MINISTRY OF HEALTH OF UKRAINE
ZAPORIZHZHIA STATE MEDICAL UNIVERSITY
Department Internal Medicine no2

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CARDIOVASCULAR DISEASE

(«INTERNAL MEDICINE» MODULE 2)

PART 4

The executive task force for students of medical faculty of 5th cource

Zaporizhzhia
2018

UDC 616.12(075.8)
B45

Ratified on meeting of the Central methodical committee
of Zaporizhzhia State Medical University
and it is recommended for the use in educational process for foreign students.
(Protocol no 5 from 24 may 2018)

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Cardiovascular diseases («Internal Medicine». Modul 2). Part 4=Серцево-судинні захворювання («Внутрішня медицина». Модуль 2). Ч. 4 : The executive task force for students of 5th course of medical faculty / A. E. Berezin, V. A. Vizir, O. V. Demidenko. – Zaporizhzhia : ZSMU, 2018. – 293 p.

The executive task force is provided for students of 5th courses of medical faculties for helping to study of some topics in the fields of cardiovascular diseases incorporated into the discipline «Internal Medicine». There is the information about the most important topics regarding diagnosis of cardiac diseases.

CONTENT

Index of acronyms

ACE	angiotensin-converting enzyme
ACEI	ACE inhibitors
ACEI	angiotensin-converting enzyme inhibitor
ACM	alcoholic cardiomyopathy
ACS	acute coronary syndrome
AHA	American Heart Association
AHF	acute heart failure
AHMD	alcoholic heart muscle disease
ANP	atrial natriuretic peptide
APA	aldosterone-producing adenomas
APAH	associated pulmonary arterial hypertension
APCs	atrial premature complexes
ARB	angiotensin receptor blockers
ARVC	arrhythmogenic right ventricular cardiomyopathy
ARVD	arrhythmogenic right ventricular dysplasia
ASD	atrial septal defect
AV	atrioventricular
AVNRT	Atrioventricular Nodal Reentrant Tachycardia
BAS	balloon atrial septostomy
BB	beta-adrenoblockers
BNP	B-type natriuretic peptide
BP	blood pressure
Bpm	beats per minute;
BSAC	British Society for Antimicrobial Chemotherapy
CA	calcium antagonists
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCB	calcium channel blocker
CCSC	Canadian Cardiovascular Society Classification
CHD	coronary heart disease
CHF	chronic heart failure
CI	cardiac index
CK	creatine kinase
CMR	cardiac magnetic resonance imaging
CNS	central nervous system
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CPR	cardiopulmonary resuscitation
CRP	C-reactive protein
CT	computed tomography
CTD	connective tissue disease
CTEPH	chronic thromboembolic pulmonary hypertension
CV	cardiovascular diseases

CVP	central venous pressure
CVVH	continuous veno-venous hemofiltration
DAD	delayed after-depolarization
DCM	dilated cardiomyopathy
DIC	disseminated intravascular coagulation
DM	diabetes mellitus
DOC	deoxycorticosterone
EA	electrical axis
EAD	early afterdepolarization;
ECG	electrocardiogram
EF	ejection fraction
EnaC	epithelial Na^+ channel
ERA	endothelin receptor antagonist
ESC	European cardiology Association
ESRD	renal failure;
GFR	glomerular filtration rate
GP	glycoprotein
GRA	glucocorticoid-remediable aldosteronism
HCM	hypertrophic cardiomyopathy
HDL- C	high-density lipoprotein cholesterol
HF	heart failure
HIV	human immunodeficiency virus
i.v.	intravenous
IABC	intra-aortic balloon counter-pulsation
ICD	implantable cardioverter-defibrillator
IDC	implantable defibrillator-cardioverter
IE	infective endocarditis
IGF	insulin-like growth factor
INR	international normalized ratio
IPAH	idiopathic pulmonary arterial hypertension
ISH	isolated systolic hypertension
IVDU	Intravenous drug use
IVUS	intravascular ultrasound
JET	functional ectopic tachycardia
LA	left arm
LAFB	left anterior fascicular block
LBBB	left bundle branch block
LL	left leg
LMWH	low molecular weight heparin
LMWH	low molecular weight heparin
LQTS	long-QT syndrome
LV	left ventricle / ventricular
LVH	left ventricular hypertrophy
LVNC	left ventricular non-compaction
LVOT	left ventricular outflow tract

MAC	mitral annular calcification
MBC	minimum bactericidal concentration
MHC	myosin heavy chain
MI	myocardial infarction
MIC	minimal inhibitory concentration
MR	mitral regurgitation
MRI	magnetic resonance imaging
MVP	mitral valve prolapsed
NBTE	nonbacterial thrombotic endocarditis
NCCLS	USA National Commmittee for Clinical Laboratory Standards
NIPPV	non-invasive positive pressure ventilation
NO	nitric oxide
NOS	nitric oxide synthase
NSTEMI	non ST-elevation MI
NT-proBNP	N-terminal fragment of pro- brain natriuretic peptide
PA	pulmonary artery
PAC	pulmonary artery catheter
PAP	pulmonary arterial pressure
PCI	Percutaneous Coronary Intervention
PDEIs	phosphodiesterase inhibitors
PDGF	platelet-derived growth factor
PEA	pulmonary endarterectomy
PH	pulmonary hypertension
PHIRST	Pulmonary arterial Hypertension and ReSponse to Tadalafil
PJT	paroxysmal functional tachycardia
PK	pharmacokinetics
PK	pharmacokinetics
PNS	peripheral nervous system
PP	pulse pressure
PPCM	peripartum cardiomyopathy
PSVTs	paroxysmal supraventricular tachycardia’s
PVCs	premature ventricular complexes
PVD	peripheral vascular disease
PVE	prosthetic valve endocarditis
PVOD	pulmonary veno-occlusive disease
PVR	pulmonary vascular resistance
PVT	prosthetic valve thrombosis
PWP	pulmonary wedge pressure
RA	right arm
RAAS	rennin-angiotensin-aldosterone system
RAP	right atrial pressure
RBBB	right bundle branch block
RCM	restricted cardiomyopathy
RCT	randomized controlled trial
RHC	right heart catheterization

RV	right ventricle/ventricular
SAECG	signal-averaging electrocardiography
$SERCA^2$	sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase pump
6MWT	6-minute walking test
SNP	sodium nitroprusside
SNS	sympathetic nervous system
SVC	superior vena cava
SVT	supraventricular tachycardia
t.i.d.	three times a day
TAPSE	tricuspid annular plane systolic excursion
TDI	tissue Doppler imaging
TEE	transesophageal echography
TEE	transesophageal echography
TF	tissue factor
TPG	transpulmonary pressure gradient (mean PAP – mean PWP)
TTE	transthoraxic echography
VA	ventriculoatrial
VF	ventricular fibrillation
VPC	ventricular premature complexes
VSR	ventricular septal rupture
VT	ventricular tachycardia
WHO	World Health Organization
WHO-FC	World Health Organization functional class

CHAPTER 1
PULMONARY THROMBOEMBOLISM

Venous thromboembolism (VTE) encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE). Diagnosis, management, and prevention of VTE can be standardized and adapted to critical pathways. Cardiologists need to be adept in detecting PE and in managing complicated cases that require catheter-directed thrombolysis, mechanical thrombectomy, or placement of an inferior vena caval filter. Furthermore, cardiologists should set the standard for recommending and implementing prophylaxis among their hospitalized patients and among patients on whom they consult preoperatively.

Cardiologists are often summoned to help diagnose suspected PE because of their familiarity with the differential diagnosis of chest pain and dyspnea, their ability to recognize clinical manifestations of acute pulmonary hypertension, and their facility with echocardiography for risk stratification. The cardiologist is often the specialist asked to manage high-risk patients with thrombolysis and, if necessary, suction catheter embolectomy. The cardiologist may also serve as the liaison with the cardiac surgeon who is summoned to perform urgent open surgical embolectomy.

Epidemiology

VTE is the third most common cardiovascular disease, after acute coronary syndrome and stroke. VTE spans a wide age range, from teenagers to the elderly. It strikes all socioeconomic groups in developed Western countries. However, rates of VTE in Japan are quickly catching up to those in North America and Europe. Factor V Leiden is an autosomal dominant single-point genetic mutation that increases the likelihood of developing DVT or PE. This mutation also contributes to placental vein thrombosis and is associated with otherwise unexplained first trimester pregnancy losses. Racially, factor V Leiden is most commonly found in Caucasians, especially Northern Europeans. The mutation expresses itself with clinical venous thrombosis more frequently as patients age. Although factor V Leiden is the most thoroughly studied hereditary thrombophilia, other mutations with similar effects have been described, such as the prothrombin gene mutation.

Acquired risk factors warrant attention. These include long-haul air travel, women's health issues (oral contraceptives, pregnancy, and hormone replacement therapy), obesity, cigarette smoking, hypertension, increasing age, and cancer. Certain combinations of genetic and acquired risk factors lead to a markedly increased likelihood of thrombosis, such as oral contraceptives in the setting of factor V Leiden. Sorting out the contributions of heredity versus environment remains challenging. Widespread genetic testing will rarely change the management of patients with thromboembolic disease. Future studies will define more precisely the interaction between genetic thrombophilia and acquired risk factors for thrombosis.

For those who survive, DVT may result in lifelong disability with painful and disfiguring venous insufficiency of the legs. Chronic leg swelling, bulging varicose veins, and occasional ulceration may ensue, along with brownish skin discoloration at the medial malleolus. Venous insufficiency is surprisingly common. It can develop in as many as one-third of patients who have DVT. Often, it becomes apparent as a late complication, years after the initial thrombotic event. Acute PE patients may develop chronic thromboembolic pulmonary hypertension within 6 weeks to several years. Chronic thromboembolic disease develops about 4% of the time. This is an upward revision from previous estimates of 1 in 500 cases. This devastating complication can cause profound dyspnea and lifestyle limitation that precludes ordinary walking and working outside the home. Patients with pulmonary hypertension are susceptible to sudden cardiac death and must cope with dyspnea at rest as well as with exertion.

There is also a huge psychological burden for many patients with VTE. They often are young and appear otherwise healthy. Yet their lifestyle is impaired by the constraints of long-term anticoagulation. They wonder whether their children or siblings will suddenly develop DVT or PE. Also, for those who discontinue anticoagulation, they can never be certain about whether VTE will recur.

VTE is underdiagnosed because it is often asymptomatic. The best clue to detection may be the clinical setting and assessment of predisposing risk factors. These include: medical risk factors such as prior VTE, cancer, surgery, trauma, bedrest, or immobilization, which are beyond control of the patient (Table 1.1), as well as envi-

ronmental factors, such as obesity, cigarette smoking, hypertension, oral contraceptives, pregnancy, hormone replacement therapy, and long-haul air travel (Table 1.1). VTE is often a chronic illness. Overall, about 30% will suffer recurrence over the ensuing 10 years unless anticoagulation is continued.

Table 1.1

Risk Factors for venous thromboembolism

Medical Risk Factors
1. Prior venous thromboembolism
2. Cancer and/or cancer chemotherapy
3. Surgery or trauma
4. Bedrest or immobilization

Environmental Risk Factors
1. Obesity
2. Cigarette smoking
3. Hypertension
4. Oral contraceptives, pregnancy, hormone replacement therapy
5. Long-haul air travel

Diagnosis

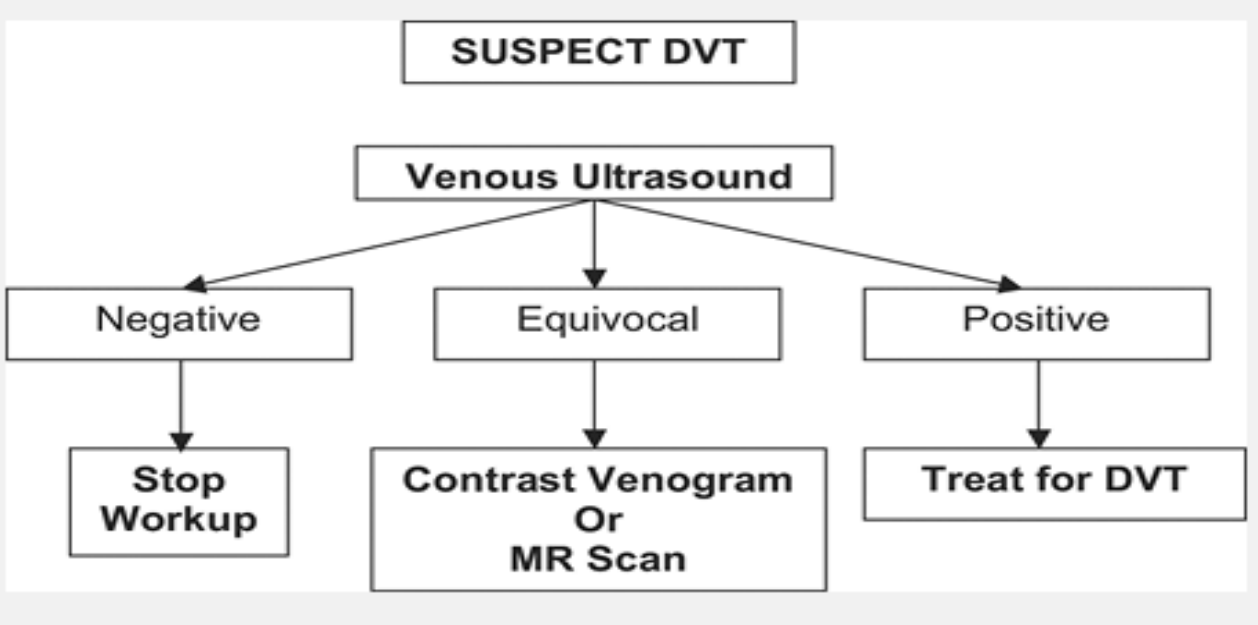
Deep Vein Thrombosis

Figure 1.1 summarizes a critical pathway for DVT diagnosis. For DVT patients, the most common chief complaint is a cramp or charley horse in the lower calf that does not abate and gradually worsens after several days. Discomfort, at first intermittent, becomes persistent. Swelling may then ensue. Occasionally, erythema accompanies the leg edema. Erythema often suggests concomitant superficial venous phlebitis with saphenous vein involvement or coexisting cellulitis.

Unexplained arm edema may herald the presence of upper extremity DVT. This condition occurs most commonly in two divergent and contrasting populations: (a) as a complication of a chronic indwelling central venous catheter, or (b) in otherwise healthy individuals who have been exerting themselves with activities such as weight lifting. Do not immediately jump to the diagnosis of DVT. Keep in mind the need to maintain a differential diagnosis. Sudden, excruciating calf discomfort is most likely due to a ruptured Baker's cyst. Fever and chills usually suggest cellulitis rather than DVT, though DVT may be present concomitantly.

Figure 1.1

Diagnosis algorithm for deep vein thrombosis



When detected early after onset, the physical findings of DVT may be minimal, consisting of mild palpation discomfort in the lower calf. If the DVT propagates proximally because it is not recognized at an early stage, one might find massive thigh swelling and marked tenderness when palpating the inguinal area over the course of the femoral vein. Such patients often have difficulty walking and may require a cane, crutches, or a walker. If a patient has upper-extremity venous thrombosis, there may be asymmetry in the supraclavicular fossae or in the girth of the upper arms. There may also be a prominent superficial venous pattern over the anterior chest wall.

If the leg is diffusely edematous, DVT is unlikely. Much more common is an acute exacerbation of venous insufficiency due to postphlebitic syndrome. When DVT is suspected, it is useful to estimate the clinical likelihood that DVT will be the final diagnosis. Clinical probability can be estimated using the formal Wells DVT Scoring System, but this approach is rarely used. Much more common is to estimate the likelihood by gestalt.

A few institutions, especially in Europe, favor stopping the DVT workup if the clinical probability is low and a D-dimer enzyme-linked immunosorbent assay (ELISA) is normal and not elevated. However, at most institutions in the United States,

including Brigham and Women's Hospital (BWH), we image with venous ultrasonography virtually all patients suspected of DVT. Of particular importance is proper interpretation of the ultrasound report. Unfortunately, the distal portion of the deep femoral vein is called the uperficial femoral vein. Even though superficial is part of the name of this vein, it is a deep vein, and patients with superficial femoral vein thrombosis should be treated for DVT. They should not be discharged home with the misdiagnosis of superficial thrombophlebitis. Superficial femoral vein thrombosis can be a lethal misnomer.

Usually, the venous ultrasound examination is definitive in detecting or excluding DVT in the large upper extremity veins as well as the deep veins from the common femoral proximally to the calf veins distally. Occasionally, the imaging test is equivocal because of the patient's body habitus, recent leg trauma or surgery, or profound edema that limits compression of vascular structures. Under these circumstances, consider pursuing other imaging. Magnetic resonance imaging (MRI) can provide surprisingly precise, detailed information about the venous system. MRI is especially useful in assessing suspected pelvic vein thrombosis and in defining the extent of upper extremity vein thrombosis. MRI can also help estimate the age of thrombus based on various spin characteristics of the image

Invasive contrast venography is rarely performed nowadays as a diagnostic test. Of necessity, invasive contrast venography is the first step when catheter intervention is planned with catheter-directed thrombolysis, suction embolectomy, angioplasty, or stenting.

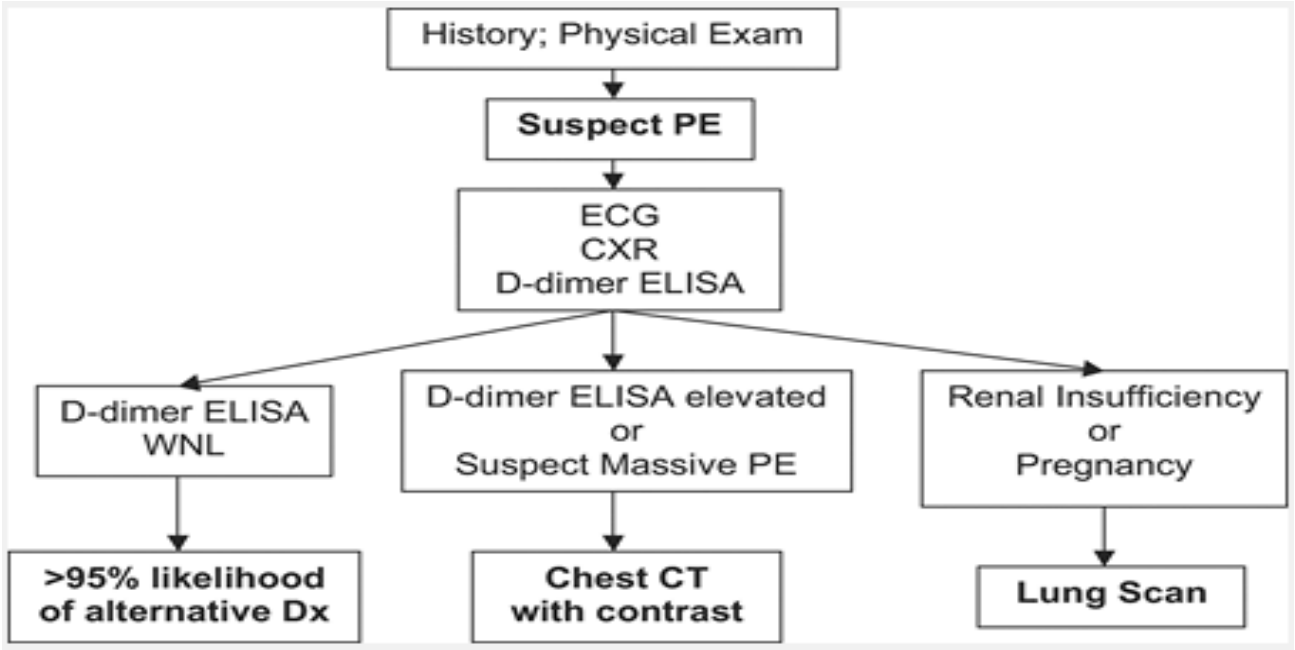
Pulmonary Embolism

Figure 1.2 summarizes a critical pathway for PE diagnosis. Unexplained dyspnea and chest pain, often pleuritic, are the most common symptoms of PE. The Wells Scoring System for PE enjoys more popularity than the DVT Scoring System. However, I have never had a patient presented to me with incorporation of the Wells Scoring System unless I asked for it to be included. This Canadian system is used for clinical research purposes, so it is worth knowing. Nevertheless, gestalt is by far the most common way that clinical probability of PE is estimated. The Wells Scoring System

is a point system where low probability for PE is less than 2 points, moderate probability is 2 to 6 points, and high probability is greater than 6 points. Seven variables comprised the point score: (a) clinical symptoms of DVT (3 points), (b) no alternative diagnosis (3 points), (c) heart rate greater than 100 beats per minute (1.5 points), (d) immobilization or surgery within the prior 4 weeks (1.5 points), (e) previous DVT or PE (1.5 points), (f) hemoptysis (1 point), and (g) cancer (1 point). The variable no alternative diagnosis is controversial because it is subjective, not objective, and is the driving forceв that makes the Wells Score an accurate predictor of the presence of absence of PE.

Figure1.2

Diagnosis algorithm for pulmonary thromboembolism



In a prospective observational study at BWH's Emergency Department, there was a trend toward increasing accuracy of PE diagnosis with increasing clinical experience. However, the difference was not as great between an intern and an attending physician as one might have expected. Physicians were asked whether they thought PE was the most likely diagnosis. The frequency of true-positive assessments was 17% for interns and 25% for attending physicians. Keep in mind that only about 10% of patients who undergo emergency imaging for PE actually have PE. Therefore, the astute clinician will formulate a differential diagnosis (Table 1.3), even when the manifestations of PE seem obvious.

Table 1.3

Adjunctive Measures for DVT Management

1	Obtain family history and consider hypercoagulable workup
2	Prescribe below-knee vascular compression stockings, 20 to 30 or 30 to 40 mm Hg, to prevent venous insufficiency
3	Provide emotional support
4	Educate subjects to use: LMWH and warfarin
5	Explain controversy concerning optimal duration of anticoagulation

The classic findings such as tachycardia, tachypnea, or hypotension actually represent unusual patients with extensive PE and impaired compensatory mechanisms. With improved imaging modalities, PE is with increasing frequency identified in normotensive patients who may appear anxious, but whose heart rate is less than 100 beats per minute and whose respiratory rate, if actually counted inconspicuously, is less than 16 breaths per minute.

Electrocardiography

All patients suspected of PE undergo electrocardiography. Although new-onset atrial fibrillation/flutter and a new S1Q3T3 sign are often cited as helpful clues, these findings are rare. The most common manifestation of right heart strain is T wave inversion in leads V1 to V4.

Chest X-Ray

The chest X-ray is useful for establishing alternative diagnoses such as pneumonia, congestive heart failure, or pneumothorax. PE patients may, however, present with an entirely normal chest x-ray.

Blood Tests

Arterial blood gases are unreliable and can be misleading. Specifically, patients who are otherwise healthy can present with large PE and yet maintain a high arterial PO_2 and a normal arterial-alveolar oxygen gradient. The only useful blood screening test is the plasma D-dimer ELISA. D-dimers are released in the presence of PE because of endogenous fibrinolysis. Plasmin dissolves some of the fibrin clot from PE, and subsequently, D-dimers are released into the plasma. The D-dimers can be recognized by commercially available monoclonal antibodies. The D-dimer has a high negative predictive value for PE. This means that if the D-dimer is normal, it is ex-

tremely unlikely that PE is present.

D-dimers are highly sensitive for the diagnosis of PE. This high sensitivity is crucially important in a screening test. However, D-dimers are nonspecific and will often be elevated in conditions that mimic PE such as acute myocardial infarction or pneumonia. They are also elevated in patients with cancer, in second or third trimester pregnancy, and in the postoperative state. Plasma D-dimer levels are usually elevated in hospitalized patients. Therefore, their contribution to diagnosis is greatest in outpatients suspected of PE; their use among hospitalized patients is minimal because the test results are rarely normal.

Imaging Tests

If the D-dimer ELISA is elevated, the next step is to order computed tomographic (CT) scanning of the chest. Chest CT scanning has revolutionized our diagnostic approach to suspected PE. By 2001, CT scanning was being used more often than lung scanning to investigate suspected PE. The clinical validity of using a CT scan to rule out PE is similar to that reported for conventional pulmonary angiography. This technology has evolved rapidly. The latest generation of scanners can diagnose submillimeter PE in sixth-order vessels. These thrombi are so tiny that their clinical significance is uncertain.

Chest CT scanning provides a satisfying dichotomous yes or no answer to whether PE is present. The CT examination can help identify the source of the clots in the legs, pelvis, or upper extremity. When PE is not present, the CT scan can help diagnose alternative pulmonary illnesses such as pneumonia, cancer, and interstitial lung diseases not apparent on the chest x-ray. The major limitation of chest CT scanning is the need to administer intravenous contrast.

Lung scanning has been the standard noninvasive imaging test for patients suspected of PE. It is highly specific when there is high probability for PE but it is not sensitive. Based on the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED), more than half of the patients with PE proven by angiography had non-high probability lung scans. The principal disadvantage of lung scanning is that the majority of the scans are of intermediate probability for PE and frustrate the clinician be-

cause they do not provide a clear-cut answer to the diagnostic dilemma of whether PE is present.

When the lung scan is equivocal, leg vein ultrasonography may be helpful. If the venous ultrasound demonstrates DVT, this usually suffices as a surrogate for PE and the diagnostic workup can stop at this point. However, it is crucial to understand that as many as half of patients with PE will have no evidence of DVT, probably because the clot has already embolized to the lungs. With a multislice CT scanner and a technologically adequate examination, the diagnosis of PE should be considered ruled out if the chest CT is negative. If a single-slice CT scanner shows no evidence of PE, it is still possible that multiple subsegmental PEs are present. Therefore, if clinical suspicion remains high, and if there is no access to a multislice CT scanner, and if a lung scan is equivocal, then invasive contrast pulmonary angiography should be considered.

MRI is promising because it can combine imaging of the pulmonary arteries with functional and structural assessment of the right ventricle. MRI is also an excellent alternative among patients who are poor candidates for receiving intravenous contrast agent because of renal insufficiency or contrast dye allergy. For now, though, this technology is not sufficiently mature to be placed on a diagnosis critical pathway.

Initial Therapy

Deep Vein Thrombosis

The treatment of DVT has changed dramatically. DVT management used to require a 5-day hospitalization with intravenous unfractionated heparin administered as a bridge to warfarin. The administration of intravenous heparin required an initial intravenous bolus followed by a continuous infusion. The dose was titrated to achieve an activated partial thromboplastin time (aPTT) two to three times control. Generally, this corresponded to an aPTT between 60 and 80 seconds. This standard approach to therapy was problematic. First, most patients were underdosed with heparin so that it required 24 to 48 hours to achieve therapeutic levels. There would be multiple changes in the dose of the continuous intravenous heparin infusion, based on emergency (STAT) aPTT values. These changes in dosing often led to medication errors.

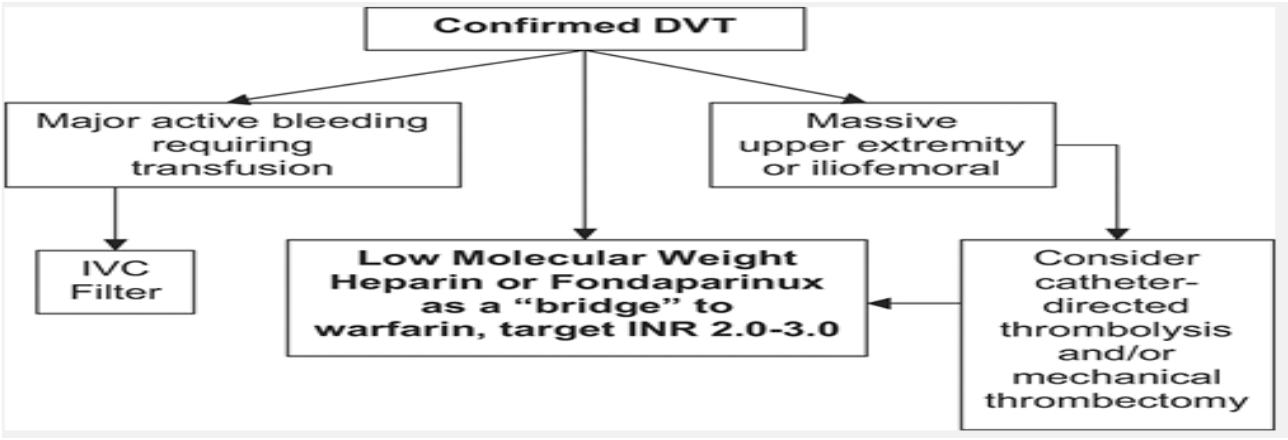
They were also extremely inconvenient and required additional physician and nurse time, often in the middle of the night. Although a robotic dosing system has been successfully tested, the need for traditional heparin appears to be limited to patients who are massively obese or in renal failure or who have an abhorrence of injections. Exposure to unfractionated heparin also increased the possibility of developing heparin-induced thrombocytopenia. Now, however, most patients receive acute DVT treatment as outpatients or with an overnight hospital stay. In the United States, immediate anticoagulation is usually achieved with the low-molecular-weight heparin enoxaparin. This strategy is safe and cost effective. Other U.S. Food and Drug Administration (FDA)-approved regimens include the low-molecular-weight heparin tinzaparin and the anti-Xa pentasaccharide fondaparinux.

Enoxaparin has received FDA approval for DVT treatment, as a bridge to warfarin because of its superior efficacy and safety compared with unfractionated heparin. Low-molecular-weight heparin is administered as a fixed dose according to weight (1 mg/kg twice daily or, among hospitalized patients, 1.5 mg/kg once daily) and is cost effective because no routine laboratory testing is required. It has become the foundation of anticoagulation of DVT patients and can facilitate complete outpatient treatment of this disease among properly selected patients.

Like low-molecular-weight heparin, fondaparinux is administered by subcutaneous injection, and no laboratory monitoring is required . Fondaparinux requires a once daily subcutaneous injection, requires only one of three possible doses based on weight, and has never been reported to cause heparin-induced thrombocytopenia. For fondaparinux, patients weighing less than 50 kg receive 5 mg, 50-kg to 100-kg patients receive 7.5 mg, and patients weighing more than 100 kg receive 10 mg. The drug is available in prefilled syringes of 5 mg, 7.5 mg, or 10 mg. Even those patients who require prolonged hospitalization (Fig. 1.3) can usually be managed with low-molecular-weight heparin or fondaparinux until they achieve a stable and therapeutic level of warfarin, based upon a target International Normalized Ratio (INR) of 2.0 to 3.0.

Figure 1.3

Deep vein thrombosis treatment



Overlap with the bridging anticoagulant should continue until two INRs are obtained in the therapeutic range. The success of an anticoagulation critical pathway depends primarily on reliable dosing and monitoring of warfarin. However, adjunctive measures for DVT management are also of paramount importance

Direct Thrombin Inhibitors

For patients with suspected or proven heparin-induced thrombocytopenia, neither unfractionated heparin nor low-molecular-weight heparin can be safely administered. The only FDA-approved alternative is the use of direct thrombin inhibitors, either argatroban or lepirudin. Argatroban, metabolized primarily by the liver, is particularly useful for patients with renal insufficiency. Lepirudin, metabolized primarily by the kidneys, is particularly useful for patients with hepatic dysfunction.

Catheter-Directed Interventions

The indications for DVT thrombolysis are uncertain and controversial. DVT thrombolysis should theoretically restore venous valve patency and function, thereby preventing the development of venous insufficiency and the postthrombotic syndrome. However, this hypothesis has not been proven. In addition, DVT thrombolysis may be especially useful in patients who have developed an upper-extremity thrombosis due to a long-term indwelling central venous catheter. For example, a patient may require completion of additional courses of chemotherapy or may need intravenous hyperalimentation. At BWH, we advise DVT catheter-directed thrombolysis for young, otherwise healthy patients who have massive iliofemoral DVT with marked leg swelling, leg tenderness, and difficulty walking (Fig. 2.3). For patients with large

DVT who require intervention in addition to anticoagulation, a combination of catheter-directed thrombolysis and catheter-assisted thrombectomy is usually utilized.

Chronic Venous Insufficiency

Venous insufficiency can first become clinically apparent several years after the initial DVT. The pathophysiological explanation is damage to the venous valves of the legs. Late onset of venous insufficiency is a separate problem from recurrent DVT. Wearing 30- to 40-mm Hg below-knee vascular compression stockings while ambulatory has proved effective in randomized clinical trials. Prescribing vascular compression stockings will halve the rate of subsequent venous insufficiency.

Emotional Support

Many patients with VTE will appear healthy and fit. They may be burdened with fear about the possible genetic implications of DVT or PE. They will often feel overwhelmed when advised to continue lifelong anticoagulation. Patients in whom anticoagulation is discontinued after 3 to 6 months of therapy may feel vulnerable to a future recurrent VTE. In addition, family, friends, and peers might not understand the implications of DVT or PE. My nurse and I help provide emotional support by running a support group one evening every third week.

Pulmonary Embolism

Risk Stratification

The clinical spectrum and severity of PE is wide. Prompt and accurate risk stratification are of paramount importance. After the diagnosis of PE is established, critical pathways are utilized to streamline, standardize, and optimize therapy (Fig. 1.4). Most patients with PE will remain hemodynamically stable and will not suffer recurrent PE or develop chronic pulmonary hypertension as long as they receive adequate anticoagulation. If the PE is anatomically small, involving less than 30% of the lungs, then it is likely that right ventricular (RV) function will not be impaired, especially if there is no underlying cardiopulmonary disease.

Cardiac Biomarkers

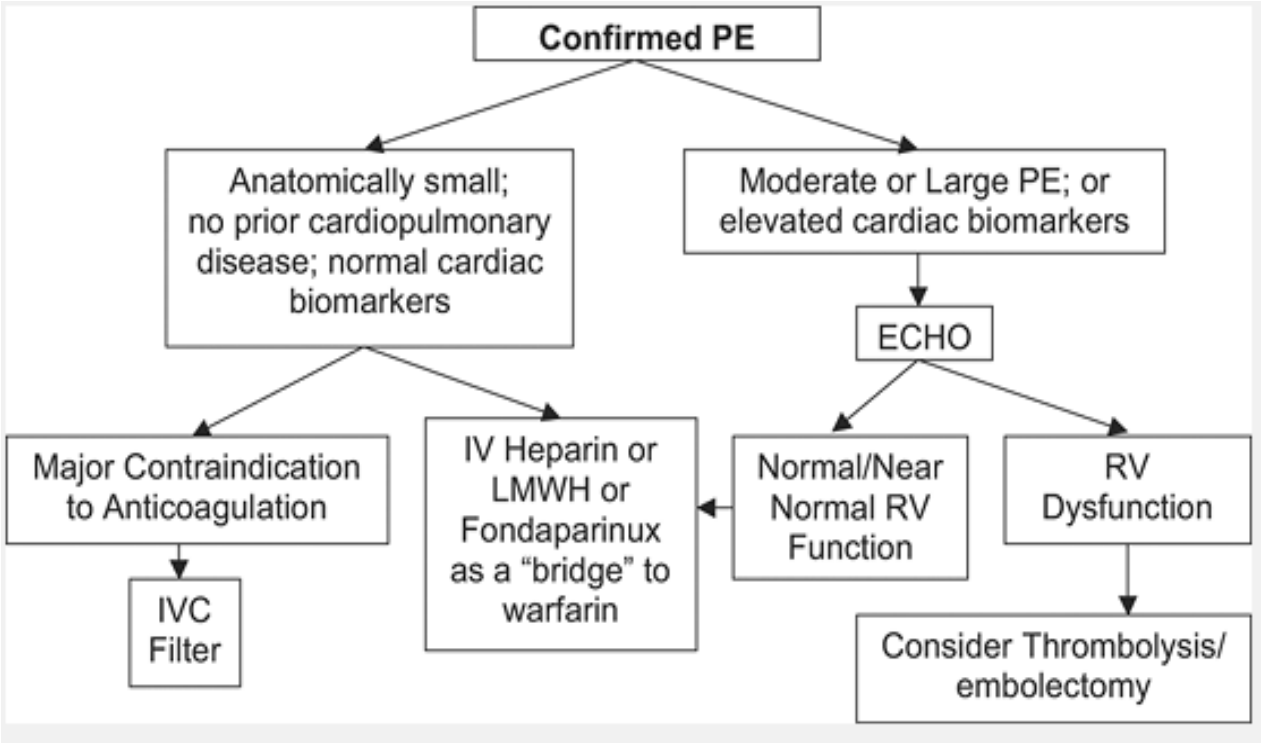
Imaging the right ventricle is probably not necessary if the patient appears clinically stable and has normal levels of cardiac biomarkers. Cardiac troponins are sensitive

and specific biomarkers of myocardial cell damage. Elevations of troponin in PE patients are mild and of short duration compared with acute coronary syndromes. In acute PE, troponin levels correlate well with the extent of RV dysfunction

Natriuretic peptides represent another class of cardiac biomarkers. The principal stimulus for synthesis and secretion of brain natriuretic peptide (BNP) is ventricular cardiomyocyte stretch. The prohormone, proBNP, has 108 amino acids.

Figure 1.4

Risk Stratification of pulmonary embolism



The biologically active BNP is a 32-amino acid peptide, with a plasma half life of 20 minutes. The remaining part of the prohormone, N-terminal (NT)-proBNP, has 76 amino acids and a half life of 60 to 120 minutes. The major role of cardiac biomarkers in risk stratification is to identify low-risk patients who do not require imaging of the right ventricle. Patients with normal levels of troponin and BNP are low risk. A simple risk stratification algorithm for PE patients is to employ either troponin or NT-proBNP testing as an initial step. Echocardiography should then be obtained if elevated biomarker levels are found. Echocardiography is not needed if both troponin and BNP (or pro-BNP) are normal.

Echocardiography

Classic risk stratification used to rely primarily on frequent assessment of systemic arterial pressure and heart rate. When patients became dependent on pressors to maintain a systolic blood pressure greater than 90 mm Hg, they were labeled as high risk. This strategy delayed intervention with thrombolysis or embolectomy until patients were developing multisystem organ failure due to evolving cardiogenic shock. By that point, the response to aggressive intervention with thrombolysis or embolectomy was often disappointing. Our approach to risk stratification has changed markedly. We now believe that among normotensive patients, assessment of RV function is pivotal to prognosticate accurately after PE is diagnosed. This assessment can at times be accomplished by finding normal cardiac biomarkers. However, patients who develop worsening RV function despite adequate anticoagulation have an ominous prognosis and are at high risk of in-hospital complications, including recurrent PE, respiratory failure, and death.

The International Cooperative Pulmonary Embolism Registry (ICOPER) enrolled 2,454 patients from 52 hospitals in 7 countries and is the largest PE registry that has ever been published. In ICOPER, age greater than 70 years increased the likelihood of death by 60%. Six other risk factors independently increased the likelihood of mortality by a factor of twofold to threefold: cancer, clinical congestive heart failure, chronic obstructive pulmonary disease, systemic arterial hypotension with a systolic blood pressure of <90 mm Hg, tachypnea (defined as >20 breaths per minute), and RV hypokinesis on echocardiogram, an especially useful sign to identify high-risk patients who might be suitable for aggressive interventions such as thrombolysis or embolectomy. It is important to emphasize that RV dysfunction on echocardiogram is an important predictor of prognosis, even in patients with a systolic blood pressure greater than 90 mm Hg. Among this population in ICOPER, the 30-day survival rate was 91% in patients without RV hypokinesis compared with 84% in those with RV hypokinesis on baseline echocardiography.

Combined Biomarkers and Echocardiography

The combination of elevated biomarkers and moderate or severe RV dysfunction can portend a lethal outcome. At BWH, the combination of echocardiographic

RV enlargement and elevated troponin significantly increased the 30-day mortality (38%) compared with patients with elevated troponin alone (23%), RV dilation alone (9%), and neither (5%).

Chest CT

Among patients with PE on chest CT scan, RV enlargement, defined as a reconstructed RV to left ventricular (LV) dimension ratio greater than 0.9, correlates with an unstable hospital course. In 431 consecutive patients, RV enlargement predicted 30-day death with a hazard ratio of 5.2, after multivariable analysis. This approach to prognosis has not been as widely verified as RV dysfunction on echocardiography.

Thrombolysis

For patients with massive PE or smaller PE accompanied by moderate or severe RV dysfunction, anticoagulation alone may not yield a clinically successful outcome. When considering thrombolysis, careful screening for potential contraindications is necessary. Pay particular attention to a history of poorly controlled hypertension or presentation with PE and systemic hypertension. Patients should also be questioned about prior head trauma, seizures, or stroke. The most feared complication from thrombolysis is intracranial bleeding. In ICOPER, 304 of the 2,454 patients received thrombolysis, and of these, 3% of the patients suffered intracranial hemorrhage. In a separate registry of 312 patients receiving thrombolysis for PE in five clinical trials, there was a 1.9% risk of intracranial bleeding. Two of the six patients had pre-existing known intracranial disease and nonetheless received thrombolysis, in violation of the exclusion criteria listed in the clinical trial protocols. Two of the six intracranial hemorrhages probably were due to administration of heparin and not thrombolysis, because they occurred late, 62 and 157 hours after thrombolysis. Diastolic blood pressure on admission was elevated in patients who developed intracranial hemorrhage compared with those who did not. The mean age of patients with major bleeding was 63 years, whereas that of patients with no hemorrhagic complication was 56 years. There was a 4% increased risk of bleeding for each additional year of

age. Increasing body mass index and pulmonary angiography were also significant predictors of hemorrhage.

Predictors of Thrombolysis Efficacy

There is an inverse association between duration of symptoms and improvement on lung scan reperfusion after thrombolysis. After controlling for age and initial lung scan defect size, there was 0.7% less reperfusion per additional day of symptoms. Thus, delay in administering thrombolysis will attenuate efficacy. Nevertheless, thrombolysis is still useful in patients who have had symptoms for 6 to 14 days.

Practical Points

The FDA approved recombinant human tissue-type plasminogen activator (rt-PA) in 1990. Heparin is not coadministered, an important difference compared to thrombolysis for myocardial infarction. After administering thrombolysis, a partial thromboplastin time (PTT) should be obtained immediately. Usually, the PTT is less than 80 seconds, and intravenous unfractionated heparin can be initiated (or resumed) as a continuous intravenous infusion, without a loading dose. If the PTT exceeds 80 seconds, heparin should be withheld, and the test should be repeated every 4 hours until it drifts down to the recommended target. Substitution of low-molecular-weight heparin or fondaparinux for intravenous unfractionated heparin following thrombolysis has not been studied. Nevertheless, in clinical practice, it is quite common after a patient has stabilized to transition from intravenous unfractionated heparin to low-molecular-weight heparin, while initiating concurrent oral anticoagulation with warfarin.

Embolectomy

Catheter-Based Embolectomy

Greenfield demonstrated that transvenous catheter pulmonary embolectomy was feasible. He devised a steerable catheter with a distal radiopaque plastic cup. Syringe suction could be applied to aspirate a portion of the embolus into the cup, and a sustained vacuum by the syringe held the embolus as the catheter was withdrawn. This 12 French (F) double-lumen balloon-tipped catheter required femoral or jugular venotomy.

Interventional angiographers favor the Meyerovitz technique for aspiration; an 8 F or 9 F coronary guiding catheter without sideholes is placed through a 10 F arrow sheath; the clot is aspirated with a 60-mL syringe. Mechanical fragmentation and pulverization of thrombus can be accomplished with a rotating basket catheter, high-pressurized jets of normal saline, or a pigtail rotational catheter embolectomy. Mechanical fragmentation can also be combined with thrombolysis. Recently, a new percutaneous catheter thrombectomy device has been tested for acute PE. The central part of the catheter system is a high-speed rotational coil within the catheter body that (a) creates negative pressure through an L-shaped aspiration port at the catheter tip, (b) macerates aspirated thrombus, and (c) removes macerated thrombus.

Surgical Embolectomy

Surgical embolectomy is best suited for patients with contraindications to thrombolysis, intracardiac thrombus, or both. Ideally, patients who have an adverse prognosis based on risk stratification with cardiac biomarkers and RV imaging will be referred prior to the onset of cardiogenic shock and multisystem organ failure.

At BWH, we have lowered our threshold for embolectomy. It is used an aggressive multidisciplinary approach to triage patients with acute PE. It is achieved rapid diagnosis with chest CT, which defines the clot burden and the surgical accessibility of thrombus. It is assessed RV function in patients with normal systemic arterial pressure. For those patients deemed at high risk, it is considered surgical embolectomy if there are contraindications to thrombolytic therapy. Surgical technique has improved. It is avoided aortic cross clamping and operate on cardiopulmonary bypass with a warm, beating heart. It is did not utilize intraoperative hypothermia. Blind instrumentation of the fragile pulmonary arteries is avoided. Extraction is limited to directly visible clot. In a series of 47 patients at BWH, there were three (6%) operative deaths, one with preoperative cardiac arrest. Actuarial survival at 1-year follow-up was 86%.

Pulmonary Thromboendarterectomy

Patients with chronic pulmonary hypertension due to prior PE may be virtually bedridden with breathlessness due to high pulmonary arterial pressures. Patients with

chronic PE and cor pulmonale should receive lifelong anticoagulation and, in addition, may be candidates for lifelong continuous oxygen therapy. However, thromboendartectomy for chronic thromboembolic pulmonary hypertension will markedly reduce pulmonary artery pressures if successful. The operation is technically more demanding and riskier than embolectomy for acute PE.

The operation involves a median sternotomy incision, institution of cardiopulmonary bypass, and deep hypothermia with circulatory arrest periods. Incisions are made in both pulmonary arteries into the lower lobe branches. Pulmonary thromboendarterectomy is always bilateral, with removal of both organized thrombus and an endarterectomy plane that includes all involved vessels. When surgery is successful, one can expect a gradual decline in the pulmonary arterial pressures during the first few postoperative months, with a concomitant improvement in quality of life among patients previously debilitated from chronic pulmonary hypertension. Among properly selected patients at experienced centers, the mortality rate from thromboendarterectomy is between 5% and 10%. The two major causes of mortality are: (a) inability to remove sufficient thrombotic material at surgery, resulting in persistent postoperative pulmonary hypertension and RV dysfunction; and (b) severe reperfusion lung injury. Thus, at designated centers, thromboendarterectomy can be performed with good results and at an acceptable risk to reduce debility from cor pulmonale due to PE.

Inferior Vena Caval Filters

Inferior vena caval filters are mechanical devices that are ordinarily placed below the renal veins to prevent embolization of thrombus from the pelvic or deep leg veins to the pulmonary arteries. The principal two indications for filter placement are (a) active bleeding (such as gastrointestinal hemorrhage requiring transfusion) that precludes anticoagulation, or (b) well-documented recurrence of PE despite therapeutic levels of anticoagulation. Other indications for PE are soft but might include situations such as preoperative insertion in a patient with recent PE who must undergo urgent or emergency surgery, such as hip fracture repair. A review of the U.S. National Hospital Discharge Survey showed a 20-fold increase in inferior vena caval filter

placement over the past two decades. Almost half the filters were placed in patients who had established DVT without pulmonary embolism. In the U.S. acute DVT registry of 5,451 patients, 14% of all patients underwent filter placement.

The largest trial of permanent vena caval filter placement followed patients for 8 years and found that filters reduced the risk of PE but increased the risk of DVT. Filters had no effect on survival.

Filters are almost always effective in preventing PE, but they do not halt the thrombotic process. Furthermore, filters appear to predispose to thrombosis and to DVT with the filter as the nidus for new clot formation. Therefore, in general, once a bleeding problem has been brought under control, anticoagulation should be initiated. Retrievable vena caval filters can be placed when it is uncertain that a patient will require a permanent filter. If not retrieved, the filter becomes a permanent filter. Such devices are especially suited for patients who have a transient risk factor for venous thrombosis or who are temporarily suffering from a bleeding problem that precludes anticoagulation.

Hospital Length of Stay

The FDA has not approved an abbreviated hospital length of stay for patients who present primarily with symptomatic PE. Some patients will be at such low risk that they can be managed as outpatients. The duration of hospitalization depends on risk assessment and clinical response to therapy. The hospital environment does have an important role for assessing response to therapy, ensuring resolution of symptoms of PE, such as shortness of breath, and providing education about PE and emotional support.

Outpatient Follow-Up

The initial office visit is ordinarily scheduled at about 2 weeks after the PE. The focus is on ensuring compliance with warfarin and discussing an optimal schedule for resumption of activities. For patients with an initial echocardiogram showing elevated pulmonary artery pressures, a repeat echocardiogram at 6 weeks may be useful. Patients with persistent moderate or severe pulmonary hypertension are susceptible to developing chronic thromboembolic pulmonary hypertension.

Oral Anticoagulant Therapy

Under certain circumstances, long-term anticoagulation with low-molecular-weight heparin rather than warfarin will be appropriate. Extended enoxaparin monotherapy for acute symptomatic PE appears feasible and safe among properly selected patients. Consider this approach when the patient has underlying cancer, cannot tolerate warfarin because of rash or alopecia, or has great difficulty maintaining warfarin within the target therapeutic range.

In the CLOT Trial, 672 patients with cancer and acute DVT or PE were randomly assigned to dalteparin, a low-molecular-weight heparin, as a bridge to oral anticoagulation versus dalteparin as monotherapy for 6 months. During the study period, the probability of recurrent VTE was 17% in the oral anticoagulant group compared with 9% in the dalteparin monotherapy group (P = 0.002). There was no significant difference in the rate of major bleeding.

Warfarin

Warfarin is one of the most difficult drugs to dose and monitor because of marked patient-to-patient variability, drug drug interactions, and drug food interactions. Warfarin is not given in a fixed dose. Instead, it is administered in an adjusted dose to achieve a target prothrombin time expressed as an INR. For most patients, the target INR is between 2.0 and 3.0.

Beware that 1% to 3% of patients have a genetic mutation that delays metabolism of the S-racemer of warfarin. These patients become fully anticoagulated with tiny doses of warfarin, in the range of 1.0 to 1.5 mg daily.

Centralized anticoagulation services help patients receiving warfarin therapy to achieve better outcomes compared to the usual care provided by their personal physicians. This approach to anticoagulation management is rapidly gaining acceptance throughout North America and Europe as a strategy that maximizes patient safety. A centralized approach allows expert nurses, pharmacists, and physicians' assistants to develop expertise and coordinate efforts that minimize bleeding and clotting complications. The core philosophy is to achieve a coordinated and systematic approach.

A centralized telephonic model provides a setting for a small number of providers to manage a large patient population dispersed over a wide geographic area. Successful services require knowledgeable and experienced providers, reliable laboratory monitoring, and an organized system for timely patient follow-up. A recent report showed that a centralized, telephone-based anticoagulation service improved the time spent in a therapeutic range of anticoagulation. This resulted in fewer complications compared with usual care. At BWH, we initiated an anticoagulation service in December 1996. Our volume increased from 72 patients staffed by 1 nurse and medical director to more than 1,900 patients staffed by 4 clinicians (nurses, physicians' assistants, and pharmacists), 1 administrator, and a medical director. This mission statement has six principles:

- Careful monitoring and dosing of anticoagulants among hospitalized patients and outpatients
- Facilitating and coordinating anticoagulation care among providers
- Transitioning (bridging) anticoagulation between the home and hospital settings
- Educating patients, families, and professionals about the most recent developments in anticoagulation therapy
- Continuous quality improvement to minimize thromboembolic and hemorrhaging complications, including tracking and critique of each complication that does occur
- Organizing and participating in clinical research projects

We assessed our major bleeding complication rate in the BWH Anticoagulation Service in 2,460 patients with 3,684 years of warfarin exposure from 2000 to 2003. Eleven patients had 12 nonfatal major bleeding complications, with no fatal bleeds during the study. The average hospitalization cost per patient was $15,988, and the average length of hospitalization was 6.0 days. The incidence of major bleeding complications was 0.12% per year. There were 0.32 bleeds per 100 patient-years of coverage. Our bleeding rate was low compared with reports from other anticoagulation services, which had major bleeding complication rates from 1.1 to 2.1 per 100 patient-years of coverage.

An increasingly popular approach to warfarin dosing is self-management with a point-of-care machine that allows patients to self-test their INRs. Patients are taught how to adjust their own doses of warfarin, analogous to home testing and dose adjustment widely practiced by insulin-dependent diabetics. In a randomized trial of 737 patients allocated to self-management versus conventional anticoagulation clinic management, achieving INR goals was similar in both groups. However, major complications and minor hemorrhages were less common in the self-management group. The dropout rate during the 1-year study was 21% in the self-management group.

New Anticoagulants under Development

There is enormous interest in developing safer and more effective oral antithrombotic agents. Oral inhibitors of thrombin or factor Xa will have to be at least as effective, at least as safe, and yet require less laboratory monitoring. To achieve these goals, the compounds will need to have high and consistent oral bioavailability. One promising approach is administration of oral heparin using a novel carrier that mediates passive gastrointestinal absorption of a noncovalent complex with heparin in a dose-dependent manner. Another strategy is use of a new oral direct thrombin inhibitor, such as dabigatran, that can be administered in a fixed dose without coagulation laboratory monitoring.

Optimal Duration of Anticoagulation

When consecutive patients with DVT receive time-limited anticoagulation, their risk of recurrence increases after anticoagulation is discontinued. A landmark cohort study by Prandoni and colleagues in Padua, Italy, followed 355 consecutive patients with a first episode of symptomatic DVT (96). The cumulative incidence of recurrent VTE was 18% after 2 years, 25% after 5 years, and 30% after 8 years. Those patients at lowest risk of recurrence had the initial DVT provoked by surgery, recent trauma, or fracture. Venous insufficiency (also known as post-thrombotic syndrome) developed in 23% after 2 years, 28% after 5 years, and 29% after 8 years. At the Mayo Clinic, VTE recurrence rates were similar with long-term follow-up: 30% at 10 years.

For uncertain reasons, the risk of recurrence is about three times higher in men than in women. In addition, patients with a first symptomatic PE have a higher risk of recurrent VTE than those who initially present with DVT alone. Counterintuitively, testing for hereditary thrombophilia does not allow prediction of recurrent VTE after anticoagulant therapy is stopped. Assessment of clinical risk factors is much more helpful in predicting the likelihood of recurrence. Unprovoked VTE is much more likely to lead to recurrence after discontinuation of anticoagulation than VTE provoked by surgery, trauma, oral contraceptives, or hormone replacement therapy.

The optimal duration of anticoagulation remains the greatest challenge in long-term management of patients with VTE. There are two different strategic approaches. An epidemiologic approach focuses on the clinical circumstances when the DVT or PE was initially diagnosed. This probing of detailed clinical events ultimately leads to a recommendation of time-limited versus indefinite duration anticoagulation. The individual approach focuses more on each patient's coagulation status and residual venous thrombosis when considering whether to discontinue anticoagulation. Currently, most practitioners use the epidemiologic approach.

For unprovoked events, the standard duration of anticoagulation is 3 months for upper-extremity or isolated calf DVT and 6 months for proximal leg DVT or PE. With 6 months of anticoagulation, the recurrence rate is halved compared with 6 weeks of anticoagulation. After a second episode of VTE, indefinite duration anticoagulation is a much better strategy than 6 months of repeated anticoagulation. With only 6 months of repeated anticoagulation, the risk of recurrence and a third VTE episode is eight times higher than with indefinite duration therapy. However, the major bleeding risk is three times higher with indefinite duration anticoagulation.

Epidemiologic Approach

Patients who receive extended anticoagulation are protected from recurrent VTE while receiving long-term therapy. In a meta-analysis of the duration of anticoagulation following VTE, the number of patients needed to treat to prevent one VTE event with lifelong anticoagulation is approximately nine. Patients with idiopathic VTE are especially likely to benefit from this strategy if their bleeding risk

from anticoagulation is low. Controversy exists over the optimal anticoagulation intensity for patients receiving indefinite duration anticoagulation. The Extended Low-Intensity Anticoagulation for Thrombo-Embolism (ELATE) Trial demonstrated a remarkably low major bleeding rate of 1.1 events per 100 patient-years with standard anticoagulation, target INR between 2.0 and 3.0. Among patients receiving low-intensity anticoagulation, target INR between 1.5 and 1.9, the major bleeding rate was exactly the same as in the warfarin-PREVENT Trial of low-intensity anticoagulation, 0.9 events per 100 person-years.

Prevention

To prevent postphlebitic syndrome, which is characterized by chronic leg swelling, calf aching, and occasionally ulceration at the medial malleolus, below-knee vascular compression stockings, 30 to 40 mm Hg, should be prescribed as soon as DVT is diagnosed. These stockings should be worn daily when out of bed. Occasionally, the stocking prescription will have to be deferred because of extreme leg pain and edema. Effective pharmacological and mechanical measures have been proven to decrease asymptomatic DVT rates among hospitalized patients. Until recently, skeptics have questioned whether a decrease in asymptomatic DVT translates into a decrease in mortality.

There appears to be gender bias against VTE prevention in women, who do not receive VTE prophylaxis as frequently as men. This finding is based on observations from the prospective U.S. registry of 5,451 patients with ultrasound-confirmed DVT. Men were 21% more likely than women to receive prophylaxis within 30 days prior to acute DVT. The observed gender difference was present in all age groups, in both academic and community hospitals and throughout all regions of the United States. The gender difference also persisted after multivariable analysis that adjusted for cancer, surgery, prior DVT, trauma, and age. These findings indicate that hospitalized women should be included when considering pharmacological VTE prevention.

There are several barriers to VTE prophylaxis. One barrier to consistent, universal prophylaxis among hospitalized patients may be the needlessly cumbersome and outdated classic approach to risk stratification. This strategy, which is not prac-

tical in contemporary clinical practice, categorizes patients into one of four risk groups and then prescribes differing prophylaxis regimens (or no prophylaxis) according to the degree of risk. This approach worked well in a previous era when low-risk patients were commonly hospitalized for prolonged lengths of stay. Nowadays, this time-consuming and often ambiguous scheme seems outdated. In modern practice, essentially all patients hospitalized for more than 1 night are at high risk of developing VTE.

Virtually every patient with an anticipated hospital stay of 48 hours or more warrants prophylaxis against VTE. The subtleties of distinguishing low risk from medium risk from high risk are distracting and impede focusing on the main task: effective and safe prophylaxis for all hospitalized patients with protocols that are routine, rapidly implemented, and practical.

Pharmacological prophylaxis should form the foundation for any VTE prevention program among hospitalized patients. For those with bleeding problems or whose risks of bleeding make this approach risky, mechanical prophylaxis should be utilized with graduated compression stockings, intermittent pneumatic compression devices, or both. Mechanical prophylaxis with graduated compression stockings or intermittent pneumatic compression devices has not been studied as extensively or rigorously as pharmacological prophylaxis.

Low-dose unfractionated heparin, administered in a fixed dosing regimen of 5,000 units injected subcutaneously every 8 hours, can halve VTE rates. For surgical patients, the first dose is administered 2 hours before the skin incision. Prophylaxis should be continued for at least a week because the peak incidence of postoperative VTE is 5 to 10 days following surgery. In medical patients, heparin 5,000 units three times daily appears equivalent in efficacy and safety to low-molecular-weight heparin administered once daily.

Low-molecular-weight heparins and fondaparinux, an anti-Xa agent, provide the convenience of once-daily dosing. They are administered as fixed doses. In general, the concentration of drug needed to prevent VTE is about one-fourth the concentration needed to treat acute DVT or PE. Low-molecular-weight heparin and fondapa-

rinux, in contrast to unfractionated heparin, also reduce the possible catastrophic side effect of heparin-induced thrombocytopenia. These agents are being used for VTE prevention in both surgical and medical patients.

With adherence to prophylaxis protocols, prevention of VTE can usually be achieved in the hospital setting. Primary prevention of VTE will be cost effective by avoiding the expenses associated with diagnosis and treatment of acute DVT and PE. To achieve a true consensus on VTE prophylaxis, we must determine how to change physician behavior. In the real world, the physician's orders on an individual patient are the real measure of whether the lessons about VTE prevention have been communicated effectively. At BWH, we have an excellent educational network, and VTE management is a major clinical interest for many physicians. For the past decade, our computer has been programmed to suggest VTE prophylaxis if a computer order is entered for bed rest. Nevertheless, audits of our own clinical practice reveal that many high-risk patients for VTE have not received prophylaxis orders. Therefore, we undertook a randomized clinical trial of high-risk patients who were not receiving VTE prophylaxis.

Conclusions

Venous thromboembolism diagnosis, management, and prevention are suited to the development and implementation of critical pathways, especially about patients with documented pulmonary embolism. D-dimer blood testing, venous ultrasonography, and chest CT scans have facilitated diagnosis. Rapid and accurate risk stratification is the key to optimal management. Most VTE that develops in the hospital can be avoided by instituting proven prophylaxis strategies.

CHAPTER 2

INFECTIVE ENDOCARDITIS. DIAGNOSIS AND MANAGEMENT APPROACHES

Foreword

Infection remains the number one killer worldwide. Nevertheless, it is the expectation that bacterial infections can be eliminated with antibiotics. Unfortunately, there remain infections due to bacteria that are difficult to detect and difficult to reach, because of minimal blood supply, with even the most potent of antibiotics. One of the diseases in this category is infections that initiate on the inner lining of a vital organ, the heart. These infections are referred to as endocarditis since they involve the endocardium, the inner lining of the heart and valves. The initial site of infection is generally in areas exposed to mechanical trauma or prosthetic device. Unfortunately the damage to the heart if not treated can be fatal and often survival requires surgical replacement of one of the valves. Despite the tremendous array of antibiotics and the marked increase in potency of these drugs to eradicate bacterial infection, the efficacy of treating the relatively a vascular lining of the heart or its valvular apparatus often eludes the desired effect. This is further complicated by the changing substrate for bacterial endocarditis, namely, artificial valves and devices and the increasing number of individuals who are imuno-suppressed because of drug use, human immuno deficiency virus infections or other debilitating conditions. Endocarditis due to bacteria and other agents remains a continuing threat as well as a challenge in terms of diagnosis, management and treatment. Despite advances in medical and surgical treatments, infective endocarditis continues to be an important clinical problem. It has an in-hospital mortality of 10–20%, and many patients will require valve surgery during long-term follow-up. The diagnosis is difficult since it is based on a constellation of findings and none of the clinical findings alone is pathognomonic. Unequivocal diagnosis is often made only at surgery or autopsy.

Introduction

Infective endocarditis (IE) may give rise to numerous extracardiac, cardiac, and valvular findings, including infected thrombi (vegetations), sequelae of local tissue

destruction, and systemic manifestations including vasculitis, emboli, and ischemic events. This is an appropriate term as the causal organisms may be bacterial, fungal, rickettsial, or even viral or mycoplasmal. Traditionally a distinction between acute and subacute infective endocarditis was made depending upon the severity and rate of disease progression. This reflected an organism's virulence and the presence of underlying cardiac disease. With antimicrobial treatment these clinical divisions have little pathologic significance, and it is preferable to think in terms of active, healing, and healed infective endocarditis. The disease is now probably best described by its anatomical location and the organism involved. Infective endocarditis may arise in normal hearts with normal valves, or more commonly in patients with abnormal cardiac anatomy. The most common preexisting cardiac valvular lesions are left-sided ones, including aortic stenosis (especially the congenitally bicuspid aortic valve), aortic insufficiency, and mitral insufficiency. Valves damaged by rheumatic fever continue to be the most common type of predisposing cardiac valvular abnormality in developing countries. However, in developed countries degenerative or age-related diseases, including mitral valve prolapse, degenerative aortic stenosis, and mitral annular calcification are becoming a more predominant background for infective endocarditis.

Other important predisposing conditions are congenital heart diseases, including ventricular septal defect, patent ductus arteriosus, coarctation, transposition of the great arteries, tricuspid and pulmonary atresia or stenosis, and tetralogy of Fallot. Hypertrophic cardiomyopathy and prosthetic grafts or valves may also predispose to infective endocarditis. For infective endocarditis to occur there are usually three features - valvular thrombus, circulating bacteria, and bacterial growth on the valve. Hearts may develop valvular thrombus due to abnormal flow and anatomy. Thrombus may develop due to regurgitant jet lesions, on contact surfaces, or other areas of mechanical trauma. It should be realized that many phenomena of modern medicine, including prolonged intubation, immunosuppression, chemotherapy, complex surgical procedures, and increased use of antimicrobial agents might contribute to increased susceptibility to develop infective endocarditis. Other predisposing conditions include

immunodeficiency, alcoholism, malnutrition, and diabetes. Intravenous drug use (IVDU) may give rise to a repetitive bacteremia and is an important risk factor for infective endocarditis.

Catheter and Line-Related infective endocarditis

Intravascular and intracardiac catheters and devices have proliferated and now include pacemakers, defibrillators, indwelling heart catheters, grafts, and valve or non-valve prostheses. These foreign bodies may be the nidus for infection and may also lead to thrombus formation on a neighboring structures or heart valves. Insertions of catheters, pacemakers, and cannulas are routine procedures in modern medical therapy for resuscitation, feeding, hemodynamic monitoring, and therapy of disease. Lines or catheters may contuse, tear, penetrate, perforate, tangle, or thrombose the intracardiac structures. Biofilms of infecting organisms and extracellular matrix may form on the surface of lines or devices and serve as a protective environment for the infective organisms.

The most common catheter- or line-related lesions involve the right atrium, right ventricle, pulmonary, and tricuspid valves. These lesions are rarely important unless they are infected. The catheter lesions are located on the atrial side of the tricuspid valve or on the ventricular side of the pulmonary valve. The lesions usually follow the line of the catheter and the catheter may be surrounded by thrombus which chronically may organize and fibrose. Infections in defibrillators and pacemakers may occur anywhere along the electrode and are not limited to the tricuspid valve. Pacemakers and defibrillators may have infection involving either the lead or the pouch, and Staphylococci are the most common pathogens involved. Fungal infection may also be seen. Septic and bland pulmonary emboli may complicate pacemaker/defibrillator infection. If the device has been in place for some time, lead extraction is usually impossible and open-heart surgery may be necessary.

Approach to Infective Endocarditis at Surgery or Autopsy

At surgery or autopsy examination of hearts, valves, and vascular prostheses, clinical suspicion that the patient has infective endocarditis may or may not be present. The presence of unexpected but suspicious valvular lesions should prompt a

proper workup for infective endocarditis. Before immersion of the heart or resected valve in fixative, a thorough examination should be made to visualize all the valves and perivalvular structures. Sterile instruments should be used if a suspicious lesion is encountered. Since the proper approach is to assume that all valvular thrombi are infected until proven otherwise (this is the author's personal practice), portions of the thrombus should be submitted for culture. Swabs of the lesions are not recommended. Cultures should never be interpreted in isolation. Pre-mortem or pre-operative blood cultures should be consulted. Microscopy of the valve or thrombus to confirm the presence of microorganisms is essential. Special stains are useful to detect microorganisms; however, treatment with antimicrobial agents has changed the utility of these stains. Gram stain is useful to detect bacteria, but after a few weeks of antimicrobial treatment the organisms may not stain. Therefore silver stains should always be performed not only to detect fungi but also to detect bacteria that have lost their positive Gram staining, yet still can be detected with silver stain of their cell walls. Care must be exercised with silver stain interpretation as this stain also highlights cellular debris and some intracellular organelles. Giemsa stain is useful to detect rickettsial organisms, which may not stain with the other stains. Correlating the blood culture result with cultures of the tissues and vegetation is essential. Communication with the clinicians may save much frustration if the special stains are negative and the organism is known from prior cultures. This is common in patients who have received prior antimicrobial agents. In culture-negative infective endocarditis, the common culprit organisms include Eikenella, Brucella, Neisseria, fungi, Chlamydia, acid-fast bacilli, or right-sided endocarditis, where the lungs filter out the organisms. HACEK (Hemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella) organisms may be particularly difficult to grow. Clinical history and history of treatment and exposures may be very relevant. Electron microscopy, immunofluorescence, polymerase chain reaction (PCR), or other molecular techniques may be contributory in the search for these often culture negative organisms. Studies have suggested that PCR may be a better diagnostic tool than culture, especially after antimicrobial therapy, but there remains concern about false positives and background contamination.

Pathological diagnosis of healed infective endocarditis can be difficult, as the findings may be nonspecific and organisms frequently cannot be found. The diagnosis can only be made with confidence when the gross and microscopic features are typical, and there are collaborative clinical findings. This is quite common in patients with adequate preoperative antibiotic treatment.

Active Infective Endocarditis Pathology

On gross examination, infected thrombi of variable size, commonly known as "vegetations," are detected along the lines of valve closure or at the low pressure end of jet lesions. They are usually gray, pink, or brown and are often friable. They may be single or multiple and may affect more than one valve. Common sites are usually on the downstream side of the intracardiac high-velocity flow jets, such as the atrial side of the mitral valve or the left atrial endocardium in cases of mitral insufficiency, the ventricular side of the aortic valve, the ventricular septum or the anterior mitral leaflet in cases of aortic insufficiency, or on the right ventricular endocardium in ventricular septal defects. Infection may also involve the intima of a blood vessel distal to a coarctation or involve the pulmonary artery side of an infected patent ductus arteriosus. Left-sided valve lesions are more common than right-sided lesions except for cases related to interventional devices, catheters, or intravenous drug use. Vegetations may be located anywhere on the valve cusp or leaflet or endocardial surface. In fact this is an important distinguishing feature to note, as valve thrombi associated with nonbacterial thrombotic endocarditis (NBTE) and those related to rheumatic fever do not have this variability in location, and are usually along the lines of valve closure. Libman Sacks lesions in lupus patients may be on both sides of the valve. Thrombi from nonbacterial thrombotic endocarditis, rheumatic fever, Libman Sacks, are not associated with valve destruction. The valve structures may also manifest destructive lesions leading to perforations, defects, aneurysms, erosions, and chordal ruptures. The amount of thrombus and destruction may completely mask the underlying predisposing valve disease. Thrombi may obstruct the valvular orifice, creating stenosis, but valvular insufficiency is a much more common complication. Chordae may rupture resulting in flail leaflets. Leaflet or cusp aneurysms bulge toward the flow sur-

face and may resemble “windsocks,” and IE is the most common cause for leaflet aneurysm or diverticulum. If the aneurysm tip ruptures, the valve may become severely regurgitant due to cusp or leaflet defects. On microscopic examination, the appearance of the vegetation depends upon both the virulence and destructiveness of the organism and the duration of the infection. Early in the disease course there are fibrin, neutrophils, and clumps of organisms . With therapy the organisms may calcify, and the thrombi organize from the base. Organizing thrombus may show no easily recognizable organisms and only show acute and chronic inflammation with neovascularization and fibroblastic proliferation. With thrombus organization giant cells may be seen. If giant cells are prominent one should consider serology for Coxiella or fungi. Pathological changes in the infected valve tissue depend on the chronicity or duration of the infection, the virulence of the organism and the status of the original valve itself. Electron microscopy, immunofluorescence, polymerase chain reaction or molecular techniques are contributory in the search for organisms.

Fungal Endocarditis

Fungal endocarditis is usually encountered when there are preexisting risk factors such as intravenous drug use, prior cardiac surgery, immunosuppression, intravenous hyperalimentation, antibiotic therapy, long-term venous catheters, pacemakers, defibrillators, and other intravascular devices. Fungi may infect either native or prosthetic valves. The common organisms are Candida and Aspergillus. Classical clinical manifestations of bacterial IE are often absent. Fungal infected thrombi are usually quite large and friable. Valve orifice obstruction leading to clinical valve stenosis may occur if the size of the thrombus is large. Embolic events are not unusual and blood cultures are often negative. The organs receiving the emboli frequently develop abscesses.

Whipple Disease

Patients with Whipple disease have been reported to have symptoms of cardiovascular disease in 58% of cases. However, at autopsy 79% have gross evidence of cardiac involvement, and of these 53% have valvular disease. The mitral valve is the most common valve affected, with the aortic and tricuspid valves also reported to be

involved at times. There are periodic acid Schiff reaction (PAS)-positive macrophages on light microscopic examination and bacilliform organisms on electron microscopy. Polymerase chain reaction performed on blood may be helpful for diagnosis. The organism is a Gram-positive actinomycete, *Tropheryma whippelii*. The infection may lead to fibrosis and chronic inflammation giving rise to a valve with similar appearance to a post-rheumatic one. The deposits may be nodular and are often not calcified. Similar pathological changes are found in the myocardium, endocardium, and pericardium. History of gastrointestinal disorder should be questioned for, as the diagnosis is usually made by small intestinal biopsy.

Chronic Infective Endocarditis Pathology

With successful medical treatment of infective endocarditis the infected vegetations may organize and the thrombi may form calcific valve nodules. Destructive sequelae of the infection are common. The valve may have defects at the edges or central defects forming irregular perforations. Around the holes or perforation there may be brown nodules of organisms that eventually form fibrocalcific nodules. The destruction of the valve tissue may lead to defects at the margins resulting in poor valve coaptation. Distinguishing a post- infective endocarditis perforation from a congenital accessory orifice may be difficult. In atrioventricular valves congenital orifices should have surrounding chordae, while a post- infective endocarditis perforation would not. Fenestrations, an age-related finding, are also confused with perforations. These fenestrations are located laterally on the valve cusps near the commissures and always beyond the line of valve closure. Chordae may rupture resulting in flail leaflets and valve regurgitation. The ruptured chords may knot and calcify along with the organizing infected thrombi. The valve itself may thicken and the chords may fuse. All these are significant contributors to chronic valve regurgitation. Ventricular papillary muscles may rupture for multiple reasons due to infective endocarditis. The infection may extend from an adjacent chord and cause myocardial necrosis and rupture. A coronary arterial embolus may cause a myocardial infarct with papillary muscle rupture, similar to any acute myocardial infarct. Finally an embolus may lead to a myocardial abscess with local tissue destruction.

Perivalvular Lesions of Infective Endocarditis

Extension of the valve infection into surrounding structures predicts a higher mortality, higher risk of significant heart failure, and the need for cardiac surgery. In the early stage, perivalvular abscess is largely composed of inflammatory infiltrate, but at later stages necrosis and cavitation usually develop leading to destruction of perivalvular tissue. Perivalvular abscess is not a static complication but is progressive and can evolve into serious perivalvular complications including perivalvular leak, fistula and pseudoaneurysm. These perivalvular complications may develop in spite of early valve surgery. Perivalvular leak due to annular abscess may be seen with native valve IE (aortic more than mitral), but are especially common adjacent to infected valve prostheses. Although a perivalvular leak may be technically related to poor tissues, suture unraveling, suture tissue cut-through, and other technical matters, it is important to keep the possibility of infective endocarditis in mind with all perivalvular leaks. These leaks may cause clinically significant congestive heart failure and sometimes hemolysis. Extension of an active valve infection to adjacent cardiac structures is common, including infected lesions where adjacent valves come in contact or are contiguous—such as from the aortic valve to the base of anterior mitral leaflet, from the posterior leaflet mitral valve to the left atrial endocardium, and from the aortic valve to the ascending aorta. Jet lesions as a result of valvular insufficiency may cause infected endocardial lesions to form along the path of the regurgitant jet. Infections may also extend from the mitral and aortic valves to the valve annuli. This complication is considerably more common in the aortic position as compared to the mitral. This may manifest as an aortic root abscess, or the mitral annulus or mitral annular calcification (MAC) may become infected. Mitral annular calcification is a common finding in the hearts of elderly patients. It is considered to be an age-related finding, but it probably represents degenerative changes in the mitral annulus. It is associated with mitral valve disease, especially mitral valve prolapse due to myxomatous/floppy mitral valve. Uncommonly the calcium extends onto the leaflet, producing a mass and the calcium may undergo liquefactive necrosis and grossly mimic infective endocarditis. Mitral annular calcification may ulcerate giving rise to thrombus

deposition with potential for embolization and infection. If infected, there is usually leaflet perforation and myocardial abscess formation. If the infection spreads into the lateral atrioventricular groove, the circumflex coronary artery may thrombose because of distortion from the local effects of the infection, and development of arteritis. Annular abscesses may also erode into to the pericardial surface, producing fibrinous or suppurative pericarditis and hemopericardium with tamponade. Aortic root abscesses may become a significant source of embolic material and they may compress adjacent structures around the aortic root. If the proximal coronary arteries are distorted, myocardial ischemic sequelae may result. The formation of annular abscess is not an end event. Rather these structures are progressive with potential formation of perforations or fistulas. Due to the central position of the aortic valve, infection of this valve may form fistulas with practically any chamber. Each aortic cusp and sinus has its own propensity for fistula formation and complication. Infection in the left aortic cusp or sinus may spread through the aortic wall and cause pericarditis or tamponade, or a fistula may extend into the left atrium. Infection of the posterior (non-coronary) aortic cusp or sinus may cause a fistula to either the left or right atrium. Infection of the right aortic cusp or sinus may cause a fistula to the right atrium, and the right ventricle or right ventricular outflow tract. An aorto-right ventricular fistula is possible due to the presence of the atrioventricular component of the interventricular septum. Extension into the myocardium and the conduction system may be found when the infection involves the valve ring or annulus. Fistulas and abscesses are important problems particularly with prosthetic infective endocarditis, as discussed below. Involvement of the coronary arteries may be due to distortion from an aortic root abscess or they may become directly infected by local extension through the coronary ostia or by formation of mycotic aneurysms. The latter may occur in normal arteries but also may be superimposed pattern or on an underlying atherosclerotic plaque. Mycotic aneurysms may thrombose and are a source of infected emboli that may seed the myocardium leading to myocardial abscesses. Myocardial abscesses may also form as a result of local valvular infective endocarditis extension into the adjacent myocardium. Aortic root abscesses and myocardial abscesses may impinge upon or

destroy the conduction system in the areas of the atrioventricular node and His bundle. Clinically this manifests as a progressively worsening degree of heart block and may be an important clinical sign that treatment is failing or disease is progressing. Extension of infection to the pericardial space may lead to hemopericardium and tamponade or to pericarditis. Fibrinous pericarditis is a common finding with infective endocarditis, but the pericardium may also become infected, leading to suppurative pericarditis.

Infective Endocarditis of Valve Prostheses

Infection of valve prostheses may manifest early after surgery or long after hospital discharge. Both bacterial and fungal organisms are important causes of prosthetic infective endocarditis. Valvular bioprostheses have vegetation, cusp thrombi, destruction, erosion, and perforation similar to native valves. With infection of mechanical prostheses, the actual prosthesis usually remains intact and the infection is mainly in the sewing ring and surrounding tissues. The thrombi on a mechanical prosthesis or bioprosthesis may interfere with normal function, as the prosthesis may become dysfunctional with disc or cusp immobility. Peripheral emboli are not uncommon. In any prosthesis, sewing ring and perivalvular tissue infection is common, and the valve prosthesis may dehisce or become loose when the surrounding tissues develop necrosis. Annular abscess and fistulas are much more common with prostheses, as compared to native valves. It is a disturbing and memorable experience to image a near totally dehisced valve prosthesis by echocardiography and for the surgeon to be able to remove such a valve prosthesis from the patient without much need for dissection. Sutures, pledgets, as well as the aortotomy site may become infected. A large perivalvular leak results in severe perivalvular regurgitation and heart failure, but even a small perivalvular leak can be significant due to the development of severe hemolysis. Destruction of the adjacent tissues may lead to intracardiac fistulas, conduction system destruction and arrhythmias, and coronary artery inflammation and thrombosis. The mortality of prosthetic IE remains high, with or without surgery, and perivalvular complications can develop despite surgery. Fungal infection of valve prosthesis is a surgical indication due to near total mortality without surgery.

Systemic Pathology of Infective Endocarditis

Systemic manifestations of infective endocarditis may be due to generalized sepsis, immune reactions—including immune complex disease - or related to emboli or ischemia with organ atrophy, ischemia, or infarction. Classic peripheral stigmata of IE may not be evident with right-sided infective endocarditis or with infections due to HACEK organisms. Similar to all disseminated infections, infective endocarditis related sepsis may present with fever (or fever of unknown origin), leukocytosis, disseminated intravascular coagulation (DIC), adult respiratory distress syndrome (diffuse alveolar damage), jaundice, and other sequelae of hypotension including multiorgan failure.

Renal manifestations include interstitial nephritis and pyelonephritis. There may be immune complex formation between bacterial antigens and antibodies, which deposits in the glomeruli leading to glomerular damage. Focal necrotizing and diffuse proliferative glomerulonephritis may manifest as acute nephritis and renal failure. Type 1 membranoproliferative glomerulonephritis may lead to nephrotic syndrome. Crescentic glomerulonephritis with rapidly progressive glomerulonephritis can also occur.

Emboli to the kidney may cause infarction, hematuria, flank pain, and renal abscesses. Emboli may occur in both right- and left-sided infective endocarditis. Emboli can occur before therapy, during therapy, or even after therapy. Emboli from left-sided valve or cardiac lesions may affect any systemic organ leading to visceral infarction, ischemia, or organ atrophy. Either bland fibrin platelet material of the vegetation or infected components containing microorganisms may embolize. The propensity for embolization may be related to the size and mobility of the vegetation, as seen on echocardiogram. The effect of the embolic material depends upon the size of the embolus, whether it contains microbes, the size of the occluded blood vessel, the degree of collaterals in the organ, and the metabolic demand of the organ. Vascular spasm may also contribute. If there are prominent numbers of organisms in the embolic material, the organ may form an abscess, in addition to an infarct, which is referred to as a septic infarct. Coronary arterial emboli may lead to angina, myocardial

infarction or sudden death. Embolic myocardial infarcts are usually large, and myocardial abscesses may develop. The central nervous system is the most common site involved by infective endocarditis and neurologic deficits may be due to many different causes. Cerebrovascular embolism may manifest as transient ischemic attacks or stroke. Cerebral infarcts may be hemorrhagic and non-hemorrhagic. Mycotic aneurysms of infected cerebral arteries may thrombose or rupture Other serious neurological complications are cerebral abscesses and meningitis. Splenic infarcts may cause abdominal, back, or flank pain. Splenic infarcts may be bland ischemic infarcts or septic infarcts both of which may lead to abscess formation. Rarely the spleen may rupture, leading to intra-peritoneal bleeding. Gut ischemia and infarction may occur if the mesenteric circulation is embolized. Emboli to the limbs may cause acute ischemia or gangrene. When a vascular surgeon performs a thrombectomy or embolectomy in a patient with acute limb ischemia the removed material should be examined for infection with bacterial and fungal stains. Right-sided endocarditis may lead to infected pulmonary emboli, pulmonary infarction, abscesses, and empyema. If large, these pulmonary emboli may cause sudden death. If there is an intracardiac shunt, either preexisting or developed due to infective endocarditis, paradoxical embolism is possible with vegetation fragments embolizing into the systemic circulation bypassing the lung.

Osler nodes (tender subcutaneous nodules on the digits), Janeway lesions (red or hemorrhagic nontender lesion on the palms or soles), and Roth spots (retinal hemorrhages) are due to emboli to small blood vessels. These are now rarely encountered with modern medical care. Petechiae and subungual hemorrhages may be seen on the skin.

Small-vessel vasculitis may be due to an infected embolus (a mycotic aneurysm) or immune complexes.

Mycotic aneurysms may occur in any circulation, but are most common in the central nervous system circulation. Cerebral vessels are commonly involved, followed by visceral arteries and arteries of the extremities. Branch points are usually affected. They may develop in the aortic wall adjacent to the valve or distant to it. These aneurysms weaken the vessel wall and may rupture and hemorrhage even after

the infection has been treated. Subclinical rupture may lead to pseudoaneurysm formation. They also may thrombose. Surgical intervention is usually required.

Microbiology of Infective Endocarditis and Microbiologic Diagnosis

Microbiology Trends

The microbiology of infective endocarditis has evolved significantly over the last century. Previously a community-acquired disease affecting predominantly patients with rheumatic heart disease, IE is now being seen in new populations including IV drug users, patients with prosthetic valves, and patients infected through health-care-associated bacteremia. Improved blood culture technologies and non-culture laboratory methods have also resulted in a lower rate of culture-negative cases. Because of differing proportions of particular risk groups, the etiologic agents responsible for causing infective endocarditis vary significantly among continents, countries, regions within countries, and even among different years in an individual hospital. This discussion of the etiologic agents of infective endocarditis will begin with native valve endocarditis followed by consideration of special situations including prosthetic valve endocarditis, infective endocarditis in injection drug users, and culture-negative endocarditis.

Community-Acquired Native Valve Endocarditis

The common causes of native valve endocarditis are members of the normal flora of the skin, oropharynx, and the gastrointestinal and genitourinary systems. The vast majority of native valve endocarditis cases are caused by *Staphylococcus* and *Streptococcus* species. Several recent publications show that *Staphylococcus aureus* seems to have overtaken the viridans group Streptococci as the most common cause of native valve infective endocarditis. However, a population-based study of IE cases in Olmstead County, Minnesota, from 1970 to 2000 revealed no significant trends over time with respect to either the overall incidence of infective endocarditis or the relative proportion of cases caused by Staphylococci and Streptococci. These apparently contradictory observations likely result from differences in patient risk factors (e.g., low IVDU rates in Olmstead County) and referral patterns (more *S. aureus* IE referred to tertiary care centers).

Prosthetic Valve Endocarditis

Overall, prosthetic valve endocarditis (PVE) accounts for 10–30% of all infective endocarditis cases. The risk of endocarditis is highest in the first few months following surgery, with cumulative rates of 1.0–1.4% at one year and 3.0–5.7% at five years after valve replacement. When compared to native valve IE, (CoNS) infection is much more common in PVE; Gram-negative bacilli, fungi and diphtheroids are also more likely to cause PVE, while *S. aureus* enterococci are less frequently causes of PVE than they are of native value infective endocarditis. The relative importance of the causative organisms in PVE depends on the timing of infection in relation to valve replacement surgery. Early PVE is most often related to intraoperative contamination of the surgical field or postoperative bacteremia. As such, the bacterial flora of the skin and hospital associated pathogens predominate.

CoNS (most frequently *S.epidermidis*) are responsible for about 30–50% of PVE within this group, *S.aureus* (with an increasing proportion of MRSA) causes 15–20%, and Gram-negative bacilli causes 10–20%. Fungi (*Candida* species), diphtheroids and enterococci (with rare cases of VRE) each cause at least 5% of early PVE cases, and the streptococci are very rare causes of prosthetic valve endocarditis in the early postoperative period. The distribution of etiologic agents causing late prosthetic valve endocarditis is very similar to that for native valve infective endocarditis, with the streptococci being the most frequently isolated organisms in most reported series. Patients with late prosthetic valve endocarditis tend to have more CoNS and less *S. aureus* when compared to those with native valve IE. The Gram-negative bacilli and fungi seen in the early period after valve replacement are recovered infrequently in late prosthetic valve endocarditis. The HACEK organisms are isolated in up to 5% of patients presenting with late onset prosthetic valve endocarditis.

Intermediate-onset prosthetic valve endocarditis includes a mixture of patients who are presenting relatively late with peri-operatively acquired infections and individuals who have developed communityacquired endocarditis. As a result, the pattern of organisms causing prosthetic valve endocarditis developing at this time is essen-

tially an average of the proportions of cases caused by each group of organisms observed in the early and late periods.

Intravenous Drug Users

The majority of infective endocarditis in the Intravenous drug use group is caused by *Staphylococcus aureus*, which is responsible for 50–75% of cases. The streptococci and enterococci are the next-most-common organisms (7–10%), with small percentages caused by CoNS, Gram-negatives, and *Candida* species. Polymicrobial infective endocarditis is relatively common in the Intravenous drug use population, occurring in up to 5% of cases. *S.aureus* most commonly causes right-sided (tricuspid) endocarditis in the intravenous drug use setting. It was definite that *S.aureus* native valve infective endocarditis cases. So, of 170 patients with right-sided *S.aureus* infective endocarditis, 131 (77%) provided a history of IV drug use. In the same study, MRSA was observed infrequently in the IVDU population: 6/43 (14.0%) patients with MRSA infective endocarditis used IV drugs compared to 136/248 (54.8%) of those with infection caused by susceptible strains. However, increasing rates of MRSA in intravenous drug use have been observed and outbreaks have been documented. Gram-negative infective endocarditis in drug users can be caused by organisms that are encountered only rarely in non- Intravenous drug use patients. *Pseudomonas aeruginosa* endocarditis is uncommon and occurs nearly exclusively in Intravenous drug use. *Pseudomonas aeruginosa* infective endocarditis is usually right sided, but can involve leftsided valves, in which case the clinical course is more complicated. A cluster of 36 cases of *Serratia marcescens* infective endocarditis was seen among heroin users in San Francisco in the 1970s, with high associated mortality. *Campylobacter fetus, Pasteurella* spp., *Brucella* spp., *Bordetella* spp., *Franciscella tularensis, Aeromonas hydrophila,* and *Yersinia enterocolitica* are other Gram-negative bacilli that are occasionally encountered in the setting of IV drug use.

Blood-Culture-Negative Endocarditis

Reported blood culture-negative endocarditis (BCNE) rates have historically varied by study population, ranging from 2.5% to 31%. These rates are still consistent among recent studies conducted in Spain (13.7%), London (12.2%), and Sweden

(20%). A recent review of 26 case series published between 1993 and 2003 showed BCNE rates of about 10%. These rates are likely artificially high because of preceding antibiotic therapy. This effect was quantified in a retrospective review of 107 definite IE cases at a center in Spain, in which 14/20 patients with negative blood cultures had received prior antibiotics, leaving 6/107 (5.6%) with BCNE. Thus, excluding the cases confounded by antibiotic therapy prior to blood cultures, the frequency of "true" culture-negative endocarditis is much less, likely around 5%. By definition, standard culture methods are inadequate to allow detection of the causative agents of BCNE. The largest study to address the etiology of BCNE involved 348 patients with suspected BCNE in France. The authors attempted to determine the causative organism using a comprehensive serology panel, shell vial cultures and analysis of valve specimens by multiple methods, including PCR. These investigations showed that 167 cases (48%) were due to *Coxiella burnetti*, 99 (28%) due to *Bartonella* spp., 5 (1%) due to rare fastidious organisms, and 73 (21%) without an identified cause. Of the 73 undiagnosed cases, 58 had received antibiotics before the blood cultures, leaving only 15 (4.3%) unexplained cases. *Coxiella burnetti* is reported to cause 3–5% of all endocarditis in France, Israel, and Great Britiain. Underlying heart disease, immunocompromising conditions and animal contact are the major risk factors. Reported outcomes of *C. burnetti* IE were previously poor with nearly two-thirds of patients developing congestive heart failure (CHF), but in this cohort only 38% developed CHF and mortality was only 3% (4/150). This improvement likely reflects better and more rapid diagnostics and more timely treatment. *Bartonella* spp. are reported to cause 3% of all endocarditis. Epidemiology was distinct for the two species, with *B. quintana* seen in patients who were homeless or alcoholic with exposure to body lice, and *B. henselae* in individuals with a history of exposure to cats. *Trophyrema whipplei*, the Whipple disease bacterium, is an emerging cause of culturenegative endocarditis.

Microbiologic Diagnosis Blood Cultures

Blood culture remains the single most important investigation in a patient suspected of having infective endocarditis. If appropriately collected prior to antibiotic administration, blood cultures can be expected to yield growth of the causative organ-

ism in over 90% of cases of infective endocarditis. Identification of the organism may allow the treating physician to determine the original source of bacteremia, and facilitates the choice of the appropriate therapeutic agent(s) and treatment duration. The Modified Duke Criteria include blood culture as one of the major diagnostic criteria. In order to fulfill the major microbiologic criterion, blood culture support for the diagnosis of IE is defined as isolation of "typical" microorganisms (viridans streptococci, *Streptococcus bovis*, HACEK group, *S.aureus*, community-acquired *Enterococcus* spp.) from at least two separate blood cultures, blood cultures persistently positive for "microorganisms consistent with IE," or a single culture positive for *Coxiella burnetti*.

Intravascular infections including IE are characterized by the presence of continuous bacteremia, and in the majority of IE cases most or all of the pre-therapy blood cultures will be positive. Demonstration of continuous bacteremia by definition requires more than one blood culture result, and the yield of blood cultures is dependent on both the number of cultures obtained and the volume of blood cultured.

For the majority of patients, one blood culture set consisted of 20 mL divided equally between one aerobic and one anaerobic bottle. The investigators found that a second 20 mL blood draw increased blood culture yield by 17–20%, and that this additional pick-up rate was the same whether the second culture set was drawn immediately after the first, or at any other time within the next 24 hours. The addition of a third 20 mL draw within 24 hours further increased the blood culture yield by 10%. Most experts agree that three separate blood culture sets (20–30 L in two or three bottles) should be sufficient to detect over 95% of IE-associated bacteremias in the absence of preceding antibiotics. In addition to maximizing the diagnostic yield, the practice of obtaining multiple blood cultures can also be useful in determining whether a positive result represents contamination, in which case only one culture would be expected to grow the contaminating organism.

The timing of blood culture draws depends on the overall clinical status of the patient. In the setting of a septic patient with suspected acute IE, therapy should not be delayed to allow blood cultures to be drawn, and two or three separate venipunc-

tures can be performed a few minutes apart while arrangements are made for initiation of empiric antibiotic therapy. Conversely, a clinically stable patient who has been ill for weeks can safely remain off antibiotics for at least 24 hours while serial blood cultures are obtained. In patients who have received antibiotic therapy before being worked up for IE, blood culture media containing antibioticinactivating resin should be used, and in selected circumstances withdrawal of antibiotics in order to allow cultures to be drawn would be appropriate. Newer blood culture media and modern automated blood culture systems represent a significant improvement over older methods. The majority of non-fastidious organisms will trigger a positive signal in blood culture instruments within 72 hours.

Most clinical laboratories incubate routine blood cultures for five days, as most positive cultures appearing after longer incubation represent contaminants. However, some fastidious organisms that cause IE, including the HACEK group, *Brucella* species and others, may require longer periods of incubation before triggering automated blood culture systems. The majority of fastidious organisms causing infective endocarditis will grow within ten days, but others (e.g., *Bartonella* species) can require several weeks to grow and may not trigger blood culture instruments even when they do grow. In the setting of clinically suspected IE, therefore, blood culture specimens require special management within the laboratory. Approaches vary among institutions and include extended incubation of the bottles collected from patients identified as suspect infective endocarditis cases, terminal subcultures of negative blood culture bottles to solid culture media at the end of the planned incubation period, or a combination of both. Highly specialized culture techniques can be used for isolation of specific rare causes of infective endocarditis such as *Coxiella burnetti*, *Bartonella* species, and *Tropheryma whipplei* when they are suspected.

Candida species cause approximately 50% of proven cases of fungal endocarditis. Although blood cultures are thought to have poor sensitivity for detection of candidemia, more specialized blood culture media have no advantage over standard blood culture bottles for detection of *Candida* species. Special fungal blood culture media such as Bactec Myco-F-lytic bottles are superior in supporting growth of fila-

mentous fungi such as *Aspergillus* species, and could be considered for use in immunocompromised patients or known IV drug users with suspected infective endocarditis. The lysis-centrifugation (Isolator) method is superior to other available processes for detection of *Histoplasma capsulatum* from blood samples. Emboli leading to operative intervention are seen relatively commonly in cases of fungal endocarditis given the typically large vegetation size. Because blood cultures are frequently negative in fungal endocarditis, these emboli can provide crucial information about the causative organism, and they should be cultured and stained for fungal organisms when they are encountered and removed.

Methods for Diagnosis in Culture-Negative IE Serology

Serologic testing can be useful in determining the cause of IE in true culture-negative cases, which are usually caused by organisms that are difficult to culture including *Coxiella burnetti*, *Bartonella* spp., *Chlamydia* spp., and *Legionella* species. The immune response to *C. burnetti* involves development of antibodies against phase 1 and phase 2 antigens. In acute infection, IgM and IgG antibodies develop against phase 2, and only IgM antibodies develop against phase 1. Endocarditis is a manifestation of chronic Q fever, which is characterized by high anti-phase 1 IgG titers. Positive Q fever serology, defined as a phase 1 IgG titer of >1:800, is listed as one of the major modified Duke criteria. A *Bartonella* antibody titer of 1:1,600 has been reported to have a positive predictive value of 88% for *Bartonella* infective endocarditis. However, titers may not be reproducible given lot-to-lot variability of antigen preparations used for testing. Patients with *Bartonella* infection also frequently develop cross-reacting antibodies that result in falsepositive *Chlamydia* spp. serology. Additional assays to be considered in culture-negative infective endocarditis cases include serologic studies for *Brucella* species and *Legionella* serology or urinary antigen testing.

Molecular Diagnostics

In spite of limitations including the potential presence of PCR inhibitors in clinical samples and the possibility of sample-to-sample contamination, molecular amplification methods can be useful in establishing the cause of IE. To date, PCR methods

have been applied with most success to surgically excised valve tissues. Because several possible etiologic agents are normally being considered in cases of culturenegative IE, the most commonly applied approach involves the use of "universal" PCR primers. These primers are directed against highly conserved sequences that are common to all bacteria, thereby allowing amplification of genetic material from virtually any species of bacteria. The segment to be amplified (most often genes encoding for 16S rRNA) is chosen based on the presence of intervening regions with sequence variability, allowing identification of organisms by sequencing of the PCR product with subsequent comparison of the result to a sequence database. PCR identification was possible in 26 of 30 cases with positive blood cultures prior to surgery, and in 5 of 6 blood culture-negative cases (four *Bartonella* species, one *S.gallolyticus*). When a particular diagnosis is suspected, species-specific PCR assays can also be employed. Protocols have been developed for many of the agents of culture-negative IE including *C.burnetti*, *Bartonella* spp., *Brucella* spp., *Tropheryma whipplei*, *Chlamydia* spp. and *Legionella* spp.

Histology

In cases of suspected infective endocarditis for which the causative organism is not known prior to surgical intervention, heart valve material should be submitted for further investigation by histology and culture. Because of preceding antibiotic therapy, bacterial cultures of valve tissue obtained at surgery are positive in only a minority (10–15%) of cases. Histologic examination of excised valve tissue can be used both to confirm the diagnosis of infective endocarditis and to determine the probable causative organism. Pathologic findings compatible with infective endocarditis are considered to be evidence of definite endocarditis within the modified Duke criteria. Routine stains, including H&E and tissue Gram stains, will show infiltrates of inflammatory cells and can allow common causative organisms to be visualized. Special stains, including Warthin-Starry (*Bartonella* spp.), periodic acid-Schiff (*T.whipplei*, fungi), Gimenez (*C.burnetti*, *Legionella* spp.), and Gomori methenamine silver (fungi) stains, are needed for detection of less common causes of infective endocarditis.

Pathogenesis and Rationale for Prophylaxis

The fundamental step in the pathogenesis of infective endocarditis is the development of bacteremia, with subsequent seeding of a previously damaged endocardial surface. Experimental studies suggest that valvular endothelial damage leads to platelet and fibrin deposition and the formation of a nonbacterial thrombotic vegetation. Circulating bacteria can then adhere to these lesions and multiply within the platelet-fibrin complex, leading to an infected vegetation. Dental treatment has traditionally been considered the major cause of the bacteremia that leads to infective endocarditis, mainly because of historical studies that demonstrated a high frequency of bacteremia after various oral invasive procedures, as well as because of previous studies documenting the viridans group streptococci (VGS, the predominant members of the oral microflora) as the leading cause of infective endocarditis. The initial recognition of a relationship between viridans streptococcal IE and dental. In 1923, Lewis and Grant proposed the hypothesis that abnormally structured heart valves may contribute to the development of IE in healthy adults by trapping and retaining organisms from the transient bacteremia. In 1935, Okell and Elliott, in a series of 138 patients, demonstrated the presence of bacteremia related to tooth extraction; in 64% of the cases, the isolate was a *Streptococcus* spp. Subsequent to the procedure, the organism was recovered in 20% of the blood cultures. One study demonstrated a "dose-dependent"-like effect, with a significant correlation found between the number of teeth extracted and subsequent positive blood cultures. Thus, it has become well established that bacteremia may occur after dental procedures that compromise mucosal surfaces, especially dental extractions and gingival surgery. This bacteremia, however, is transient, lasting typically no more than 15–30 minutes, as well as low grade (usually < 100 colony-forming units/mL of blood). Transient asymptomatic bacteremia also occurs after a variety of other procedures and manipulations, particularly those associated with trauma to the mucous membranes of the respiratory, esophageal, gastrointestinal, and genito-urinary tracts. If the bacteremia following these procedures is a major cause of infective endocarditis, in theory, maneuvers that decrease the magnitude and/or the

duration of this bacteremia could prevent the development of IE in patients at risk for the disease.

Prophylaxis of Experimental Endocarditis

The evidence supporting the use of prophylactic antibiotic regimens in humans derives from its proven efficacy in animal models. Experimental infective endocarditis has been typically produced in rabbits via **c**atheter-induced damage to cardiac valves and subsequent intravenous challenge with various amounts of bacterial inocula. These experimental conditions allowed infective endocarditis to be more effectively and reliably induced than in other models, with a predictable time of onset, thus facilitating analyses. Antibiotics are administered at the same or similar weight-based dose as in humans. The experimental infective endocarditis is followed with serial blood cultures, with eventual sacrifice of the animal and quantitative culture of the valvular vegetations. Such experiments have helped to elucidate a hierarchy in the infectivity of the pathogens. Adherence of circulating bacteria to the valvular endothelium/thrombotic vegetation is the most critical factor early in the pathogenesis of infective endocarditis. Indeed, *S.aureus*, the VGS, and *Enterococcus* spp., which collectively account for the majority of cases of infective endocarditis, do so specifically because of virulence factors that permit ligand-receptor interactions between bacterial surface components and constituents of damaged valves. However, the inoculum size (i.e., magnitude of the bacteremia), as well as the duration of the bacteremia after inoculation, are also important determinants of infectivity. Based on such models, antimicrobial prophylactic regimens should be predicted to be efficacious by interfering with one or more of these factors.

Patients at Risk

The American Heart Association (AHA), British Cardiac Society (BCS), and French guidelines stratify cardiac conditions into high- and moderate-risk categories, based on studies that have shown that certain types of structural heart disease are associated with higher risks of developing IE. Although the exact degree of risk for IE for certain cardiac lesions is difficult to assess, conditions deemed high-risk are inferred from the relative frequencies that particular cardiac lesions occur in a large se-

ries of patients with IE. For example, the incidence rates for IE are highest for patients with a previous history of native valve endocarditis (300–740/100,000 patient-years) and for patients with mechanical or bioprosthetic cardiac valves (300–600/100,000 patient-years); these rates are approximately 60–185-fold higher than that of the general population. Presumably, damaged valvular endothelium from a previous IE episode predisposes to subsequent nidus formation for a second episode. In the case of prosthetic valves, infective endocarditis can occur by seeding of the foreign-body valvular apparatus. Patients with congenital cyanotic cardiac disease (i.e., single ventricle states, transposition of the great vessels, tetralogy of Fallot) also have higher incidence rates of infective endocarditis, estimated at 100–200/ 100,000 patient-years; this represents a rate approximately 50-fold higher than that of the general population. The increased incidence of disease in this group is likely related to turbulent, high-velocity flow and stagnant eddies from right-to-left shunts. It should be noted that stratification of cardiac conditions is also determined not only by risk of developing infective endocarditis, but on the attendant morbidity or mortality should infective endocarditis develop.

Non-cyanotic congential heart disease includes conditions such as bicuspid aortic valve and coarctation of the aorta, as well as atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA). Surgical repair of the latter three conditions has been reported to be associated with a negligible risk for infective endocarditis (i.e., no greater risk than the general population). It should be noted, however, that the risk becomes negligible typically six months after surgical correction, provided that no other abnormality exists and no residual shunt is found by Doppler echocardiography, during which time endothelialisation of the material is complete.

Acquired valvular dysfunction includes aortic sclerosis, aortic stenosis (AS), aortic insufficiency (AI), mitral stenosis (MS), and mitral regurgitation (MR). The prevalence of these valvulopathies increases with age. Of these, AS, jet streams which can damage the endothelial lining and predispose to platelet aggregation and fibrin deposition on the valves, forming a nonbacterial thrombotic endocardial lesion.

These vegetations can act as a nidus for infection when seeded by circulating bacteremia. Therefore, the ACC/AHA Guidelines for the management of patients with valvular heart disease recommends that such patients, identified by physical examination or by echocardiography demonstrating at least moderate AS or MS or mild AI, receive infective endocarditis prophylaxis.

Mitral valve prolapse (MVP), defined as a systolic displacement of all or part of a mitral valve leaflet at least 2 mm into the left atrium in a long-axis view on echocardiography, occurs in < 5% of the general population. MVP, however, is not uniformly associated with increased risk for infective endocarditis. In fact, if auscultation reveals only the characteristic mid-systolic click and the valves are normal on echocardiography, the risk of infective endocarditis in patients in this situation is negligible. However, if the valves are insufficient, such that the characteristic murmur of MR is produced, or there is echoradiographically demonstrable MR, prophylaxis is warranted. If echocardiography demonstrates thickened, redundant mitral valve leaflets, such patients are also at increased risk for infective endocarditis and prophylaxis should be administered. In addition, male sex and age >45 years have been identified as predictors of increased risk for development of infective endocarditis.

Procedures Producing Bacteremia

High-risk procedures, in this context, are those procedures associated with a high incidence of bacteremia, with “bacteremia” acting as a surrogate marker for infective endocarditis risk. There is much controversy, however, about the role of invasive procedures, especially dental procedures, as the causative event leading to infective endocarditis. The evidence for causality of odontogenic bacteremia is circumstantial, based on a temporal relation between dental procedures and subsequent manifestation of disease, and the identification of oral microflora (predominantly VGS, occasionally bacteria of the HACEK group) as the major pathogens. However, the mere presence of a temporal relation does not constitute proof of causation, particularly because of the influence of reporting bias: dental procedures are extremely common , whereas infective endocarditis is relatively uncommon (e.g., 3.3 cases/100,000 population/ year in the United Kingdom, with similar figures for the United States and

France).

Furthermore, identification of the same type of bacteria in the mouth and in cardiac vegetations supports the hypothesis that the offending pathogens derive from a mucosally lined source, but it again may be unfairly blaming dental procedures. There is no doubt that certain odontogenic procedures may occasionally cause transient bacteremias that lead to infective endocarditis. However, it has been estimated that dental treatment causes no more than 4% of all cases of infective endocarditis. Therefore, although it is convenient to think that gingival instrumentation with bleeding permits oral microflora to access the circulation and establish IE, the evidence that dental manipulation causes IE is weak. How then do the oral bacteria end up on the vegetation? The history of a "recent" dental procedure may, in fact, be a surrogate marker of poor oral hygiene. Patients with poor oral hygiene are at increased risk for bacteremia in the absence of dental procedures, with the size of the inocula likely related to the degree of gingival inflammation. Such transient bacteremia occurs with daily, trivial activities, such as chewing or tooth brushing.

Further supporting the refutation of dental procedures as a major cause of IE are studies which raise doubt about the efficacy of pre-dental treatment antibiotic prophylaxis. In a nationwide, case-control study in the Netherlands was estimated that the protective efficacy of chemoprophylaxis was 49% for first-ever infective endocarditis occurring within 30 days of a procedure. The same group, in a prospective, population-based case study, demonstrated that medical and dental procedures cause only a small fraction of infective endocarditis cases; furthermore, full compliance with prophylaxis might have prevented infective endocarditis in 47 (17.1%) of 275 patients with late prosthetic or native valve infective endocarditis involving a previously known cardiac lesion who underwent a procedure with an indication for prophylaxis.

For an incubation period of 30 days, prophylaxis might have prevented infective endocarditis in 23 (8.4%) of these 275 patients, or 5.3% of all patients with endocarditis (i.e., total of 427 cases). However, three points need to be emphasized: Firstly, some of the studies still demonstrated an association between procedures in at risk patients and the subsequent development of infective endocarditis. Secondly, the stu-

dies were population-based, case- or case-control study design, raising the possibility of ecological fallacy in analysis interpretation, where the effect of antibiotic prophylaxis at the population level may be negligible, but may continue to be worthwhile for the individual patient.

Although anaerobic bacteria are the principal components of the oral microflora and are released into the circulation after dental/oral procedures, they rarely cause IE. The predominant organisms of concern are the VGS, which are the targets for prophylaxis. A fundamental component of prophylaxis is good oral hygiene through daily, proper self-care and regular professional care. Antiseptic mouth rinses, either chlorhexidine- or povidone-iodine-based, may reduce the incidence and/or magnitude of bacteremia prior to dental procedures and are recommended by the current AHA and French guidelines prior to invasive oral procedures to reduce the risk of infective endocarditis.

Prophylaxis is recommended for procedures associated with significant bleeding. As well, it is recognized that unanticipated bleeding may occur on occasion in patients who did not receive prophylaxis prior to the procedure; in these cases, experimental data suggests that the appropriate pre-procedure regimen can still be administered within two hours of the procedure with similar efficacy. Interestingly, however, visible bleeding may not be a clinically relevant tool, as a previous study has demonstrated that bleeding is a poor predictor of odontogenic bacteremia. In cases where multiple consecutive dental interventions are required, repeated prophylaxis is also required. Because repeated single-dose antibiotic administration may select for resistant organisms which persist in the mouth, multiple procedures are recommended to be carried out in one sitting (if possible) or separated by 9–14 days. Streptococcal bacteremia can also occur via manipulation of other mucosal surfaces lining the upper respiratory tract (e.g., tonsillectomy, mastoidectomy, septoplasty). Although the use of a rigid bronchoscope is suggested to be a potential bacteremic-inducing procedure via mucosal damage and for which prophylaxis is recommended, there is no literature to support this opinion.

The esophageal procedures with the highest associated bacteremia rates are sclerotherapy of esophageal varices and esophageal dilation of a stricture. Endoscopic retrograde cholangiopancreatography (ERCP) has become a commonly performed procedure. The diagnostic and therapeutic utility of ERCP has been well demonstrated for a variety of disorders, including the management of biliary obstruction, predominantly due to choledocholithiasis or biliary malignancies. The rate of bacteremia after contrast injection or instrumentation of unobstructed pancreatic or bile ducts ranges from 0% to 15% (mean frequency of 6.4%). Biliary obstruction, however, may lead to infection of the biliary system with a variety of organisms. Although the predominant organisms are Gram-negative bacillary enterics (e.g., *E.coli*, *Klebsiella* spp.), which are common causes of cholangitis/biliary sepsis, they are uncommon causes of IE, although they may cause disease in high-risk patients (e.g., those with prosthetic valves). The major organisms from an infected biliary tree that can cause bacteremia with the potential for IE are *Enterococcus* spp. and VGS. The enterococci are particularly more common among patients with previous biliary endoprosthesis. Instrumentation of an obstructed biliary system has resulted in bacteremia rates as high as 26.5% (mean 18.0%), hence the rationale for prophylaxis.

Endoscopic ultrasound (EUS) is a relatively new procedure. One of its greatest benefits is the ability to perform fine-needle aspiration (FNA), the two procedures referred to as EUS-FNA. EUS-FNA has been used to aspirate fluid from cystic lesions, pseudocysts, and fluid collections for both diagnostic and therapeutic purposes. Some experts recommend prophylactic antibiotics as well as 48 hours of antibiotics after the procedure for EUS-FNA of the perirectal space. Colonoscopy has a surprisingly low rate of bacteremia (2–5%), most commonly with organisms that are not typically causes of infective endocarditis. Therefore, antibiotic prophylaxis is not recommended for this procedure, including when it involves biopsy or polypectomy.

Genitourinary (GU) instrumentation is necessary for the diagnosis and treatment of benign and malignant urological diseases. However, instrumentation and catheterization of the GU tract is also the leading cause of nosocomial urinary tract infections (UTIs) Less frequently, bacteremia can result from these interventions, the rates vary-

ing with different procedures. Development of bacteremia directly attributable to the GU procedure typically occurs after colonization of the urine.

Antimicrobial Prophylaxis

Because VGS are felt to be the predominant pathogens potentially to cause IE after dental/oral, respiratory, and esophageal procedures, aminopenicillins are the recommended prophylaxis. In the past, VGS were nearly uniformly susceptible to penicillin and other β-lactams, as well as to lincosamides and macrolides. Therefore, the current AHA guidelines on IE prophylaxis, which were published in 1997, recommend the use of amoxicillin (ampicillin if the patient is unable to tolerate oral intake). Amoxicillin was recommended over penicillin because it is better absorbed from the GI tract and because it provides higher and more sustained levels. In humans, the elimination half-life of amoxicillin is 50–60 minutes. Clindamycin or macrolides are alternatives in those unable to tolerate β-lactams. A contemporary review of the antimicrobial susceptibility of VGS demonstrated that amoxicillin at a concentration of ≤ 0.5 μg/mL inhibited 87%, 64%, and 100% of isolates in the *S.sanguis*, *S.mitis*, and *S.milleri* groups, respectively, as well as two of the three isolates in the *S.salivarius* group. Hence, the use of amoxicillin as a prophylactic regimen was justified. However, several studies have since demonstrated increasing rates of VGS isolates from oropharyngeal specimens and bloodstream infections that are not susceptible to penicillin, macrolides, or lincosamides.

Furthermore, resistance to these antibiotics can occur with repeated prophylaxis doses for serial procedures distributed closely in time. Therefore, continued monitoring of such resistance patterns is mandatory, and modifications of future guidelines may be necessary. Until such time, amoxicillin remains the recommended prophylaxis regimen for the above-mentioned procedures. When comparing the AHA guidelines from those of Europe (BSC, French), differences in amoxicillin dose is seen. The latter recommend a single 3-g oral dose, which produces serum levels above the MIC of most oral streptococci for a period of 6–14 hours . The AHA proposes 2-g, instead of 3-g, because the serum kinetics produced by the two different doses are very similar, although the lower dose is associated with fewer side effects. For pa-

tients with a history of penicillin allergy, clindamycin remains appropriate. Alternatives include macrolides, such as clarithromycin or azithromycin, which have demonstrated efficacy in experimental models and have convenient dosing regimens, although they are more expensive. Cephalosporins also have demonstrated efficacy, but should not be used in patients with a history of type 1 (immediate- type/anaphylaxis) hypersensitivity reaction to β-lactams. For patients unable to take medication orally, intravenous regimens are recommended, and administration of the full dose should be completed within 30 minutes of the procedure.

For procedures involving the biliary system or the gastrointestinal or genitourinary tracts, the predominant pathogen of concern is *Enterococcus* spp. Previous studies have reported that among cases of enterococcal IE, ~40% were associated with a recent gastrointestinal or genitourinary procedure (i.e., within 2–6 weeks). Enterococci however, are notoriously more resistant than VGS, with typically higher MICs to β-lactams.

Thus, after administration of amoxicillin, the corresponding serum levels fall below the MIC of enterococci sooner than for VGS, resulting in a decreased period of bacterial growth inhibition. To overcome this issue in high-risk patients, a second dose of the β-lactam is currently recommended six hours after the first dose to ensure prolongation of adequate serum levels and to enhance protective efficacy.

Alternatively, administration of a single dose of vancomycin (in conjunction with gentamicin) can be used in high-risk patients unable to tolerate β-lactams. The evidence for this recommendation derives from experimental studies in which vancomycin demonstrated prolonged serum half-life, producing serum levels greater than MIC for a longer period of time (compared to ampicillinbased regimens), which resulted in significantly greater area under the curve (AUC) and serum inhibitory activity, and more consistent protective effect. Because of vancomycin's pharmacokinetics, a second dose is not considered necessary. For moderate-risk patients, the second dose of aminopenicillins is optional.

Thus, guidelines exist to assist clinicians in stratifying their patients' risk of infective endocarditis with regard to various procedures. Unfortunately, most of the recommendations are not based on robust, scientific evidence, but, instead, are con-

sensus expert opinion. In addition, emergence of antimicrobial resistance and a changing epidemiology of infective endocarditis will likely necessitate revision of current guidelines.

Diagnostic Criteria.

General Investigations

Laboratory investigations may reveal anemia, leukocytosis with a left shift, elevated erythrocyte sedimentation rate, and glomerulonephritis (with hematuria or active urinary sediment). Immunologic perturbation may also occur in subacute or chronic cases leading to high titers of rheumatoid factor. The chest x-ray may show evidence of preexisting valvular disease (valvular calcification or cardiomegaly) or a complication arising from the infection (congestive heart failure or septic pulmonary emboli). Rarely, suppurative pericardial effusion from periannular abscess formation may produce a globular heart on x-ray. A careful examination of the electrocardiogram should be made to rule out heart block (as this is one of the complications of IE as the infectious process involves the aortic valve annulus and membranous interventricular septum).

Bacteriologic Investigations

Three aerobic blood cultures (with a minimum of 10mL per bottle), from separate venipuncture sites, should be obtained over at least an hour before beginning therapy. Blood cultures inoculated with at least 5 mL of blood had a 92% detection rate for bacteremia compared to only 67% for bottles inoculated with less than 5 mL in one study The estimated yield from blood cultures increased approximately 3% per mL of blood cultured. Anaerobic cultures may be performed but only rarely will the organism be anaerobic. If a patient has not been treated with antibiotics prior to obtaining the blood cultures there is minimal benefit beyond three cultures. However, there may be additional diagnostic yield if antibiotics had been administered or if the initial blood cultures were negative. Not all bacteremias imply the presence of IE. Certain species are more commonly associated with the disease.

Echocardiographic Investigations

Prior to the availability of echocardiography the only way to visualize a vegetation was by surgery or autopsy. The development of echocardiography and the identification of criteria for the diagnosis of infective endocarditis have significantly improved our ability to diagnose and treat this disease. Echocardiography has become one of the major diagnostic procedures available today. The echocardiographic hallmark of infective endocarditis is an endocardial mass lesion usually referred to as a "vegetation" (as mentioned earlier). This is usually defined as an oscillating mass attached to an endocardial surface, such as a valve or supporting structure, or a structure in the path of regurgitant jets. Additionally, echolucency, suggesting the presence of abscess formation, and Doppler evidence of valvular dysfunction should be sought.

A series of diagnostic criteria have been developed by Pelletier and Petersdorf (1977), von Reyn (1981), and the Duke group (1994). The Pelletier and Petersdorf criteria required pathological confirmation of the diagnosis of IE and thus, were not very useful for prospective clinical diagnosis. Von Reyn and colleagues improved the case definitions to make them more clinically relevant. In 1994, investigators from Duke University modified the von Reyn criteria to include echocardiographic findings in the diagnosis of infective endocarditis (Table 2.1, 2.2, 2.3).

Table 2.1

Diagnostic Criteria by Pelletier and Petersdorf

Definite: Histologic evidence of endocarditis on autopsy or surgery

Probable

Uniformly positive blood cultures AND all of
- Underlying valve disease
- Evidence of skin or visceral emboli

OR

- Negative blood cultures AND all of
- Fever > 38 °C
- New regurgitant murmur
- Evidence of skin or visceral emboli

Possible

- Uniformly positive blood cultures AND
- Underlying valve disease OR evidence of skin or visceral emboli

OR

- Negative blood cultures AND all of

Fever > 38 °C
Underlying valve disease
Evidence of skin or visceral emboli

Their classification scheme by Pelletier and Petersdorf consisted of three diagnostic categories: definite, probable, and possible. These diagnostic criteria were quite specific but were not very sensitive. Many patients with clinically suspected IE failed to meet diagnostic criteria.

Table 2.2

von Reyn Criteria for Diagnosis of Infective Endocarditis

Definite

Direct histologic evidence of infective endocarditis from surgery or autopsy

OR

Bacteriology (Gram stain or culture) of valvular vegetation or peripheral embolus

Probable

Persistently positive blood cultures plus ONE of the following:

New regurgitant murmur

Predisposing heart disease AND vascular phenomena

OR

Negative or intermittently positive blood culture plus ALL of the following:

- Fever
- New regurgitant murmur
- Vascular phenomena (petechiae, splinter hemorrhages, conjunctival hemorrhages, Roth spots, Osler's nodes, Janeway lesions, aseptic meningitis, glomerulonephritis, peripheral emboli, central nervous system emboli, coronary emboli, peripheral emboli)

Possible

Persistently positive blood culture plus ONE of the following:

- Predisposing heart disease (definite valvular or congenital disease or cardiac Prosthesis excluding permanent pacemakers)
- Vascular phenomena

OR

Negative or intermittently positive blood culture plus ALL of the following:

- Fever
- Predisposing heart disease
- Vascular phenomena

Rejected

Endocarditis unlikely, alternative diagnosis generally apparent

Endocarditis likely, empiric antibiotic therapy warranted

Culture negative endocarditis diagnosed clinically but excluded by postmortem

The von Reyn system was designed to make the diagnostic criteria more clinically applicable. The classification scheme consisted of four categories: definite, probable, possible, and rejected. Pathological confirmation of vegetations, or of an abscess, was still required to define a case as definite. Thus many cases were classified as probable or possible since many patients did not have pathological confirmation.

At the present time, the Duke criteria are the standard diagnostic criteria for patients with suspected infective endocarditis, while there are some criteria that are listed above. Duke criteria: Investigators at Duke University further refined the diagnostic criteria to make the case definitions more clinically applicable to patients suspected of having acute infective endocarditis. This group has since published modifications of their original criteria after the validation studies were completed. The new criteria include the addition of the presence of *Coxiella burnetii* as a major criterion and the elimination of echocardiographic minor criterion. Possible infective endocarditis has been redefined to include one major plus one minor criterion or three minor criteria. In addition, the role for transesophageal echocardiography for the diagnosis of infective endocarditis has been made more explicit to include patients with prosthetic valves and those suspected of having complicated infective endocarditis (such as a paravalvular abscess)

Table 2.3

Modified Duke Criteria for Diagnosis of Infective Endocarditis

Major Criteria

Positive blood cultures for infective endocarditis

In the absence of a primary focus, positive cultures from two separate blood cultures of one of the following typical organism:

- *Streptococci viridans*
- *Streptococcus bovis*
- HACEK group (*Haemophilus* species, *Actinobacillus actinomycetes comitants*, *Cardiobacterium hominis, Eikenlla* species, *Kingella kingae*)
- Community-acquired *Staphylococcus aureus* or entercocci

OR

Persistently positive blood cultures of a microorganism consistent with infective endocarditis

OR

Single blood culture for Coxiella burnetii or antiphase I IgG antibody titre > 1:800.

Evidence of endocardial involvement

New valvular regurgitation

OR

Positive echocardiogram (oscillating intracardiac mass in the absence of an alternative anatomic explanation

OR abscess

OR new partial dehiscence of prosthetic valve)

Minor criteria

Predisposing heart condition OR intravenous drug use

Fever (at least 38.0 °C)

Vascular phenomena (major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctivae hemorrhage, Janeway lesions)

Immunologic phenomena (glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor)

Microbiologic evidence of positive blood culture not meeting major criterion but excluding single positive culture for coagulase negative *Staphylococci* and organisms that do not cause endocarditis OR serologic evidence of active infection with organism consistent with IE.

Definite

Two major criteria

OR

One major and three minor criteria

OR

Five minor criteria

OR

Microorganism demonstrated by culture or histology of a vegetation, embolized vegetation or in an intracardiac abscess

OR

Histologic evidence of active endocarditis (vegetation or intracardiac abscess)

Possible

One major and one minor critieria

OR

Three minor criteria

Rejected

Firm alternative diagnosis

OR

Resolution of manifestations of endocarditis with 4 or less days of antibiotics

OR

No pathologic evidence of infective endocarditis at surgery or autopsy after 4 or less days of antibiotics

OR

Does not meet criteria for possible infective endocarditis

So, when appropriately used, echocardiography (TTE and TEE) is extremely useful in defining both the diagnosis and prognosis of infective endocarditis. Categorization of patients into strata of clinical probability of disease and into strata of clinical risk for morbidity and mortality may help to determine the most appropriate timing of the echocardiographic examination and the choice of the initial echocardiographic modality.

Surgical Management: Indications and Technical Issues

Surgical procedures for "active" or "acute" infective endocarditis are technically more demanding than operations for acquired non-infected valvular lesions. The main challenge in acute infective endocarditis is to address the two coexisting aspects of the disease:

1. the infectious process that requires removal of all infected tissues to prevent recurrence of infective endocarditis,
2. the altered valvular anatomy and function that should be corrected or restored.

This may require extremely complex and high-risk surgical procedures, although operations in "healed" infective endocarditis with no residual infection or perivalvular involvement can be handled similar to conventional valve operations. The decision-making process is key to the final surgical outcome, underlining the critical need for each individual case to be carefully assessed for the infectious process and evaluated for valvular dysfunction in order to decide on when and how to operate.

Indications and Evaluation for Surgery

Generally speaking, major absolute indications for surgical intervention in IE include:

1. hemodynamic compromise,
2. persistent and/or uncontrolled infection despite aggressive medical therapy
3. embolization.

Significant anatomical changes and complications caused by infective endocarditis, such as aneurysm, fistula, and atrioventricular discontinuity, may also be considered an indication, as they usually indicate the imminent occurrence of hemodynamic compromise. Some authors have advocated other relative indications for

surgery. The most common indication for surgery is usually heart failure, followed by persistent sepsis. Surgical outcomes are better in healed infective endocarditis operations than in acute infective endocarditis surgeries. However, in the presence of a major indication, or when clinical judgment strongly suggests that surgical indication is imminent, there should be no delay in carrying out the operation, even with active infective endocarditis. Hemodynamic stability takes priority over infection control by medical treatment. When to operate for infective endocarditis remains a controversial issue and is often addressed on a case by case basis. Surgical timing strategies have evolved considerably over the recent years, owing to the developments in the medical management of infectious diseases and in diagnostic tools, echocardiography in particular. The more routine use of transesophageal Echo, beginning in the 1990s, has especially led to earlier and more accurate identification of surgical indications and more optimal timing of operation. Early diagnosis by echocardiography and blood cultures, identification of the causative microorganisms, detection of localized foci of infection by advanced imaging techniques, and availability of more effective antimicrobials have all definitely changed the decision-making process and timing for surgery. Such improvements have even enhanced the frequency of successful medical management without the immediate need for cardiac surgery. On the other hand, improvements in operative techniques, postoperative care, availability and quality of prosthetic valves, and the accuracy in early prediction of inevitable surgery are all in favor of earlier surgical intervention. Many situations that were once considered high-risk for surgery have demonstrated better outcomes with surgical intervention than with conservative medical management. Significant acute aortic or mitral regurgitation with heart failure in the setting of NVE is an obvious indication for surgery. Finally, like any other open-heart surgery, the patient should also be evaluated from other cardiac and non-cardiac standpoints. Hepatic and renal functions are of particular importance, as they have a great impact on the surgical outcomes. Unjustified delay of the operation, when surgery is indicated, may cause deterioration in renal and/or hepatic function due to both the disease itself and the toxicity of medications, antibiotics in particular. This underscores, once again, the significance of the right

timing for surgery. Comorbidities (diabetes, etc.) should be considered and properly addressed. In patients with a high risk of CAD, preoperative angiography should be performed to assess for the possible need of coronary artery bypass grafting at the same operative session.

The fact that cardiac surgery is an integral part of infective endocarditis management, early consultation with the cardiac surgery team is strongly recommended following the diagnosis of infective endocarditis. This will allow the surgical team to be fully familiar with the patient, in case surgery is eventually needed. It will also enable medical and surgical teams to join forces in determining the need and optimum timing for surgery. The American College of Cardiology/American Heart Association Guidelines for the Management of Patients with Valvular Heart Disease also support early surgical consultation in infective endocarditis cases.

Treatment of Native Valve Endocarditis: General Principles and Therapy for Specific Organisms

Infective endocarditis, if inadequately treated, is fatal. Even with appropriate management, overall mortality rates range from 10% to 25%. Clinical outcome is influenced by multiple factors, including valve characteristics, host factors, causative organism, development of intracardiac or systemic complications, and management options available.

The therapeutic modality initially used in the treatment of infective endocarditis is medical. The role of surgery, however, continues to expand; aggressive surgical intervention, particularly in the early stages of developing complications, can be associated with a reduction in mortality.

The principles of antimicrobial selection for infective endocarditis are based on the understanding of the behavior of the causative pathogen, proper interpretation of antibiotic susceptibility testing, an understanding of vegetation characteristics, and proper application of antimicrobial pharmacokinetic and pharmacodynamic data. These considerations are complemented by animal experimental models and by clinical outcomes of published observational studies to form consensus-based guidelines for the optimal management of infective endocarditis.

Optimal management aims to eradicate the infecting organism as soon as possible, to operate with correct timing if surgical intervention should be required, and to treat complications. Because infective endocarditis carries a significant risk of death even when well managed, it is important that treatment be continued long enough to ensure that relapse will not occur. In contrast, patients with the more easily cured forms of endocarditis should not be subjected to unnecessarily long, expensive, and potentially toxic treatment in a hospital. This can happen when physicians treat on the basis of outdated rules, such as the one stating that "endocarditis should be treated for 6 weeks". In fact, many patients can be cured in or 4 weeks, while some require treatment for 6 weeks or longer.

Fundamental to the management of infective endocarditis is early diagnosis and prompt initiation of effective antimicrobial therapy. Therefore, proper laboratory identification of the pathogen to the species level is essential, with subsequent antimicrobial susceptibility testing using standardized protocols to determine the minimal inhibitory concentration (MIC). Testing for synergistic combinations of antibiotics (e.g., highlevel aminoglycoside resistance for *Enterococcus* spp.) using standardized protocols should also be done where appropriate. The MIC of an antimicrobial agent is defined as the lowest concentration which results in maintenance or reduction of inoculum viability; it is the lowest concentration of the drug needed to prevent microbial growth in vitro The MIC can then be compared to a reference standard database, such as that from the Clinical and Laboratory Standards Institute (formerly the National Commmittee for Clinical Laboratory Standards (NCCLS)), to interpret whether the pathogen is “susceptible”, “intermediate”, or “resistant” to the tested antimicrobial. Definitions of these terms are provided Table 2.4.

Table 2.4

Definitions of Terms Used in Antimicrobial Susceptibility Testing

Categories	Performances
Susceptible	implies that infections may be treated appropriately with the dosage of antibiotic recommended for the type of infection and infecting species, unless otherwise indicated.
Intermediate	implies that infections may be treated if the antibiotic is able to reach specific tissues where the drug will be concentrated (for ex-

	ample, quinolones in the urine) or when the drug can be used in higher than usual doses without adverse effects. This category also includes a "buffer zone," which should prevent small, uncontrolled technical factors from causing major discrepancies in interpretation
Resistant	isolates are not inhibited by the usually achievable systemic concentrations of the drug in normal dosage and/or fall in the range where specific microbial resistance mechanisms are likely (for example, β-lactamases) and clinical efficacy has not been reliable in treatment studies. These categories are not mutually exclusive, but rather represent a continuum of antimicrobial activity

It is important to note that the MIC represents a unique relation between a particular bacterial species and the tested antimicrobial agent. Because different antibiotics are tested at different concentrations, the MIC numbers cannot be directly compared.

The minimum bactericidal concentration (MBC) is the lowest concentration of an antibiotic, expressed in mg/L, that under defined in vitro conditions reduces by ≥ 99.9% (3 log10) the number of organisms in a medium containing a defined inoculum of bacteria, within a defined period of time. Although the MBC is an in vitro microbiological method to determine the killing efficacy of antibacterial agents, its routine use in clinical practice is precluded by inaccuracy of measurement, as well as technical limitations (e.g., suboptimal inocula, difficulties with interpretation of a 99.9% bactericidal endpoint) that produce varying and thus invalid results. As such, various working groups for endocarditis, including the British Society for Antimicrobial Chemotherapy (BSAC) and the American Heart Association committee (AHA), do not recommend its routine determination.

The value of the MBC, however, allows for the definition of antimicrobial agents as bactericidal, bacteriostatic, or tolerant. Bactericidal antibiotics, generally speaking, are those that kill bacteria, whereas bacteriostatic agents are those that prevent the growth of bacteria (i.e., keeps them in the stationary phase of growth). In IE, a bactericidal regimen (either monotherapy or combination therapy) is considered necessary for cure.

The actual microbiological definition of "bactericidal" is a ≥ 99.9% reduction in viable bacterial density in an 18–24-hour period, producing an MBC to MIC ratio

≤ 4, whereas "bacteriostatic" is defined as a ratio of MBC:MIC > 4. Tolerance occurs among bacterial strains when a bactericidal antibiotic loses its killing efficacy but retains its bacteriostatic activity (i.e., MIC unchanged) and is defined as a ratio of MBC:MIC > 32.

Bactericidal activity is not an invariable property of an antibiotic; it is also influenced by the organism, inoculum burden, as well as growth conditions. To enhance the bactericidal activity of a selected antibiotic regimen further requires an understanding of pharmacokinetics and pharmacodynamics, with subsequent optimization of these parameters. Pharmacokinetics (PK) refers to the factors that determine the drug concentrations at the site of infection after a dose of an antimicrobial drug is given; it is affected by the absorption, distribution, and elimination of the drug However, with newer antibiotics in which the oral formulation has high (near 100%) bioavailability, this dogma in the management of IE may change. The concentration of an antibiotic in the serum is also affected by its volume of distribution, its metabolism, and its elimination. With infective endocarditis, the site of infection is an intravascular vegetation enclosed in a layer of biofilm that renders penetration of antibiotics difficult. This phenomenon may explain the superiority of some antibiotics over others in the management of infective endocarditis, depending on their degree of vegetation penetration. It also provides the rationale for using high doses of antibiotics and a prolonged duration of treatment. Another factor that determines efficacy of antibiotic at the site of infection is protein binding. All drugs bind to some extent to serum proteins; however, it is the free (unbound) drug that is active. Antibiotics that are highly protein bound in vivo may actually be clinically ineffective, even though they demonstrate significant in vitro killing activity. Such was the case with cefonicid, a second-generation cephalosporin that was clinically inadequate for the treatment of infective endocarditis due to *S. aureus*. Lastly, an understanding of how a certain antibiotic is metabolized or excreted, and whether this clearing system is impaired in the host, will allow for optimal dosing while minimizing toxicity. Pharmacodynamics relates drug exposure (i.e., pharmacokinetics) to the antimicrobial effect of the drug, to provide a more rational basis for determination of optimal dosing regimens in

terms of the dose and the dosing interval. The two major components of antibiotic activity are its pattern of kill and its post-antibiotic effect (PAE). The pattern of bactericidal activity can be concentration-dependent, in which the rate of kill is directly dependent on the amount of drug (peak serum concentration) relative to the MIC, or time-dependent, in which the bactericidal efficacy is dependent on the amount of time the serum antibiotic concentration exceeds the MIC. For time-dependent antibiotics such as β-lactams and glycopeptides, further increasing antibacterial concentrations above the MIC does not result in proportional increases in killing. The PAE refers to a variety of persistent effects that last after antimicrobial exposure. Examples include the in vitro PAE, which is the extent of growth retardation of bacteria that occurs when drug levels are suddenly eliminated, as well as the post-antibiotic leukocyte effect, in which organisms in the postantibiotic state of growth are more susceptible to the antimicrobial activity of white blood cells. As the vegetations in IE are composed of fibrin, platelets, and bacteria, with few phagocytes, the post-antibiotic leukocyte effect would be intuitively negligible in infective endocarditis. The clinical significance of other PAE in IE remains to be elucidated.

Based on the pattern of bactericidal activity and the PAE, antibiotics can then be divided into three categories:

(1) concentration dependent killing and moderate to prolonged persistent effects (examples include aminoglycosides, quinolones, and daptomycin);
(2) timedependent killing and minimal to no persistent effects, such as β-lactams;
(3) time-dependent killing and moderate to prolonged persistent effects, including glycopeptides, oxazolidinones, clindamycin, macrolides, and tetracyclines.

This framework will determine subsequent modifications of dosing regimens to optimize bactericidal efficacy.

For the first group, enhancing peak serum concentration (while avoiding or minimizing toxicity) would be the preferred intervention.

For β-lactams, adjusting the interval between infusions or using agents with longer half-lives would be undertaken to increase the duration of exposure.

For the third group, enhancing the amount of drug is predicted to be an important determinant of clinical efficacy.

As mentioned previously, in addition to bactericidal and bacteriostatic activity, antibiotics can also be tolerant (i.e., inhibit bacterial growth but without killing activity). Although the clinical relevance of tolerance in endocarditis is unknown (as MBC is not routinely tested), retrospective microbiological studies have demonstrated this phenomenon among clinical isolates in treatment failures of β-lactams and glycopeptides. It may also provide additional rationale for the use of synergistic combination therapy in certain cases of infective endocarditis.

Selecting the appropriate antibiotic regimen at the start of therapy is but the first step. Reassessment of antmicrobial performance is continuously required. The only reliable measure of clinical efficacy is ultimate cure without relapse. In the interim, it is important to monitor for evidence of improvement, including defervescence, sterilization of blood cultures, and normalization of inflammatory markers. Failure to demonstrate such features, in the presence of correct clinical and laboratory diagnosis, may reflect pharmacological error (e.g., insufficient dose, dosing interval, or antibiotic serum levels) or the development of IE complications. To ensure pharmacological optimization, consultation with a pharmacist with experience in antimicrobial therapy should be considered. As well, therapeutic drug level monitoring, especially for aminoglycosides and glycopeptides, is recommended (table 2.5).

Table 2.5.

Conditions for Two-Week Combination Therapy for Penicillin-Sensitive and Aminoglycoside-Sensitive Streptococcal Endocarditis

№	Characteristics
1	Penicillin-sensitive oral (or viridans group) streptococcus or *S. bovis* (penicillin MIC ≤0.1 μg/mL)
2	Native valve infective endocarditis
3	No cardiac complications (e.g., intra-cardiac abscess, heart failure, aortic insufficiency, conduction abnormalities)
4	No extra-cardiac complications (e.g., septic embolic foci)
5	No vegetation >5 mm in diameter on echocardiography
6	Clinical response within 7 days: there should be resolution of fever, the patient should feel well, and the appetite should return

Recognition of syndromes indicating the presence of infective endocarditis complications is crucial in patient management. These complications can be classified into cardiac and extra-cardiac. The cardiac manifestations include congestive

heart failure (CHF), periannular extension of infection (with subsequent abscess or fistula formation, or rupture), valve obstruction, or prosthesis instability. The extracardiac manifestations result from embolic phenomena; the major sequelae include neurological compromise (e.g., stroke with or without hemorrhage, mycotic aneurysm) and metastatic infections. The presence of these complications can assist in determining the need and timing for surgical intervention.

In summary, the appropriate treatment of infective endocarditis requires early diagnosis, as well as prompt effective antmicrobial therapy, and is best managed via a multidisciplinary team approach, involving at least specialists in infectious disease, cardiologists, pharmacists, and cardiac surgeons.

Empiric Therapy

When the etiologic organism is not known, the choice of empiric therapy should depend on whether the patient has acute or subacute disease. ABE requires broad-spectrum therapy that covers *Staph.aureus* as well as many species of streptococci and gram-negative bacilli. SBE requires a regimen that treats most streptococci, including *E.faecalis.* To meet these requirements, the following suggestions are offered: l For ABE: nafcillin 2.0 g IV q 4 h plus ampicillin 2.0 g IV q 4 h plus gentamicin 1.5 mg/kg IV q 8 h. If methicillin-resistant *Staph.aureus* is considered likely (for example, in a hospital-acquired case), vancomycin 1.0 g IV q 12 h should be substituted for nafcillin in this regimen until the antibiotic sensitivity is known. For SBE: ampicillin 2.0 g IV q 4 h plus gentamicin 1.5 mg/kg IV q 8 h. Treatment should be adjusted as appropriate when the etiologic organism is identified and again when antibiotic sensitivity is known. In those few cases where empiric therapy is administered as a therapeutic trial to help confirm a diagnosis, treatment should be continued without interruption or unnecessary changes for at least 2 weeks; otherwise, no useful diagnostic information will be gained.

Duration of Therapy

Extensive experience with treatment of the common forms of endocarditis provides the basis for recommendations on duration of therapy. In the case of *Staph.aureus* endocarditis, the response to appropriate treatment can be variable;

some patients recover swiftly without complications, especially young IDUs, who can often be cured within 2 weeks. In contrast, some patients remain febrile for 10 to 14 days due to complications such as abscesses or other extracardiac manifestations of disseminated staphylococcal disease. Although 4 weeks of therapy is adequate in most cases, this should not be regarded as a rigid rule, because some patients with *Staph.aureus* endocarditis require treatment for 6 weeks or longer to achieve a cure. For *E.faecalis* endocarditis, 4 weeks of treatment is usually adequate. The relapse rate, however, seems to be higher in patients with mitral valve infection and in those who have had symptoms for more than 3 months, where treatment should continue for 6 weeks. Parenteral treatment can be completed in the patient's home or in the outpatient clinic in carefully selected cases. Availability of antibiotics with long half-lives, such as vancomycin or ceftriaxone, allows once-daily administration. Supervised parenteral treatment outside the hospital should be fully effective in achieving a microbiologic cure and offers obvious benefits: convenience for the patient and cost containment. The risks posed by a possible late complication, such as an embolic stroke or the sudden onset of heart failure, must be balanced against these benefits in selecting candidates for home parenteral therapy. Further trials are needed to refine the criteria and proper applications for outpatient therapy for endocarditis, but current experience indicates that more than one-half of endocarditis patients could receive at least some of their treatment as outpatients. In general, the less extensive the published experience with a particular organism and treatment regimen, the more one should lean toward prolonging treatment in order to provide a reasonable margin of safety. Guidelines for the duration of treatment of the more common etiologic organisms are listed in Table 2.6.

Table 2.6

Treatment Regimens and Duration of Management for Infective Endocarditis

Organism	Treatment Regimen: Dose, Route and Duration in Weeks	Notes
Fully penicillin-sensitive streptococci: MIC 0.1 g/mL viridans (hemolytic) streptococci; *Strep.bovis; Strep.pneumoniae; Strep.pyogenes* group A, C, etc.; *Strep.agalactiae* group B	1. Penicillin G 4 million units every 6 h IV alone (4 weeks) *or* 2. Penicillin G 4 million units every 6 h IV with gentamicin (2 weeks)	Suitable for hospitalized patients but less convenient for outpatient therapy For patients allergic to penicillins but not cephalospo-

	3. Ceftriaxone 2 g IV or 1 M once daily alone (2 weeks) *or* 4. Ceftriaxone 2 g IV or 1 M once daily or with gentamicin 1 mg/kg twice a day or 3 mg/kg 4 times a day (2 weeks) 5. Vancomycin 15 mg/kg IV every 12 h (4 weeks	rins or for outpatient therapy in selected patients For patients allergic to penicillins and cephalosporins
Relatively penicillin-resistant streptococci: MIC > 0.1 < 1.0 g/mL, some viridans (- hemolytic) streptococci; some *Strep. pneumoniae;* etc.	1. Penicillin G 4 million units IV every 4 h *plus* gentamicin 1.0 mg/kg every 12 h IV or IM (for first 2 weeks only during 4 weeks) *or* 2. Vancomycin 15 mg/kg IV every 12 h (4 weeks)	For outpatient therapy in selected patients, ceftriaxone 2 g IV once daily may be substituted for penicillin if ceftriaxone MIC 4 g/mL, *plus* gentamicin 2.0 mg/kg given once daily For patients allergic to penicillins
Staphylococci (in the absence of prosthetic material)	Methicillin-susceptible staphylococci: 1. Nafcillin 2 g IV every 4 h IV 4-6 weeks *or* 2. Nafcillin 2 g IV every 4 h IV . 4-6 weeks plus gentamicin 1.0 mg/kg every 8 h IV . 3-5 days 3. Vancomycin 15 mg/kg IV every 12 h 4-6 weeks	β-lactam-containing regimens preferred over vancomycin unless patient is definitely hypersensitive to penicillins and cephalosporins; for patients with severe disseminated staphylococcal infection, antimicrobial synergy may be advantageous during early stages of treatment; therefore, gentamicin 1.0 mg/kg IV every 8 h for first 3-5 days only may be added to any of these regimens
Penicillin-resistant streptococci: MIC 1.0 g/mL, *E. faecalis, E.faecium,* other enterococci; some other streptococci	1. Penicillin G 18-30 million units/day IV continuously or in divided doses *plus* gentamicin 1 mg/kg IV or IM every 8 h (4-6 weeks) *or* 2. Ampicillin 12 g/day IV continuously or in divided doses *plus* gentamicin 1.0 mg/kg IV every 8 h, (4-6 weeks) *or* 3. Vancomycin 15 mg/kg IV every 12 h *plus* gentamicin 1.0 mg/kg IV every 8 h (4-6 weeks)	Susceptibility testing needed; do not use penicillin- or ampicillincontaining regimen if strain produces - lactamase. 4-week regimen recommended for most cases with symptoms for <3 months, otherwise 6 weeks For patients allergic to penicillin; 4 weeks should be adequate for most cases; serum levels should be monitored
In right sided uncomplicated tricuspid endocarditis	Nafcillin 2 g IV every 4 h and gentamicin 1 mg/kg twice a day or 3 mg/kg 4 times a day	

	2 weeks Methicillin-resistant staphylococci: Vancomycin 15 mg/kg IV every 12 h during 4-6 weeks	
Staphylococci (associated with prosthetic valve or other prosthetic material)	Methicillin-susceptible staphylococci: Nafcillin 2g IV every 4h *plus* gentamicin 1.0mg/kg IVevery 8h plus rifampin 600 mg orally 4 times a day during > 6 weeks Methicillin-resistant staphylococci: Vancomycin 15 mg/kg IV every 12 h *plus* gentamicin 1.0 mg/kg IV or IM every 8 h *plus* rifampin 300 mg orally every 8 h during >6 weeks	Cefazolin or vancomycin may be substituted for nafcillin if necessary due to drug hypersensitivity
HACEK group organisms: *Haemophilus* species *Actinobacillus actinomycetemcomitans* *Cardiobacterium hominis* *Eikenella* species *Kingella kingae*	1. Ceftriaxone 2 g IV or IM once daily 4 weeks *or* 2. Ampicillin 12 g/day IV continuously or in divided doses *plus* gentamicin 1.0 mg/kg every 12 h IV or IM 4 weeks	Other third generation cephalosporins may be substituted, using appropriate dose adjustment Less convenient for outpatient therapy
Pseudomonas aeruginosa, other gram-negative bacilli	Extended-spectrum penicillin *or* third generation cephalosporin *or* imipenem *plus* aminoglycoside during 4-6 weeks	Combination therapy recommended; final choice of antibiotic regimen to be made after sensitivity results available
Neisseria species	1. Penicillin G 2 million units IV every 6 h during 3-4 weeks *or* 2. Ceftriaxone 1 g IV or IM once daily during 3-4 weeks	Organisms often highly sensitive to penicillin, but must be tested for –lactamase production; 3 weeks should be adequate for most patients without complications

For less common organisms, the optimal duration of treatment required may vary according to individual circumstances.

Anticoagulant Therapy

Even though the infected vegetation is essentially a thrombotic lesion, there is no evidence that anticoagulation has any useful therapeutic effect on the course of the endocarditis itself. On the contrary, early experience showed that simultaneous treatment with penicillin and heparin carried an increased risk of fatal intracerebral hemorrhage. For this reason, anticoagulation was considered to be strongly contraindicated in patients with endocarditis, until further experience showed that warfarin

could usually be given safely during the treatment of patients with prosthetic valve infections.

Currently available information suggests the following guidelines for patients with infective endocarditis:

- Avoid use of heparin except for urgent indications, such as treatment of massive pulmonary embolism.
- Discontinue or avoid oral anticoagulants if possible, especially in patients with intracranial complications and if *Staph. aureus* is the cause of infective endocarditis.
- Anticoagulate with warfarin if there is a clear-cut indication, such as a mechanical prosthetic heart valve, taking care to regulate the prothrombin time between International Normalized Ratio (INR) 2.5 and 3.5.
- Choose an antibiotic treatment regimen that does not require intramuscular injections if anticoagulation is instituted.
- Thrombolytic agents theoretically could promote lysis or resolution of vegetations. Adjunctive treatment with recombinant tissue plasminogen activator decreased vegetation size and improved the results of short-term penicillin therapy in rabbits with fresh vegetations. Similarly, aspirin therapy can reduce the size of experimental vegetations and improve rate of sterilization by antibiotics. The potential value of antithrombotic agents, however, has not been demonstrated in human beings; thrombolytic therapy might not work on the older vegetations typical of SBE in human beings and could possibly cause serious hemorrhagic complications.

Management of Complications

HEART FAILURE

The development of moderate or severe cardiac failure due to structural valvular damage indicates the need for **prompt surgical intervention** in most patients with endocarditis, even if the intracardiac infection is still active. In patients with mild heart failure, the decision should be individualized, always remembering that lives may be lost unnecessarily if cardiac function suddenly worsens, so that surgery becomes either hazardous or unfeasible.

EMBOLI

The occurrence of one or more significant arterial emboli during the treatment of endocarditis is a relative indication for surgery. The predictable early and long-term mortality and morbidity rates of valve replacement must be weighed against the highly unpredictable likelihood of further emboli. For this reason, embolization is a weaker indication for valve replacement than is cardiac failure. In the author's opinion, operative intervention during antibiotic treatment should seldom be undertaken solely to prevent further emboli unless the patient has suffered more than one or two proved major emboli. Because the frequency of emboli falls rapidly after 1 to 2 weeks of antibiotic therapy, the most logical time to operate for the purpose of preventing emboli would be early, within 1 week of diagnosis.

RENAL FAILURE

In the preantibiotic era, patients with SBE frequently developed chronic renal failure before they died. Subsequently, both the incidence of renal failure and its importance as a cause of death have greatly diminished. In one series, up to one-third of patients with infective endocarditis developed evidence of acute renal failure, however. Risk factors for renal failure were increased age, hypertension, thrombocytopenia, infective endocarditis caused by *Staph. aureus*, and PVE. While the earlier diagnosis and antibiotic treatment have forestalled the development of immune-complex glomerulonephritis, in those (about 5 to 10 percent) who still develop this complication of SBE, timely dialysis can maintain the patient until antibiotic treatment results in disappearance of the bacterial antigens that triggered immune-complex nephritis. Renal function usually normalizes smoothly once infection has been controlled, but recovery may take weeks or months. In a few cases, creatinine clearance worsens for a time despite effective antibacterial treatment, perhaps reflecting persistence of bacterial antigen in vegetations after bacteriologic cure. Corticosteroids may have been of value in a small number of cases. Some patients with septicemia, shock, or disseminated intravascular coagulation associated with ABE develop acute renal failure and require dialysis as part of their intensive care.

MYCOTIC ANEURYSM

This complication is diagnosed in less than 5 percent of patients with IE, but the local consequences of aneurysm expansion and rupture can be very serious, especially in the brain. Small aneurysms will often thrombose or resolve spontaneously during or after antibiotic therapy. Once aneurysms exceed 0.5 to 2 cm in diameter, they are likely to enlarge and eventually rupture despite eradication of the etiologic bacteria by antibiotic therapy. Surgery is indicated for accessible aneurysms before this complication occurs. Intracranial mycotic aneurysms are especially difficult to manage. They may present with headaches, subarachnoid hemorrhage, or stroke, but many are asymptomatic. Even small aneurysms may bleed at any time; they may be multiple and/or located in inaccessible sites. This presents a therapeutic dilemma: whether to treat conservatively with antibiotics and hope for resolution (risking serious or fatal hemorrhage) or to operate (risking neurologic damage and permanent sequelae). Symptoms or signs consistent with an intracranial aneurysm indicate the need for prompt imaging, using computed tomography and/or magnetic resonance imaging. Cerebral angiography may be needed if the findings are inconclusive. In general, large (over 0.5 cm in diameter) or expanding aneurysms or aneurysms that have already leaked or begun to bleed should be clipped if a surgical approach is feasible. An individualized decision must be made on whether or not to operate for smaller aneurysms that have not leaked or ruptured.

PROGNOSIS

Infective endocarditis is one of the few infectious diseases that are virtually always fatal if untreated. Spontaneous recovery was reported occasionally in the preantibiotic era, but most of these patients probably had illnesses other than IE. The interval between the onset of symptoms and death in patients with untreated subacute disease varied widely, with a median time to death of about 6 months. Almost all patients with acute infective endocarditis died within less than 4 weeks. Heart failure is the leading adverse prognostic factor. Other adverse factors include central nervous system complications, renal failure, culture-negative disease, gram-negative bacillary or fungal infection, prosthetic valve infection, and development of abscesses in the valve ring or myocardium. Survival 6 months after PVE in one series was only 54

percent. Six-month survival after early-onset PVE (37 percent) was significantly worse than it was for late-onset PVE (65 percent). Because modern treatment methods, including valve replacement, are effective for treatment of heart failure, central nervous system complications have replaced heart failure as the most important adverse prognostic factor in some case studies. Favorable prognostic factors include youth, early diagnosis and treatment, infection involving a prolapsing mitral valve, and penicillin-sensitive streptococcal infection. The prognosis is good for young IDUs with *Staph. aureus* infection of the tricuspid valve. With earlier diagnosis and appropriate therapy, including surgery, the prognosis for elderly patients can be substantially improved. Eradication of the etiologic organisms (microbiological cure) can be achieved in a high proportion of all patients with bacterial endocarditis. Both early and long-term mortality rates remain significant, however, due to any preexisting disease and added damage caused by endocarditis before the organisms were eradicated. Survival curves after admission with infective endocarditis show a significant number of late deaths despite microbiologic cure.

RECURRENT ENDOCARDITIS

Recurrent endocarditis is a general term that includes both relapses and reinfections. The term *relapse* refers to recurrence of infection with the same organism because treatment failed. The frequency of relapse can be predicted from published experience for each of the various forms of infective endocarditis. Because relapses occasionally occur even after an optimal treatment regimen has been used, follow-up clinical evaluation should be meticulously performed during the first 2 months after treatment. Any clinical suspicion that relapse might have occurred indicates the need to draw blood cultures. Most relapses occur within a few weeks of ending treatment, but living organisms can persist in seemingly healed vegetations for many months and may occasionally cause late relapse. The term *reinfection* refers to a new episode of endocarditis occurring after the cure of a previous episode. Usually a different etiologic organism is involved, but if the new isolate appears similar to the initial etiologic organism, molecular typing techniques can be used to determine if the case is a relapse or an infection. Patients remain permanently at risk of reinfection after cure of

infective endocarditis because of residual valve damage superimposed on the original predisposing lesion. Recurrent episodes are fairly common, being recorded in from 2 to 31 percent of cases. This wide variation in reported incidence is partly due to variable duration of follow-up. IDUs and patients with severe periodontitis are at highest risk for reinfection. Occasionally, a patient may suffer three or more separate episodes of infective endocarditis. Patients who have previously had NVE and have required valve replacement, are at high risk to develop prosthetic valve infection (often with a different organism) for reasons that are not yet understood.

Prophylaxis of Endocarditis

Infective endocarditis is a potentially fatal disease. Even with appropriate antimicrobial treatment, mortality rates range from 10% to 25%; therefore, prevention of disease is very important. Guidelines have been created to estimate which patients with certain risk factors would most benefit from infective endocarditis prophylaxis. However, there have been no controlled, clinical trials to demonstrate the protective efficacy of antibiotic regimens in the prophylaxis of infective endocarditis in humans. Such trials will not likely ever be done for two major reasons: From a study-design perspective, the relative rarity of infective endocarditis developing after a single transient bacteremic episode would require $\geq$ 6,000 patients, all with predisposing cardiac disease. Secondly, such a study would also be considered unethical.

Because various invasive procedures induce bacteremias with bacterial species that often cause infective endocarditis, prophylactic antibiotics are frequently given to susceptible patients in an attempt to prevent bacterial endocarditis. Although antibiotics definitely can prevent endocarditis in experimental animals, its effectiveness in human beings has not been proved in prospective randomized clinical trials and likely never will be. Many relevant questions remain unanswered. These include the following:

- Is antibiotic prophylaxis effective?
- Does the prophylactic effect (benefit) outweigh the potential side effect of the drug cost and influence the emergence of drug-resistant bacteria?
- Which operations and diagnostic procedures should be covered?
- Which patients should receive antibiotics?
- What antibiotic regimens will be most effective?

Although the risk of infection has not been quantitated, it is sufficiently low that most of these questions cannot be answered by clinical trials; the number of susceptible patients required to provide significant results would be too large. Less than 15 percent of SBE cases and even fewer of ABE cases follow identifiable medical procedures that cause transient bacteremias; therefore, the proportion of cases that is potentially preventable by antibiotics is vanishingly small. Because endocarditis causes serious morbidity and mortality, the American Heart Association and the practicing medical community have accepted the practice of using antibiotic prophylaxis without evidencebased studies. It has been accepted that prevention of even a few cases could be worthwhile. For this reason, currently accepted standards of practice require that an antibiotic regimen be administered before certain dental and surgical procedures in patients with known heart lesions that pose a significant risk of endocarditis. Because several hundred cases of streptococcal endocarditis following dental and genitourinary tract procedures have been recorded, the potential causative role of these procedures is certainly suggested. A rather short "incubation period" for endocarditis is typical, in that most of these patients noticed symptoms within 2 weeks of the procedure. It should be emphasized that the link between a case of endocarditis and a recent procedure causing bacteremia cannot be proved, because the infection could have been caused by one of the transient, asymptomatic, low-grade bacteremias that occur very commonly, induced by everyday events such as chewing and cleaning the teeth. In fact, when 273 cases of endocarditis are examined retrospect from 1, 2, and 3 months prior to endocarditis, no correlation to dental procedures were found. In the absence of prospective controlled trials, empirical recommendations for prophylaxis of bacterial endocarditis have been made on the basis of indirect information. This information includes the reported frequency of bacteremia after various procedures; the relative risk posed by the patient's cardiac lesion; case reports of prophylaxis failures in vitro susceptibility studies on the relevant organisms, especially streptococci; experimental studies in laboratory animals; and retrospective studies in human beings.

Information from these sources indicates that experimental endocarditis in animals can be prevented by bactericidal antibiotics; that prevention is probably effective in human beings; that only a small proportion of total cases is potentially preventable by use of antibiotics 370,374; and that the cost per prevented case would be very high.

Thus, prevention probably would not be cost-effective as a general strategy, but it might be effective for selected individuals (namely patients with previous IE and patients with prosthetic valves), especially for high-risk procedures such as tooth extractions. For the individual patient, the decision to administer prophylaxis should be made by assessing two main factors: the risk posed by the preexisting cardiac lesion and the risk posed by the procedure that might cause bacteremia. For example, if a patient with a prosthetic valve undergoes prostate resection, antibiotic prophylaxis is recommended because both factors present a significant risk of endocarditis.

In contrast, if a patient with mitral valve prolapse is scheduled for gastroscopy, prophylaxis is not necessary because the risk for endocarditis in this setting is very low. Such risk assessments may be difficult or inaccurate; in many situations uncertainties will remain. For these, there is no one "correct" answer; the patient's and the physician's attitudes and preferences may influence the decision to use prophylaxis.

Updated consensus recommendations by the AHA may be useful in guiding decision making. These guidelines emphasize the following points:

1. Most cases are not attributable to an invasive procedure.

2. Cardiac conditions should be stratified into light, moderate, and negligible risk categories; these are primarily based on potential outcomes if endocarditis occurs.

3. There are procedures that may cause high grade bacteremia and for which prophylaxis is most likely to be effective.

4. There is an algorithm to use in deciding on prophylaxis in patients with mitral valve prolapse.

5. The initial dose of amoxicillin is reduced to 2 g for oral and dental procedures and a follow-up dose is no longer recommended; clindamycin (not erythromycin) is recommended as an alternative therapy in penicillin-allergic individuals.

6. Prophylactic recommendations in gastrointestinal and genitourinary procedures have been simplified.

Attempted prophylaxis does not always succeed. So, it's surprisingly appiered, in one series 12 of 16 patients with known cardiac abnormalities who developed IE with organisms of dental origin and who had a dental procedure within 3 months of onset of infective endocarditis received prophylactic antibiotics according to AHA guidelines. In fact, only 10 percent of cases of infective endocarditis in this study would qualify for prophylaxis according to the AHA standards. Even if a prophylaxis was 100 percent effective, it would reduce the incidence of infective endocarditis by only 2.0 cases per 1,000,000 person-years. Common errors in attempted prevention of endocarditis are starting antibiotics too early, continuing for too long, using low doses, covering tooth extractions but not lesser dental procedures, and confusing prevention of rheumatic fever (requiring long-term, low-dose antimicrobial drugs) with prevention of endocarditis (short-term, high-dose).

In the absence of pelvic infection, prophylaxis for endocarditis in patients with heart lesions is not recommended to cover normal delivery, therapeutic abortion, dilation and curettage, and insertion or removal of intrauterine contraceptive devices. Similarly, antibiotics are not recommended before many common procedures, such as cardiac catheterization, insertion of temporary pacemakers, endotracheal intubation, bronchoscopy, endoscopy, or radiographic contrast studies of the upper and lower gastrointestinal tract. In comparison, some physicians choose to cover even these low-risk procedures in patients with prosthetic valves because they are at higher risk for endocarditis than are patients with native valves.

The paradigms that have been proposed by various expert bodies (including the AHA) for the use of antibiotics to prevent infective endocarditis have developed over time and have been based on indirect evidence derived from studies in animals that demonstrated that prevention was possible, on case reports tying IE to various proce-

dures known to cause bacteremia, and from a concern about the dire consequences of the disease. These recommendations have been accepted as "standard of care" and failure to follow them has taken on medicolegal implications. Various authors have questioned this practice and new information has emerged calling into question the clinical benefit of prophylactic antibiotics in this setting. This is especially important in an era where overuse of antimicrobials is fueling the dangerous epidemic of antibiotic-resistant bacteria. Therefore, it seems prudent for the various expert committees who write such recommendations to carefully weigh the apparent minimal benefits with the downsides of toxicity, cost, and resistance that has come with excessive use of antibiotics.

Conclusions.

There have been major advances in the diagnosis and treatment of endocarditis over the past 60 years. The advent of antibiotics has dramatically improved the prognosis of patients with endocarditis. Endocarditis remains an elusive diagnosis because of its many disguises. Early diagnosis and prompt antibiotic therapy are the most effective way to minimize mortality and morbidity in this patients population.

CHAPTER 3
DISEASES OF THE PERICARDIUM

Definition.

The pericardium is a closed, fibroserous membrane sac in the middle mediastinum posterior to the sternum and the second to sixth costal cartilages and anterior to the fifth to eighth vertebrae. During embryologic development, the heart invaginates the sac, based on a pedicle of the great vessels, cavae, and pulmonary veins. A layer of the serous sac becomes densely adherent to the myocardium, forming the visceral pericardium or epicardium. This layer envelops the entire heart apart from a bare area on the posterior aspect of the left atrium between the pulmonary veins in the oblique sinus. The visceral layer reflects back on itself and is continuous with the parietal pericardium. This reflection forms a second cleft between the great vessels and the left atriumв the transverse sinus.

The parietal pericardium consists of an outer fibrous layer composed of multiple layers of collagen, aligned in different directions, interspersed with elastin fibrils. This fibrous layer has ligamentous attachments with the central tendon of the diaphragm inferiorly, the sternum anteriorly by the superior and inferior sternopericardial ligaments, and the pleural membranes laterally. The inner layer of the parietal pericardium is a serous mesothelial membrane, with microvilli, to aid fluid secretion. The normal pericardium contains about 50 mL of pale serous fluid to minimize friction and restrict excessive cardiac motion. The fluid is low in protein and has a relatively high proportion of albumin, consistent with a transudate. The pericardium is innervated by branches via the phrenic nerve. This may explain the perception of pericardial pain in the left shoulder tip. Arterial supply to the pericardium is via the internal (thoracic) mammary arteries and multiple branches of the bronchial, esophageal, and phrenic arteries. Venous drainage is via the azygous system.

Normal Physiology of Pericardium

For the pericardium as a whole, there is an exponential stress of strain relationship. At normal cardiac volumes, the pericardium is on the flat portion of the curve, and physiologic changes in volume are associated with minimal changes in intraperi-

cardial pressure. However, with abrupt large increases in volume (such as in acute overhydration or valve rupture), the pericardium quickly reaches the exponential portion of the curve and significantly restricts further cardiac dilation. In this way, it can be argued that the pericardium has a very little role in limiting cardiac filling at normal physiologic volumes and only exerts a constraining effect on filling when abrupt changes in volume occur. The pericardial pressure usually approximates pleural pressure and varies with the respiratory cycle, being approximately -6 mm Hg at end-inspiration and -3 mm Hg at end-expiration. The lowering of pericardial pressure more than atrial pressure and transmural pressures in inspiration allows increased filling of the right heart while there is increased aortic transmural pressures and pooling of the right ventricular output and consequently decreased left heart filling.

As the heart slowly enlarges in the face of a chronic process such as cardiomyopathy or chronic valvular insufficiency, so too the pericardium increases in volume and mass. Thus, even in cardiomegalic states, the pericardial stress in When the cardiac volume causes the pericardium to reach the steep portion of its pressure - volume curve, a phenomenon of ventricular interdependence is observed. Put simply, the ventricles, with their common interventricular septum, are forced to exist in a finite-volume cavity. Therefore, increased filling of one chamber (e.g., right ventricle during inspiration) will shift the septum into the left ventricle, impeding its filling and therefore output. A similar effect is seen in cardiac tamponade and constrictive pericarditis and is the pathophysiologic mechanism underlying pulsus paradoxus and flow paradoxus.

Clinical Presentations of Pericardial Disease

Acute Pericarditis

Inflammation of the layers of the pericardium from any of a myriad of causes yields a common clinical syndrome termed acute pericarditis. The causes of acute pericarditis are listed in Table 3.1. The classical symptom complex represents an important differential diagnosis in the assessment of chest pain presentations. However, the relatively common finding of pericardial inflammation at autopsy suggests that the majority of cases are subclinical.

Table 3.1.

An etiology of acute pericarditis

I. **Idiopathic**

II. **Infectious**

Bacterial, Tuberculous, Viral: *Coxsackie, Influenza, HIV, etc.* Fungal, Rickettsial, Mycoplasma, Leptospira, Listeria, Parasitic, Other

III. **Vasculitis/Connective Tissue Disease:** Rheumatoid Arthritis, Rheumatic Fever, SLE, Scleroderma, Sjogren's Syndrome, Reiter Syndrome, Ankylosing Spondylitis, Wegener's Granulomatosis, Giant Cell Arteritis, Polymyositis (Dermatomyositis), Behcet Syndrome, Familial Mediterraneun Fever, Dermatomyositis, Polyarteritis, Churg-Strause Syndrome

IV. **TTP**, Leukoclastic Vasculitis, Other

V. **Diseases in Adjacent Structures:** myocardial infarction, aortic dissection, pneumonia, pulmonary embolism, empyema

VI. **Metabolic Disorders:** Uraemic, Dialysis-Related, Myxoedema, Gout, Scurvy

VII. **Neoplastic**

A. *Secondary* (Metastatic, or Direct Spread): Carcinoma, Lymphoma, Carcinoid, Other

B. *Primary* Mesothelioma, Sarcoma, Fibroma, Lipoma, Other

VIII. **Trauma**

Direct:

1. Pericardial Perforation: Penetrating Injury, Esophageal or Gastric Perforation
2. Cardiac Injury: Cardiac Surgery, Percutaneous Procedures

Indirect

Radiation, Non-Penetrating Chest Injury

IX. **Association with Other Syndromes**

Clinical Presentation

Acute pericarditis classically presents with progressive, often severe, chest pain over hours. This mechanical pain is typically postural, being worse on lying supine and relieved by sitting forward. It is often pleuritic and aggravated by coughing, motion, and swallowing. It is described as sharp, stabbing, or knifelike in character. The pain may radiate to the neck or shoulder in the region of the trapezius ridge and less frequently to the arms and back and even left shoulder, making differentiation from coronary ischemic pain more difficult. There is often a low-grade fever associated with viral and idiopathic pericarditis, whereas purulent pericarditis is associated with very high fevers and systemic sepsis. In strain curve shifts to the right; during normal daily living, it exerts very little constraining effect to filling. Similarly, abrupt changes in cardiac volume superimposed on a chronically dilated heart will

move the pericardium into the steep portion of the pressure - volume curve, and a constrictive effect on cardiac filling will be observed.

Post-Myocardial and Pericardial Injury Syndromes, Inflammatory Bowel Disease, Loffler Syndrome, Stevens-Johnson Syndrome, Giant Cell Aortitis, Hypereosinophilic Syndromes, Acute Pancreatitis, etc.

The presence of a pericardial rub is pathognomonic for pericarditis, although its absence does not exclude the syndrome. This rasping sound has a timing consistent with the cardiac cycle and is creaking in nature, like the sound of leather on leather. It is best appreciated with the diaphragm of the stethoscope applied to the lower left sternal edge and with the patient leaning forward in end-expiration. The sound classically has a triple cadence with components related to atrial systole, ventricular systole, and ventricular diastole. The rub is triphasic in nearly 50% of the cases, biphasic in 33% of the cases, and monophasic in 10% of the cases. The intensity of the sound can be attenuated by subcutaneous tissue thickness and hyperinflated lung volume. Furthermore, the development of a pericardial effusion as part of the inflammatory syndrome can lead to waxing and waning of the rub over days, although a loud pericardial rub can still be heard occasionally in the presence of a significant effusion. The sound should be differentiated from a pleural rub (which is similar in character and timed with the respiratory cycle), subcutaneous emphysema (which may be an associate in postsurgical or traumatic cases), and loud intracardiac murmurs (such as ventricular septal defects).

Investigations

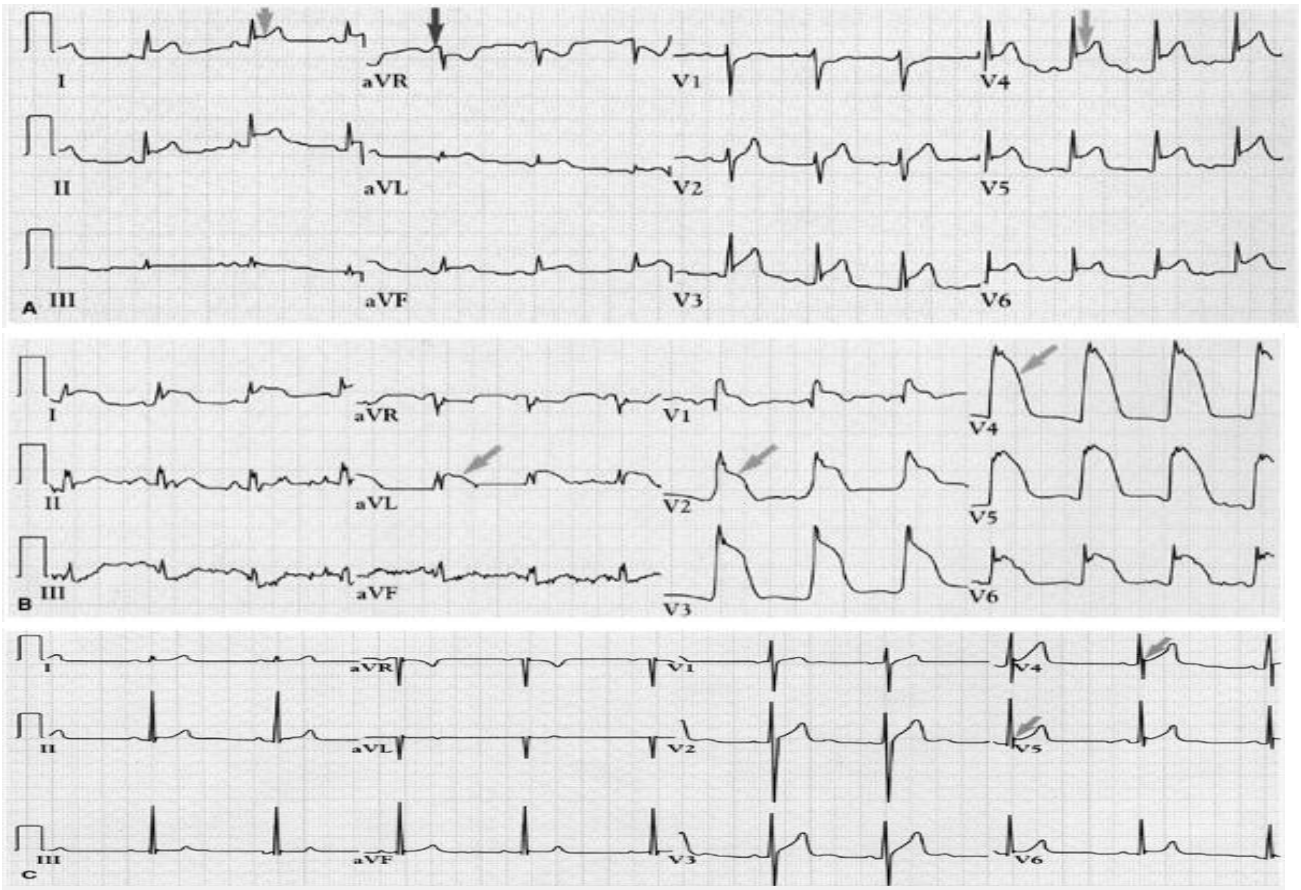
The electrocardiogram represents the most useful diagnostic test in acute pericarditis. Inflammation of the subepicardial myocardium is thought to be the mechanism producing ST and T-wave changes, whereas inflammation of the atrium is thought to cause the PR-segment changes. The PR-segment deviations may precede the ST changes. In contrast to the regional ST changes of myocardial ischemia, pericarditis generally produces widespread electrocardiogram (ECG) changes in limb and precordial leads. Four phases of ECG abnormalities have been recognized: ST elevation and upright T waves (stage 1) is present in 90% of cases. Over time, the ST

changes resolve and the ECG may look normal (stage II). There may be further evolution to T-wave inversion (stage III) and finally to normal (stage IV).

The ECG abnormalities should be differentiated most importantly from acute myocardial ischemia (Fig.3.1). The ST changes are more widespread in pericarditis and have a typical saddle-shaped or upward concave appearance. Unlike myocardial infarction, there are no Q waves or loss of R-wave progression. The other important differential diagnosis of these ECG changes is the early-repolarization pattern. Although difficult without clinical correlation, differentiation can be made by the presence of PR-segment elevation (especially aVR) and ST elevation in V6, which is uncommon in the early-repolarization syndrome. Most patients with acute pericarditis remain in sinus rhythm.

Figure 3.1.

ECG for acute pericarditis



Chest radiography contributes relatively little to the diagnosis of acute pericarditis. The presence of cardiomegaly may be seen in the minority of cases where a significant pericardial effusion has accumulated. Laboratory analysis of blood often shows a modest leukocytosis and raised C-reactive protein and sedimentation rate.

Radionuclide scanning with indium-111 and gallium-67 has been reported to be useful in identifying the pericardium as the source of an inflammatory syndrome of unknown diagnosis in some patients. MRI with gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) enhancement has identified specific regions of the pericardium involved in the inflammatory process.

Serum troponin I has been reported to be elevated in patients with ST elevation and acute pericarditis, reflecting a degree of epicardial myocardial injury. Elevations in troponin I among patients with viral or idiopathic pericarditis are most common in younger patients, men, and patients with ST elevations and pericardial effusions at presentation. However, for patients with acute pericarditis, elevated troponin I is not a negative prognostic marker.

Diagnostic algorithm

The following sequence has been proposed. All patients should have a complete history and physical examination, electrocardiography, and chest radiography. Diagnostic specific testing may include tuberculin skin testing, rheumatoid factor and antinuclear antibody, and viral studies. HIV testing should be considered. In more complex cases (i.e., symptoms and signs lasting >1 week, clinical evidence of tamponade, or purulent pericarditis), echocardiography and blood cultures should be considered. Pericardiocentesis (either percutaneous or surgical) is indicated for clinical tamponade, evidence for purulent pericarditis, high suspicion of tumor, or illness lasting longer than 1 week.

Pericardial Effusion

Pericardial effusion is diagnosed in routine echocardiography practice in almost 1 in 10 patients. Large pericardial effusions that develop slowly can be remarkably asymptomatic, whereas rapidly accumulating smaller effusions can present with tamponade. Massive chronic pericardial effusion is a diagnosis ascribed to a syndrome consisting of a large pericardial effusion present for at least 3 months and not attributable to any systemic cause. These effusions can be present for many years and were well tolerated in one series, with tamponade a rarity. However, in two series, cardiac tamponade occurred in near one third of patients. In the larger study, 28 pa-

tients with large idiopathic chronic pericardial effusions were followed for a median of 7 years. Unexpected tamponade occurred in 8 patients (29%), and pericardiectomy was performed in 20 patients. Chronic nonspecific pericarditis was found in all patients evaluated by histology.

Clinical Presentation

Pericardial effusions that are not causing hemodynamic embarrassment to the heart are usually asymptomatic. Patients may describe dyspnea or dysphagia due to space-occupying effects in the chest. Physical compression may cause hoarseness (recurrent laryngeal nerve), hiccups (phrenic nerve), or nausea (diaphragm). Physical examination of patients with large effusions demonstrate muffled heart sounds. Ewart's sign, dullness on auscultation under the left scapula, is a result of compression of the base of the left lung. This may be associated with coarse crepitations due to local atelectasis. Chest x-ray findings include cardiomegaly, which may be massive, often with a characteristic globular shape to the heart silhouette. The cardiac margins are unusually sharp because the pericardium is free of the cardiac motion that usually blurs the silhouette radiographically. Electrocardiography demonstrates diminished QRS and T-wave voltages. Electrical alternans is a marker of massive pericardial effusion.

Echocardiography is the diagnostic tool of choice for pericardial effusion. Initially, M-mode was the standard, with a high sensitivity for posterior pericardial fluid. The advent of two-dimensional echocardiography has shown the various presentations of effusion, including circumferential, posterior, and loculated. The last are more common when scarring has supervened, for example, after surgery, trauma, or purulent pericarditis. The size of effusions can be graded as small (<10 mm of echo-free space in systole and diastole), moderate (>10 mm at least posteriorly), large (>20 mm), or very large (compression of the heart). Furthermore, two-dimensional echocardiography can give information about the nature of the fluid, suggesting the presence of fibrin, clot, tumor, air, and calcium. Care must be taken to differentiate pericardial fluid from pleural fluid and ascites. Left pleural effusions can be difficult to differentiate from pericardial fluid. By transthoracic echocardiography in the paras-

ternal long-axis view, pericardial fluid can be seen to reflect at the posterior atrioventricular groove, whereas pleural fluid continues under the left atrium, posterior to the descending aorta. Spin-echo and cine MRI can also be used to assess the size and extent of simple and complex pericardial effusions similar to echocardiography. The effusions seen by MRI may tend to be larger than those detected by echocardiography.

Management

The action taken after the finding of a significant pericardial fluid collection depends on the underlying etiology, the presence of hemodynamic compromise, and the volume of fluid. Pericardiocentesis may not be necessary in all cases, particularly when the diagnosis can be made based on other systemic features. Where doubt remains, particularly where malignancy or purulent pericarditis is suspected, pericardiocentesis is indicated. Hemodynamic compromise is an absolute indication for drainage (see later discussion).

Pericardial Tamponade

Fluid accumulation in the finite pericardial space will cause an increase in pressure with subsequent cardiac compression. Tamponade is not a binary phenomenon, and exhibits a spectrum from mild cardiac compression and embarrassment to cardiovascular collapse.

Pathophysiology

Systemic venous flow occurs in two phases: systolic, related to filling of the atrium with a closed tricuspid valve (x descent on central venous pressure trace, S wave on hepatic venous Doppler), and diastolic, related to filling of the right atrium as it empties through the open tricuspid valve (y descent on central venous pressure trace, D wave on hepatic venous Doppler). In tamponade, the heart is compressed and remains in a finite volume. Ventricular ejection decreases the relative proportion of the pericardial space occupied by the heart, allowing a fall in intrapericardial and atrial pressure and a rapid inflow of blood (large x descent and S wave). During diastole, the pericardium contains filled ventricles, which increases its pressure and thus decreases forward flow from the systemic veins (blunted y descent and D waves). The systemic venous flow in cardiac tamponade should be distinguished from con-

strictive pericarditis with prominent x and y descent (S and D on hepatic venous Doppler).

Pulsus paradoxus, defined as an inspiratory drop of systolic blood pressure of greater than 10 mm Hg, is a hallmark of cardiac tamponade. With inspiration, intrathoracic pressure becomes subatmospheric. Intrapericardial pressure, pathologically high in this syndrome, is reduced during inspiration (as it is physiologically reduced in the normal state), allowing increased right ventricular filling. Systemic venous diastolic flow (y descent, hepatic vein D wave) increases and right ventricular size and stroke volume increase. Again, due to the finite volume of the pericardium, the left ventricle is partially compressed by the enlarging right ventricle (due to leftward displacement of the intraventricular septum), causing an inspiratory decrease in systemic stroke volume. An alternative mechanism is that the pulmonary venous-to-left atrial pressure gradient is decreased because the changes in intrathoracic pressure are not transmitted to the left ventricle due to shielding by the pericardial fluid and the increased pulmonary vascular compliance. There is reciprocally increased flow on the right side of the heart due to interventricular interdependence. Pulsus paradoxus can also be detected in noncardiac conditions such as severe lung disease (in which intrathoracic pressure swings are supraphysiologic) as well as pulmonary embolus (in which right ventricular filling pressures are disproportionately higher than left pressures).

Clinical Presentation

The spectrum of presentation of patients with cardiac tamponade ranges from dyspnea and edema to frank circulatory collapse. The classic triad of cardiac tamponade is hypotension, elevated jugular venous pressure, and distant heart sounds. Early tamponade is manifested by tachycardia, tachypnea, dyspnea, edema, elevated venous pressure, and quiet cardiomegaly. Examination of the central venous waveform shows a prominent x descent and absence of the y descent.

Pulsus paradoxus is examined using the stethoscope over the brachial pulse and measuring the pressure gap between the appearance of the Korotkoff sounds during expiration only and their continuous presence. It is defined by an inspiratory fall

in systolic blood pressure of 10 mm Hg with inspiration, an exaggeration of the normal situation. False-positive pulsus paradoxus without cardiac tamponade may occur with obstructive lung disease, right ventricular infarction, and pulmonary embolism; and a false-negative finding may occur with high left ventricular pressures as with left ventricular dysfunction or hypertrophy, severe hypotension, and severe aortic regurgitation or in the case of an atrial septal defect.

Profound circulatory collapse or shock is more common in patients with acute tamponade related to cardiac or pericardial trauma. In the most extreme cases, such as acute aortic dissection into the pericardium, patients may present with electromechanical dissociation. Patients who develop the syndrome subacutely tend to present in a less dire status and manifest signs of right heart failure with edema, hepatomegaly, ascites, and pleural effusion. Rarely, low-pressure cardiac tamponade without the typical signs can develop in the presence of dehydration and hypovolemia. Other variant forms of tamponade may include hypertensive cardiac tamponade (with high blood pressure), tamponade with ventricular dysfunction (right or left ventricular dysfunction), regional cardiac tamponade (localized effusions), or effusive constriction.

With an increase in invasive cardiac procedures in the electrophysiology and cardiac catheterization laboratories, the complication of cardiac tamponade is more frequent. A report of nearly 7,000 patients undergoing percutaneous coronary intervention found an incidence of 0.2%, with cardiac tamponade developing 2 to 36 hours after the procedure.

Investigations

The electrocardiogram and chest x-ray do not differentiate tamponade from noncompressive pericardial effusion. Large pericardial effusions allow swinging of the heart on its vascular pedicle, causing electrical alternans in some cases. Echocardiography is a fast and noninvasive modality for accurately diagnosing tamponade. The presence of pericardial fluid should be documented and its location defined. The classic signs of cardiac tamponade are right atrial and right ventricular collapse. Postsurgical effusions may be loculated (e.g., behind the left atrium) and sometimes difficult to visualize from the transthoracic window. Indeed, if the diagnosis of tampo-

nade is suspected in this scenario, transesophageal echocardiography is indicated. Two-dimensional echocardiography can also exclude pericardial masses and ventricular and valvular dysfunction as the cause of hemodynamic compromise. Doppler echocardiography allows direct quantitation of mitral and tricuspid inflows, pulmonary venous and systemic venous flows, and, with the use of a respirometer, their variation with respiration. Respiratory variation of transmitral E waves is minimal in normal individuals, and greater than 25% variation (increasing on the first beat of expiration and conversely on inspiration) is highly suggestive of significant tamponade. Tricuspid E waves often will exhibit some degree of respiratory variation in normal individuals, and greater than 40% variation is required (opposite pattern to the left side), and prominent hepatic venous flow reversals in expiration is required to suggest tamponade.

Cardiac catheterization has historically been the diagnostic standard for tamponade and remains useful, particularly when noninvasive modalities are inconclusive. Right heart catheterization is often performed simultaneously with pericardiocentesis, allowing monitoring of improvement as the effusion is drained. Typically, patients demonstrate an elevated right atrial pressure, with a prominent x descent and diminished or absent y descent. The PCWP is also elevated and is often equal to intrapericardial and right atrial pressure. As pericardial fluid is drained, intrapericardial pressure falls below biatrial pressure. If this does not occur, the diagnosis of effusive constrictive disease should be considered (see later discussion).

Pericardiocentesis

While the equipment for pericardiocentesis is being prepared, the patient in tamponade may be supported with cautious fluid loading and inotropes. Percutaneous pericardiocentesis should be performed in an environment in which advanced cardiac life support equipment and personnel are immediately available. Historically, these procedures have been performed in the cardiac catheterization lab with arterial and right heart catheters in situ. More recently, the procedure has tended to be performed in the procedure room of the cardiac or intensive care unit, or even at the bedside, using echocardiographic guidance. Surgical drainage of the pericardium (either by a

subxiphoid approach or utilizing a complete pericardiectomy) is indicated for loculated effusions, patients at risk of excessive bleeding, and in situations in which fluid has recurred after previous drainage procedures.

Echocardiography can demonstrate the most accessible window for passage of the needle. Historically, the subxiphoid approach has been used most commonly with a long needle passed under the xiphoid and directed toward the left shoulder at a 30B° angle to the skin. Echocardiography performed at the cardiac apex can often identify a window through which the pericardium can be entered (usually in the sixth or seventh rib space in the anterior axillary line) without risk of cardiac puncture. A short needle is passed through the rib space under constant negative pressure until fluid is aspirated. It is important to confirm that the fluid aspirated is intrapericardial, that is, the blood should not clot.

Once the pericardial space is reached by either approach, a soft-tipped guide wire is passed and the needle removed. A multiholed catheter is then introduced and the pericardial fluid suctioned out. It is prudent to drain the fluid in steps of less than 1 liter at a time to allow cardiovascular equilibrium to be restored at each stage and to avoid the rare complication of acute right ventricular dilation. Clinical improvement usually occurs after the aspiration of only 100 to 200 mL of fluid. The fluid should be drained completely and specimens sent for chemistry, cytology, culture, cell counts, and acid-fast bacilli (AFB) staining. It is common practice to leave the catheter in for some hours, connected to a free drainage bag, to allow further drainage as the patient assumes different postures. It is important to avoid the allowance of air into the pericardium because this is most uncomfortable for the patient.

Percutaneous pericardiocentesis is a rapid and safe procedure when performed by trained personnel. In a recent study of patients undergoing urgent pericardiocentesis after cardiac perforation, tamponade was relieved in 99% of patients. A major complication rate of 3% occurred and included pneumothorax and right ventricular laceration. No deaths resulted directly from pericardiocentesis. A similar review of 245 pericardiocenteses performed in patients with postoperative effusions showed that anticoagulant therapy was the most common contributing factor to early pericar-

dial effusions (<7 days), and postpericardiotomy syndrome contributed most often to late effusions. The rate of major complications from pericardiocentesis was 2% in this study.

Surgical Procedures

A median sternotomy or anterolateral thoracotomy approach provides good visualization for pericardial surgery including pericardiectomy for constrictive and effusive disease. However, less invasive procedures are available for drainage of pericardial effusions when pericardiocentesis is not feasible or recurrent fluid accumulates.

Subxiphoid pericardiectomy is a safe and efficacious method of draining large pericardial effusions. A small incision is made in the upper epigastrium and the pericardium is approached by posterior retraction of the diaphragm from the sternum. A pleuropericardial window is often created to allow ongoing drainage. This approach, although still safe, has the advantage over pericardiocentesis due to a higher diagnostic yield, allowing for fluid analysis and pericardial biopsy.

Alternative nonthoracotomy techniques for formation of a pericardial window include percutaneous pericardiotomy using an inflatable balloon from a subxiphoid approach and a video-assisted thoracic surgical (VATS) pericardiectomy. These procedures are effective for the management of malignant and other large pericardial effusions. In addition, pericardial biopsy can be performed via a pericardioscopy technique, establishing a diagnosis or etiology in near 50% of patients.

Constrictive Pericarditis

Dense fibrosis and adhesion of the parietal and visceral layers of the pericardium creates a rigid case around the heart, limiting its filling and causing profound disturbances of cardiac function. This final common pathway may be the end result of one (or more) of many etiologic agents, including infection, post cardiac surgery, and radiation. The constrictive process can follow the etiology acutely, subacutely (months), or chronically (years). The clinical presentation is well recognizable, with debilitating right heart failure and a poor prognosis. A voluminous literature exists

about the many methods of differentiating this constellation from that of restrictive cardiomyopathy, which presents with similar clinical signs and symptoms.

Pathophysiology

The fundamental abnormality in constrictive pericarditis is the limited filling and enhanced interventricular dependence of the heart due to the rigid encasement of the heart by a thickened pericardium, which effectively isolates it from the normal respiratory swings in pressure and allows a finite filling volume for the ventricles. Within the pericardium, the myocardium is intrinsically normal (unless there is a combined abnormality such as in radiation myocarditis), with no specific abnormality of systolic or diastolic function. In constriction, the ventricle fills abruptly on valve opening (often more abruptly than normal due to elevated atrial filling pressures). However, in mid-diastole, the chambers reach the maximum volume that the constraining pericardium will allow and filling abruptly ceases. This can be appreciated visually on two-dimensional echocardiography as wall motion ceases with a shudder in mid-diastole. In contrast, restrictive myocardial diseases involve abnormal ventricular filling from the very onset of diastole as the chamber relaxes slowly and stiffness increases with a compensatory increase in left atrial pressure.

However, it is the effect of respiration on cardiac flows that is the major hallmark for differentiating constrictive from restrictive cardiac diseases. Because the heart is effectively isolated from the thorax by its rigid encasement, it does not experience marked respiratory swings in pressure. Thus, on inspiration, intrathoracic (and therefore pulmonary vein) pressure decreases but left atrial pressure does not. Thus, the pulmonary vein-to-left atrial pressure gradient that drives left atrial inflow diminishes, as does mitral inflow. The resultant decreased left ventricular filling during diastole allows more room for right ventricular filling due to a septal shift and enhanced ventricular interdependence, and thus right-sided inflows increase. The exact opposite sequence occurs in expiration.

Filling pressures rise to compensate for the decrease in cardiac output via renal retention of salt and water. The finite space of the pericardium causes the filling pressure of the four chambers (and the pulmonary wedge pressure) to equalize. Intraven-

tricular pressure recordings demonstrate the classic dip-and-plateau or square-root sign morphologies. The dip represents the abrupt early filling at the atrioventricular valve opening related to high filling pressures and corresponds to a deep y descent on the central venous tracing. The plateau phase represents a period of unchanging pressure and volume related to the finite volume of the pericardial encasement. The x descent on the venous trace may also be prominent as systolic emptying of the ventricles allows filing of the atria. The x and y descents are sometimes referred to as the W-pattern.

Differentiating Restriction from Constrictive Pericarditis

Hemodynamics

Cardiac catheterization has been traditionally the gold standard in distinguishing between these two similar diseases; however, there can be overlap of the hemodynamics. Simultaneous recordings of the right and left heart pressures have revealed elevation and equalization (within 5 mm Hg) of the right atrial pressure, right ventricle diastolic pressure, PCWP, and pre-a-wave left ventricular diastolic pressure. The right atrial pressure contour typically shows an M or W configuration with a preserved systolic x descent and a prominent y descent and with small a and v waves. The right ventricular and left ventricular pressure tracings show a dip-and-plateau contour. The right ventricular and pulmonary artery systolic pressure is mildly elevated at less than 50 mm Hg compared to greater than 50 mm Hg in restriction. Administration of saline over 6 to 8 minutes can enhance the classic findings of constriction in a patient with occult constriction.

One small study of 11 patients with hemodynamic correlation demonstrated that brain natriuretic peptide (BNP) levels in isolated constrictive pericarditis are near normal compared to significantly elevated levels in patients with restriction.

Echocardiography

There have been many M-mode and two-dimensional signs that have been used to differentiate these two conditions; however, these signs have proven to be nonspecific and insensitive. The important two-dimensional echocardiographic features of constriction that may provide clues to the diagnosis include pericardial thick-

ening, myocardial tethering, a septal bounce with respiration, and inferior vena cava plethora.

Doppler echocardiography

As described earlier, Doppler echocardiography with respirometry has emerged as a useful tool in these conditions. Limited ventricular filling and enhanced ventricular interaction account for the Doppler findings in constrictive pericarditis, whereas decreased distensibility of the ventricles accounts for the Doppler findings in restriction. The similarities with restriction examined by Doppler echocardiography include a short deceleration time indicative of the dip-and-plateau hemodynamic pattern and limited filling. The main differences include enhanced respiratory variation in mitral inflow and pulmonary venous flow (at the onset of inspiration and expiration) in constriction but not restriction (unless a concomitant pericardial effusion accounting for respiratory variation is present). In restriction, there is a markedly blunted pulmonary venous systolic flow, with greater diastolic forward flow indicative of a prominent y descent and elevated left atrial pressures; in constriction, usually both systolic and diastolic flows are present. Due to enhanced ventricular interdependence, there is a decreased transtricuspid flow in expiration and enhanced expiratory flow reversals in the hepatic vein with constriction; there is increased inspiratory flow reversal in restriction. Respiratory variation in the tricuspid regurgitation peak velocity and velocity duration has been noted in constriction but not in restriction. Superior vena cava Doppler can help to distinguish respiratory variation of mitral inflow in patients with chronic obstructive lung disease and constrictive pericarditis. The systolic forward component of superior vena cava flow varies significantly with chronic obstructive lung disease, whereas there is little change with constrictive pericarditis. Color M-mode Doppler and tissue Doppler echocardiography have provided complimentary information in the evaluation of patients with constrictive pericarditis. The velocity of propagation from color M-mode and the tissue Doppler E annular velocity are normal or supranormal in constriction, representing normal compliance but abnormal relaxation. Exceptions to the finding of a normal tissue Doppler E annular

velocity include patients with extensive annular calcification, LV dysfunction, or segmental differences in velocities.

There are several pitfalls in using Doppler echocardiography with respiratory monitoring for distinguishing constriction from restriction. Factors including depth of respiration, position of the sample volume, level of left atrial pressure, presence of concomitant myocardial disease or tricuspid regurgitation, and atrial fibrillation may influence the accuracy of the diagnosis. Transesophageal echocardiography may be used to delineate the anatomy (pericardial thickening) as well describe the physiology better than transthoracic echocardiography.

Preload reduction maneuvers may be useful in lowering the left atrial pressure to enhance the respiratory variation, and volume loading may be used if the filling pressures are decreased. Mixed restriction/constriction may occur postirradiation and may have features of localized pericardial thickening with restrictive physiology. In addition, atrial fibrillation may make it difficult to perform a Doppler evaluation of constriction and restriction. However, a series of 31 patients with constrictive pericarditis showed a similar respiratory variation of pulmonary venous flow and mitral inflow in patients with atrial fibrillation compared to normal sinus rhythm. Occasionally, ventricular pacing can be used to regularize the RR intervals in patients with atrial fibrillation. Constrictive pericarditis can also be evaluated in the operating room during mechanical ventilation. In a study with 15 patients, it was noted that positive-pressure ventilation reversed the pattern of respiratory variation of the mitral inflow and pulmonary venous flow velocities

Magnetic Resonance Imaging for Pericardial Disease

Direct visualization of the pericardium is possible with MRI in healthy and diseased states. This imaging modality is evolving as part of the routine work-up of suspected pericardial disease. In constrictive pericarditis, the pericardium is seen as a thickened, low-intensity signal band related to its fibrocalcific nature. The increased pericardial thickening can be measured easily by MRI but does not necessarily indicate pericardial constriction. Ancillary findings by MRI include the conical or tubular narrowing of the ventricular cavities by the thickened pericardium, atrial dilation, in-

ferior vena cava enlargement, hepatomegaly, and ascites. The sensitivity, specificity, and accuracy of MRI imaging in the diagnosis of constrictive pericarditis were 88%, 100%, and 93%, respectively, in one study. Cine MRI is useful in assessing the functional impairment of the abnormal filling in constriction compared to restriction, and phase flow mapping may show abnormal flow patterns in the superior vena cava that improve after pericardial stripping. However, MRI may have difficulty in distinguishing between calcification and fibrous tissue; thus, CT scanning may be better for assessing pericardial thickening when calcification is present. Gadolinium-enhanced MRI has been used in the diagnosis of tuberculous constrictive pericarditis.

Clinical Presentation

Patients with significant pericardial constriction present with congestive heart failure. Gross dependent edema, effusions, and ascites, hepatic congestion with dysfunction, splenomegaly, poor exercise tolerance, and cachexia constitute anasarca, of which constriction is one of the few remaining causes in developed nations. Jugular venous distention is common, with a prominent y descent (Friedreich's sign); the classic Kussmaul sign (a rise in central venous pressure with inspiration due to the inability of the right atrium to receive additional volume) is seen in some cases. The syndrome is relentless and progressive, responding poorly to conservative medical therapy. Pulsus paradoxus is seen when effusive constriction is present. Auscultation of the chest reveals quiet heart sounds, often with a pericardial knock, which correlates with the abrupt cessation of early diastolic filling (E wave) when the ventricles reach their finite-volume limit.

The ECG demonstrates low voltages with nonspecific T-wave changes. Atrial fibrillation is seen in a minority of patients. Chest roentgenography may demonstrate “egg-shell” calcification of the pericardium, particularly in tuberculous pericarditis, and pleural effusions. There may be variation in the presentation of constriction. These variants include localized constriction (localized scarring), effusive constriction (after the pericardial fluid is drained), elastic constriction (thick pericardial fluid), latent or occult constriction (volume depleted), transient constriction, and constriction with normal pericardial thickness.

Effusive-constrictive pericarditis is a variation of constrictive pericarditis that is infrequently recognized. Confirmation of this diagnosis requires pericardiocentesis and cardiac catheterization. Patients present with predominant cardiac tamponade with elevated intrapericardial and intracardiac pressures. After pericardiocentesis with a fall to baseline intrapericardial pressure, the hemodynamics of constriction remains. Pericardiectomy is often required. Transient constrictive pericarditis occurs in a subset of patients presenting with constrictive physiology due to almost all etiologies with the possible exception of radiation. Complete resolution of hemodynamic abnormalities and symptoms occurs after medical therapy for approximately 3 months. Pericardiectomy is not required.

Treatment

Conservative medical management of constrictive pericarditis is at best palliative, with no substantial effect on the natural history of the disease. Diuretics decrease the intensity of fluid overload symptoms, and atrioventricular blocking agents and antiarrhythmics are useful for the management of atrial fibrillation. Surgical pericardiectomy remains the only definitive management of this problem and should be performed before calcification and myocardial involvement progress. In one series, a worse prognosis following pericardiectomy was associated with inadequate resection, higher NYHA functional class, radiation, myocardial involvement, residual coronary artery disease, older age, chronic disease, and arrhythmias. A second contemporary series of 135 patients with constrictive pericarditis found a 6% 30-day perioperative mortality for pericardiectomy and 78% and 57% 5- and 10-year survival, respectively, with improvement in functional class in most patients. Similar to prior studies, predictors of poor prognosis included advanced age, NYHA class, and postradiation etiology. Symptomatic benefit postpericardiectomy has been correlated with improvement in diastolic filling pattern and shorter duration of symptoms. Furthermore, the prognosis of patients after pericardiectomy largely depends on etiology, with a 30-day perioperative mortality of 2.7% for idiopathic constriction, 8.3% for postsurgical constriction, and 21.4% for postradiation constriction (overall 6%).

Idiopathic and Viral Pericarditis

The majority of cases of acute pericarditis have no specific cause detected and are designated idiopathic. Many of these cases represent acute viral pericarditis. Attacks of this syndrome follow the seasonal epidemics of enterovirus infection (Coxsackie B and echovirus). Proven viral cases are more likely to occur in immunocompromised hosts. Cytomegalovirus pericarditis has increased in frequency in association with immunocompromised hosts and early HIV infection. Most recently, myopericarditis has been reported associated with smallpox vaccination.

Clinical Presentation

Idiopathic or viral pericarditis in the immunocompetent host is typically self-limited beginning with a nonspecific flulike illness. There is often a history of a prodromal upper respiratory tract infection. There may be associated arthralgias and myalgias. Patients present with a syndrome of chest pain as described earlier. The pain is often severe, distressing, and associated with sympathetic activation of clamminess, pallor, and tremor. There is often an associated low-grade fever. Significant dyspnea is uncommon in simple cases unless there is hemodynamic compromise by a large pericardial effusion or associated viral pneumonitis.

The specific diagnosis of viral pericarditis should be entertained in all cases after other etiologic agents have been considered. However, the identification of the viral agent from serologic markers or from pericardial fluid occurs infrequently in clinical practice. A fourfold rise in serum antibody levels is highly suggestive of an underlying viral cause. Associated myocarditis is often associated with modest elevation of cardiac isozymes.

Uncomplicated acute pericarditis is a self-limited benign illness with few sequelae and a course ranging from days to a few weeks. Complications are infrequent and include relapsing attacks of acute pericarditis (see later discussion), acute tamponade, acute myocarditis with ventricular dysfunction and late cardiomyopathy, and chronic constrictive pericarditis.

Management

Specific antiviral therapy is not indicated for viral/idiopathic pericarditis in the immunocompetent host. Treatment is directed toward symptomatic relief. The mains-

tay of therapy centers on the oral antiinflammatory drugs, particularly aspirin (650 mg twice daily or three times daily) or most often on the nonsteroidal antiinflammatory agents indomethacin (25 to 50 mg four times daily) and ibuprofen (800 mg three times daily). Most regimens are given for 7 to 10 days followed by a gradual tapering over 2 to 4 weeks to reduce recurrence and include gastric protection for patients at high risk of bleeding. Indomethacin should be reserved in adults due to deleterious effects on coronary blood flow and myocardial infarcts. Thus, other nonsteroidal agents are commonly used. No specific studies have used the COX-2 inhibitor agents. Colchicine (0.6 mg every 12 hours), with or without a load of 2 to 3 mg, may be used when added to the antiinflammatory agent or by itself in treating the initial attack or preventing recurrences. There is no role for antibiotics unless purulent pericarditis has been documented. Systemic steroid therapy with prednisone has been used in severe and intractable cases but generally should be avoided during a first episode due to concern for recurrence after tapering. Some patients may have recurrent or incessant pericarditis that may be related to an immunopathic etiology. Not infrequently, these patients may be steroid dependent. Colchicine may be an effective drug to use when attempting to wean patients off steroids. Outpatient management of acute pericarditis is safe in patients without poor prognostic predictors, which include fever greater than 38B°C, subacute onset, immunodepression, trauma, oral anticoagulants, myopericarditis, severe effusion, and cardiac tamponade.

Controversies and Personal Perspectives

Decades ago the study of diastology, restrictive cardiomyopathy, and pericardial disease was largely limited to tertiary centers, required invasive diagnostic procedures, and was associated with poor outcomes and few treatment options. Now it is recognized that disorders of diastology are highly prevalent and that diastolic heart failure occurs often as a manifestation of common clinical problems. Over the last several years, many pivotal basic and clinical studies have furthered our understanding of the pathophysiology of diastolic dysfunction, aided in the characterization of specific disorders, and advanced the management of patients with diastolic heart failure.

Although some investigators have supported a broader classification of heart failure with a normal ejection fraction (HFNEF), in recent work using invasively determined pressure-volume loops has confirmed that abnormalities in active relaxation and passive stiffness are operative in patients with heart failure and a normal ejection fraction. Therefore, diastolic heart failure should be accepted as a well-defined entity with heart failure symptoms, abnormalities of diastolic impairment, and normal or near-normal ejection fraction.

Echocardiography remains the cornerstone of the study of diastology. Additional lessons regarding the fundamentals of diastolic dysfunction have been learned with the use of newer, ultrasound-based technologies including strain, strain rate, tissue-tracking, and torsion imaging. These technologies have allowed for earlier recognition of diastolic dysfunction as well as aided in distinguishing primary forms of pathologic hypertrophy and restrictive cardiomyopathies and predicting preclinical deterioration to heart failure in select patient groups.

Concomitant with advances in cardiac ultrasound technology is the emergence of computed tomography and most notably cardiac magnetic resonance imaging for the evaluation and diagnosis of pericardial disease and restrictive cardiomyopathy. MRI with gadolinium enhancement has become an important test for the diagnosis of cardiac sarcoidosis, hemochromatosis, and amyloidosis and may predict cardiac events among patients with hypertrophic cardiomyopathy. Although these technological advances are not available to all clinicians, simple laboratory tests, such as BNP, have helped in the diagnosis of diastolic abnormalities including diastolic heart failure and correlated with filling pressures and stages of diastolic dysfunction.

CHAPTER 4
CARDIOMYOPATHIES

Foreword

Cardiomyopathy is literally defined as a "disease of heart muscle." Goodwin first proposed a clinicopathological classification of cardiomyopathy designed to assist in the differential diagnosis of heart failure in 1964 and further modified it in 1972. Categories included dilated (congestive, fibrotic), hypertrophic, and restrictive categories, and their use has proven valuable in identifying etiological factors, determining prognosis, and planning treatment. Nonetheless, some have considered even this system too complex; in 1970, it was suggested that the cardiomyopathies were in danger of being classified into oblivion. Certainly, any attempt to classify any disease into subcategories should remain as simple as possible. At the same time, it is absolutely essential that any classification be meaningful if it is to be useful.

WHO's first proposal to classify cardiomyopathies and thus develop "order from chaos" was published in 1968; this document suggested that the term "idiopathic cardiomegaly" be used for cardiomyopathies. This definition was easily applicable in developing countries but did nothing to facilitate an understanding of heart muscle disease in either these developing countries or in more medically sophisticated societies. In 1980, WHO/ISFC followed this initial effort by recommending that cardiomyopathies be divided into "cardiomyopathy," in which the causes were unknown, and "specific heart muscle diseases," in which a definite etiology could be identified.

Specific cardiotoxic agents such as viruses and chemicals produce heart muscle disease and dysfunction and thus by definition, cardiomyopathy. In 1982, only 10 345 deaths in 410 000 days of hospital care were attributed to cardiomyopathy; this illustrates the difficulty of applying this nomenclature generally.

WHO/ISFC now suggests that the cardiomyopathies be "defined as diseases of the myocardium associated with cardiac dysfunction" and that they be "classified by the dominant pathophysiology, or, if possible, by etiological/pathogenetic factors." Thus, cardiomyopathies would be pathophysiologically classified as dilated, hypertrophic, restrictive, and arrhythmogenic right-ventricular cardiomyopathies. The term

"specific cardiomyopathies" is now used to describe heart muscle diseases that are associated with specific cardiac or systemic disorders." Disease categories include ischemia, valvular heart disease, inflammatory cardiomyopathy, metabolic cardiomyopathy, general system disease, muscular dystrophies, neuromuscular disorders, sensitivity and toxic reactions, and peripartal cardiomyopathy.

It is not clear why the WHO/ISFC definition of cardiomyopathy was ever restricted to heart muscle diseases of unknown cause. All cardiomyopathies have causes, regardless of whether the specific etiology can be identified. The limitations of this initial restriction have been recognized and removed. However, it is now just as unclear why the use of the term "cardiomyopathy" should be restricted only to heart muscle disease associated with cardiac dysfunction. While the clinicopathological classification of dilated, hypertrophic, and restrictive cardiomyopathy is useful in formulating differential diagnoses and selecting therapeutic regimens, the classification only recognizes the advanced stages of the cardiomyopathic process.

The classification process must remind both clinician and clinical investigator that cardiomyopathy is present before the cardiac anatomy and physiological function are altered and that the cardiomyopathic process begins with the first diseased myocardial cell(s), which in 1996 and beyond may be subject to therapeutic salvage or treatment. Yet, the WHO/ISFC definitions would not permit recognition of the process of geometric remodeling in a hypertensive individual's heart as cardiomyopathic. A parallel situation using coronary artery disease as the disease process would be the failure to recognize that the heart of a 45-year-old, overweight, smoking, hypercholesterolemic man with a strong family history of coronary artery disease is likely to be atherosclerotic until myocardial infarction has occurred.

Cardiomyopathy and clinical heart failure are closely linked. However, heart failure is but one possible clinical outcome of cardiomyopathy. The recognition of latent cardiomyopathy may well allow therapeutic intervention designed to delay or prevent the development of clinical heart failure. For example, the realization that latent or early cardiomyopathy may be present in the hypertensive individual, despite the absence of symptoms or clinical evidence of cardiac dysfunction, should be a

strong indicator for antihypertensive therapy to prevent the development of advanced hyperten-sive cardiomyopathy that would lead to clinical heart failure.

The listing of specific cardiomyopathies is too limited to reflect current understanding of the causes of heart muscle disease. Surprisingly, there is no category to cover heredofamilial cardiomyopathy. Although this etiological consideration of a genetic basis overlaps categories such as neuromuscular disorders, the absence of such a category ignores the vast amount of progress in understanding the molecular biological basis of cardiomyopathy. Also missing from the classification scheme is a category of hyperergopathic cardiomyopathy (cardiomyopathy of overwork, pathological hypertrophy, cardiac remodeling). This hypertrophic process occurs in virtually all the other cardiomyopathies, once sufficient myocardial damage results from the initial insult. Finally, the classification does not include the descriptive category "idiopathic." Clearly, certain patients presenting with heart failure cannot be specifically diagnosed regarding the etiology of the underlying cardiomyopathy, nor should the treating physician apologize for using the term "idiopathic." In fact, use of the term should encourage investigators to explore possible new etiologies and develop better tests for those already identified.

WHO/ISFC now defines ischemic cardiomyopathy as "a dilated cardiomyopathy with impaired contractile performance not explained by the extent of coronary artery disease or ischemic damage." This would appear to represent a contradiction in terms; if myocardial dysfunction cannot be explained by the extent of ischemia, how, then, can the etiology be attributed to ischemia? The intent of the original description by Burch et al in 1970 was not to limit the definition of ischemic cardiomyopathy to unexplained factors but rather to define the disease as heart muscle damage resulting from inadequate perfusion of the myocardium relative to metabolic demands, usually due to obstructive changes in the coronary circulation. Myocardial ischemia produces biochemical abnormalities and significant resultant cellular dysfunction even when ischemia is not prolonged or severe enough to produce myocardial necrosis in the well-described processes of myocardial hibernation and stunning. Technically, ischemic cardiomyopathy begins with the onset of excessive cellular anaerobiosis and

eventually encompasses a broad spectrum of disease.

Although many cases of cardiomyopathy are clearly pluricausal (eg, ischemia and diabetes mellitus), the WHO/ISFC classification does not allow for such multiple etiologies. Again, analogous to the pathogenesis of atherosclerosis, multiple risk factors may be present for the development of cardiomyopathy.

As recommended previously, cardiomyopathy should be defined simply as diseases of heart muscle. The natural progression of the disease should be recognized by establishing potential (latent), early, and advanced clinical categories. The knowledgeable physician will understand that the pathophysiological process is a continuum and that the final expression may be characterized as dilated, hypertrophic, nondilated, nonhypertrophic (restrictive), and so forth. Thus the presence of clinical dysfunction represents a late stage in the development of cardiomyopathy, and therapeutic emphasis should be on prevention or early interruption of the pathophysiological process. The classification scheme also should emphasize that the cardiomyopathies may be multifactorial.

At least three additional categories should be added to the classification scheme: heredofamilial, hyperergopathic (overwork), and idiopathic. On the one hand, these represent recognition of the vast progress made in understanding the basis and progression of many cardiomyopathies and, on the other, allow for the classification of cardiomyopathies that have eluded the diagnostic and investigative processes. The process of progression should be reemphasized among the etiological/pathogenetic factors. For example, ischemic cardiomyopathy begins with the first episode of myocardial ischemia (clinically apparent as angina or silent) and ends with terminal heart failure or sudden death.

Progress reclassifying the cardiomyopathies has been slow. The current WHO/ISFC Task Force is certainly to be congratulated for making substantive changes and for recognizing that the classification process is dynamic. Nevertheless, it is time now to finish the course and remove the remaining stumbling blocks the current classification places in the way of the investigation, diagnosis, and treatment of this important group of diseases. The treatment of asymptomatic and early myo-

cardial dysfunction has already been shown to benefit patients. Ideally, we will soon be conducting clinical trials to investigate the treatment of specific cardiomyopathies rather than the end-stage processes of heart failure and sudden death.

Introduction

Historically, most cardiomyopathies have been defined by the *absence* of particular features or associated disorders, but it is increasingly apparent that many patients with unexplained heart muscle disease in fact have rare, but well described diseases that can involve the myocardium. In this new classification system, we propose a move away from the concept of diagnosis by exclusion and focus solely on the morphology and function of the heart. This simple but radical departure from the existing convention means that the differentiation between cardiomyopathies and specific heart muscle diseases is abandoned (with the exceptions of hypertension, coronary artery disease, valve disease, and congenital heart anomalies).

Remarkably, it was not until 50 years ago (1957) that the term *cardiomyopathy* was used for the first time. Over the next 25 years, a number of definitions for cardiomyopathies were advanced. Indeed, in the original 1980 WHO classification, cardiomyopathies were defined only as "heart muscle diseases of unknown cause," reflecting a general lack of available information about basic disease mechanisms. In 1968, the WHO defined cardiomyopathies as "diseases of different and often unknown etiology in which the dominant feature is cardiomegaly and heart failure." The final WHO classification published in 1995 proposed "diseases of myocardium associated with cardiac dysfunction" and included for the first time arrhythmogenic right ventricular cardiomyopathy/dysplasia, as well as primary restrictive cardiomyopathy.

Therefore, why was it necessary to offer yet another classification scheme for cardiomyopathies in 2006 under the auspices of the American Heart Association (AHA)? In fact, the international expert consensus panel (and writing group) found several very important reasons to take on this project. The last formal effort at developing a consensus for the classification of cardiomyopathies had been published 12 years previously in the form of a very brief and rudimentary document. Most importantly, it was apparent that with the identification of several new disease entities over

the prior decade and a virtual explosion in diagnostic capability with the introduction and penetration of modern molecular biology into cardiovascular medicine and more precise knowledge of the basic causes and phenotypic expression of cardiomyopathies, the WHO classification had been rendered obsolete.

Indeed, out of this genomic revolution the ion channelopathies emerged as important causes of sudden death in the young, caused by mutations in proteins leading to dysfunctional sodium, potassium, and calcium ion channels and predisposed to potentially lethal ventricular tachyarrhythmias. These are, by definition, molecular diseases of heart muscle and without gross structural abnormalities.

The rationale for a new classification

When the classification system for cardiomyopathies was originally conceived, the lack of knowledge about the underlying cause and pathophysiology of different types of cardiomyopathy was recognized, but there was an implicit assumption that they were distinct entities. Cardiomyopathies were defined as primary myocardial disorders of unknown cause; heart muscle disorders of known aetiology or associated with systemic disorders were classified as secondary or specific heart muscle diseases. With the passage of time, the distinction between primary and secondary heart muscle disease has become increasingly tenuous, as the aetiology of previously idiopathic disorders has been discovered. Recently, an expert committee of the American Heart Association proposed a new scheme in which the term primary is used to describe diseases in which the heart is the sole or predominantly involved organ and secondary to describe diseases in which myocardial dysfunction is part of a systemic disorder. However, the challenge of distinguishing primary and secondary disorders in this way is illustrated by the fact that many of the diseases classified as primary cardiomyopathies can be associated with major extra-cardiac manifestations; conversely, pathology in many of the diseases classed as secondary cardiomyopathies can predominantly (or exclusively) involve the heart.

As many cardiomyopathies are caused by mutations in genes that encode various cardiac proteins, an alternative approach is to reclassify cardiomyopathies according to the causative genetic defect. However, in clinical practice the pathway from di-

agnosis to treatment rarely begins with the identification of an underlying genetic mutation; more usually, patients present with symptoms or are incidentally found to have clinical signs or abnormal screening tests. Even when the genetic defect is known in a family, the identification of clinically relevant disease in gene-carriers still requires the demonstration of a morphological phenotype. Thus, we believe that a clinically oriented classification system in which heart muscle disorders are grouped according to ventricular morphology and function remains the most useful method for diagnosing and managing patients and families with heart muscle disease.

Contemporary nomenclatura.

The cardiomyopathies are an important and complex group of heart muscle diseases with multiple etiologies and heterogeneous phenotypic expression. Awareness and knowledge of these diseases in both the public and medical communities have historically been impaired by periodic confusion surrounding definitions and nomenclature. Therefore, formal and systematic classifications have traditionally been viewed as useful exercises promoting greater understanding of the heart muscle diseases. Indeed, a multitude of such cardiomyopathy classifications have been advanced over the years by individual investigators and consensus panels sanctioned by medically related organizations such as the World Health Organization (WHO).

By virtue of these novel insights into the morphological and functional expression of the heart muscle diseases, older entrenched disease definitions and classifications are no longer relevant. In particular, the popular clinical classification for cardiomyopathies of "hypertrophic-dilated-restrictive" poses major limitations by mixing anatomic designations (ie, hypertrophic and dilated) with a functional one (ie, restrictive) into the same construct, and this classification probably should be abandoned. An example of confusion in nomenclature caused by "mixed phenotypes" arises with regard to hypertrophic cardiomyopathy (the most common of the purely genetic cardiomyopathies), given that this disease may appear in 2 or all 3 of the categories. Hypertrophic cardiomyopathy is characterized by left ventricular hypertrophy, is usually restrictive in the sense that impaired diastolic filling is a common and important disease component, and furthermore may evolve into a dilated phase with systol-

ic dysfunction as part of a remodeling process. Similarly, amyloid and other infiltrative cardiomyopathies do not adopt uniformly static phenotypic expression, and as part of their natural history they may evolve from a nondilated (often hyperdynamic) state with ventricular stiffness to a dilated form with systolic dysfunction and heart failure.

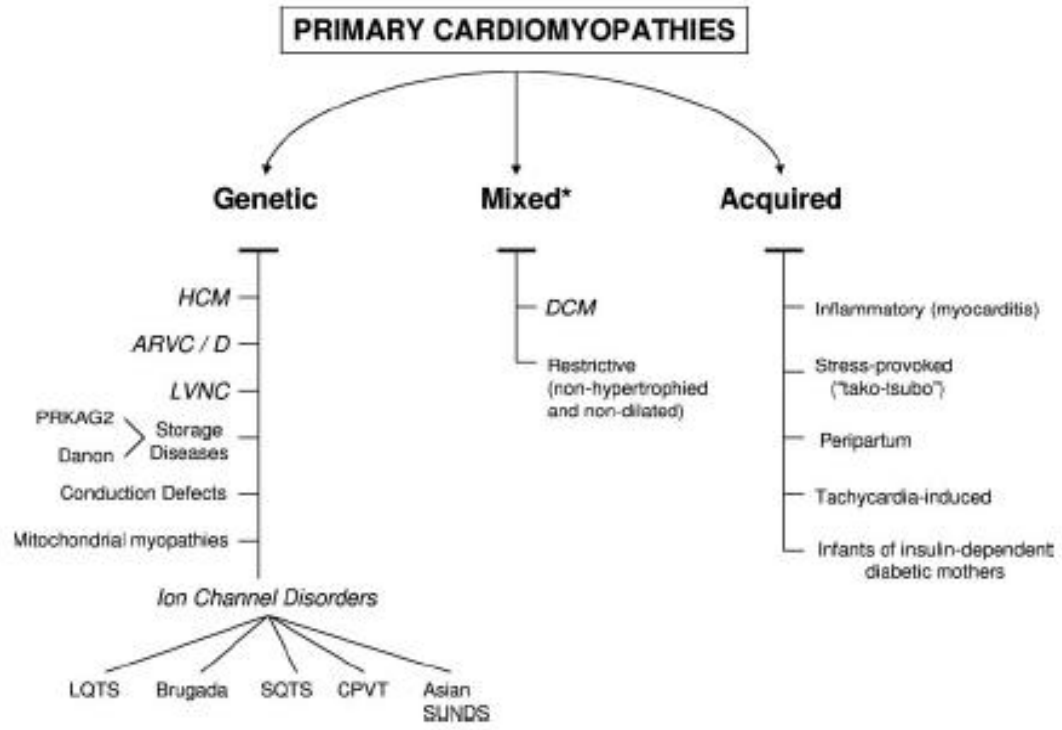
In addition, it is often difficult to reliably distinguish dilated from nondilated forms of cardiomyopathy given that quantitative assessments of ventricular chamber size represent a continuum and patients can vary widely in their degree of cavity enlargement (often deviating only slightly from the upper limits of normal). Indeed, such ambiguities may also arise with regard to some rare and/or newly identified cardiomyopathies for which few quantitative cardiac dimensional data are available. In other conditions, such as stress (tako-tsubo) cardiomyopathy and the transient cardiomyopathy in infants of diabetic mothers, the dynamic remodeling that occurs with clinical recovery substantially changes (and normalizes) cardiac morphology. Finally, the pure form of restrictive (nonhypertrophied) cardiomyopathy is extraordinarily rare and should not be confused with the myriad of myocardial diseases that have a component of restrictive physiology, usually with associated left ventricular hypertrophy (such as hypertrophic cardiomyopathy).

AHA Definition

The proposed definition of cardiomyopathies offered by the AHA expert consensus panel is as follows: "a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction, which usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation, due to a variety of etiologies that frequently are genetic. Cardiomyopathies are either confined to the heart or are part of generalized systemic disorders, and often lead to cardiovascular death or progressive heart failure–related disability." This definition of cardiomyopathies, similar to that reported by the European Society of Cardiology (ESC), under the auspices of the Working Group on Myocardial and Pericardial Diseases, excludes myocardial involvement secondary to coronary artery disease, systemic hypertension, and valvular and congenital heart disease. Primary cardiomyopathies (ie, those solely or predominantly confined to heart muscle) are shown in the Figure 4.1 from the

AHA classification.

Figure 4.1



Note: AHA classification model for primary cardiomyopathies (disease processes solely or predominantly confined to the working myocardium). These conditions are segregated according to their genetic or nongenetic acquired etiologies in accord with contemporary definitions. *Regarded as predominantly nongenetic on the basis of current knowledge, ie, familial disease has been reported in only a minority of cases. ARVC/D indicates arrhythmogenic right ventricular cardiomyopathy/dysplasia; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; LVNC, left ventricular noncompaction; SQTS, short QT syndrome; and SUNDS, sudden unexplained nocturnal death syndrome.

Points of Departure With ESC

Three major considerations relevant to the AHA cardiomyopathy definitions and classification will be addressed here because they have been the source of controversy and also some criticism from the writing panel of the recent ESC classification of cardiomyopathies,.

Genetic Diagnosis

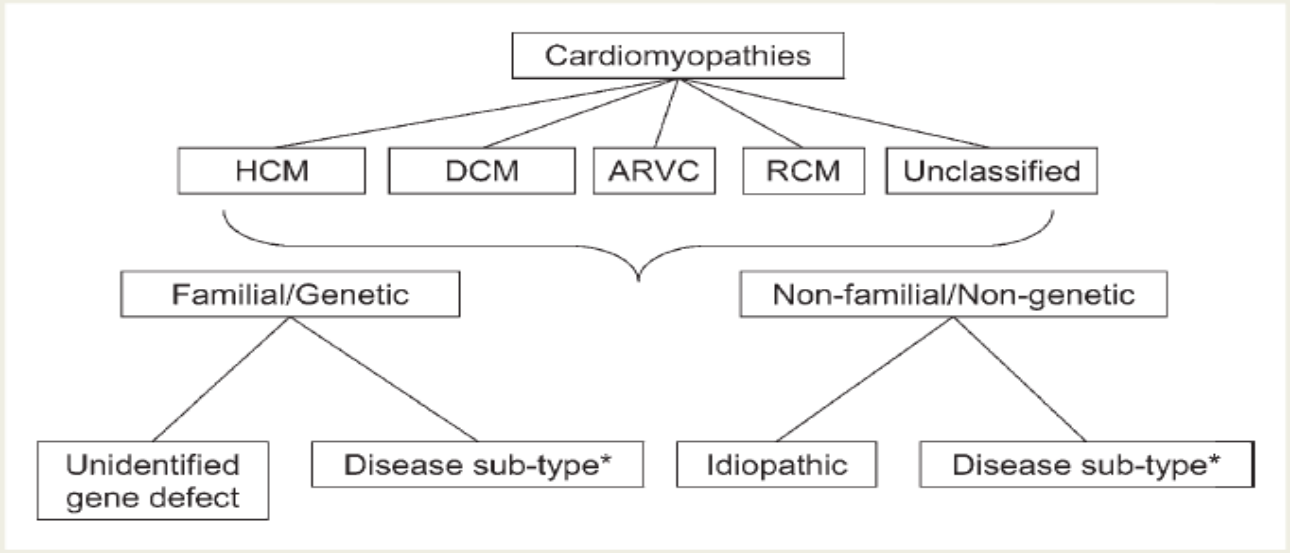
It seemed self-evident and unavoidable to the AHA panel that contemporary definitions and a classification for heart muscle diseases should rely substantially on a genetic model, taking into account encoded protein expression and underlying gene

mutations. Nevertheless, the panel also recognized that the penetration of commercial diagnostic genetic testing into routine clinical practice is far from complete, and molecular biology of the cardiomyopathies will also evolve considerably over the next several years.

Indeed, the AHA recommendations represent (and function as) a robust but flexible "living document" that will continue to be largely relevant in the future as new data emerge and genetic testing becomes more routine. The ESC inference (in 2008) that contemporary understanding of the cardiomyopathies is only confused by genetic diagnostic labeling seems to be a reversion to the old 1995 WHO classification. Furthermore, the ESC classification (Figure 4.2) itself segregates the cardiomyopathies into "familial/genetic" and "nonfamilial/nongenetic" categories seemingly indistinguishable from the AHA nomenclature, which also uses "genetic/acquired (nongenetic)." Therefore, at least in this respect, the AHA and ESC presentations do not appear to differ significantly.

Figure 4.2

The ESC classification



Note: ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy

Clinical Utility

Neither the AHA nor the ESC presentations represent comprehensive guides that dictate precise, clinical diagnostic strategies for each of the cardiomyopathies. Nevertheless, the ESC promotes their document as an improved "clinically oriented"

classification with "utility for "everyday practice," which serves as an improved guide for diagnosis emphasizing specific morphological and functional phenotypes. However, on close inspection, the ESC and AHA do not differ substantially in this regard because both in fact rely on specific structural disease states (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia) as the basis for the classification.

Inclusion of Ion Channelopathies

Given the basic definition for cardiomyopathies established by the AHA consensus panel, inclusion of ion channelopathies (ie, clinically expressed long QT syndrome, short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia) in the classification scheme seems reasonable and appropriate (if not unavoidable), although admittedly a distinct departure from prior efforts. Within the AHA definition, cardiomyopathies are associated with failed myocardial performance that may be either mechanical (eg, diastolic or systolic dysfunction) or electrical. Indeed, the ion channelopathies are a constellation of related primary electrical diseases that do not express gross or histopathological abnormalities, in which the structural and functional myocardial abnormalities responsible for arrhythmogenesis exist at the molecular level within the cell membrane. Therefore, the basic pathological abnormality in this group of diseases cannot be identified by conventional noninvasive imaging or myocardial biopsy, or by autopsy examination of tissue.

Nevertheless, the AHA panel was justified in including ion channelopathies in a contemporary classification of cardiomyopathies on the basis of the scientific assertion that ion channel mutations are responsible for altering biophysical properties and protein structure, thereby creating structurally abnormal ion channel interfaces and architecture. The fact that mutations in genes encoding ion channel proteins have been reported in patients with other cardiac diseases, a criticism made by the ESC, is not a particularly compelling argument against our inclusion of the ion channelopathies.

Nonspecific idiopathic cardiomyopathies.

A cardiomyopathy should be defined as: A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary ar-

tery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality.

Cardiomyopathies are grouped into specific morphological and functional phenotypes; each phenotype is then sub-classified into familial and non-familial forms. In this context, familial refers to the occurrence, in more than one family member, of either the same disorder or a phenotype that is (or could be) caused by the same genetic mutation and not to acquired cardiac or systemic diseases in which the clinical phenotype is influenced by genetic polymorphism. Most familial cardiomyopathies are monogenic disorders (i.e. the gene defect is sufficient by itself to cause the trait). A monogenic cardiomyopathy can be sporadic when the causative mutation is *de novo*, i.e. has occurred in an individual for the first time within the family (or at the germinal level in one of the parents). In this classification system, patients with identified *de novo* mutations are assigned to the familial category as their disorder can be subsequently transmitted to their offspring.

Non-familial cardiomyopathies are clinically defined by the presence of a cardiomyopathy in the index patient and the absence of disease in other family members (based on pedigree analysis and clinical evaluation). They are subdivided into idiopathic (no identifiable cause) and acquired cardiomyopathies in which ventricular dysfunction is a complication of the disorder rather than an intrinsic feature of the disease. In a departure from the 1995 WHO/ISFC classification, we exclude left ventricular dysfunction secondary to coronary artery occlusion, hypertension, valve disease, and congenital heart disease because the diagnosis and treatment of these disorders generally involves clinical issues quite different from those encountered in most cardiomyopathies.

The expert panel of the American Heart Association has suggested that ion channelopathies and disorders of conduction should also be considered as cardiomyopathies. This suggestion was predicated on the fact that these genetic disorders ‘are responsible for altering biophysical properties and protein structure, thereby creating structurally abnormal ion channel interfaces and architecture'. However, recent studies suggesting that genes encoding ion channels may be implicated in subgroups of

patients with dilated cardiomyopathy (DCM), conduction disorders, and arrhythmias do not provide an argument for the redesignation of channelopathies as cardiomyopathies at the present time.

Hypertrophic cardiomyopathy

Historically, hypertrophic cardiomyopathy (HCM) has been defined by the presence of myocardial hypertrophy in the absence of haemodynamic stresses sufficient to account for the degree of hypertrophy and systemic diseases such as amyloidosis and glycogen storage disease. The aim of this distinction was to separate conditions in which there is myocyte hypertrophy from those in which left ventricular mass and wall thickness are increased by interstitial infiltration or intracellular accumulation of metabolic substrates. In everyday clinical practice, however, it is frequently impossible to differentiate these two entities using non-invasive techniques such as echocardiography or magnetic resonance imaging. One approach to this conundrum is to include the histological demonstration (on myocardial biopsy) of myocyte hypertrophy in the definition of HCM; unfortunately, the patchy and complex nature of most myocardial pathologies means that this distinction can only be reliably made at post-mortem. In order to provide a common starting point for clinical investigation, the presence of intramyocardial storage material is not an exclusion criterion for HCM in this classification scheme. Instead, hypertrophic cardiomyopathies are simply defined by the presence of increased ventricular wall thickness or mass in the absence of loading conditions (hypertension, valve disease) sufficient to cause the observed abnormality.

Inevitably, this approach will be controversial, but it reflects the terminology that is already in use in paediatric practice and avoids the circular arguments and contradictions that arise when trying to confine the term HCM to one narrow phenotype and aetiology (i.e. sarcomere protein disease). The potential inaccuracy (in a pathological sense) of the term ‘hypertrophic’ in some clinical settings is, in our view, outweighed by a shift in the clinical emphasis towards the development of appropriate diagnostic strategies based on clues from the history, physical examination, and non-invasive investigations.

The working group considered at some length the issue of cardiac amyloid, historically regarded as an exemplar of restrictive cardiomyopathy (RCM), in spite of the fact that, in strict morphological terms, it frequently fails to fulfil most of the features listed in previous definitions. The arguments for continuing with this convention are that interstitial (rather than intracellular) accumulation of amyloid protein precludes use of the term 'hypertrophy' and that, unlike other causes of myocardial thickening, amyloid has distinct features on electrocardiography and cardiac imaging that suggest the diagnosis. The counterargument is that the logic of a morphological classification dictates that increased ventricular wall thickness caused by amyloidosis should be listed as HCM. The final consensus was that amyloidosis should be listed in the differential diagnosis of both HCM and RCM, acknowledging that this still leaves a degree of nosological ambiguity.

Left ventricular hypertrophy in the absence of hypertension and valve disease occurs in approximately 1:500 of the general population. Many individuals have familial disease with an autosomal dominant pattern of inheritance caused by mutations in genes that encode different proteins of the cardiac sarcomere. The majority of patients with sarcomeric protein gene mutations have an asymmetrical pattern of hypertrophy, with a predilection for the interventricular septum and myocyte disarray. Left ventricular cavity size is usually diminished and fractional shortening typically higher than normal. Progression to left ventricular dilatation and systolic failure occurs in a minority of patients (up to 10% in some series). All patterns of hypertrophy are consistent with the diagnosis of sarcomeric protein disease, but concentric hypertrophy is more frequent in patients with metabolic disorders such as Anderson–Fabry disease, mitochondrial cytopathy, and glycogen storage disease. Additional diagnostic clues in these patients include the inheritance pattern (X-linked, autosomal recessive) and the presence of signs and symptoms of multi-system disease. Athletic training to national or international level is associated with physiological changes in left ventricular morphology that can be confused with a pathological phenotype, but myocardial thickness similar to those seen in patients with HCM are rare (less than 2% of male athletes). In the young, HCM is often associated with congenital syndromes, inherited

metabolic disorders, and neuromuscular diseases. In familial cases, various patterns of inheritance are observed; autosomal disorders that present in the young include Noonan and LEOPARD syndrome (dominant) and Friedreich's ataxia (recessive)

Natural history including sudden cardiac death

HCM may be identified clinically at virtually any age, from infancy to old age (with even a few patients >90 years of age). Understanding the clinical course of HCM, particularly when viewed in the context of predicting outcome for individual-patients, has for 40 years been constrained by three obstacles:

- uncommon occurrence of the disease (i.e., 0.2 percent inthe general population);
- heterogeneity of disease expression;
- tertiary center referral bias.

Indeed, because much of the considerable published literature on HCM is based on studies performed at tertiary referral centers, the overall clinical picture of HCM that has emerged is profoundly influenced by the biases created by highly selective patient referral patterns, which has led to an overestimation of the overall risk for premature death and morbidity. This concept is substantiated by the fact that annual mortality figures from such referral centers are considerably higher (3 to 4 percent and up to 6 percent in children) than those more recently reported in relatively unselected regional populations (about 1 percent per year). Indeed, patient referral patterns are probably the strongest determinants of our prevailing perceptions regarding the clinicalexpression and impact of HCM. In general terms, it is reasonable to characterize HCM as a complex disorder capable of important clinical consequences, including causing premature death in some patients. However, the disease has a more favorable overall clinical course than previously thought, as many patients achieve normal life expectancy with little or no disability and often without the aid of therapeutic interventions. These observations emphasize the need to provide many HCM patients, including many children, with reassurance regarding their clinical outlook, as well as prudence concerning possible adverse consequences.

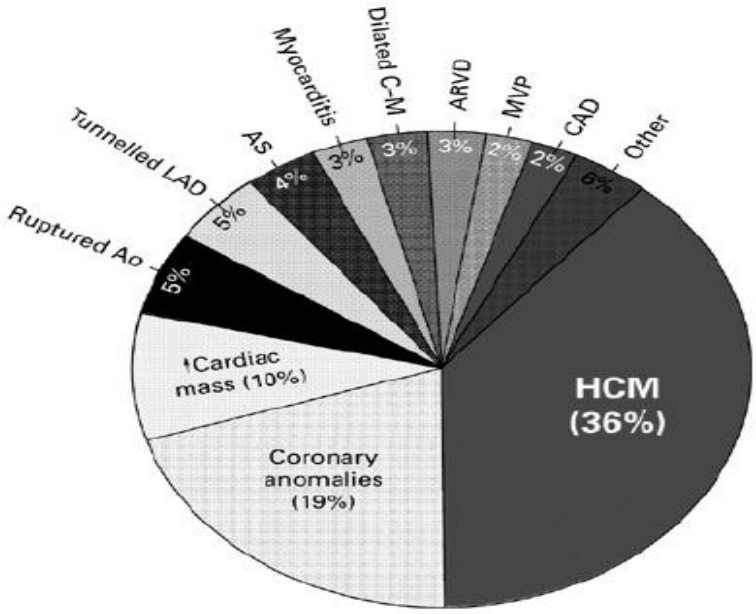
On the other hand, when HCM is viewed in terms of patient subgroups (rather than the overall disease), some individuals are clearly at much higher risk and may be subject to three modes of death:

- sudden and unexpected, often in the young;
- progressive heart failure in midlife; and
- stroke associated with atrial fibrillation, largely in the elderly.

While frequent in children and young adults, sudden death is not confined to these age groups and may also occur in midlife and beyond, without a statistically significant predilection for any particular age group. Therefore the potential risk period in HCM is particularly long. However, reports of sudden death in infants and very young children are exceedingly rare. Sudden death in HCM usually occurs in previously asymptomatic (or only mildly symptomatic) patients, and such catastrophes are often the first clinical manifestation of the disease. Although most patients die in the morning hours while engaged in sedentary pursuits or during mild exertion, a substantial proportion collapse during or just after vigorous physical activity. The latter observation-as well as the fact that HCM is the most common cause of sudden death among young competitive athletes (Fig. 4.3) supports the view that intense physical activity can act as a trigger for sudden death in the presence of underlying cardiovascular disease. Therefore it is prudent to recommend the disqualification of young athletes with HCM from intense competitive sports, in accord with the standards of the 26th Bethesda Conference, in an effort to decrease the risk of exercise-related sudden death.

Figure 4.3

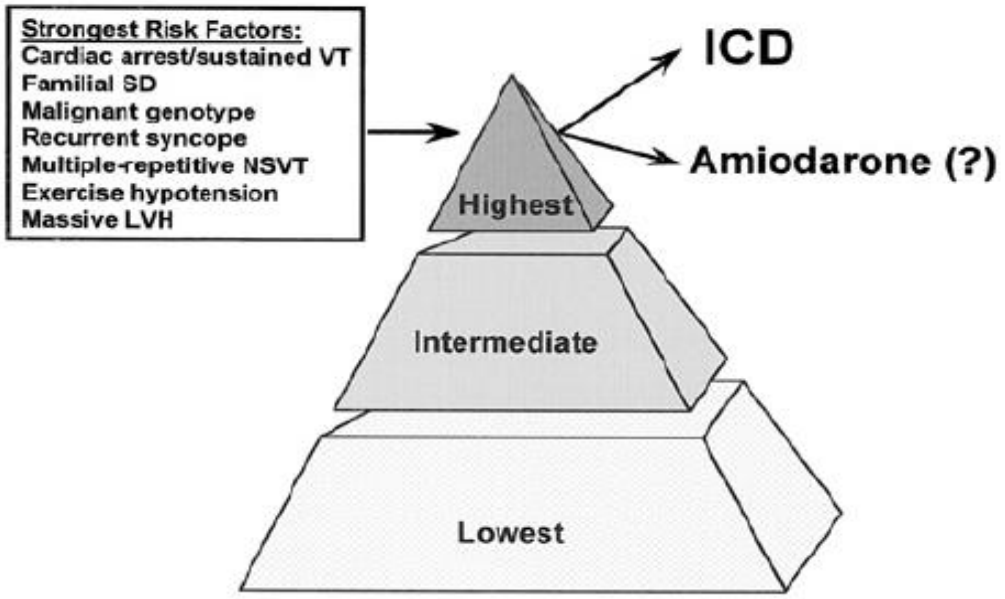
Causes of sudden cardiac death in young competitive athletes.



Note: Ao = aorta; LAD = left anterior descending coronary artery; AS = aortic stenosis; C-M = cardiomyopathy; ARVD = arrhythmogenic right ventricular dysplasia; MVP = mitral valve prolapse; CAD = coronary artery disease; HCM = hypertrophic cardiomyopathy.

Figure 4.4

Assessment of risk for sudden cardiac death in HCM population.



Note: ICD = implantable cardioverterdefibrillator; LVH = left ventricular hypertrophy; NSVT = nonsustained ventricular tachycardia; SD = sudden death; VT = ventricular tachycardia

Based on stored electrogram data from HCM patients experiencing appropriate implantable cardioverter-defibrillator discharges, ventricular tachycardia/fibrillation appears to be the primary mechanism most commonly responsible for sudden death in HCM, although a number of other mechanisms may also be involved. No particular symptom complex has been shown to be reliably associated with subsequent sudden death in HCM with the exception of recurrent or exertional syncope, particularly in the young. Furthermore, patients with or without subaortic obstruction may die suddenly, and some patients appear to tolerate marked outflow obstruction for virtually their entire lives without adverse consequences. Indeed, the presence or magnitude of the outflow gradient has not been independently associated with increased risk for sudden death. However, other disease variables have been associated with an increased likelihood of sudden death. The most important of these proposed risk fac-

tors include the following: prior cardiac arrest or sustained ventricular tachycardia, "malignant" genotype or family history of premature HCM death, multiple-repetitive (or prolonged) bursts of nonsustained ventricular tachycardia on ambulatory ECGs, massive degree of left ventricular hypertrophy (wall thickness, 30 mm). A hypotensive blood pressure response to exercise may also be informative regarding risk but is encumbered by a low positive predictive accuracy and is much more powerful as a negative predictor of outcome.

A recent retrospective analysis of children with HCM suggested that an intramural course of a segment of the proximal left anterior descending coronary artery (i.e., myocardial bridging) constitutes a risk factor for sudden cardiac arrest. It was proposed that such muscular bridges could produce systolic coronary arterial narrowing, residual diastolic compression, and myocardial ischemia, thereby justifying surgical unroofing when detected. The data available at this time do not provide convincing evidence that programmed electrical stimulation has a major role in risk stratification in HCM. Particularly aggressive programmed stimulation protocols with triple ventricular premature depolarizations seldom induce monomorphic ventricular tachycardia but frequently trigger polymorphic ventricular tachycardia or ventricular fibrillation in patients with HCM. Based on experience in HCM as well as in coronary artery disease and dilated cardiomyopathy, these latter arrhythmias are generally regarded as nonspecific responses.

A final phase of disease evolution occurring in about 10 percent of symptomatic patients in a referral-based population has been variously referred to as the "end-stage," "burned-out," or "dilated" phase of HCM61. This distinctive clinical course is characterized by progressive congestive symptoms with marked exercise limitation and atrial arrhythmias, associated with substantial left ventricular remodeling-i.e., enlarging left ventricular cavity size (occasionally with marked absolute dilatation), thinning of portions of the wall, systolic dysfunction, and-in a few patients-spontaneous reduction of the subaortic gradient. Therefore, the disease in end-stage patients is transformed from the typical morphologic and functional appearance of HCM (hyperdynamic, hypertrophied, and nondilated left ventricle) to a clinical state

that is more suggestive of a dilated form of cardiomyopathy in which the thickness of the left ventricular wall may be virtually normal. Many such patients exhibit irreversible myocardial perfusion abnormalities, which undoubtedly represent areas of extensive myocardial scarring

It is possible that the morphologic and functional changes that result in end-stage depression of left ventricular contractile function are due to impaired coronary blood flow and myocardial ischemia resulting from small-vessel coronary artery disease. Patients evolving into the end-stage phase of HCM or experiencing sudden and unexpected cardiac death may coexist in the same family (and share the identical disease-causing mutation). Also, a few patients with aborted episodes of cardiac arrest have themselves died many years later in the end-stage phase.

Hypertrophic cardiomyopathy in the elderly

Older patients (over age 60 to 65) with morphologic and clinical features consistent with HCM have been reported. In certain of these patients, HCM may be well tolerated to particularly advanced ages (i.e., 80 to 90 years) and therefore should be regarded as a disease compatible with normal longevity. In an unselected HCM population, about 20 percent of patients had achieved the age of 75 years. In other elderly patients, symptoms are not present early in life, but severe functional limitation and heart failure may intervene abruptly for the first time after age 60 to 65. This prolonged period of symptomatic latency is notable for a disease usually expressed morphologically by age 20 and in which symptoms are usually evident by age 40 to 50. Older patients with HCM differ in many respects from many younger patients with regard to certain morphologic features. Older patients characteristically have relatively small hearts with only modestly increased left ventricular wall thickness (usually 20 mm) and severely distorted outflow tract morphology, with greatly reduced size, and exaggerated anterior displacement of a normal-sized mitral valve. Substantial deposits of calcium in the mitral annular region are frequently present and may contribute to anterior displacement of the valve in some patients. Outflow obstruction often occurs in the presence of restricted mitral valve systolic anterior motion, with contact between ventricular septum and anterior mitral leaflet produced by a combination of

anterior excursion of the mitral valve toward the septum and posterior movement of septum toward the mitral valve. It is uncertain whether the HCM phenotype in such older patients always conveys the same genetic etiology as in younger patients; however, some older patients have been documented to carry the same mutant genes encoding sarcomeric proteins characteristic of other (younger) HCM patients.

Medical treatment

Asymptomatic Patients and Prevention of Sudden Cardiac Death Those patients with clear evidence of high risk should be offered treatment for the prevention of sudden cardiac death. The implantable cardioverter/defibrillator effective and reliable in relatively young and high-risk HCM patients by virtue of sensing ventricular tachycardia/fibrillation and restoring sinus rhythm by appropriate defibrillation shocks or antitachycardia pacing at an overall rate of 7 percent per year. The ICD may be lifesaving, both in the context of secondary prevention after cardiac arrest or in sustained ventricular tachycardia (11 percent per year) or for primary (prophylactic) prevention due to the perception of high risk based on 1 sudden death risk factors. Alternatively, long-term prophylactic treatment with amiodarone 158 would seem less realistic in relatively young HCM patients, given the potential side effects and the long risk period in HCM as well as the paucity of data substantiating amiodarone as affording effective protection against sudden cardiac death specifically in this disease. Prophylactic and empiric administration of beta blockers or verapamil to asymptomatic patients for the primary purpose of reducing the risk for sudden death, for which there are no or little data, now seems outdated in view of the availability of more definitive therapeutic measures such as the ICD. Drug treatment to prevent or delay progression of congestive symptoms is empiric, with a complete lack of any controlled data.

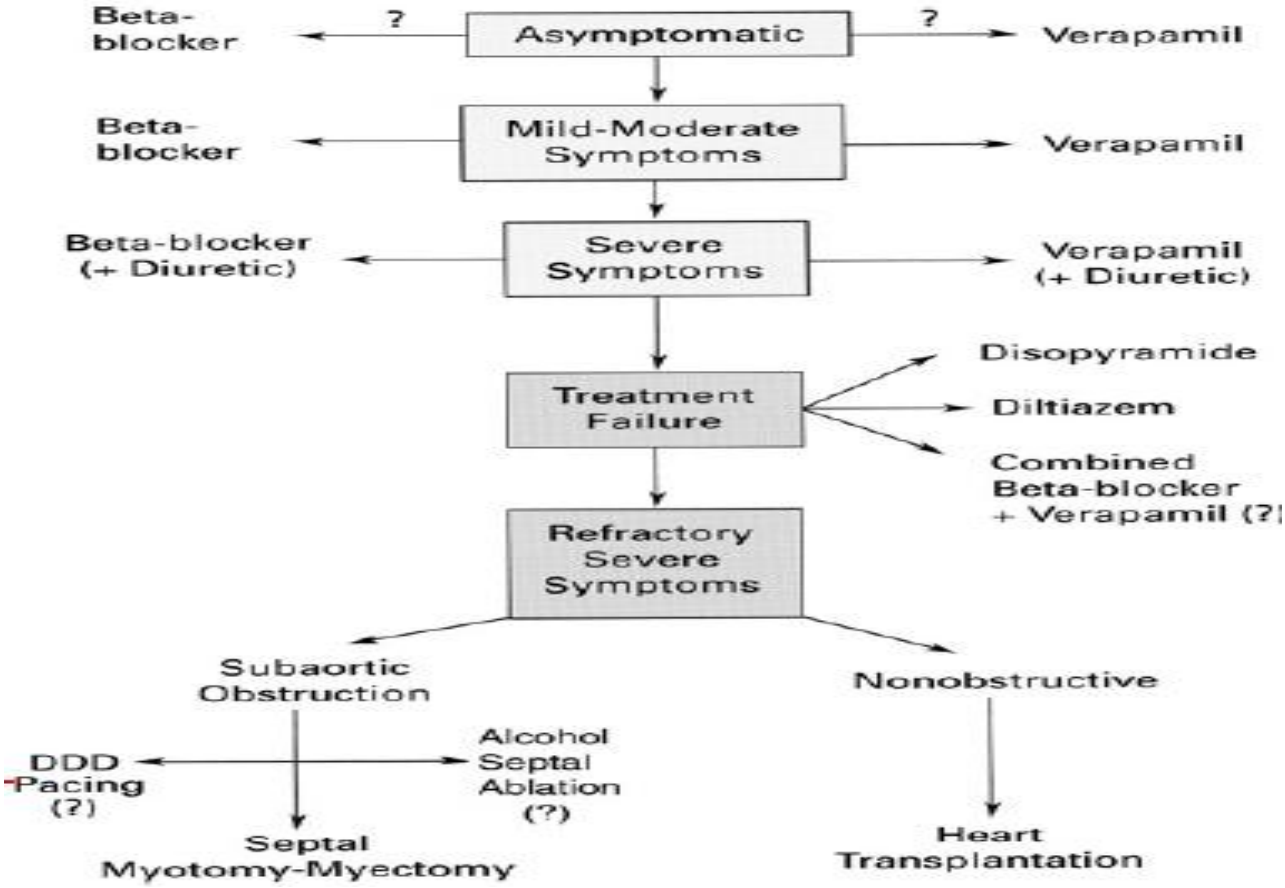
Alleviation of Symptoms Therapeutic strategies for symptomatic patients with HCM are summarized in Fig. 4.5.

Responses of HCM patients to medical treatment are highly variable; consequently, therapy must often be tailored to the individual requirements of symptomatic patients. Historically, beta-adrenergic blocking drugs (propranolol or more cardiose-

lective agents such as atenolol, metoprolol, or nadolol) have been utilized extensively to relieve symptoms in patients with either the obstructive or nonobstructive form of HCM.

Figure 4.5.

Therapeutic strategies for patients with HCM.



The beneficial effects of beta blockers on symptoms (principally exertional dyspnea and chest pain) and exercise capacity appear to be due largely to decreased heart rate, with consequent prolongation of diastole, increased passive left ventricular filling, and decreased filling pressures. By reducing inotropic state, beta blockers may also lessen myocardial oxygen demand and decrease the left ventricular outflow gradient during exercise when sympathetic tone is increased.

Calcium channel blockers (principally verapamil) are also important therapeutic agents in the management of symptomatic patients with HCM. Orally administered verapamil provides improvement in cardiac symptoms and exercise tolerance for many patients with HCM, including those who have failed to benefit from beta

blockers. This symptomatic improvement with verapamil appears to be due largely to normalization of left ventricular filling parameters. Beta blockers and verapamil are usually administered empirically at the onset of symptoms by titrating drug dosage to the historical assessment of functional disability, although some investigators utilize exercise testing with or without measurement of oxygen consumption to gauge the effect of medications on symptoms. Furthermore, there is no consensus on the sequence with which beta blockers and verapamil should be administered; usually a trial with one or the other drug is initiated and should a benefit fail to result, the patient is converted to the other drug. Excessive dosages of either a beta blocker or verapamil should be avoided (e.g., >480 mg/day of verapamil), since such drug levels rarely achieve beneficial results and can incur side effects. There is no evidence that the effect of using beta blockers and verapamil together is superior to that of either drug alone, and this combination should be avoided.

At selected centers, disopyramide has been an alternative medication for patients with obstructive HCM and severe symptoms otherwise unresponsive to standard therapy. Disopyramide may reduce outflow gradient and improve symptoms by virtue of its negative inotropic properties, although the potential for proarrhythmia has constituted an obstacle to its use in HCM for some investigators. The aforementioned negative inotropic agents have been shown to reduce outflow gradient in HCM by slowing left ventricular ejection acceleration. Some patients with particularly severe symptoms of heart failure despite treatment with beta blockers or verapamil may show symptomatic improvement with the judicious addition of diuretic agents. The aforementioned therapeutic considerations apply to those patients with HCM in whom symptoms of congestive failure typically occur in the presence of normal or hyperdynamic systolic performance. Conversely, in the subgroup of patients experiencing congestive symptoms secondary to systolic dysfunction (i.e., end-stage HCM), therapeutic strategy is similar to that employed for heart failure in other diseases with impaired systolic function, including the use of diuretics, angiotensin-converting enzyme inhibitors, and digitalis; ultimately, heart transplantation should be considered in this subgroup of patients.

Prevention of Infective Endocarditis.

Bacterial endocarditis, a recognized complication of HCM, is virtually confined to patients with the obstructive form of the disease (and mitral valve systolic anterior motion) with a prevalence of about 0.5 percent. Vegetations most commonly involve the anterior mitral leaflet or septal endocardium at the site of mitral valve contact (likely a consequence of the high-velocity outflow jet) and less commonly the aortic valve. Atrial Fibrillation Atrial fibrillation is a particularly important arrhythmia in HCM, reportedly occurring in up to about 20 percent of patients followed longitudinally with this disease. Atrial fibrillation is associated with an increased risk for systemic thromboembolism, heart failure, and death.

Of note, HCM patients with atrial fibrillation usually show substantial left atrial enlargement but, paradoxically, usually only relatively mild left ventricular hypertrophy. Onset of atrial fibrillation may importantly impair the clinical course in HCM, probably because absence of the atrial systolic contribution to ventricular filling is critical to cardiac function in patients with such poorly compliant ventricles. In many patients, however, chronic atrial fibrillation appears to be reasonably well tolerated as long as ventricular rate is controlled. Beta-adrenergic blocking agents or verapamil are usually efficacious in controlling heart rate in patients with chronic atrial fibrillation. Recurrent atrial fibrillation is managed by restoring sinus rhythm with electrical cardioversion, if necessary, or alternatively by drugs-with amiodarone probably the most effective antiarrhythmic agent for the prevention of recurrent atrial fibrillation. Because of the risk of peripheral embolism and stroke, anticoagulant therapy should be administered (and continued indefinitely) in most patients once atrial fibrillation has been documented.

Surgical treatment

Operation is regarded as the standard treatment for those HCM patients with obstruction to left ventricular outflow under basal conditions (gradient 50 mmHg), and severe drug-refractory symptoms.Therefore surgery is performed to relieve incapacitating symptoms and subaortic obstruction by normalizing the markedly increased systolic intraventricular pressures. General agreement is lacking, however, as

to whether symptomatic patients with marked outflow gradients-which are present solely or predominantly under provokable conditions such as exercise or with maneuvers in the catheterization laboratory (e.g., isoproterenol infusion, amyl nitrite inhalation, or Valsalva maneuver)-are appropriate operative candidates. Ventricular septal myotomy-myectomy (Morrow operation) is the surgical procedure of choice; a small amount of muscle is removed from the basal anterior septum (usually about 2 to 6 g) through an aortotomy. However, mitral valve replacement has been employed in selected patients when the operative site for muscular resection in the basal anterior portion of the septum is relatively thin (i.e., 18 mm) or when the distribution of septal hypertrophy is atypical

Occasionally, patients have outflow obstruction from a mechanism other than mitral valve systolic anterior motion. For example, anomalous papillary muscle insertion directly into anterior mitral leaflet without the interposition of the chordae tendineae producing muscular midventricular obstruction should always be contemplated prior to surgery, since the operative strategy may require a more extensive myectomy or possibly mitral valve replacement. Suture plication of the anterior mitral leaflet (in combination with myotomy-myectomy) has also been introduced in patients judged to have a greatly enlarged mitral valve, so as to reduce the likelihood that mitral valve systolic anterior motion will persist postoperatively. Intraoperative 2D echocardiography is an important guide to mapping the distribution and magnitude of septal hypertrophy and determining how the muscle resection should be tailored to the distribution of septal hypertrophy in the individual patient to achieve the desired hemodynamic result and avoid iatrogenic complications such as ventricular septal defect. Transesophageal echocardiography may also be useful in assessing morphologic and functional abnormalities during surgery, particularly of the mitral valve. Results from a number of North American and European centers employing septal myotomymyectomy over the past 40 years, in about 2000 patients, have demonstrated salutary hemodynamic as well as symptomatic effects. Operative mortality at the most experienced centers has improved over the past several years and is presently less than 1 to 2 percent. Older patients with associated cardiac lesions, such as coronary artery

disease requiring bypass grafting, may be at greater operative risk. Several important effects of operation have been defined in patients with HCM. First, in more than 90 percent of patients, myotomy-myectomy (or mitral valve replacement) abolishes or substantially reduces the basal subaortic gradient and mitral valve systolic anterior motion without importantly compromising left ventricular function; this consequence of surgery appears to be permanent, with no evidence that the gradient recurs post-operatively or that spontaneous growth of septal musculature recurs in the area of the resection. Second, the reduction in left ventricular systolic pressure is associated with a significant and persistent improvement in symptoms and exercise capacity in 70 percent of patients 5 years after operation as well as with a demonstrable increase in myocardial oxygen consumption and improvement in lactate metabolism. In a minority of patients, even after surgical relief of outflow obstruction, symptoms may nevertheless return (presumably due to persistently impaired left ventricular filling or ischemia, atrial fibrillation, or conduction abnormalities), and premature cardiac death can still ensue many years postoperatively. Traditionally, surgery has not been recommended for asymptomatic (or mildly symptomatic) patients with outflow obstruction since, in addition to the operative risk, definitive evidence is lacking that prophylactic relief of outflow obstruction prolongs survival, diminishes risk for sudden death, or mediates the development of symptoms.

Alternatives to surgery

Dual-Chamber Pacing Although the septal myotomy-myectomy operation is the first therapeutic option for severely limited patients without obstructive HCM, perhaps the major limitation of surgery is the restricted availability of surgeons with the necessary experience to readily afford patients with low operative mortality and a high expectation of hemodynamic and symptomatic success with myotomymyectomy. In addition, some patients are not ideal surgical candidates, either due to advanced age, insufficient personal motivation, or a limiting medical disability unrelated to HCM. Therefore it is a reasonable aspiration to develop and pursue alternatives to operation for this small but important subgroup of patients. However, proper patient selection for such procedures is a paramount consideration. Over the past sev-

eral years there has been some interest in the application of permanent dualchamber pacing, as an alternative to operative intervention, for severely symptomatic patients with obstructive HCM who are refractory to drug therapy. Observational and uncontrolled studies have reported pacing to be associated with reduction in outflow gradient and amelioration of symptoms in many patients over relatively short time periods. However, this reported symptomatic benefit has not been consistently accompanied by improved exercise tolerance documented by objective parameters (e.g., treadmill exercise duration and measured oxygen consumption). Randomized, double-blind, crossover pacing studies have shown that the subjectively perceived symptomatic improvement reported by patients is largely due to a placebo effect. In addition, the effect of pacing on outflow gradient and symptoms is variable and reduction in obstruction is often much more modest than that achieved with surgery. Other laboratory catheterization studies report dual-chamber pacing to have deleterious effects on left ventricular systolic and diastolic function. For these reasons and because the underlying HCM disease process and the risk for sudden death do not appear to be altered by permanent dualchamber pacing, this potential treatment modality cannot be regarded as a primary treatment for the diverse clinical and functional spectrum of HCM. However, there may well be a therapeutic role for certain subsets of patients with this disease.

Alcohol Septal Ablation

A second, recently introduced potential alternative to surgery is alcohol septal ablation, in which about 2 mL of alcohol is injected directly into the first septal perforator coronary artery for the purpose of producing an MI, septal thinning, and reduced mitral valve systolic anterior motion. This procedure is intended to mimic the morphologic and functional consequences of ventricular septal myotomy-myectomy. At present the septal ablation technique is associated with a risk similar to that of surgery but is capable of producing a substantial reduction in the basal gradient. As yet, there is little objective substantiation for the improvement in symptoms reported by many patients over short-term follow-up. This is of particular importance in assessing symptomatic and functional changes for a disease in which pathophysiology is com-

plex and symptoms are variable, often difficult to assess by history, and subject to a placebo effect. As is the case with pacing, alcohol ablation should not be regarded as a primary treatment for the disease or one capable of reducing the risk of sudden death. Indeed, there is concern that this intervention could paradoxically increase the future long-term risk for life-threatening ventricular tachyarrhythmias and sudden death-a risk directly attributable to the intramyocardial scar produced by alcohol ablation (which is not present following myotomy-myectomy) in a patient population that already harbors an arrhythmogenic substrate and often a particularly long period of risk.

Dilated cardiomyopathy

DCM is defined by the presence of left ventricular dilatation and left ventricular systolic dysfunction in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment. Right ventricular dilation and dysfunction may be present but are not necessary for the diagnosis.

The prevalence of DCM in the general population is unknown, but it clearly varies with age and geography. At least 25% of patients in Western populations have evidence for familial disease with predominantly autosomal dominant inheritance. Familial disease should also be suspected when there is a family history of premature cardiac death or conduction system disease or skeletal myopathy. Autosomal dominant forms of the disease are caused by mutations in cytoskeletal, sarcomeric protein/Z-band, nuclear membrane and intercalated disc protein genes. X-linked diseases associated with DCM include muscular dystrophies (e.g. Becker and Duchenne) and X-linked DCM. DCM may also occur in patients with mitochondrial cytopathies and inherited metabolic disorders (e.g. haemochromatosis). Examples of acquired causes of DCM include nutritional deficiencies, endocrine dysfunction, and the administration of cardiotoxic drugs

DCM can occur at a late stage following cardiac infection and inflammation. In contrast to active or fulminant myocarditis, which is by definition, an acute inflammatory disorder of the heart, often with preserved left ventricular size, inflammatory DCM is defined by the presence of chronic inflammatory cells in association with left

ventricular dilatation and reduced ejection fraction; histology and/or immunocytochemistry are, therefore, necessary for the diagnosis. A proportion of individuals with inflammatory DCM have persistence of viral proteins in the myocardium; viral persistence can also be observed in the absence of inflammation.

Etiologic Classification of DCM

1. Ischemic
2. Valvular
3. Hypertensive
4. Inflammatory
5. Metabolic
6. General Systemic Diseases
7. Muscular Dystrophies
8. Neuromuscular
9. Sensitivity and Toxic Reactions
10. Peripartum

The term mildly dilated congestive cardiomyopathy (MDCM) has been used to describe patients with advanced heart failure and severe left ventricular systolic dysfunction occurring with neither restrictive haemodynamics nor significant left ventricular dilatation (less than 10–15% above normal range). A family history of DCM is present in over 50% of patients. Although some pathological findings differ, the clinical picture and prognosis of MDCM are very similar to those of typical DCM.

At the moment it has identified 5 Phenotypes of DCM:

- DCM with muscular dystrophy
- Juvenile DCM in male relatives no MD
- DCM with segmental wall motion of LV
- DCM with conduction defects
- DCM with sensorineural hearing loss

Clinical presentation

The first presentation of IDC may be with systemic embolism or sudden death, but patients more typically present with signs and symptoms of pulmonary congestion and/or low cardiac output, often on a background of exertional symptoms and fatigue for many months or years before their diagnosis. Intercurrent illness or the development of arrhythmia, in particular atrial fibrillation, may precipitate acute decompensation in such individuals. Increasingly, IDC is diagnosed incidentally in asymptomatic

individuals during routine medical screening or family evaluation of patients with established diagnosis.

Electrocardiography

The ECG in patients with IDC may be remarkably normal, but abnormalities ranging from isolated T wave changes to septal Q waves in patients with extensive left ventricular fibrosis, prolongation of atrioventricular (AV) conduction, and bundle branch block may be observed. Sinus tachycardia and supraventricular arrhythmias are common, in particular atrial fibrillation. Approximately 20-30% of patients have non-sustained ventricular tachycardia and a small number present with sustained ventricular tachycardia.

Echocardiography

An echocardiogram is essential for the diagnosis of IDC. In patients with poor echo windows other imaging modalities such as radionuclide scans and magnetic resonance may be useful. Recently suggested echocardiographic criteria for IDC are shown in the adjacent box. When making the diagnosis of IDC it is important to take into account sex and body size. The most widely applied criteria in family studies are based on the Henry formulae, with a left ventricular cavity dimension of >112% of predicted normal values used to define left ventricular enlargement and a shortening fraction of <25% defining abnormal systolic function. These criteria have some limitations, in particular the use of only short axis dimensions and a relatively low specificity in young patients, but they are practical and reproducible.

Diagnostic criteria for IDC

- Ejection fraction <0.45 and/or a fractional shortening of <25%, and a left ventricular end diastolic dimension of >112% predicted value corrected for age and body surface area

Exclusion criteria for IDC:

- Absence of systemic hypertension (>160/100 mmHg)
- Coronary artery disease (>50% in one or more major branches)
- Chronic excess alcohol (>40 g/day female, >80 g/day male for more than five years after six month abstinence
- Systemic disease known to cause IDC

- Pericardial diseases
- Congenital heart disease
- Cor pulmonale

Exercise testing

Symptom limited upright exercise testing is of considerable value when assessing functional limitation in patients with IDC, particularly when combined with respiratory gas analysis. Metabolic exercise testing provides an objective measure of exercise capacity, facilitates assessment of disease progression, helps assess prognosis, and is useful in selecting patients for cardiac transplantation. Metabolic exercise testing may also provide diagnostic information in patients with left ventricular impairment caused by primary metabolic abnormalities such as mitochondrial disease, by detecting severe acidaemia.

Viral serology

In children and adults with acute myocarditis, viral culture and serology may be useful in establishing a diagnosis of viral myocarditis by demonstrating rising titres of neutralising antibodies, or virus specific IgM class antibodies to enteroviruses indicative of recent infection. In adults with IDC the relation between viral infection and disease is more uncertain. Many studies purporting to demonstrate a positive association between viral infection and IDC are very small, and have failed to control for cross contamination with laboratory controls. The source of disease and control populations is also important as the most commonly implicated enterovirus, coxsackie B, is ubiquitous in most communities and causes small subclinical epidemics. At present, the detection of viral antibodies in patients with stable chronic IDC has little impact on management, but viral studies may become more important in the future if current trials suggest a role for immunosuppressive/modulatory treatments in IDC.

Endomyocardial biopsy

Although endomyocardial biopsy can be used to diagnose a wide range of myocardial diseases, most are rare causes of IDC and can often be diagnosed by other means. Even the detection of an inflammatory cardiomyopathy is of limited use, given the uncertainties and inconsistencies surrounding its diagnosis using conventional light microscope criteria. Endomyocardial biopsy may be of use in selected pa-

tientsfor example, those with suspected cardiac haemochromatosis and other infiltrative or malignant diseasesbut in general it should be confined to carefully conducted clinical trials. A number of immunohistological studies have already demonstrated increased numbers of T cells and increased expression of endothelial and interstitial MHC (major histocompatibility complex) antigens and cell adhesion molecules in IDC hearts, consistent with previous observations of immune activity in IDC. As our understanding of the clinical significance of immunohistochemical markers improves, it is likely that endomyocardial biopsy will become more important in guiding immunomodulatory treatment.

Treatment.

Specific treatments are not available for most patients with IDC. Therefore, the primary aims of treatment are to control symptoms and to prevent disease progression and complications such as progressive heart failure, sudden death, and thromboembolism. Diuretics remain central to the management of congestive symptoms, but they should not be used as monotherapy as they exacerbate neurohumoral activation and may contribute to disease progression unless administered concomitantly with neurohumoral antagonists. ACE inhibitors, angiotensin-2 receptor antagonists, bête-adrenoblockers, spironolactone, eplerenone are recommended.

Novel potential pharmacological treatments

Natriuretic peptides. Atrial natriuretic peptide (ANP) is released from atrial myocytes in response to stretch, and induces diuresis, naturesis, vasodilatation, and suppression of the renin-angiotensin system. Circulating concentrations of ANP are increased in congestive cardiac failure and correlate with NYHA functional class and prognosis. Both ANP and brain natriuretic peptide are potent vasodilators and diuretics, but clinical trials have shown that tolerance frequently develops during intravenous ANP administration. This problem may be overcome by the development of drugs that inhibit neutral endopeptidase, the enzyme responsible for breakdown of natriuretic peptides.

Cytokine antagonists. Tumour necrosis factor (TNF) or cachectin is a proinflammatory cytokine released from activated macrophages, T cells, and failing myo-

cardium. It circulates at high concentrations in patients with congestive cardiac failure and in experimental models causes pulmonary oedema, cardiomyopathy, cachexia, and reduced peripheral blood flow. Raised plasma concentrations of TNF and other proinflammatory cytokines such as interleukin 6 have been interpreted as epiphenomena of heart failure, but it is increasingly thought that cytokines may promote heart failure progression. Endothelins are another family of locally acting peptides with profound vasoconstrictor effects found in high plasma concentrations in patients with heart failure. Experimental data using the endothelin antagonist bosentan have shown favourable haemodynamic effects in heart failure patients, although the drug is associated with dose related hepatic dysfunction, prompting the investigation of more selective endothelin antagonists.

Anticoagulants. Although the annual risk of thromboembolism in patients with IDC is relatively low, many patients are young and are exposed to an appreciable cumulative risk of systemic embolisation. At present there are no trial data to guide anticoagulant treatment in IDC, but warfarin is advised in patients with a history of thromboembolism or evidence of intracardiac thrombus. Patients with more than moderate ventricular dilatation and moderate to severe systolic dysfunction should also be advised to take warfarin.

Non-pharmacological treatment of advanced heart failure

Heterotopic heart transplantation is still the cornerstone of advanced heart failure management in patients with intractable heart failure symptoms and end stage disease. However, transplantation remains limited by the scarcity of suitable organs and the development of graft vasculopathy. In response to this dilemma several novel approaches are being evaluated.

Partial left ventriculectomy ("Batista" procedure) is based on the hypothesis that as wall tension is related to left ventricular diameter (Laplace's law), reducing the left ventricular size by excision of a portion of its circumference should reduce wall stress and improve ventricular haemodynamics. In the best centres results from this intervention were initially remarkably good given the nature of the procedure. It is clear, however, that even with careful patient selection many patients survive only

with the benefit of left ventricular assist devices and subsequent transplantation. Late sudden death is also described in a proportion of survivors. The difficulties associated with patient selection and subsequent postoperative care suggest that, at best, this form of treatment will be confined to a very small number of experienced centres.

Left ventricular assist devices (LVADs) have recently received approval from the US Food and Drug Administration for use in patients with end stage heart failure as a bridge to cardiac transplantation. Experience in patients with IDC suggests that LVAD treatment can result in an apparent improvement in left ventricular function that may persist when the device is removed. However, there are as yet no reliable markers that distinguish the minority of patients that sustain useful recovery from the majority that deteriorate following explantation of the device. Technical advances in LVAD design now raise the possibility of using these devices as an alternative to transplantation in patients who are not transplant candidates. This mode of treatment is currently being evaluated in the REMATCH study, which if positive will have substantial clinical and resource implications for centres managing advanced heart failure.

Multisite ventricular pacing

Many patients with advanced IDC have abnormal left ventricular activation that in turn results in prolonged and incoordinate ventricular relaxation. In some patients ventricular conduction delay is also associated with prolongation of atrioventricular conduction, resulting in a loss of atrioventricular synchrony and a predisposition to prolonged functional mitral regurgitation. Dual chamber pacing has been advocated as a method for restoring AV synchrony and improving left ventricular coordination in patients with severe congestive heart failure. Although initially favourable haemodynamic results using conventional right ventricular pacing were not confirmed by later studies, there has been a more consistent response in studies that have used biventricular pacing, the outcome depending critically on the native QRS duration and the paced AV delay. Patients should be considered for biventricular pacing if they have QRS duration greater than 150 ms, PR interval prolongation, and symptoms refractory to conventional medical treatment.

Immunomodulation/immunosuppression

While there is considerable evidence to suggest that autoimmunity plays a significant role in the pathophysiology of IDC, there has been little evidence to suggest that immunosuppressive treatment is of any benefit. This lack of response is, perhaps, not that surprising given the limitations of criteria used to select patients for treatment in immunosuppresive studies and the heterogeneity of the underlying aetiology of the condition. Immunosuppression is also a rather indiscriminate weapon, as it may suppress potentially beneficial immune responses such as neutralising antibody production in patients with chronic viral myocarditis. New approaches to the diagnosis of chronic myocarditis and the treatment of inflammatory cardiomyopathy should improve this situation. There are already interesting preliminary data suggesting that high dose immunoglobulin and immunoadsorption may result in short term improvement in left ventricular performance in patients with dilated and peripartum cardiomyopathy.

Peripartum cardiomyopathy (PPCM) is a form of DCM that presents with signs of cardiac failure during the last month of pregnancy or within 5 months of delivery. Suggested aetiological factors in PPCM include myocarditis, autoimmunity caused by chimerism of haematopoetic lineage cells from the foetus to the mother and the haemodynamic stress of pregnancy. PPCM can occur at any age but is more common in women older than 30 years. It affects women of all ethnic groups, is almost equally associated with first/second and multiple pregnancies and is strongly associated with gestational hypertension, twin pregnancy and tocolytic therapy.

In conclusion, IDC is a disease of diverse causes and pathophysiology. Among the many challenges facing clinicians treating patients with the disorder are the detection of early disease, the identification of the predominant mechanism of left ventricular dysfunction, and the development of treatments that target the initiating mechanism of disease. Nevertheless, there have been major advances in our understanding of the genetic and immunological basis of IDC, and recent advances in the pharmacotherapy of heart failure have substantially improved the outlook for many patients. The rapid pace of current research and the development of new treatments for the management of both early and late disease augur well for the future.

Restrictive cardiomyopathy

The World Health Organization (WHO) and World Heart Foundation define cardiomyopathies as heart muscle diseases of unknown etiology and classify them according to hemodynamic and pathophysiologic criteria. Although this definition differentiates primary cardiomyopathies from other pathologic processes that disturb myocardial function-such as ischemic, hypertensive, valvular, and congenital heart diseases-the WHO classification, despite recent modifications, remains controversial. The clinicopathologic classification scheme initially proposed by Goodwin is similar and includes dilated or congestive, hypertrophic, and restrictive forms. *Restrictive cardiomyopathy* refers to either an idiopathic or systemic myocardial disorder characterized by restrictive filling, normal or reduced left ventricular (LV) and right ventricular (RV) volumes, and normal or nearly normal systolic (LV and RV) function. Thus, the clinical and hemodynamic picture thus simulates constrictive pericarditis and is characterized by elevated venous pressure with prominent X and Y descents, a small or normal sized LV, and pulmonary congestion.

Restrictive left ventricular physiology is characterized by a pattern of ventricular filling in which increased stiffness of the myocardium causes ventricular pressure to rise precipitously with only small increases in volume. Restrictive cardiomyopathy (RCM) has always been difficult to define because restrictive ventricular physiology occurs in a wide range of different pathologies. In this classification system, restrictive cardiomyopathies are defined as restrictive ventricular physiology in the presence of normal or reduced diastolic volumes (of one or both ventricles), normal or reduced systolic volumes, and normal ventricular wall thickness. Historically, systolic function was said to be preserved in RCM, but is rare for contractility to be truly normal. Restrictive physiology can occur in patients with end-stage hypertrophic and DCM but we do not believe that these entities require their own sub-category.

Restrictive cardiomyopathy may be noninfiltrative or infiltrative and occurs with or without obliteration; infiltration may be interstitial (e.g., amyloid, sarcoid) or cellular (e.g., hemochromatosis). Restrictive cardiomyopathy has assumed importance in clinical cardiology for several reasons. First, these myocardial disorders epi-

tomize diastolic heart failure; thus, abnormal ventricular diastolic compliance and impaired ventricular filling constitute their central pathophysiologic components and congestion and elevated diastolic pressure are their major clinical and hemodynamic manifestations. Second, the hemodynamic and clinical manifestations may mimic those produced by constrictive pericarditis, which, in contrast to restrictive cardiomyopathy, is a surgically curable disorder. Accordingly, its lack of recognition may have dire consequences. Third, restrictive cardiomyopathy may present with interventricular conduction delays, heart block, or skeletal muscle disease, often making the diagnosis difficult. Fourth, diagnostic criteria for restriction are not universally accepted, and the morphologic spectrum overlaps with hypertrophic cardiomyopathy challenges our traditional concepts of classification.3 Finally, a comprehensive echo Doppler assessment has become an important, noninvasive means of detecting the pathophysiology, morphology, and prognosis of the restrictive cardiomyopathies

The exact prevalence of RCM is unknown but it is probably the least common type of cardiomyopathy. RCM may be idiopathic, familial, or result from various systemic disorders, in particular, amyloidosis, sarcoidosis, carcinoid heart disease, scleroderma and anthracycline toxicity. Familial RCM is often characterized by autosomal dominant inheritance, which in some families is caused by mutations in the troponin I gene; in others, familial RCM is associated with conduction defects, caused by mutations in the desmin gene (usually associated with skeletal myopathy). Rarely, familial disease can be associated with autosomal recessive inheritance (such as haemochromatosis caused by mutations in the HFE gene, or glycogen storage disease), or with X-linked inheritance (such as Anderson–Fabry disease).

Restrictive ventricular physiology can also be caused by endocardial pathology (fibrosis, fibroelastosis, and thrombosis) that impairs diastolic function. These disorders can be sub-classified according to the presence of eosinophilia into *endomyocardial diseases with hypereosinophilia* [now grouped under hypereosinophilic syndromes (HES)] and *endomyocardial disease without hypereosinophilia* [e.g. endomyocardial fibrosis (EMF)]. Parasitic infection, drugs such as methysergide, and inflammatory and nutritional factors have been implicated in acquired forms of EMF.

Fibrous endocardial lesions of the right and/or left ventricular inflow tract cause incompetence of the atrioventricular valves. Isolated left ventricular involvement results in pulmonary congestion and predominant right ventricular involvement leads to right heart failure.

EMF should be distinguished from endocardial fibroelastosis, occurring in early childhood, characterized by thickening of mural endocardium mainly of the left ventricle, secondary to proliferation of fibrotic and elastic tissues. It is often associated with congenital malformations and some data suggest an aetiologic role for viral infection, in particular, mumps virus.

Clinical Features of Restrictive Cardiomyopathy

Involvement of the myocardium (or endomyocardium), and ventricular obliteration, may occur either in isolation or in the setting of systemic or iatrogenic disease (Table 4.1).

Table 4.1

Classification of the Restrictive Cardiomyopathies

Type of cardiomyopathu	Performances
Myocardial	Noninfiltrative cardiomyopathies
	• Idiopathic • Familial • Pseudoxanthoma elasticum • Scleroderma
	Infiltrative cardiomyopathies
	• Amyloidosis • Sarcoidosis • Gaucher's disease
	Storage disease
	• Hemochromatosis • Fabry's disease • Glycogen storage diseases
Endomyocardial	Obliterative
	• Endomyocardial fibrosis • Hypereosinophilic syndrome
	Nonobliterative
	• Carcinoid • Malignant infiltration • Iatrogenic (radiation, drugs)

Thus, in the strictest sense, restrictive cardiomyopathy is not necessarily a primary disease of heart muscle. Irrespective of the etiology, terminology, or the nature of myocardial process, the ventricles are small (generally <110 mL/m2), and stiff, restricting ventricular filling. Despite normal (or near normal) systolic function, ventricular diastolic, jugular, and pulmonary venous pressures are increased. Typically, LV filling pressures exceed RV filling pressures by more than 5 mmHg, but equalization of the diastolic pressures and a "square root" dip and plateau of early diastolic pressures of the RV and LV may be seen if the compliances of these chambers are similarly affected. Importantly, the hemodynamics of constrictive pericarditis may be simulated. Moreover, elevated atrial pressures produce symptoms of systemic and pulmonary venous congestion (dyspnea, orthopnea, edema, abdominal discomfort), and relatively underfilled ventricles are responsible for reduced cardiac output and fatigue. In patients with restrictive cardiomyopathy as part of a systemic disorder, cardiac symptoms may dominate or overshadow symptoms referable to other organ systems. Patients with constrictive cardiomyopathy generally have lower RV systolic pressures (<40 mmHg) and an RV end-diastolic pressure greater than one-third of the pressure RV systolic pressure as opposed to patients with restrictive cardiomyopathy but these differences are far from absolute.

Physical Findings

Physical examination reflects the elevated systemic and pulmonary venous pressure. Striking elevation of the jugular venous pulse and prominent X and especially Y descents are characteristic. A *diastolic* arterial pulse, owing to a reduced stroke volume and tachycardia, may be seen in severe cases. The apical impulse is not displaced and systolic murmurs of atrioventricular regurgitation and filling sounds marking the abrupt cessation of rapid early diastolic filling may be present. Electrocardiographic (ECG) abnormalities such as abnormal voltage, atrial and ventricular arrhythmias, and conduction disturbances are frequent; when restrictive cardiomyopathy is due to amyloid infiltration, low voltage is usual. The chest radiograph usually reveals normal-sized ventricles, although atrial enlargement and pericardial effusion may produce an enlarged cardiac silhouette. Pleural effusions and signs of

pulmonary congestion may also be present. Echocardiographic findings are nonspecific but in many cases are useful to exculpate other, more common causes of heart failure.

Differentiation from constrictive pericarditis

Although several clinical, imaging, and hemodynamic features are helpful in distinguishing restrictive cardiomyopathy from constrictive pericarditis (Table 4.2), considerable overlap and diagnostic confusion exist.

Table 4.2

Clinical and Hemodynamic Features That Help Distinguish Restrictive Cardiomyopathy from Constrictive Pericarditis

	Restrictive Cardiomyopathy	Constrictive Pericarditis
History	Systemic disease that involves the myocardium, multiple myeloma, amyloidosis, cardiac transplant	Acute pericarditis, cardiac surgery, radiation therapy, chest trauma, systemic disease involving the pericardium
Chest radiograph	• Absence of calcification • Massive atrial enlargement	• Helpful when calcification persists • Moderate atrial enlargement
ECG	Bundle branch blocks, AV block	Abnormal repolarization
Visualisation procedures (CT/MRI)	Normal pericardium	Helpful if thickened (>4 mm) pericardium
Hemodynamics	• Helpful if unequal diastolic pressures • Concordant effect of respiration on diastolic pressures	Diastolic equilibration Dip and plateau
Biopsy	Fibrosis, hypertrophy, infiltration	Normal

The pathophysiologic basis for this distinction includes:

- transmission of intrathoracic pressure to the ventricles (limited by the stiff pericardium in constrictive pericarditis but not in restrictive cardiomyopathy);
- the principal determinant of the diastolic ventricular pressure-volume relation (ventricular versus pericardial compliance in restrictive cardiomyopathy as compared to constrictive pericarditis, itself);

- involvement of the ventricular septum in restrictive cardiomyopathy versus the capacity for ventricular interdependence in constrictive pericarditis.

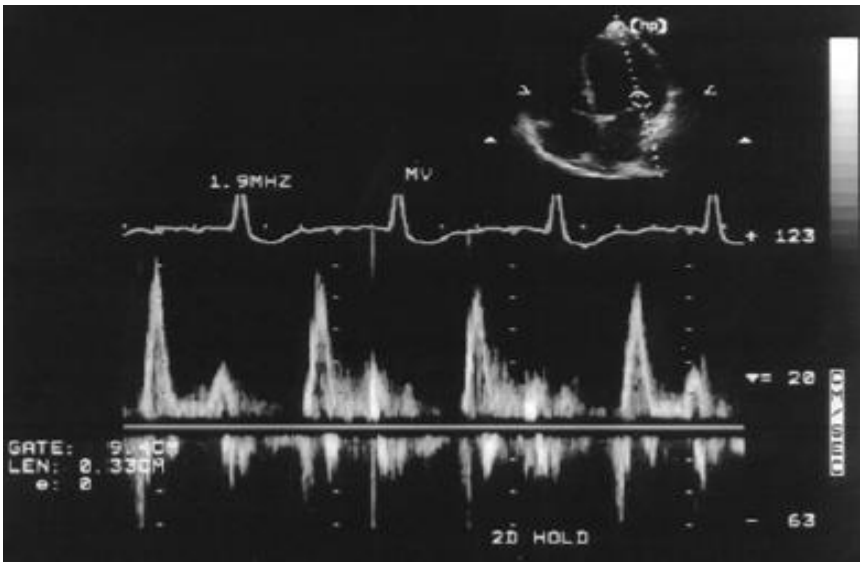
Recently, Doppler techniques (spectral Doppler, color M-mode, and Doppler tissue imaging) have assumed an important role in characterizing the nature of transvalvular filling and in clinically distinguishing between constrictive pericarditis and restrictive cardiomyopathy. In the *normal subject*, the early filling wave (E) of mitral flow is greater than the late, atrial systolic wave (A), and neither change significantly with respiration. In contrast, the E and A velocities of tricuspid valve flow increase slightly with inspiration. The deceleration time of the LV early diastolic wave ranges from 150 to 240 ms, and the LV isovolumic relaxation time ranges from 70 to 110 ms. Pulmonary venous flow is generally biphasic, with a dominant wave during systole (S) and a smaller wave during diastole (D); respiratory changes are minimal and atrial systolic reversals are generally small. Hepatic vein flow consists of a larger S and smaller D wave with small reversals (Vr and Ar) after each wave, respectively. With expiration, S and D waves decrease and Vr and Ar increase. Doppler tissue imaging (DTI) shows a prominent longitudinal axis velocity in early diastole (Ea >8 cm/s) and a smaller velocity after atrial contraction (Aa). The slope of early diastolic LV filling on color M-mode (Vp) is >45 cm/s.

In the patient with *restrictive cardiomyopathy*, mitral valve flow shows an increased E/A ratio (>2) with a short (<150 ms) deceleration time and a short (<70 ms) isovolumic relaxation time (a "restrictive" pattern of filling) without respiratory variation (Figure 4.6).

The tricuspid valve flow shows an increased E/A ratio without respiratory variation, a shortened deceleration time, and a short isovolumic relaxation time that shortens further with inspiration. The S/D ratio of pulmonary venous flow is <1, atrial reversals are increased, and there is little respiratory variation. The S/D ratio of hepatic venous flow is <1 and prominent reversals are seen during inspiration. Doppler tissue imaging shows a striking decrease in Ea (<8 cm/s) and the propagation velocity on color M-mode is <45 cm/s.

Figure 4.6

Doppler record of mitral inflow velocity from a patient with idiopathic restrictive cardiomyopathy.



Note the dominant early diastolic wave

In *constrictive pericarditis*, mitral and tricuspid valve flows are also "restrictive," but unlike those in restrictive cardiomyopathy, they display marked respiratory variation. The isovolumic relaxation time shortens during expiration. The S/D of pulmonary venous flow is <1, with increased velocities (especially diastolic) in expiration, resulting in a further decrease in the S/D ratio. In contrast to restrictive cardiomyopathy, hepatic venous flow reversals occur in expiration, early diastolic tissue velocities (Ea) are normal on DTI, and the transmitral propagation velocity is >45 cm/s. Despite the considerable interest and potential clinical value in the ability to discriminate restrictive cardiomyopathy from constrictive pericarditis, there is no uniform agreement regarding the characteristic features of the Doppler indices, especially those of venous flows. Moreover, rigorous studies of the sensitivity and specificity of these Doppler findings are lacking and relatively few patients have been examined. Thus, the diagnostic certainty is related to the number of "pathognomonic" findings in concert with clinical information and additional imaging studies. One report suggested that radionuclide ventriculographic indices of LV diastolic function could differentiate constrictive pericarditis and restrictive cardiomyopathy.

However, measurements of LV filling-such as the peak filling rate, time to peak filling, and various filling fractions-require careful attention to technical detail. The need for stable heart rates, the lack of venous flows, and the inability to observe the influence of respiration on cardiac blood flows are important limitations of the radionuclide ventriculographic technique. Magnetic resonance imaging (MRI) and computed tomography (CT) are useful for accurately assessing pericardial thickness; a pericardium >4.0 mm thick can distinguish the two entities Recent preliminary data suggest that constrictive pericarditis is associated with severe autonomic dysfunction that involves all segments of the autonomic nervous system, whereas in restrictive cardiomyopathy the autonomic dysfunction is localized to the parasympathetic efferent pathway. Invasive hemodynamics may be helpful, and occasionally a histologic diagnosis is necessary.

It is important to remember that clinical and laboratory testing, including imaging and pathologic studies, may produce results consistent with mixed constrictive pericarditis and restrictive cardiomyopathy; indeed, the two entities may coexist [for example, after mediastinal irradiation or after coronary artery bypass grafting (CABG)]. In these cases, a decision to treat conservatively or surgically explore a patient requires experienced clinical judgment.

Cardiac Catheterization

Most patients in whom restrictive cardiomyopathy is a serious consideration should undergo rightand left-sided heart catheterization to document the diagnosis, assess severity, and, in some patients, establish the etiology by means of endomyocardial biopsy. As in patients with constrictive pericarditis, extra care must be taken to obtain high-quality pressure recordings with appropriate gain and optimal damping conditions, and to attend to details such as the transducer height and system calibration. The venous pressure is elevated and the deep and rapid fall of the right atrial Y descent is striking. During inspiration, the descent of the V wave in the right atrium becomes deeper, steeper, and more pointed, whereas the other waves of the venous pulse and the mean atrial pressure do not vary throughout the respiratory cycle. The RV systolic pressure is often within the range of 35 to 45 mmHg, and the early por-

tion of diastole is characterized by a deep, sharp dip followed by a plateau, during which no further increase in RV pressure occurs. These hemo dynamic features are identical to those of constrictive pericarditis and may cause diagnostic confusion. There is usually only modest pulmonary hypertension and the pulmonary arterial diastolic pressure is a few millimeters higher than the pulmonary wedge pressure, which is often quite elevated. It is not uncommon for the pulmonary wedge and the right atrial pressures to be identical and to simulate further the hemodynamics of constrictive pericarditis; however, a higher LV than RV filling pressure strongly favors the diagnosis of restrictive cardiomyopathy rather than constrictive pericarditis. LV systolic pressure is normal, while the LV diastolic pressure tracing shows the same abnormalities as those of the RV Left ventriculography usually shows a normal ejection fraction and the absence of major regional wall motion abnormalities. Endomyocardial biopsy is an integral part of the workup of many patients with restrictive cardiomyopathy. When distinction from constrictive pericarditis is particularly difficult, the biopsy may furnish proof of myocardial disease and establish the cause of restrictive cardiomyopathy (e.g., amyloidosis), or (by virtue of unremarkable histology) suggest the need for surgical exploration, even in the absence of a thickened pericardium.

Treatment of Restrictive Cardiomyopathy (General Considerations)

The treatment of restrictive cardiomyopathy is empiric and directed toward the treatment of diastolic heart failure. Reduction in the elevated ventricular diastolic pressures produces substantial improvement in pulmonary and systemic congestion, but judicious use of diuretics is warranted in view of the steep pressure-volume relation of the ventricles and the need to maintain a relatively high filling pressure. Vasodilators may also jeopardize ventricular filling and should be used cautiously. Calcium channel blockers are used by some because of their beneficial effect in hypertrophic cardiomyopathies, but improvement in ventricular compliance with their use has not been demonstrated in restrictive cardiomyopathy.

Specific restrictive cardiomyopathic diseases

Myocardial Diseases

Noninfiltrative cardiomyopathies

Idiopathic and Familial Restrictive Cardiomyopathy

Recent data suggest that idiopathic restrictive cardiomyopathy may be an autosomal dominant disorder involving myocardium, conduction tissue, and skeletal muscle, with resultant restrictive ventricular filling and heart failure, AV block, and distal skeletal myopathy. Deposition of the intermediate filament desmin has been linked to this syndrome and may represent a distinct pathologic entity; accumulation of desmin immunoreactive material on heart biopsy may be confirmed ultrastructurally. Changes in collagen subtypes and matrix metalloproteinase activity may play an important role in the genesis of increased LV stiffness. Myocyte hypertrophy and fibrosis on endomyocardial biopsy characterize idiopathic restrictive cardiomyopathy, and the absence of myocyte disarray is an important pathologic distinction from hypertrophic cardiomyopathy. However, overlap syndromes characterized by physiologic evidence of restriction and myocyte hypertrophy but without myocyte disarray or LV hypertrophy on echocardiography are reported. Moreover, it was recently postulated that primary restrictive and hypertrophic cardiomyopathies may represent different phenotypic expressions of the same genetic disease. An echocardiographic feature distinguishing primary restrictive cardiomyopathy from cardiac amyloidosis (in addition to the associated clinical features) is the increased LV wall thickness in the latter. In both disorders (and restrictive cardiomyopathies in general), ventricular dimensions are normal or reduced, systolic function is variable, and atrial dimensions are increased.

Two-dimensional and Doppler echocardiography are reliable, noninvasive techniques for diagnosing primary restrictive cardiomyopathy. A dominant mitral early diastolic "E" velocity, an increased pulmonary venous atrial systolic "A" reversal velocity and duration, and shortened mitral deceleration time are present in both children and adults with primary restrictive cardiomyopathy. On CT or MRI scans, evidence of restrictive filling (e.g., right atrial and caval enlargement) are common in both restrictive cardiomyopathy and constrictive pericarditis. MRI may differentiate

primary restrictive cardiomyopathy from amyloidosis on the basis of tissue characterization.

Pseudoxanthoma Elasticum. Pseudoxanthoma elasticum is a rare, genetically heterogeneous disorder characterized by fragmentation and calcification of elastic fibers involving the skin, eyes, and gastrointestinal and cardiovascular systems. Although endocardial fibroelastosis uncommonly causes restrictive cardiomyopathy, coronary artery disease with premature death is a major problem in these patients.

A useful classification of the restrictive cardiopathies is shown in Table 1. This scheme is based upon the cardiac compartment predominantly involved (i.e., myocardial versus endomyocardial) and subdivides the myocardial diseases into the noninfiltrative, infiltrative, and storage and the endomyocardial diseases into obliterative (i.e., endomyocardial fibrosis and the hypereosinophilic syndrome), carcinoid, infiltrative, and iatrogenic.

Progressive Systmic Sclerosis. Myocardial fibrosis, which may have a patchy distribution and be present in both ventricles, is found in the majority of patients with scleroderma at autopsy. On echocardiography, LV wall thickening in the absence of hypertension and evidence of LV dysfunction may be seen, but heart failure due to either restrictive or dilated cardiomyopathy is rare. Pericardial involvement and electrocardiographic abnormalites (heart block, supraventricular and ventricular tachycardia, and pseudoinfarction patterns) are common. Pulmonary hypertension is a leading cause of morbidity and mortality in patients with scleroderma.

Infiltrative cardiomyopathies

Amyloidosis

Amyloidosis is a systemic disorder characterized by interstitial deposition of linear, rigid, nonbranching amyloid protein fibrils in multiple organs (e.g., heart, kidney, liver, nerve). Although there are several types of amyloidosis, cardiac involvement is most common in primary amyloidosis (AL type), which is caused by plasma cell production of immunoglobulin light chains; the latter occurs often in association with multiple myeloma. Multiple myeloma is also reported to cause diastolic heart failure in the absence of amyloidosis. Cardiac deposition of amyloid protein (protein

A, a nonimmunoglobin) mayalso occur in secondary amyloidosis due to chronic inflammation (such as tuberculosis or rheumatoid arthritis). Amyloidois may also be familial and is commonly present (especially at postmortem examination) in the elderly as senile amyloidosis. Mutations of the protein transthyretin (formerly prealbumin) are usually inherited as an autosomal dominant trait and produce peripheral and autonomic neuropathy in addition to cardiac disease; over 50 mutations have been described. Cardiac involvement occurs late in the disease and, although present in less than one-third of cases, it is responsible for over half of the deaths. A transthyretin mutation at isoleucine was recently reported as a cause of late-onset cardiac amyloidosis in African Americans.

Clinical features

Amyloid deposits may be interstitial and widespread, resulting in restrictive cardiomyopathy, or localized to (1) conduction tissue, resulting in heart block and ventricular arrhythmias (especially familial amyloid); (2) the cardiac valves, causing valvular regurgitation; (3) the pericardium, producing constriction; and (4) the coronary arteries, resulting in ischemia. Amyloid may be isolated to the subendocardium in senile amyloid and amyloid secondary to chronic disease. Deposition of amyloid and atrial natriuretic factor (ANF) in the atria is frequent in aged hearts. Despite sinus rhythm, atrial mechanical failure and thrombus formation may result due to electromechanical dissociation. Atrial and brain natriuretic peptide are expressed in ventricular myocytes in patients with cardiac amyloidosis. In some cases, the clinical picture is dominated by autonomic neuropathy (orthostatic hypotension, syncope, diarrhea, lack of sweating, and impotence) and nephropathy and cardiac involvement are unrecognized. Cardiac manifestations define a spectrum, often progressive through stages of severity, from the asymptomatic to biventricular failure.

Diagnostic/imaging studies

The cardiac silhouette on the chest radiograph may be normal or moderately enlarged. The ECG typically shows decreased voltage, a pseudoinfarction pattern, left axis deviation; arrhythmias and conduction disturbances may predominate the clinical course. The M-mode echocardiogram may reveal symmetrical wall thickness involv-

ing the right and left ventricles, a small or normal LV cavity, variable (but often depressed) systolic function, left atrial enlargement, and a small pericardial effusion. Digitized M-mode tracings may reveal decreased rates of systolic wall thickening and diastolic wall thinning and increased isovolumic relaxation time, especially in the early stages.

Two-dimensional echo findings include thickening of the ventricular myocardium, the interatrial septum and valves (especially the AV valves), enlarged papillary muscles, and dilated atria and inferior vena cava. LV wall thickness is an important prognostic variable; in one study, patients with biopsy-proven amyloidosis having a mean wall thickness 15 mm had a median survival of 0.4 years, whereas patients with a mean wall thickness 12 mm had a median survival of 2.4 years. Highly reflective echoes producing a granular or sparkling appearance and occurring in a patchy distribution are characteristic echocardiographic findings but are neither sensitive nor specific; concentric hypertrophy, as occurs in hypertension or aortic stenosis, may produce a uniformly speckled or echolucent appearance of the myocardium; and idiopathic hypertrophic cardiomyopathy may display a patchy, granular sparkling. Although they correlate with wall thickness, granular echoes may not be seen. Importantly, their recognition is subjective and is affected by ultrasound instrument settings. Thus, granular sparkling alone is an unreliable finding. The infiltrative pathology associated with amyloidosis may be detected by tissue characterization using MRI. Amyloid cardiomyopathy may exist despite the absence of echocardiographic evidence of infiltration.

Doppler studies may show the restrictive pattern of LV filling-i.e., a transmitral E/A ratio 2 without respiratory variation, transmitral diastolic deceleration time <150 ms, and an isovolumic relaxation time 70 ms. The RV filling pattern is often abnormal. The systolic-todiastolic pulmonary venous flow ratio is <1 and atrial reversals increase with inspiration in the pulmonary and hepatic veins. However, the *earliest sign* of amyloid cardiomyopathy is impaired LV relaxation, manifest by an E/A ratio <1, and increased isovolumic relaxation and transmitral diastolic deceleration times. The severity of combined systolic and diastolic abnormalities can be determined with

an echo Doppler index using isovolumic contraction and relaxation and ejection times. In addition, Doppler has shown utility in prognosis; a deceleration time <150 ms and an increased E/A transmitral ratio are strong predictors of cardiac death. Abnormalities of LV filling are also demonstrated with the LV time-activity curve from radionuclide ventriculography. Moreover, radionuclide imaging using technetium-^{99m} pyrophosphate or Indium-^{111} antimyosin may be useful in diagnosis. The variable clinical, diagnostic, and prognostic features reflect the location, nature, and extent of amyloid deposition and the temporal course of the disease. Serum and urine protein electrophoresis is diagnostic in most cases of primarily amyloidosis, but monoclonal protein is not secreted in 10 percent of cases. Endomyocardial biopsy of the RV (most helpful if an abdominal fat aspirate is negative) provides the diagnosis, establishes the histochemistry, and quantifies myocardial damage and atrophy.

Treatment of amyloidosis

The treatment of amyloidosis is unrewarding and symptomatic therapy is fraught with hazard; patients are sensitive to digoxin and calcium channel blockers, and hypotension with vasodilators and diuretics is a threat due to the steep LV pressure-volume relation. Immunosuppressive therapy with melphalan and prednisone is the established treatment regimen for primary (AL) amyloidosis. In a recent study, multiple alkylating agents failed to increase the response rate or survival time over this conventional regimen. Orthotopic cardiac transplantation is generally not recommended because of the systemic nature of amyloidosis and the possibility of recurrence in the transplant, but successful cases have been reported. Liver transplantation may be lifesaving in patients with familial amyloidosis, since the liver is the site of transthyretin production.

Sarcoidosis is a disorder of unknown etiology characterized by the presence of noncaseating granulomas that involve many organs (e.g., lung, skin, lymph nodes, liver, spleen). Granulomas involve the heart in sarcoidosis in as many as 25 percent of patients but are frequently subclinical. Nevertheless, in approximately half of the fatalities, cardiac involvement is responsible. Rarely, sarcoid is confined to the heart. The combination of extracardiac manifestations and cardiac abnormalities favors a

presumptive diagnosis of sarcoidosis without biopsy. Interstitial granulomatous inflammation initially produces diastolic dysfunction, but later, when the disease is more extensive, it may produce systolic (at times focal) abnormalities. Localized thinning and dilatation of the basilar LV resembling ischemic heart disease are characteristic. Restrictive cardiomyopathy is uncommon. However, sarcoid pulmonary involvement is frequent and produces echo and Doppler findings of pulmonary hypertension and right heart failure. High grade AV block, due to involvement of the conduction system, and ventricular arrhythmias are the principal manifestations and may result in sudden cardiac death; syncope is common. The ECG commonly demonstrates T-wave and conduction abnormalities. Pseudoinfarct patterns may appear with extensive myocardial involvement.

Echocardiographic findings include evidence of systolic and diastolic LV dysfunction, LV aneurysm formation, abnormal ventricular wall thickness, pericardial effusion, regional wall motion abnormalities in the basal septum with apical sparing, and evidence of cor pulmonale. Thallium ^{201} and gallium ^{67} have been used to indicate areas of myocardial involvement and serve to predict the response to corticosteroids. MRI may detect mass lesions due to sarcoid granuloma or scar. Endomyocardial biopsy is useful but may be falsely negative. An important entity in the differential diagnosis is giant-cell myocarditis, which is characterized by a more aggressive and fatal course than cardiac sarcoid. Treatment with prednisone is warranted in highly suspicious or proven cases because the cardiac granuloma may be sensitive. In patients at high risk for sudden cardiac death, an automatic implantable cardioverter defibrillator (AICD) may be appropriate, and cardiac transplantation is an appropriate consideration in some cases.

Gaucher's Disease is due to an inherited deficiency of the enzyme - glucocerebroside, which results in accumulation of cerebroside in the reticuloendothelial system, brain, and heart. Diffuse interstitial infiltration of the left ventricle occurs, with reduced LV wall compliance and cardiac output, but is often subclinical. LV and left-sided valvular thickening and pericardial effusion are seen on echo.

Storage diseases

Hemochromatosis

Primary hemochromatosis is an autosomal recessive iron-storage disease that involves the heart, pancreas, skin, liver, and gonads. Myocardial iron deposition in hemochromatosis, either primary or secondary (e.g., resulting from multiple transfusions, ineffective erythropoesis), usually produces dilated cardiomyopathy but may cause restrictive cardiomyopathy. Arrhythmia and conduction disturbances are common; indeed, congestive heart failure, conduction abnormalities, and supraventricular and ventricular arrhythmias occur in one-third of patients. Interstitial fibrosis is variable and unrelated to the extent of iron deposition, which occurs in the myocyte; secondarily, myocardial fibrosis may develop. Bronze diabetes and hepatic dysfunction, reflecting iron deposition in the skin, pancreas and liver are frequent associated manifestations. One report suggests that cardiac involvement progresses temporally from a small, concentrically hypertrophied LV with diastolic dysfunction to a dilated LV with systolic dysfunction. However, this sequence of events is not universally accepted, and systolic abnormalities may require provocation. Findings consistent with either dilated or restrictive cardiomyopathy may be seen; the presence of systolic dysfunction indicates a poor prognosis. Granular sparkling and atrial enlargement may be observed, but these are nonspecific signs. Quantitative ultrasonic analysis of integrated backscatter has been used experimentally to detect changes in the echo reflectivity of the myocardium due to iron deposition in thalassemia major. Computed tomography and magnetic resonance imaging may demonstrate subclinical cardiac involvement, and tissue characterization may be possible with MRI. Endomyocardial biopsy is confirmatory; in selected instances, it may be useful in excluding the diagnosis.

Repeated phlebotomy is recommended for primary hemochromatosis, and the chelating agent desferrioxamine is often beneficial in secondary hemochromatosis. Cardiac transplantation (with or without liver transplantation) may be considered in selected cases.

Fabry's Disease is an X-linked, genetically heterogeneous disorder of glycosphingolipid metabolism caused by lysosomal ceramide (α-galactosidase) deficiency

that leads to accumulation of glycolipid in the heart, skin, and kidneys. Glycolipid accumulation in the myocardium and vascular and valvular endothelium may present with either a restrictive, hypertrophic, or dilated cardiomyopathy, mitral regurgitation, ischemic heart disease, or aortic degeneration. Echocardiographic findings in restrictive cardiomyopathy mimic those seen in amyloid, and LV mass correlates with the severity of disease. Arterial hypertension, mitral valve prolapse, and heart failure are common clinical presentations. Definitive diagnosis may require endomyocardial biopsy.

Pompe's Disease (glycogen storage type II) is due to an inherited (autosomal recessive) metabolic abnormality due to acid maltase deficiency that causes massive amounts of glycogen deposition in the heart and skeletal muscles. A hypertrophied, hypokinetic LV in an infant with muscle hypotonia, hyperreflexia, and failure to thrive are characteristic findings. The echocardiographic manifestations may be indistinguishable from hypertrophic obstructive cardiomyopathy. The diagnosis can be made by absence of -1,4-glucosidase activity on skeletal muscle biopsy. Adults with glycogen storage type III disease (debranching enzyme deficiency) may have marked LVH on echocardiography.

Endomyocardial Diseases

Obliterative endomyocardial diseases

Endomyocardial Fibrosis and Hypereosinophilic Syndrome

Endomyocardial diseases that cause restrictive obliterative cardiomyopathies include endomyocardial fibrosis (EMF) and hypereosinophilic (Loeffler's) syndrome. The former accounts for 10 to 20 percent of deaths due to heart disease in equatorial Africa but is seen throughout the world. In contrast, Loeffler's endocarditis is seen mainly in countries with a temperate climate. Although it shares similar pathological features with EMF, it affects mainly men; is usually related to parasitic infections, leukemia, and immunologic reactions; and is characterized by intense eosinophila and thromboembolic phenomena. The two conditions may represent different forms of the same disease (Loeffler's endocarditis representing an early and EMF an advanced stage), but considerable differences exist. Moreover, the endemic variety EMF may

be related to high levels of cerium and low levels of magnesium; it may be pathophysiologically distinct from Loeffler's.

Hypereosinophilic syndrome

Cardiac involvement occurs in the majority of patients with the hypereosinophilic syndrome (unexplained eosinophilia exceeding 1500 eosinophils/mm3 for at least 6 months and symptoms of organ involvement) and often has a biventricular distribution. Cardiotoxic eosinophils (abnormal cells containing vacuoles and having fewer than the normal number of granules) are central to the pathogenesis. The cardiac pathology consists of an acute eosinophilic myocarditis, fibrinoid vasculitis of the intramural coronary arteries, mural thrombosis (often with eosinophils), fibrotic endocardial thickening, and ventricular obliteration. In addition to symptoms due to cardiac involvement, patients have skin rash and constitutional symptoms. The disease is aggressive and rapidly progressive. Electrocardiographic abnormalities (especially involving the T wave) are common but nonspecific. Hemodynamic findings are typical of restrictive cardiomyopathy.

Endomyocardial fibrosis

In contrast to Loeffler's, EMF has a more insidious onset, has no gender predilection, and most often affects children and young adults. The disease is more indolent than Loeffler's, and biventricular involvement occurs in only about half the cases. LV involvement produces symptoms due to pulmonary congestion, whereas the less common isolated RV involvement (about 10 percent) may simulate constrictive pericarditis. Atrioventricular valve regurgitation and embolic episodes are frequent complications, and atrial fibrillation is common.

Echocardiographic features

Endomyocardial disease is characterized by endocardial fibrosis of the apex and subvalvular regions of one or both ventricles, resulting in restriction to inflow to the affected ventricle. Although their clinical presentations differ, the pathology, and therefore the cardiac imaging studies, are generally similar in the endomyocardial diseases. M-mode echo findings are nonspecific and digitized M-mode studies reveal a decreased peak filling rate and a decreased duration of the peak filling. On two-

dimensional echo, apical obliteration of the right and/or left ventricle, apical thrombus, preservation of ventricular systolic function with thickening of the posterior atrioventricular valve apparatus and posterobasilar LV wall, echo densities in the endocardium, and small ventricular and large atrial cavities are noted. Involvement of the posterior mitral and tricuspid valve leaflets results in mitral and tricuspid regurgitation; less commonly, restricted motion may produce stenosis. Sparing of the outflow tracts is characteristic.

Doppler interrogation yields typical patterns of restriction (increased E/A, decreased IVRT, decreased deceleration time), mitral and tricuspid regurgitation, and, less often, stenosis. Not surprisingly, the location, extent, and severity of involvement determine the clinical picture.

Treatment of the obliterative restrictive cardiomyopathies

Medical therapy of Loeffler's is often ineffective and frustrating. Treatment consists of symptomatic relief, anticoagulants, corticosteroids, and hydroxyurea for myocarditis (interferon has had some success55), and palliative surgery in the late, fibrotic stage. Surgical excision of fibrotic endocardium and valve replacement may offer symptomatic improvement, but at the expense of high (15 to 25 percent) operative mortality. The prognosis of advanced disease is grim (50 percent 2-year mortality), but it is considerably better in those with milder disease.

Nonobliterative endomyocardial diseases

Carcinoid Syndrome

Carcinoid syndrome results from metastatic carcinoid tumors (most commonly arising in the small bowel and appendix, but also the bronchus and other sites) and consists of cutaneous flushing, diarrhea, and bronchoconstriction; involvement of the heart occurs as a late complication of carcinoid syndrome in approximately 50 percent of patients. Hepatic metastases produce serotonin, bradykinin, and other substances that affect right heart structures but are inactivated in the lungs. Thus, LV involvement is distinctly uncommon and its presence suggests a right-to-left intracardiac shunt. Fibrous endocardial plaques comprising smooth muscle cells in a stroma of collagen and acid mucopolysaccharide on the tricuspid and pulmonic valves and

right heart endocardium are characteristic. Although tricuspid and pulmonic stenosis and regurgitation dominate the clinical picture, restrictive cardiomyopathy may occur. The chest radiograph is often normal, but cardiomegaly, pleural effusions, and nodules may be evident; unlike the case with congenital pulmonic stenosis, poststenotic dilatation of the pulmonary artery trunk does not occur. Electrocardiographic abnormalities are common, but nonspecific. Two-dimensional echocardiography reveals thickened, retracted tricuspid and pulmonic valves and right atrial and ventricular enlargement; right atrial wall thickening may be seen on transesophageal echo. Low-velocity tricuspid and pulmonic regurgitation on Doppler indicates normal pulmonary arterial pressures, which is typical of carcinoid heart disease. In one series, echocardiographic findings were detected in two-thirds of patients with carcinoid. In another study, cardiac involvement was associated with a reduced 3-year survival as compared with those without cardiac involvement. Catheterization findings are usually those of tricuspid regurgitation and/or pulmonic stenosis. Therapy is symptomatic, and valvular replacement (mechanical) or repair is warranted in patients with severe valve dysfunction.

Malignant Infiltration

Infiltrating tumors of the heart are generally metastatic (lung, breast, melanoma, lymphoma, leukemia) and rarely produce restriction to ventricular filling unless the pericardium is involved. Infiltration on echocardiography is suggested by a localized increase in wall thickness, often associated with abnormal wall motion and pericardial effusion. CT and MRI scans are also useful.

Iatrogenic Disease frequently complicates radiation therapy to the chest and may produce constrictive pericarditis; however, endo- and myocardial involvement may produce restrictive cardiomyopathy, at times presenting years after radiation therapy has been completed. Anthracyclines and methysergide can cause endomyocardial fibrosis. Oils containing L-tryptophan were withdrawn from the market when they were implicated in the genesis of the eosinophiliamyalgia syndrome; this syndrome was associated with restrictive cardiomyopathy. Finally, a restrictive pattern of

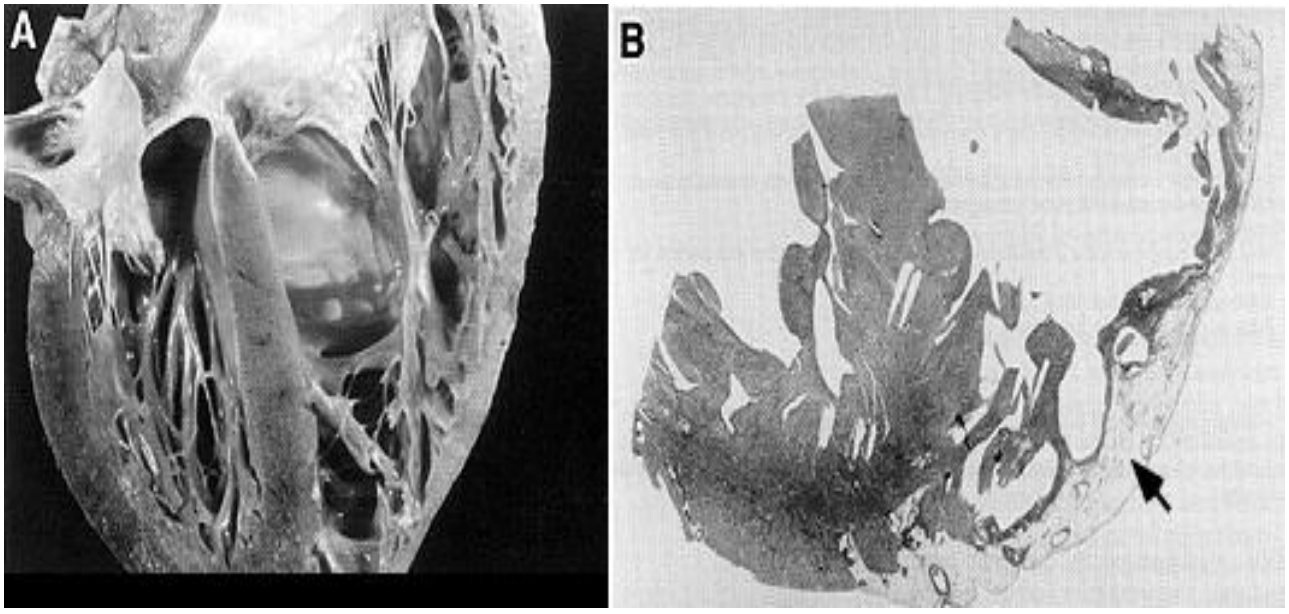
LV filling is common soon after orthotopic cardiac transplantation and may persist for at least 1 year in as many as 15 percent.

Arrhythmogenic right ventricular cardiomyopathy

Unlike HCM, DCM, and RCM, arrhythmogenic right ventricular cardiomyopathy (ARVC) is defined histologically by the presence of progressive replacement of right ventricular myocardium with adipose and fibrous tissue often confined to a *'triangle of dysplasia'* comprising the right ventricular inflow, outflow, and apex (Figure 4.7). While these pathologic abnormalities can result in functional and morphological right ventricular abnormalities, they also occur in the left ventricle, producing a DCM phenotype, or can be present in the absence of clinically detectable structural changes in either ventricle. For the purposes of this classification, ARVC is defined by the presence of right ventricular dysfunction (global or regional), with or without left ventricular disease, in the presence of histological evidence for the disease and/or electrocardiographic abnormalities in accordance with published criteria.

Figure 4.7

Arrhythmogenic right ventricular cardiomyopathy



Notes. Left: Increased Fatty or fibrofatty RV infiltrate,
Right: EM demostrates Desmosomal Abnormalities plakoglobin, desmoplakin, and plakophilin-2.

Although uncommon (estimated prevalence 1:5000), ARVC is a frequent cause of sudden death in young people in some areas of Europe. Autosomal recessive forms

of ARVC (e.g. Naxos and Carvajal syndromes caused by mutations in genes encoding plakoglobin and desmoplakin, respectively) are recognized, but the majority of cases are caused by autosomal dominantly inherited mutations in genes encoding plakophilin 2 and other proteins of the desmosome of cardiomyocytes. Mutations in TGF-ß and Ryanodine receptor genes may be associated with an ARVC phenotype.

Unclassified cardiomyopathies

Left ventricular non-compaction

Left ventricular non-compaction (LVNC) is characterized by prominent left ventricular trabeculae and deep inter-trabecular recesses. The myocardial wall is often thickened with a thin, compacted epicardial layer and a thickened endocardial layer (Figure 4.8).

Figure 4.8

Non-compaction left ventricle

In some patients, LVNC is associated with left ventricular dilatation and systolic dysfunction, which can be transient in neonates.

It is not clear whether LVNC is a separate cardiomyopathy, or merely a congenital or acquired morphological trait shared by many phenotypically distinct cardiomyopathies. LVNC occurs in isolation and in association with congenital cardiac disorders such as Ebstein's anomaly or complex cyanotic heart disease and some neuromuscular diseases. The population prevalence of isolated LVNC is not known, but it is reported in 0.014% of consecutive echocardiograms. In large paediatric series,

LVNC is reported to be the commonest cause of unclassified cardiomyopathies. LVNC is frequently familial, with at least 25% of asymptomatic relatives having a range of echocardiographic abnormalities. Genes in which causative mutations have been identified include G 4.5 encoding taffazin (X-linked), alpha dystrobrevin, ZASP, actin, lamin A/C and a locus on chromosome 11 p 15.

Takotsubo cardiomyopathy

Stress-induced cardiomyopathy—also known as Takotsubo cardiomyopathy, apical ballooning syndrome, or ampulla cardiomyopathy—is an acute, reversible condition characterized by LV systolic dysfunction generally involving the mid and apical segments. Transient left ventricular apical ballooning syndrome or takotsubo cardiomyopathy is characterized by transient regional systolic dysfunction involving the left ventricular apex and/or mid-ventricle in the absence of obstructive coronary disease on coronary angiography. Patients present with an abrupt onset of angina-like chest pain, and have diffuse T-wave inversion, sometimes preceded by ST-segment elevation, and mild cardiac enzyme elevation. Originally described in Japan, the condition is reported in Caucasian populations in Europe and North America. Most reported cases occur in post-menopausal women. Symptoms are often preceded by emotional or physical stress. Norepinephrine concentration is elevated in most patients and a transient, dynamic intraventricular pressure gradient is reported in 16% of cases. Left ventricular function usually normalizes over a period of days to weeks and recurrence is rare. The same kind of reversible myocardial dysfunction is occasionally encountered in patients with intracranial haemorrhage or other acute cerebral accidents (neurogenic myocardial stunning).

Associated electrocardiographic abnormalities suggest ischemia or myocardial injury, but occur in the absence of obstructive epicardial coronary artery disease. The majority of patients present after an acute emotional or physical stressor, which implicates a catecholamine surge in the pathophysiology. Stress-induced cardiomyopathy mimics an acute coronary syndrome and is estimated to account for approximately 1–2% of all presentations with symptoms of myocardial infarction. The in-hospital mortality rate is lower than that for myocardial infarction. Long-term survival is simi-

lar to that of an age-matched and gender-matched population. The diagnosis of stress-induced cardiomyopathy in the patient in this case was confirmed by the presence of all four Mayo Clinic diagnostic criteria: transient contractile dysfunction of the mid-LV segments with or without apical involvement, extending beyond a single epicardial vascular distribution; absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; new electrocardiographic abnormalities (either ST-segment elevation, T-wave inversion, or both) or elevated cardiac troponin; and the absence of a pheochromocytoma or myocarditis.

To our knowledge, this case is the first published report of PET imaging with ^{11}C hydroxyephedrine in stress-induced cardiomyopathy. Although limited to a single patient, the PET findings are compatible with the proposed pathophysiological hypothesis focusing on direct myocardial effects of high catecholamine levels.

^{11}C hydroxyephedrine is a norepinephrine analog that provides a measure of cardiac presynaptic sympathetic activity. Plasma hydroxyephedrine is transported into cardiac sympathetic nerve terminals by the uptake-1 mechanism. Unlike norepinephrine, hydroxyephedrine is not metabolized by monoamine oxidase or catecholamine-O-methyltransferase enzymes. Vesicular storage of hydroxyephedrine occurs, but to a lesser extent than norepinephrine, owing to the higher lipophilicity of hydroxyephedrine. Myocardial retention of hydroxyephedrine, therefore, reflects a continuous release and reuptake of hydroxyephedrine in the presynaptic neuron. The acutely reduced myocardial ^{11}C hydroxyephedrine retention in segments with contractile dysfunction is compatible with the hypothesis of increased sympathetic activity, with associated increased norepinephrine release and competitive inhibition of ^{11}C hydroxyephedrine reuptake. The higher ^{11}C hydroxyephedrine retention at follow-up is indicative of the reversible nature of this effect. An alternative explanation for the acutely reduced ^{11}C hydroxyephedrine uptake is transient dysfunction of the uptake-1 mechanism secondary to myocardial injury. Other imaging studies have demonstrated abnormal myocardial fatty acid and glucose metabolism using single photon emission computed tomography (SPECT) with ^{123}iodine--methyl-p-iodophenyl pentadecanoic acid and PET with ^{18}F-fluorodeoxyglucose, respectively, during the acute phase of

presentation. Impaired MBF could also contribute to these imaging findings, but was excluded in this case and other studies by demonstrating normal perfusion at the time of imaging. It remains to be established whether the sympathetic abnormality is a primary event or an epiphenomenon in stress-induced cardiomyopathy.

Evidence to support the pathophysiological role of the sympathetic nervous system in stress-induced cardiomyopathy includes the temporal relationship between the presentation and preceding emotional or physical stress, elevated plasma catecholamine levels in some patients, and the inability to reproduce the syndrome in animal models of stress-induced cardiomyopathy in the presence of adrenergic blockage. Cardiac sympathetic imaging in this condition has been limited to SPECT studies using ^{123}iodine metabenzylguanidine (MIBG), which have reported findings consistent with cardiac sympathetic abnormalities. Like the patient in this case, other individuals have exhibited persistent MIBG defects for several months and even at 1 year after presentation with stress-induced cardiomyopathy, indicating prolonged cardiac sympathetic abnormalities despite resolution of contractile dysfunction. SPECT with MIBG has two notable limitations when compared with ^{11}C hydroxyephedrine. First, SPECT has lower spatial and temporal resolution than PET, which precludes absolute quantification of regional differences in tracer uptake by kinetic modeling. Second, interpretation of MIBG cardiac behavior is also confounded by a considerable amount of non-neuronal tissue uptake.

Proposed mechanisms by which catecholamines might induce myocardial stunning include direct myocyte effects, such as intracellular calcium overload, or indirect effects, such as epicardial spasm, microvascular dysfunction, and hyperdynamic contractility with midventricular cavity obstruction. Epicardial spasm and cavity obstruction are not common findings, but impaired microvascular perfusion has been reported in up to two-thirds of patients at presentation. Notably, the acute cardiac sympathetic abnormality in this patient was not accompanied by reduced MBF, as measured by PET, which suggests mechanisms other than widespread microcirculatory dysfunction or resolution by the time of PET imaging. Regional differences in -adrenergic receptor density and sympathetic innervation have been proposed as po-

tential explanations for the unique pattern of contractile dysfunction observed in stress-induced cardiomyopathy, although supporting data in humans are lacking. In addition, the apparent female predisposition for the disorder also suggests gender differences in myocardial catecholamine sensitivity. Lyon and colleagues have hypothesized that high levels of circulating epinephrine could trigger a switch in intracellular signal trafficking, from G_s protein to G_i protein via the $_2$-adrenoreceptor, which might be negatively inotropic. Although it is not possible to determine whether the observed reduction in hydroxyephedrine retention index in the patient in this case is a direct or indirect effect of catecholamines, our findings clearly demonstrate acute cardiac sympathetic abnormalities in stress-induced cardiomyopathy and provide impetus for further investigation.

Treatment and management

Individuals with stress-induced cardiomyopathy generally recover spontaneously. However, approximately 40% of patients develop congestive heart failure, and a minority (10%) can present with acute cardiogenic shock or major hemodynamic compromise necessitating hemodynamic support. As catecholamines could have a causative role in stress-induced cardiomyopathy, therapy with epinephrine, inotropic agents such as dobutamine, or both might lead to worsening of the condition, although in the absence of clinical studies this is a theoretical concern. In the presence of LV outflow tract obstruction, as occurs in some patients, inotropic agents can also be deleterious. Currently, there is no proven therapy that augments recovery or improves outcomes in stress-induced cardiomyopathy. The potential role of catecholamines has prompted the empirical use of -blockers, with the goal of preventing recurrence. Theoretically, some -blockers could promote stimulus trafficking of $_2$-adrenergic receptors to G_i protein coupling, but whether this is clinically relevant is unknown. Finally, it remains to be established whether complete adrenergic blockade with a combined -blocker and -blocker, such as labetalol, is superior to -blockade alone.

Specific forms of cardiomyopathies.

The diagnosis of cardiomyopathy encompasses a wide spectrum of diseases with widely divergent pathogenic mechanisms, that have as their final common

pathway the syndrome of congestive heart failure. These heart muscle diseases may be primary or secondary-i.e., resulting from specific cardiac or systemic disorders. Coronary artery disease, hypertension, valvular heart disease, and cardiomyopathy are the most common causes of heart failure for both sexes. Inflammatory cardiomyopathies, particularly viral myocarditis, have served as a model to understand the development of heart failure. More than 70 different specific cardiomyopathies associated with general systemic disease, neuromuscular disorders, sensitivity and toxic reactions, and the peripartum state have been described. When considered as a group, these disorders are infrequent; when considered individually, they are rare.

Ischemic cardiomyopathy

Hypertensive cardiomyopathy

Cardiac hypertrophy due to long-standing arterial hypertension is associated with a high incidence of heart failure. Initially, myocyte hypertrophy occurs to reduce wall stress and to accommodate the increased pressure load imposed on the heart. This increase in myocyte wall thickness is accompanied by biochemical and molecular changes, such as a shift to fetal phenotype gene expression and alterations in the intracellular handling of calcium. Alterations in the nonmyocyte compartment-such as excessive myocardial fibrosis-also ensue. In concert these changes lead to an altered contractile performance of the heart. Although the precise mechanisms that accelerate the progression from compensated hypertrophy to failure are not known, activation of the renin-angiotensin system has been postulated to play a major role. In vivo, angiotensin II has been shown to increase left ventricular mass and contributes to cardiac phenotype modulation independently from its effect on arterial pressure. In vitro, studies have demonstrated that angiotensin II causes myocyte hypertrophy and promotes interstitial fibrosis. This clinical prevention trial further confirms the deleterious effects of the renin-angiotensin axis on cardiac function. The patient with hypertensive cardiomyopathy typically presents with left ventricular hypertrophy in association with features of dilated or restrictive cardiomyopathy. The prognosis is generally better than that of other forms of cardiomyopathy; however, the prognosis is significantly worsened by the presence of comorbid conditions such as diabetes

mellitus, coronary artery disease, and persistent hypertension. Hypertensive cardiomyopathies are common in the elderly and may be related to an increased prevalence of hypertension due to central arterial stiffness and inherent myocardial changes that occur with normal aging. Recent advances in molecular biology and in echocardiographic and Doppler techniques have led to an improved understanding of the various distinct causes of hypertrophic heart disease in the elderly and the realization that the process is not solely due to the changes associated with aging. Hypertrophic obstructive cardiomyopathy, once thought to be a familial disorder affecting primarily younger individ uals, has been diagnosed in older individuals with increasing frequency.

Similarly, hypertensive hypertrophic cardiomyopathy is another significantly unappreciated cause of hypertensive cardiomyopathy in the elderly. In contrast to the hypertrophic obstructive form, there is a higher female predominance, which is thought to be due to gender-specific differences in the degree of myocyte hypertrophy to intraventricular pressure-overload previously described in women with aortic stenosis. There is no apparent familial component, and patients give a long history of isolated systolic hypertension. In comparison to the prevalence of hypertension in patients over age 65, which varies from 50 to 70 percent, hypertensive hypertrophic cardiomyopathy remains relatively rare, suggesting a unique and currently poorly understood pathophysiology. Many postulate that in hypertensive hypertrophic cardiomyopathy, as in the hypertrophic obstructive form, the development of senescent hypertension may act influentially on an already genetically altered substrate to lead to the respective phenotypes.

Valvular cardiomyopathy

Valvular cardiomyopathy is defined as systolic dysfunction out of proportion to the wall stress imposed by the initial valvular lesion. It occurs most commonly with left-sided regurgitant (mitral and aortic insufficiency) rather than stenotic lesions (aortic and mitral stenosis). The prognosis depends on the nature and extent of the valvular abnormality but more importantly on the degree of left ventricular dysfunction at the time of the proposed surgical repair. Generally even severe left ventricular dysfunction due purely to aortic stenosis will have a favorable prognosis after surgic-

al repair. This is in marked contrast to a surgical approach for similar degrees of left ventricular dysfunction due to mitral or aortic regurgitation. Owing to high surgical risks, medical therapy with afterload reduction-and, if indicated, cardiac transplantationare acceptable modes of therapy in these instances. Cardiac reduction surgery with valve repair has become an increasingly popular modality for treatment of these high-risk patients. No largecenter randomized trial is currently available to evaluate the efficacy and safety of this approach.

Alcohol cardiomyopathy

Long-term heavy alcohol consumption (of any beverage type) is the leading cause of a nonischemic, dilated cardiomyopathy, herein referred to as alcoholic cardiomyopathy (ACM). ACM is a specific heart muscle disease of a known cause and is classified as a dilated cardiomyopathy. ACM is also frequently referred to as alcoholic heart muscle disease (AHMD), because at one time the World Health Organization/International Society and Federation of Cardiology Task Force suggested the term cardiomyopathy be reserved for labeling heart muscle diseases of unknown origin that are limited to the heart. The more recent report of the World Health Organization/International Society and Federation of Cardiology Task Force suggests that cardiomyopathies be classified by the dominant pathophysiology, or if possible by the etiologic/pathogenetic factor. Consequently, ACM is considered both a dilated and specific cardiomyopathy and is usually discussed in the category of agents that is toxic to the myocardium. Similar to other dilated cardiomyopathies (*ie*, idiopathic, viral/immune), ACM is characterized by a dilated left ventricle (LV), normal or reduced LV wall thickness, and increased LV mass. The point at which these abnormalities appear during the course of an individual's lifetime of drinking, such that the abnormalities can be called a dilated cardiomyopathy, is not well established and is highly individualized. Also, unlike other cardiomyopathies, such as immunologic cardiomyopathies, there are no specific immunohistochemical, immunologic, or other criteria for the diagnosis of ACM. Therefore, the diagnosis of AHMD is often considered presumptive and is usually one of exclusion. The key factor in ruling in AHMD is a long-term history of heavy alcohol abuse.

Incidence, Prevalence, and Morbidity

The occurrence of ACM correlates with a high daily level and duration of alcohol consumption; however, the prevalence of ACM is variable and, fortunately, not all heavy drinkers have ACM develop. ACM represents about 3.8% of all cardiomyopathy cases. This statistic may seem rather insignificant; however, long-term heavy alcohol consumption is the second-leading cause of a dilated cardiomyopathy. Furthermore, if one considers the incidence of dilated cardiomyopathy in the general population, the incidence of a dilated cardiomyopathy in alcoholics is much greater. The incidence of ACM has remained constant over the last several decades, despite a gradual downward trend in per capita alcohol consumption in the United States.

The prevalence of ACM is variable and ranges from 23 to 40%. Among ACM cases, men represent the largest percentage, whereas women represent approximately 14%. In all races, death rates due to ACM are greater in men compared to women, and are greater in African-American men and women compared to white men and women with ACM.

Etiology

Alcoholics can present with either a preclinical (asymptomatic) or symptomatic ACM (the latter is primarily distinguished from the former by signs and symptoms of heart failure). Therefore, a question clinicians often ask is: What duration and level of alcohol consumption produces an asymptomatic ACM, as well as symptomatic ACM? Even after decades of study, the exact amount and duration of alcohol consumption that is required to produce asymptomatic and symptomatic ACM has not been clearly established. There appears to be no simple linear alcohol concentration-to-injury relationship that clinicians can use when assessing their patients for alcohol-induced changes in myocardial structure or function. In general, others have reported that the duration and amount of alcohol consumed by asymptomatic alcoholics does not correlate with changes in myocardial structure and function.

Even though there is lack of a specific dose-response relationship, as well as variability among studies in terms of the amount of alcohol consumed and duration of alcohol abuse, some general conclusions can be made regarding alcohol consumption

and ACM. In general, asymptomatic alcoholic patients with changes in cardiac structure and function had a history of consuming > 90 g/d of alcohol (some studies report > 200 g/d) for > 5 years. However, the average duration of drinking reported in the majority of studies was 15 years. As a point of reference, there is 12 g of alcohol in a standard drink; therefore, these alcoholics self-reported consuming from 8 to 21 standard drinks per day.

In terms of the amount and duration required to produce symptomatic ACM and heart failure, the data are very limited. Therefore, the key variable linked to the development of heart failure appears to be the duration of heavy daily alcohol consumption. However, it is possible that other morbidities or variables, such as hypertension or arrhythmias, may predispose alcoholic patients to the development of heart failure.

Pathophysiologic Mechanisms

Even though there is a substantial amount of work documenting the adverse affects of alcohol on the myocardium, the exact pathogenesis of ACM is incompletely understood. Animal models of ACM have contributed a great deal to our understanding of ACM. These models have demonstrated that long-term alcohol consumption produces a number of histologic and cellular changes. These changes fall into the following categories: myocyte loss, intracellular organelle dysfunction, contractile proteins, and calcium homeostasis. These changes can alter several aspects of myocyte function and therefore may lead to myocyte dysfunction. This may represent the primary injury caused by alcohol, which eventually culminates in reduced myocardial function and ACM. However, it is also possible that other cell types or systems are activated, such as the sympathetic nervous system (norepinephrine), renin-angiotensin system (RAS), cytokines, and natriuretic peptide (NP) system. In the section that follows, these categories of alcohol-induced changes are reviewed with an emphasis on more recent data.

Myocyte Loss

In many organ systems, including the heart, myocyte loss or cell death may be an important component of organ dysfunction and pathology. Cell death can result

from either necrosis or apoptosis (programmed cell death). Others have shown that ethanol-induced apoptosis is probably a critical mechanism underlying ethanol-induced disorders such as fetal alcohol syndrome. There are several early reports in humans with ACM and animal models of cardiomyopathy that support a role for myocyte loss as a mechanism underlying alcohol-induced cardiac dysfunction. Apoptosis was induced by rinsing cells twice in phosphate-buffered saline solution and then replacing the medium with a serum-free suspension. Both concentrations of alcohol potentiated the apoptotic effect of serum withdrawal (as measured by DNA acid fragmentation). In addition, both alcohol concentrations increased the protein levels of the pro-apoptotic protein Bax and increased caspase-3 enzyme activity (the latter is a member of a family of intracellular proteases activated in apoptosis). Interestingly, in this same experiment, the application of insulin-like growth factor (IGF)-1 attenuated the apoptotic effects of ethanol on serum withdrawal. It is important to note that these concentrations of alcohol are very high (in human beings who cannot tolerate alcohol, 500 mg/dL can be associated with respiratory depression and death); however, these investigators also found lower concentrations of alcohol, 200 mg/dL, potentiated the effects of serum withdrawal. It is interesting that IGF-1 attenuated the effects of alcohol. IGF-1 has multiple effects on the cell, some which include cell proliferation and differentiation, whereas activation of signaling components downstream to the IGF receptor are linked to the development of hypertrophy.

In summary it remains unknown whether the process of apoptosis is important in the pathogenesis of ACM. However, further studies are clearly needed, even though speculative apoptosis may indeed be an early inciting event that precedes other events, such as myocyte hypertrophy and activation of neurohormonal systems.

Intracellular Organelle Dysfunction

There are many early reports documenting the adverse effects of long-term alcohol consumption on mitochondrial and sarcoplasmic reticulum function. In fact, changes in mitochondria structure/function have been one of the most ubiquitous findings among studies. There are many reports of mitochondrial enlargement that is accompanied by disorganization and degeneration of the cristae. These changes in

structure have been supported by the findings of others in animal models of ACM, who have found changes in mitochondrial function, exemplified by decreases in indexes of mitochondria respiration and/or calcium uptake by the mitochondria. Others have found an increased level of fatty ethyl esters in the alcoholic heart, which can attach to the mitochondria and disrupt mitochondria function. Changes in mitochondria function can affect cell function in many ways and therefore maybe a key contributor to intrinsic cell dysfunction. Intrinsic cell dysfunction may also arise from impaired sarcoplasmic reticulum function. There are reports of decreases in sarcoplasmic reticulum calcium biding and uptake. These findings corroborate those of others who have found electron micrographic evidence of sarcoplasmic reticulum swelling and disorganization.

Contractile Proteins

Changes in the structure and/or function of the contractile proteins can affect many aspects of cross-bridge cycling as well as force production. As a potential mechanism of alcohol-induced cardiac damage. Shifts in the relative expression of the contractile proteins, ß-myosin heavy chain (MHC) have been reported in animal models of pressure overload, thyroid deficiency, and heart failure. The author and colleagues have also demonstrated that a short period of alcohol consumption is associated with a myosin isoform change. It has been postulated that this shift in the myosin isoforms allows the heart to reduce the rate of contraction, as well as reduce the level of adenosine triphosphate consumption, allowing the heart to reside in a more energy efficient state.

Calcium Homeostasis

At least in the latter stages of ACM, contractile function is depressed, and similar to other cardiovascular diseases, abnormalities in Ca^{2+} homeostasis have been implicated as a cellular mechanism. Calcium homeostasis is essential for normal cellular function, and similar to other cell types, the myocyte tightly regulates intracellular shifts in Ca^{2+}. Calcium is critical in the initiation of cross-bridge cycling and in regulating myocardial force. Myocardial contractility can be regulated by altering the Ca^{2+} transient or myofibrillar sensitivity to Ca^{2+}. Normal Ca^{2+} regulation is rather complex

and depends a number of factors, such as the abundance and functioning of sarcolemmal L-type Ca^{2+} channels, sarcolemmal transport pumps (Na/Ca exchanger), and the sarcoplasmic reticulum (storage and release Ca^{2+}). Therefore, changes in any one of these modulating factors can alter Ca^{2+} homeostasis. With regard to calcium transients, others have examined cytosolic Ca^{2+} transients in hearts isolated from rats fed alcohol (36% v/v in drinking water) for 7 months and found no differences in systolic or diastolic intracellular Ca^{2+} rise and fall between alcohol and control hearts. There were also no differences between groups in the protein levels of sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase pump (SERCA2) and phospholamban (a protein attached to SERCA2 that modulates the function of SERCA2). These findings suggest that other factors, such as myofilament sensitivity, may be altered after long-term alcohol consumption. In support of this idea, data from the author's laboratory indicate that a relatively short period of alcohol consumption (2 months of a liquid alcohol diet) is associated with decreases in myofilament Ca^{2+} sensitivity.

However, the maximal Ca^{2+}-induced force development was similar between the groups (*ie*, force at the greatest concentration of Ca^{2+}). Therefore, a relatively short period of alcohol consumption altered the sensitivity of the myofilaments to physiologic levels of calcium.

Others have also speculated that alcohol may increase the threshold of the heart for calcium overload and mitochondrial dysfunction. Co-treatment with the calcium antagonist verapamil prevented the development of the contractile and metabolic dysfunction. Based on this abnormal contractile response to calcium, these investigators speculated that alcohol induces an upregulation of L-type calcium channels, which then increases the threshold of the heart for calcium overload. It is important to note that their model is one of short alcohol exposure and these changes are found in the absence of detectable hypertrophy (*ie*, no change in heart weight-to-body weight ratios). This is an intriguing hypothesis; however, one would predict that, as time progressed and drinking continued, heart failure and early death would ensue similar to the Syrain hamster model of cardiomyopathy, in which calcium overload is considered a key pathologic factor. However, work of the author and others has shown that

12 months of alcohol consumption in rats is associated with a dilated cardiomyopathy and contractile dysfunction, but there are no signs of heart failure and, at least in the author's experience, early death has never occurred.

Neurohormonal Systems

As noted earlier, as a consequence of myocyte dysfunction, other cell types or systems might be activated, such as sympathetic nervous system (norepinephrine), RAS, and NP system. Reviewed below is the potential role of these systems in ACM pathophysiology. Sustained and high levels of norepinephrine exert adverse effects on the myocardium, some of which include myocyte hypertrophy, toxicity, and apoptosis. All of these cellular events are linked to LV remodeling. However, this duration of alcohol consumption was associated with depressed contractile function (as exemplified by a decrease in developed twitch tension in alcoholic atria compared to control atria).

Recently, in a rodent model of ACM, the author examined whether changes in cardiac structure corresponded to activation in the RAS and the NP system. Using echocardiography, it was shown that 8 months and 12 months of alcohol consumption in male Sprague-Dawley rats was associated with a dilated cardiomyopathy, exemplified by increases in the EDD, ESD, LV mass, and heart weight to body weight ratio. It is important to note, though, that these structural changes were not significantly different from the control group until the 12-month time point. In addition, the pressure-volume relationship in the alcohol-treated animals was shifted down and to the right, which is characteristic of a dilated heart.

Myocardial Structural and Functional Changes Associated With ACM

Similar to other dilated cardiomyopathies, ACM is characterized by an increased LV mass, dilation of the ventricles, wall thinning, and ventricular dysfunction, and these changes are present in the absence of coronary artery disease and nutritional deficiencies. As will be discussed in more detail, the degree of LV dilation and change in LV mass, wall circumference, and LV function may depend on the stage and severity of ACM. AHMD occurs in stages, beginning with a preclinical or asymptomatic stage, and then progressing to a symptomatic stage and eventually

heart failure. In the late 1970s, the concept emerged of a preclinical (asymptomatic) form of ACM that may precede the more severe form of symptomatic ACM. Since that period of time, numerous studies have been conducted to determine the changes in LV structure (remodeling) that are in involved in the progression of ACM. In general, early signs of ACM appear to be LV dilation, exemplified by increased end-diastolic dimension (EDD) and increased systolic dimension, increased LV mass, and modestly increased posterior and septal wall thickening. Other reports suggest that hypertrophy, exemplified by either an increase in posterior and/or septal wall thickness and LV mass rather than LV dilation, are early findings in asymptomatic alcoholics.

In summary, it appears that in asymptomatic male alcoholic patients, the most prominent early finding was LV dilation and an increase in LV mass. Diastolic dysfunction appears to be an early finding; however, patients may have both diastolic and/or systolic dysfunction. Some patients may also have a modest degree of wall thickening; the former change coupled with LV dilation would serve to offset wall tension and therefore would lead to a compensated and asymptomatic form of ACM. More than likely, both the drinking histories and other unidentified individual variables may account for differences in the studies.

Clinical Characteristics of ACM

Clinical characteristics as well as age of onset are similar in patients with idiopathic dilated cardiomyopathy (IDCM) and ACM. An equal percentage of dilated cardiomyopathy and ACM patients presented with either New York Heart Association (NYHA) class I-II or class III-IV functional status, and all echocardiographic and hemodynamic parameters were similar between the groups. These latter investigators also examined smoking and not surprisingly found that larger percentage of ACM patients were current, intermediate, and heavy smokers compared to the IDCM group.

How do clinicians distinguish asymptomatic from symptomatic ACM? Others have found that symptomatic ACM is characterized by a greater degree of LV dilation and increased cardiac mass. Symptomatic ACM patients are also likely to be in NYHA class III-IV, have systolic dysfunction (decreased EF), and have signs and

symptoms of heart failure, such as elevated jugular venous pressure, S_3-S_4 heart sounds, pulmonary rales, and peripheral edema.

Outcomes and Treatment of Patients With ACM

Some reports indicated prognosis (survival) was better in ACM patients compared to patients with other types of cardiomyopathies. However, these studies did not examine the effect of alcohol abstinence; in one study, a percentage of the patients classified as having ACM also had coronary artery disease or hypertension.

Genomic/post-genomic of cardiomyopathies

Many cardiomyopathies are the consequences of a single gene defect and are thus inherited according to Mendelian law. The extraordinary advances accomplished in the last two decades in molecular genetics has allowed the identification of the gene defect for some forms of dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy. These are clearly structural heart diseases, with or without arrhythmias. Familiar dilated cardiomyopathies have been found to be due to defects of the cytoskeleton impairing force transmission. Familiar hypertrophic and restrictive cardiomyopathies have been related to defective sarcomere proteins impairing force production. The genetic basis of arrhythmogenic right ventricular cardiomyopathy has recently been found to be linked to abnormal cytoskeleton proteins regulating cell junctions, both in the autosomal and recessive (Naxos disease) forms. Mutations in the genes encoding for intercellular junctions have been also discovered to account for the other cardiocutaneous syndromes which are characterised by the association of cardiomyopathy and skin abnormalities. On the other hand, non-structural heart disease manifesting with arrhythmias or conduction disturbances are mostly the consequence of ion channel gene mutations, either at the level of the cell membrane or intracellular organelles. Long and short QT syndrome are sodium or potassium ion channel diseases of the cell membrane, Brugada syndrome is a sodium ion channel disease, and polymorphic ventricular tachycardia is related to an abnormal ryanodyne receptor 2 regulating calcium release from the sarcoplasmic reticulum for electromechanical coupling. Thus, if we want to reconsider the classification of inherited cardiomyopathies, which

is currently based upon the phenotypic expression, a genomic/post-genomic classification could be postulated taking into account the underlying gene mutations and the cellular level of expression of encoded proteins, thus distinguishing cytoskeleton (cytoskeletalopathies), sarcomeric (sarcomyopathies) and ion channel (channelopathies) cardiomyopathies (Table 4.3). What was considered for years as idiopathic and was at the base of early classification (of unknown cause), was recently largely elucidated by finding a genetic background.

Table 4.3

A genomic/post-genomic classification of inherited cardiomyopathies

Cytoskeletal cardiomyopathy (‘‘cytoskeletalopathy’’)	Dilated cardiomyopathy, Arrhthmogenic right ventricular cardiomyopathy, Cardiocutaneous syndromes
Sarcomeric cardiomyopathy (‘‘sarcomyopathy’’)	Hypertrophic and restrictive cardiomyopathy
Ion channel cardiomyopathy (‘‘channelopathy’’)	Long and short QT syndromes, Brugada syndrome, catecholaminergic polymorphic VT

In summary, cardiomyopathies are remained as poor identifiable disease in clinical cardiology. Summarize efforts of specialists with different areas can improve diagnostics and treatment of this diseases.

CHAPTER 5

CONGENITAL AND AQUIRED HEART DISEASE

Introduction

Congenital heart disease (CHD) is defined as a gross structural abnormality of the heart, great arteries, or great veins that is present at birth. Congenital cardiac malformations are relatively uncommon. Multiple studies have demonstrated an incidence of 0.6% of live births for moderate to severe defects. The prevalence is higher in stillbirths and spontaneous abortions. There are approximately 32,000 new cases per year in the United States and greater than 1,000,000 new cases per year worldwide. Although the prevalence is low, the population of patients with CHD continues to expand. Because of the dramatic advances made in medical, surgical, and interventional device therapy, survival into adulthood is now the rule for the vast majority of patients with congenital cardiac defects.

Etiology

The etiology of CHD is multifactorial. Recurrence risks vary with the gender of the proband and the specific cardiac defect, with an overall recurrence risk of 3% to 5% in the offspring of patients with congenital heart disease. The exact proportion of patients with a specific genetic etiology is unknown. There are reports of familial defects following Mendelian patterns of inheritance. Certain chromosomal abnormalities are associated with congenital heart defects. The most common of these is trisomy 21 (Down syndrome). At least 50% of patients with Down syndrome have CHD (most commonly atrioventricular septal defects or ventricular septal defects), often associated with early pulmonary vascular obstructive disease. Despite the identification of many candidate genes on chromosome 21, the key genes contributing to the cardiac phenotype in Down syndrome have yet to be defined. Other syndromes associated with CHD include Turner syndrome, Noonan syndrome, Williams syndrome, Marfan syndrome, and trisomy 13, 14, 15, and 18.

Deletions of 22q11 are seen in DiGeorge syndrome (thymic aplasia, hypoparathyroidism, congenital heart defects involving the outflow tracts, and a dysmorphic appearance). From transgenic studies with a mouse model, TBX1 has been identified

as the likely gene responsible for the cardiac and hypoparathyroid phenotype. 22q11 deletions are now recognized as the cause of a broader group of defects and are seen in 50% of patients with conotruncal abnormalities. CATCH-22, a syndrome due to microdeletion at chromosome 22q11, consists of cardiac conotruncal abnormalities, abnormal facies, thymic abnormalities, cleft palate, and hypocalcemia. Some patients may have the gene deletion without accompanying syndromic features.

Mutations in a few specific genes have been identified in some cases of congenital heart defects. Mutations in TBX5 are seen in the majority of patients with Holt-Oram syndrome, an autosomal disorder with cardiac septal defects and upper limb defects. Mutations in the elastin gene (ELN) have been identified as a cause of supravalvular aortic stenosis. Mutations in NKX2.5 have been associated with the autosomal dominant phenotype of atrial septal defect or tetralogy of Fallot.

Fetal and Neonatal Circulation

In fetal life, the placenta is a low-resistance structure that acts as a respiratory organ and receives the largest amount of fetal blood flow. Blood from the placenta returns to the fetus through the ductus venosus, entering the inferior vena cava (IVC) to the right atrium (RA). A portion of the IVC blood flow is directed across the patent foramen ovale (PFO) to the left atrium (LA), bypassing the right heart. Blood from the superior vena cava (SVC) is directed into the right ventricle (RV) along with the remaining blood return from the IVC and is then pumped out into the pulmonary artery. Because of high pulmonary vascular resistance in the fetus, most pulmonary blood flow crosses the ductus arteriosus and enters the descending thoracic aorta. At birth, the relatively low resistance placental circulation is removed, and systemic vascular resistance increases within minutes. With respiration, the pulmonary vascular bed dilates in response to inspired oxygen, and pulmonary vascular resistance decreases while pulmonary blood flow increases. Pulmonary venous blood return increases, which increases systemic ventricular output and helps to close the foramen ovale. The ductus arteriosus is patent at birth, but begins to constrict shortly after birth and usually closes within hours to several days. Defects in which pulmonary blood flow depends on flow through the ductus are characterized as ductal dependent.

With closure of the ductus in these patients, progressive hypoxemia, acidosis, and death invariably occur. Prostaglandin E_1 infusion to maintain patency of the ductus is used as a temporizing measure until more definitive therapy can be undertaken.

Diagnostic Tools

The physical exam is critical in the evaluation of patients with known or suspected CHD and includes elements that may not be routinely performed in patients with acquired forms of heart disease. In addition to precordial palpation, assessment of venous waveforms, and careful cardiac auscultation, it is also important to assess for cyanosis (including differential cyanosis), palpate pulses and measure blood pressure in both upper and lower extremities, and check oxygen saturation. Evidence of phenotypes associated with CHD (e.g., Down syndrome, William syndrome) should be sought. Although the electrocardiogram (ECG) and chest x-ray (CXR) are a routine part of the evaluation of patients with CHD, they are not specific enough for diagnostic purposes. Imaging studies by qualified personnel play a critical role in the evaluation of these patients. A careful review of prior data, including catheterization data, imaging, and operative reports, is essential as well.

Transthoracic echocardiography (TTE) is the most widely used diagnostic tool for establishing the initial diagnosis and following patients serially. Studies in these patients are complex and time-consuming and should be performed by sonographers and physicians with expertise in CHD. Transesophageal echocardiography (TEE) is particularly useful in adults with poor acoustic windows, providing excellent visualization of the atrial septum, pulmonary veins, interatrial baffles, and Fontan connections. Intraoperative TEE plays a critical role for patients undergoing surgical repair. TEE is also used to guide catheter interventions and device deployment. Increasingly, intracardiac echocardiography is being used for these procedures. Three-dimensional echocardiography is an evolving technology that may be helpful in evaluating patients with congenital heart disease.

Cardiac magnetic resonance imaging (MRI) is an extremely useful tool for the assessment of patients with congenital heart disease, providing high-quality images with a wide field of view in nearly all patients. MRI is particularly useful for assess-

ment of extracardiac anatomy, including delineation of the great vessels, branch pulmonary arteries, and surgical shunts, as well as systemic and pulmonary venous connections. MRI allows quantitation of ventricular mass, volumes, and ejection fraction and can be used to calculate shunt flow and regurgitant flow. Contrast is not required for routine imaging but may be particularly useful in assessing vascular structures. The role of cardiac computed tomography (CT) imaging is evolving. Cardiac CT provides excellent visualization of anatomy (particularly extracardiac anatomy) but does use ionizing radiation.

Cardiac catheterization plays a critical role in the management of patients with congenital heart disease, as both a diagnostic and a therapeutic tool. Due to the complex hemodynamic data and difficult anatomy in many of these patients, catheterization is best performed by experienced personnel. There is an expanding role for interventional catheterization procedures, including closure of shunts, pulmonary and aortic valvotomy, pulmonary artery stenting, stenting of conduits, and balloon aortoplasty for aortic coarctation.

Specific Defects

Left-to-Right Shunts

Atrial Septal Defect

An atrial septal defect (ASD) is a direct communication between the atrial chambers. ASDs are common, accounting for 5% to 10% of all congenital heart defects and one third of all congenital defects diagnosed in adulthood. They are usually sporadic, but familial cases have been reported. They are more common in female than male individuals (2:1). An associated congenital defect may be seen in up to 30% of cases. ASDs are seen in association with skeletal deformities of the upper extremities, including Holt-Oram syndrome. Ostium secundum and primum defects are also associated with Down syndrome.

There are several morphologic types of ASDs. The most common is the ostium secundum defect (seen in 75% of cases). Secundum defect occurs in the region of the fossa ovalis, may extend in any direction, and may be multiple. Partial anomalous pulmonary venous connections are seen in 2% of patients with secundum defects. Os-

tium primum defects account for 15% of ASDs. Primum defects are part of the spectrum of atrioventricular (AV) septal defects and are associated with a common AV junction. A common AV valve is usually present with fusion of the inferior and superior bridging leaflets, leading to separate mitral and tricuspid orifices. This results in a trileaflet appearance of the anterior mitral leaflet, sometimes referred to as cleft in the anterior leaflet. Mitral regurgitation may be associated with this abnormal valve. Sinus venosus defects account for 10% of ASDs. Sinus venosus defects occur in the superior portion of the septum near the insertion of the SVC and are frequently associated with anomalous pulmonary venous drainage of the right pulmonary veins, most commonly the right upper pulmonary vein. Inferior sinus venosus defects are rare. They occur at the mouth of the IVC and may have right-to-left shunting and cyanosis due to preferential shunting of IVC blood to the LA. The rarest form of ASD is the coronary sinus defect, which may occur at the mouth of the coronary sinus or in the body of the coronary sinus itself (known as unroofing of the coronary sinus). Coronary sinus ASDs are often associated with a persistent left superior vena cava connecting to the LA. Some patients may have absence of most of the interatrial septum, resulting in a common atrium.

With unrestricted defects, there is no pressure gradient between the atria. Left-to-right shunting across the ASD occurs in late systole and diastole. The magnitude of the shunt depends on the size of the defect and the relative of compliance of the right and left ventricles as well as the pulmonary and systemic vascular resistance. Diseases that affect left ventricular (LV) compliance (e.g., hypertension, coronary artery disease) can increase the magnitude of the left-to-right shunt. The left-to-right shunt results in right ventricular volume overload with increased pulmonary blood flow. Large shunts may result in pulmonary hypertension. Spontaneous closure of ASDs may occur. Small ASDs (<3 mm) usually close by 18 months, and as many as 80% of defects in the range of 5 to 8 mm close by 18 months. Larger defects rarely close spontaneously

The cardiac exam demonstrates a right ventricular lift with significant volume overload. S1 is normal. S2 is widely split and does not vary with respiration, although

this pathognomonic finding is not universally present. A systolic flow murmur is common due to increased flow across the right ventricular outflow tract. A diastolic rumble across the tricuspid valve may be heard with large shunts. With the development of pulmonary hypertension, splitting of S2 narrows and the intensity of P2 increases. With shunt reversal (the Eisenmenger syndrome), cyanosis and clubbing develop. Cyanosis may also be seen in the absence of pulmonary hypertension in patients with very large defects, a prominent Eustachian valve, a coronary sinus defect, or in association with pulmonic stenosis, RV dysfunction, or Ebstein's anomaly. Typical ECG findings include right-axis deviation (except in ostium primum defects) and an rSR or rsR pattern in lead V1. There may be evidence of right ventricular hypertrophy (RVH). Some patients have prolongation of the PR interval. Inverted P waves in the inferior leads suggest a sinus venosus type of defect. A superior QRS axis (extreme right- or left-axis deviation) suggests a primum atrial septal defect. The CXR shows right-sided chamber enlargement, a dilated pulmonary artery, and increased pulmonary vascular markings in patients with significant shunts.

The diagnosis is made by echocardiography, which demonstrates the location and size of the defect as well as the direction of shunting. The presence of a dilated RA and RV consistent with right-sided volume overload should suggest the presence of an ASD, prompting thorough interrogation of the atrial septum and a bubble study. Ostium secundum and primum defects are well visualized by transthoracic imaging, particularly on subcostal views. Sinus venosus defects may be more difficult to demonstrate and require additional views. TEE is frequently used in the adult populations to fully interrogate the interatrial septum.

Cardiac catheterization is not usually required in patients with an ASD unless there is associated pulmonary hypertension or the noninvasive assessment is inconclusive. The presence of an ASD is confirmed by catheter passage across the atrial septum and a step up in oxygen saturation at the level of the atrium. Systemic and pulmonary blood flow, ratio of pulmonary to systemic blood flow (Qp/Qs), pulmonary pressure, and pulmonary vascular resistance should be assessed. If anomalous pulmonary venous drainage is suspected, levophase pulmonary artery injections

should be obtained. Coronary angiography is usually performed for patients over the age of 40 years if surgical correction is planned. ASDs can also be diagnosed by cardiac MRI, which is also excellent for assessing pulmonary venous connections.

ASDs are often diagnosed in childhood, but they can also present in adulthood. Patients with an ASD are usually asymptomatic in childhood, but patients may have decreased exercise tolerance and increased respiratory infections. Symptoms usually occur in adulthood by the third or fourth decade. Seventy percent of patients will have symptoms by the fifth decade, and annual mortality increases to 10% by the sixth decade for patients with untreated ASDs. The most common symptoms are dyspnea and decreased exercise tolerance. Patients may present with atrial arrhythmias, congestive heart failure, or symptoms associated with pulmonary vascular disease. There is some increased risk of stroke due to paradoxical embolism, but this is usually seen only in patients with atrial arrhythmias and/or right ventricular dysfunction. Pulmonary vascular obstructive disease (the Eisenmenger syndrome) is uncommon with ASDs, occurring in 5% to 10% of cases, more commonly in female patients. Patients with the Eisenmenger syndrome secondary to an ASD typically present in their twenties or thirties.

Closure of the defect is recommended for ASDs with a Qp/Qs greater than 1.5:1 and a pulmonary to systemic vascular resistance ratio less than 0.7 units. In children, closure is usually recommended between the ages of 2 and 4 years to allow for spontaneous closure. In adolescents and adults, closure is usually undertaken when the diagnosis is made. The surgical approach has low morbidity and mortality (<1%) and is done by patching the defect or with direct suture closure.

Surgical closure of an ASD in childhood or early adulthood (before the age of 25 years) results in a long-term mortality similar to that of an age- and sex-matched control population. These patients can be considered cured. Patients undergoing surgery after the age of 25 years have reduced survival compared to control subjects, most strikingly in those older than the age of 40 years. Surgical closure between the ages of 25 and 40 years in asymptomatic patients is controversial but is generally presumed to prevent symptomatic deterioration. For symptomatic patients older than the

age of 40 years, surgical closure improves exercise capacity, improves survival compared to medically managed patients, and prevents further deterioration in functional capacity. However, it does not reduce the risk of supraventricular arrhythmias, heart failure, or cerebrovascular accidents. Surgical closure in symptomatic patients with a significant shunt who are over the age of 60 years results in symptomatic improvement in 80% (54). Patients with older age at repair require surveillance for atrial arrhythmias, heart failure, stroke, and progressive pulmonary vascular disease. Seventy percent of patients with preoperative arrhythmias have persistent arrhythmias postoperatively, and 10% to 25% of patients without arrhythmias will develop them postoperatively. An increased risk of systemic arterial hypertension of unclear etiology has been demonstrated after ASD closure in older patients. Preoperative pulmonary vascular resistance (PVR) is predictive of outcome. Patients with a PVR of less than 7 Wood units have improvement in symptoms and New York Heart Association (NYHA) functional class, whereas a PVR of greater than 15 Wood units is associated with a high surgical mortality. If PVR is greater than two thirds of systemic vascular resistance, patients must have a large shunt or evidence of pulmonary vascular reactivity before surgery is considered.

The role of device closure is increasing. First attempted in 1976, device systems have undergone continuous evolution in terms of material, design, shape, and delivery method. Devices available or in clinical trials include the Amplatzer septal occluder, the Atrial Septal Defect Occlusion System (ASDOS), the Buttoned Device, the Guardian Angel, the Helex Septal occluder, and the Cardioseal. Success rates vary but generally are in the range of 90% to 97% for initial successful deployment. Residual leaks are common on initial assessment but usually decrease or disappear with longer-term follow-up. Choice of the device type depends on the location of the defect and the degree of aortic rim tissue (must have 4- to 5-mm rim). There are no comparative studies between device and surgical closure.

There is no consensus for long-term follow-up after device closure, and long-term outcomes are largely unknown (including the risk for atrial arrhythmias, heart failure, and stroke). Because there is ongoing morbidity and mortality in adults un-

dergoing surgical closure of ASDs, it is reasonable to postulate that a similar outcome may be seen in adults undergoing device closure. Potential complications specific to device closure include the potential for obstruction of pulmonary or systemic venous drainage, interference with the mitral valve, and erosion of the atrial wall or the aortic wall.

Ventricular Septal Defect

Ventricular septal defects are the most common form of congenital heart defect, accounting for 25% to 30% of all patients with congenital heart disease. The male:female ratio is 1. VSDs are the most common defect seen in the pediatric population. VSDs are usually a single defect, but they can occur in the setting of more complex congenital heart defects. Defects can be divided into restrictive defects (flow restricted between the LV and the RV with right ventricular pressure less than half of systemic levels) or nonrestrictive defects (with equal left and right ventricular pressures). From 70% to 80% of VSDs can be characterized as restrictive, with the potential to close or become smaller. Nearly half of all VSDs are small, and up to 75% may close spontaneously. Even large defects can decrease in size. VSDs usually close by the age of 10 years. Spontaneous closure in adults is rare but has been reported.

The ventricular septum consists of the trabecular muscular septum, the inlet septum (formed from the endocardial cushion), the outlet or infundibular septum, and the membranous septum. Failure of growth, alignment, or fusion of these components results in a VSD. Perimembranous VSDs are the most common type, accounting for 75% to 80% of cases. A perimembranous defect occurs at the junction of the inlet, outlet, and trabecular septum and may extend variably into these regions. The perimembranous VSD underlies the septal leaflet of the tricuspid valve and may decrease in size or close spontaneously due to adherence of septal leaflet tissue to the defect, resulting in a ventricular septal aneurysm. Inlet septal defects account for 5% to 10% of VSDs. They occur in the muscular septum, under the mitral and tricuspid leaflets, due to deficiency of tissue from the endocardial cushion. Inlet VSDs rarely close spontaneously. Muscular defects or defects of the trabecular septum account for 20% of all VSDs. They may be located in various positions within the trabecular septum and may be multiple. Muscular VSDs tend to decrease in size with muscle growth

and may close spontaneously. Outlet defects (also known as doubly committed subarterial defects or supracristal VSDs) account for 5% of all VSDs. They occur in the right ventricular outlet or conal portion of the septum, underlying both the pulmonary and aortic valves. Outlet defects do not close spontaneously, but their size can decrease due to prolapse of aortic cusp tissue through the defect (also resulting in aortic regurgitation).

The degree of left-to-right shunting depends on the size of the defect and the relative resistance of the systemic and pulmonary vascular beds. VSDs are characterized as small when the defect size is less than one-third of the aortic root size, and these are always restrictive. Pulmonary vascular resistance remains normal. With moderate restrictive defects, the defect is approximately half the size of the aortic valve, and there is moderate to severe left-to-right shunting. Patients with moderate defects may develop symptoms associated with LV volume overload and are at risk for developing pulmonary vascular disease. Large VSDs are nonrestrictive, with equal pressures in the left and right ventricles. There is a large left-to-right shunt initially, and the pulmonary circulation is exposed to systemic pressures early in the course of the disease. Patients with nonrestrictive VSDs usually develop irreversible pulmonary vascular disease within the first decade of life, eventually resulting in shunt reversal and Eisenmenger physiology.

The natural history of VSDs depends on the size and location of the defect. Small, restrictive defects with a Qp/Qs less than 1.5 to 1 do not place a hemodynamically significant load on the LV. Moderate or large defects cause pulmonary congestion and LV volume overload, which may lead to LV dysfunction and congestive heart failure. Pulmonary hypertension may occur with moderate defects. Larger defects are associated with a significant risk of pulmonary hypertension and pulmonary vascular obstructive disease. The Eisenmenger syndrome occurs in 10% of patients with VSDs. All patients are at risk for bacterial endocarditis and require antibiotic prophylaxis. Other complications include aortic cusp prolapse through the defect, resulting in aortic regurgitation and/or subaortic obstruction, and the development of a

double-chambered RV due to hypertrophy of muscle bundles within the mid-right ventricular cavity.

The physical exam findings vary with the size of the defect. A patient with a small defect has a normal PMI, a normal S1 and S2, and a harsh pansystolic murmur associated with a systolic thrill. In addition to the murmur and thrill, patients with larger defects have evidence of LV enlargement with prominence and/or displacement of the apical impulse, a diastolic mitral inflow rumble, and frequently a gallop rhythm. With the development of pulmonary hypertension, the intensity of P2 increases, splitting of the second heart sound becomes narrowed, and the murmur decreases or disappears.

ECG findings are nonspecific. The ECG is normal with small defects. Larger defects are usually associated with the development of left ventricular hypertrophy (LVH) and ST-T wave changes. RVH may be seen with large defects or with the Eisenmenger syndrome. The CXR is normal with small defects, but cardiomegaly and pulmonary plethora are seen with larger defects. Patients with severe pulmonary vascular disease and shunt reversal (Eisenmenger physiology) have mild cardiomegaly or normal heart size with large central pulmonary arteries, peripheral pruning of the pulmonary vessels, and oligemic lung fields.

The diagnosis can be made by echocardiography with Doppler color flow mapping. With careful interrogation of the septum, the site and size of defects can be demonstrated. The pressure gradient between the LV and the RV can be assessed by continuous-wave Doppler interrogation of the VSD jet, and right ventricular systolic pressure can be indirectly estimated from continuous-wave Doppler interrogation of the tricuspid regurgitation (TR) jet. Care must be taken with the latter approach because the TR jet may be contaminated by the VSD jet (particularly with perimembranous defects), resulting in inaccurate right ventricular pressure estimation. The interventricular pressure gradient may be inaccurate in the setting of tortuous or serpiginous defects where the modified Bernoulli equation is not applicable. Echocardiography may also reveal other associated defects, including aortic regurgitation. Cardiac catheterization is generally reserved for patients in whom there is uncertainty re-

garding the size of the shunt and the pulmonary vascular resistance. The reversibility of pulmonary hypertension can be assessed with the administration of oxygen, nitric oxide, prostaglandins, or adenosine. Selective coronary angiography is usually performed for patients older than the age of 40 years if surgical repair is planned.

The clinical presentation depends on the size of the shunt. Patients with small defects are asymptomatic and have normal growth and development. The diagnosis in usually made on the basis of finding a loud holosystolic murmur. Larger shunts may result in symptoms of congestive heart failure in infancy as well as an increased susceptibility to pulmonary infections. The diagnosis of a VSD in adulthood is usually based on the incidental finding of a murmur or the development of a complication related to the VSD (e.g., endocarditis, aortic valve prolapse and regurgitation, or the Eisenmenger syndrome). Overall, the 25-year survival for all patients is 87%. Mortality increases with the size of the VSD.

Patients with symptomatic heart failure initially are treated with medical therapy, including diuretics and afterload reduction. Digoxin is often used in the pediatric setting. There are no randomized trials of medical therapy, but its use is indicated to stabilize the patient until surgical repair can be performed. Indications for surgery include severe intractable heart failure within the first 3 months of life, the presence of symptoms in older infants and children, and the presence of a moderate or large defect with a Qp/Qs greater than 2:1. Repair is also recommended for subarterial defects regardless of the shunt size due to the risk of aortic valve prolapse. Pulmonary vascular resistance should be below 8 Wood units (less than two-thirds systemic vascular resistance) for surgery to have long-term success. Repair is usually performed from the RA but occasionally through the RV, with placement of a patch or direct suture closure. Pulmonary artery banding is rarely performed. It is used to decrease pulmonary blood flow in patients with multiple defects or complex malformations that are not otherwise amenable to repair. Transcatheter device closure of VSDs appears to be feasible in some cases but is not widely available.

The prognosis is normal for patients with spontaneous closure of their VSD. Unoperated patients with an isolated small VSD and normal PVR have an excellent

long-term prognosis, although they remain at risk for endocarditis. Unoperated patients with moderate to large shunts are at risk for multiple complications, including endocarditis, aortic regurgitation, LV dysfunction from chronic volume overload, arrhythmias, development of the Eisenmenger syndrome, and sudden death. Patients with subarterial VSDs (and occasionally perimembranous defects) may develop prolapse of the aortic cusp through the defect with the development of progressive aortic regurgitation.

Overall, late outcome after early surgical closure of a VSD is excellent. Residual shunts are common, seen in up to 20% of cases after surgery, but are usually small. Late complications after surgical repair include endocarditis (if a residual shunt persists after surgery), surgically induced aortic or pulmonary regurgitation, and tricuspid regurgitation (if the septal leaflet was manipulated during the VSD repair). Arrhythmias and conduction disturbances may be seen. Right-bundle-branch block occurs in 30% to 60% of patients after surgical closure, first-degree AV block is seen in 10%, and complete heart block in 1% to 3% over long-term follow-up. Patients may have LV dysfunction with late repair of the defect or with significant aortic regurgitation. Patients may have persistent pulmonary hypertension after surgery or may develop progressive pulmonary hypertension despite successful closure of their shunt. There is an increased risk of sudden cardiac death after VSD closure, seen in 2% of patients. The etiology for sudden death has not been defined. In general, patients undergoing early repair without a residual shunt, evidence of pulmonary hypertension, arrhythmias, or conduction block do not require long-term follow-up. Later repair of VSDs is associated with a risk of pulmonary hypertension and LV dysfunction, making long-term follow-up of these patients mandatory.

Patent Ductus Arteriosus

Patent ductus arteriosus (PDA) refers to continued patency of a normal structure in fetal circulation. The ductus arteriosus is derived from the left sixth aortic arch and is usually a left-sided structure, but may be right sided or bilateral. PDA occurs in 5% to 10% of congenital defects and is often present in premature infants. An increased incidence is also seen in cases of maternal rubella. A PDA is associated with

a left-to-right shunt that is predominantly systolic in early infancy but becomes continuous as PVR decreases. Thus, in the newborn with a significant shunt, there is an active precordium and only a systolic murmur. In older children and adults, a continuous machinery murmur is present at the left upper sternal border. A PDA may close spontaneously before the age of 6 months.

The clinic presentation of a PDA is similar to that of a VSD. With small shunts, there is a loud murmur but the ECG and CXR are normal. In patients with a moderate to large shunt, the clinical exam is remarkable for an enlarged apical impulse and bounding pulses in addition to the continuous murmur from the shunt. With a moderate to large shunt, the ECG may show LVH and the CXR will demonstrate cardiac enlargement and pulmonary plethora. Patients with moderate to large shunts may develop atrial arrhythmias, left heart failure, and pulmonary hypertension, including the development of the Eisenmenger syndrome. In patients with the Eisenmenger syndrome, the continuous murmur disappears as the aortic-to-pulmonary pressure gradient decreases. Patients with Eisenmenger syndrome secondary to a PDA have preferential shunting of deoxygenated blood to the descending thoracic aorta through the ductus while oxygenated blood is ejected into the ascending aorta. This leads to the differential cyanosis, with cyanosis and clubbing in the feet but not in the upper extremities. Because of the proximity of the left subclavian artery to the ductus, there may be some clubbing and cyanosis in the left hand. All patients are at risk for endarteritis, regardless of the size of the shunt. An exception to this rule is the silent ductus, which refers to a trivial shunt seen by color flow Doppler without an associated murmur. Asilent ductus has no hemodynamic significance, and the risk of endocarditis is extremely low.

Echocardiography demonstrates continuous flow from the aorta to the pulmonary artery by color Doppler. Direct visualization of the ductus by echocardiography is usually possible in children but difficult in adults. The aortic-to-pulmonary artery pressure gradient can be measured from the continuous-wave Doppler tracings. The presence of other associated congenital defects should be a routine part of the exam. The diagnosis can also be made and/or confirmed at cardiac catheterization by the

presence of an oxygen saturation step-up at the level of the pulmonary artery and demonstration of the ductus by aortography. In premature infants, closure of the ductus arteriosus can be promoted with the use of indomethacin (once coarctation and ductal-dependent congenital defects are excluded). Closure of the ductus is generally recommended for all shunt sizes (except silent PDA) to reduce the risk of endarteritis as well as that of LV volume overload in moderate to large shunts. Closure of a PDA is contraindicated in the setting of Eisenmenger physiology.

Closure of a PDA can usually be accomplished with percutaneous closure devices. The Rashkind double umbrella device was introduced in 1979 and had an occlusion rate of 82.5% at 1 year and 94.8% at 20 months but a fairly high rate of complications. The device is not currently approved by the Food and Drug Administration (FDA). Coils may be used to close a PDA. Coils have been available since 1976 (never applied for FDA approval) and can be deployed using small delivery systems. Closure rates of 93% to 97% have been reported with coil embolization after 6-month follow-up. Embolization into the pulmonary circulation was reported in 3% to 8% of initial studies, but the incidence is lower after modifications in technique. The Amplatzer duct occluder has shown excellent early outcomes, with a 98% closure rate at 6 months. The U.S. experience with the Amplatzer device reported in 2004 demonstrated a 99% success rate for device implant, with 76% occlusion on initial angiogram, 89% occlusion by postprocedure day 1, and 99.7% occlusion at 1 year. Serious adverse events were seen in 2.3% of cases. Patients after device closure still require bacterial endocarditis prophylaxis for at least 6 months, lifelong if there is a residual shunt. There are rare reported cases of hemolysis after device implant.

Surgical ligation and division of the ductus can be done with low morbidity and mortality but is rarely needed. Surgical closure is required for a PDA that is too large for device closure and for those patients with distorted ductal anatomy (e.g. aneurysm or calcification). A patient with a PDA repaired in childhood can be considered cured. Patients repaired in adolescence or adulthood remain at risk for complications such as pulmonary hypertension, LV dysfunction, and arrhythmias and should

have routine follow-up. Although rare, an aneurysm of the PDA may occur with risk of rupture. The natural history of device closure is unknown. Intermittent follow-up is advisable.

Atrioventricular Septal Defects

Partial and complete atrioventricular septal defects (AVSDs) are seen in 2% to 3% of patients with congenital heart disease. Also known as AV canal defects or endocardial cushion defects, they are characterized by a common atrioventricular junction guarded by a common atrioventricular valve. There is absence of the atrioventricular septum that separates the RA from the LV. The aorta is unwedged from its usual position between the atrioventricular orifices, which results in a narrowing of the subaortic region and a longer outflow dimension of the interventricular septum. There is considerable variation in the features of AVSDs, including variations in the common atrioventricular valve, differences in the degree and direction of shunting, and the relative вЂњbalanceвЂќ of the atrioventricular valves and the ventricles. With a partial atrioventricular septal defect (partial AVSD), the common AV valve is divided into separate right and left orifices, which are separated by fusion between the superior and inferior bridging leaflets. This gives a three-leaflet appearance to the mitral valve, often mistaken as a cleft in the anterior leaflet. On echocardiography, the mitral and tricuspid valves appear at the same level at the AV junction. Partial AVSDs may have attachment of the bridging leaflets of the common AV valve to the ventricular septum, resulting in only interatrial shunting (the so-called ostium primum defect). Alternatively, the bridging leaflets may be attached to the atrial septum, resulting in only an interventricular shunt (inlet-type VSD). With a complete atrioventricular septal defect (complete AVSD), the common AV valve floats between the atrial and ventricular septum, allowing shunting at both atrial and ventricular levels. Patients with a complete AVSD may have a common valve with a single orifice or may have separate left and right orifices. When the common AV valve is equally committed to both ventricles, this is referred to as a balanced defect. In unbalanced forms, there is commitment of the common AV valve to one ventricle with resultant hypoplasia of the other ventricle. Many other associated malformations may coexist, including left ventricular outflow obstruction, other congenital deformities of the AV

valve, and association with other forms of congenital heart disease (e.g., tetralogy of Fallot, double-outlet right ventricle, etc.). There is a distorted arrangement of atrioventricular node (located in the posterior atrial wall) and the bundle of His (located under the inferior bridging leaflet), which makes these patients prone to conduction block.

AVSDs are particularly common in patients with Down syndrome (seen in 30% to 40% of Down patients with CHD), usually as the complete form of AVSD. Conversely, Down syndrome is present in 70% to 80% of patients with a complete AVSD. The risk of developing associated pulmonary vascular disease appears to be greater and more rapidly progressive in patients with Down syndrome. This is due, at least in part, to a tendency toward airway obstruction (due to macroglossia, a small hypopharynx, and poor pharyngeal muscle tone), abnormal capillary bed morphology in the lungs, and possible pulmonary hypoplasia.

The clinical presentation depends on the specific malformation. Partial AVSDs of the ostium primum type present similar to other ASDs, except for the unusual QRS axis (leftward and superior counterclockwise axis). Patients may have first-degree AV block as well. Partial AVSDs of the inlet VSD type present similar to other VSDs. Patients with complete AVSDs typically present with breathlessness and heart failure in infancy due to excessive pulmonary blood flow. Symptoms usually becomes manifest after PVR falls, usually within a few weeks of birth. These patients are also at significant risk for pulmonary hypertension if not repaired. The magnitude of left-to-right shunting and the degree of regurgitation through the common AV valve determine the clinical presentation. Patients with large shunts and/or significant AV valve regurgitation present earlier with symptoms of heart failure and/or evidence of pulmonary hypertension. Varying degrees of cyanosis may be present if there is significant right-to-left shunting.

The ECG in patients with a complete AVSD shows left-axis deviation due to an abnormal activation sequence of the ventricles (due to deficiency of intermediation radiation of left bundle branch). First-degree AV block is common, and right-bundle-branch block and right ventricular hypertrophy (RVH) are invariably present. Left

ventricular hypertrophy (LVH) may be present as well. The CXR shows cardiomegaly and pulmonary plethora.

Echocardiography places a critical role in the diagnosis, including the anatomy and function of the common AV valve, the location and degree of intracardiac shunts, the balance of the ventricles, and the presence of other associated conditions. Cardiac catheterization with angiography is often warranted to assess hemodynamic parameters and the magnitude of the intracardiac shunts. In patients with significant pulmonary hypertension, a lung biopsy is occasionally required to determine operability.

Surgical repair should be undertaken at the time of diagnosis if pulmonary vascular disease is not prohibitive. Surgical repair of complete AV septal defects is complex, requiring closure of the shunts and creation of two competent AV valves. In some cases, a pulmonary artery band is placed to prevent pulmonary hypertension if repair of the defect cannot be performed. When diagnosis of made in adolescence or adulthood, there is usually a partial AV septal defect or the patient has developed severe pulmonary vascular obstructive disease. Patients who present in adulthood with a partial AVSD are usually candidates for surgery. Device closure is not an option. Patients with a complete AVSD and severe pulmonary hypertension should be treated as having Eisenmenger physiology once the diagnosis is confirmed. The long-term outcome after surgical repair is good. All patients are at risk for endocarditis and require antibiotic prophylaxis. Despite a good prognosis after surgery, patients remain at risk for left-sided AV valve regurgitation and need long-term follow-up. Surgical series have indicated that as many as 10% to 12% of patients will need further surgery for left-sided AV valve regurgitation. Patients may also have a residual VSD, may develop subaortic or subpulmonary obstruction, or may develop progressive pulmonary vascular disease (especially with вЂњlateвЂќ closure of VSD). Patients are also at risk for development of complete heart block, sinus node dysfunction, and atrial arrhythmias. Sudden death has been reported, although the risk is largely unknown.

Aortopulmonary Window

The aortopulmonary window is a rare form of congenital heart disease, manifested by a communication between the ascending aorta and the pulmonary trunk

above the level of the coronary arteries. An aortopulmonary window can occur as an isolated defect but is often associated with other anomalies. The defect is usually very large, resulting in a large left-to-right shunt and a high likelihood of developing pulmonary hypertension. Thus, patients usually present in infancy with symptoms of heart failure or with cyanosis due to pulmonary hypertension with right-to-left shunting. The diagnosis is made by echocardiography demonstrating the defect and the associated shunting. Occasionally, defects may be small enough to be closed with catheter intervention, but surgical closure is required for the majority. Presentation in adulthood is nearly always associated with the Eisenmenger syndrome.

Partial Anomalous Pulmonary Venous Connection

Partial anomalous pulmonary venous connection is defined as one or more (but not all) pulmonary veins connecting to a systemic vein, the RA, or the coronary sinus. Examples include connection of the right upper lobe and right middle lobe veins to the SVC, right upper lobe and right middle lobe veins to the RA, right pulmonary veins to the IVC, right lower lobe vein to the IVC (scimitar syndrome), left upper or lower pulmonary veins to the coronary sinus, and left lower pulmonary veins to the RA or IVC. Partial anomalous pulmonary venous connection is relatively uncommon, accounting for less than 1% of all congenital defects. An ASD is usually present, and the clinical presentation is similar to that of an uncomplicated ASD. Partial anomalous pulmonary venous connection can be seen with any type of ASD but is most commonly associated with the sinus venosus type of ASD. Other associated defects may occur. The exam findings, ECG, and CXR findings in patients with partial anomalous pulmonary venous connection are similar to those of a secundum ASD. The CXR findings in the scimitar syndrome are addressed later.

Patients are usually asymptomatic in childhood. They may remain undiagnosed in adulthood if the anomalous pulmonary venous connection is an isolated defect. If more than 50% of the total pulmonary blood flow drains to the right heart, symptoms are common. Thus, symptomatic patients usually have more than one anomalous connection or an associated lesion. Symptoms are similar to those of ASD, with dyspnea, arrhythmias, and (rarely) pulmonary hypertension. The diagnosis can be

made by echocardiography if care is taken to identify the pulmonary vein connections. TEE is usually required in adult patients to adequately define the pulmonary vein anatomy. Cardiac MRI is an excellent tool for the diagnosis of partial anomalous pulmonary venous connections.

Treatment depends on the magnitude of shunting. Isolated anomalous pulmonary venous connection with a small shunt does not require surgery. For larger shunts, surgical closure of the ASD and rerouting of pulmonary venous return to the left atrium is performed to prevent long-term complications such as atrial arrhythmias, right heart failure, and pulmonary hypertension. Pulmonary venous drainage should be assessed in any patient with an ASD who is being considered for either device or surgical closure. The presence of an anomalous pulmonary venous connection is a contraindication to device closure. Inspection of the pulmonary venous connections should be a routine part of surgical closure of an ASD, and anomalous pulmonary venous connections should be repaired when present.

The long-term outcome after surgical repair of partial anomalous pulmonary venous connection is excellent. Bacterial endocarditis prophylaxis is not required after surgical repair. Obstruction of the reimplanted pulmonary veins or obstruction of the vena cava at the site of pulmonary vein explantation is uncommon but may require surgical or catheter intervention.

Scimitar Syndrome

The scimitar syndrome refers to the presence of anomalous drainage of the right pulmonary veins to the IVC with a characteristic appearance on CXR resembling a scimitar or Turkish sword. There is usually some degree of hypoplasia of the right lung and the right pulmonary artery, usually with an aberrant systemic artery from thoracic aorta supplying part of the right lung. Surgical correction removes the left-to-right shunt and may improve blood flow to the right lung. There is a risk of postoperative pulmonary venous obstruction.

Obstructive Lesions

Pulmonary Stenosis

Pulmonary stenosis (PS) is a common defect, occurring in 7% to 10% of patients with congenital heart disease. Obstruction may be subvalvular, valvar, or supravalvular. Valvar stenosis is the most common (90%). The pulmonary valve morphology varies. The valve may be unicommissural with an eccentric orifice (extremely rare), bicuspid or trileaflet with commissural fusion, or dysplastic. Dysplastic valves have markedly thickened leaflets with disorganized myxomatous tissue but minimal commissural fusion. Bicuspid or trileaflet valves with commissural fusion are usually amenable to balloon dilation or surgical valvotomy, whereas dysplastic valves are less amenable to these procedures. Dysplastic valves are commonly associated with Noonan syndrome. PS is usually an isolated lesion. Associated cardiac and noncardiac malformations are more common when the valve is dysplastic. Chronic obstruction of the right ventricular outflow tract leads to RVH, which may be particularly prominent in the infundibular region, further contributing to RV outflow tract obstruction. Severe PS presenting in infancy is associated with severe RVH and a small right ventricular cavity size. Lesser degrees of PS are associated with RVH, but the RV cavity is usually well formed. The degree of stenosis is classified by peak systolic gradient, with trivial stenosis defined as a peak gradient less than 25 mm Hg, mild stenosis with a gradient of 25 to 49 mm Hg, moderate stenosis with a gradient of 50 to 79 mm Hg, and severe stenosis with a peak gradient above 80 mm Hg.

Infants with critical PS present in neonatal period, usually with cyanosis due to right-to-left shunting across a PFO or ASD. Mortality is high in neonates with critical PS unless intervention is prompt. Lesser degrees of stenosis usually present later in childhood or in adulthood. Patients with trivial or mild stenosis with a peak gradient of less than 25 mm Hg have a good outcome. There is usually no significant progression of disease, and therefore no treatment is warranted. Patients with more significant stenosis may present with exertional dyspnea, chest pain, fatigue, or syncope, occasionally with cyanosis.

The physical exam findings in valvar PS include an RV lift, a thrill along the left sternal border, and a harsh crescendo-decrescendo systolic ejection murmur in the pulmonary area, which is louder in expiration. A systolic ejection click is often

present. The intensity of P2 is reduced in patients with severe stenosis. The ECG reflects the degree of RVH (except in the neonatal period). The ECG is normal with mild degrees of obstruction and shows right-axis deviation and RVH with moderate to severe obstruction. Poststenotic dilation of the main pulmonary artery and the left pulmonary artery (due to a more parallel take-off of the left pulmonary artery) may be seen on CXR with all degrees of PS. Heart size is normal with mild to moderate obstruction, but right-sided enlargement is seen with severe stenosis. Echocardiography is the diagnostic method of choice and can demonstrate valvular and infundibular anatomy. Continuous-wave Doppler is used to quantitate the transvalvular gradient. A complete study includes an assessment of the integrity of atrial septum as well as assessment of RV size and function. In the Second Natural History Study of Congenital Heart Defects, patients with mild PS (peak gradient 25 to 49 mm Hg) had a 20% chance of requiring intervention at some point. Patients with moderate stenosis treated medically were at risk for progressive obstruction with symptoms warranting intervention. Most patients with a peak gradient greater than 50 mm Hg required intervention, with better outcomes demonstrated in those patients undergoing intervention than in those treated medically.

The earliest surgical interventions on the pulmonary valve were performed using a closed technique with blunt dilation of the right ventricular outflow tract (Brock procedure). Currently, pulmonary valvotomy is performed using cardiopulmonary bypass. Transcatheter intervention with balloon valvuloplasty has now largely replaced operative intervention and has become the therapy of choice. Balloon valvuloplasty can be performed with a low rate of complications and outcomes similar to surgery with a similar reduction in gradient. An infundibular gradient may be present after successful pulmonary valvotomy but often regresses over 3 to 12 months. Long-term outcomes for both surgical and balloon valvotomy are excellent. Long-term complications of both procedures include pulmonary regurgitation and residual or recurrent RV outflow tract obstruction. Reintervention is required in some cases for recurrent RV outflow obstruction with symptoms or significant arrhythmias. The presence of severe pulmonary regurgitation with decreasing exercise capacity, deteriorat-

ing RV function, or the development of significant arrhythmias is an indication for pulmonary valve replacement. Subpulmonary stenosis is usually seen in complex defects, such as tetralogy of Fallot. Isolated subpulmonary stenosis is rare.

Supravalvular obstruction with pulmonary arterial stenosis may be seen in rubella syndrome and Williams syndrome and in association with other complex congenital cardiac defects (e.g., tetralogy of Fallot). Pulmonary arterial stenosis may also occur as an isolated defect. Stenosis may occur in the main pulmonary artery, at the bifurcation of the pulmonary artery branches, and at the secondary or more distal branches. The obstruction may be focal or diffuse (often a manifestation of more widespread vasculopathy such as rubella, cutis laxa, or Ehlers-Danlos syndrome).

The clinical presentation is similar to that of valvar PS. Patients have a systolic ejection murmur, but there is no ejection click, and P2 is normal. The ECG and CXR findings are usually nonspecific. Echocardiography may demonstrate the presence of RV pressure overload and may demonstrate the site of stenosis, but the branch pulmonary arteries may be difficult to visualize by TTE. Doppler study of the main and branch pulmonary arteries is used to quantitate the severity of stenosis. CT or MRI scans offer excellent visualization of the main pulmonary artery trunk and the pulmonary artery branches. Angiography can also be used to demonstrate the obstruction, and the localized pressure gradient can be demonstrated at catheterization. Perfusion imaging helps in assessing perfusion imbalance. Although pulmonary artery stenosis may be managed surgically with pericardial or prosthetic patch repair to enhance stenotic vessels, stenting of pulmonary vessels is playing an increasing role.

Obstruction of the Left Ventricular Outflow Tract

Left ventricular outflow tract obstruction may occur at the level of the valve, below the valve, or in the ascending aorta. Valvar aortic stenosis (AS) is the most common cause of congenital LV outflow obstruction, and bicuspid valves are by far the most common type. The bicuspid aortic valve is usually not included in epidemiologic studies of congenital heart disease but is the most common type of congenital cardiac defect, seen in 1% to 2% of the general population. A bicuspid aortic valve results from fusion of two commissures, resulting in two rather than three valve leaf-

lets. There is a high incidence of bicuspid valves in a mouse model of nitric oxide synthase deficiency, suggesting a role of nitric oxide in the development of the normal trileaflet aortic valve. Bicuspid aortic valves may be familial, but most appear to be spontaneous mutations. Bicuspid valves and coarctation of the aorta are the most common defects found in patients with Turner syndrome (XO).

Considered a normal variant by some, a bicuspid aortic valve may function normally throughout life or may develop either stenosis or regurgitation. There are autopsy reports of normally functioning bicuspid valves in octogenarians. The abnormal opening of the valve leaflets is presumed to cause an abnormal flow profile across the valve, resulting in valve thickening, fibrosis, and calcification. This, in turn, may result in either progressive stenosis or regurgitation. Although it is usually an isolated abnormality, associated cardiac defects are seen in up to 20% of patients (including coarctation of the aorta, PDA, and VSD). Left-dominant coronary circulation is seen in 30% to 60% of cases. Patients with bicuspid aortic valves may have associated abnormalities within the media of the aorta, placing them at risk for aortic root dilation and dissection. The degree of aortic root abnormality may be out of proportion to the severity of the valvular dysfunction. Congenital AS presenting in infancy is unusual (occurs in 10% to 15% of patients with congenital AS) and may be associated with other lesions. The valve morphology in isolated valvar AS in the neonate may be bicuspid, unicuspid, or severely dysplastic. Neonates with severe AS typically present with severe decompensation, and prompt intervention is required. Children with less severe degrees of AS are usually asymptomatic, and the diagnosis is usually made based on the presence of a murmur. Bicuspid aortic valves are often seen in adults as an incidental finding.

Children and adults with congenital AS usually have a systolic ejection click and a systolic ejection murmur. The aortic closure sound (A2) may be normal or decreased due to decreased leaflet mobility. The second heart sound may be normal or narrowly split. Paradoxical splitting of the second heart sound may be present with severe obstruction. The ECG may be normal or may demonstrate LVH. There is poor correlation between the degree of stenosis and the ECG findings. The CXR may

demonstrate a normal heart size or cardiomegaly. Poststenotic dilation of the ascending aorta may be seen.

The clinical manifestations of AS are similar for congenital and acquired forms. Chest pain, congestive heart failure symptoms, and syncope (often exertional or postexertional) are the presenting symptoms. Unlike acquired forms of AS, symptomatic congenital AS tends to present earlier in life (in the forties or fifties). In the adult population, bicuspid aortic valves account for half of all surgical cases of isolated AS. Patients with associated abnormalities of the aortic media may present with aortic root dilation, dissection, and rupture. All patients are at risk for endocarditis, particularly those with bicuspid aortic valves.

Echocardiography is the diagnostic tool of choice for the diagnosis of AS. Patients with a bicuspid aortic valve typically have two unequal-size aortic cusps with an eccentric closure line. Valve anatomy can be determined, and the presence of associated regurgitation or stenosis can also be demonstrated and quantitated, with assessment of the transvalvular gradient, and calculation of valve area. LVH and LV function (both systolic and diastolic) should be assessed. Cardiac catheterization is usually reserved for patients in whom either surgical or catheter intervention is contemplated or for additional quantitation of the severity of valvular disease. Coronary angiography is usually performed in patients older than the age of 40 years. Visualization of the aortic root by echo, angiography, or MRI is an important part of the diagnostic evaluation. All patients with congenital AS need bacterial endocarditis prophylaxis. The indications for catheter or surgical intervention differ between the pediatric and adult populations. In children, there is a risk of sudden death in the absence of definable symptoms related to the aortic valve disease. For this reason, catheter or surgical intervention is recommended for those patients with severe stenosis as defined by a valve area of less than 0.5 cm^2/m^2 or a mean gradient of greater than 50 mm Hg. Exercise testing is also used, with the development of ST-segment depression or significant ventricular ectopy considered to be a reasonable indication for intervention. For mild stenosis (gradient <40 mm Hg), observation is recommended because the risk of sudden death is low. In the adult population, the indications for

surgical intervention are the same as for those patients with acquired forms of AS, namely chest pain, congestive heart failure, and syncope. Unlike the pediatric population, sudden death occurs rarely in asymptomatic adult patients with AS. In symptomatic adults, survival is poor without surgical intervention, with 5-year survival rates ranging from 15% to 50%. Because of the associated aortic root abnormalities, the initial presentation of a patient with a bicuspid aortic valve may be in the setting of aortic dissection or rupture.

In the pediatric and adolescent populations, balloon valvotomy is a reasonable option for many patients. Successful balloon valvotomy requires a pliable, noncalcified valve. Surgical options in the pediatric age group include valvotomy and valve replacement. The Ross procedure is usually preferred in the pediatric population because of the potential for growth of the вЂњneoaorticвЂќ valve in proportion to patient's somatic growth. In adolescents and young adults, balloon valvotomy may be an option if the valve appears pliable and has little or no calcification. In most adult patients, there is usually significant calcification and leaflet thickening, making balloon and surgical valvotomy unattractive. Thus, aortic valve replacement is usually required. Late complications of both balloon valvotomy and surgical valvotomy are well recognized. Series of surgical valvotomy have similar outcomes to catheter-based procedures, with a 40% to 50% incidence of reoperation for recurrent stenosis or regurgitation. Aortic regurgitation is common postvalvuloplasty (either surgical or balloon). The degree of aortic regurgitation (AR) is usually mild, but it is moderate in 20% to 30% of cases, with a potential to progress over time. LV dysfunction may occur, usually in patients with a later age at repair and/or a history of prolonged, severe obstruction. The reported risk of sudden death in the postsurgical valvotomy population is 0.4% per year, usually associated with residual or progressive aortic valve disease. All patients remain at risk for endocarditis.

Subaortic stenosis may take many forms, ranging from a discrete fibrous or muscular ridge to a more diffuse (tunnel) form of muscular hypertrophy. Subaortic obstruction may be isolated or may occur in association with other defects (in 60%). The most common associated defects are VSD, coarctation, Shone syndrome, PDA,

and valvar AS. Subaortic obstruction occurs due to an accumulation of fibroelastic tissue and may be an acquired lesion. Subtle abnormalities of the LV outflow tract may result in altered shear stress, triggering cell proliferation. Progression of stenosis is common, although the rate of progression is variable and often difficult to predict. Downstream turbulent flow may result in damage to the aortic leaflets, resulting in aortic regurgitation in as many as 50% of patients.

The clinical presentation varies. Patients with mild obstruction are usually asymptomatic. Dyspnea, chest pain, or syncope is seen with moderate to severe obstruction. The diagnosis is made by echocardiography demonstrating narrowing of the LV outflow tract. A discrete membrane may be visualized, or there may be more diffuse narrowing and obstruction. Measurement of the severity of subaortic stenosis by Doppler is accurate, with discrete forms of obstruction, but it may be inaccurate in long, tunnel-like stenosis. Cardiac catheterization is used to measure the subaortic gradient and to visualize the subvalvular anatomy by angiography. Management is controversial for asymptomatic patients. Patients are at risk for progressive obstruction and progressive aortic valve damage. Some experts suggest waiting for symptoms, whereas others propose early intervention to prevent aortic valve damage. In general, a resting gradient greater than 50 mm Hg and/or progressive AR are indications for surgery. Surgery is more complicated for tunnel-type stenosis, which has a higher operative mortality. In addition to resection of subaortic tissue, some patients may need augmentation of the LV outflow tract (aortoventriculoplasty or Konno procedure). These patients are at risk for complete AV block as a complication of surgery. All patients are at risk for progressive AR, even after successful relief of subaortic obstruction, which occurs in as many as 25% to 40% of cases. Recurrence of LV outflow tract obstruction after successful surgical excision occurs frequently, and is reported to be as high as 27%.

Supravalvular AS is the rarest form of LV outflow tract obstruction, and is caused by a variety of different pathologic lesions. All forms of supravalvular obstruction tend to progress over time. Supravalvular AS is frequently seen in Williams syndrome (supravalvar AS, intellectual impairment, and distinct facial features). Su-

pravalvular stenosis may also occur as an isolated sporadic case and occasionally in familial form. The most common manifestation is narrowing of aorta at the level of the sinotubular junction. There is potential for involvement of the coronary artery ostia, including dilation of coronary arteries and obstruction, aneurysms of the ascending aorta, pulmonary artery stenosis, and involvement of other major arterial branches, including the cerebral circulation. The aortic valve is abnormal in 35% to 50% of cases, with bicuspid valves and aortic regurgitation or stenosis. The diagnosis of supravalvar obstruction may be made by echocardiography, MRI, or catheterization.

Surgery is performed for all symptomatic patients. Other indications for intervention include a gradient of greater than 50 mm Hg or progressive aortic valve dysfunction in asymptomatic patients. Surgery involves relieving obstruction while preserving aortic root geometry and aortic valve function. The Ross procedure is often recommended for those patients requiring aortic valve replacement. Recurrence of supravalvular stenosis is uncommon after repair. Reoperation is required in 17% to 40% of patients undergoing surgery at an early age, usually aortic valve replacement for progressive AR.

Coarctation of the Aorta

Coarctation of the aorta is defined as a narrowing or obstruction of the aortic arch. Coarctation is a common defect and occurs in 8% to 10% of all congenital defects; it is more common in male than in female individuals (2:1). Aortic coarctation may occur in isolation but is often associated with other congenital defects (bicuspid aortic valve in up to 85% of cases; also VSD and mitral valve abnormalities). Aortic coarctation is common in Turner syndrome, occurring in 30% of cases.

Aortic obstruction usually occurs at the level of the ligamentum arteriosus and is due to thickened intima and increased tissue in the media consisting of collagen, smooth muscle cells, and varying degrees of elastin. A more diffuse arteriopathic process appears to be involved because some patients have a propensity to aortic aneurysm formation and dissection or may have associated aneurysms in the circle of Willis (seen in 10% of cases).

The clinical presentation depends on the location and severity of the obstruction. More than half of patients present with symptoms in the first year of life. In the infantile type, systemic blood flow depends on flow through the ductus to the descending thoracic aorta. In these infants, ductal closure can result in circulatory collapse. The use of prostaglandin E_1 to maintain ductal flow is a temporizing measure, and immediate intervention is required due to the absence of adequate collateral circulation. After repair in infancy, these patients remain at risk for premature atherosclerosis, late hypertension, and premature death. Presentation in older children and adults is different. In these patients, blood flow to the descending thoracic aorta is supplied by the LV through the ascending aorta. Collateral circulation gradually develops between the proximal and distal aorta. These patients are usually asymptomatic and present with upper limb hypertension.

The physical exam findings depend on the age of presentation. In the infantile form, the infant is usually in circulatory shock and may have differential cyanosis. In adolescents and adults, the exam is remarkable for a blood pressure difference between the upper and lower extremities and diminished or absent femoral pulses. A short systolic murmur from the coarctation is common and may be heard in the left interscapular area. Faint, continuous murmurs from collateral vessels may also be audible. The ECG is often normal but may show LVH. On CXR, the heart size may be normal or mildly enlarged. Rib notching from the fourth to eighth ribs may be seen in older children and adults due to hypertrophied intercostal arteries as part of the collateral circulation. A sign representing a pre- and poststenotic dilation of the aorta at the level of the coarctation may be seen.

Echocardiography is a good technique for the diagnosis of coarctation, demonstrating the area of obstruction in the aorta and demonstrating disturbed flow by Doppler techniques. Continuous-wave Doppler with the expanded Bernoulli equation is needed to accurately assess the degree of obstruction. For patients with severe stenosis and extensive collaterals, the Doppler gradient may underestimate the degree of obstruction due to decreased blood flow through the coarctation segment (206). MRI is excellent for demonstrating aortic anatomy and is particularly useful in the adult

population in whom echocardiographic imaging of the aortic arch and descending thoracic aorta may be difficult.

The long-term outcome for patients with coarctation of the aorta is poor without intervention. Sixty percent of patients with symptomatic coarctation and 90% with complicated coarctation (associated with other lesions) will die within the first year of life without intervention. The average life expectancy for simple coarctation without surgery is 35 years. Presentation in adulthood suggests mild to moderate postductal coarctation. Indications for intervention beyond the neonatal period include congestive heart failure, the presence of upper extremity hypertension, and/or a gradient greater than 20 mm Hg across the obstruction. Exercise testing may be used to provoke a gradient across the area of obstruction.

Surgery for native coarctation in children can be done with an end-to-end anastomosis, a subclavian flap (to augment the aortic arch), or an interposition graft. In adults, resection of the obstructed segment with end-to-end anastomosis is the procedure of choice. An interposition tube graft may be needed if there is a long segment of coarctation. A bypass jump graft is occasionally required in older patients with fragile aortic tissue or a long segment of obstruction. Postoperative complications include hypertension, abdominal pain, chylothorax, late aneurysm formation, and, rarely, spinal cord ischemia.

Percutaneous transcatheter angioplasty of native or recurrent coarctation has an increasing role. In native coarctation, balloon procedure with or without stent placement is a treatment alternative. Acute and long-term results for native aortic coarctation are similar to those of surgery, but aortoplasty is associated with higher rates of aneurysm formation and restenosis than surgery. Balloon aortoplasty appears to be a better option than surgery for recurrent coarctation. Complications of catheter procedures include femoral artery injury and thrombosis, aneurysm formation, embolic events, and, rarely, aortic rupture. Hypertension is common, even after successful relief of obstruction. Hypertension is seen in as many as 75% of patients after repair and is more common in those patients with older age at repair. The incidence of hypertension appears to increase with longer follow-up. Patients with normal resting

blood pressure often demonstrate an abnormal blood pressure response to exercise as well as increased left ventricular mass. Although the pathophysiology is not well understood, the hypertension is likely to be related to structural changes in the central and peripheral vessel walls, abnormalities of endothelial reactivity, and alterations in the reninвЂ“angiotensin system. In some patients, there is persistent hypoplasia of the aortic arch, which contributes to persistent hypertension. Chronic hypertension places patients at risk for premature coronary artery disease (CAD), LV dysfunction, rupture of aortic or cerebral aneurysms, and sudden death. Meticulous blood pressure control is mandatory. Beta-blockers are usually recommended as first-line therapy, although there are no randomized trials.

Lifelong follow-up with imaging of the aorta is mandatory but not often employed. Even after successful repair, there is evidence of ongoing morbidity and mortality in these patients. In one long-term follow-up of postoperative coarctation repair, the overall 30-year survival was only 72%. Thirteen percent of patients required reoperation for either aortic valve replacement or recurrent coarctation (228). Residual or recoarctation may be seen in 3% to 41% of patients and can occur with any surgical technique or after angioplasty (seen in 8% to 11% of patients undergoing angioplasty for native coarctation). Residual or recurrent obstruction is associated with hypertension, increased LV mass, and the development of CAD and congestive heart failure. Angioplasty is usually recommended for recoarctation after previous surgery, with a good success rate (65% to 100%) and an acceptable (13%) complication rate. Stents are increasingly being used for recurrent coarctation, although only short-term data are available.

Patients may have aneurysm formation at site of repair (seen in 5% to 9% of surgical patients and 4% to 12% of patients after balloon procedures) and are also at risk for dissection and rupture. Both repaired and unrepaired patients may have evidence of a diffuse arteriopathy of the aorta of unclear etiology and may develop aneurysm formation and dissection at a site remote from the original site of coarctation. All patients (repaired and unrepaired) are at risk for endarteritis or endocarditis on an associated bicuspid valve. As many as 10% of patients with coarctation of the aorta

will have aneurysms of circle of Willis. Their growth appears to be promoted by uncontrolled hypertension. Screening for intracranial aneurysms is not routinely recommended.

Interruption of the Aortic Arch

Interruption of the aortic arch is defined as the absence of continuity between the transverse arch and the descending thoracic aorta. This uncommon defect produces symptoms in the neonatal period as the ductus arteriosus closes. There are rare cases of survival to adulthood. Interrupted aortic arch may be associated with DiGeorge syndrome and is nearly always associated with other defects (e.g., VSD, PDA, and complex defects). The diagnosis is made by echocardiography. Prostaglandin E_1 is administered to maintain ductal patency and to temporize until surgery can be performed. After repair, patients may develop LV outflow obstruction and obstruction at the site of the surgical repair.

Other Obstructive Lesions

Shone Syndrome

Left ventricular inflow and outflow obstructive lesions frequently occur together. Shone syndrome was originally described as supravalvular mitral membrane, parachute mitral valve, subaortic stenosis, and coarctation of the aorta. Currently, the term Shone syndrome is applied to patients with some or all of these features.

Congenital Mitral Stenosis

Congenital mitral stenosis is rare. When present, it often coexists with other left-sided stenotic lesions (i.e., LV outflow tract obstruction and coarctation of the aorta). The obstruction may be supravalvular, at the annulus, at the leaflet margins, or at the level of the chordae and papillary muscle. Typically, congenital mitral stenosis has rolled leaflet edges, short, thick chordae, and hypoplastic papillary muscles. If the papillary muscles fuse to form a single papillary muscle, the term parachute mitral valve is applied. The age at presentation depends on the severity of obstruction and the presence of other associated lesions. Congenital mitral stenosis is usually diagnosed in childhood, rarely in adulthood. Patients typically present with symptoms of heart failure and signs of pulmonary hypertension. Echocardiography is diagnostic.

Treatment consists of medical management, with surgery for symptoms refractory to medical management. Balloon valvotomy may be considered, but results are less satisfactory than for rheumatic mitral stenosis. There are limited data on long-term surgical outcomes.

Cor Triatriatum

Cor triatriatum is a rare congenital defect in which a membrane divides the LA into a superior pulmonary venous chamber and an inferior chamber including the LA appendage and inflow portion of the LA. This occurs due to embryologic failure of the common pulmonary vein to become incorporated into the LA. An associated ASD is common, either above or below the membrane, but the atrial septum may be intact. From 70% to 80% of patients have other associated defects. The clinical presentation depends on the severity of obstruction (size of the orifice) and the presence of associated defects.

Patients may present in infancy or adulthood. Patients presenting in infancy have dyspnea, cyanosis, exercise intolerance, and failure to thrive. Patients who present in adulthood may have atrial arrhythmias, dyspnea, syncope, chest pain, or symptoms caused by pulmonary hypertension. The diagnosis may be also be made incidentally during echocardiography. TTE or TEE demonstrates a nonmobile membrane in the left atrium. Echocardiography is also used to define the location, size, and number of membrane openings, the transmembrane gradient, and the presence of associated defects including anomalies of pulmonary venous connection. In some cases, it may be necessary to volume load the patient in order to assess the significance of the transmembrane gradient. Surgical excision is therapy of choice. There is a high mortality in symptomatic patients who do not undergo intervention. Reoperation is rarely necessary.

Pulmonary Vein Stenosis

Congenital pulmonary vein stenosis and atresia is uncommon, usually consisting of diffuse hypoplasia of the pulmonary veins. Surgical results are disappointing, with recurrence of stenosis and progressive pulmonary hypertension commonly seen after surgery. Transcatheter approaches with balloon dilation have also been disap-

pointing. There is some preliminary data suggesting that cutting balloon technology may be helpful.

Vascular Rings

Vessels encircling the trachea and the esophagus cause vascular rings. In contrast, vascular slings partially encircle these structures. Compression of the trachea and esophagus may cause dysphagia, wheezing, and respiratory distress, or these vascular abnormalities may be incidental findings. Imaging by echocardiography or magnetic resonance imaging is usually diagnostic.

Complex Lesions

Transposition Complexes

In transposition complexes, the great arteries arise from the wrong ventricles (ventriculoarterial discordance), with the aorta arising from the RV and the pulmonary artery from the LV. The aorta is usually anterior to the pulmonary artery, and there are many variations in the spatial relationship of the two great vessels. The terms D and L refer to the cardiac loop or position of the ventricles.

Complete Transposition

In complete transposition of the great arteries (also known as D-transposition), there is atrioventricular concordance (the RA connected to the RV and the LA to the LV) but ventriculoarterial discordance (the RV connected to the aorta and the LV to the pulmonary artery). This results in two parallel circulations. Complete transposition is the second-most-common cyanotic lesion overall and the most common cyanotic lesion presenting in neonates. Two thirds of patients are male.

Most cases are not associated with a specific gene defect. There is an increased incidence in infants of diabetic mothers, leading to speculation that complete transposition may be related to a maternal intrauterine hormone imbalance. Associated defects are common. From 60% to 70% of patients with complete transposition have an intact ventricular septum, whereas 30% to 40% have a moderate to large VSD. Other abnormalities may be present, including LV outflow tract obstruction (subpulmonary obstruction), which is seen in 25% of cases, and coarctation of the aorta, which is seen in 5%.

With complete transposition and intact ventricular septum, there is complete separation of the pulmonary and systemic circulations, and the only intracardiac mixing occurs through the foramen ovale and the ductus arteriosus. Because the foramen ovale allows only limited interatrial shunting, the infant is dependent on shunting through the ductus arteriosus. These infants are severely cyanotic within hours to days after birth. Without intervention, mortality is 90% in the first year of life. Treatment involves prostaglandin E_1 to maintain patency of ductus and balloon atrial septostomy to improve oxygenation by increasing intracardiac mixing. Patients with complete transposition and a VSD tend to have less cyanosis and be less critically ill in the neonatal period.

The cardiac exam in neonates with complete transposition is remarkable for severe cyanosis, no murmur, and a single S2. The ECG typically shows RVH and right-axis deviation, and the CXR shows cardiomegaly with increased pulmonary vascular markings. Although the ECG and CXR findings are suggestive, the diagnosis is made by echocardiography. Cardiac catheterization may be performed to define anatomy but is usually not required.

Surgery during the late 1950s and early 1960s was performed using the atrial switch procedure (the Senning or Mustard procedure). These procedures rerouted venous return to allow systemic venous flow to be returned to the LV and then ejected into the pulmonary artery and pulmonary venous blood to be returned to the RV and ejected into the aorta. The Senning procedure used right atrial wall and atrial septal tissue to create the baffle, whereas the Mustard procedure used pericardium or synthetic material to create the baffle. Although they were lifesaving, many long-term complications of these procedures have been described.

Sinus node dysfunction is common after the atrial switch procedure. Late loss of sinus rhythm has been estimated to occur at a rate of 2.4% per year. In one series, 72% of patients remained in sinus rhythm at 1 year after surgery, 56% at 5 years, 50% at 10 years, and 43% at 13 years. The heart rate response to exercise is variable. Exercise capacity in post-atrial switch patients is usually reduced relative to normal, with chronotropic incompetence the most common limitation. In the absence of

symptoms, a resting heart rate less than 40 beats per minute while awake or less than 30 beats per minute while asleep has been proposed as an indication for permanent pacing. Pacemaker implantation is usually done by a transvenous approach. In post-atrial switch patients, it is critical to evaluate for baffle leaks (transvenous leads relatively contraindicated) or SVC baffle stenosis before attempting transvenous lead placement. When present, baffle obstruction can frequently be managed with balloon dilation and stenting. Transvenous lead placement may be challenging due to the postoperative anatomy and is best performed by an operator experienced in congenital heart disease. Supraventricular tachycardia, often an intraatrial reentrant tachycardia or atrial fibrillation, occurs in up to 50% of patients after the atrial switch procedure. Although catheter ablation may be successful in these patients, it is technically very challenging due to the postoperative anatomy.

Right ventricular dysfunction is major concern in postвЂ“atrial switch patients. In most series, 10% to 20% of patients are reported to develop severe RV dysfunction. Abnormal coronary perfusion in the setting of RVH has been suggested as a possible etiology for the development of RV dysfunction. Tricuspid regurgitation is common after the atrial switch operation, usually seen in the setting of systemic ventricular dysfunction. Although medical therapy (angiotensin-converting-enzyme inhibitors and beta-blockers) for RV dysfunction is commonly used, there are no systematic studies of their efficacy. Attempts to convert these patients to a late arterial switch (removal of atrial baffle, recreation of atrial septum, and switching the great arteries) has been proposed by some but appears to be associated with high mortality. Transplantation remains the other surgical option for patients with symptomatic systemic ventricular dysfunction.

Reoperation is needed in as many as 20% of cases for baffle complications (usually obstruction), progressive subpulmonary outflow obstruction, or tricuspid (systemic AV valve) insufficiency . Late development of pulmonary vascular disease occurs in 7% of cases and is more common in patients undergoing late repair or in patients with a ventricular septal defect.

Late-term studies have demonstrated an increased mortality after the atrial switch operation. The 20-year survival rate was 76% in one series and 80% in another series. The most common mechanism of death was sudden death, followed by systemic RV failure. The incidence of late death is 2.7 times higher for patients with complete transposition and a VSD as compared to patients with an intact ventricular septum. The incidence of sudden death has been reported to range from 2% to 3% to as high as 16%. Risk factors for sudden death include systemic (right) ventricular dysfunction, tricuspid regurgitation (systemic AV valve), and atrial arrhythmias.

Patients who have undergone an atrial switch procedure are challenging to manage. Routine arrhythmia surveillance with Holter and exercise treadmill testing every 1 to 2 years is recommended. Pacemakers are indicated for symptomatic bradycardia, and electrophysiologic study is recommended for patients with syncope. New arrhythmias should also prompt a search for hemodynamic derangement, often a change in right ventricular function. Serial imaging studies to follow RV function are recommended, and serial cardiopulmonary stress tests are useful for following functional capacity.

In 1975, the arterial switch operation with coronary relocation began to replace the atrial switch procedure. With this procedure, the great arteries are transected above the aortic and pulmonary valves and switched, then the coronaries are removed from the aorta and implanted into the neoaorta. Since the 1980s, the arterial switch has been performed in infancy (often in the neonatal period) with very low mortality. Although it is technically challenging, there are far fewer long-term complications than with the atrial switch procedure. Potential long-term complications of the arterial switch operation include pulmonary artery stenoses, supraaortic obstruction (rare), and abnormalities of the neoaortic valve and aortic root. Neoaortic valve regurgitation and mild degrees of aortic root dilation are possible but are usually mild. Patients have a potential risk of coronary abnormalities (including ostial narrowing if ostial growth is impaired). In one prospective angiographic study, coronary artery abnormalities were seen in 18% of patients, including coronary occlusions and major stenoses. Coronary abnormalities may be related to specific surgical techniques and may

be treated with surgical revascularization or catheter techniques. After the arterial switch operation, the LV is left in the systemic circulation, and normal LV function is seen in greater than 95% of patients postoperatively. There is limited long-term survival data. One review of more than 1,000 survivors showed an 88% survival at 10 and 15 years with isolated complete transposition and 80% for transposition with associated lesions. Sinus node dysfunction and heart block are uncommon. Supraventricular arrhythmias are uncommon (seen in 5% or cases in one series), and ventricular tachycardia is rare (0.5%). Sudden death is unusual. Most cases of sudden death are related to coronary obstruction and myocardial infarction.

The Rastelli operation is used for patients with complete transposition complicated by pulmonary outflow obstruction and a VSD. This procedure involves baffling blood flow from the LV through the VSD to the aorta and inserting a conduit between the RV and the pulmonary artery while the pulmonary valve/subpulmonary region is oversewn. Although the LV is left in the systemic circulation, the development of conduit stenosis is inevitable, necessitating further surgeries for conduit replacement. Long-term survival rate after the Rastelli operation is 82% at 5 years, 80% at 10 years, 68% at 15 years, and 52% at 20 years. Patients undergoing the Rastelli operation are at risk for supraventricular and ventricular arrhythmias, heart block, and sudden death. Left ventricular dysfunction occurs in up to 25% of patients at late follow-up. Right ventricular dysfunction is also common, often related to conduit dysfunction.

Congenitally Corrected Transposition

Congenitally corrected transposition is characterized by atrioventricular and ventriculoarterial discordance, resulting in systemic venous return to the RA, LV, and pulmonary artery, and pulmonary venous return to the LA, RV, and aorta. Thus, the tricuspid valve and the RV are in the systemic circulation. The aorta is positioned anterior and leftward of the pulmonary artery. Also known as L-transposition or ventricular inversion, congenitally corrected transposition is uncommon, occurring in less than 1% of patients. Associated defects are common, with VSD, pulmonary outflow tract obstruction, and morphologic abnormalities of the tricuspid valve seen most commonly. An Ebstein-type malformation of the tricuspid valve may be seen, and

tricuspid regurgitation (systemic AV valve regurgitation) is likely to progress with time. Other defects may occur, including ASD, PDA, double-outlet right ventricle, and subaortic stenosis. The AV node and bundle of His are abnormally located in patients with congenitally corrected transposition, placing patients at risk for conduction system abnormalities. Patients are particularly prone to develop spontaneous heart block (occurs in 2% to 4% of patients per year) or complete heart block with surgery. Left-sided accessory bypass tracts with preexcitation and AV reentrant tachycardia are seen in 2% to 4% of cases. Dextrocardia is present in 20%. The diagnosis may be made by echocardiography, angiography, and cardiac MRI.

Infants and children with congenitally corrected transposition may present with congestive heart failure, usually in the setting of a large VSD or severe tricuspid regurgitation. Treatment includes initial medical management, followed by surgical repair. VSD closure is performed with sutures placed on the RV side to avoid heart block. Tricuspid valve repair is rarely successful in these patients, and tricuspid valve replacement is usually required. Children with a VSD and severe pulmonary outflow obstruction usually present with cyanosis. Initial management often includes a shunt in infancy, followed by surgical repair done at a later stage. These patients often require placement of a conduit to relieve pulmonary outflow obstruction and thus will require further surgery for conduit replacement at some point. The double-switchв operation may be undertaken, which includes an atrial switch combined with a baffle to direct blood from the LV to the aorta (intraventricular Rastelli) and a RV-to-pulmonary artery conduit. The double-switch operation is complicated, and the long-term outcome is largely unknown. Complications include conduit obstruction, baffle obstruction, and rhythm problems.

Patients with isolated congenitally corrected transposition (no associated defects) may remain symptom-free until well into adulthood. There are some cases of survival into the seventh and eight decades. Symptoms occur in more than 50% of patients in adulthood, with heart block, tricuspid regurgitation, congestive heart failure, and supraventricular arrhythmias commonly seen. Complete heart block is seen in 24% to 39% of cases, tricuspid regurgitation in 40% to 44%, and congestive heart

failure in 17% to 34%. From 30% to 50% of adults with congenitally corrected transposition will require surgery over long-term follow-up. All patients are at risk for progressive dysfunction of the systemic ventricle (morphologic RV), regardless of the presence of associated anomalies.

Permanent pacing is required for complete heart block, with DDD mode preferred due to the presence of the RV as the systemic ventricle. Transvenous pacing should be avoided in the presence of an uncorrected shunt. Surgery is indicated for closure of a VSD, relief of subpulmonary obstruction, and repair or replacement of tricuspid valve for severe regurgitation. The timing of tricuspid valve surgery is difficult due in part to the difficulty in assessing RV function. The presence of moderate or greater tricuspid regurgitation in the face of diminishing RV function is an indication for tricuspid valve surgery. The preoperative ejection fraction is predictive of postoperative survivorship, with a poor outcome associated with an RV ejection fraction less than 40% to 45%, thus emphasizing the importance of timely surgical referral. Some surgeons have proposed the double-switch operation to restore the LV to the systemic circulation. This complicated procedure involves rerouting the systemic and pulmonary venous return to the right and left atria, respectively (atrial switch), and connecting the LV to the aorta and the RV to the pulmonary artery (arterial switch). In many cases, a pulmonary artery band must be placed first to promote hypertrophy of the LV and prepare it to tolerate systemic pressure. Surgical procedures may be quite complex, and experience is limited.

Tetralogy of Fallot

Tetralogy of Fallot is the most common cyanotic malformation, accounting for 10% of all congenital heart disease. There is a slight male preponderance. Fifteen percent of patients with tetralogy of Fallot have a deletion on chromosome 22q11. Tetralogy of Fallot is characterized by malalignment of the infundibular outlet septum, which results in a VSD, obstruction of the right ventricular outflow tract, and an aorta that overrides the VSD. Right ventricular hypertrophy, the fourth component, occurs as a consequence of both RV outflow obstruction and the large nonrestrictive VSD. Multiple variations of RV outflow obstruction can be seen, including infundi-

bular stenosis, hypoplastic pulmonary valve annulus, bicuspid pulmonary valve, and varying degrees of hypoplasia of the main pulmonary trunk and its branches. The branch pulmonary arteries may be confluent or nonconfluent, with origin of one vessel from the ductus or from the aorta. Alternatively, one branch pulmonary artery may be absent. Extreme variants of tetralogy of Fallot may be seen with an absent pulmonary valve (seen in DiGeorge syndrome and velocardiofacial syndrome) or with pulmonary atresia. Coronary anomalies are present in 3% of cases. The most significant of these is origin of the left coronary artery from the right coronary artery, with the left coronary artery crossing the right ventricular outflow tract (important surgical implications). From 25% to 30% of cases have a right-sided aortic arch. Multiple VSDs are seen in 5% to 7% of cases. An ASD or PFO may be present as well (pentalogy of Fallot).

Most patients present with cyanosis in infancy. Cyanosis occurs due to the right-to-left shunt across the nonrestrictive VSD and the obstruction to pulmonary blood flow. The severity of the RV outflow tract obstruction determines the severity of cyanosis. With mild degrees of RV outflow tract obstruction, patients usually have minimal cyanosis (pink tetralogy) and may present in adulthood. In most cases, survival to adolescence and adulthood is uncommon without treatment. Only 10% of patients with unoperated tetralogy of Fallot survive to 10 years of age.

Prior to the era of surgical repair, shunts were commonly used to increase pulmonary blood flow and decrease cyanosis. Shunts used included the Pott shunt (descending thoracic aorta to left pulmonary artery), the Waterston shunt (ascending aorta to right pulmonary artery), and the Blalock-Taussig shunt (subclavian artery to pulmonary artery). These shunts were designed to decrease cyanosis but did not result in physiologic cure. Long-term complications of these shunts include pulmonary hypertension (especially with the Potts shunt), distortion of pulmonary artery branches, and LV dysfunction from chronic volume overload. Cardiologists may encounter adults with tetralogy of Fallot who have had only a palliative shunt procedure. These patients remain cyanotic and are at risk for pulmonary hypertension, biventricular dysfunction, and premature death due to heart failure or sudden cardiac death. Currently,

shunts may be performed as a bridge to total repair or in patients not amenable to complete repair. Currently, most patients undergo complete repair at the time of diagnosis. Surgery involves closure of the VSD and relief of RV outflow obstruction. Corrective surgery was first performed in 1955, and surgical techniques have evolved over time. Earlier approaches involved large incisions across the RV outflow tract with a transannular patch. This approach often leads to progressive pulmonary regurgitation and also places patients at risk for reentrant ventricular tachycardia originating around the patch. Current surgical techniques are designed to avoid annular incisions. Preoperative assessment for coronary anomalies is important to avoid coronary injury during surgery.

Long-term follow-up after tetralogy of Fallot repair has been reported in more than 1,000 patients, with 90% to 95% survival at an average of 10 years. The best long-term results are seen with repair before the age of 5 years. Thus, early repair is advocated without prior palliative shunts. There are smaller series of adult patients undergoing repair of tetralogy with low mortality and favorable long-term outcomes.

Despite fairly good long-term outcomes, patients are at risk for multiple complications, including pulmonary regurgitation, residual RV outflow obstruction, residual shunts, atrial and ventricular arrhythmias, AR with or without aortic root dilation, left and right ventricular dysfunction, and late sudden death. RV dysfunction is usually related to residual lesions in the RV outflow tract (obstruction or regurgitation). LV dysfunction may be secondary to chronic volume overload from prior shunts or a residual VSD or from inadequate myocardial preservation at the time of surgical repair. Reintervention is needed in approximately 10% of patients over a 20-year follow-up.

Pulmonary regurgitation is a particular problem in patients with repaired tetralogy of Fallot, particularly in patients with large transannular incisions or placement of a transannular patch. Pulmonary regurgitation is usually well tolerated but results in chronic volume overload of the RV, ultimately resulting in deterioration of RV function. Patients are often asymptomatic until significant RV dysfunction is present. They may present with arrhythmias (atrial or ventricular), symptoms of right heart

failure, or sudden death. The timing of pulmonary valve replacement is controversial. The presence of progressive RV enlargement, worsening tricuspid regurgitation, arrhythmias, and evidence of deteriorating exercise tolerance are all indications for pulmonary valve replacement. Although pulmonary valve replacement in symptomatic patients usually results in subjective improvement, there may not be a significant change in RV volumes or systolic function. Some authors advocate early pulmonary valve replacement to reduce the risk of late morbidity and mortality. Right-bundle-branch block is present in 80% to 90% of patients after repair, related to the right ventriculotomy. Bifasicular block is seen in 15%. The presence of bifasicular block with PR prolongation suggests a risk of high-grade block, and a permanent pacemaker is warranted. The overall risk of sudden death is small, with a reported incidence of 2% to 6%. A recent study reported a risk of sudden death of 1.2% after 10 years, 2.2% at 20 years, 4% at 25 years, and 6% at 35 years. A QRS width greater than 180 msec has been shown to be predictive of increased risk for sustained ventricular tachycardia and sudden death. The QRS width corresponds to the degree of RV enlargement and the severity of pulmonary insufficiency. The rate of QRS change with time or the QT dispersion (a difference of >60 msec between the longest and shortest QT intervals on 12-lead ECG) may be a better predictor of patients at risk for sustained ventricular arrhythmia and sudden death than QRS duration alone.

Premature ventricular contractions (PVCs) are common after repair of tetralogy of Fallot, and are seen in 40% and 60% of cases on Holter monitoring (365,367,368). Sustained ventricular tachycardia is seen in 4% to 7% of cases and may originate as a reentrant tachyarrhythmia from the right ventricular outflow tract scar. The prognostic significance of PVCs and nonsustained ventricular tachycardia is unclear. Currently, treatment is only recommended for symptomatic patients. The role of electrophysiologic studies is unclear. Such studies are largely used for evaluation of syncope. Failure to induce ventricular arrhythmias with programmed stimulation does not accurately predict the subsequent development of clinical ventricular arrhythmias. Reentrant ventricular tachycardia originating around the RV outflow tract scar may be successfully treated with ablation. However, it is not clear whether ablation will

protect patients from sudden death. Current indications for implantable cardioverter defibrillator (ICD) implantation include secondary prevention of sudden death in survivors of sudden cardiac death, patients with syncope and inducible ventricular tachycardia, and those patients with sustained monomorphic ventricular tachycardia. The role of ICDs for primary prevention of sudden death has not been explored.

Atrial arrhythmias are an important cause of morbidity in patients after tetralogy repair, and are often correlated with congestive heart failure and tricuspid regurgitation. Patients may have reentrant atrial tachycardia (incision tachycardia) or atrial fibrillation or flutter. Atrial arrhythmias are seen in up to one third of adult patients and are associated with long-standing shunts, older age at surgical repair, reoperation, and the presence of moderate to severe tricuspid regurgitation. There are no good data on the choice of antiarrhythmic therapy. Reentrant atrial tachycardia and atrial flutter have been successfully ablated. The new onset of an arrhythmia should always prompt investigation of the patient's hemodynamic status, with correction of lesions as indicated (pulmonary valve replacement or tricuspid valve replacement/repair) with concomitant intraoperative cryoablation. Recommendations vary for follow-up. Serial ECGs, Holter monitoring, and exercise testing may be useful. The patient's hemodynamic status may be a better predictor of arrhythmias and other adverse outcomes. The presence of residual/recurrent pulmonary obstruction or severe pulmonary regurgitation with RV volume overload predicts worse outcome, and these complications should be evaluated with serial imaging.

Ventricular Septal Defect with Pulmonary Atresia

Ventricular septal defect with pulmonary atresia is a rare lesion. It is characterized by a biventricular heart with a VSD and no continuity between the ventricular chambers and the pulmonary arterial tree. Patients must have some source of pulmonary blood supply (usually via the ductus or from collateral vessels from the aorta or its branches). The native pulmonary arteries are often hypoplastic and may or may not communicate with one another. Some of these sources of pulmonary blood flow will be underperfused due to small size or stenosis within the vessel, whereas other sources may be unprotected, with excessive pulmonary blood flow resulting in pul-

monary vascular obstructive disease. Most unoperated patients die in infancy or childhood, although some survive to adulthood. Surgical repair is complicated due to the fragile pulmonary circulation. Multiple surgeries may be required. Long-term prognosis for these patients is more guarded than that for patients with repaired tetralogy of Fallot. Long-term surgical after repair has been reported to be 92% at 5 years, 86% at 10 years, 83% at 15 years, and 75% at 20 years in one series.

Pulmonary Atresia with Intact Ventricular Septum

Pulmonary atresia with intact ventricular septum is another rare congenital defect. There is either an imperforate pulmonary valve (80%) or muscular obliteration of the RV infundibulum with no pulmonary valve. There are varying degrees of hypoplasia of the tricuspid valve and the RV cavity. Pulmonary blood flow is provided through the ductus (or, less commonly, through aortopulmonary collaterals) with an obligatory right-to-left shunt at the atrial level. The severity of the defect ranges. Some patients have a nearly normal RV cavity with mild infundibular narrowing that is amendable to pulmonary valvotomy or catheter perforation of valve. Other patients have more significant RV hypoplasia with tricuspid stenosis. In other patients, the tricuspid valve is dysplastic or absent, with severe tricuspid regurgitation and a thinned, underdeveloped RV. In patients with severe RV hypoplasia, the high-pressure RV is decompressed through a dilated coronary circulation, the coronary sinusoids. Echocardiography is critical in the initial diagnosis, but cardiac catheterization is usually required to define the coronary circulation. Surgical options are complicated, and long-term survival is poor, with only 30% to 35% survival at 15 to 20 years of age. There are preliminary reports of intervention in the fetus (perforation of pulmonary valve) to permit normal growth of RV and improve long-term outcome.

Double-Chambered Right Ventricle

Double-chambered RV is an uncommon defect. The RV is divided or septated by muscular or fibrous structures into a high-pressure proximal chamber and a lower-pressure distal chamber (397). The RV outflow obstruction appears to be an acquired lesion, but probably results from a congenitally abnormal substrate. A double-chambered RV is often associated with a perimembranous VSD (seen in >75% of

cases). A double-chambered RV may also be seen with other abnormalities of the RV outflow tract, including valvar PS, tetralogy of Fallot, and double-outlet right ventricle. The degree of RV outflow obstruction ranges from trivial to severe. The clinical presentation depends on the size of the VSD and the degree of RV outflow obstruction, with a clinical appearance similar to that of tetralogy of Fallot. In some cases, the VSD may close spontaneously, and these patients present similarly to patients with isolated PS. Symptoms associated with double-chambered RV include exertional dyspnea, cyanosis, angina, dizziness, and syncope. The clinical exam includes an RV heave and a harsh systolic ejection murmur with a thrill. Unlike patients with tetralogy, the second heart sound is normal, with physiologic splitting. Patients may be cyanotic due to right-to-left shunting across an ASD, or PFO or may shunt right to left across the VSD proximal to the RV obstruction. The diagnosis is made by echocardiography or MRI. The severity of obstruction can be assessed by Doppler or at catheterization. Operative intervention is recommended for those patients with significant obstruction. Surgery consists of resection of the obstructing muscle bundles in the RV and RV outflow tract, closure of the VSD, and repair of other associated defects.

Tricuspid Atresia

Tricuspid atresia is defined as the absence of a right-sided atrioventricular connection, usually associated with underdevelopment of the RV (absence of inlet portion). An ASD is invariably present for the obligatory right-to-left shunt. If the interatrial communication is restrictive, patients have severe cyanosis in infancy. A nonrestrictive ASD may become restrictive over time. The great arteries may be normally related (70%) or transposed (30%). With normally related great arteries, the pulmonary artery arises from the RV and there is usually valvular or subvalvular PS. With transposed great arteries, the aorta arises from the RV and there may be associated PS, pulmonary atresia, and subaortic obstruction (due to a small VSD restricting blood flow into the RV).

Tricuspid atresia is an uncommon lesion (seen in 1% to 3% of all congenital defects) and is usually sporadic, although some familial cases have been described.

The diagnosis is suspected in a cyanotic infant with decreased pulmonary blood flow on CXR. Echocardiography is diagnostic. Catheterization may be required to define hemodynamics before surgical intervention.

Tricuspid atresia has a very high mortality in infancy, with few patients surviving beyond 6 months of age without some type of palliation. Rare survival into adulthood without surgery has been reported. In critically ill infants, medical therapy with prostaglandin E_1 is used to maintain patency of the ductus, and a balloon atrial septostomy may be used for patients with restrictive ASDs to improve right atrial-to-left atrial shunting. Patients with tricuspid atresia are now routinely treated with staged palliative surgical procedures. A palliative shunt may be required initially to improve pulmonary blood flow in patients with severe PS. A systemic-to-pulmonary artery shunt (Blalock-Taussig or modified Blalock-Taussig shunt) or a cavopulmonary shunt (bidirectional Glenn shunt) is used.

The Fontan procedure is now considered the definitive procedure for patients with tricuspid atresia. First done in 1971, the Fontan procedure separates the pulmonary and systemic circulation by creating a direct connection of the systemic venous blood to the lungs without an intervening ventricle. Multiple modifications of the surgical technique have been made. Overall, the Fontan procedure is excellent for long-term palliation. The procedure is most commonly performed with direct anastomosis of the systemic venous return to the pulmonary arterial circulation, bypassing the systemic venous ventricle (modified Fontan) or completely bypassing both the systemic venous atrium and ventricle with a total cavopulmonary anastomosis using an intracardiac or extracardiac conduit. The Fontan operation is typically performed at the age of 2 to 3 years. Risk factors for poor outcome from the Fontan operation include high pulmonary vascular resistance (>2 Wood units/m^2), high mean pulmonary artery pressure (>18 mm Hg), distorted pulmonary artery anatomy, systolic or diastolic dysfunction with an LV end-diastolic pressure greater than 12 mm Hg, and atrioventricular regurgitation. A patient with two or more risk factors is considered to be at high risk.

Multiple long-term complications of the Fontan procedure may occur, include-

ing RA enlargement, atrial arrhythmias, thrombus formation within the Fontan circuit, conduit obstruction due to deterioration of prosthetic materials, hepatic congestion potentially leading to cirrhosis, progressive ventricular dysfunction, atrioventricular valve regurgitation, development of systemic venous collaterals and/or pulmonary arteriovenous fistula, right-to-left shunts at the atrial level, and protein-losing enteropathy. Older versions of the Fontan procedure with a direct RA-to-pulmonary artery anastomosis often result in progressive dilation of the RA, contributing to arrhythmogenesis. Atrioventricular valve regurgitation and ventricular dysfunction also contribute to arrhythmias. Sinus node dysfunction is common after the Fontan operation and is seen in 10% to 15% of cases. For patients requiring permanent pacing, epicardial lead placement is required for ventricular pacing and may be required for atrial pacing because the placement of transvenous atrial leads may be complicated. Sinus node dysfunction and bradycardia increase the risk for atrial tachycardias.

Re-entrant atrial tachycardia, atrial fibrillation, and atrial flutter are reported in nearly half of Fontan patients in long-term outcome studies. Sustained atrial arrhythmias tend to be poorly tolerated and may result in the development of atrial thrombus (occasionally causing Fontan pathway obstruction) as well as congestive heart failure. Anticoagulation is critical in these patients. TEE is particularly useful for visualizing thrombus within the Fontan circuit. Catheter ablation of arrhythmias in patients after the Fontan operation is technically very challenging. Multiple circuits are usually present, and ablation may have limited effectiveness due to extensive fibrosis and scarring. Although acute success rates are good in small series, arrhythmia recurrence is common in long-term follow-up. Drug therapy is likewise complicated for these patients. They often require a combination of drug therapy and pacing. Amiodarone may have an increased incidence of thyroid and hepatic toxicity in the Fontan population. On occasion, patients with refractory arrhythmias may require surgical revision to a total cavopulmonary connection with intraoperative electrophysiologic mapping to guide surgical cryoablation.

Protein-losing enteropathy is an uncommon complication that is presumed to result from increased systemic venous pressure causing intestinal lymphangiectasia.

Patients develop a debilitating gastrointestinal protein loss resulting in malnutrition, edema, effusions, ascites, and hypogammaglobulinemia. Protein-losing enteropathy is very difficult to treat. Multiple treatments have been tried with varying success. The 5-year survival rate is less than 50%. The 5- to 10-year survival is reported to be 60% to 70% after a Fontan operation. Patients usually report good functional status but have abnormal exercise capacity with a lower maximal workload, lower maximal oxygen consumption, and a blunted heart rate response. Patients are at risk of developing cyanosis due to pulmonary arteriovenous fistulas in the setting of a classic Glenn shunt or may have anomalous systemic venous connections. Patients have an ongoing mortality after the Fontan procedure despite a successful operation, with the precise mechanism of death not clearly identified. A small number of successful pregnancies have been reported after the Fontan operation.

Total Anomalous Pulmonary Venous Connection

Total anomalous pulmonary venous connection is defined as connection of all of the pulmonary veins to one or more of the systemic veins, draining to the RA or coronary sinus. There is no direct communication of the pulmonary veins to the LA. Pulmonary venous drainage may return to the heart above the level of the diaphragm (supracardiac type) or below the diaphragm (infracardiac type), or it may occur in a mixed pattern. An ASD or PFO is necessary for survival, allowing blood to enter the LA and LV. There may be associated obstruction of the common pulmonary venous channel, which is more commonly seen with the infracardiac types. Patients with obstructed forms of total anomalous pulmonary venous connection present in the neonatal period with progressive hypoxemia, marked pulmonary edema, and a small heart on chest x-ray. Patients with unobstructed total anomalous pulmonary venous connection usually present in infancy with congestive heart failure and mild hypoxemia. Less commonly, they may present later in childhood or adolescence, rarely in adulthood.

The diagnosis is made by echocardiography. Cardiac catheterization with angiography is usually not required unless pulmonary venous drainage patterns are complex. MRI is an excellent tool for defining the pulmonary venous connections. Cor-

rective surgery to redirect the pulmonary venous return to the LA and close the associated ASD is necessary for all patients with this condition (427). For severely ill infants with the obstructed form, medical therapy with digoxin, diuretics, and mechanical ventilation may help to stabilize the patient until corrective surgical repair can be accomplished. The development of postoperative pulmonary venous obstruction is uncommon but carries a poor prognosis.

Ebstein's Anomaly

Ebstein's anomaly is an uncommon defect (<1.0% of all congenital defects), and is characterized by varying degrees of dysplasia and apical displacement of the septal and mural (posterior) leaflets of the tricuspid valve. The anterior leaflet is often malformed and excessively large and may be adherent to the RV free wall. Tricuspid leaflet displacement results in atrialization of the inlet portion of the RV. The true RV or functional RV (apical and outflow segments) may be quite small. The degree of leaflet displacement varies, resulting in wide differences in the clinical presentation. Patients have varying degrees of tricuspid regurgitation, whereas tricuspid stenosis is unusual. There is an increased incidence in Ebstein's malformation in the offspring of mothers treated with lithium carbonate in the first trimester of pregnancy.

Ebstein's malformation may occur as an isolated defect or in association with other complex congenital heart defects (e.g., tetralogy of Fallot, AV septal defect, etc.). Ebstein's anomaly is commonly seen with congenitally corrected transposition. The most common associated congenital defect is an ostium secundum ASD or a PFO, which is present in greater than 50% of patients. Poor RV compliance and elevated RA pressure cause right-to-left shunting across the ASD. In addition, patients may have some degree of RV outflow obstruction. Wolff-Parkinson-White (WPW) syndrome is frequently seen in Ebstein's anomaly and is often associated with multiple pathways (usually right-sided) due to discontinuity of the central fibrous body associated with the septal leaflet displacement.

The clinical spectrum of patients with Ebstein's anomaly varies from severe disease presenting in utero or in infancy to an incidental diagnosis made in the seventh to eighth decades of life (433). The clinical exam demonstrates variable de-

grees of cyanosis. A soft systolic murmur of tricuspid regurgitation is usually present, and a middiastolic murmur may be present. The characteristic triple or quadruple gallop rhythm is caused by splitting of S1, wide splitting of S2, and the presence of an S3 and S4. Multiple clicks may be heart. The ECG is usually abnormal, with tall P waves and right-bundle-branch block seen frequently. First-degree AV block is seen in 40% to 50% of cases, and 25% have WPW. On CXR, heart size varies from normal to massively enlarged. Echocardiography is diagnostic. Specific criteria have been defined for the diagnosis of Ebstein's anomaly, requiring septal leaflet displacement greater than 8 mm/m^2 from the annulus. The size of the functional RV, the degree of tricuspid valve regurgitation or stenosis, and the presence of an interatrial shunt can be demonstrated.

The long-term prognosis depends on the age at presentation. Presentation in infancy with cyanosis and congestive heart failure is usually associated with a poor prognosis (432,433,434). Adolescents and adults are more likely to present with arrhythmias, usually SVT (reentrant supraventricular tachycardia, atrial fibrillation, and atrial flutter). There is an increased risk of sudden death in patients with Ebstein's anomaly, occurring in 3% to 4% of patients. Predictors of poor outcome include a diagnosis in infancy, NYHA class III or IV, systemic arterial saturation less than 90%, and a cardiothoracic ratio greater than 0.65.

WPW syndrome is present in 20% to 25% of patients with Ebstein's anomaly. The bypass tracts are usually right-sided or posterior septal, along the atrialized portion of the RV, and multiple bypass tracts are seen in 30% to 50% of cases. Ablation of these accessory pathways in Ebstein's anomaly is often complicated, with the success rate for ablation lower than that for ablation of WPW in the general population (75% vs. 95%). The recurrence rate is also higher. For patients with WPW syndrome who require tricuspid valve surgery (repair/replacement) and/or closure of their ASD, intracardiac mapping and surgical elimination of pathway has a high success rate with low risk of recurrence.

Morbidity and mortality for neonates with severe Ebstein's anomaly is quite high. Indications for surgery include critically ill neonates who fail intensive medical

therapy, advanced functional class (III or IV) with significant cardiomegaly, the presence of significant cyanosis, and paradoxical emboli. The initial surgical approach may be creation of a palliative systemic-to-pulmonary artery shunt to relieve cyanosis, with later conversion to a Fontan-type operation. The mortality for surgical repair remains significant, particularly in the neonatal population (6% to 14%). Less than 20% of patients require surgery within first decade of life, and surgical outcomes are much better in older patients (who tend to be less ill, with more suitable valve anatomy). For older children, adolescents, and adults, the surgical options include tricuspid valve repair or tricuspid valve replacement (bioprosthesis preferred) along with closure of the atrial septal defect. For some patients, cardiac transplantation may be appropriate. It is unclear whether surgery affects the risk of sudden death. For patients with significant cyanosis, closure of the ASD or PFO is usually done at the time of surgical repair of the tricuspid valve. ASD device closure has been rarely reported and may result in hemodynamic deterioration.

Double-Outlet Right Ventricle

Double-outlet right ventricle (DORV) is an uncommon defect in which more than half of each great artery is connected to the morphologic RV. DORV is nearly always associated with a large, nonrestrictive VSD, which provides the only outlet from the LV. There is a wide variety of spatial orientations of the great arteries, as well as variation in the location of the VSD. The VSD may be subaortic, subpulmonary, doubly committed (beneath both great arteries), or noncommitted. Patients may have pulmonary or aortic outflow obstruction, abnormalities of the atrioventricular junction, and ventricular hypoplasia. The clinical presentation depends on the specific morphology of the VSD and the presence or absence of PS. Patients may present with a large left-to-right shunt and congestive heart failure or may have cyanosis. There are only rare survivors to adulthood without prior surgical repair. The diagnosis requires echocardiography and cardiac catheterization with angiography. Surgical treatment is a primary repair for most patients.

There are four major types of DORV, each of which requires a different type of surgical repair. The most common form is the subaortic VSD without associated PS.

In this case, oxygenated blood from the LV is directed through the VSD into the aorta. These patients present with mild or no cyanosis. Their clinical presentation resembles that of a large VSD, with patients at risk for congestive heart failure and pulmonary hypertension. Surgical treatment involves a primary repair, tunneling left ventricular blood through the VSD to the aorta. Surgery is performed early in infancy to prevent the development of pulmonary hypertension. Patients with a subaortic VSD may have valvar or subvalvar PS (so-called Fallot type), causing desaturated blood to enter the aorta. The clinical presentation with this type is similar to that of tetralogy of Fallot. Surgical treatment includes an intraventricular tunnel from the LV to the aorta, along with relief of pulmonary obstruction by a patch graft or extracardiac conduit. This surgery is done in older infants and children. With a subpulmonary VSD (the Taussig-Bing malformation), oxygenated blood from the LV is directed into the pulmonary artery while desaturated blood is directed to the aorta. The clinical picture resembles that of complete transposition of the great arteries. Patients are at risk for severe pulmonary vascular obstructive disease early in life. Surgical treatment is performed early in infancy, usually by tunneling left ventricular blood through the VSD to the pulmonary artery combined with an arterial switch operation. Patients with DORV with a remote VSD (located away from the aorta and pulmonary artery) usually present with mild cyanosis and increased pulmonary blood flow. There may be associated abnormalities of the atrioventricular valves, including AV valve straddling, making surgical repair complex. Patients with ventricular hypoplasia or severe AV valve straddling may not be candidates for biventricular repair and may require a Fontan-type operation.

Single Ventricle

Single ventricle is an uncommon defect in which both atria are connected to one ventricle. There are usually two atrioventricular valves (double inlet), although rarely there may be a common atrioventricular valve (common inlet). The morphology of the single ventricle is usually that of an LV with a rudimentary RV (outlet chamber). On occasion, the single ventricle may have the morphology of an RV, often associated with a double outlet (both aorta and pulmonary artery arising from the

RV). In some cases, the ventricular morphology is indeterminate. The great arteries are transposed in the majority of cases, with the aorta arising anteriorly from the rudimentary outlet chamber. The connection between the single ventricle and the outlet chamber (the bulboventricular foramen) may become obstructed, causing decreased systemic blood flow and increased pulmonary blood flow.

There is complete mixing of blood in the common ventricle, and the degree of cyanosis is determined by the amount of pulmonary blood flow. Infants without PS have markedly increased pulmonary blood flow with symptoms of heart failure. These patients are at risk for the development of pulmonary vascular obstructive disease and have a high mortality in infancy. Infants may have valvar or subvalvar PS, which protects the pulmonary circulation by limiting pulmonary blood flow but results in more severe cyanosis.

Surgical management for patients with a single ventricle is complex. Patients with severe cyanosis often require a palliative shunt to increase pulmonary blood flow. Patients without PS may have a pulmonary artery band to decrease pulmonary blood flow, but this procedure may worsen obstruction of the bulboventricular foramen. Patients with a single ventricle are usually treated with a Fontan-type repair. On occasion, a patient may have biventricular repair with creation of a ventricular septum, although this operation carries a high operative risk. Long-term outcomes for unoperated and palliated patients with a single ventricle have been reported. For unoperated patients, survival is only 30% to 50% at 14 to 16 years. Survival depends on the morphology of the ventricle, with better survival seen in patients with an LV morphology. Two thirds of palliated patients were alive at 15 years.

Common Arterial Trunk

Common arterial trunk or persistent truncus arteriosus is an uncommon defect (33,200), and is characterized by a single great vessel arising from the ventricular mass that gives rise to the coronary arteries, at least one pulmonary artery, and the brachiocephalic arteries. A VSD is invariably present, directly below the truncus. The pulmonary arteries may arise from a common pulmonary trunk off the ascending portion of the arterial trunk or may have separate origins of the branch pulmonary arte-

ries from either the ascending portion of the truncus, the descending aorta, the ductus arteriosus, or an aortopulmonary collateral. The truncal valve may be bicuspid, tricuspid, or quadricuspid and may be stenotic, regurgitant, or both. The coronary artery origins have a variety of abnormalities. Some forms are associated with other severe anomalies of the aorta, including coarctation, aortic arch atresia, and aortic interruption.

In most patients, there is excessive pulmonary blood flow that ultimately leads to congestive heart failure and severe pulmonary vascular obstructive disease. Mortality is high in childhood without surgical intervention, and only rare patients survive to adulthood. Surgery is the only definitive therapy and is usually undertaken shortly after diagnosis. Surgery includes separation of the pulmonary arteries from the arterial trunk, creation of continuity between the RV and the pulmonary arteries with a valved conduit, and closure of the VSD. Long-term survival after initial successful repair is good (85% at 20 years in one series), but reoperation rates are high (90% at 10 years). Reoperation is most commonly performed for conduit replacement or for truncal valve insufficiency. Reoperation is the most important predictor of late death, with 50% of late deaths occurring at time of reoperation .

Hypoplastic Left Heart Syndrome

Hypoplastic left heart syndrome (HLHS) occurs in 1% of all congenital defects and is the most common cardiac cause of death in the first month of life. HLHS is characterized by aortic atresia or severe stenosis, mitral atresia or severe stenosis, and left ventricular hypoplasia with varying amounts of endocardial fibroelastosis. An ASD is seen in 15% to 20% of cases, a VSD in 10%, and coarctation of the aorta in 70% to 80%. In most cases, the entire circulation depends on flow through the ductus arteriosus from the RV. With closure of the ductus in the first few hours to days, the neonate develops a relentless low-output state with metabolic acidosis and death. An immediate diagnosis can be made by echocardiography, and prostaglandin E_1 therapy is initiated to maintain ductal flow. A balloon atrial septostomy may provide some temporary relief to improve oxygenation, but surgery is required for survival. Two major surgical options are the Norwood procedure and cardiac transplantation. The Norwood operation is a complex staged surgical therapy, culminating in a Fontan op-

eration. In stage 1, an atrial septectomy is performed to allow intracardiac mixing, the main pulmonary artery is divided with the distal stump closed, and a neo-ascending aorta is created from the proximal main pulmonary trunk and the native ascending aorta. Augmentation of the aortic isthmus may be performed to relieve coarctation. A modified Blalock-Taussig shunt (Gore-Tex graft) is used to provide pulmonary blood flow to the distal confluent pulmonary arteries. In stage 2, a bidirectional Glenn shunt is created (SVC to the right pulmonary artery). Stage 3 is the creation of a modified Fontan. The long-term outcome and complications from these complicated repairs are only beginning to be studied. There are preliminary data on fetal intervention for HLHS, with intrauterine perforation of the fetal aortic valve to permit normal growth of the LV and improve long-term outcome.

Heterotaxy Syndromes

Heterotaxy refers to an abnormal arrangement of the viscera, with incompletely or nonlateralized abdominal viscera. The liver is symmetric and midline, and the thoracic contents are more symmetric (either bilateral trilobed lungs with bilateral eparterial bronchi or bilateral bilobed lungs with bilateral hyparterial bronchi). Visceral heterotaxy is frequently associated with severe cardiac malformations. Atrial isomerism (bilateral right- or left-sidedness) is usually present. In patients with right atrial isomerism (bilateral morphologic right atria), the spleen is often absent (asplenia). The most commonly associated cardiac lesions in right atrial isomerism are total anomalous pulmonary venous connection, a common atrioventricular valve, and abnormalities of ventriculoarterial connections. In patients with left atrial isomerism (bilateral morphologic left atria), there are usually multiple spleens (polysplenia). The most common associated cardiac lesions with left atrial isomerism are anomalous systemic venous connections (absence of the IVC, bilateral SVC, absence of the coronary sinus, and partial anomalous pulmonary venous connections), AVSD, VSD, and DORV.

Eisenmenger Syndrome

Eisenmenger syndrome is a term applied to any large communication between the systemic and pulmonary circulation that results in irreversible changes in the

pulmonary vascular bed, with reversal of the shunt direction. The Eisenmenger syndrome may occur with any congenital defect that results in a large left-to-right shunt, with aortopulmonary collaterals, and with surgically created aortopulmonary anatomizes.

The pulmonary vascular changes begin in childhood (often within the first 2 years of life) and are progressive. Any nonrestrictive communication at any level will result in increased pulmonary blood flow and transmission of near-systemic pressures to the pulmonary circulation, resulting in the development of pulmonary vascular disease. Increased activity of endogenous vascular elastase in the pulmonary vascular bed has been shown to induce other mediators, resulting in smooth muscle migration and hypertrophy and stimulation of elastin and collagen synthesis. These steps are critical in the formation of irreversible pulmonary vascular disease.

The pathologic changes in the pulmonary vascular bed correlate with the hemodynamic status and can be graded in terms of severity. Grade A is characterized by increased pulmonary blood flow but normal mean pulmonary artery pressure. Pathologically, extension of muscle into nonmuscular peripheral arteries is seen. Grade B is characterized by increased mean pulmonary artery pressure. Pathologically, medial hypertrophy is seen in more proximal vessels as a result of smooth muscle hypertrophy and proliferation as well as increased connective tissue elements. With grade C, there is increased pulmonary vascular resistance, which correlates pathologically with a reduced concentration of distal pulmonary vessels. The Heath-Edwards classification has been used to grade the severity of pulmonary vascular obstructive disease on a histopathologic basis (grades I to VI). The presence of grade II changes or greater predicts persistence of pulmonary vascular resistance in the postoperative state.

The Eisenmenger syndrome is most commonly seen in association with large communications such as large VSDs, large PDA, and aortopulmonary windows. The Eisenmenger syndrome was seen in only 9% of patients with ASD in Wood's initial description. Early and progressive pulmonary vascular disease leading to the Eisenmenger syndrome is frequently seen in patients with Down syndrome (102). The prevalence of the Eisenmenger syndrome is declining with improved diagnosis and therapy for congenital defects. In large adult congenital heart disease clinics, approx-

imately 4% of patients have the Eisenmenger syndrome. The prevalence is higher in clinics with a concentration in cyanotic lesions, and is seen in 19% of one such clinic.

Although the pathologic changes of pulmonary vascular obstructive disease are present in childhood, the age at diagnosis varies. Patients with large shunts at the ventricular or aortopulmonary level are usually diagnosed in childhood, whereas those with shunts at the atrial level are more likely to be diagnosed in adulthood. A history of congestive heart failure in childhood suggests a large left-to-right shunt. Symptoms disappear as pulmonary vascular resistance increases and the magnitude of the shunt decreases. Shunt reversal and cyanosis appear later. Patients may have minimal symptoms in childhood and present with severe pulmonary vascular disease in adulthood. Pulmonary vascular disease may also occur as a late complication of palliative shunts performed for cyanotic lesions in childhood.

Because the development of pulmonary vascular disease is gradual, symptoms related to the Eisenmenger syndrome usually occur gradually. While most patients are symptomatic, they usually report fairly good functional capacity. The most common symptoms are dyspnea, fatigue, palpitations, edema, and syncope. The physical findings in the Eisenmenger syndrome include cyanosis and clubbing, an RV heave (and often a palpable pulmonary artery impulse), a pulmonary ejection sound, and a loud P2. The pulmonary component of the second heart sound moves earlier as pulmonary pressures increase, and the second heart sound may be single (fusion of A2 and P2). Murmurs of pulmonary and tricuspid regurgitation may be present secondary to pulmonary hypertension. The murmurs associated with the original shunt are absent. Differential cyanosis is present in patients with the Eisenmenger syndrome secondary to a PDA.

The natural history of patients with the Eisenmenger syndrome is significantly different from that of patients with primary pulmonary hypertension. Despite high pulmonary pressures, patients with the Eisenmenger syndrome have more favorable hemodynamics and a better prognosis than those with primary pulmonary hypertension. In one study comparing the two patient populations, the actuarial survival was 77% at 3 years for Eisenmenger syndrome as compared to 35% for patients with pri-

mary pulmonary hypertension. In one case series, the actuarial survival rate for 201 Eisenmenger patients was 80% at 10 years and 77% at 15 years after the initial diagnosis. In another series with a combined pediatric and adult population, the actuarial survival was 75% at 30 years of age, 70% survival at 40 years, and 55% survival at 50 years. Simple defects had better survival than complex defects. There are no prospective studies of long-term outcome in patients with the Eisenmenger syndrome.
Risk factors that have been identified from retrospective studies include syncope, age at presentation, poor functional class, complex underlying disease, supraventricular arrhythmias, oxygen saturation less than 85%, increased serum creatinine, RV dysfunction, and increased serum uric acid concentration.

Many of the complications seen in the Eisenmenger syndrome are related to the presence of chronic cyanosis and are discussed in a subsequent section. Supraventricular arrhythmias are common, and are seen in 36% of Eisenmenger patients on Holter monitoring. The development of supraventricular arrhythmias predicts clinical deterioration and death in some series. In general, sinus rhythm should be restored promptly when possible. Ventricular arrhythmias are less common. There is no published experience with implantable cardiodefibrillators in the Eisenmenger population.

The management of patients with the Eisenmenger syndrome is deceptively simple. Physicians should вe avoid therapies not proven to be beneficial, alleviate symptoms, and intervene only when neededвЂќ to avoid destabilizing the balanced physiology. Afterload reduction should be avoided because it may worsen right-to-left shunting. Arterial hypertension should be treated, however, because untreated hypertension may increase the risk of intrapulmonary bleeding and hemoptysis. Beta-blockers are usually well tolerated. Pregnancy is associated with a high maternal mortality and a high risk of fetal complications and should be avoided, preferably with permanent sterilization.

Hemoptysis may occur in patients with the Eisenmenger syndrome and may be life-threatening. The amount of hemoptysis does not necessarily reflect the extent of intrapulmonary hemorrhage. Therefore, CXR and CT scans of the chest are required to define the extent of pulmonary hemorrhage. Treatment is conservative in most cas-

es, consisting of bed rest, cough suppressants, avoidance of antiplatelet and anticoagulant agents, and treatment of hypovolemia. For severe or incessant bleeding, aortography with selective embolization of bleeding source may be successful in some cases. Routine phlebotomy should be avoided (see management of chronic cyanosis). Potentially nephrotoxic agents (including nonsteroidal antiinflammatory drugs) should be avoided.

Patients with the Eisenmenger syndrome have increased morbidity and mortality during noncardiac surgery. Careful anesthetic management is required for these patients. Medical therapy for patients with the Eisenmenger syndrome differs from that for patients with primary pulmonary hypertension. Anticoagulation has a proven role in primary pulmonary hypertension, but there are no data to support its use in the Eisenmenger syndrome. Anticoagulation is generally avoided in these patients due to their increased risk of bleeding. However, anticoagulation is indicated for atrial fibrillation, atrial flutter, recurrent thromboembolic events, mechanical heart valves, or other high-risk anatomy. Obviously, anticoagulation in this patient population requires meticulous management. Although it is often used, oxygen therapy does not have proven efficacy in patients with the Eisenmenger syndrome. In a single small study of nocturnal oxygen therapy in Eisenmenger patients, there were no benefits in terms of exercise capacity, quality of life, or degree of erythrocytosis. The drying effects on the nasal mucosa may predispose patients to epistaxis.

Pulmonary vasoactive therapy has been extensively studied in patients with primary pulmonary hypertension but there is only limited experience in the Eisenmenger population. Rosenzweig et al. studied continuous intravenous prostacyclin therapy in 20 patients with Eisenmenger syndrome over a 1-year period. Exercise capacity improved, pulmonary pressures decreased slightly, and 8 of 12 patients listed for transplant were removed from the transplant list. In three small, nonrandomized reports of patients with Eisenmenger syndrome treated with bosentan, an endothelin antagonist, improvement in functional class and improved exercise capacity were seen without obvious adverse effects.

The role of transplantation for patients with the Eisenmenger syndrome is con-

troversial. Patients are invariably symptomatic with decreased exercise tolerance, but the long-term outcomes for patients with the Eisenmenger syndrome are better than often appreciated and referral may be premature. One report suggests that patients with the Eisenmenger syndrome awaiting transplant have a very low mortality, raising the issue of the appropriateness of transplant for some of these patients. Patients require either lung transplantation with repair of the cardiac defect or heart-lung transplantation. With 3- to 5-year survival rates in the range of 50% to 60% for combined heart-lung transplant, transplant should be considered only in those patients whose predicted life expectancy without transplant is less than 2 years.

Miscellaneous Defects

Congenital Anomalies of the Coronary Arteries

Congenital anomalies of the coronary arteries may occur in isolation or in association with other congenital anomalies. Multiple variations exist. A rare but potentially lethal condition is the anomalous origin of the left coronary artery from the pulmonary artery. As pulmonary pressures fall in newborns with this condition, myocardial perfusion becomes dependent on collaterals from the right coronary circulation. These infants may present with ischemic symptoms or symptoms of heart failure from an ischemic cardiomyopathy. They may present in the neonatal period or later in infancy or childhood. This coronary anomaly is rarely seen in adults. In children, the diagnosis of coronary anomalies may often be made by echocardiography with color flow Doppler. Other patients may require catheterization with aortography and angiography. The treatment is surgical, with reimplantation of the anomalous coronary or aortocoronary bypass. Postoperatively, patients may have persistent problems with abnormal myocardial perfusion.

Congenital Pericardial Defects

Congenital pericardial defects may be partial or complete. Partial absence of the left side of the pericardium may cause chest pain. An unusual cardiac silhouette may be seen on CXR due to herniation of the left atrial appendage or the ventricles through the defect. Herniation of the right lung through a partial right-sided defect

may result in obstruction of the SVC. Alternatively, right heart structures may herniate through right-sided defects.

Sinus of Valsalva Aneurysms

Sinus of Valsalva aneurysms are defined as enlargement of one of the aortic sinuses between the valve annulus and sinotubular ridge. Absence of the elastic lamellae results in focal weakening of the aortic wall. This leads to aneurysmal dilation of the weakened portion and may ultimately lead to rupture. Sinus of Valsalva aneurysms are rare, and are seen in 0.09% of the general population at autopsy. They are four times more common in male individuals. Aneurysms occur in the right coronary sinus in 65% to 85% of cases, in the noncoronary sinus in 10% to 30%, and in the left coronary sinus in less than 5%. Sinus of Valsalva aneurysms may be associated with VSD, AR, bicuspid aortic valve, or connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome. The diagnosis can be made by echocardiography demonstrating the aneurysm and color flow mapping to demonstrate flow in ruptured aneurysms. Patients are usually asymptomatic until the aneurysm ruptures, which usually occurs in the third and fourth decades. A sinus of Valsalva aneurysm may cause local obstructive symptoms (compression of the right ventricular outflow tract or the coronary ostium).

Classically, rupture of a sinus of Valsalva aneurysm occurs with exertion or after trauma. The usual site of rupture is into the RV (in 90% of cases). Patients typically present with chest pain, cough, and breathlessness. Over time, they may develop LV volume overload and symptoms of congestive heart failure and may present late. Patients often have a continuous/machinery murmur, but this is not invariably present. Without surgical intervention, there is usually progressive deterioration with LV failure. Surgical repair is recommended for ruptured aneurysms or symptomatic aneurysms with compression, arrhythmias, or evidence of infection. Unruptured aneurysms without symptoms do not warrant surgical intervention.

Absent Pulmonary Valve

The absent pulmonary valve syndrome is an uncommon defect usually associated with tetralogy of Fallot or a ventricular septal defect. When the defect occurs

in isolation, it may result in fetal heart failure and death or may be associated with survival to the seventh or eighth decade. **Pulmonary valve replacement is indicated for right heart failure.**

Special Management Issues in Congenital Heart Disease

Postoperative Patients

Truly corrective surgery for congenital heart disease is uncommon. Most patients have had reparative or palliative surgery and require lifelong surveillance for long-term complications. Table 30.1 lists common surgical procedures in CHD patients, including the anatomy and associated complications. Palliative procedures include pulmonary artery banding (to decrease pulmonary blood flow) and the creation of shunts to increase pulmonary blood flow. Both systemic venous-to-pulmonary artery or arterial-to-pulmonary artery shunts may be used. Older systemic arterial-to-pulmonary artery shunts were fraught with complications. Currently, the modified Blalock-Taussig shunt or a systemic venous-to-pulmonary artery shunt is used to provide a controlled source of pulmonary blood flow. The modified Blalock-Taussig shunts use a prosthetic tube graft between the subclavian artery and the pulmonary artery to provide a controlled source of blood flow. The Glenn shunt diverts part of the systemic venous return to the lungs (SVC to the pulmonary artery with an end-to-side anastomosis). Actuarial survival with the Glenn shunt in patients with a single ventricle is 84% at 10 years and 66% at 20 years. Patients may develop pulmonary arteriovenous malformations (AVMs) in the lung with the shunt due to the exclusion of inferior vena cava blood from that lung. Pulmonary AVMs may result in cyanosis due to intrapulmonary shunting. The bidirectional Glenn shunt consists of an end-to-side anastomosis of the SVC to the pulmonary artery, leaving the right and left pulmonary arteries in continuity. The bidirectional Glenn shunt is often used en route to the Fontan procedure. Venous-to-pulmonary shunts are favored and have fewer complications and more balanced pulmonary blood flow than the systemic arterial-to-pulmonary artery shunts. Physiologic repair of congenital defects results in separation of the pulmonary and systemic circulations. Examples of physiologic repairs include the atrial switch operations for complete transposition and the Fontan procedure for

tricuspid atresia. Prosthetic materials are usually used, resulting in a risk for long-term complications associated with these prosthetic materials. Physicians caring for these postoperative patients must understand the specific details of the operative repair in order to monitor for long-term complications.

Management of Patients with Chronic Cyanosis

Chronic cyanosis associated with the Eisenmenger syndrome or other cyanotic congenital heart defect is a multisystem disorder. Erythrocytosis (an isolated increase in the red cell line) occurs in chronic cyanosis as a physiologic response to hypoxia, resulting in increased oxygen-carrying capacity. The increase in red cell mass also increases whole-blood viscosity and may result in symptoms of hyperviscosity such as headaches, fatigue, myalgias, paresthesias, and transient visual disturbances.

Most patients with chronic cyanosis are in a compensated state, with a stable hemoglobin and hematocrit and minimal symptoms of hyperviscosity. Phlebotomy is not appropriate for these patients. Patients may develop decompensated erythrocytosis with an unstable, rising hematocrit associated with severe hyperviscosity symptoms. Phlebotomy is indicated only for severe symptoms with a hematocrit greater than 65 in a well-hydrated patient in an iron-replete state. Patients with chronic cyanosis may have anemia with a hemoglobin level above 15 g/dL, often due to iron deficiency from phlebotomy or heavy menses. Because iron-deficient red cells are less deformable than normal biconcave red cells, patients with iron deficiency may have hyperviscosity symptoms with lower hematocrit levels. Careful iron repletion may be indicated in iron-deficient patients. Certain laboratory precautions are necessary for patients with erythrocytosis. The relatively low plasma volume in patients with a high hemoglobin and hematocrit may give spurious results for hematocrit unless appropriate adjustments are made. Measurements of blood glucose may also be spuriously low due to increased glycolysis from the increased number of red blood cells.

Patients with cyanotic congenital heart disease are at increased risk for both bleeding and thrombosis. Thrombocytopenia is commonly seen due to shortened platelet survival (increased peripheral consumption or destruction). Chronic cyanosis is associated with qualitative platelet disorders and also affects coagulation factors

(decreased levels of factors V, VII, IX, and X), leading to an increased risk of bleeding. Increased blood viscosity stimulates the release of endothelium-derived nitric oxide and prostaglandins, leading to increased tissue vascularity, which further contributes to an increased risk of bleeding. The measured prothrombin time and partial thromboplastin time are usually normal. The bleeding time is often normal as well, despite abnormal platelet function. Fortunately, bleeding is usually mild and self-limited in patients with chronic cyanosis. The exception is hemoptysis, which may be life-threatening.

Patients with chronic cyanosis are also at increased risk of thrombosis, which may be promoted by sluggish flow through cardiac chambers and the presence of prosthetic material such as valves and conduits. Although there is some increased risk of cerebral venous thrombosis in cyanotic children with elevated hematocrits, there is no increased risk of arterial thrombosis in either children or adults. Prophylactic phlebotomy is contraindicated and actually increases the risk of stroke.

Hyperuricemia is common in patients with chronic cyanosis and occurs as a consequence of increase urate production and decreased renal clearance. Arthralgias are common, and gout may occur. However, urate nephropathy and uric acid stones are uncommon. The degree of hyperuricemia is useful as a marker of impaired renal function in these patients. Functional and structural abnormalities of the kidneys are common in patients with chronic cyanosis. Serum creatinine is usually a poor indicator of renal function, and significant renal dysfunction may be seen in patients with a normal serum creatinine. Patients with right-to-left shunts are at risk for paradoxical embolization, and meticulous care must be taken when intravenous access is used. Filters should be used on all intravenous lines. These patients are also at increased risk of cerebral abscess due to the potential for paradoxical embolization of infected material. Patients commonly present with a headache.

Endocarditis

All patients are at increased risk for endocarditis. This is particularly true for those patients with bicuspid aortic valves, prosthetic shunts and conduits, and restrictive ventricular septal defects. Low-pressure lesions (e.g., ASDs) tend to have low

risk. In a series of CHD patients with endocarditis, LV outflow tract obstruction was most common underlying cardiac defect, followed by unoperated small VSDs, then cyanotic congenital heart disease. Antibiotic prophylaxis is required for most patients with CHD.

Contraception and Pregnancy

Most patients with CHD will reach child-bearing age and will need to address the risks of pregnancy. Patients can be stratified into high, moderate, and low risk for complications during pregnancy. The highest-risk group includes patients with the Eisenmenger syndrome, severe pulmonary hypertension, severe LV outflow tract obstruction (including unrepaired coarctation of the aorta), Marfan syndrome with a dilated aortic root, and class III or IV congestive heart failure. Low-risk lesions include uncomplicated left-to-right shunts, mild left-sided obstructive lesions, isolated pulmonic or tricuspid valve disease, and repaired tetralogy of Fallot. Nearly all other types of congenital heart defects fall in the moderate-risk category. There are only limited data regarding pregnancy outcomes for specific cardiac defects.

Maternal functional class is also a risk factor for fetal outcome, with fetal mortality rates of 30% for mothers in New York Heart Association class IV. Cyanosis is a significant risk factor for fetal and maternal complications. In one series of pregnancy in mothers with chronic cyanosis, live births occurred in only 43% of pregnancies, and maternal complications occurred in 32%. Fetal risks are strongly related to the degree of maternal cyanosis. A risk stratification scheme has been proposed to predict cardiac events in pregnancy that can be applied to mothers with CHD. Preconceptual counseling is important so that a potential mother can understand the risks to herself and her fetus. Offspring of patients with CHD have a higher risk of congenital heart defects, generally in the range of 5% to 6%. The defect in the offspring is usually not the same as in the mother except for autosomal dominant and familial syndromes. Prenatal cardiac ultrasound is recommended to screen for fetal cardiac malformations.

Contraception is complicated in patients with CHD, and the risks of different forms of contraception must be understood. Barrier methods have a high failure rate

(10% to 20%). Intrauterine devices have a lower failure rate (4%) but are associated with an increased risk of infection and are generally contraindicated in patients with CHD. Oral contraceptives have a low failure rate (1% to 3%) but are associated with increased risk for thromboembolism and are contraindicated in patients with cyanosis or pulmonary hypertension. Progesterone-only contraceptives are associated with a risk of fluid retention and irregular bleeding. Sterilization is the most effective means of contraception and is recommended for high-risk patients.

Functional Capacity and Exercise Limitations

Despite reported good functional class, many patients with CHD have significant exercise limitations. Even patients with simple lesions and repaired lesions usually have decreased exercise capacity when formally tested. In general, patients with simple shunts who are status post repair with no evidence of pulmonary hypertension can participate in all sports. In the presence of pulmonary hypertension, intense activity should be prohibited, and competitive sports are not permitted. For patients with obstructive lesions, exercise limitations depend on the severity of stenosis. The presence of pulmonary hypertension, ventricular dysfunction, and rhythm abnormalities must be considered. Specific exercise recommendations were recently updated.

Noncardiac Surgery

Patients with CHD may be at increased risk for noncardiac surgery due to abnormal cardiac anatomy, the presence of shunts (both systemic-to-pulmonary and pulmonary-to-systemic shunts), cyanosis, and the presence of poor ventricular function, clinical heart failure, or pulmonary hypertension. There may be a poor correlation between clinical status and functional reserve. Cardiac anatomy must be clearly defined before surgery, and anesthesia must be carefully planned, based on the cardiac anatomy and hemodynamic state. Antibiotic prophylaxis against bacterial endocarditis is usually recommended. Preoperative phlebotomy to a hematocrit less than 65 may be considered to improve hemostatic function. Dehydration should be avoided in patients with cyanosis or severe pulmonary hypertension.

In patients with severe pulmonary hypertension, any decrease in systemic vascular resistance will cause systemic output to fall or will increase the magnitude of the right-to-left shunt in patients with a pulmonary to systemic shunt. Patients with a Fontan circulation pose a particular challenge. Because pulmonary blood flow depends on systemic preload, pulmonary blood flow and oxygenation may be adversely affected by changes in pulmonary vascular resistance, hemorrhage, vasodilator drugs, inadequate volume replacement, and positive-pressure ventilation causing increased intrathoracic pressure. Intravenous access must be meticulously managed in all patients with shunts to avoid paradoxical embolization.

Transplantation in Congenital Heart Disease

Patients with complex CHD may require heart transplant, lung transplant with cardiac repair, or a combined heart-lung transplant, depending on their particular anatomy and hemodynamics. Complex anatomy may make transplant surgery technically more challenging. Cyanotic patients and other patients with complex anatomy are at increased risk of bleeding from collaterals. Significant comorbidities may be present, including pulmonary vascular disease, renal dysfunction, and liver disease. The optimal timing of transplant is difficult. Maximum oxygen uptake is usually abnormal in patients with CHD, even in the absence of symptoms. A specific cutoff predicting poor outcome in CHD patients has not been defined. Because many patients are not candidates for ventricular assist devices, late referral may pose a significant problem because there is only limited therapy to bridge the patient to transplant.

There are limited data for outcome of transplantation in these patients. In the 2001 Registry of the International Society for Heart Lung Transplantation (ISHLT), only 1.6% of adult heart transplants were performed for CHD. Similar data was reported for lung transplant, whereas CHD accounted for one third of all heart-lung transplants. The most common diagnoses were the Eisenmenger syndrome and postoperative complex CHD (including the Fontan operation and postoperative atrial baffle for transposition of the great arteries). In the pediatric population, survival for patients with transplanted for CHD is not different from those with cardiomyopathy.

However, in adults, survival is worse for patients with CHD than for patients with acquired heart disease.

Controversies and Personal Perspectives

The majority of patients with CHD will survive to adulthood, with a population of nearly one million in the United States. The population of adult patients with CHD is estimated to be larger than the pediatric population. Although many patients who underwent intervention in childhood may consider themselves cured, few can be truly considered cured. Most patients are at risk for long-term complications and will require long-term follow-up. At least half of these patients will have significant defects, and more than 25% will have complex defects requiring long-term expert care. Traditionally, pediatric cardiologists have provided the care for most of these patients.

Adult patients with CHD often have little knowledge about their disease or its complications and may mistakenly consider themselves cured. When these patients develop complications related to their CHD, they frequently present to adult cardiologists who traditionally have had little training or exposure to patients with more complicated forms of CHD, and thus these patients may receive suboptimal care.

The Thirty-Second Bethesda Conference recommended the close collaboration of adult and pediatric cardiologists and the establishment of regional referral centers to provide expert care for this patient population. Such regional referral centers are designed to optimize the care of adult patients with congenital heart disease, as well as facilitate research and training in this area. Although there is an increasing number of adult CHD centers, access to expert care for most patients is limited.

Many questions remain regarding the optimal treatment of these patients. There are no large randomized, controlled trials in this patient population, and most of the literature involves case series or retrospective caseвЂ“control series. The role of angiotensin-converting-enzyme inhibitors and beta-blockers for patients with ventricular dysfunction in the setting of a single ventricle or a systemic RV is unknown. Optimal treatment of arrhythmias is largely undefined, and the role of ICDs in primary prevention of sudden death is completely unknown. Because of the relatively small

numbers of patients, collaborative efforts are needed to create large databases, potentially even a national CHD database to effectively address clinical questions.

Conclusions.

Many challenges remain. The genetic control of cardiac development is being intensely studied with efforts aimed at identifying specific gene defects and altered signals that result in cardiac malformations. Although gene therapy ultimately holds tremendous potential for altering cardiac development in the future, current possibilities of using interventional techniques on the fetal heart provide a unique opportunity for altering the morphology of the developing heart. Although there have been dramatic advances in the care of infants and children with CHD, there is still significant mortality for some patients and inadequate surgical options for some complex defects. Further advances in both surgical and catheter techniques will widen the spectrum of defects that can be treated and potentially minimize the long-term risk of complications. Survivors of palliative or reparative procedures remain at risk for complications and sequelae of their original operation(s). Advances in our diagnostic tools (including echocardiography, cardiac MRI, and CT scanning) have improved our ability to define cardiac anatomy and may ultimately allow us to identify patients at risk for complications so that treatment interventions may be made in a timelier manner. Dramatic advances have been made in transcatheter techniques, and the role of the catheterization lab as a therapeutic location continues to evolve. Because arrhythmias are one of the most common complications seen in adult patients with CHD, advances in catheter ablation techniques, pacemaker technology, and defibrillators will likely contribute to significant improvements in the long-term outcomes of this patient population.

CHAPTER 5
ACUTE AND CHRONIC MYOCARDITIS

After implementation into routine clinical practice the endomyocardial biopsies diagnosis of myocarditis could be established during life of the patients. Multiple infectious etiologies (Table 5.1) have been implicated as the cause of myocarditis, with the most common being viral, specifically, Coxsackie B. In the majority of patients, active myocarditis remains unsuspected because the cardiac dysfunction is subclinical, asymptomatic, and self-limited. Endomyocardial biopsy is essential for definite diagnosis of idiopathic myocarditis. However, since endomyocardial biopsy is guided by fluoroscopy, whether or not the diseased myocardium is biopsied depends on chance, and this may lead to misdiagnosis. If the endocardial surface represents changes indicative of stages of myocarditis, staging of myocarditis and targeted cardioscope-guided biopsy could be used for accurate histological diagnosis. Histologic evidence of myocarditis following traumatic death is identified in 1 to 3 percent of autopsies, suggesting that the frequency of myocarditis is underestimated by analyzing data only from symptomatic patients.

Table 5.1

Causes of Myocarditis

Main reasons	Type of causes	Examples
Infectious	Viral	Coxsackie virus, echovirus, HIV, Epstein-Barr virus, influenza, cytomegalovirus, adenovirus, hepatitis (A and B), mumps, poliovirus, rabies, respiratory syncytial virus, rubella, vaccinia, varicella zoster, arbovirus
	Bacteria	Cornyebacterium diptheriae, Streptococcus pyogenes, Staphylococcus aureus, Haemophilus pneumoniae, Salmonella spp., Neisseria gonorrhoeae, Leptospira, Borrelia burgdorferi, Treponema pallidum, Brucella, Mycobacterium tuberculosis, Actinomyces, Chlamydia spp., Coxiella burnetti, Mycoplasma pneumoniae, Rickettsia spp.
	Fungi	Candida spp., Aspergillus spp., Histoplasma, Blastomyces, Cryptococcus, Coccidioidomyces

	Parasites	Trypanosoma cruzii, Toxoplasma, Schistosoma, Trichina
Noninfectious	Drugs causing hypersensitivity reactions	Antibiotics: sulfonamides, penicillins, chloramphenicol, amphotericin B, tetracycline, streptomycin
		Antituberculous: isoniazid, para-aminosalicylic acid
		Anticonvulsants: phenindione, phenytoin, carbemazepine
		Anti-inflammatories: indomethacin, phenylbutazone
		Diuretics: acetazolamide, chlorthalidone, hydrochlorothiazide, spironolactone
		Others: amitriptyline, methyldopa, sulfonylureas
	Drugs not causing hypersensitivity reactions	Cocaine, cyclophosphamide, lithium, interferon alpha
	Nondrug causes	Radiation, giant-cell myocarditis

Pathogenesis

Infection by cardiotropic viruses prompted the initial hypothesis that the viral infection was responsible for myocardial injury. However, several investigators noted that cardiac dysfunction increased after the eradication of the infective agent and speculated that the pathogenesis may be due to the immunologic responses initiated by the virus. Support for this theory comes initially from the work of Woodruff, who noted that the histologic evidence of cardiac injury in Coxsackie B infection occurred only after the virus was no longer detectable in the myocardium. Subsequently, demonstration of T-lymphocyte and macrophage infiltration, perforin granules, and a variety of cytokines known to depress myocardial contractility in endomyocardial biopsies of patients with active carditis strengthened the concept of immune-mediated injury. Furthermore, immunosuppressive therapy in animal models attenuated inflammation-with improved survival, less cellular infiltrate, and less necrosis. The specific immune responses that lead to the myocardial injury are incompletely defined. A murine model of myocarditis induced by coxsackie B has provided some insight into immunologic sequence of events. Following infection with coxsackie B3 virus, ma-

crophages are present in the infiltrate until day 8. After macrophage activity decreases, both effector (CD8) and helper (CD4) T cells are identified within myocardial lesions. At peak infiltration, some murine strains showed a predominance of CD8-positive cells while in others CD4 cells predominate, suggesting participation of both humoral- and cell-mediated immune responses. In human subjects, T-lymphocyte and macrophage infiltration characterizes the immunohistochemical picture, whereas B lymphocytes and natural killer cells are absent. T-lymphocyte subset analysis of human serum does not demonstrate consistency in dominance of CD4 or CD8 cells. The mechanisms of injury when lymphocytes infiltrate the myocardium are unknown. In the murine model, messenger ribonucleic acid (m-RNA) of perforin, the pore-forming protein mediating cytotoxicity, was identified in cytoplasmic granules of infiltrating cells by in situ hybridization. Similarly, biopsy samples from patients with active myocarditis contain perforin granules in infiltrating cells, implying that direct cytotoxicity can occur. Alternatively, release of cytokines such as interleukin-1, interleukin-6, interleukin-8, and tumor necrosis factor alpha may cause reversible depression of myocardial contractility without resulting in cell death. Therefore, the effect of T cell-mediated immune injury may be either irreversible as a result of cell death through cytotoxicity (perforin) or reversible as a result of injury mediated by cytokines. A marked reduction in myocardial cell damage is noted in T cell-depleted mice inoculated with encephalomyocarditis virus. Antiheart antibodies in the serum of patients with myocarditis have been reported but may reflect nonspecific myocardial damage. When serum from patients with myocarditis was screened for autoantibodies, high-titer immunoglobulin G (IgG) with cardiac specificity was detected in 59 percent of patients with myocarditis and in none of the normal samples. Antibodies with specificity for contractile and energy-transport proteins have been identified. In sera from patients with active myocarditis, Western immunoblotting demonstrated reactivity of a fraction that includes antibody to the heavy chain of cardiac myosin. In a murine myocarditis model, cardiac myosin antibodies are observed following coxsackie B virus infection. Moreover, injection of cardiac antimyosin antibodies without infection results in myocarditis that is histologically similar to that seen following

coxsackie B3 virus infection. The role of viral infection has been deemphasized following the popularization of the immune injury hypothesis. Viral infection is the trigger for the immune response that is deleterious. Attempts to culture virus from human myocardial tissue generally have been unsuccessful. Only a single case report of Coxsackievirus identified in a myocardial biopsy specimen in an adult has been described. However, identification of viral genomic fragments in myocardial samples by in situ hybridization and polymerase chain reaction from patients with myocarditis and dilated cardiomyopathy have been reported. These genomic fragments may not be capable of replicating as intact cardiotropic virus but probably serve as a persistent source of antigen to drive the deleterious immune responses. In addition to the tropism of the virus, host immune responses play an important role in determining the severity of the clinical disease. When quantitative peripheral T- and B-lymphocyte populations were analyzed in patients with dilated cardiomyopathy and myocarditis, no consistent changes were detected. However, immunologic assays demonstrate a reduction in the function of natural killer cells, antibody-dependent cellular cytotoxic cells, and suppressor cells and an increase in circulating levels of interleukin-1 and tumor necrosis factor alpha. These immunoregulatory defects may predispose the host with a high antigenic load to develop immune responses that are not modulated by the natural inhibitory immunoregulatory mechanisms. In addition to chronic inflammatory immune mechanism or persistent viral infection, apoptotic cell death may be another mechanism by which myocarditis can result in cardiomyopathy. Several different viruses have been reported to be triggers for apoptosis. The association between acute myocarditis and dilated cardiomyopathy has been recognized for the past two centuries. However, the link between these two diseases remains circumstantial. Autoreactive antibodies and interleukin-2 receptors are identified commonly in both patients with myocarditis and those with dilated cardiomyopathy. Serologic titers to cardiotropic viruses are more common in patients with cardiomyopathy than in normal subjects. Viral genomic material can be detected more frequently by polymerase chain reaction (PCR) in patients with dilated cardiomyopathy versus other cardiac diseases. Animal models of myocarditis can progress to dilated cardiomyopathy, as

can patients with clinically suspected or biopsy-proven myocarditis. However, the percentage of patients with idiopathic dilated cardiomyopathy that represent the end stage of an active myocarditis is unknown.

Clinical Presentation.

The clinical manifestations of myocarditis are variable. Most patients have a self-limited disease, whereas others present in profound cardiogenic shock. The most obvious symptom suggesting myocarditis is an antecedent viral syndrome. Flu-like symptoms occur in approximately 60 percent of patients.Chest pain may occur in up to 35 percent of patients and may be typically ischemic, somewhat atypical, or pericardial in character. Occasionally patients will present with a clinical syndrome identical to an acute myocardial infarction, with left ventricular asynergy, electrocardiographic evidence of injury or Q waves, and ischemic cardiac pain. In this syndrome, at autopsy, the coronary arteries are widely patent, although viral coronary arteritis has been reported. Coronary vasospasm has also been associated with acute myocarditis. Patients may present with syncope or palpitations with atrioventricular (AV) block or ventricular arrhythmia. Complete AV block is common with some patients presenting with Stokes-Adams attacks. The complete heart block is generally transient and rarely requires a permanent pacemaker. Sudden cardiac death can be the initial presentation of myocarditis in some patients, presumably from complete heart block or ventricular tachycardia. In a 20-year review of sudden death among Air Force recruits, 20 percent had myocarditis documented at autopsy. In some patients with refractory ventricular arrhythmias, endomyocardial biopsy or autopsy has revealed myocarditis. Systemic or pulmonary thromboembolic disease is also associated with myocarditis. A familial tendency for the development of myocarditis may be present. In one report, a suppressor cell defect was detected, predisposing to development of active myocarditis. Patients with peripartum cardiomyopathy have a high frequency of myocarditis on endomyocardial biopsy. The immunoregulatory changes during and following pregnancy may heighten susceptibility to viral myocarditis, and exposure to trophoblastic antigens may predispose to immune-mediated myocardial injury. Patients with new-onset left ventricular dysfunction given the di-

agnosis of idiopathic dilated cardiomyopathy may actually have active myocarditis despite the absence of clinical signs and symptoms of acute infection.

Diagnosis

Laboratory findings are generally not diagnostic. Sixty percent of patients will have an elevated erythrocyte sedimentation rate and 25 percent an elevated white blood cell count. Elevated titers to cardiotropic viruses may be present. However, a fourfold rise in IgG titer over a 4- to 6-week period is required to document acute infection. Elevated IgM antibody titer may denote an acute infection more specifically than a rise in IgG antibody titer. Unfortunately, a rise in antibody titer documents only the response to a recent viral infection and does not indicate active myocarditis. Abnormalities in peripheral T- and B-lymphocyte counts have been reported, but these findings have not been consistent and cannot be used as diagnostic adjuncts. Increase in the MB band of CPK is observed in approximately 12 percent of patients. Troponin levels may also increase. In the Myocarditis Treatment Trial, elevated troponin levels were found in 32 percent of the patients and were predictive of inflammatory involvement. The electrocardiogram most frequently shows sinus tachycardia. Diffuse ST-T-wave changes, prolongation of the QTc interval, low voltage, and even an acute myocardial infarct pattern has been noted in some patients with myocarditis. Conduction delay is common, with left bundle branch block identified in 20 percent of patients. Cardiac arrhythmias are frequently observed in patients with myocarditis, including complete heart block, supraventricular arrhythmias-especially in the presence of congestive heart failure or pericardial inflammation, and ventricular arrhythmias. Echocardiography can reveal left ventricular systolic dysfunction in patients with a normal-sized left ventricular cavity. Segmental wall motion abnormalities may be observed. Wall thickness may be increased, particularly early in the course of the disease, when inflammation is fulminant. Ventricular thrombi are detected in 15 percent of those studies. Echocardiographic findings in active myocarditis can mimic restrictive, hypertrophic, or dilated cardiomyopathy. Endomyocardial biopsy is the critical test to confirm the diagnosis. Endomyocardial biopsy techniques enable the repetitive sampling of the human myocardium with minimal discomfort and minor mor-

bidity. Right ventricular myocardial specimens can be obtained by accessing the right internal jugular or femoral vein. Intravascular biopsy of the left ventricle is infrequently performed due to the higher morbidity associated with this approach. The right ventricular bioptome is positioned under fluoroscopy or echocardiography to sample the interventricular septum. As the myocarditis can be focal, a minimum of four to six fragments are obtained. Sampling error is reduced by less than 5 percent. Using the Stanford bioptome, typical samples are 2 to 3 mm in maximal diameter and 5 mg in wet weight. Samples are processed, paraffin-imbedded, sectioned, and stained with hematoxylin-eosin and trichrome. Special stains are employed if other diagnoses are considered. Diagnoses that can be made or confirmed by endomyocardial biopsy are listed in Table 5.2.

Table 5.2

Diagnoses That Can Be Made by Endomyocardial Biopsy

1. Myocarditis
    - Giant cell
    - Cytomegalovirus
    - Toxoplasmosis
    - Chagas
    - Rheumatic
    - Lyme
2. Infiltrative
    - Amyloid
    - Sarcoid
    - Hemochromatosis
    - Carcinoid
    - Hypereosinophilic
    - Glycogen storage
    - Cardiac tumors
3. Toxins
    - Doxorubicin
    - Chloroquine
    - Radiation injury
4. Genetic
    - Fabry
    - Kearns-Sayre syndrome

- Right ventricular dysplasia

Several investigators have performed endomyocardial biopsies in patients with unexplained congestive heart failure and/or ventricular arrhythmia. The percentage of patients with biopsies interpreted as myocarditis varied widely, primarily owing to the different diagnostic criteria for active myocarditis used by the investigators. This variability of endomyocardial biopsy criteria prompted a meeting of cardiac pathologists to reach a consensus on the pathologic definition of myocarditis, now known as "the Dallas criteria." Active myocarditis was defined as "an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease." Examination of a minimum of four to six fragments from each patient is required for interpretation. The term borderline myocarditis is applied when the inflammatory infiltrate is too sparse or myocyte injury is not demonstrated. Repeat biopsy is then suggested. A high frequency of active myocarditis is confirmed by repeat biopsy in patients whose initial histologic samples demonstrated borderline myocarditis. When right ventricular endomyocardial biopsy has failed to establish the diagnosis, sampling the left ventricle may improve diagnostic yield (Fig. 5.1).

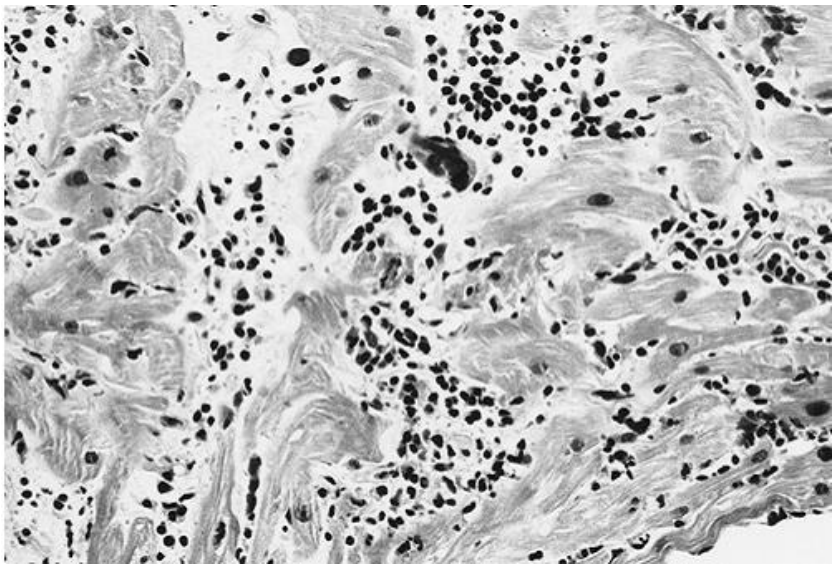


Figure 5.1. Photomicrograph showing extensive interstitial infiltrates of lymphocytes and myocytes with focal myocyte necrosis (×60).

Endomyocardial biopsy must be applied as quickly as possible to maximize the diagnostic yield. Biopsies in patients with peripartum cardiomyopathy have the high-

est yield when performed early after onset of symptoms. Resolution of active myocarditis has been documented within 4 days of initial biopsy, with progressive clearing over several weeks on serial biopsy. Progression of active myocarditis to dilated cardiomyopathy has been documented when serial biopsies are performed. Newer molecular biology techniques are being applied to the analysis of endomyocardial tissue for the detection of viral nucleic acid. The usefulness of PCR amplification of viral genomic material from endomyocardial tissue in children with suspected myocarditis was shown in a study that found PCR amplified viral product in 67 percent of the children studied.

Although technetium-99m-pyrophosphate scintigraphy has proved useful in the detection of myocarditis in a murine model, it has not been effective in diagnosing myocarditis in humans. Imaging with gallium 67, an inflammation-avid radioisotope, has shown promise as a screening method for active myocarditis, with a specificity and sensitivity of 83 percent and a negative predictive value of 98 percent in biopsy-proven myocarditis. Indium 111-labeled antimyosin antibody scans can be used to detect myocyte necrosis. Application of this technique in patients with myocarditis has demonstrated a sensitivity of 83 percent, a specificity of 53 percent, and a positive predictive value of a normal scan of 92 percent. In those patients who were antimyosin antibody-positive and biopsy-negative, the possibility of inflammation undetected by biopsy has been considered. Antimyosin imaging, however, detects myocyte injury independent of etiology, and noninflammatory causes of heart muscle injury in young patients may cause false-positive scans. The usefulness of scintigraphy in diagnosing myocarditis is limited by low specificiy, radiation exposure, and expense Tissue alterations associated with myocarditis may be identifiable using magnetic resonance imaging (MRI). Preliminary results suggest that myocardial inflammation may induce abnormal signal intensity of the myocardial walls. Use of T2-weighted images to visualize tissue edema has been described in several case reports of patients with active myocarditis. More recently, contrast media-enhanced MRI has been used to characterize myocardial changes in myocarditis. The MRI imaging contrast agent gadopentetate dimeglumine accumulates in inflammatory lesions. It is a

hydrophilic agent that accumulates in the extracellular space of water-containing tissues. Gadolinium increases the signal of T1-weighted images. A total of 19 patients with clinically suspected myocarditis and 18 normal subjects underwent contrast-enhanced MRI. Global relative enhancement was higher in patients than controls. Contrast MRI also visualized the area of inflammation and the extent of inflammation and may prove to be a valuable technique in both the diagnosis and monitoring of disease activity. Despite the promise of noninvasive techniques, endomyocardial biopsy remains the diagnostic standard.

Treatment

The immune injury hypothesis generated application of potential therapies, including immunosuppression. Anecdotal success with immunosuppression in active viral myocarditis led to the large Multicenter Myocarditis Treatment Trial. In this study, patients with biopsy-proven myocarditis were randomized between conventional medical therapy versus steroid/azathioprine or steroid/cyclosporine immunosuppression. The primary end point of the study was change in ejection fraction over 28 weeks. For all patients, the average increase in ejection fraction over baseline was 9 percent. Treatment assignment was not predictive of improvement in left ventricular ejection fraction, attenuation of clinical disease, or mortality.

Recently, immune modulatory therapy with immune globulin has been shown to be an effective treatment for Kawasaki's disease and new-onset cardiomyopathy in pediatric patients. Subsequently, a small open-label study was performed in 10 adult patients with new-onset heart failure. Significant improvement in left ventricular function was observed in 9 of 10 patients. These findings formed the basis for a multicenter study investigating the use of this treatment modality. The IMAC trial (Intervention in Myocarditis and Acute Cardiomyopathy with immune globulin) used a single infusion of high-dose immunoglobulin (2 g/kg) to treat presumed inflammatory cardiomyopathies. In this placebo-controlled 6-month trial, the improvement in left ventricular ejection fraction and symptoms was similar in both groups. Thus no benefit of immunomodulation could be demonstrated. Despite the experimental data supporting the immune injury hypothesis, no randomized study has yet demonstrated the

efficacy of immunosuppressive therapy in myocarditis. Immunosuppressive therapy is therefore not routinely recommended for infective myocarditis. Standard heart failure treatment remains the mainstay of therapy.

Prognosis

About one-third of those who present with clinical carditis and recover will be left with some cardiac abnormality ranging from mild changes on electrocardiography (ECG) to significant heart failure. The multicenter myocarditis trial provided insight into the natural history of myocarditis with current treatment. The degree of left ventricular dysfunction at initial presentation was most predictive of recovery. Approximately 40 percent of patients fully recovered. Other predictors of recovery included shorter duration of disease and less intensive conventional drug therapy. One-year survival in this study was 80 percent, with a 4-year survival of only 44 percent. The prognosis of myocarditis depends to some extent on the causative agent, but if clinical heart failure develops, 5-year mortality rates are in the 50 to 60 percent range, comparable with figures seen in idiopathic cardiomyopathy. Chronic inflammation, viral persistence, or both may affect disease progression and prognosis. Future therapies will need to identify the predominant factor to target treatment and hopefully improve survival.

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) is increasingly recognized as a cause of dilated cardiomyopathy. In some inner-city hospitals, it may represent a very common diagnosis. The relatively recent emergence of this virus in the early 1980s has provided a unique opportunity to prospectively monitor the development of heart failure to chronic viral infection. The etiology of this cardiomyopathy may be from infection of myocardial cells with HIV or coinfection with other cardiotropic viruses, postviral autoimmune response, or cardiotoxicity from illicit drugs or drug therapy. Patients with a history of illicit drug use, prior cardiac disease, previous treatment with antiretroviral or immunomodulating drugs, or with an ejection fraction less than 50 percent were excluded from prospective study. In the 60 months of follow up, 8 percent of the patients developed cardiomyopathy, with annualized incidence rate of

16 cases per 1000 patients. A predisposing factor to cardiomyopathy development was a CD4 cell count below 400/mL. In 83 percent of the patients, a histologic diagnosis of myocarditis was made. In 92 percent of these positive biopsies, HIV nucleic acid sequences were detected by in situ hybridization. Coexistent infection with coxsackie virus group B, cytomegalovirus and Epstein-Barr virus was detected in a small segment of this cohort. Other studies suggest that disease duration and illicit drug use as factors contributing to the development of this disease. As the symptoms of heart failure and HIV can be very similar (i.e., fatigue, wasting, etc.), careful cardiologic follow-up of these patients is probably indicated to detect early development of left ventricular dysfunction. Conventional heart failure management can then be instituted to alleviate cardiac-related symptoms.

Cytomegalovirus

Cytomegalovirus may lead to myocarditis in the general population, but ordinarily the myocarditis is self-limited and asymptomatic. In the cardiac transplant recipient, however, cytomegalovirus myocarditis may become a more serious disease resulting in cardiac dysfunction. The treatment of cytomegalovirus myocarditis is intravenous ganciclovir, which effectively eradicates the virus. Early cytomegalovirus infection correlates with the development of allograft coronary artery disease, the major cause of death beyond the first year after cardiac transplantation. It is proposed that infection of either subintimal fibroblasts or endothelial cells results in immunologic injury that predisposes to this potentially fatal condition.

NONVIRAL CAUSES OF MYOCARDITIES

Chagas' Disease

American trypanosomiasis, or Chagas' disease, is the most common cause of congestive heart failure in the world. This condition results from the bite of the reduviid bug, leading to infection with Trypanosoma cruzi, and is endemic to rural South and Central America.

Pathogenesis

The pathogenesis of chronic, chagasic cardiomyopathy is controversial because the parasite is rarely present in the myocardium. As in the viral cardiomyopathy

model, the cardiac injury is thus thought to be immunologically mediated. Both cellular and humoral immune responses have been implemented in the myocardial injury. Myocardial biopsies demonstrate that the inflammatory infiltrate in chronic Chagas' disease consists mainly of CD8+ T cells, with a low number of CD4+ T cells. This suggests some degree of immunologic depression in the host, since the activation of T-helper cells is known to be the most effective mechanism of defense against the parasites. Some have postulated that the diminished expression of CD4+ T cells during acute T. cruzi infection may be related to a mechanism of tolerance induced by the parasite Evidence for this comes from studies that have shown that the addition of interleukin-1 (IL-1) in vitro restores helper T-cell function, thus implementing a macrophage defect in this process. Furthermore, IL-2 and the IL-2 receptor are absent or scarce in the inflammatory infiltrate, attesting to the attenuated role of the T-helper subset in this disease.

Clinical Presentation

This parasitic disease has an acute phase, where hematogenous spread of the parasite leads to invasion of various tissues and organ systems. The invasion is accompanied by an intense inflammatory reaction with mononuclear cells and is characterized by fever, sweating, myalgias, myocarditis, hepatosplenomegaly, and a case fatality rate of about 5 percent. Most patients recover from the acute illness and enter an asymptomatic latent phase, but 20 to 30 percent will develop a chronic form of the disease up to 20 years after the initial infection.

The chronic stage is a result of gradual tissue destruction. The gastrointestinal tract and the heart are the most common sites of involvement, with the primary cause of death being cardiac failure. In the gut, the destruction of the myenteric plexus is responsible for the development of megaesophagus and megacolon. In the heart, the myofibrils and the Purkinje fibers are replaced by fibrous tissue, leading to cardiomegaly, congestive heart failure, heart block, and arrhythmia. The microscopic findings are those of extensive fibrosis, but a chronic cellular infiltrate composed of lymphocytes, plasma cells, and macrophages is often present and parasites are found in about a quarter of the patients.

The diagnosis of the acute disease depends on the discovery of trypomastigotes in the blood of the infected individual. In chronic infection, direct diagnosis is less useful due to less circulating trypomastigotes. Xenodiagnosis (where the patient is bitten by reduviid bugs bred in the laboratory and subsequent identification of the parasites in the intestine of the insect) is the most useful test, which will detect infection in about half the patients. The complement-fixation test (Machado-Guerreiro test) also has high sensitivity and specificity for identification of chronic Chagas' disease. In the other lab tests, it is necessary to rely on positive serologic tests (such as the indirect immunofluorescent antibody, the enzyme-linked immunosorbent assay, and the hemagglutination tests) together with symptoms and signs compatible with Chagas' disease.

Endomyocardial biopsy may show active myocarditis using the Dallas criteria. Noninvasive assessment commonly shows segmental wall motion abnormalities, specifically apical aneurysms. Electrocardiographic findings include complete heart block, atrioventricular block, or right bundle branch block with or without fascicular block in 11 percent of infected individuals. Ventricular arrhythmias may require antiarrhythmic drugs, including amiodarone. The treatment of chronic Chagas' disease is symptomatic and includes a pacemaker for complete heart block, an implantable cardioverter-defibrillator for recurrent ventricular arrhythmia, and standard therapy for congestive heart failure as outlined for other forms of myocarditis. Antiparasitic agents such as Nifurtimox and benzimidazole eradicate parasitemia during the acute phase and are typically curative. They should be administered if the disease has not previously been treated and may be used as prophylaxis if there is a high likelihood of recurrence, such as following immunosuppressive therapy. The role of immunosuppression therapy for chagasic myocarditis is controversial, and heart transplantation is effective for end-stage refractory cardiac disease.

Lyme Carditis

Lyme disease may result from infection with the spirochete Borrelia burgdorferi, introduced by a tick bite. The initial presenting symptom in patients with the disease who progress to cardiac involvement is frequently complete heart block. Left

ventricular dysfunction may be seen but is unusual. Endomyocardial biopsy may show active myocarditis. Rarely are spirochetes seen on biopsy. Corticosteroid administration is helpful in treating Lyme carditis following therapy with tetracycline. Among other infectious etiologies is Toxoplasma gondii, which is curable by pyrimethamine and sulfadiazine and occurs most commonly in the immune-deficient host. Leptospirosis is yet another common cause in fatal cases of myocarditis. Fifty percent of cases have ST- and T-wave changes on electrocardiography.

Rheumatic Carditis

One form of myocarditis that has declined dramatically in the latter half of the twentieth century is rheumatic carditis. The availability of antibiotics and changes in the virulence and serotypes of group A streptococcus may explain the decreasing frequency of this disease. Acute rheumatic fever can occur in children and young adults. It generally follows a group A streptococcal pharyngitis, but only indirect evidence linking the two has been found. Rheumatic carditis may result from a direct toxic effect of some streptococcal product versus an immunologic mechanism. Group A streptococci have a number of structural components similar to those of human tissue. Antibodies to streptococci cross-react with the glycoproteins of heart valves. The serum of patients with rheumatic fever contains autoantibodies to myosin and sarcolemma. The Aschoff body, pathognomic for this disorder, represents persistent focal inflammatory lesions in the myocardium. These nodules can persist for years after an acute attack. Macrophages containing myosin have been identified in these nodules.

Clinical diagnosis is made using the Jones criteria. The major manifestations are carditis, polyarthritis, chorea, erythema marginatum, subcutaneous nodules, and evidence of preceding streptococcal infection (i.e., positive throat culture, history of scarlet fever, elevated antistreptolysin titers). Minor criteria are nonspecific findings such as fever, arthralgia, previous rheumatic fever or rheumatic heart disease, elevated ESR or reactive protein, and prolonged PR interval. Diagnosis is made by the presence of two major criteria or one major and two minor criteria. Debate into whether the Jones criteria should be modified to incorporate Doppler-Echo indices are ongoing.

Two-thirds of patients present with an antecedent pharyngitis, followed by the symptoms of rheumatic fever in 1 to 5 weeks, with a mean presentation of 18.6 days. Severe carditis resulting in death can occur but is unusual. CHF is observed in only 5 to 10 percent of cases. Usually the carditis is mild, with the predominant effect being scarring of the heart valves. Physical exam is notable for fever and heart murmurs reflecting the acute valvulitis. The mitral valve is involved three times as frequently as the aortic valve; therefore mitral murmurs are more common. Mitral regurgitation is the most common finding. A mid diastolic murmur over the apical area can frequently be heard. This is called the Carey Coombs murmur, and its presence almost certainly confirms mitral valvulitis. Aortic insufficiency can be auscultated with aortic valvulitis. There are no characteristic ECG findings through PR prolongation, and nonspecific ST-T-wave changes are frequently described. Endomyocardial biopsy demonstrates the Aschoff nodules as well as a diffuse cellular interstitial infiltrate including lymphocytes, polymorphonuclear cells, histiocytes, and eosinophils.

Laboratory tests suggestive of rheumatic fever include antibodies to antistreptolysin O and anti-DNAase B, an elevated sedimentation rate, and elevated C-reactive protein. Extracardiac manifestations generally predominant with an acute migratory polyarthritis of the large joints. Aspirin and penicillin are the mainstays of therapy. Corticosteroids can also provide symptomatic relief. Once rheumatic fever is diagnosed, antibiotic prophylaxis is required to prevent recurrent episodes. The most effective method is a single monthly intramuscular injection of 1.2 million units of benzathine Penicillin G until age 21.

NONINFECTIVE CAUSES.

Hypersensitivity reasons

Hypersensitivity myocarditis is an example of the early phase of eosinophilic myocarditis and is thought to be due to an allergic reaction to a variety drugs. Methyldopa, the penicillins, sulfonamides, tetracycline, and the antituberculous drugs are the pharmaceuticals most commonly associated with this entity. It is characterized by peripheral eosinophilia and infiltration into the myocardium by eosinophils, multinucleated giant cells, and leukocytes. The major basic protein of the eosinophil gra-

nule may be detected in the presence of acute necrotizing myocarditis, suggesting toxicity of the granule contents. Good success has been reported with stopping the offending agent and treatment with corticosteroids. Unfortunately, the presence of this condition often goes unnoticed and the first manifestation of cardiac involvement is sudden death due to arrhythmia.

GIANT-CELL MYOCARDITIS

Giant-cell myocarditis is an extremely rare but aggressive form of myocarditis, typically progressive and unresponsive to medical therapy. This disease is most prevalent in young adults, with a mean age at onset of 42 years (and a range of 16 to 69 years). Association with other autoimmune disorders is reported in approximately 20 percent of cases. Diagnosis is made by endomyocardial biopsy. Widespread or multifocal necrosis with a mixed inflammatory infiltrate including lymphocytes and histiocytes is required for histologic diagnosis. Eosinophils are frequently noted, as are multinucleated giant cells in the absence of granuloma (Fig. 5.2). Immunophenotyping of the cellular infiltrate has shown lymphocyte populations composed of T-helper or in some cases T-suppressor cells.

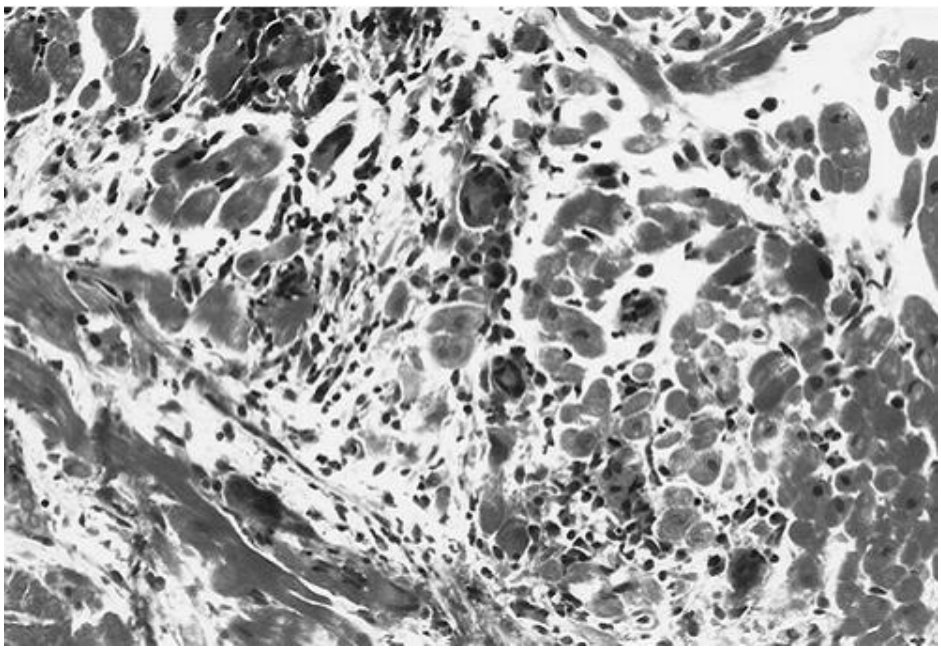


Figure 5.2. Photomicrograph showing extensive myocyte damage and infiltrates of mononuclear cells and numerous multinucleated giant cells (×60).

The clinical course is usually characterized by progressive CHF and is frequently associated with refractory ventricular arrhythmia. It is almost uniformly and

rapidly fatal. Comparison of survival of patients with giant-cell myocarditis with that of patients with lymphocytic myocarditis demonstrates significantly worse survival in those patients with giant-cell disease. There have been rare reports of response to aggressive immunosuppressive regimens that include cyclosporine and azathioprine in addition to corticosteroids. Use of immunosuppressive therapy in these patients appears to prolong survival. Cardiac transplantation represents the best treatment option, though most patients expire prior to identification of a suitable donor. Giant-cell myocarditis may recur following cardiac transplantation, but the frequency of recurrence is unknown. Giant cells can be detected on routine surveillance biopsies up to 9 years posttransplant. This cellular infiltrate may respond to an increase in immunosuppressive therapy.

Idiopathic myocarditis

Idiopathic myocarditis is an inflammatory myocardial disease, the aetiology of which is not well known (Table 5.3). The Dallas criteria or Japanese Circulation Society criteria have been used to diagnose this disease.With both criteria, the diagnosis is based on clinical manifestations and histology of the endomyocardial biopsy specimen. Since endomyocardial biopsy is guided by fluoroscopy and not by direct observation, whether or not the biopsied specimens are obtained from the inflamed areas and exhibit histological inflammatory changes is dependent on chance. This uncertainty means that myocarditis cannot be diagnosed from histological changes alone, and is the reason why clinical manifestations must also be included in the diagnostic criteria. If endocardial surface colour can be shown to represent the stages of myocarditis, percutaneous cardioscopy, which enables observation of the cardiac chambers from inside, could be used for diagnosis and staging of myocarditis. This procedure would also make it possible to obtain myocardial specimens from the diseased myocardium, with direct observation of where inflammation is actually occurring. A definite histological diagnosis of myocarditis could therefore be attained.

Table 5.3

Classification of acute and chronic idiopathic myocarditis by clinical manifestations and endomyocardial biopsy

A. Classification by clinical manifestations

1. Acute idiopathic myocarditis

- Within 1 month from the onset of signs and symptoms
- Preceding common cold-like symptoms
- Signs and symptoms indicating cardiac involvement (arrhythmia,
- murmur, gallop rhythm, and friction rub)
- Electrocardiographic abnormality
- Ventricular contraction disturbance by echocardiography
- Elevated C-reactive protein and/or troponin T.
- Endomyocardial biopsy findings.

2. Chronic idiopathic myocarditis

Cardiac symptoms and signs persisting for a few months or more (2 months)

a) Active (persistent) type

- Elevated troponin T or C-reactive protein.
- Endomyocardial biopsy findings shown in B.

b) Inactive (subsided) type

- No signs of inflammation.
- No elevation of troponin T or C-reactive protein.
- With or without DCM-like appearance by ventriculography.
- Endomyocardial biopsy findings shown in B.

B. Classification by endomyocardial biopsy findings

1. Acute idiopathic myocarditis

- Polynuclear cell infiltration.
- Mononuclear cell infiltration (≥20/f) (massive; grouping).
- Mononuclear cell infiltration (≥5≤ to ,20/f) (moderate to minimal).
- Cardiomyocytes: degeneration, disruption, lysis, and/or loss.
- No interstitial fibrosis.
- Interstitial and/or endocardial oedema.

2. Chronic idiopathic myocarditis

a) Active (persistent) type

- Mononuclear cell infiltration (≥14 to ,20/f) (moderate).
- Cardiomyocyte: degeneration, disruption, irregular size, and/ or disarray.
- Interstitial oedema,
- Interstitial fibrosis (≥5%/f) and/or fat deposition.

b) Inactive (subsided, or healed) type

- Mononuclear cell infiltration (≥5to ,14/f) (minimal)
- Cardiomyocyte: degeneration, hypertrophy, irregular size, and/or disarray.
- Interstitial fibrosis (≥5%/f) and/or fat deposition.

There are two established criteria for the diagnosis of idiopathic myocarditis, the Dallas criteria and the Japanese Circulation Society criteria. Since chronic idi-

opathic myocarditis (CM) is not included in the Dallas criteria, the Japanese Circulation Society criteria, which include both acute idiopathic myocarditis (AM) and CM, were adopted in the present study. In the Japanese Circulation Society criteria, idiopathic myocarditis is classified based on clinical manifestations, by excluding giant cell myocarditis and other secondary myocarditis, into AM and CM, and histologically into three stages, namely AM, active CM, and inactive CM. Polynuclear cell infiltration, which appears in the super-acute phase of inflammation, is included in the histological criteria. Mononuclear cell infiltration, which also indicates inflammation, was classified according to cell density into massive (≥20/f × 400: number of cells per microscopic field at ×400 magnification), moderate (≥14 to ,20/f × 400), and minimal (≥5to ,14/f × 400). A density below 5/f × 400 was considered to indicate no infiltration and accordingly no inflammation.

How is the myocardium affected by viral infections? First, virus infection directly contributes to cardiac tissue destruction by cleaving the cytoskeletal protein dystrophin, leading to a disruption of the dystrophin-glycoprotein complex. It is hypothesised that this mechanism is crucial for enteroviral replication in the heart and for the development of viral associated chronic cardiomyopathy. If extensive damage occurs, it is conceivable that the heart is functionally impaired and heart failure develops. This might be the case during fulminant myocarditis. Interestingly, patients with fulminant myocarditis that survive acute disease and probably clear the virus do not develop progressive heart failure. In mouse strains, susceptible and resistant to chronic myocarditis, viral genome and transcript are present. This indicates that the persistence of virus alone may not be the single determining factor in the development of chronic cardiomyopathy and that the viral damage itself may not be as important as the viral associated immune response. Indeed it appears that progression to overt heart failure reflects an ongoing process due to the development of heart-specific autoimmunity, virus persistence or both. In this context several clinical studies and insights from animal models provide evidence that autoimmune mechanisms significantly contribute to chronic cardiac inflammation. Autoimmune features in patients with inflammatory cardiomyopathy include familiar aggregation, abnormal ex-

pression of HLA-class II on cardiac endothelial cells, a weak but significant association with HLA-DR4 and the detection of organ- and disease-specific autoantibodies of the Ig G class by indirect immunfluorescence (IFL) in approximately 30% of patients with myocarditis and dilated cardiomyopathy. Two of the autoantigens recognised by the antibodies found by IFL could be identified as alpha and beta myosin heavy chain isoforms. The low frequency of cardiac specific autoantibodies in patients with heart failure not due to myocarditis or dilated cardiomyopathy, the decrease of autoantibody titers during disease progression in dilated cardiomyopathy and the deterioration of cardiac function in myosin antibody positive patients indicate that these antibodies are not merely an epiphenomenon but represent specific markers of immune pathogenesis. Animal models further support the idea that autoimmune mechanisms triggered by viral infection contribute to the pathogenesis of inflammatory and post-inflammatory cardiomyopathy. Comparable to human myocarditis infection of genetically defined mice strains with cardiotropic virus results in ongoing myocarditis and dilated cardiomyopath. Development of myocarditis is associated with polyclonal heart-specific autoantibody responses and heart-specific, autoaggressive T cell responses. The evidence available indicates a key role for alpha-myosin as a target antigen in development of myocarditis and dilated cardiomyopathy as the same susceptible mouse strains develop autoimmune myocarditis in the absence of virus infection after immunization with activated dendritic cells loaded with alpha-myosin peptide. The finding that in some susceptible mouse strains like DBA/2 mice virus- or myosin-induced myocarditis is an antibody-mediated disease may also apply to humans which means that the heart-specific antibodies may be directly pathogenic in some patients with myocardits and dilated cardiomyopathy. In this context further randomized studies examining the therapeutic value of non-antigen-specific Ig G adsorption as well as antibody-specific plasmapheresis and affinity adsorption are needed.

Taken together it is still a matter of debate, whether the presence of persistent virus by itself or infection-triggered autoimmunity is of more relevance to the development of heart failure. In order to refine current treatment strategies it is more im-

portant to define diagnostic criteria that allow us to recognise which mechanism is of relevance in the setting of an individual patient.

The clinical picture of acute / chronic myocarditis/myopericarditis is of importance in differential diagnosis, especially in younger patients with suspected myocardial infarction. Myocarditis/myopericarditis commonly presents with chest pain, and the diagnosis is usually established on clinical grounds. However, endomyocardial biopsy is necessary to confirm the diagnosis. In general, endomyocardial biopsy of the right ventricle is carried out because biopsy of the left ventricle is difficult. By improving the guiding catheter and bioptome system, left ventricular biopsy was easier and safer in the present study. The left ventricle was selected for biopsy in the present study because it is the main chamber that contributes to cardiac pump function. Ventriculography is always carried out during routine catheterization; and simply replacing the angiographic catheter with a cardioscope-guided bioptome is sufficient for biopsy.

The majority of patients clinically diagnosed as having acute / chronic myocarditis exhibited acute or chronic heart failure. Nature evolution of acute / chronic myocarditis to end stage of cardiovascular disease across dilated cardiomyopathy is presented on Figure 5.3.

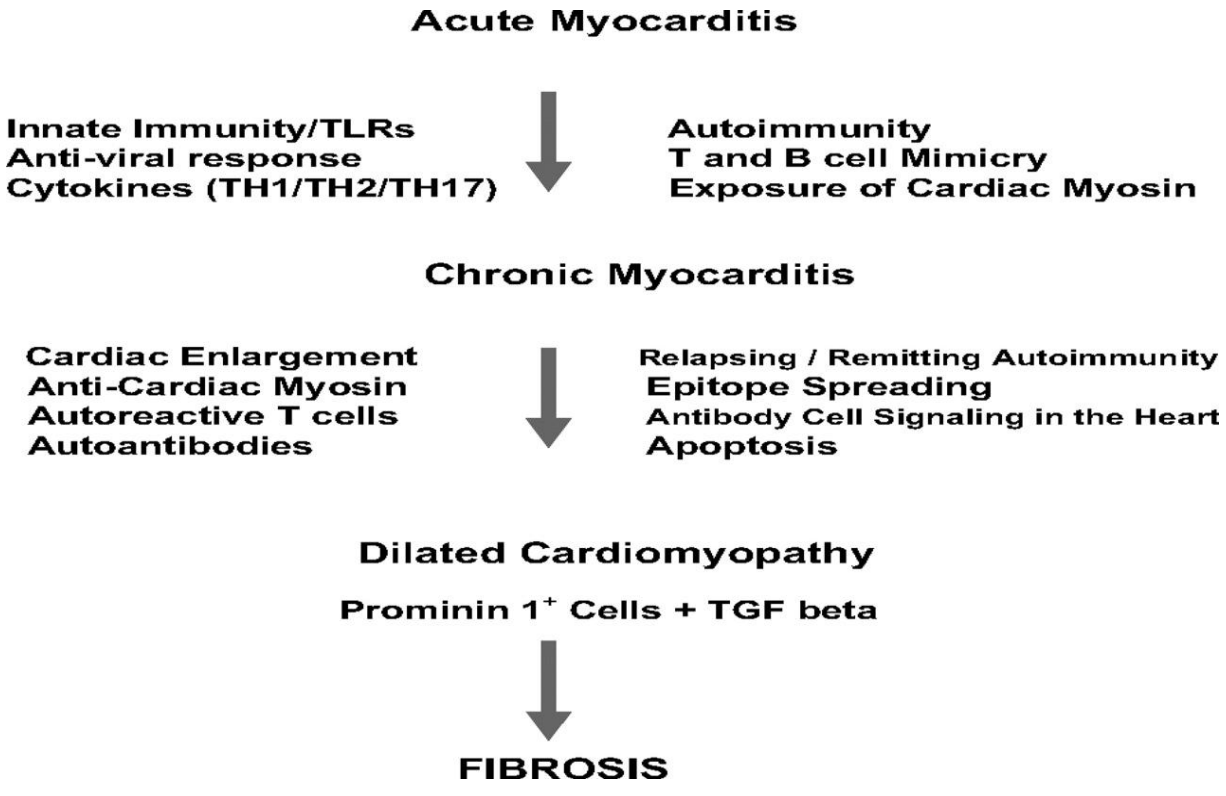


Figure 5.3. Potential mechanisms in progression of myocarditis to cardiomyopathy.

Supportive treatment

Over the last years myocarditis therapy has been restricted to supportive options facing the clinical syndroms of heart failure or arrhythmias [6], including basic medications with angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blocking agents, diuretics, beta-blockers and Amiodarone. Patients with persistently impaired cardiac ejection fraction and/or life threatening arrhythmias take survival advantage from ventricular assist devices and implantable cardiac defibrillators (ICD). In severe and rapidly progressive cases, however, heart transplantation still represents the only therapeutic option.

Immunosuppression

The idea that autoimmune mechanisms play an important role in the pathogenesis of myocarditis and post-viral cardiomyopathy has suggested a potential beneficial effect of immunosuppression in affected patients. Unfortunately, large randomised clinical trials have failed to prove that immunosuppression indeed improves survival in myocarditis, The largest study, the Myocarditis Treatment Trial, did not show beneficial effects of a combined immunosuppressive regimen on primary endpoints such as left ventricular function or survival. However, inclusion criterion was a histological diagnosis of myocarditis according to the Dallas criteria without further risk stratification for virus persistence and markers of immunoactivation on biopsy samples or cardiac autoantibodies. In contrast, several just recently published studies showed beneficial effects of immunosuppressive treatment for certain subgroups of patients with myocarditis. A large retrospective multi-centre study suggested that an immunosuppressive treatment regimen combining Cyclosporine and/or Azathioprin with corticosteroids improved outcome such as time to death or transplantation for patients with histological proven Giant-cell myocarditis. In a prospective single centre study immunosuppression together with a gluten-free diet improved left ventricular function and clinical status of patients with Celiac disease-associated myocarditis. Another study on patients with impaired cardiac function for more than 6 months and

biopsy-proven active lymphocytic myocarditis suggested a favourable effect of immunosuppression for patients with no detectable viral genome on heart biopsy samples but elevated titers of cardiac autoantibodies in the serum. Interestingly, the same study revealed a good response to immunosuppressive therapy for patients with Hepatitis C Virus-related myocarditis. In addition, a large randomised, prospective 2-centre study on patients with dilated cardiomyopathy selected for HLA up-regulation as a marker for immunoactivation on endomyocardial biopsy samples showed beneficial effects of a combined immunosuppressive therapy regarding ejection fraction, end-systolic and end-diastolic dimensions as well as NYHA score after 24 months of treatment. Of note, functional improvement always became evident within the first months of immunosuppressive treatment in most responders. Despite these encouraging data, however, there is no evidence so far that immunosuppression has a beneficial effect on primary end-points, such as heart transplantation or death.

Taken together, recent clinical and experimental data suggest that immunosuppression might become a reasonable option for defined subgroups of patients with myocarditis or dilated cardiomyopathy.

SQUEEZE FOR PULMONARY THROMBOEMBOLISM

1. Determaine the leading acquired causes of venous thromboembolism in generally populations. Choose all appropriate reason.
    a. oral contraceptives
    b. pregnancy
    c. hormone replacement therapy
    d. arterial hypertension
    e. obesity
2. Determaine the main inhered causes of venous thromboembolism in generally populations. Choose all appropriate reason.
    a. Factor V Leiden
    b. Factor VII deficiency
    c. Proconvertasa enzyme deficiency
    d. Prothrombin gene mutation
    e. Factor X gene mutation
3. Determaine the vulnerable population to pulmonary thromboembolism. Choose all appropriate reason.
    a. Cancer subjects

b. Patients with immobilization
c. Senior subjects
d. Pregnancy women
e. Obesity patients

4. Determaine environmental risk factors to pulmonary thromboembolism. Choose all appropriate reason.

a. Obesity
b. Arterial hypertension
c. Cigarette smoking
d. Surgery or trauma
e. Obesity patients
f. Cancer and/or cancer chemotherapy

5. Determaine more common signs and symptoms of deep venous thrombosis. Choose all appropriate reason.

a. asymmetry in the supraclavicular fossae
b. diffusely edematous of legs
c. difficulty walking
d. asymmetry in the girth of the upper arms
e. mild palpation discomfort

6. Determaine more appropriate method for visualization of pelvic veen thrombosis. Choose all appropriate reason.

a. Magnetic resonance imaging
b. Ultrasound examination
c. X-ray examination
d. Invasive contrast venography
e. Computer tomography

7. Determaine more appropriate method for visualization of deep veen thrombosis. Choose all appropriate reason.

a. Venous ultrasound examination
b. Magnetic resonance imaging
c. X-ray examination
d. Invasive contrast venography
e. Computer tomography

8. Determaine indications for invasive contrast venography as a diagnostic test. Choose all appropriate reason.

a. catheter intervention is planned
b. catheter-directed thrombolysis is expected
c. suction embolectomy is planned
d. angioplasty or stenting are pending
e. all answeres are correct

9. Determaine adjunctive measures for deep veen thrombosis management. Choose all appropriate reason.

a. Obtain family history and consider hypercoagulable work-up
b. Provide emotional support
c. Prescribe below-knee vascular compression stockings
d. Explain controversy concerning optimal duration of anticoagulation
e. all answeres are correct

10. Determaine a role of D-dimers for both veen thrombosis and venous thromboembolism. Choose all appropriate reason.

a. D-dimers are highly sensitive for the diagnosis of pulmonary thromboembolism
b. D-dimers are released in the presence of deep veen thrombosis
c. D-dimer is usful as screening test only
d. D-dimer has a high negative predictive value for pulmonary thromboembolism
e. all answeres are correct

SQUEEZE FOR INFECTIVE ENDOCARDITIS

1. Determine all possible important predisposing conditions for infective endocarditis.

a. congenital heart diseases
b. prosthetic grafts and valves
c. arterial hypertension
d. mitral annular calcification
e. coronary artery disease

2. Determine all possible important clcinical conditions for infective endocarditis.

a. Immunodeficiency
b. Alcoholism
c. Malnutrition
d. Diabetes mellitus
e. All mentioned are correct

3. Determine the most common catheter- or line-related lesions occurred in infective endocarditis.

a. right atrium,
b. left ventricle,
c. pulmonary valve,
d. tricuspid valve
e. mitral valve

4. Determine all intravascular and intracardiac devices that can induce infective endocarditis.

a. pacemakers,
b. defibrillators,
c. indwelling heart catheters,
d. allografts

e. prosthesis velves

5. Determine the common culprit organisms that considered as causes of culture-negative infective endocarditis.

a. Streptococci,
b. Enterobacterium,
c. Fungi
d. Chlamydia
e. HACEK organisms (Hemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella)

6. Determine the common culprit organisms that considered as causes of culture-positive infective endocarditis.

a. Brucella,
b. Neisseria,
c. Streptococci,
d. Straphylotococci
e. Fungi

7. Determine more optimal methods to be identifying culture organisms suspected for infective endocarditis.

a. immunofluorescence,
b. polymerase chain reaction,
c. electron microscopy,
d. typical culture
e. serological tests

8. Determine all perivalvular complications of infective endocarditis.

a. perivalvular leak,
b. fistula
c. pseudoaneurysm
d. vegetations
e. abscess

9. Determine complications of infective endocarditis that can destroy the conduction system in the areas of the atrioventricular node and His bundle.

a. myocardial abscesses,
b. aortic root abscess
c. fibrinous pericarditis
d. pseudoaneurysm
e. vegetations

10. Determine peripheral stigmata of infective endocarditis.

a. adult respiratory distress syndrome,
b. small-vessel vasculitis
c. nephritis
d. embolic complications
e. vegetations

SQUEEZE FOR DISEASES OF THE PERICARDIUM

1. Determine normal pericardium fluid volume.
    a. about 50 mL
    b. about 100 mL
    c. about 150 mL
    d. about 200 mL
    e. about 250 mL
2. Determine leading reasons for pericardium fluid volume accumulation.
    a. Heart failure
    b. hypotireosis
    c. cancer
    d. limphoproliferative diseases
    e. all answeres are correct
3. Determine the main causes for acute pericarditis.
    a. infections
    b. vasculities
    c. cancer
    d. limphoproliferative diseases
    e. idiopathic
4. Determine the main infectious causes for acute pericarditis.
    a. tuberculosis
    b. fungal
    c. viral
    d. rickettsial
    e. parasitic
5. Determine the main metabolic causes for acute pericarditis.
    a. Uraemic
    b. Dialysis-Related
    c. Myxoedema
    d. Gout
    e. All answeres are correct
6. Determine the main ECG signs for acute pericarditis.
    a. PR-segment deviations
    b. ST elevation
    c. Non-specific T wave changes
    d. ST depression and PR-segment deviations
    e. All answeres are correct

7.Determine the main reason that contribute ST-segemtn elevation on ECG in acute pericarditis.

    a. epicardial myocardial injury
    b. metabolic disorders

c. subendocardial ischemia
d. inflammatory syndrome
e. All answeres are correct

8.Determine the most sensitivity diagnostic tools for acute pericarditis.

a. Echo-cardiography
b. ECG
c. X-ray
d. physical examination
e. serology

9.Determine a small size of pericardial effusions in Echo-exam figure in acute pericarditis.

a. >10 mm of echo-free space in systole and diastole
b. >15 mm of echo-free space in systole and diastole
c. >20 mm of echo-free space in systole and diastole
d. >25 mm of echo-free space in systole and diastole
e. >30 mm of echo-free space in systole and diastole

10.Determine the main cause of constrictive pericarditis.

a. tuberculosis
b. fungal
c. Viral
d. Cancer
e. paracistic

SQUEEZE FOR CARDIOMYOPATHIES

1. What kind of cardiomyopathy is characterized by inadequate compliance causing abnormalities of diastolic filling? Choose one corrected answer only.
   a. Restricted form
   b. Dilated form
   c. Hypertrophic form
   d. Non-classified form
   e. Arrhythmogenic right ventricular dysplasia
2. What kind of cardiomyopathy associates with high risk of sudden death due to inhered ion channel disorders? Choose one corrected answer only.
   a. Brugada syndrom
   b. Peripartum form
   c. Hypertrophic form
   d. Non-compacted form
   e. Infants of insulin-dependent diabetic mothers
3. What kinds of cardiomyopathies associate with peripheral muscle disorders? Choose one corrected answer only.
   a. Mitochondrial form
   b. Peripartum form

c. Stress-provoked form
d. Non-compacted form
e. Tachycardia-induced form

4. What kinds of the main reasons of dilated cardiomyopathies are not important for adolescents and adults? Choose one uncorrected answer only.

a. Kawasaki disease
b. Familial IDC
c. X linked
d. Alcohol
e. Infective/toxic

5. What kind of the main reason of dilated cardiomyopathies is not important for children? Choose one incorrected answer only.

a. Infective/toxic
b. X linked
c. Idiopathic
d. Familial IDC
e. Alcohol

6. What kind of family reason of dilated cardiomyopathies is important for children? Choose one uncorrected answer only.

a. Infective/toxic
b. X linked
c. Idiopathic
d. Mitochondrial
e. Selenium deficiency

7. What kinds of features of mitochondrial disease are considered as main reasons of dilated cardiomyopathies? Choose one incorrected answer only.

a. Infective/toxic
b. maternal inheritance
c. epilepsy
d. Familial diabetes
e. Concomitant muscular dystrophy

8. What kind of phenotype is the most common for idiopathic dilated cardiomyopathy? Choose one corrected answer only.

a. Autosomal dominant
b. Autosomal recessive
c. X linked
d. Autosomal dominant + skeletal diaosders
e. Conduction defects

9. What kind of diagnostic criteria of dilated cardiomyopathy is non common? Choose one corrected answer only

a. Left ventricular hypertrophy
b. Ejection fraction < 0.45

c. Fractional shortening of < 25%
d. Left ventricular end diastolic dimension of > 112% predicted value corrected for age and body surface area
e. Spherical transformation of ventricular cavities.

10. What does non-pharmacology approach provide in advance heart failure due to dilated cardiomyopathy? Choose one corrected answer only

a. Defibrillator / cardioverter implantation
b. Mechanical support devise implantation
c. Orthotropic heart transplantation
d. Multisite ventricular pacing
e. Partial left ventriculectomy.

SQUEEZE FOR VALVULAR HEART DISEASES

1. What kinds of clinical conditions are common for acute mitral regurgitation? Choose one uncorrected answer only.

a. systemic thromboembolism
b. acute severe left ventricular failure.
c. pulmonary edema
d. cardiogenic shock
e. mitral chords rupture

2. What kinds of drugs are often effective in reducing pulmonary vascular congestion in acute mitral regurgitation? Choose one uncorrected answer only.

a. Aminophylline i.v.
b. Nitroglycerin i.v.
c. Furosemide i.v.
d. Digoxin i.v.
e. Nitroprusside i.v.

3. Degenerative reasons for chronic mitral regurgitation usually include some conditions. Choose one uncorrected answer only.

a. Gout
b. Myxomatous degeneration of the valve
c. Calcification of the mitral valve annulus
d. Marfan syndrome
e. Pseudoxanthoma elasticum

4. Structural causes for chronic mitral regurgitation are referred as follow. Choose one uncorrected answer only.

a. Hypertrophic cardiomyopathy
b. Ruptured chordae tendineae
c. Ischemic dysfunction of a papillary muscle
d. Dilatation of mitral valve annulus secondary to left ventricular dilatation
e. Paravalvular prosthetic valve leak

5. What kinds of the main causes for congenital valvular aortic stenosis? Choose one uncorrected answer only.

a. Marfan syndrome
b. senile calcific valve
c. bicuspid form
d. rheumatic processes
e. congenital varieties

6. What kinds of the most common cause of adult-acquired valvular aortic stenosis? Choose one uncorrected answer only.

a. congenital varieties
b. rheumatic processes
c. chronic nonspecific inflammatory
d. fibrotic process of the aortic valve similar to arterial atherosclerosis
e. aortic valve calcification

7. What kinds of the most common cause of adult-acquired mitral stenosis? Choose one uncorrected answer only.

a. rheumatic processes
b. syphilitic processes
c. congenital varieties
d. fibrotic process of the aortic valve similar to arterial atherosclerosis
e. aortic valve calcification

8. What kinds of the most common cause of supraortic stenosis? Choose one uncorrected answer only.

a. rheumatic processes
b. syphilitic processes
c. congenital varieties
d. fibrotic process of the aortic valve similar to arterial atherosclerosis
e. family inhared reasons

9. What kinds of the most common cause of subaortic stenosis? Choose one uncorrected answer only.

a. rheumatic processes
b. muscle hyperetrophy
c. congenital varieties
d. fibrotic process of the aortic valve similar to arterial atherosclerosis
e. family inhared reasons

10. What kinds of the most common cause of aortic dissection? Choose one uncorrected answer only.

a. media necrosis
b. muscle hyperetrophy
c. congenital varieties
d. fibrotic process
e. atherosclerosis

SQUEEZE FOR MYOCARDITIS

1. Determine more essential for definite diagnosis of acute / chronic myocarditis:
    a. Endomyocardial biopsy
    b. ECG
    c. Fluoroscopy
    d. Eco- and Doppler examination
    e. Inflammation-avid radioisotope
2. Determine the most common causes of acute myocarditis:
    a. Viruses
    b. Fungi
    c. Parasites
    d. Antibiotics
    e. Drugs
3. Determine the most important causes of infiltrative changes in materials obtained be endomyocardial biopsy
    a. Amyloid
    b. Sarcoid
    c. Hemochromatosis
    d. Carcinoid
    e. Siphilitic
4. Determine the most important toxins that can induce acute myocarditis
    a. Doxorubicin
    b. Chloroquine
    c. Radiation
    d. Botulinux
    e. Viral
5. Determine indications for immune modulatory therapy in myocarditis
    a. Acite myocarditis due to Kawasaki's disease
    b. Acite myocarditis in pediatric patients
    c. Infective myocarditis
    d. AIDS associated myocarditis
    e. Viral myocarditis
6. Determine predictors of recovery in patients with acute myocarditis
    a. preserved left ventricular function at initial presentation
    b. short duration of disease
    c. lack of symptomatic heart failure
    d. viral persistence
    e. intensive conventional drug therapy

7. Determine leading cause of viral acute myocarditis
    a. Cytomegalovirus
    b. Hepatit C virus
    c. Coronavirus
    d. Epstein-Barr virus
    e. Coxsackie virus group B
8. Determine more optimal diagnostic test for chronic Chagas' disease
    a. xenodiagnosis
    b. complement-fixation test
    c. indirect immunofluorescent antibody test
    d. hemagglutination tests
    e. enzyme-linked immunosorbent assay
9. Determine all diagnostic criteria for acute idiopathic myocarditis
    a. Preceding common cold-like symptoms
    b. Signs and symptoms indicating cardiac involvement (arrhyth-mia,murmur, gallop rhythm, and friction rub)
    c. Electrocardiographic abnormality
    d. Endomyocardial biopsy findings
    e. Ventricular contraction disturbance by echocardiography
10. Determine endomyocardial biopsy findings for acute myocarditis accordingle Dallas’criteria
    f. Polynuclear cell infiltration
    g. degeneration, disruption, lysis, and/or loss of cardiomyocytes
    h. Interstitial and/or endocardial oedema
    i. interstitial fibrosis
    j. Massive mononuclear cell infiltration

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