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

A. E. Berezin, V. A. Vizir, O. V. Demidenko

CARDIOVASCULAR DISEASE

(«INTERNAL MEDICINE» MODULE 2)

PART 1

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)

Reviewers:

V. V. Syvolap - MD, PhD, professor, Head of Department of Propedeutics of Internal Diseases with the Course of Patients' Care, Zaporizhzhia State Medical University;

O. V. Kraydashenko - MD, PhD, professor, Head of Department of Clinical Pharmacology, Pharmacy and Pharmacotherapy with the Course of Cosmetology, Zaporizhzhia State Medical University.

Authors:

A. E. Berezin - MD, PhD, professor, Department of Internal Diseases 2;
V. A. Vizir - MD, PhD, professor, Department of Internal Diseases 2;
O. V. Demidenko -MD, PhD, Head of Department of Internal Diseases 2.

B45 **Berezin A. E.**

Cardiovascular diseases («Internal Medicine». Modul 2). Part 1=Серцево-судинні захворювання («Внутрішня медицина». Модуль 2). Ч. 1 : The executive task force for students of 5th course of medical faculty / A. E. Berezin, V. A. Vizir, O. V. Demidenko. – Zaporizhzhia : ZSMU, 2018. – 220 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
HACEK	group organisms: Haemophilus species, Actinobacillus actinomyce-temcomitans, Cardiobacterium hominis, Eikenella species, Kingella kingae.
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
WPW	Wolff-Parkinson-White syndrome

PREFACE

The task force is addressed to students of 5th course of medical university for helping to study of some parts of internal medicine in field of cardiovascsular diseases. It includes the use of contemporary tools for identification of congenital and acquired heart diseases, coronary artery disease, arterial hypertension, heart failure, arrhythmias, pericardial diseases etc., including objectives, laboratory studies, genetic investigations, biopsy materials, X-ray, multidetector CT, angiography, MRI procedures. Etiology and pathophisiology are discussed also separately for each of cardiovascular disorders. Diagnostic algorithm and procedures choosing are considered obligatory with an elucidation of contemporary management and prevention of cardiovascular diseases. This book has been written in a concise and easy assimilable style to enable rapid understanding of the cardiovascular diseases. It has been structured in a format that incorporates information for quickly reminding and squeezes are applied also. Hopefully, in some way, all of the effort and expertise brought together here will help advance this field.

Authors.

CHAPTER 1

THE RESTING ELECTROCARDIOGRAM

Foreword.

What is commonly called an *electrocardiogram* (ECG) is the graph obtained when the electrical potentials of an electrical field originating in the heart are recorded at the body surface. Although the ECG gives very useful clinical information, it only provides an approximation of the voltage produced by the source. The ECG has not been able to achieve interesting new insights into its own *basic* theoretic limitations, which some have considered as the solutions of the "forward" problem and the "inverse" problem of electrocardiography. Whereas the former seeks the description of a specific electrocardiographic pattern in response to a specific local or regional intracardiac change in electrical activity, the latter seeks to predict the behavior of the cardiac generator from potentials recorded at the body surface. Nevertheless, recent experimental studies have provided new information capable of expanding the clinical usefulness of the ECG, as will be discussed throughout this chapter. The ECG has many uses: It may serve as an independent marker of myocardial disease; it may reflect anatomic, hemodynamic, molecular, ionic, and drug-induced abnormalities of the heart; and it may provide information that is essential for the proper diagnosis and therapy of many cardiac problems. In fact, it is the most commonly used laboratory procedure for the diagnosis of heart disease. Underreading or misreading due to insufficient knowledge of pathologic conditions, overreading due to an inability to recognize technical errors, and most important, failure to correlate ECG findings with the clinical findings may result in iatrogenic heart disease. Every physician interpreting ECGs as well as those learning electrocardiographic interpretation should read the *Guidelines for Electrocardiography of the American College of Cardiology, American Heart Association; European Cardiology Society Task Force*.

Ventricular depolarization and repolarization

Fluxes of ions across the cell membranes cause the differences in voltage between resting and activated myocardial cells. To understand the electrical forces produced by the heart as a whole at the body surface, it has been conventional to first

discuss the electrical properties of a hypothetical muscle strip from the free wall of the left ventricle extending from endocardium to epicardium. In the resting or polarized state, the charges are at rest. A unipolar electrode facing the epicardial side of the strip, such as V6, registers an isoelectric line. If activation of this relatively large muscle strip starts in the endocardial side, it initiates the process called *depolarization*. The *sequence* of this process is thus from endocardium to epicardium. Depolarization has been described as a moving wave *with the positive charges in front of the negative charges*. The previously mentioned lead V6 overlying the epicardium of the left ventricle will record a positivity because it consistently faces positive charges throughout the entire depolarization sequence. On the other hand, the *sequence* of ventricular repolarization is from epicardium to endocardium. The *negative charges*, however, travel *in front* because repolarization tends to reestablish the resting, polarized state of the previously depolarized cells. As a consequence of the latter, V6 will record a positive deflection (T wave) because it constantly faces positive charges throughout the entire repolarization sequence. The earlier epicardial end of repolarization has been attributed to the shorter duration of repolarization that epicardial cells have in comparison with endocardial cells. Thus repolarization finishes at the epicardium while it still has not been completed at the endocardium. Hence the *sequence* of repolarization is, as noted previously, from epicardium to endocardium. M cells play a determining role in the inscription of the T wave because currents flowing down voltage gradients on either side of the usual (but not necessarily) mid-myocardial cells determine both the height and width of the T wave, as well as the degree to which the ascending or descending limbs of the T wave are interrupted.

Electrocardiographic leads

To record an ECG, an electric circuit between the heart and the electrocardiograph must be completed. For this purpose, electrodes are placed on different parts of the body surface and are connected to the instrument by means of cables. Thus the whole system consists of an instrument, electrodes, cables, and leads.

Bipolar Standard Leads

An ECG lead can be defined as a pair of terminals with designated polarity, each of which is connected either directly or via a passive-active network to recording electrodes. In 1913, Einthoven developed a method of studying the electrical activity of the heart by representing it graphically in a *two-dimensional* geometric figure, namely, an equilateral triangle. There are several simplifying assumptions on which Einthoven's hypothesis is founded:

1. The body is a homogeneous volume conductor. Although the conductivity of the various tissues is not the same, the differences are not great enough to invalidate that the body can be considered as a homogeneous volume conductor.

2. The sum of all the electric forces, or the mean of all the forces generated during the cardiac cycle, can be considered as originating in a dipole located in the electrical center of the heart.

3. Electrodes placed on the right arm (RA), left arm (LA), and left leg (LL) are used to pick up the potential variations on these extremities. Standard (bipolar) leads (I, II, and III) are obtained by recording, respectively, the potential differences between LA and RA, LL and RA, and LL and LA. These leads record potential variations in a single frontal plane only.

4. Attachment between these limb electrodes, on the forearms and limbs, corresponds to a position in the root of the corresponding limb. For example, an electrode in the right forearm records the electrical activity that reaches the right shoulder. It should be pointed out that when the electrodes are placed proximally to the roots of the extremities, they lose their relatively "far" distance from the heart.

Hence Einthoven's equilateral theory does not hold. The latter is of importance to understand why leads placed proximally to the roots of the extremities, such as those used for exercise testing and coronary care unit and Holter monitoring, by being only "equivalent" to the corresponding bipolar leads, are in some cases markedly different from the "true" standard bipolar leads.

Wilson Central Terminal

The sum of the potentials from the right arm (RA), left arm (LA), and left leg (LL) is equal to zero throughout the cardiac cycle with respect to any point at the

body surface. Lead wires attached to electrodes on each limb are connected together, through 5000-W resistors, at a point. When this common point-*Wilson's central terminal*-is attached to the negative pole of the ECG machine and an "exploring" electrode is connected to the positive pole, the potential variations recorded will be those of the latter only. A lead taken by this method is called a *unipolar lead.* Actually, the central terminal is not zero because the RA, LA, and LL are not equidistant from each other and from the heart, the body tissues vary in resistance, and the heart and extremities do not lie in exactly the same plane in the body. The potential of the central terminal has been said to average around 0.3 mV.

Unipolar Extremity Leads

At present, unipolar extremity leads are obtained by disconnecting the input to the central terminal of Wilson from the extremity being explored. This results in a one-and-a-half increase in their voltage. These *augmented* (a) extremity leads are the ones usually used for clinical electrocardiography and are labeled aVR, aVL, and aVF.

Unipolar Precordial Leads

The unipolar precordial ECG is obtained by placing the exploring electrode (connected to the positive pole of the ECG machine) on the classic six locations of the anterior and left portions of the chest. The central terminal is used as the indifferent electrode. Precordial (V) leads yield a positive deflection when facing positive charges and negative deflections when facing negative charges. They do this according to what Wilson called the *solid-angle concept*. A solid angle is merely an imaginary cone extending from the site in the chest throughout the heart. The precordial electrode is at its apex, and its base is at the opposite epicardial surface. This concept is most important to understand precordial lead morphologies. According to Wilson's scalar concept of electrocardiography, this occurs because the solid angle subtended by the corresponding lead records the electrical activity from the regions of the heart over which the lead is placed as well as from distant regions.

Thus, if V_2 is placed over (thereby facing) the right ventricle, part of the initial positive ventricular deflection reflects right ventricular activation, with the corres-

ponding electrical forces moving toward the electrode. Most portions of the terminal S wave represent activation of muscle other than the right ventricle (septum and free left ventricular wall), reflecting electrical forces moving away from the electrode. Acceptance that the amount of muscle activity recorded by various unipolar leads is not the same implies different "real" duration of depolarization and repolarization, irrespective of that supposedly resulting from the projections of a vector on an idealized horizontal lead axis (see sections on QT dispersion and vectorcardiography). For practical purposes, the peak of the r (or R) wave in precordial leads gives a rough estimate of the moment of arrival of excitation (*intrinsicoid* deflection) at the muscle underneath the electrode. This encompasses a considerable number of muscle fibers (given by the solid-angle concept), however-in fact, a greater number than if the electrode is placed directly on the epicardial surface. In the latter case, the moment of arrival of excitation at the electrode affects a lesser number of fibers and is thus given by the *intrinsic* deflection.

Special Leads

Some leads are not considered part of the standard ECG but are useful in specific circumstances. Posterior leads (V_7, V_8, and V_9) increase the ECG sensitivity for injury in the posterior wall. Right precordial leads (V_{3R}, V_{4R}) are particularly useful for the diagnosis of right ventricular infarcts and of some congenital abnormalities. A routine use of the negative aVR (at 30 degrees) would add useful information to the standard ECG, and it would be less likely to be overlooked during routine ECG interpretation. The P wave is not always distinctly seen in the 12-lead ECG, but it may be easily identified with special leads. Distinct P waveforms can be seen by placing the right and left arm leads in various chest positions (if possible, parallel to the vector of atrial depolarization) while recording lead I (the Lewis lead). Atrial activity can also be recorded semiinvasively from leads placed in the esophagus because the anterior wall of the esophagus lies against the left atrium. In patients with dual-chamber pacemakers, atrial electrograms can be recorded by telemetry from the pacing electrodes. In patients recovering from cardiac surgery, the placement of temporary epicardial pacing electrodes allows the direct recording of atrial activity.

Equipment

Electrocardiographers are calibrated to give a deflection of 10 mm/mV (this calibration is seen at the beginning or end of the ECG). ECG paper is graph paper divided in little squares of 1 mm each and bigger squares of 5 mm each. The paper speed is standardized to 25 mm/second. One mm equals 0.1 mV.

Commercial systems provide ECG programs with stereotyped methodologies of measurement. The only limb ECG leads that digital electrocardiographs record are leads I and II; the remaining limb leads are calculated in real time based on the Einthoven law (I + III = II) and using relationships derived from lead vectors for the aV leads. For the calculation of the electrical QRS axis, the entire QRS complex area is used. This is an advantage over the manual QRS axis estimation, based mainly on R-wave measurements.

Current electrocardiographs use digital technology. Analog data are converted into digital signals that are later processed. The use of compression techniques allows storage and subsequent retrieval of serial ECG recordings, as well as remote transmission of ECG data

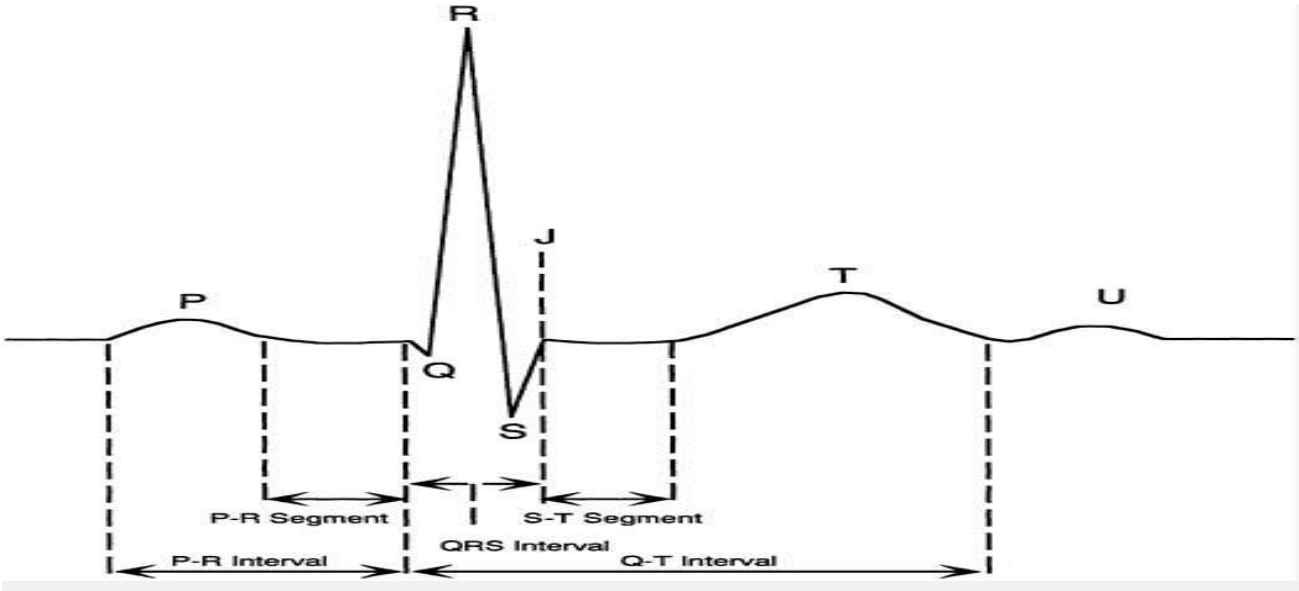
Normal activation of the heart: ventricular depolarization

After emerging from the sinus node, the cardiac impulse propagates throughout the atria in its journey toward the atrioventricular (AV) node. The *normal* P wave (resulting from activation of the myocardium of both atria) is a consequence of, but does not directly represent, sinus node activity. During sinus rhythm, the right atrium is activated before the left atrium. This explains why high-fidelity recordings of the P waves of some normal persons show a small notch at the top. The latter simply reflects the normal asynchrony existing between the atria. Because of the anatomic position of the sinus node, the sequence of atrial depolarization occurs in an inferior, leftward, and somewhat posterior direction. The normal P waves are always positive in leads I, II, aVF, and V_3 to V_6 and negative in lead aVR. According to the anatomic position of the heart, the P wave may be diphasic in V_1 and aVL or negative in the latter lead.

Atrial repolarization, also called Ta, is directly opposite in polarity to the P wave. It is usually not seen because it coincides with the PR segment (not to be confused with the PR interval) and QRS complex. The PR interval (used to estimate AV conduction time) includes conduction through the "true" AV structures (AV node, His bundle, bundle branches, and main divisions of the left bundle branch), as well as through those parts of the atria located between sinus and AV nodes. The onset of ventricular depolarization (given by the beginning of the normal q wave) reflects activation of the left side of the interventricular septum. This has been attributed to the fact that the left bundle system is shorter than the right bundle branch. In addition, the large fanlike distribution of the ramifications of the fascicles of the left bundle branch on the left septal surface produces activation of a greater number of ordinary muscle cells per unit of time. For this reason, the normal initial depolarization is oriented from left to right, therefore explaining the small q wave in lead V_6 and the small r wave in lead V1. After the cardiac impulse descending through the right bundle branch reaches the right septal surface, the interventricular septum is activated in both directions. Septal activation is thereafter encompassed within or neutralized by free-wall activation. The most distal ramifications of both bundle branches (Purkinje fibers) form networks within the subendocardial regions of both ventricular walls. The latter are activated as soon as the multiple ramifications emerge from the Purkinje fibers. The greater mass of the left ventricular (LV) free wall explains why LV free-wall events overpower those of the interventricular septum and right ventricular free wall. Normal intervals and waves on ECG are presented in Figure 1.1.

Figure 1.1

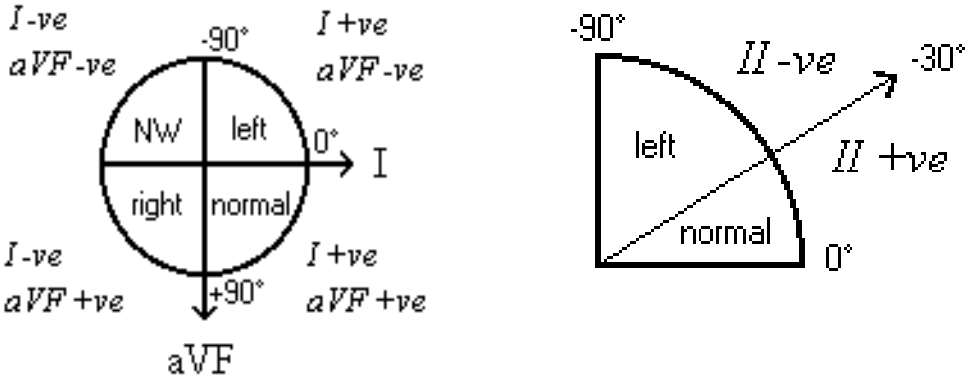
Normal intervals and waves on ECG.



Electrical axis

The *electrical axis* (EA) may be defined as a vector originating in the center of Einthoven's equilateral triangle (Figure 1.2). A *vector* is a mathematical value expressed as an arrow that has magnitude, sense, and direction. On the other hand, *scalar* values only have magnitude.

Figure 1.2.



- both I and aVF +vector = normal axis
- both I and aVF - vector = axis in the Northwest Territory
- lead I - vector and aVF + vector = right axis deviation
- lead I + vector and aVF - vector
  - lead II + vector = normal axis
  - lead II - vector = left axis deviation

Note: using leads I and aVF the axis can be calculated to within one of the four quadrants at a glance. If the axis is in the "left" quadrant take your second glance at lead II.

When applied to the EA of the QRS complexes, the vector that represents it also gives the direction of the activation process as projected in the plane of the limb leads. Its length represents the manifest potential of the dipole in the center of the triangle. These general considerations apply either to the instantaneous EA (the vector indicating the direction of the impulse at the instant at which it is determined) or to the mean EA (which is the resultant of all instantaneous electrical axes). Although the term *EA* can be used in reference to any of the major components of the ECG (P, T, or QRS), it is generally applied to the QRS. There are many methods for determining the mean EA. The one recommended by electrocardiographers of the classical school consists of calculating the net areas enclosed by the QRS complex in leads I, II, and III. The net area is the absolute sum of the positive and negative areas of the QRS complex in the corresponding lead. One of the drawbacks of this method is that the absolute values of the net area cannot be determined *accurately* by inspection. Since the absolute magnitude of the EA is not of fundamental clinical importance, it has been recommended that arbitrary units be used.

When this is done, the results can be counterchecked by using Einthoven's law. For example, if in a given case lead I is +4 units, lead II is +2 units, and lead III is -2 units, the calculation is accurate because the sum of leads I and III (+4 plus -2) must always equal lead II (+2). After having determined the net area, the results are plotted on the sides of the triangle, and perpendiculars are dropped from two or all three leads. The perpendiculars will meet at a point away from the center of the triangle. A line drawn from the latter to the former defines the mean EA. A simpler, though less precise, method of calculating the quadrant (or parts of a quadrant) in which the EA is located consists of using the maximal QRS deflection in leads I and aVF and, when necessary, lead II. This method is inexact from the mathematical viewpoint but has the value of simplicity.The main causes of axis deviation are presented in Table 1.1.

Table 1.1.

The main causes of axis deviation

The main causes of a Northwest axis

- emphysema
- hyperkalaemia
- lead transposition
- artificial cardiac pacing
- ventricular tachycardia

The main causes of right axis deviation

- normal finding in children and tall thin adults
- right ventricular hypertrophy
- chronic lung disease even without pulmonary hypertension
- anterolateral myocardial infarction
- left posterior hemiblock
- pulmonary embolus
- Wolff-Parkinson-White syndrome - left sided accessory pathway
- atrial septal defect
- ventricular septal defect

The main causes of left axis deviation

- left anterior hemiblock
- Q waves of inferior myocardial infarction
- artificial cardiac pacing
- emphysema
- hyperkalaemia
- Wolff-Parkinson-White syndrome - right sided accessory pathway
- tricuspid atresia
- ostium primum ASD
- injection of contrast into left coronary artery

Ventricular gradient

The relationship between the EA of the QRS complex and the T wave was referred to by Wilson as the *ventricular gradient*. In contrast to what occurs in an epicardial-to-endocardial muscle strip (as mentioned previously), in the isolated muscle strip, the *sequence* of ventricular depolarization occurs in the same direction as that of repolarization. Although the QRS and T deflections have opposite polarity, the algebraic sum of QRS and T *areas* is zero. In the human heart, however, not only is the sequence different, but the pathways of ventricular depolarization and repolarization

are not exactly the same. Thus the algebraic sum of QRS and T *areas* is no longer zero.

Therefore, a *gradient* is said to exist. The ventricular gradient can be calculated by determining the electrical axis of the QRS and T (using *areas*) and then obtaining the resultant by the parallelogram method. Wilson considered that the ventricular gradient could be of help in differentiating between T-wave inversion of various causes (primary changes) and the obligatory secondary T-wave changes resulting from abnormalities in depolarization, such as bundle branch block, ventricular hypertrophy, ventricular pacing, and preexcitation syndromes. In practice, calculation of the ventricular gradient is difficult and time consuming because it has to be determined by areas and not maximal amplitude. The type was attributed to modulated electrotonic interactions occurring during cardiac activation in such a way that repolarization was accelerated at ventricular sites where depolarization begins and delayed in areas where depolarization terminates. T-wave changes appearing after prolonged depolarization was no longer present showed accumulation and (fading) *long-term* memory for variable time.

Cardiac Rhythm

The rhythm is sinus if there is a P wave in front of every QRS and if the P wave is upright in leads I and aVF (Figure 1.3). The rhythm is low right atrial if there is a P wave in front of every QRS but if the P wave is upright in lead I and inverted in lead aVF (Figure 1.4). This is not an abnormal rhythm. It is a variant of normal and requires no special evaluation or treatment. The rhythm is left atrial if there is a P wave in front of every QRS and the P wave is inverted in lead I (Figure 1.5). This rhythm can be associated with situs inversus totalis, in which the morphologic right atrium and the normal sinus node are to the left of the left atrium. In this case, the rhythm requires no treatment. A left atrial rhythm can also occur with normal situs when a left atrial electric focus supplants the normal sinus rhythm. In the absence of a left atrial ectopic focus tachycardia associated with this condition, no treatment is required.

Figure 1.3

Sinus rhythm

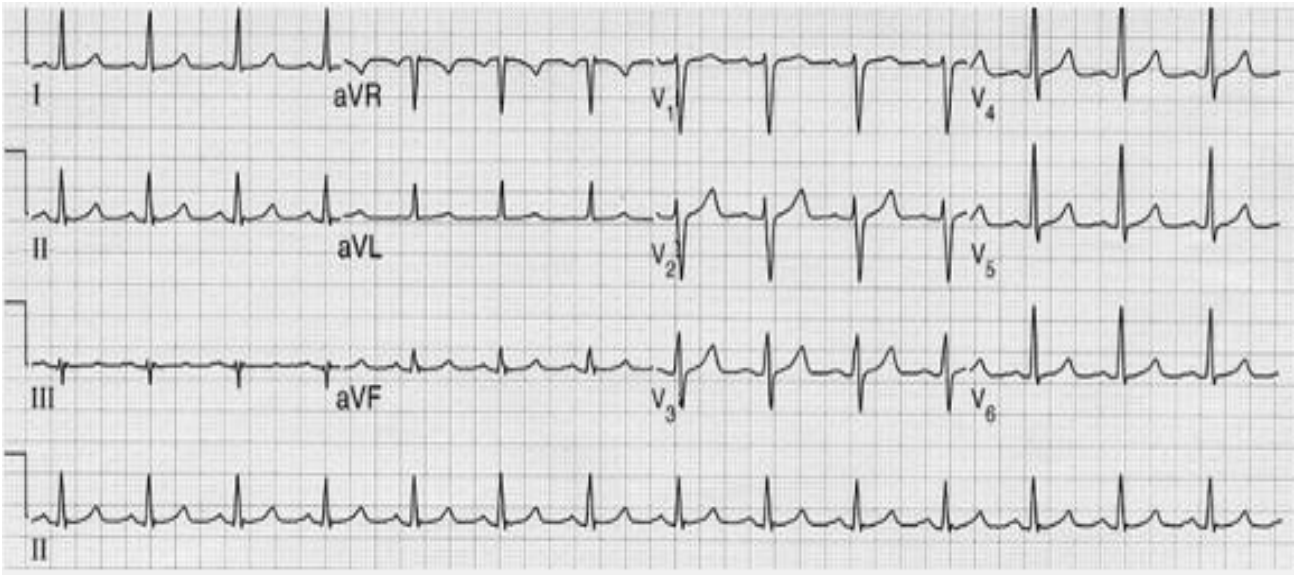


Figure 1.4

Low right atrial rhythm

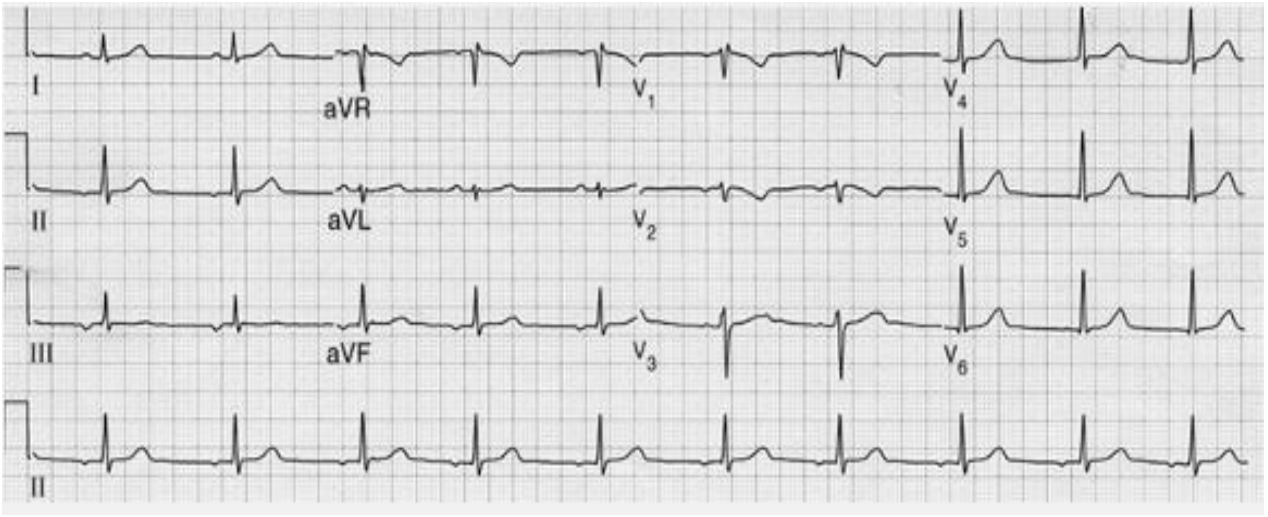
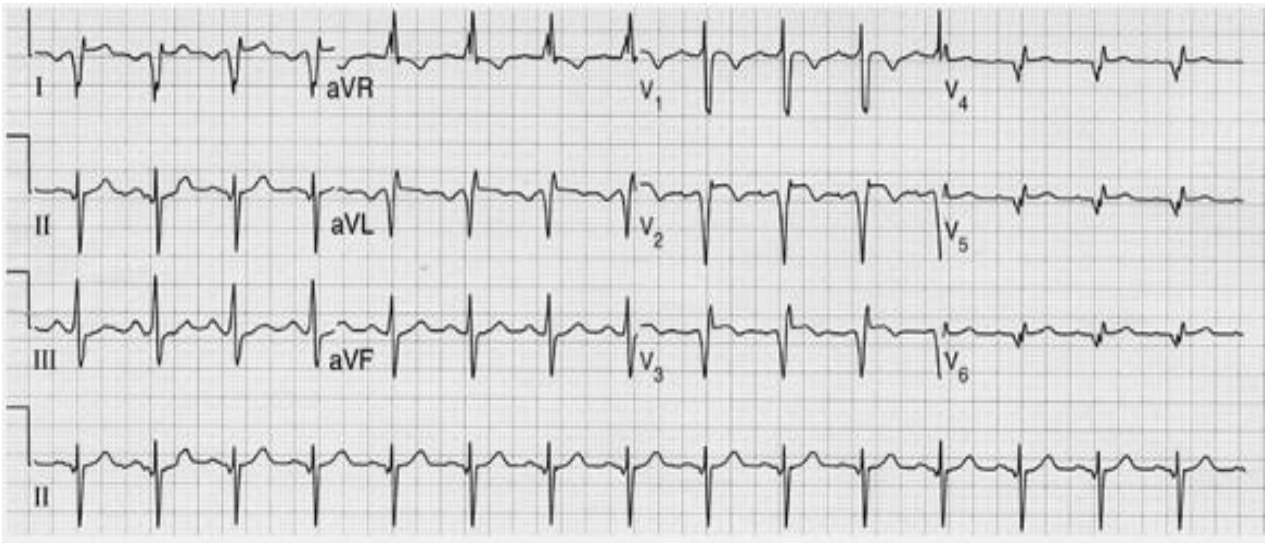


Figure 1.5

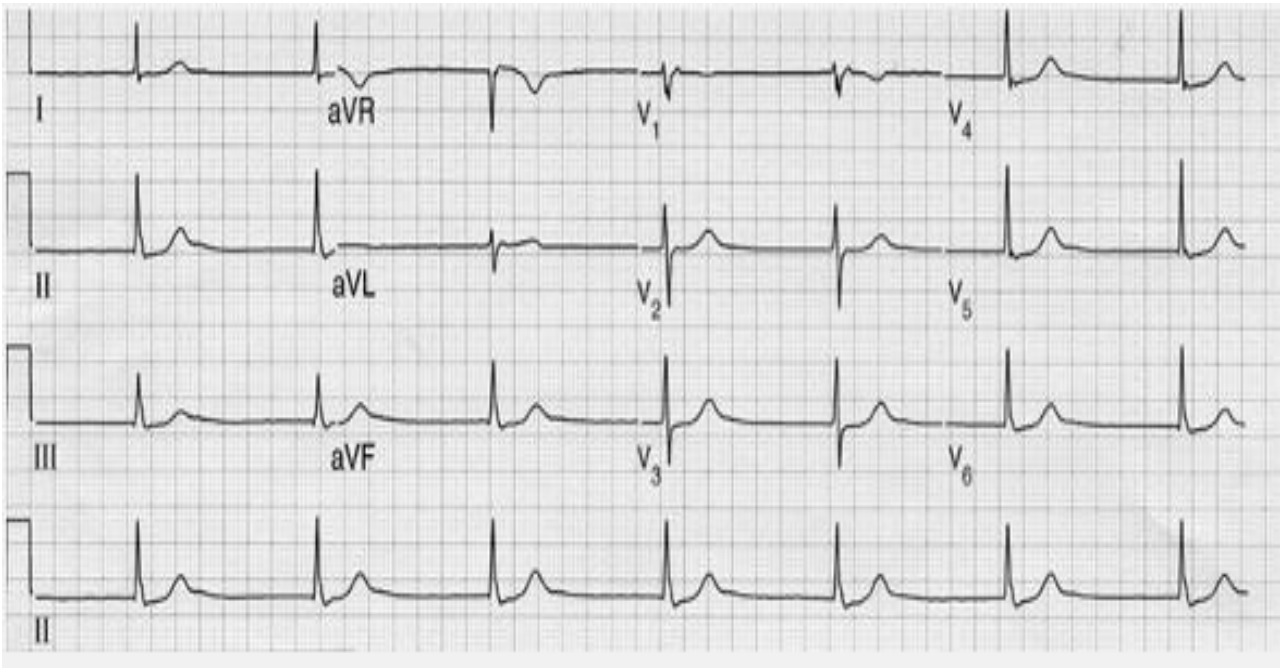
Left atrial rhythm



The rhythm is functional if there is no P wave in front of the QRS and if the QRS is narrow (<80 msecond; two small boxes) (Figure 1.6). Usually, functional rhythm is slower than the expected sinus rate. Intermittent functional rhythm can be normal, especially during sleep. The treatment for functional rhythm in the absence of any sinus rhythm may involves insertion of a pacemaker. However, it is difficult to identify patients who require a pacemaker. When functional rhythm is a complication of cardiac surgery, most experts recommend insertion of a pacemaker. If functional rhythm is particularly slow or is associated with symptoms of lightheadedness or syncope, insertion of a pacemaker is indicated.

Figure 1.6

Functional rhythm

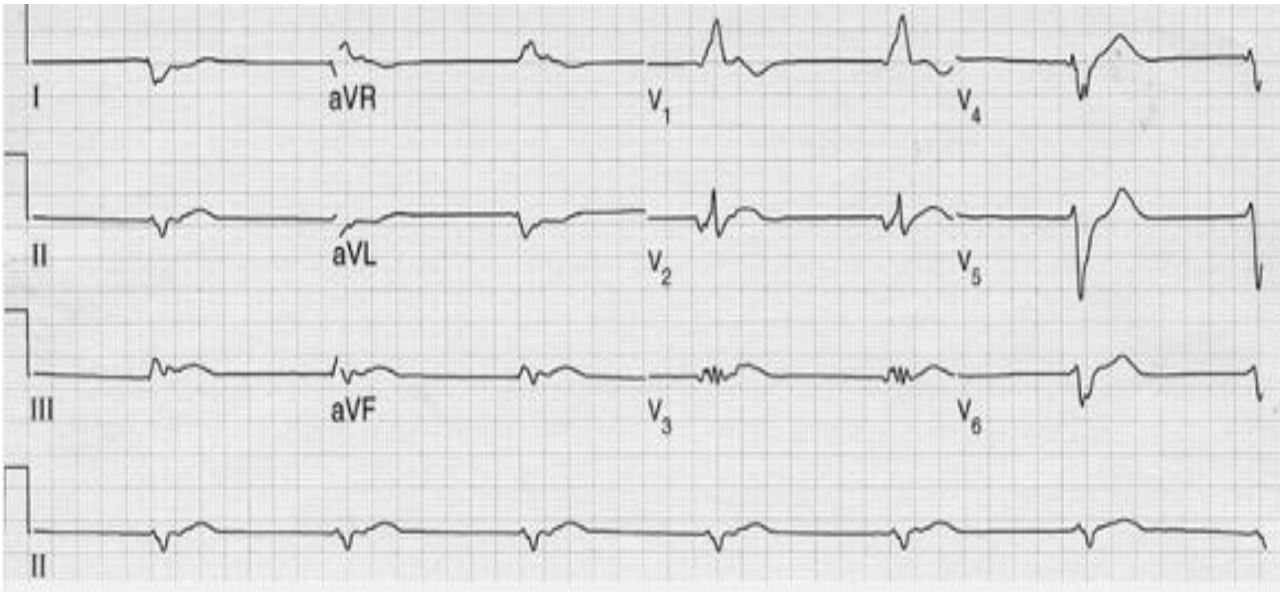


If there is no P wave in front of the QRS and if the QRS is wide (>120 msecond), the rhythm likely is originating distal to the His bundle (Figure 1.7). The rhythm most likely is ventricular in origin. Alternatively, the rhythm could be originating from the junction if there is bundle branch block. The treatment of this condition depends upon many factors. Firstly, one must determine whether the rhythm is functional with aberrant conduction or is ventricular or fascicular in origin. If a previous ECG is available when the patient was in sinus rhythm and if the morphology of the QRS complex in sinus rhythm is identical to that when there is no sinus rhythm, then the rhythm is functional and treated accordingly (see preceding text).

Secondly, if the rhythm is ventricular or fascicular, its cause must be determined. The causes of ventricular or fascicular rhythms include myocarditis, electrolyte imbalance, long QT-interval syndrome, Brugada syndrome, and myocardial ischemia, among others. The treatment will depend upon the underlying cause but might include correction of metabolic abnormalities causing the arrhythmia, drugs to suppress the rhythm, and/or an implantable cardiac defibrillator (ICD). There is a condition of benign ventricular tachycardia (VT) of childhood that requires no treatment. However, before arriving at this diagnosis, all other causes of ventricular rhythms must be excluded.

Figure 1.7

Rhythm likely originating distal to the His bundle



Abnormal ST-segment changes

In orthodox ECG language, *injury* implies *abnormal* ST-segment changes, *necrosis* implies *abnormal* Q waves, and *ischemia* implies *symmetric* T-wave inversion (or elevation). Following conventional ECG theory, several authors consider that ECG "injury" occurs because the affected cells are unable to maintain their normal polarization during diastole. Various hypotheses have been postulated to explain how this diastolic hypopolarization or generalized diastolic depolarization is manifested as abnormal ST-segment shifts in the surface ECG. One hypothesis is based on the existence of a diastolic current of "injury." During the control (diastolic) period, both membrane resting potential and surface ECG baseline are at their normal level. At the

onset of injury, the resting intracellular potential decreases (e.g., from 90 to 70 mV), and the ECG baseline shifts below its preinjury level. Because the injured cells leak negative ions, their *exterior* becomes relatively negative (or less positive) than that of the normal cells.

Thus, a "current of injury" flows between the negative ("injured") zone and the positive ("normal") region. This produces a negative displacement of the surface ECG *baseline* in the leads facing the injured region. In the surface ECG, depolarization (by virtue of the electrical negativization of the nonaffected area) practically reduces the potential difference between noninjured and injured regions. Therefore, the ST segment remains at the preinjury level, which is relatively *elevated* in reference to the injury baseline.

Consequently, the ST segment appears to be abnormally displaced above the latter. Note that the apparent presence of a systolic current of injury actually reflects disappearance of the diastolic current of injury. Finally, after the end of repolarization, the current of injury between injured and noninjured regions is reestablished, and the ECG baseline is again depressed (as it was immediately before depolarization). Since the precise moment at which injury starts is not recorded in the usual alternating-current (ac) electrocardiographic recordings, the baseline that is almost invariably recorded is the postinjury baseline. It also has been shown that the abnormal ST-segment elevation in leads facing the affected zone does not merely represent the (passive) return of the baseline to its preinjury level but reflects a true, active, positive displacement.

Thus, when depolarization of both normal and injured regions has occurred, the surface of the normal cells will (on account of their greater initial polarization) be able to accumulate more negative ions. Hence the normal regions become more negative than the injured regions, which are relatively more positive.

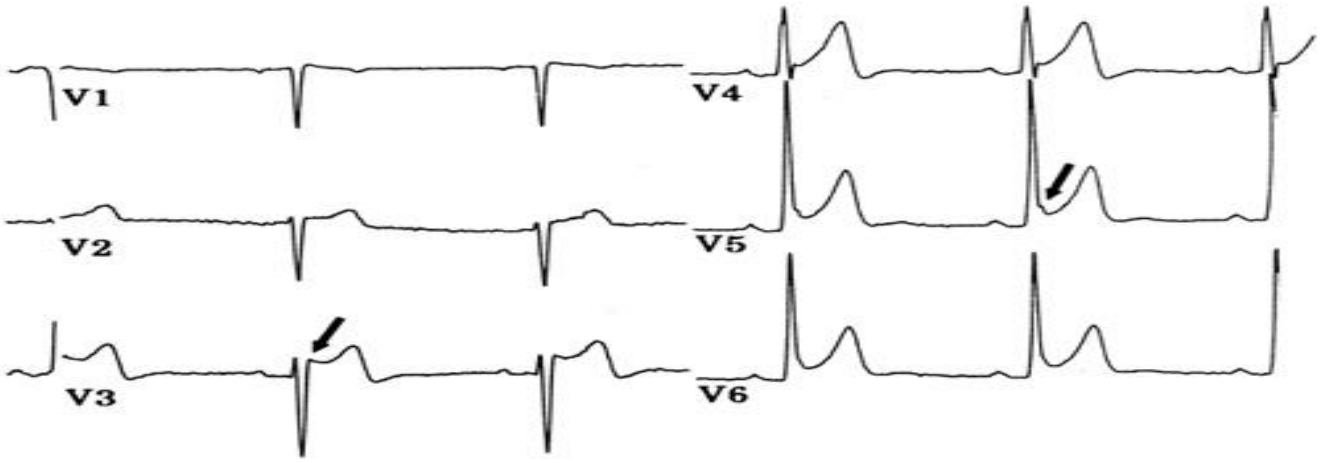
In consequence, the ST segment becomes actively elevated above and beyond the preinjury baseline because of the relative potential difference existing at the end of depolarization. Most likely, injury reflects both disappearance of diastolic baseline shifts and active ST-segment elevation.

According to the current-of-injury theory, this process results in ST-segment elevation when the injured muscle is located between normal muscle and the corresponding unipolar electrode. On the other hand, ST-segment depression occurs when normal muscle is located between the injured tissue and the corresponding electrode. The mechanism of abnormal ST-segment elevation in anatomically defined ventricular aneurysms has not been fully established. Some authors consider that it results from the earlier repolarization of a ring of persistently viable (but nevertheless affected) tissue surrounding the aneurysm. For other investigators, chronic ST-segment elevation reflects functional (echocardiographic) dyskinesia, thus not necessarily being due to a pathologic ventricular aneurysm.

Coronary artery disease is the most frequent cause of abnormal ST-segment elevation. The latter, when generalized, also can be due to epicardial injury due to pericarditis. Both should be differentiated from the benign "early repolarization" pattern, a normal variant. In its classic form, there is J-point elevation (of no more than 3 mm) with an upwardly concave ST segment. R waves may be tall and at times have a distinct notch and slur on the downstroke (Figure 1.8). ST-segment elevation is more frequent in chest leads but can occur in leads I and II. These dynamic ECG changes may be affected by exercise and hyperventilation. Isoproterenol reduces and propranolol increases ST-segment elevation. Although the mechanism of early repolarization has not been fully elucidated, it has been related to enhanced activity of the right sympathetic nerves.

Figure 1.8

Early repolarization.



Note: This normal variant is characterized by narrow QRS complexes with J-point and ST-segment elevation in the chest leads. Left chest leads often show tall R waves with a distinct notch or slur in their downstroke (*arrow* in V5), while the right chest leads may display ST segments having a "saddleback" or "humpback" shape (*arrow* in V3).

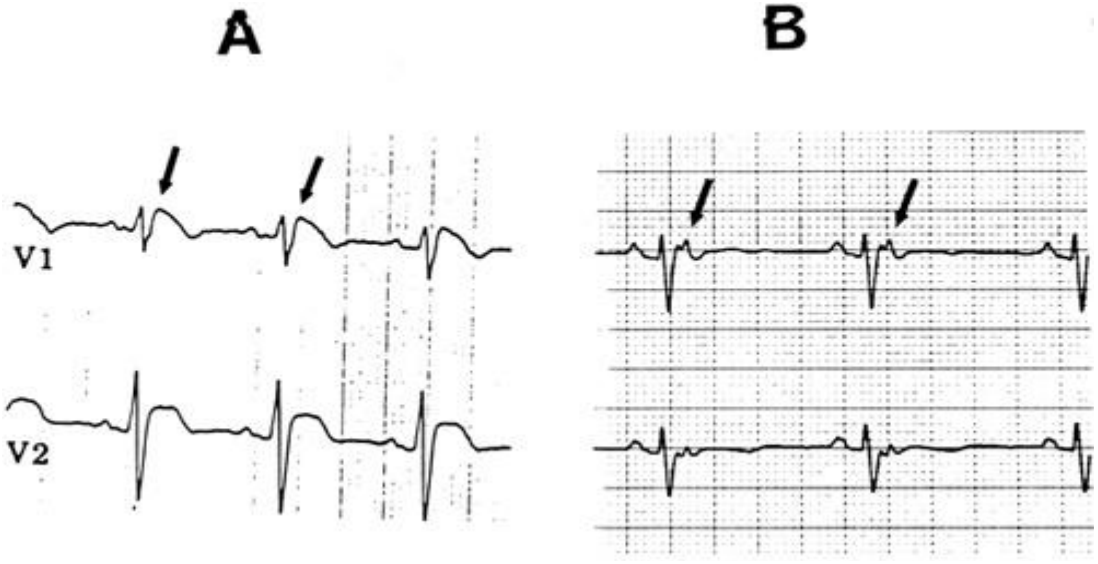
Selective nonischemic st-segment elevation in the right precordial leads

High-takeoff ST segments of either the caved or saddleback type localized to the right chest leads associated with different degrees of right bundle block with or without T-wave inversion and sudden death due to ventricular fibrillation are seen in the *Brugada syndrome* (Figure 1.9 left).

This is a familial entity ascribed to a "primary" electrophysiologic abnormality. Similar findings were reported in the familial cardiomyopathy and sudden cardiac death syndrome described by Corrado et al. Strong Na channel blocking drugs can produce ST-segment elevations even in patients without any evidence of syncope or ventricular fibrillation. The changes produced by potassium are discussed in the section of hyperkalemia (below). Slight ST-segment elevation with an incomplete right bundle branch block pattern showing an epsilon wave has been described in arrhythmogenic right ventricular dysplasia (Figure 3 right).

Figure 11. 9.

Nonischemic ST-segment elevation in the right precordial leads in a young patient with the Brugrada syndrome. *B.* Epsilon wave of a patient with arrhythmogenic right ventricular dysplasia.



Abnormal Q waves

Abnormal Q waves appearing several hours after total occlusion of a coronary artery result from necrosis secondary to the decreased blood supply. The number of affected cells has to be large enough so as to produce changes reflected at the body surface. In general, the depth of the Q wave is proportional to wall-thickness involvement.

Thus, in lead aVF a QS complex was said to reflect transmural necrosis. On the other hand, clinical myocardial infarction (MI) without abnormal Q waves was categorized as subendocardial infarction. Presently, MIs are no longer classified as transmural or subendocardial (but as Q or non-Q MIs). The duration of the Q wave is proportioned to the extent of the area of necrosis parallel to the epicardial surface. If the latter is large enough, starts in the subendocardium, and extends toward (but not quitereaching) the epicardium, the corresponding unipolar leads will record QR or Qr complexes depending on the amount of living tissue located between dead tissue and the recording electrode. Therefore, abnormal Q waves may occur in MIs that are not completely transmural. The following changes have been said to be equivalent to Q waves in non-Q-wave MI: R/S ratio changes, acute frontal plane right-axis deviation, new left-axis deviation or left bundle branch block, initial and terminal QRS notching, and some types of "poor r-wave progression." Although the concept of non-Q-wave MI as a discrete clinicopathologic entity, different from Q-wave MI, has gained almost universal acceptance, it was challenged recently by a group of respectable electrocardiographers.

In the course of the clinical entity known as *acute myocardial infarction* (MI), persisting Q waves are usually (but not invariably, as will be discussed subsequently) due to anatomic (lack of blood flow-related) necrosis. Abnormal Q waves also can occur transiently in unstable angina, Prinzmetal's angina, coronary artery spasm (without chest pain), and exercise-induced ischemia. This has been attributed to an intensity of cellular affectation ("injury") severe enough to produce a significant degree of hypopolarization (to, let us say, around 60 mV). Because the cells become electrically unexcitable (even though they are not anatomically, irreversibly necrotic),

abnormal Q waves occur. Spontaneous recanalization of an occluded vessel, spontaneous reversion of the ischemia, or spasm and interventions (pharmacologic or mechanical) that improve cellular metabolism and oxygenation can restore the normal polarization. If these cells become again excitable, the abnormal Q waves may disappear or vanish. Ischemic necrosis usually takes longer to appear than the accelerated abnormal Q waves seen in the majority of patients with Q-wave MI after successful thrombolysis or effective coronary artery angioplasty performed early in the course of the process. The genesis of these Q waves is not well understood. Some authors consider them an expression of the acceleration of necrosis secondary to explosive cell swelling in already irreversibly injured tissue. Because some of these Q waves also tend to disappear quickly, other authors consider that they reflect factors other than myocardial necrosis, such as reversal of regional dysmetabolism or the occurrence of transient interstitial ischemia or hemorrhage. Profound and prolonged ischemia can cause myocardial stunning with reversible functional, metabolic, ultrastructural, and electrophysiologic abnormalities. Thus transient Q waves may be the ECG counterpart (electrical stunning) of the corresponding mechanical stunning. It is possible for myocardial stunning to lag behind electrical recovery. *Myocardial stunning* should be differentiated from *myocardial hibernation*. The latter is a term used in reference to mechanical dysfunction of an ischemic area that is not transient but chronic. Although the ECG counterpart of this type of mechanical dysfunction requires further study, it is conceivable that (in some cases) the disappearance of chronic Q waves after coronary artery bypass surgery with improvement of wall motion abnormalities indicates that these Q waves were due not to cellular death but to cellular hibernation.

Finally, abnormal Q waves need not be the end result of coronary artery disease because they may be seen after primary (due to infections or drugs) cellular necrosis and in other pathologic processes such as myocardial infiltration and certain types of interventricular septal (and LV) hypertrophy, Wolff-Parkinson-White syndrome, and muscular dystrophies.

Ischemic T-wave changes

Symmetric T waves, inverted or upright (as in "hyperacute" T waves), characteristic of ECG "ischemia," have been considered to reflect a type, or degree, of cellular affection resulting only in action potentials of increased duration. Because the QT interval recorded at the body surface can be considered as the sum of all action potentials (i.e., of the QT intervals of individual cells), any process (such as ECG ischemia) that increases action potential duration will cause prolongation of ventricular depolarization and QT interval. T-wave inversions do not always reflect "physiologic" ischemia (due to decreased blood supply) because they also can be seen in evolving pericarditis, myocardial contusion, and increased intracranial pressure, as well as in the right chest leads of young patients (persistent juvenile pattern).

Secondary ST-T-wave changes

Alterations in the sequence of (and sometimes delay in) ventricular depolarization (such as those produced by bundle branch blocks, ventricular pacing, ectopic ventricular impulse formation, preexcitation syndromes, and ventricular hypertrophy) result in a change in the sequence of ventricular repolarization. The latter causes nonischemic T-wave inversions (secondary T-wave changes) in leads showing a predominantly positive QRS deflection. As mentioned earlier in the discussion of ventricular gradient and cardiac memory, disappearance of these alterations in ventricular depolarization may be followed by narrow QRS complexes with negative T waves. After disappearance of "complete" left bundle branch block (LBBB) and in right ventricular pacing, inverted T waves appear in leads (such as V_1 and V_2) where the S wave predominates. Finally, marked ST-segment changes may occur *during* rapid supraventricular tachycardias, even in young patients without metabolic evidence of (physiologic) ischemia.

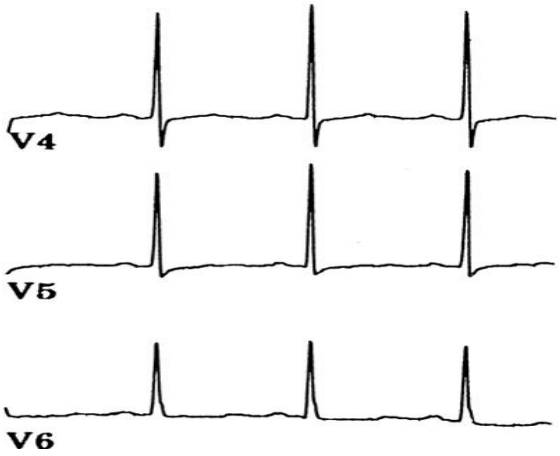
Nonspecific ST-segment-T-wave changes

While it seems more appropriate to discuss ST-segment and T-wave changes separately, they will be dealt with together because of their often coexistence. While nonspecific (or rather, nondiagnostic) ST-segment-T-wave changes are the most commonly diagnosed ECG abnormalities, they have not been categorized adequately and represent different findings for various interpreters (Figure 1.10). Depth of ST-

segment depression and T-wave inversion as well as their contour. When analyzed without clinical information, this diagnosis was made in 40 percent of 410 abnormal ECGs. The number was reduced to 10 percent, however, when clinical data became available. In the absence of structural heart disease, these changes can be due to a variety of physiologic (i.e., hyperventilation, anxiety, body position, food, neurogenic influences, and temperature), pharmacologic (i.e., antiarrhythmic and psychotropic drugs, digoxin), and extracardiac (i.e., electrolyte abnormalities, upper gastrointestinal processes, allergic reactions, etc.) factors.

Figure 1.10

Nonspecific (nondiagnostic) ST-segment-T-wave changes, the most common abnormalities in ECG interpretation



U wave

A number of hypotheses have been advanced to explain the genesis of the U wave. Foremost among them is the relationship to late repolarization of the Purkinje system. A criticism of this hypothesis is that the conducting system does not have sufficient mass to generate a large deflection at the body surface. The recent identification of another population of (M) cells between epicardium and endocardium may provide the necessary mass to produce not only U waves but also the J (or Osborn) wave characteristic of hypothermia. What sometimes appears to be a U wave merging with a T wave simple may be a notched T wave whose ascending or descending limbs are interrupted by differences in the end of the composite action potential of epicardial and M cells. The normal U wave, most prominent in leads V_2 and V_3, has the same polarity as the T wave and is approximately 10 percent of its amplitude. A

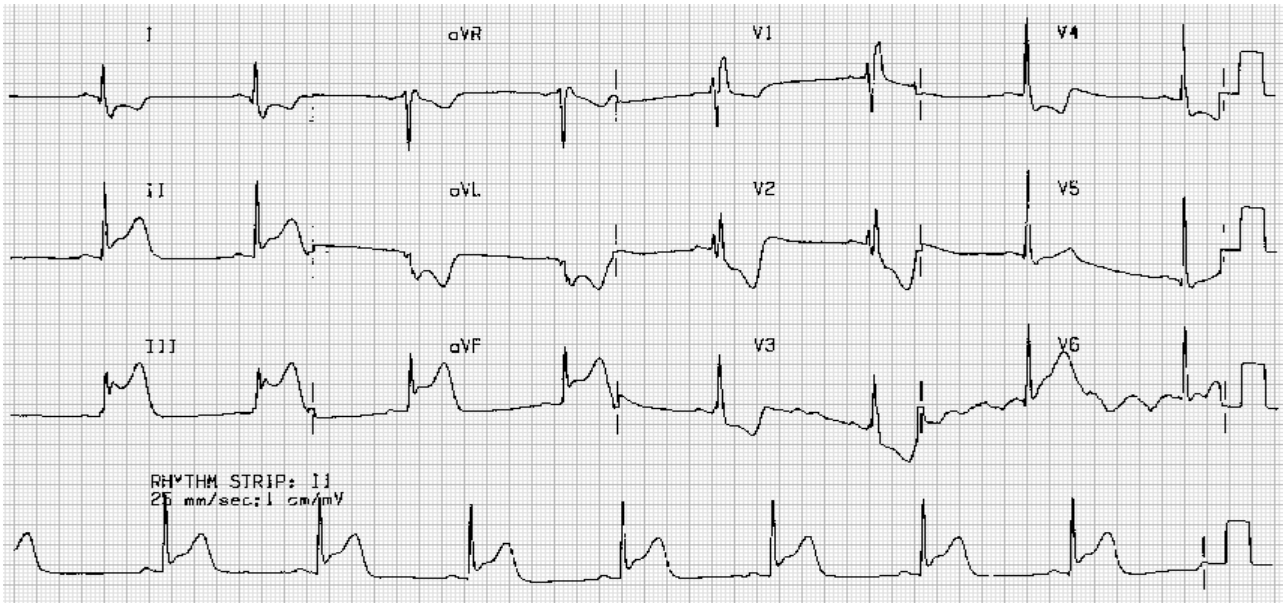
large positive U wave may be due to hypokalemia and multiple antiarrhythmic drugs. In orthodox ECG interpretation, merging of T and U is still considered a stage in hypokalemia but can result from such drugs as quinidine and sotalol. Repolarization of the His-Purkinje system was first suggested by Watanabe as the most likely cause of the "real" U wave. Causes of negative U waves are ischemia, hypertension, and occasionally, right ventricular enlargement.

Acute MI

Although a recent article challenged this distinction, MIs are no longer classified as transmural and subendocardial but as Q-wave and non-Q-wave. In the thrombolytic era, the prevalence of the latter seems to be greater than that of the former, presumably due to a reduction in infarct size (Figure 1.11). The prethrombolytic "classic" evolution of acute MI has been transformed by pharmacologic therapy and interventional techniques. The succession of events in the course of a Q-wave MI is from hyperacute positive T waves (on occasion) to ST-segment elevation to abnormal Q waves to T-wave inversion. Commonly, two or more of these findings appear together, depending on the timing of the first recorded static ECG. Acceleration of these phases can occur with effective reperfusion. The time course of ST-segment elevation is a good predictor of reperfusion.

Figure 1.11

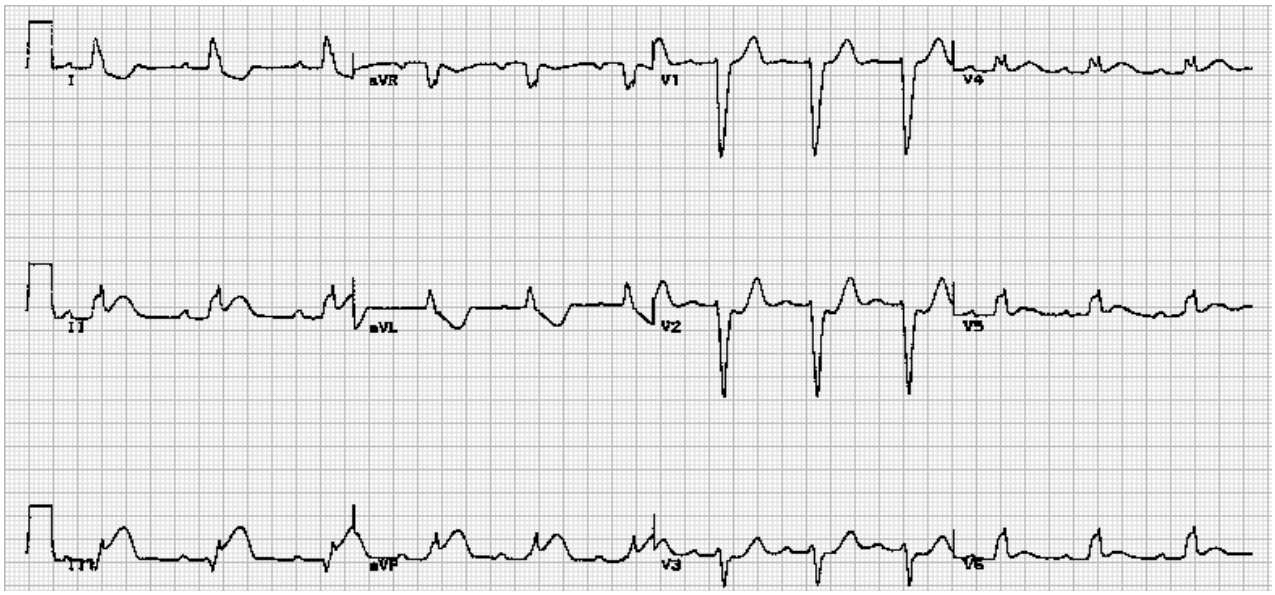
ECG in patient with acute inferior myocardial infarction



Sometimes, acute onset LBBB can mask acute MI (Figure 1.12).

Figure 1.12

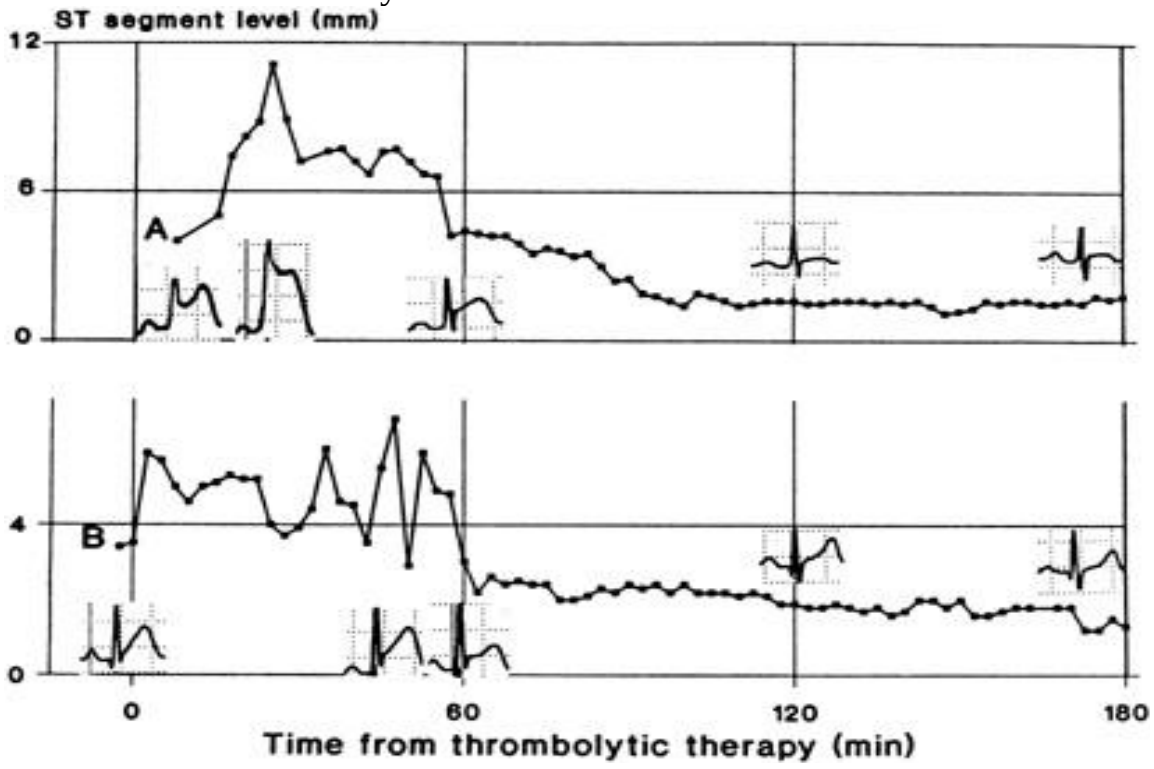
Acute myocardial infarction in the presence of left bundle branch block



Because prethrombolytic 12-lead ECG studies on ST-segment evolutions were based on static recordings obtained at fixed time intervals, it became clear that continuous monitoring in the coronary care unit (which falls outside the realm of this chapter) was essential to adequately record the dynamics of ST-segment trends. Sensitivity increases as frequency of monitoring increases (Figure 1.13).

Figure 1.13.

Plots of ST-segment levels versus time from therapy in two selected patients with patency of the infarct-related vessel at 60 min.



Note that a 50 percent decrease in ST-segment levels within 60 min occurred only when measurements were made from the peak ST-segment level (highest ST-segment level measurement within the first 60 min).

Continuous monitoring is thus essential to evaluate occurrence of reperfusion. Resolution of ST-segment elevation has been defined as a progressive decrease within 40 to 60 min to less than 50 percent of its maximally elevated value. It has been suggested that in patients treated with thrombolytics, the dichotomization for Q-wave and non-Q-wave MI should be made by the predischarge, rather than the 24^{-h}, ECG due to possible crossover from one group to another. Aspects of the ECG other than ST-segment changes may be altered particularly during acute, anterior-wall MI. In fact, the same degree of ST-segment elevation in V_2 and V_3 with disappearance of the S waves indicates a greater degree of affectation than with preservation of this negative wave.

Clinical Value of the Electrocardiogram in Established Myocardial Infarction

Autopsy, echocardiographic, and angiographic studies have shown that the 12-lead ECG has a limited capability to diagnose established myocardial infarction. The accuracy of the ECG depends on both the infarct location and size, and it may be hampered by the presence of intraventricular conduction defects, LAFB, Q-wave regression, multiple infarctions (e.g., an anterior infarct may reduce tall R waves in V_1 to V_2 from a previous posterior infarct), and LVH.

Infarct Location

The presence of abnormal Q waves in two or more leads of the same group has been classically associated to infarct areas that, anatomically, may not be accurately correlated. For example, in ventriculograms, abnormal Q waves in leads I, aVL, V_5, and V_6 are often associated with apical, rather than lateral, wall motion abnormalities. Anteroseptal infarct has classically been defined by the presence of Q waves in leads V_1 to V_3, yet in patients with ST-segment elevation in V_1 to V_3, echocardiographic and angiographic data have shown anteroapical infarcts and normal septa. Anatomically defined septal infarcts result instead in disappearance of septal Q waves in inferior leads and in I, V_5, and V_6. These changes are preceded by ST-segment depression

in the same leads during the acute phase or, if the infarction was inferoseptal, by precordial ST-segment depression. Initial R waves may be reduced in V_1 to V_3.

Prominent right precordial R waves have been classically attributed to posterior infarct, but this may be a misnomer. The term posterior may apply better to the thoracic wall facing these areas of the LV than to the LV itself. Prominent R waves in V_1 (R/S >1) are highly specific and have a high positive predictive value for basal lateral asynergy of the LV. Specificity and positive predictive value drop slightly for prominent R waves in V_2. Abnormal R waves in V_1 in patients with chest pain are 96% specific for circumflex occlusion. In both posterior and inferoposterior infarcts, the culprit artery is usually the circumflex. In some patients, a taller R wave in V_1 and prominent R waves in V_2 to V_3 may develop after LAD occlusion. The R-wave amplitude and duration may also be used for the diagnosis of established infarction. Because the electrical activation of the right ventricular free wall is insignificant in comparison with that of the LV myocardium, infarction of the right ventricle rarely alters the QRS complex beyond a slight voltage reduction. When present, Q waves in both V_{3R} and V_{4R} are highly specific markers for right ventricular infarction.

Table 1.2 shows an acceptable classification for the ECG location of MI according to leads showing abnormal Q waves. In addition, it depicts other processes that may result in false patterns of Q-wave MI. During the acute phase, ST-segment changes give a clue to the area at risk, but because of the normal variability in coronary anatomy and the presence of previous occlusions, there is sometimes more than one possible explanation for a specific ECG pattern.

Table 1.2

Electrocardiographic Location of Infarction Sites Based on the Presence of Abnormal Q Waves

Site	Leads	False Patterns
Inferior (diaphragmatic)	II, III, aVF	WPW (PSAP), HCM
Inferolateral	II, III, aVF, V_4-V_6	
'True' posterior (postero-basal)	V1	RVH, 'atypical' incomplete RBBB, Left AP
Inferoposterior	II, III, aVF, V_1	WPW (left PSAP), HCM
Inferior-right ventricular	II, III, aVF plus	ASMI as defined from axis

	V_4RV_6R or V_1-V_3	
Anteroseptal	V_1, V_2, V_3	LVH, chronic lung disease, LBBB, chest electrode misplacement
Anterolateral	I, II, V_4-V_6	HCM, ventricular septal defect
Extensive anterior	I, aVL, V_1-V_6	
High lateral	I, aVL	
Anterior (apical)	V_3-V_4	
Posterolateral	V_4-V_6, V_1*	WPW (LFWAP)
Right ventricular	V_4R with V_4R-V_6R or V_1-V_3	ASMI

NOTE: ASMI = anteroseptal myocardial infarction;
HCM = hypertrophic cardiomyopathy;
LBBB = left bundle branch block;
LFWAP = left free-wall accessory pathway;
PSAP = posteroseptal accessory pathway;
WPW = Wolff-Parkinson-White syndrome;
RVH = right ventricular hypertrophy.

Reciprocal ST-segment changes

In an inferior MI with abnormal ST-segment elevation limited to this wall, the reciprocal STsegment changes will occur in diametrically opposed leads located in the *same* plane. For example, "indicative" ST-segment elevation in leads III and aVF,which record the electrical activity of the inferior (posteroinferior or diaphragmatic) wall, yields "reciprocal" ST-segment depression in leads I and aVL because they face the superior (anterolateral) wall. ST-segment depression in lead V2 may reflect injury in the anterior subendocardial wall as well as injury in the posterobasal (or true) posterior wall.

The ECG by itself cannot distinguish with absolute certainty between these two possibilities. The differential diagnosis perhaps can best be made by performing cardiac catheterization or radionuclear studies in the acute phase of the MI, when the ST-segment changes are still present. Another way is by analyzing ST-segment changes occurring during percutaneous transluminal coronary angioplasty in patients with proven single-vessel disease. This has shown that reciprocal ST-segment depression in leads V_2 and V_3 can occur during balloon occlusions of dominant right, as well as of dominant left, coronary arteries.

Right ventricular MI

An ST-segment elevation of at least 1 mm in lead V4R in patients with *acute inferior MI* had a sensitivity of 100 percent, a specificity of 87 percent, and a predictive accuracy of 92 percent for the diagnosis of right ventricular infarction in patients with ST-segment elevation in leads II, III, and aVF. These changes disappeared within 10 to 18 h after the onset of chest pain in 50 percent of their patients and after 72 h in the remaining patients. In addition to V_4R, ST-segment elevation can be seen in leads V_5 and V_6R and in some cases (with decreasing amplitude) in V_1, V_2, and even V_3. It is possible for ST-segment depression in V_5 and V_6 to be reciprocal to right ventricular involvement.

Atrial Infarction

Atrial infarction is rarely recognized in the ECG; however, it may occur in 1% to 17% of patients with acute myocardial infarction. The injury current affects atrial repolarization and results in elevation of the Ta wave with reciprocal changes in opposite leads. This produces displacement of the PR segment, better appreciated in patients with AV block.

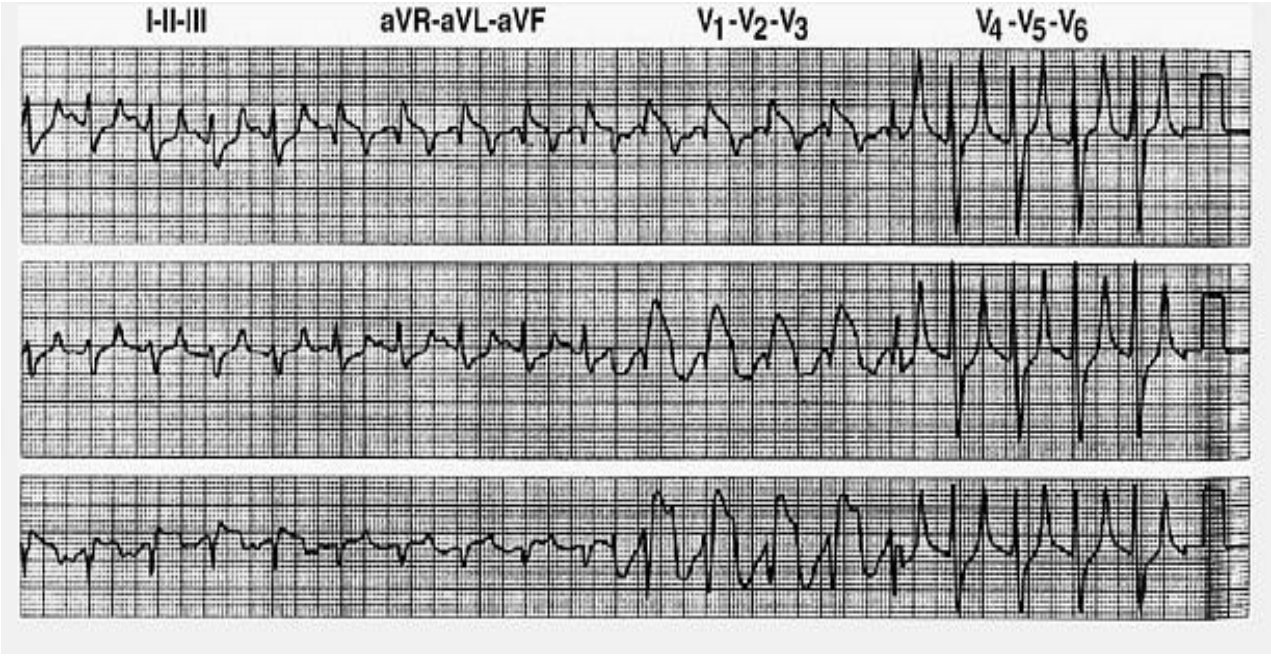
Pseudoinfarction Patterns

Aside from the setting of acute myocardial injury, in some conditions the ECG shows ST-segment elevation, usually with a concave pattern. These conditions include severe hyperkalemia, pericarditis, uncomplicated LBBB, primary and secondary cardiac tumors, acute pulmonary embolism, early repolarization, ventricular aneurysm, and implantable defibrillator shocks.

Pathologic Q waves or decreased R-wave amplitude mimicking myocardial necrosis may occur in LVH, fascicular blocks, ventricular preexcitation, infiltrative heart disease, lead misplacement, acute pulmonary embolism, pulmonary emphysema, pleural effusion, and epicardial implantable defibrillator systems. LBBB and ventricular pacing may present the ECG appearance of acute or remote myocardial infarction. Figure 1.14 shows pseudoinfarction patterns mimicked by hyperkalemia.

Figure 1.14

Acute pseudoinfarction patterns mimicked by hyperkalemia.



Pericarditis

The ECG pattern of acute (generalized) pericarditis not due to MI is produced by the associated epimyocarditis, which in turn results in diffuse epicardial "injury." The ST segments can be elevated in all leads except aVR and, rarely, in V_1. Symmetric T-wave inversion (due to epicardial "ischemia") usually develops after the ST segments have returned to the baseline (but can appear during the injury stage). Neither reciprocal ST-segment changes nor abnormal Q waves are seen. In most cases of acute pericarditis, the PR segment is depressed. Average ECG resolution occurs in close to 2 weeks. The ECG pattern of acute pericarditis has to be differentiated from the normal variant referred to as early repolarization.

Myocardial Stunning from Sudden Emotional Stress (Stress Cardiomyopathy or Takotsubo Syndrome)

Emotional stress can induce clinical manifestations similar to those of an acute coronary event. This entity has been called stress cardiomyopathy, Takotsubo syndrome, and broken heart syndrome. It affects mainly postmenopausal women. Patients present with chest pain, sometimes accompanied by ST-segment elevation, negative T waves, QT prolongation, pathologic Q waves, relatively minor elevation of cardiac enzyme and biomarker levels, and reversible LV dysfunction despite the

absence of epicardial coronary disease. Plasma levels of catecholamines and stress-related neuropeptides are increased. Prognosis is good.

Electrocardiographic Features of Sinus Nodal Dysfunction

Sinus tachivardia. Sinus tachivardia (sinus rate > 90 beats per minute) is asymptomatic resting sinus rhythm and it is considered as nodal dysfunction.

Sinus arrhythmia. Sinus arrhythmia is considered as nodal dysfunction in adults and as normal variant in chidren.

Inappropriate Sinus Bradycardia. Sinus bradycardia (sinus rate <60 beats per minute) is considered inappropriate when it is persistent and does not increase appropriately with exercise. This arrhythmia should be distinguished from asymptomatic resting sinus bradycardia in young athletes and in normal adults during sleep. Chronotropic incompetence is not present in these individuals, as it is in patients with sinus nodal dysfunction.

Sinus Arrest. The terms sinus arrest and sinus pause are used interchangeably and refer to the condition in which the sinus node's principal pacemaker cells fail to fire. The pause is not an exact multiple of the preceding PP interval. Pauses greater than 3 seconds are rare in normal individuals and may or may not be associated with symptoms but are usually caused by sinus nodal dysfunction. In contrast, asymptomatic pauses greater than 2 seconds (but <3 seconds) are seen in 11% of normal patients during 24-hour Holter monitoring and are especially common in trained athletes.

Chronic Atrial Fibrillation. The presence of chronic atrial fibrillation in a patient with a slow ventricular response not secondary to drug therapy is a sign of sinus nodal dysfunction. In some cases, cardioversion results in a long sinus pause before the appearance of sinus rhythm, or functional escape rhythm. Although a combination of sinus nodal and AV nodal conduction disease may be present in many instances, examples of rapid ventricular responses during atrial tachyarrhythmias can frequently be found.

Tachycardia-Bradycardia Syndrome. Tachycardia-bradycardia syndrome refers to the presence of intermittent sinus or functional bradycardia alternating with

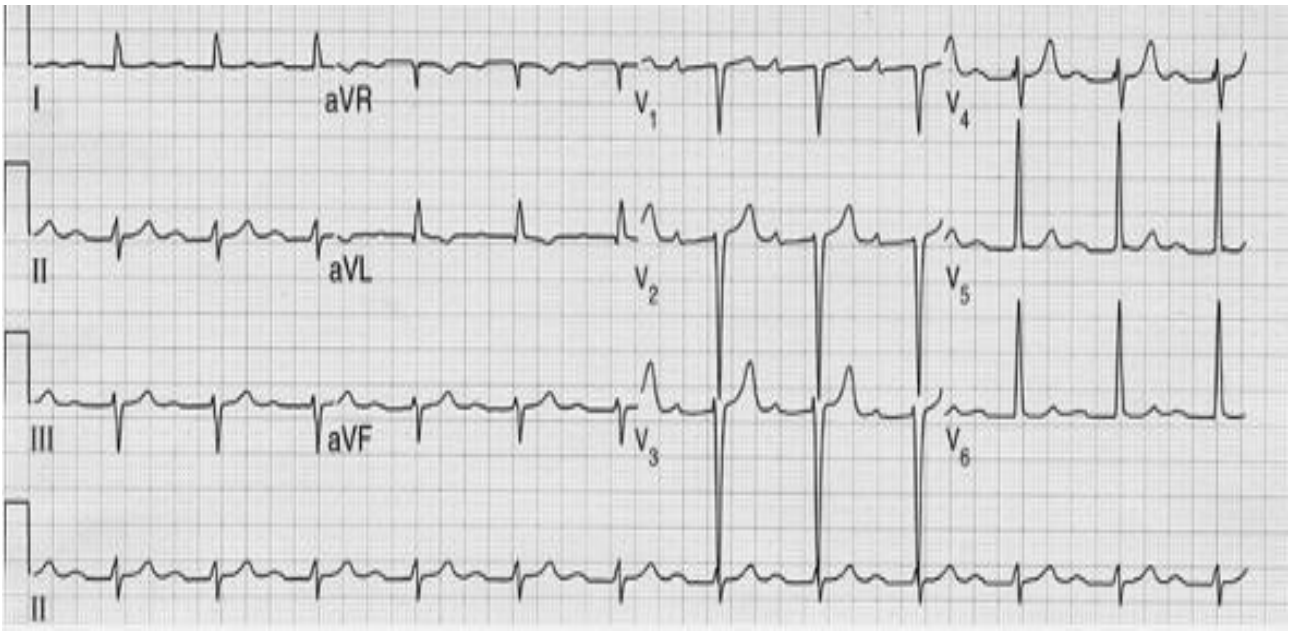
atrial tachycardia (usually paroxysmal atrial fibrillation) in the same patient. This condition, frequently referred to as sick sinus syndrome, is a common manifestation of sinus nodal dysfunction. The highest incidence of syncope associated with sinus nodal dysfunction probably occurs in this group. Syncope typically occurs secondary to a long sinus pause after the spontaneous termination of atrial fibrillation

Atrioventricular Nodal Dysfunction

First-Degree Atrioventricular Block. First-degree AV block on the surface ECG is seen as a PR interval greater than 0.20 second. Each P wave is followed by a QRS complex with a constant, prolonged interval (Figure 1.15).

Figure 1.15

First-degree AV block, indicated when the PR interval is prolonged.



Although the conduction delay can be anywhere along the system, the PR prolongation is usually caused by delay within the AV node (87% when the QRS complex is narrow). On the bundle of His electrogram, this would be seen as an AH interval greater than 130 msec with a normal HV interval.

In cases in which first-degree AV block is seen in the presence of a bundle branch block, a bundle of His electrogram is necessary to localize the site of block. Infranodal conduction delay is present in 45% of these cases. A combination of delay within the AV node and in the His-Purkinje system must also be considered.

In certain cases of congenital structural heart disease, such as Ebstein anomaly of the tricuspid valve or endocardial cushion defects, intraatrial conduction delay can

cause first-degree AV block. In addition, intra-Hisian conduction delay can cause first-degree AV block. On the bundle of His electrogram, a split His potential can be seen, resulting in a prolonged His potential, HV, and PR intervals. Dual-AV-nodal physiology can produce transient, abrupt, or alternating first-degree block caused by block in the fast AV nodal pathway (which is normally used), with conduction down the slow pathway instead.

Second-Degree Atrioventricular Block

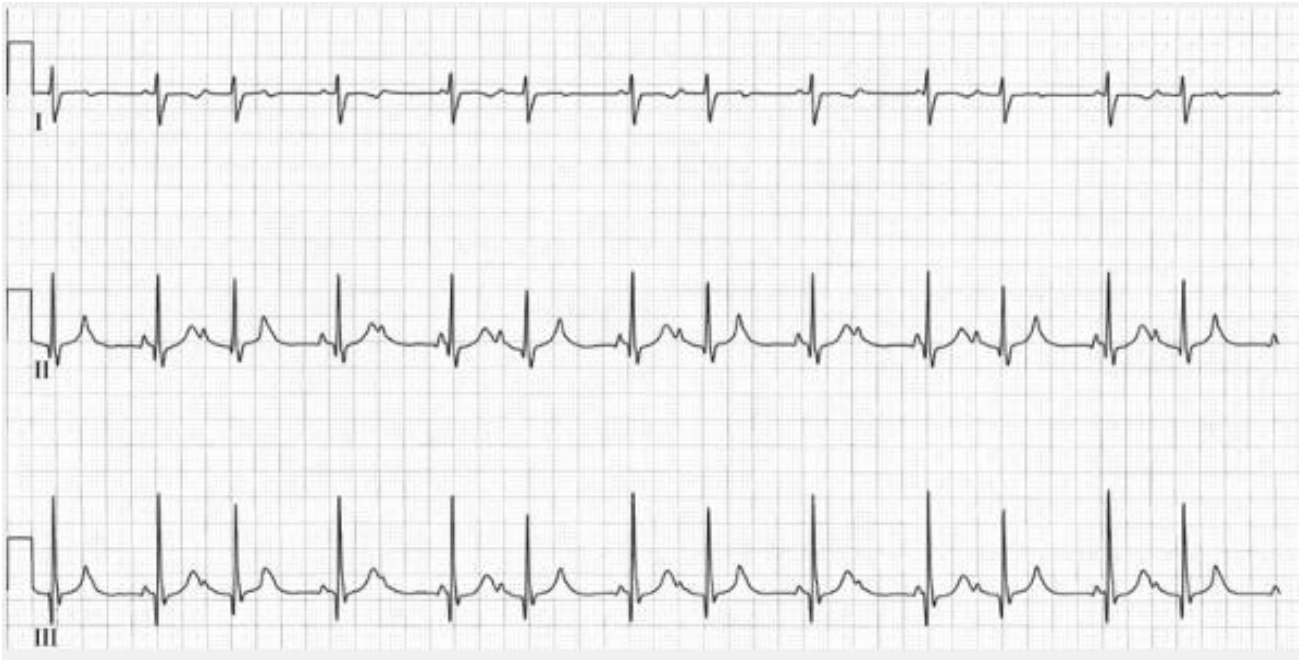
Type I second-degree AV block, or Wenckebach block, manifests on the surface electrogram as progressive prolongation of the PR interval before failure of an atrial impulse to be conducted to the ventricles (Figure 1.16). The PR interval immediately postblock returns to its baseline interval, and the sequence begins again. Features of typical Wenckebach periodicity include the following:

- Progressive lengthening of the PR interval throughout the Wenckebach cycle.
- Lengthening of the RR interval occurring at progressively decreasing increments, resulting in progressive shortening of the RR intervals.
- A pause including the nonconducted P wave that is less than the sum of any two consecutively conducted beats.
- Shortening of the PR interval postblock compared with the PR interval just preceding the blocked cycle.

Wenckebach block is almost always within the AV node when a narrow QRS complex is present. Intra-Hisian block is the rare exception. When type I block is seen with a bundle branch block, the block is still more likely to be in the AV node, but it could also be localized below the bundle of His. A bundle of His electrogram would be needed to accurately identify the level of block. Wenckebach block in the AV node is characterized by progressive prolongation of the AH interval until an atrial deflection is not followed by a bundle of His or ventricular deflection. In type I block secondary to block below the bundle of His, progressive prolongation of the HV interval is followed by an H deflection without an associated ventricular depolarization.

Figure 1.16

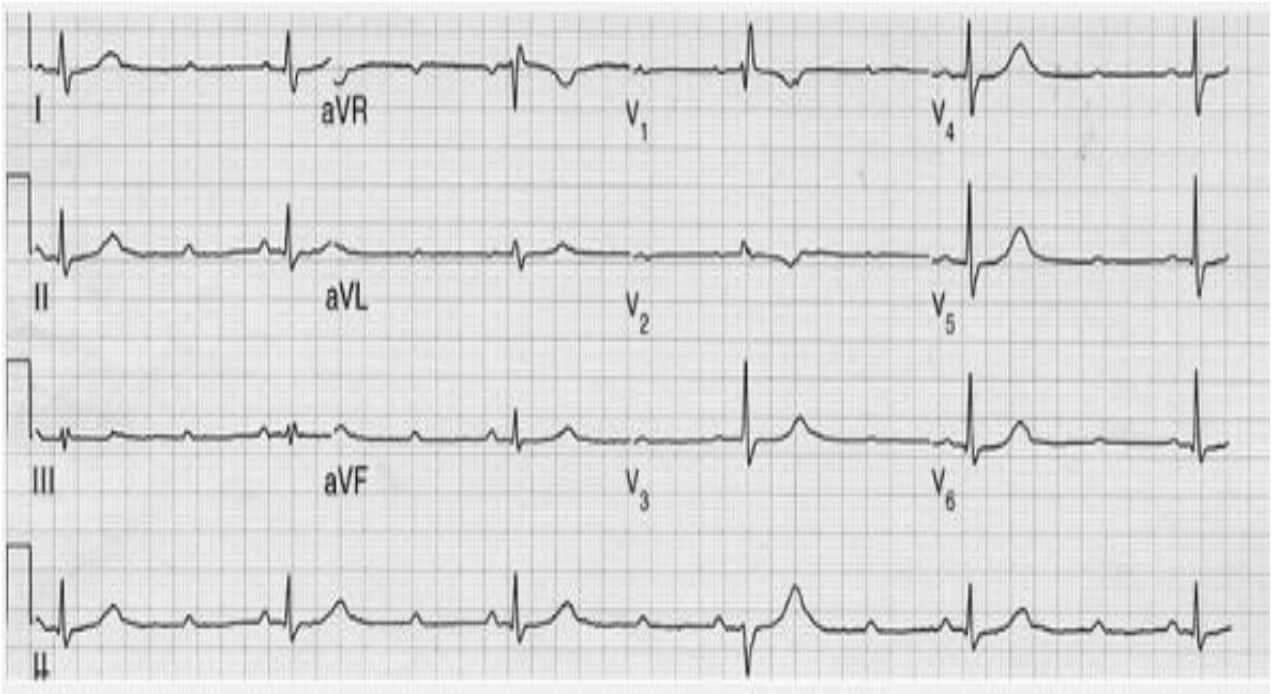
Mobitz I or Wenckebach type of second-degree AV block.



Type II, or Mobitz II, second-degree AV block is characterized on the surface electrogram by a constant PR interval followed by sudden failure of a P wave to be conducted to the ventricles. The PP intervals remain constant and the pause including the blocked P wave equals two PP intervals (Figure 1.17).

Figure 1.17

Mobitz II type of second-degree AV block.



Therefore, Mobitz II block should not be confused with a nonconducted premature atrial complex. Mobitz II block is usually associated with bundle branch block or bifascicular block. In a majority of these cases, the site of block is within or below the bundle of His. When presumed Mobitz II block is seen in conjunction with a narrow QRS complex, Mobitz I with only minimal PR variation should be suspected. Only rarely is Mobitz II found with a narrow QRS complex and is caused by intra-Hisian block. The bundle of His electrogram is useful in verifying the site of the Mobitz II block. The blocked cycle features atrial and bundle of His deflections without a ventricular depolarization. The conducted beats usually show evidence of infranodal conduction system disease, with a prolonged HV interval, or even a split bundle of His potential.

2:1 Atrioventricular Block

Fixed 2:1 AV block poses a diagnostic dilemma because it is usually impossible to classify as type I or II block by a surface electrogram alone. A narrow QRS complex and recently seen Wenckebach block is highly suggestive of block at the AV nodal level. A 2:1 block associated with a wide QRS complex is likely infranodal, but it could still be at the level of the AV node. A definitive diagnosis can only be made with an intracardiac recording at the bundle of His region.

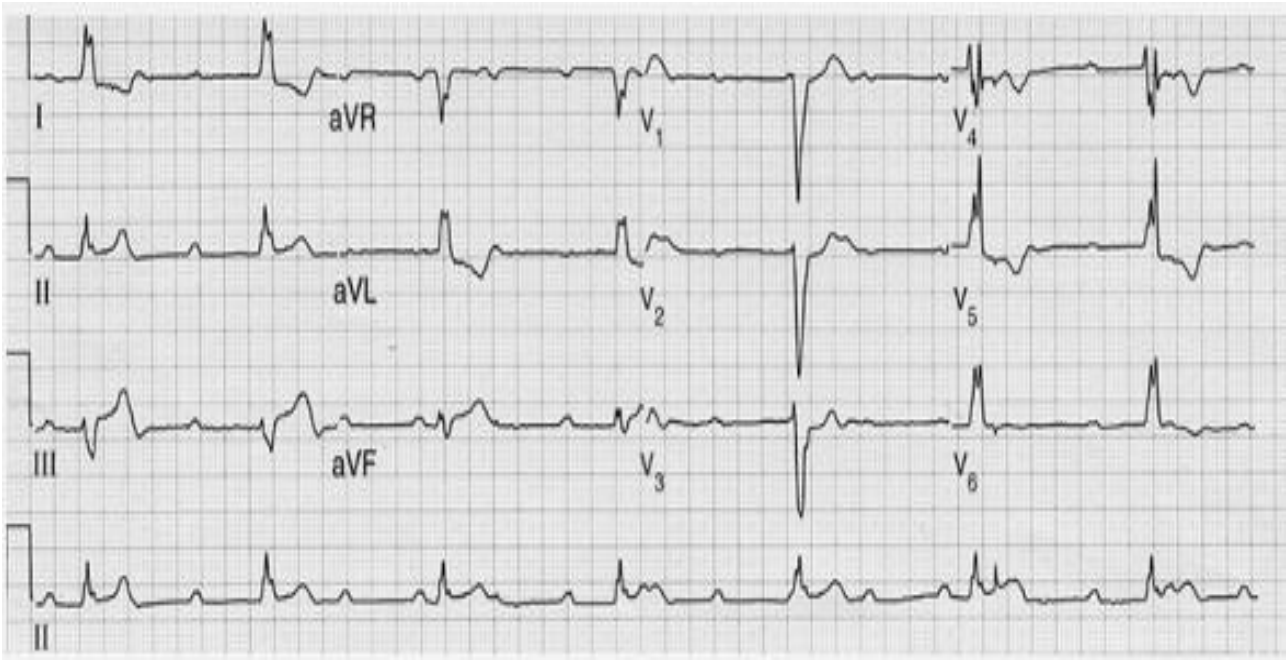
Nonconduction of two or more consecutive P waves when AV synchrony is otherwise maintained is sometimes termed high-degree AV block. The level of block can be at the AV node or the His-Purkinje system. When high-degree AV block is caused by block in the AV node, QRS complexes of the conducted beats are usually narrow. Wenckebach periodicity is also seen, and atropine administration produces 1:1 conduction. Features pointing toward block in the His-Purkinje system are conducted beats with bundle branch block and no improvement in block with atropine. Bundle of His recordings are sometimes needed to confirm the site of block.

Third-Degree Atrioventricular Block

Third-degree, or complete, AV block is seen on the surface electrogram as completely dissociated P waves and QRS complexes, each firing at its own pacemaker rate (Figure 1.18).

Figure 1.18

Third-Degree Atrioventricular Block



The atrial impulse is never conducted to the ventricles, but different levels of block are possible. The level of block determines the QRS morphology along with the site and rate of the escape rhythm. Congenital complete heart block is characterized by a narrow QRS complex with an escape rate between 40 and 60 beats per minute, which tends to increase with exercise or atropine. This is consistent with block within the AV node. Acquired complete heart block is usually associated with block in the His-Purkinje system, resulting in a wide QRS complex with an escape rate between 20 and 40 beats per minute. The intracardiac electrogram shows bundle of His deflections consistently following the atrial electrograms, but the ventricular depolarization is completely dissociated from these. Block below the bundle of His is thus demonstrated. In contrast, complete heart block at the AV nodal level is seen on the intracardiac tracings as bundle of His potentials consistently preceding each ventricular depolarization. The atrial electrograms are dissociated from the HV complexes. The sinus rate is faster than the ventricular rate in patients with complete heart block. Data collected from patients with congenital complete heart block have shown the atrial rate to usually be age appropriate. It is important to note that complete antegrade AV block does not always predict retrograde (VA) conduction. Retrograde conduction may be intact in an individual with complete antegrade AV block.

Atrioventricular Dissociation

AV dissociation is a secondary phenomenon that results from a primary conduction disorder. It is characterized by the atria and ventricles depolarizing independently of each other. By definition, there is no retrograde conduction from the ventricles to the atria. AV dissociation may be complete or incomplete. In complete AV dissociation, both the atrial and ventricular rates remain constant, and therefore the PR interval varies with none of the atrial complexes conducted to the ventricles. In incomplete AV dissociation (interference dissociation), ventricular capture beats occur because some of the atrial impulses arrive at the AV junction when the AV junction is no longer refractory. This phenomenon is common in advanced AV block with periodic capture beats.

Atrial Fibrillation

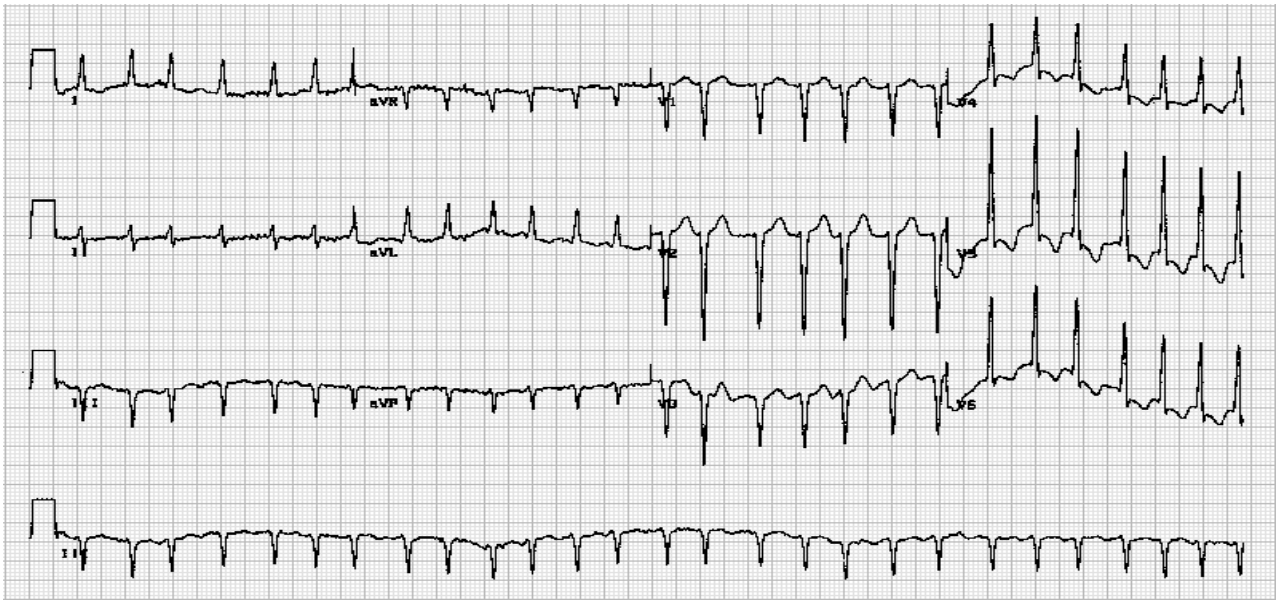
Arrhythmias require an initiating event, for example, a premature atrial or ventricular complex, and a sustaining substrate, for example, one or more reentrant circuits. The initiating event and sustaining substrate may be all due to automaticity such as a rapidly firing atrial focus. In AF, both automaticity and reentry appear to play a role. The ectopic focus theory for AF was essentially smothered by the overwhelming weight of observations indicating that reentry was the mechanism of AF. However, observations made during intracardiac radiofrequency catheter ablation of AF have rekindled interest in the ectopic focus theory. In patients with AF, PVs have shorter refractory periods than in control patients, and refractory periods are also shorter in the left atrium outside of the PVs.

However, it is often possible to observe in ECG lead V_1 well-defined P waves with a short cycle length that is irregular. The presence of a grossly irregular, very rapid, wide QRS complex ventricular response during AF with rare exceptions is diagnostic of conduction over an accessory pathway (Figure 1.19).

At very fast heart rates, a tendency toward regularization of the RR intervals is present, but careful measurement always discloses definite irregularities. It would be rare for such rapid responses to result from conduction over the AV node, and the only other alternative is ventricular tachycardia.

Figure 1.19

Irregular rhythm with wide QRS complex ventricular response during atrial fibrillation



It is axiomatic that rapid, irregular ventricular tachycardia is unstable and quickly degenerates into ventricular fibrillation. Thus, when a rapid, irregular, wide QRS complex tachycardia is noted in a patient who has a reasonably stable hemodynamic state, preexcitation is the most likely diagnosis. The ability to conduct rapidly over an accessory pathway is determined primarily by the intrinsic conduction and refractory properties of the accessory pathway. However, as with AV node conduction, factors such as spatial and temporal characteristics of atrial wavefronts during atrial fibrillation, autonomic tone, and concealed conduction influence activation over the accessory pathway

Atrial Flutter

The term atrial flutter has traditionally referred to an atrial tachycardia with monomorphic P waves, sometimes referred to as flutter waves, without an isoelectric baseline, having rates in the range of 240 to 300 beats per minute. The term atrial tachycardia has frequently been used for atrial rates less than 240 beats per minute because these tend to have an isoelectric baseline between individual P waves. However, with increasing understanding of the mechanisms of atrial reentrant rhythms, the modern use of the term atrial flutter refers to a regular reentrant tachycardia within the atria having a definable reentrant circuit by our current mapping techniques, also called a macro reentrant atrial tachycardia. The term atrial tachycardia or focal atrial

tachycardia tends to be used to describe a tachycardia with an automatic mechanism arising from a narrow focus or, perhaps, a reentrant mechanism confined to a narrow region too limited for current mapping systems to resolve. Although atrial flutter as a phenomenon was described around a century ago, the mechanisms of this arrhythmia in the human heart have only relatively recently been elucidated with the development of activation mapping systems capable of displaying the reentrant activation wave front.

The most common form of atrial flutter is the so-called typical form of atrial flutter. The reentrant circuit involves cranial-caudal conduction over the crista terminalis, continuing across the cavo-tricuspid isthmus, breaking out onto the interatrial septum and posterior atrial wall, conducting up to the roof of the right atrium anterior to the superior vena cava opening, and then entering the superior end of the crista again. When viewed from the ventricular side of the tricuspid annulus, the reentrant waveform rotates around the tricuspid annulus in a counterclockwise direction. Thus, this common form of typical flutter is sometimes called counterclockwise flutter. Early mapping studies of this type of flutter demonstrated that the wave front propagated cranio-caudally along the lateral right atrium and caudo-cranially along the septal portion of the right atrium, with slow conduction occurring along the inferior portions of the right atrium. This reentrant pathway in the human heart was also described by Feld and colleagues in their report on the use of radiofrequency ablation to interrupt the tachycardia circuit. The slow area of conduction in the low right atrium was identified to be the isthmus of atrial myocardium located between the tricuspid valve and the inferior vena cava.

In the case of the typical flutter circuit, the re-entrant loop around the tricuspid valve can be accompanied by a lower loop circulating around the inferior vena cava. Although less often seen clinically, the same circuits can also rotate in the opposite direction, creating the so-called clockwise typical flutter.

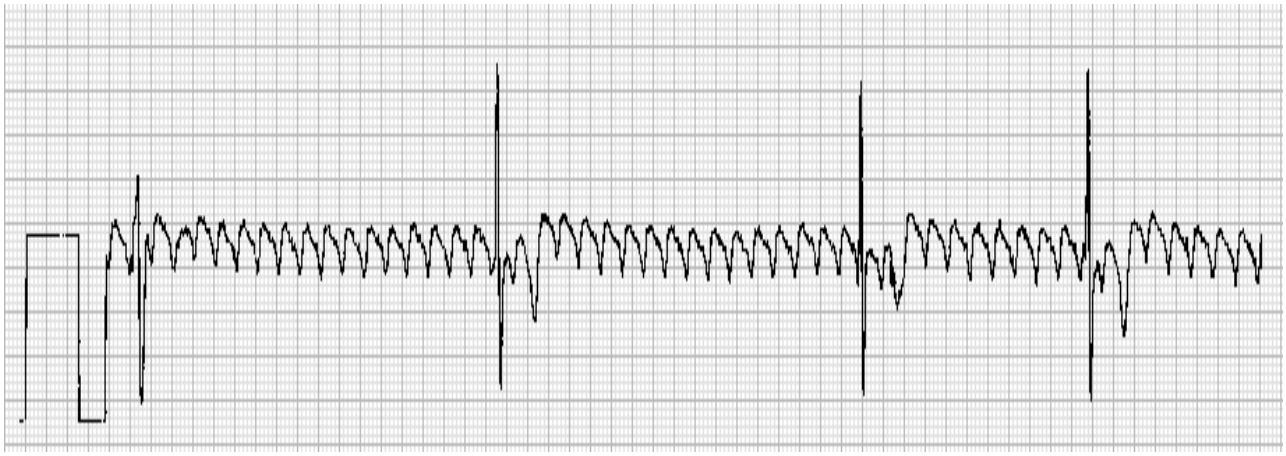
The two types of circuit rotation result in different atrial activation patterns, generating somewhat different ECG morphologies of the flutter wave (F-waves). With the typical pattern, atrial activation starts with septal breakout of the waveform

emanating from the cavotricuspid isthmus. The remainder of the right and left atria tends to be activated more or less simultaneously. This results in the flutter wave having a superiorly directed vector on the surface ECG. In the less common clockwise version, wave front breakout occurs at the lateral portion of the tricuspid annulus. It then spreads cranially and then across the right atrial roof before propagating across to the left atrium. The leftward ECG leads (lead I and lead aVL) generally show a positive flutter wave. Catheter ablation of these two types of flutter is typically accomplished by interrupting the reentrant pathway within the cavotricuspid isthmus.

Identification of the common limb in this circuit is important for ablation because interruption at this limb is most likely to create successful interruption of the flutter. The ECG of the flutter waves in left atrial flutters can vary considerably depending on the reentrant circuit. Figure 1.20 shows an example of a left atrial flutter circulating around the mitral valve.

Figure 1.20

The ECG of the flutter waves



Premature complexes

Atrial premature complexes

Atrial premature complexes (APCs) can be found on 24-h Holter monitoring in over 60% of normal adults. APCs are usually asymptomatic and benign, although at times they may be associated with palpitations. In susceptible patients, they can initiate paroxysmal supraventricular tachycardias (PSVTs). APCs may originate from any location in either atrium, and they are recognized on the electrocardiogram as early P waves with a morphology that differs from the sinus P wave. While APCs

usually conduct to the ventricles when they occur late in the cardiac cycle, early APCs may reach the AV conduction system while it is still in its relative refractory period, resulting in a conduction delay manifested by a prolonged PR interval following the premature P wave. Very early APCs may even be blocked in the AV node if this structure is encountered during its effective refractory period. APCs, whether conducted or not, are usually followed by a pause before a return to sinus activity. Most commonly, an APC enters and resets the sinus node, so the sum of the pre- and postextrasystolic PP intervals is less than the sum of two sinus PP intervals. In this case, the pause is said to be less than fully compensatory. The QRS complex following most APCs is normal, although early APCs may be followed by aberrantly conducted QRS complexes due to the premature complex falling within the relative refractory period of the His-Purkinje system. Since most APCs are asymptomatic, treatment is not required. When they cause palpitations or trigger PSVTs, treatment may be useful. Factors that precipitate APCs, such as alcohol, tobacco, or adrenergic stimulants, should be identified and eliminated; in their absence, mild sedation or the use of a beta blocker may be tried.

AV functional complexes

The site of origin of these complexes is thought to be in the bundle of His, since the normal AV node in vivo possesses no automaticity. AV functional complexes are less common than either atrial or ventricular premature complexes and are more often associated with cardiac disease or digitalis intoxication. Functional premature impulses can conduct both antegradely to the ventricles and retrogradely to the atrium and, on rare occasions, may fail to conduct in either direction. Premature AV functional complexes can be recognized by normal-appearing QRS complexes that are not preceded by a P wave. Retrograde P waves (inverted in leads II, III, and aVF) may be observed after the QRS complex. While often asymptomatic, functional premature complexes may be associated with palpitations and cause cannon *a* waves, which may result in distressing pulsations in the neck.

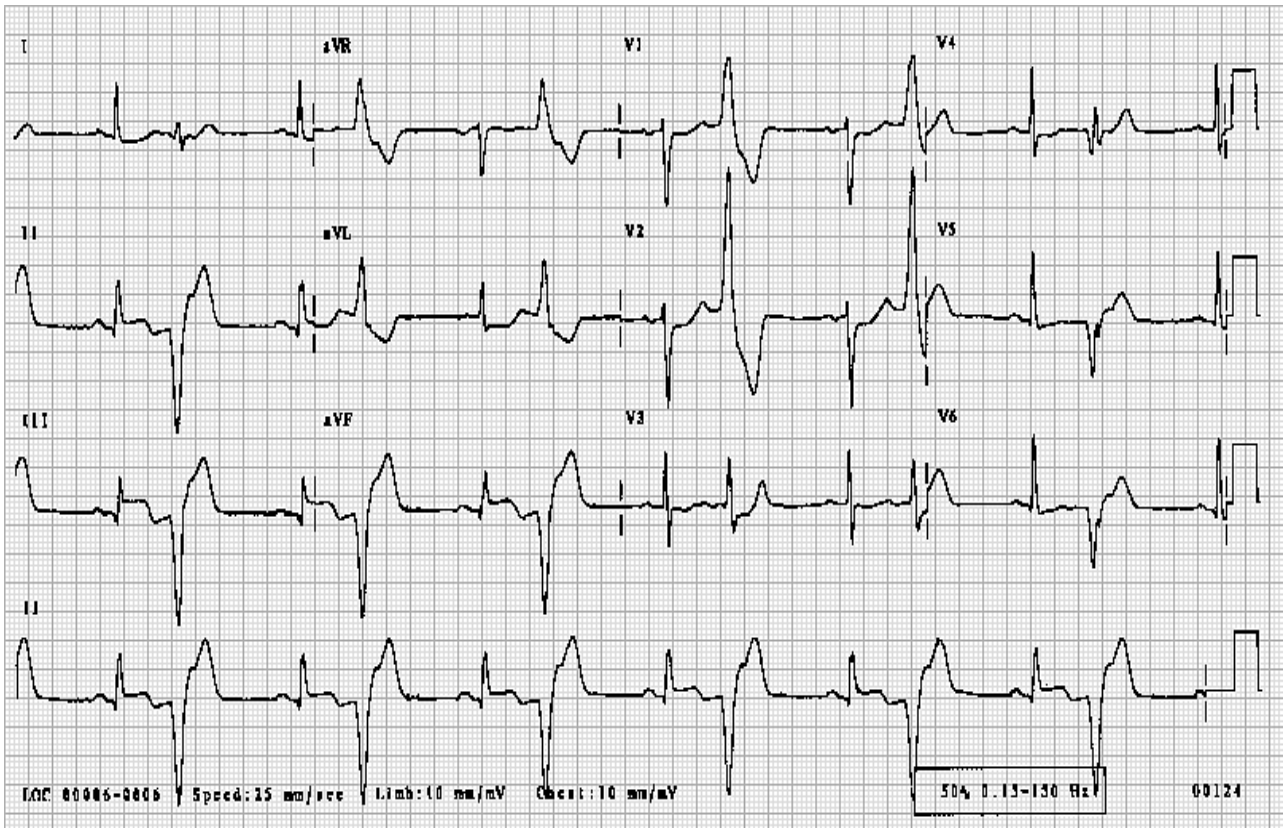
Ventricular premature complexes (VPCs)

These are among the most common arrhythmias and occur in patients with and without heart disease. Of adult males, >60% will exhibit VPCs during a 24-h Holter monitoring. In patients without heart disease, VPCs have not been shown to be associated with any increased incidence in mortality or morbidity. VPCs may occur in up to 80% of patients with previous myocardial infarction, and in this setting, if frequent (>10per hour) and/or complex (occurring in couplets), they have been associated with increased mortality. However, cardiac mortality in such patients usually occurs in association with significantly impaired ventricular function. While frequent and complex ventricular ectopy is an independent risk factor, it is not as strong a risk factor as is impaired ventricular function. Moreover, even though VT and/or ventricular fibrillation (VF) may be the basis for the sudden death in these patients, this does not a priori establish a cause-and-effect relation between spontaneous ectopy and life-threatening VT or VF. Very early cycle (R-on-T) VPCs have been stated by some to increase the risk of sudden death. Although this has been observed during acute ischemia and in the setting of QT prolongation, frequently, VT or VF is precipitated by VPCs that occur after the T wave of the prior beat.

VPCs are recognized by wide (usually >0.14 s), bizarre QRS complexes that are not preceded by P waves. However, when they arise in the specialized conduction system (e.g., fascicles) they may be >0.12 s in duration. They may bear a relatively fixed relationship to the preceding sinus complex (i.e., fixed coupled VPCs). When fixed coupling is not present and the interval between VPCs has a common denominator, *ventricular parasystole* is said to be present. Under these circumstances, the VPCs are a manifestation of abnormal automaticity of a protected ventricular focus. Because this focus is not penetrated by sinus impulses, it is not reset by them, and the interectopic intervals remain relatively fixed (>120ms variation of mean RR cycle length). VPCs may occur singly; in patterns of bigeminy (Figure 1.21), in which every sinus beat is followed by a VPC; in trigeminy, in which two sinus beats are followed by a VPC; in quadrigeminy, etc.

Figure 1.21

Ventricular bigeminia



Two successive VPCs are termed *pairs* or *couplets*, while three or more consecutive VPCs are termed *ventricular tachycardia* when the rate exceeds 100 beats/min. VPCs may have similar morphologies (monomorphic, or uniform) or different morphologies (polymorphic, or multiformed). Most commonly, VPCs are not conducted retrogradely to the atrium to reset the sinoatrial node. Thus they result in a fully compensatory pause, i.e., the interval between conducted sinus beats that bracket the VPC equals two basic RR intervals. Ventricular impulses may also manifest retrograde conduction to the atrium and cause inverted P waves in leads II, III, and aVF. This retrograde atrial activation can reset the sinus node, and the pause that results may therefore be less than compensatory. In many instances, the VPC will not be associated with retrograde ventriculoatrial (VA) conduction but may block retrogradely in the AV node. This renders the AV node refractory to the subsequent sinus beat and causes slowed conduction (i.e., prolonged PR interval) or block of the next sinus P wave. This prolonged PR interval is said to be a manifestation of concealed retrograde conduction of the ventricular impulse into the AV node. A VPC that does not produce any manifestation of retrograde concealed conduction and fails to influence the oncoming sinus impulse is termed an *interpolated VPC*.

VPCs can cause palpitations or neck pulsations secondary to either the occurrence of cannon *a* waves or the increased force of contraction due to postextrasystolic potentiation of ventricular contractility. Patients with frequent VPCs or bigeminy may rarely develop syncope or lightheadedness because the VPCs do not result in an adequate stroke volume and the cardiac output is reduced by the "halving" of the heart rate.

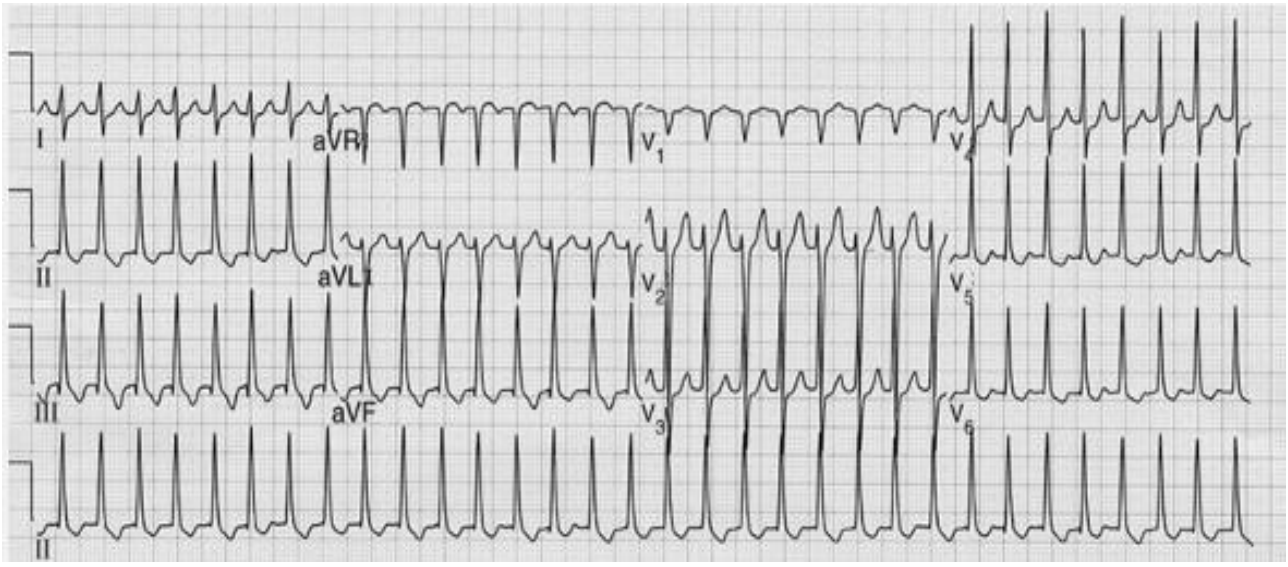
Tachyarrhythmias exist if the heart rate is faster than it should be on the basis of the patient's activity. Tachyarrhythmias can be classified into supraventricular tachycardia (SVT), functional tachycardia (paroxysmal functional tachycardia [PJT] or functional ectopic tachycardia [JET]), and VT.

Supraventricular tachycardia

In supraventricular tachycardia, the QRS is narrow, and P waves, if discernible, will be related to the QRS (Figure 1.22).

Figure 1.22

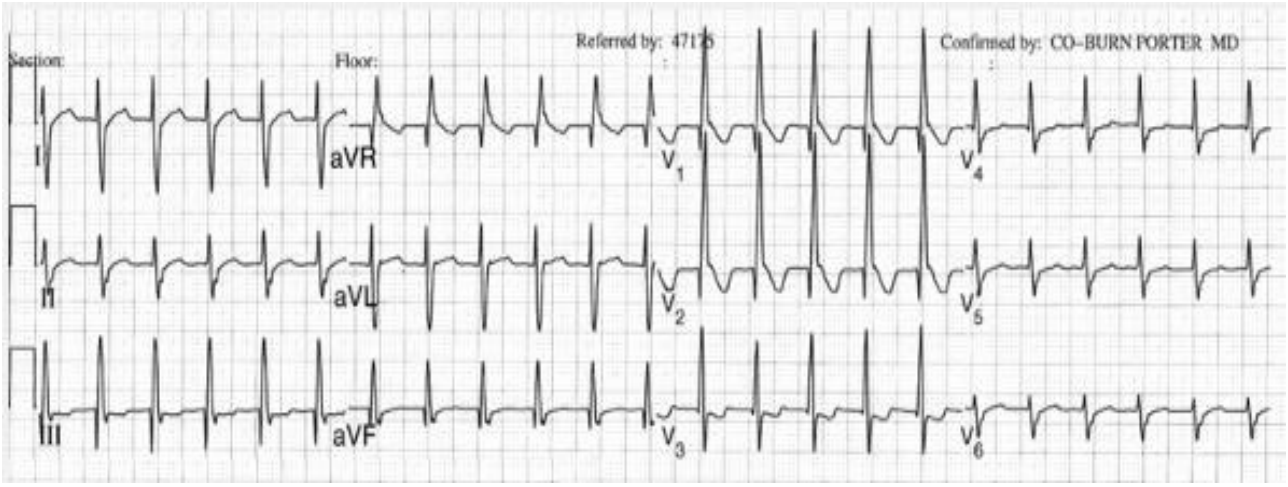
The electrocardiogram in SVT



Functional tachycardia also is characterized by a narrow QRS complex but, in contrast to SVT, the P waves and QRS complexes are dissociated from one another (Figure 1.23). JET usually occurs in infants immediately following intracardiac surgery. One usually is faced with treatment of JET in infants following cardiac operation.

Figure 1.23

Functional tachycardia



Ventricular Tachycardia

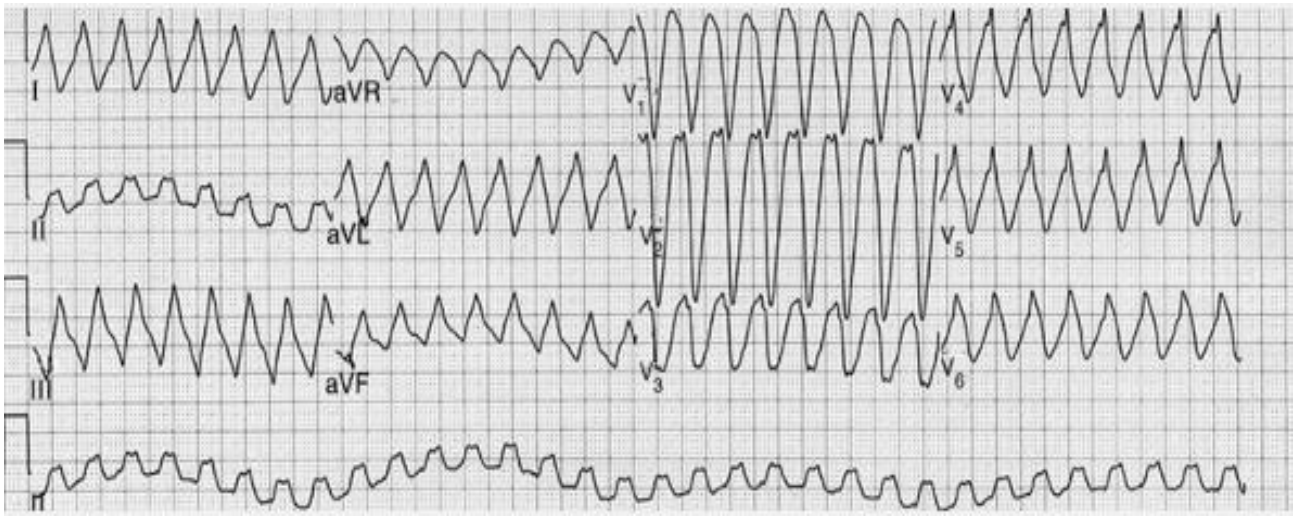
Ventricular tachycardia (VT) remains an important cause of morbidity and mortality in cardiac patients. Symptoms may be mild (palpitations and dyspnea), or they may reflect rapid and severe hemodynamic compromise (syncope, cardiac arrest). In occasional patients, congestive heart failure may be the initial presentation when VT of prolonged duration remains unrecognized. Structural heart disease (SHD) is present in 85% to 90% of patients, with healed myocardial infarction the most common cause. The specific underlying myocardial substrate has an important influence on long-term outcome and therapeutic options, and it is discussed in detail in subsequent sections.

Although rapid rates (>200 beats per minute) are more likely to produce hemodynamic compromise, autonomic compensatory mechanisms (particularly the baroreceptor reflex) play a major role independent of heart rate or pre-VT hemodynamic status. Impairment of this reflex has been associated with more rapid hemodynamic deterioration. Unstable VT is an important, but by no means exclusive, cause of cardiac arrest and sudden death.

Identification of VT begins with the recognition of three or more consecutive wide complexes (Figure 1.24).

Figure 1.24

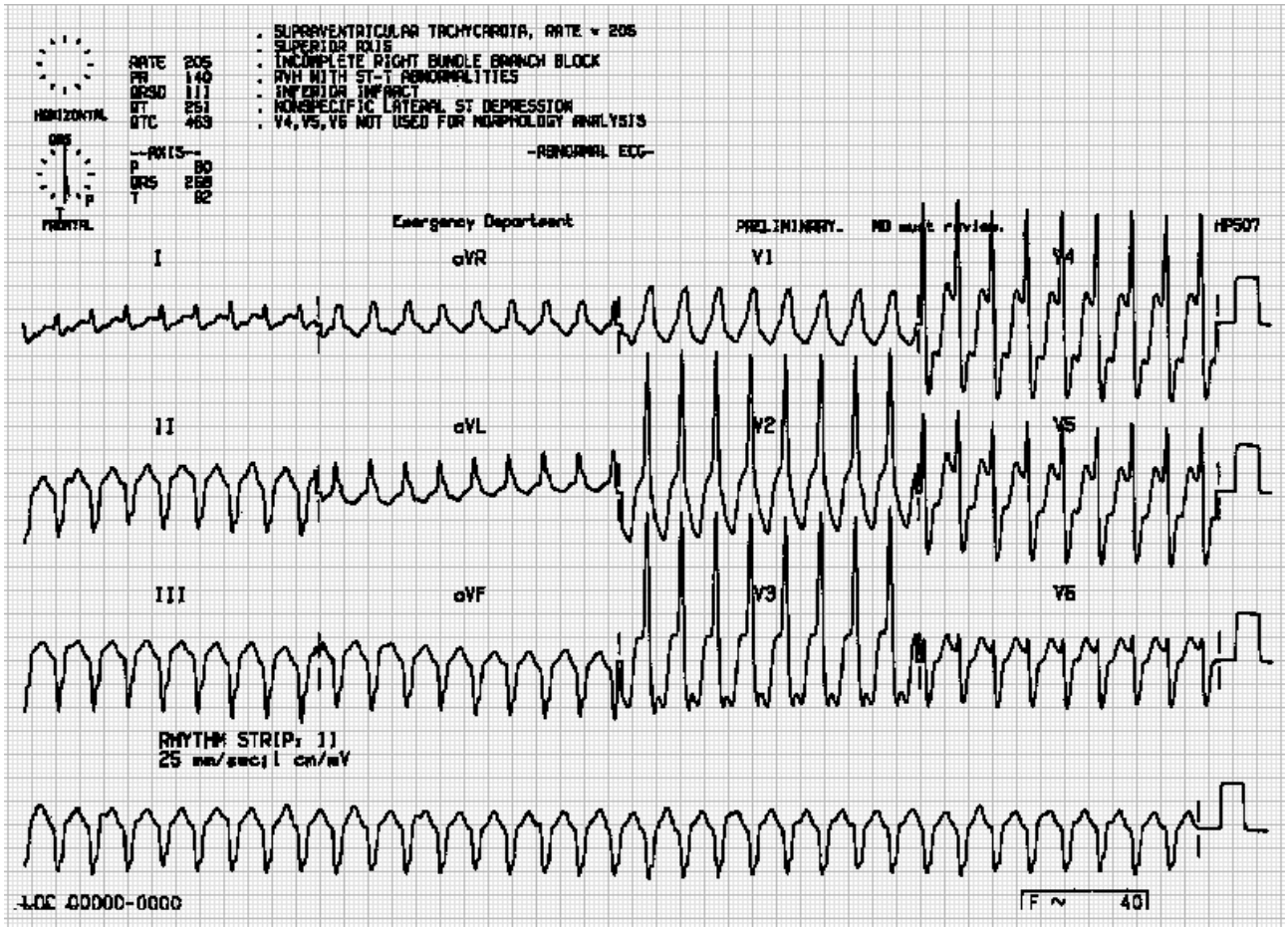
Ventricular tachycardia



Rarely, the QRS complex may be slightly narrower if the focus is within or adjacent to the proximal Purkinje system or bundle branches, with rapid early engagement of conduction over this network. These complexes may have a uniform appearance from beat to beat (monomorphic VT) (Figure 1.25), or consecutive complexes may vary, often widely, in QRS configuration (polymorphic VT) (Figure 1.26).

Figure 1.25

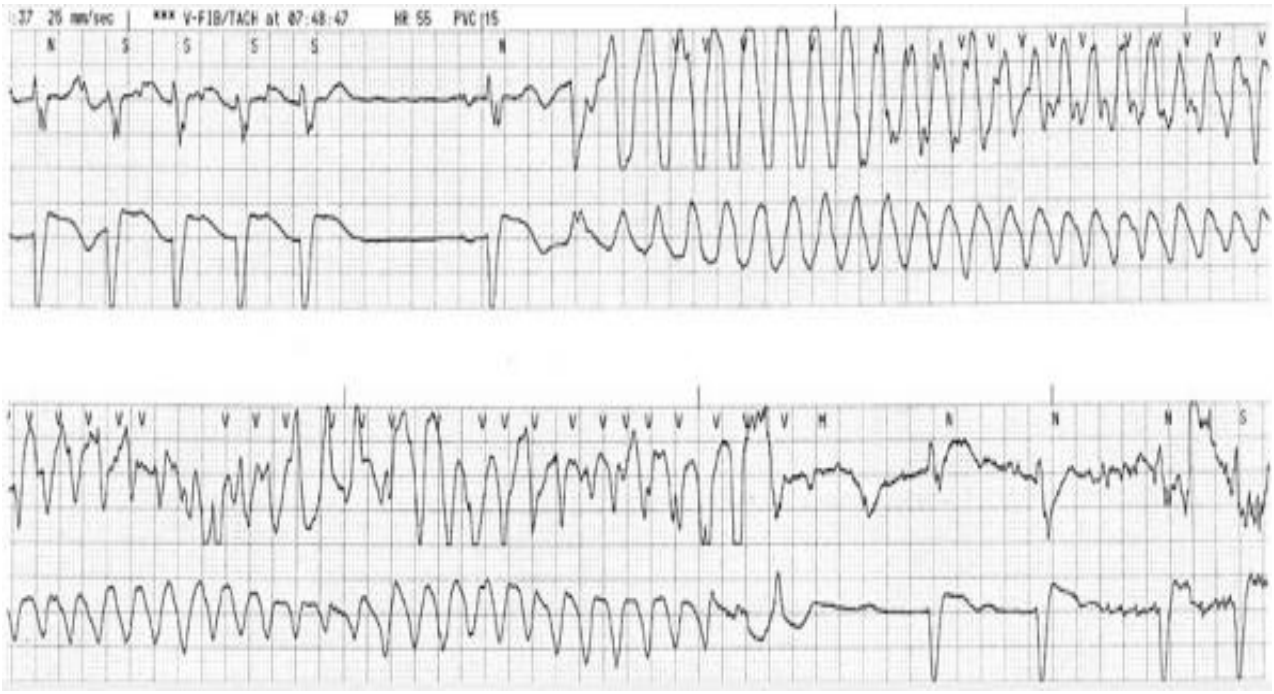
Monomorphic ventricular tachycardia



A specific pattern of polymorphic VT, termed torsade de pointes, manifests a periodic reversal of QRS polarity associated with waxing and waning QRS amplitude. The distinction between monomorphic and polymorphic VT has important implications in terms of mechanism, underlying substrate, and prognosis that are discussed in subsequent sections. Spontaneous termination within 30 seconds is generally designated nonsustained VT, with longer durations considered sustained. Very rapid rates (>270 beats per minute) are seldom associated with discrete identifiable QRS complexes and are usually designated VF.

Figure 1.26

Polymorphic ventricular tachycardia with the features of torsade de pointes.



Most wide complex tachycardias (~80%) are ventricular in origin, particularly in the presence of known SHD, and this prior probability should influence subsequent decision making.

Supraventricular tachycardia (SVT) may be associated with a wide QRS complex resulting from

- preexisting intraventricular conduction defects,
- aberrant conduction (from incomplete repolarization of some portion of the His-Purkinje system during tachycardia),
- conduction over an accessory pathway,

- conditions associated with depressed conduction (drugs, metabolic or electrolyte abnormalities, ischemia).

Rarely, ventricular pacing at rapid rates may cause diagnostic confusion because of failure to recognize the often imperceptibly small pacing artifacts on the surface electrocardiogram (ECG).

Distinction between VT and SVT with aberration can be difficult in individual patients, but several general principles are useful. Capture beats and fusion beats are generally diagnostic for VT, but they are present in only a small number of cases. Rarely, a ventricular ectopic beat during aberrantly conducted SVT can incorrectly suggest VT. Atrioventricular dissociation indicates VT with rare exceptions. It is present in up to 70% of VTs and is more common at rapid rates. It also can be suspected if cannon A waves are observed during inspection of the jugular venous pulse during physical examination. The wider the QRS duration, the more likely the rhythm is VT. Durations of 160 milliseconds or longer during left bundle branch block patterns and of 140 milliseconds or longer during right bundle branch block patterns are useful guidelines. A frontal plane axis between - 90 and + 180 degrees strongly favors VT. The precordial R/S criterion originally proposed by Brugada is relatively specific for VT. The criterion is present if either no RS complexes occur in the precordial leads, or, if R/S complexes are present, the interval from onset of the R wave to the nadir of the S wave is greater than 100 milliseconds. The absence of a typical bundle branch block pattern or rapid precordial intrinsicoid deflection favors VT. In the setting of preexisting intraventricular conduction defects, differences in QRS morphology between the baseline ECG and that of tachycardia favor a diagnosis of VT; however, similarity between the two does not exclude VT. Although numerous additional criteria have been proposed based on QRS configuration in specific leads, most have relatively low positive predictive value or are applicable only if the baseline QRS complex is normal.

Fascicular blocks

Generalities

There are several ways of proving that a given QRS pattern is due to a specific type of conduction abnormality. First is extrapolation from animal experiments. Second is ECG-pathologic correlation. Third is an analysis of QRS changes produced by the inadvertent section of the conduction fascicles during open heart surgery or catheter-induced trauma. Fourth is a comparison of tracings obtained before, during, and after the appearance or disappearance of conduction disturbances that are either persistent or (spontaneously or iatrogenically) intermittent. Under such circumstances, the QRS changes produced by fascicular block occur side by side with the control morphologies. The various criteria proposed for diagnosis of fascicular blocks, though empirical, have been accepted for a very pragmatic reason: the need to interpret clinical ECGs (Table 1.3).

Table 1.3.

Causes of Abnormal (-30° to -90°) Left-Axis Deviation

Cause	Characteristic Features
1. Left anterior fascicular block	1. rS complexes in lead II with positive T waves
2. Extensive inferior wall (AC5) MI	2. Qr complexes in lead II with ST-segment elevation and/or T-wave inversion
3. Extensive inferior wall MI with possible (AC7) LAFB	3. QS pattern in leads II, III, and aVF with ST-segment elevation and/or T-wave inversion
4. Wolff-Parkinson-White syndrome (posteroseptal accessory pathway)	4. Short PR interval; delta wave
5. Hyperkalemia	5. Wide QRS complexes; peaked T waves
6. Pulmonary emphysema	6. Low voltage; peaked P waves, S waves in standard and precordial leads
7. Right ventricular apical pacing	7. Pacemaker spikes; predominantly negative ventricular deflections in V1
8. Middle cardiac vein pacing	8. Pacemaker spikes; predominantly positive QRS deflections in V1
9. Left coronary arteriography	9. Knowledge that dye was injected in left coronary artery

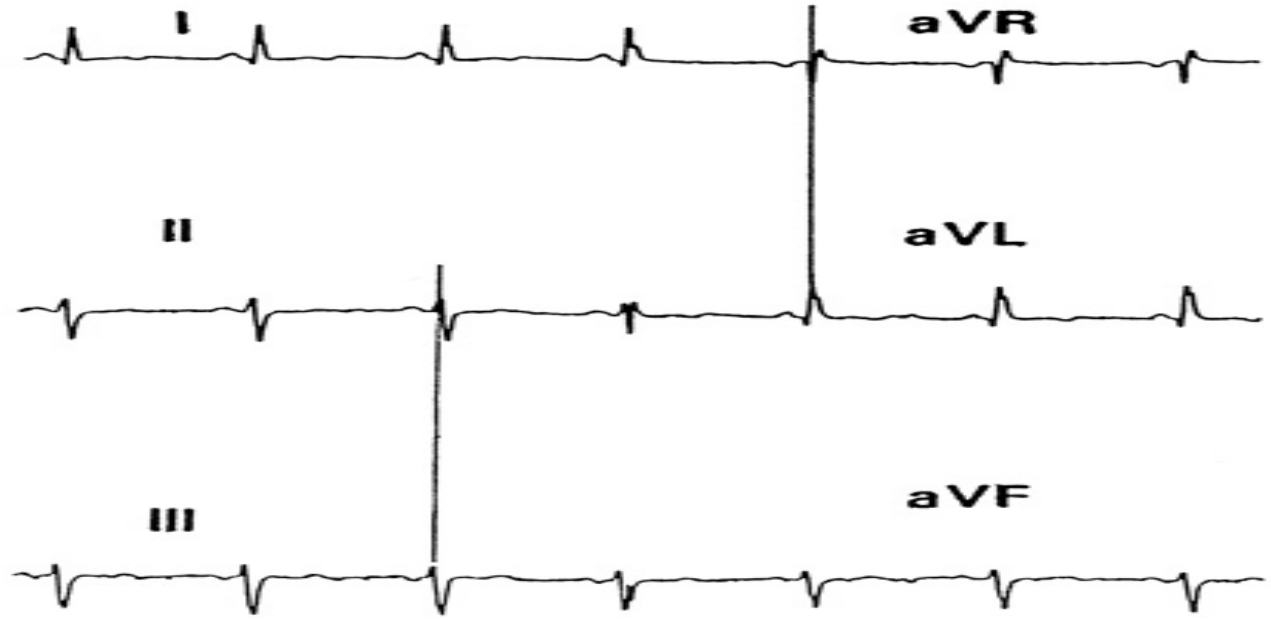
In reality, the sensitivity and specificity of these criteria require independent confirmation. One can speculate that the latter may be provided by newer methods of intraoperative and body surface mapping and refinements in the technique of phase imaging or even perhaps Carto mapping, since few centers in the United States are currently performing histopathologic studies of the distal intraventricular conduction system.

Left Anterior Fascicular Block

In left anterior fascicular block (LAFB), the posteroinferior regions of the LV endocardium are activated abnormally before the anterosuperior LV area. After emerging from the posteroinferior division of the left bundle branch, the impulse first propagates in an inferior, rightward, and usually anterior direction for a short period of time, producing q waves in leads I and aVL and r waves in leads II, III, and aVF. Thereafter, the general direction of the activation process (which determines the direction of the EA) occurs in a superior and leftward direction. Consequently, from the ECG viewpoint, the fascicles of the left branch behave more as if they were "superior" and "inferior" rather than "anterior" and "posterior" (Figure 1.27).

Figure 1.27.

LAFB in a patient with primary conduction system disease.



Note: QRS duration: 0.10 s. At normal paper speeds (25 mm/s), the relationship between the peaks of the R waves (*vertical lines*) in simultaneously recorded leads II and III and aVL and aVR cannot be determined with the desired accuracy.

For this reason, the most significant abnormalities produced by LAFB, in the absence of complete right bundle branch block (RBBB), occur in the standard and unipolar extremity leads rather than in the precordial leads. S waves frequently are recorded V_5 and V_6 because the depolarization wave first moves towards them and later, because of their relatively low position, away, in a more superior direction. The degree of left-axis deviation required for the diagnosis of complete LAFB has been a

subject of debate and speculation. It should be remembered that LAFB is but one of the causes of left-axis (superior and leftward) deviation (Table 1.4).

Table 1.4.

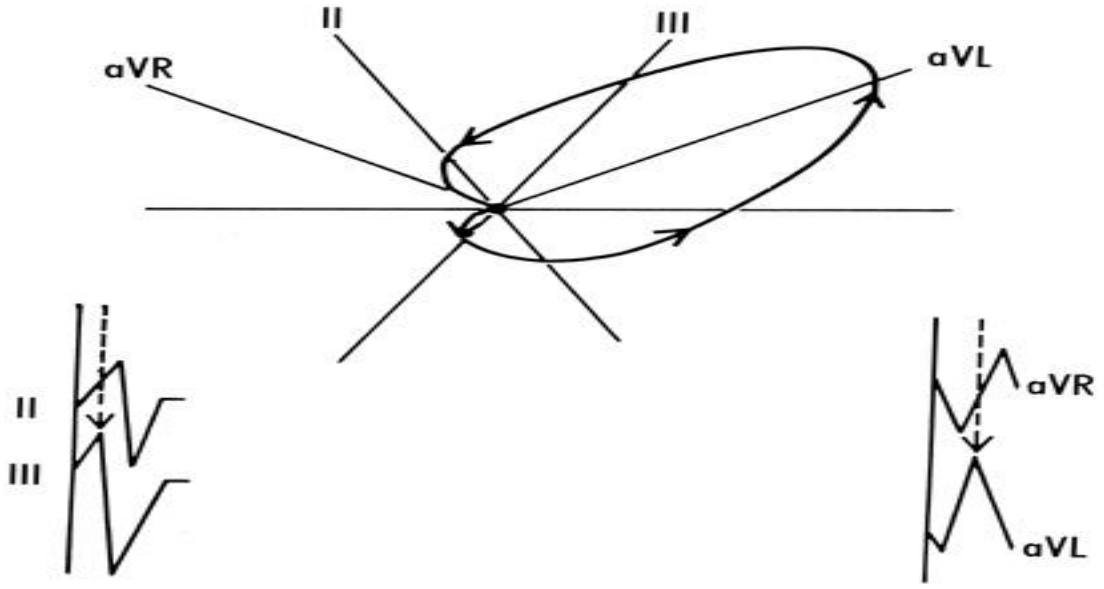
Criteria for Diagnosis of Pure Left Anterior Fascicular Block

1. Abnormal left-axis deviation (usually between -45 and -60°)
2. rS complexes in leads II, III, and aVF and qR complexes in leads I and aVL
3. Delayed intrinsicoid deflection in leads I and aVL
4. Peak of r wave in lead III occurring earlier than peak of r wave in lead II
5. Peak of R wave in lead aVL occurring earlier than peak of R wave in aVR

When LAFB coexists with certain congenital types of right ventricular enlargement and extensive anterolateral MI, the EA can be shifted to the "undeterminate" (right superior) quadrant. Thus the constant feature of the axis deviation produced by LAFB is its *superior* orientation, not its superior and leftward orientation (abnormal left-axis deviation) (Figure 1.27). Because of the multiple interconnections between the fascicles of the left bundle branch system, the appearance of LAFB does not increase QRS duration by more than 0.025 s. Therefore, a LAFB pattern with a wider QRS complex generally indicates the presence of additional conduction disturbances such as RBBB, MI, or intraventricular conduction delays due to free wall fibrosis (Figure 1.28).

Figure 1.28.

Derivation of electrocardiographic leads from a frontal plane QRS loop showing LAFB.



Note: Due to the counterclockwise rotation of the left superior loop, the peak of the R in aVL preceded the peak of this deflection in aVR (lower right). Furthermore, because the initial portion of the loop was inscribed on the positive half of the axis of lead III before it was inscribed on the positive half of the axis of lead II, the peak of the R in the former lead occurred before that in the latter lead.

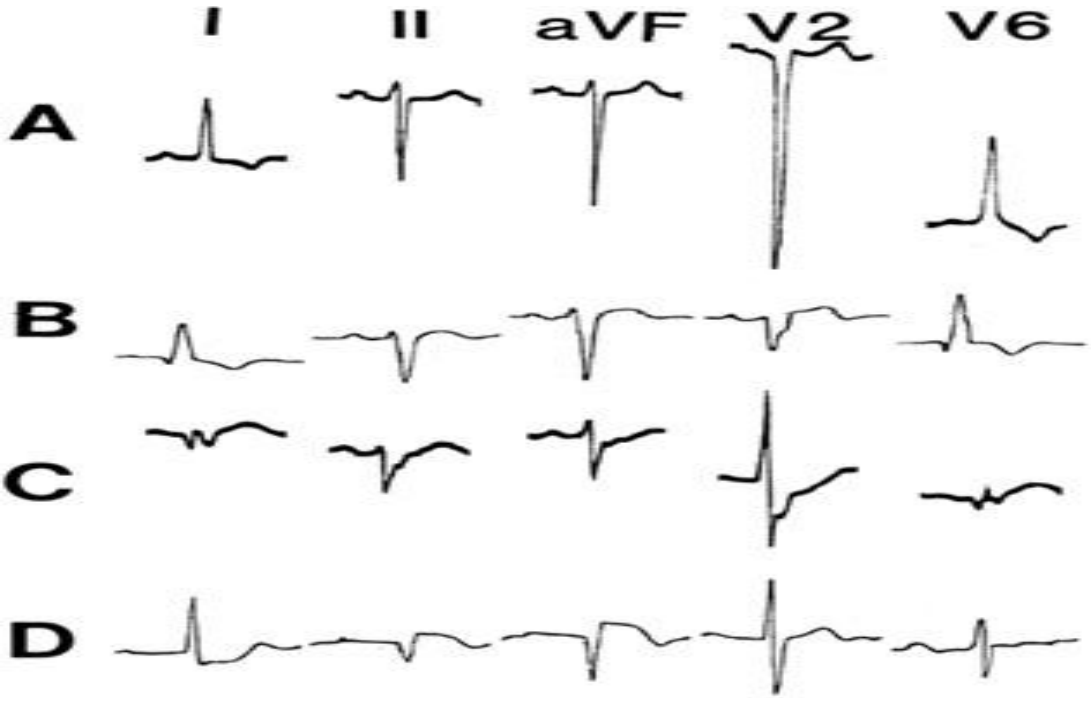
Masquerading RBBB is said to be present when (with the classic findings in lead V_1) lead I shows what seems to be a left bundle branch block (LBBB) due to the absence of q and S waves. This pattern has been attributed to a terminal delay perpendicular to lead I associated with diffuse intramyocardial fibrosis.

Left Anterior Fascicular Block Coexisting with MI

The ECG changes imposed by MIs of different locations on the LAFB are shown in Figure 1.29. An inferior wall MI can be masked by a LAFB if the infarction does not involve the areas first depolarized by the impulse emergency from the unaffected fascicle. In these cases, an r (slurred or not) can be seen in leads III and aVF. It also has been stated that the change in left septal activation produced by the fascicular block may produce small r waves in V1, V2, and V3 capable of modifying the characteristics QS complexes produced by anteroseptal MI in these leads.

Figure 1.29.

Diagnosis of LAFB associated with MI. Diagnostic feature given in parentheses.



Note: *A*. LAFB and anteroseptal MI (QR or QS complex in right chest leads). *B*. LAFB and anterolateral MI (abnormal Q wave in leads I and V6). *C*. LAFB and anterolateral MI with electrical axis in the right superior quadrant (Q wave in leads I and V6). *D*. LAFB and inferior wall MI (QR or QS complexes and elevation of J point and ST segments in leads II and III).

Nonspecific Intraventricular Conduction Delays

Several names have been applied to the conduction disturbances occurring in the left-sided Purkinjemyocardial junctions, left septal surface, or free wall of the left ventricle: *arborization block, diffuse (nonspecific) intraventricular block, peri-infarction block, parietal block, focal block,* etc. These conduction disturbances have different electrogenetic mechanisms. Thus the cellular "affectation" due to acute injury resulting from coronary artery disease, hyperkalemia, drugs, and intracoronary injections of contrast material occurs within (inside) the affected regions. Blocks occurring in subacute or chronic MI after the appearance of abnormal Q waves (peri-infarction block), as well as those occurring in the presence of diffuse myocardial fibrosis, are due to the circuitous and irregular activation of living cells surrounding areas of fibrotic tissue.

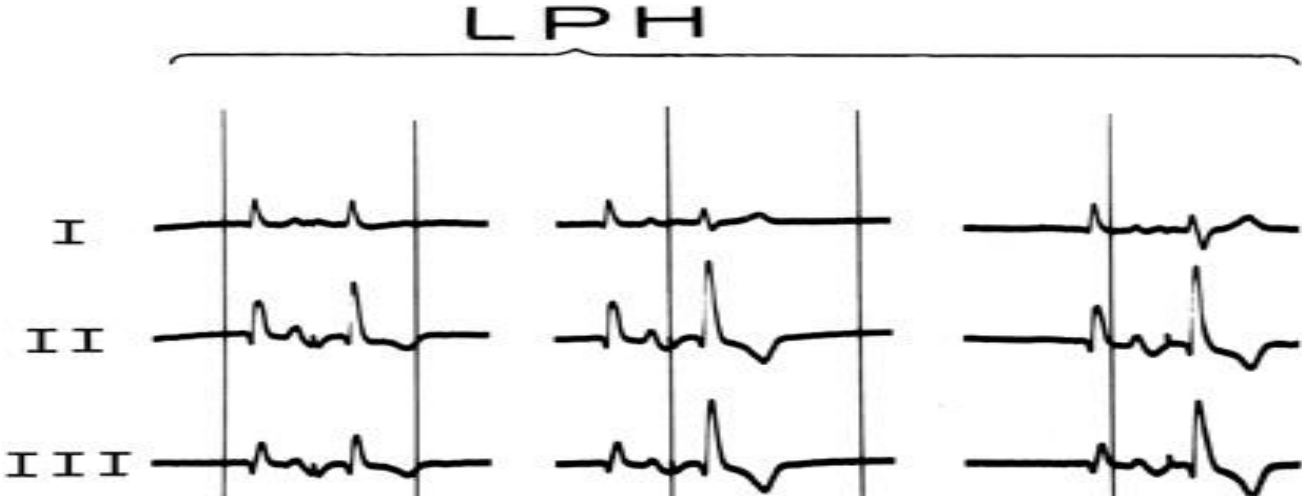
Left Posterior Fascicular Block

In pure left posterior fascicular block (LPFB), the impulse emerges from the unblocked anterosuperior division, thus producing small q waves in leads II, III, and aVF. Thereafter, the impulse moves through the electrically predominant left ventricle in an inferior and rightward direction, thus explaining the S waves in leads I and aVL as well as the R waves in leads II, III, and aVF. Radiologic studies of the human heart in situ have shown that the paraseptal regions of the posteroinferior (diaphragmatic) surface of the anatomic *left* ventricle are spatially located more to the *right* than certain (anterior) portions of the anatomic right ventricle. Since the portions of the left ventricle that are spatially located to the right are less than those located superiorly, the degree of right-axis deviation produced by pure LPFB is of lesser magnitude than that of left-axis deviation produced by LAFB. The hallmark of LPFB, therefore, is an "inferior" axis shift as much as "right" axis deviation (Figure 9). Because a similar sequence of ventricular activation also can occur in right ventri-

cular hypertrophy, pleuropulmonary disease (acute or chronic), and extremely vertical anatomic heart positions due to a slender body build or chest wall deformities, it is evident that the diagnosis of "pure" LPFB cannot be made from the ECG alone. Additional clinical, radiologic, or pathologic information is required for this purpose. The changes imposed in LPFB by MIs of different locations are depicted in Figure 1.30.

Figure 1.30.

Premature atrial beats showing increasing degrees of (incomplete and complete) LPFB aberration.



Note: The first beats in all panels are escape beats with the same morphology as that of sinus beats. The second, aberrantly induced ventricular complexes show different degrees of right-axis shift with an increase in size of the R waves in leads II and III. Note that the fundamental characteristic of LPFB was not right-axis deviation (beyond +90°) but an inferior-axis shift.

Left Fascicular Blocks Produced by Intra-His Bundle Lesions

It was attributed surgically induced LAFB (coexisting with RBBB) to a lesion of the "pseudobifurcating" part of the His bundle. The production of LBBB and LPFB by catheters located in the right-sided cavities, however, cannot be explained by assuming direct affectation of these left-sided structures. Nevertheless, they have been reported and attributed to the His bundle trauma produced by Swan-Ganz catheters. In fact, certain clinical and experimental studies have shown that some bundle branch block patterns could be normalized by distal His bundle pacing. Longitudinal dissociation of conduction within a usually diseased His bundle should be present for this to occur. There is, however, disagreement as to the mechanism involved, especially in regard to the predestination of fibers (within the His bundle) to specific

right- or left-sided structures and to the role played by the transverse fibers connecting the various longitudinal strands.

Left-Middle (Septal) Fascicular Blocks

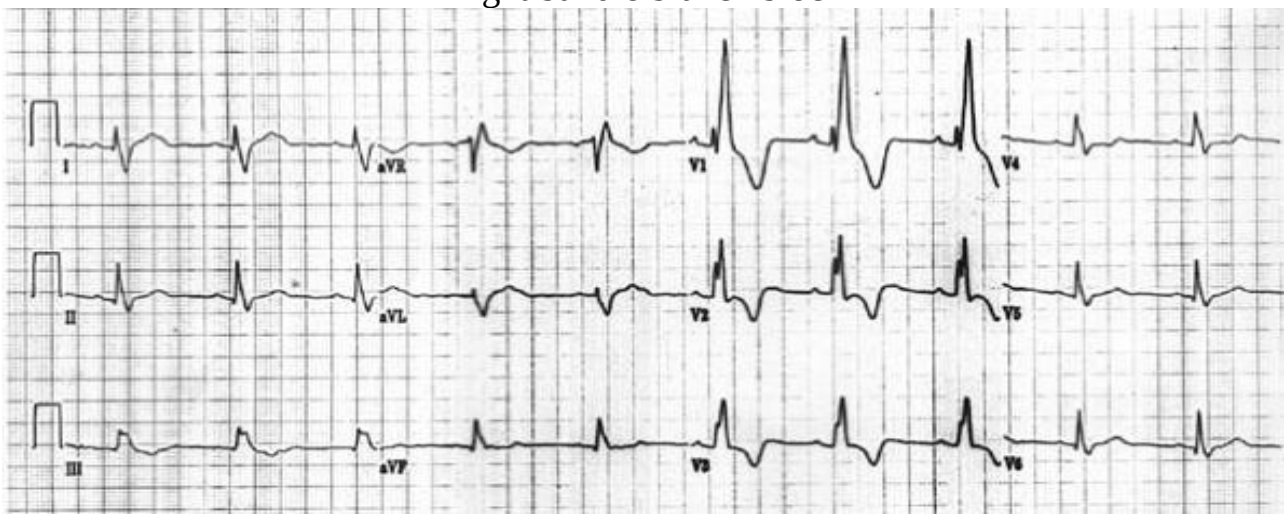
This disorder has been demonstrated anatomically and is associated with ischemic heart disease and fibrosis of the middle (septal) fascicle of the left branch. While some authors consider that the right precordial leads show prominent R waves (similar to those found in true posterior, basal, myocardial infarction), others have described Q waves in leads V1, V2, and V3. It also has been considered that left-middle (septal) fascicular blocks are manifested by the absence of the expected q waves in leads V5 and V6 in ECG intermediate or horizontal hearts. Such a diversity of diagnostic criteria shows that there are marked discrepancies regarding the ECG characteristics of this conduction disturbance.

Complete RBBB

A "complete" RBBB pattern (with QRS duration of 0.12 s) does not necessarily reflect the existence of a total conduction block in the right branch. This pattern only indicates that the entire or major parts of both ventricles are activated by the impulse emerging from the left branch. Thus, a significant degree of conduction delay ("high grade" or "incomplete" RBBB) can produce a similar pattern. In pure complete RBBB, the EA should not be deviated *abnormally* either to the left or to the right. These axis deviations reflect coexisting fascicular block or right ventricular hypertrophy (Figure 1.31).

Figure 1.31

Right bundle branch block



Incomplete RBBB Pattern

For many years what has been proven with endocardial (catheter) and epicardial mapping has been recognized-namely, that incomplete RBBB "patterns" can be produced by various mechanisms:

- different degrees of conduction delays through the main trunk of the right bundle branch,
- an increased conduction time through an elongated right bundle branch that is stretched because of a concomitant enlargement of the right septal surface,
- a diffused Purkinje-myocardial delay due to right ventricular (RV) stretch or dilatation,
- surgical trauma or disease-related interruption of the major ramifications of the right branch ("distal" RBBB),
- congenital variations of the distribution of the major distal ramifications resulting in a slight delay in activation of the crista supraventricularis in arrhythmogenic RV dysplasia, the S wave in V1 is followed by a sharp, wide, positive deflection attributed to delayed ventricular activation (postexcitation) in some RV myocardial fibers.

Wide QRS complexes in this lead (wider than in other precordial leads) were attributed to a "parietal" block superimposed on a RBBB.

Concealed RBBB

A minor conduction delay in the main trunk of the right bundle branch or in its major ramifications may be "concealed" (not manifested in the surface ECG) when there are coexisting (and of greater degree) conduction disturbances in the main left bundle branch, the anterosuperior division of the left bundle branch, and/or the free LV wall. An RBBB also can be concealed in some patients with Wolff-Parkinson-White syndrome if the ventricular insertion of the accessory pathway causes preexcitation of the RV regions that would be activated late because of the RBBB.

Nonspecific Intraventricular Block

A QRS duration of 0.11 second or greater that does not satisfy the criteria for either RBBB or LBBB is considered a nonspecific intraventricular block.

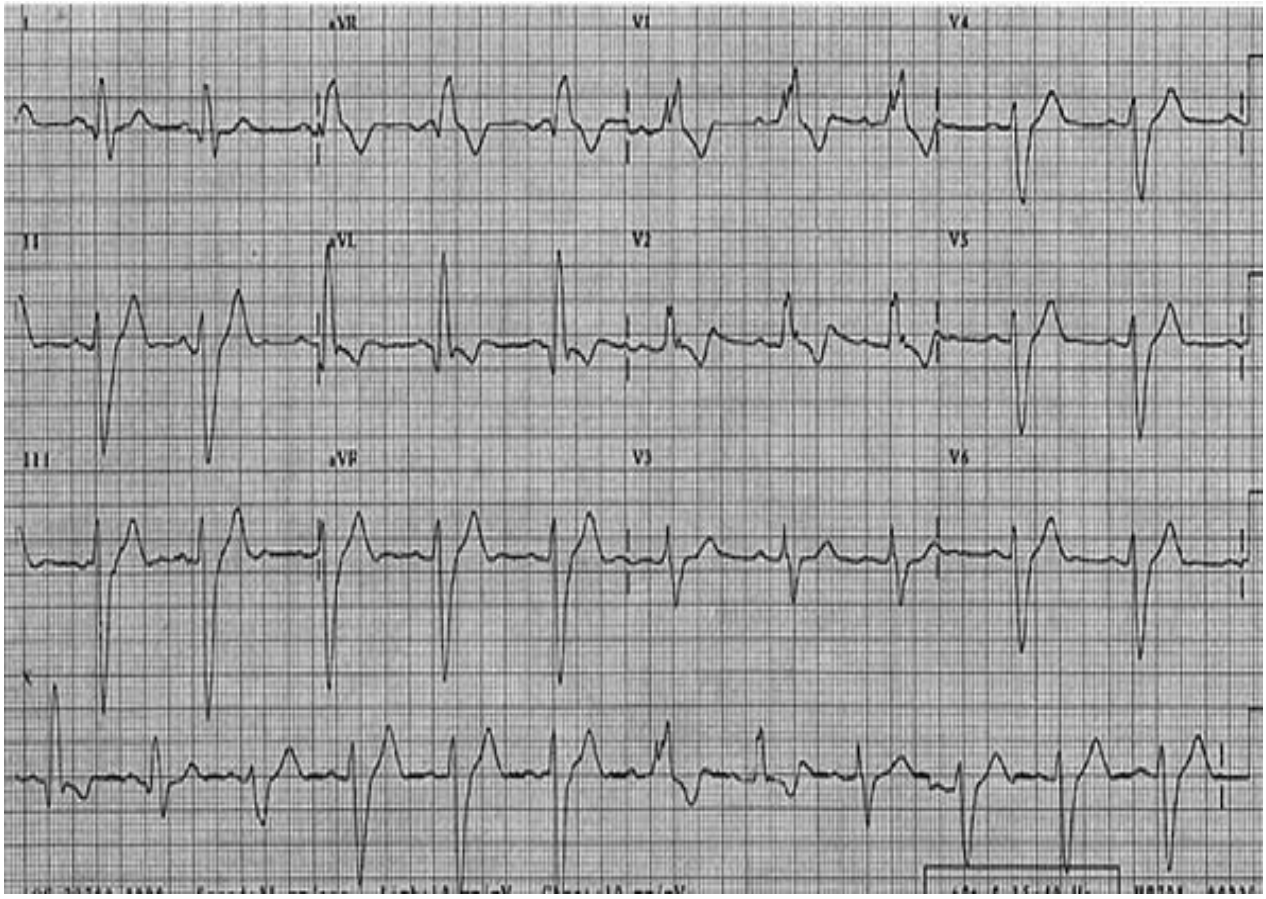
Right Bundle Branch Block with Left Anterior Fascicular Block

LAFB often accompanies RBBB. The diagnosis is made by the late prominent R wave in V_1 typical of RBBB and by the initial R waves and prominent S waves in

leads II, III, and aVF seen in LAFB. The QRS duration should be at least 0.12 second, and the frontal plane axis should be between -45 and -120 degrees (Figure 1.32).

Figure 1.32

Right bundle branch block and left anterior fascicular block



Right Bundle Branch Block with Left Posterior Fascicular Block

This combination is less common. The diagnosis can be made only if there is no clinical evidence of right ventricular hypertrophy. The diagnosis of RBBB with LPFB should be considered when in V_1 there is typical RBBB, and leads I and aVL show the initial R waves and prominent S waves of LPFB. The QRS duration should be 0.12 second or greater, and the frontal plane axis should measure 90 degrees or more.

Trifascicular Blocks

ECG documentation of trifascicular block during 1:1 AV conduction is rare and requires the presence of alternating RBBB and LBBB or fixed RBBB with alternating LAFB or LPFB. When both bundle branches are simultaneously affected by block, the ECG shows complete AV block. When the degree of block differs between

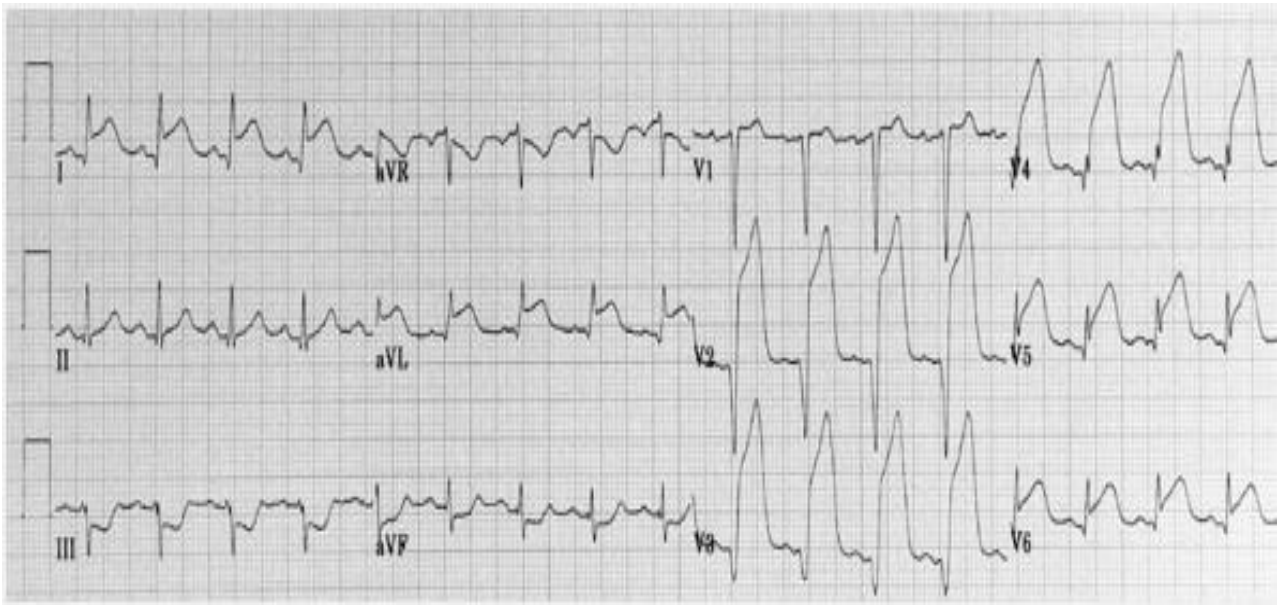
the two bundle branches, ECG manifestations vary and include, for example, a shorter PR interval preceding either RBBB or LBBB or a complete BBB with a prolonged PR interval.

Aberrancy

Aberrant intraventricular conduction is the abnormal, asynchronous propagation of an impulse through the His-Purkinje system resulting in an altered QRS complex. This definition excludes conduction of supraventricular impulses via accessory pathways that bypass the AV node. Changes in the QRS complex may affect its duration, axis, or amplitude; successive aberrant beats may mimic ventricular tachycardia (Figure 1.33).

Figure 1.33

Aberrant intraventricular conduction

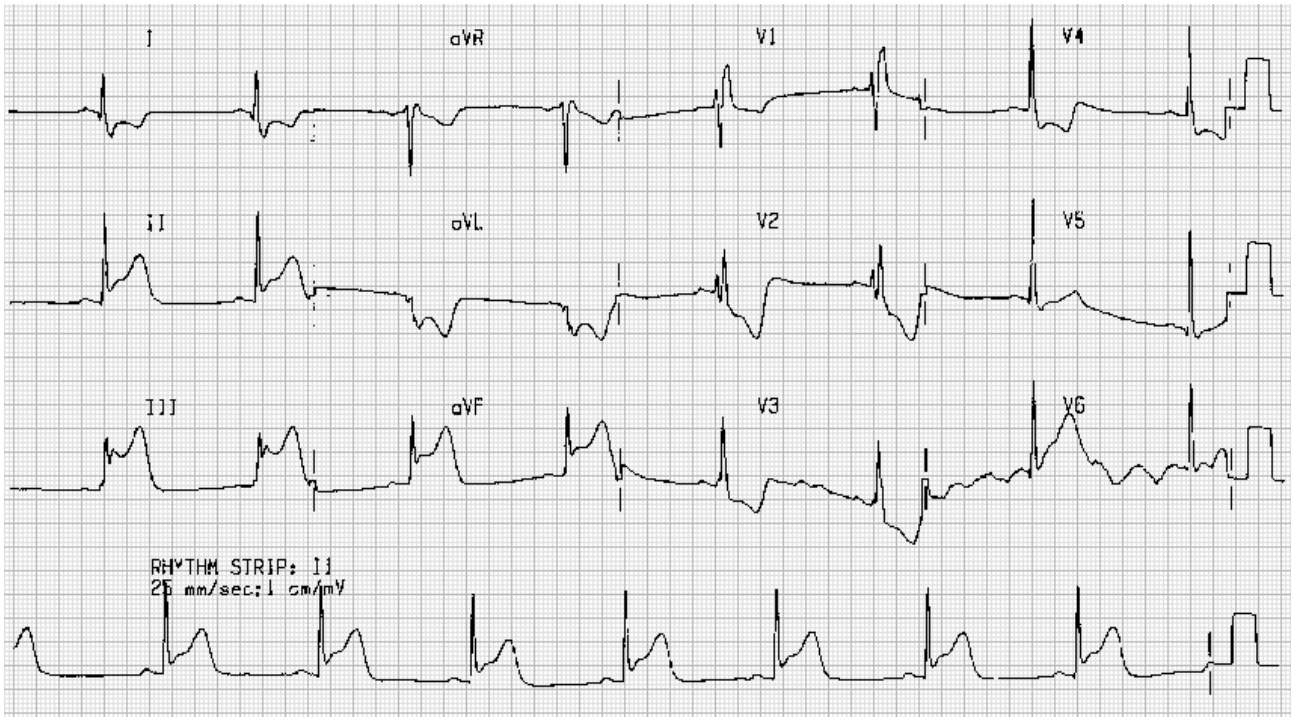


Complete LBBB

This conduction disturbance is characterized by wide (>0.11s) QRS complexes. The diagnostic criteria consist of prolongation of the QRS complexes (>0.11s) with neither a q nor an S wave in leads I, aVL, and a *properly placed* V6. A wide R wave with a notch on its top ("plateau") is seen in these leads (Figure 1.34). Apparently, the EAs of most *uncomplicated* complete LBBBs usually are not located beyond 30°. Complete LBBB with abnormal left-axis deviation indicates a great degree of left Purkinje and myocardial disease.

Figure 1.34

Complete LBBB.



Complete LBBB with Acute MI

The classic pattern of LBBB may not be modified by a small area of myocardial necrosis. This explains why thrombolytics may be given if clinical findings characteristic of MI occur in patients with a LBBB pattern. Recent studies, however, have shown that occlusions of a coronary artery by either an angioplasty balloon or (a presumably large) MI can produce ST-segment changes as in the absence of a conduction disturbance. The above-mentioned criteria also can be applied to diagnose acute MI in patients with pacemakers.

Complete LBBB with Old MI

Normally, in complete LBBB, the impulse emerges from the right bundle branch and propagates inferiorly, to the left, and slightly anteriorly. This orientation of the initial forces tends to abolish previously present inferiorly and laterally located abnormal Q waves characteristic of inferior and lateral wall MIs. If the infarction is anteroseptal, however, the impulse cannot propagate toward the left. Instead, the initial vectors point toward the free wall of the right ventricle because now the RV free-wall forces are not neutralized by the normally preponderant septal and/or initial LV free-wall forces. Thus, a small q wave will be recorded in leads I, V_5, and V_6, where

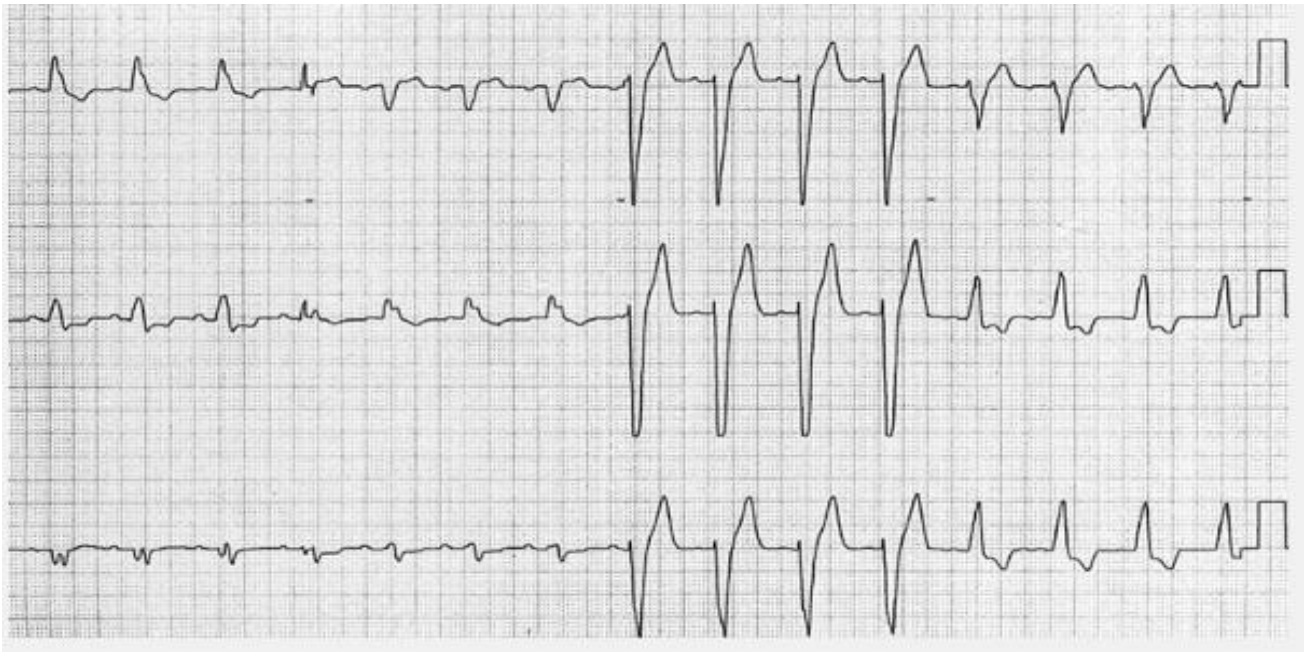
it is not normally present in complete LBBB. Similar findings can be seen in paced beats when in lead I the spike is followed by a well-defined q wave. Several studies reported that Q waves in lead I or in two or more lateral leads (I, aVL or V_5 and V_6) have high specificity but moderate sensitivity. Notching of the upstroke of the R wave in leads I, aVL, V_5, and V_6 has a sensitivity of 21 percent and a specificity of 82 percent.

Incomplete LBBB Pattern

An incomplete LBBB pattern can be diagnosed if leads I and an *appropriately placed* V6 show an R wave not preceded by a q wave. Lead V1 shows rS or QS complexes, and lead V_2 shows rS complexes. Although QRS duration usually ranges between 0.08 and 0.11 s, this *pattern* can be observed with QRS durations of 0.12 and 0.13 s (Figure 1.35).

Figure 1.35

Uncomplicated left bundle branch block.



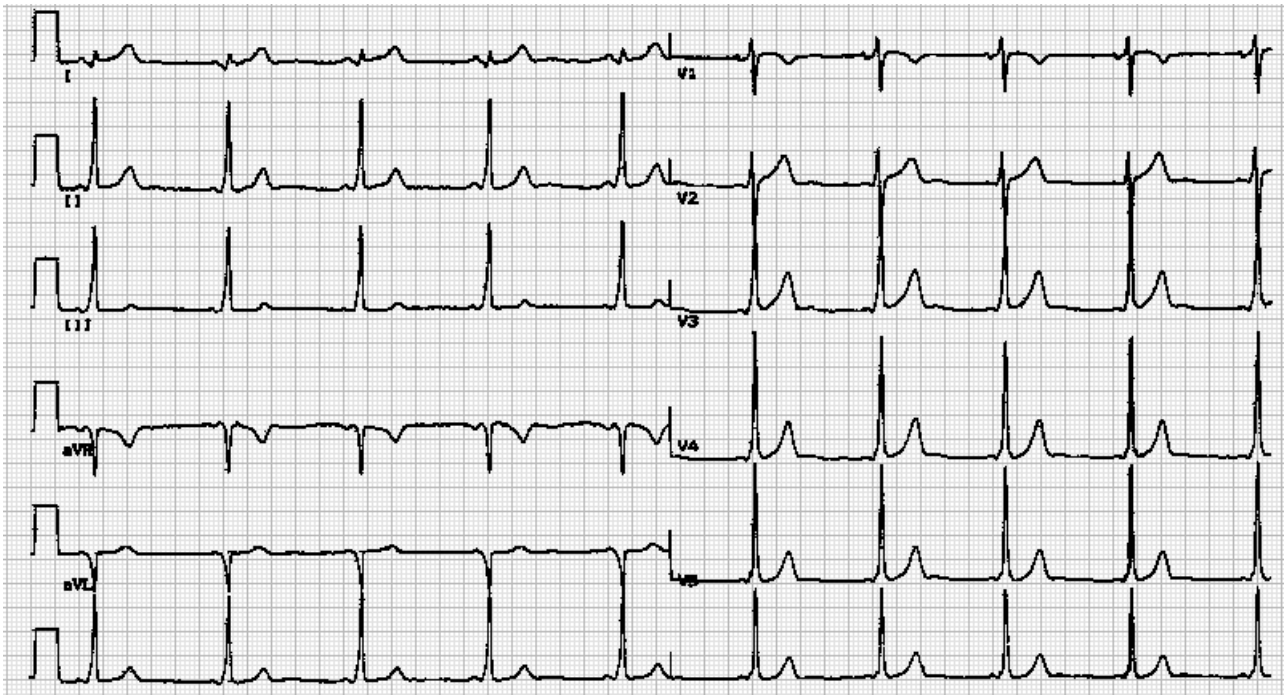
Wide QRS Complexes in Patients with Manifest Preexcitation Syndromes

The characteristic pattern of manifest Wolff-Parkinson-White syndrome during sinus rhythm is well known. The ventricular complex is a fusion beat resulting from ventricular activation by two wave fronts. The degree of preexcitation (amount of muscle activated through the accessory pathway) is variable and depends on many

factors. Foremost among these are the distance between the sinus node and atrial insertion of the accessory pathway and, more important, the differences in refractory period duration and in conduction time through the normal pathway and the accessory pathway. Other things being equal, a patient with rapid (enhanced) AV nodal conduction will have a smaller delta wave than a patient with slow conduction through the AV node. Moreover, if there is total block at the AV node or His-Purkinje system, the impulse will be conducted exclusively via the accessory pathway bundle. Consequently, the QRS complexes are different from fusion beats, although the direction of the delta wave remains the same. Moreover, the QRS complexes are as wide as (and really simulating) those produced by artificial or spontaneous beats arising in the vicinity of the ventricular end of the accessory pathway (Figure 1.36).

Figure 1.36

Wolff-Parkinson-White syndrome on ECG.



The original ECG classification of manifest Wolff-Parkinson-White syndrome proposed by Rosenbaum et al. is now of historical interest only. Nevertheless, initial noninvasive determination of the anatomic position of the accessory pathway is of great clinical importance because of the introduction of surgical and catheter ablative techniques for symptomatic cases of preexcitation. Left free-wall accessory pathways are characterized by isoelectric and even positive delta waves in leads I, aVL, V_5, or

V_6. Lead V_1 shows R or Rs complexes. During sinus rhythm, the electrical axis may be normal, but when atrial fibrillation develops and exclusive accessory pathway conduction occurs, the EA is deviated to the right and inferiorly. Posteroseptal accessory pathways show negative delta waves in leads III and aVF and R waves in V_2. An Rs (or RS) wave in V_1 suggests a left posteroseptal pathway; a QS complex in the same lead may correspond to a right posteroseptal pathway. Right freewall accessory pathways display an LBBB pattern defined, for purposes of accessory pathway localization, by an R wave greater than 0.09 s in lead I and rS complexes in leads V_1 and V_2 with an electrical axis ranging between +30 and -60°.

Right anteroseptal accessory pathways show an LBBB pattern (as defined) with an electrical axis ranging between +30 and +120°. A q wave may be present in lead aVL but *not* in leads I and V_6. Mixed patterns resulted from the existence of two separate accessory pathways. Since accessory pathways can traverse almost any part of the atrioventricular annulus, this classification is obviously insufficient when catheter ablation is contemplated.

As mentioned earlier, multiple algorithms have been proposed. Since the most useful are complex, electrocardiographers find them difficult to memorize. They are also not completely satisfactory, since smaller degrees of preexcitation seem to limit diagnostic accuracy, and the polarity of delta waves [positive, biphasic (+ or -), negative, and isoelectric] has to be properly categorized.

Step 1: Analysis of R/S ratio in V2.
Step 2: Existence of positive (+) delta wave in lead III (initial 40 ms).
Step 3: Existence of positive or negative (-) delta wave in V1 (initial 60 ms).
Step 4: Delta-wave polarity in aVF (initial 40 ms) or analysis of R/S ratio in V1 (± = biphasic or isoelectric).

Wide QRS Complexes Produced by Ventricular Pacing from Different Sites

In determining the location of the stimulating electrodes, one should take special care not to consider that the distortion produced by large unipolar spikes constitutes parts of the pacing-induced QRS complexes. It is best *not* to describe the electrically produced ventricular beats as having an RBBB or LBBB morphology, since what is relevant is the polarity of the *properly positioned* V_1 and V_2 electrodes and

the direction of the EA. For example, endocardial or epicardial stimulation of the *anteriorly* located right ventricle at any site [apical (inferior), or mid/outflow tract (superior)] yields predominantly negative deflections in the right chest leads due to the *posterior* spread of activation. The reverse (positive deflections in V_1 and V_2) occurs when the epicardial stimulation of the superior and lateral portions of the posterior left ventricle by catheter electrodes in the distal coronary sinus or great and middle cardiac veins (or by implanted electrodes in the nearby muscle) results in *anteriorly* oriented forces. Right ventricular apical pacing may produce positive deflections in V1 if this lead is (mis)placed above its usual level. On the other hand, *superior* deviation of the electrical axis only indicates that a spatial *inferior* ventricular site has been stimulated, regardless of whether this site is the apical portion of the right ventricle or the inferior part of the left ventricle, the latter being paced through the middle cardiac vein. Conversely, an *inferior* vertical axis is simply a consequence of pacing from a *superior* site, which can be the endocardium of the RV outflow tract or the epicardium of the posterosuperior and lateral portions of the left ventricle. The changes produced on the basic ECG patterns of paced beats produced by MI were briefly discussed in the section of LBBB and MI. The method discussed above to locate the site of impulse initiation during pacing is simpler than the more complicated ones used to determine the ventricular sites of exit from accessory pathways (crossing the AV junction), which require the use of right anterior oblique and, specially, left anterior oblique projections. The currently used nomenclature for accessory pathway location was discussed recently and challenged by a group of notable experts in the field of preexcitation

Left Atrial Hypertrophy

With help using M-mode echocardiography as the "gold standard," it has been evaluated the specificity and sensitivity of the most important clues for determining left atrial hypertrophy. These included:

- P wave duration greater than 0.11 s and notched P wave with an interpeak interval in excess of 0.04 s
- negative phase of P in V_1 longer than 0.04 s and greater than 1 mm in lead V_1.

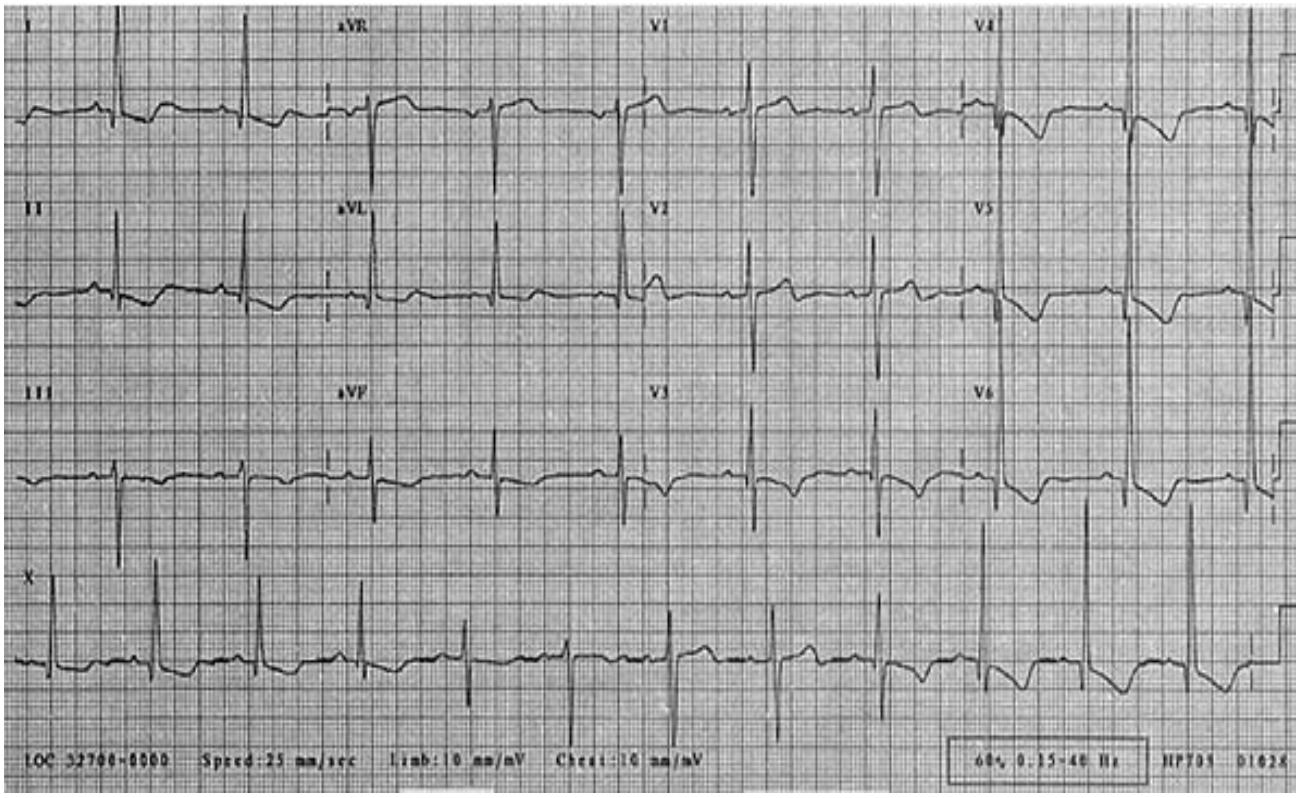
There are, however, problems when applying these criteria in a given ECG. A negative P wave in lead V1 may reflect improper (high) placement of this lead, a common error made by ECG technicians. Generally, if the previously mentioned findings are found in patients with LV enlargement or mitral stenosis, left atrial hypertrophy is most likely present, but in their absence, such findings usually indicate an intra atrial conduction defect. In any case, the ECG pattern of left atrial hypertrophy results from a hypertrophy-induced (stretching) intraatrial conduction delay.

Left Ventricle hypertrophy

Echocardiography is also a better method for the serial follow-up of changes during progression or regression of LV hypertrophy. Multiple criteria have been proposed to diagnose LV hypertrophy using necropsy or echocardiographic information. Of these, the Sokolow-Lyon criterion (SV_1 +RV5-6 35 mm) is the most specific (>95 percent) but is not very sensitive (>45 percent) (Figure 1.37).

Figure 1.37

Left ventricular hypertrophy



The Romhilt-Estes score has a specificity of 90 percent and a sensitivity of 60 percent in studies correlated with echocardiography (Table 1.5).

Table 1.5.

Point Score System of Romhilt and Estes for Diagnosis of Left Ventricular Hypertrophy

1. Amplitude, 3 points Any of the following:
    a. Largest R or S wave in the limb leads 20 mm
    b. S wave in V1 or V2 30 mm
    c. R wave in V5 or V6 30 mm
2. ST-T-segment changes (typical pattern of left ventricular strain with the ST-T-segment vector shifted in direction opposite to the mean QRS vector)
    - Without digitalis, 3 points
    - With digitalis, 1 point
3. Left atrial involvement, 3 points Terminal negativity of the P wave in V_1 is 1 mm or more in depth with a duration of 0.04 s or more
4. Left-axis deviation: -30° or more, 2 points
5. QRS duration 0.09 s, 1 point
6. Intrinsicoid deflection in V5, V6 = 0.05 s, 1 point

Note: sensitivity, 54%; specificity, 97%.

The following are some of the other criteria: The Casale (modified Cornell) criterion ($RaVL+SV_3$ >28 mm in men and >20 in women) is somewhat more sensitive but less specific than the Sokolow-Lyon criterion. The Talbot criterion (R >16mm in aVL) is very specific (> 90 percent), even in the presence of MI and ventricular block, but not very sensitive. The Koito and Spodick criterion ($RV_6 > RV_5$) claims a specificity of 100 percent and a sensitivity of more than 50 percent. According to Hernandez Padial, a total 12-lead QRS voltage of greater than 120 mm is a good ECG criterion of LV hypertrophy in systemic hypertension and is better than those most frequently used. With echocardiography as the "gold standard," several authors postulated ECG criteria for diagnosis of LV hypertrophy in the presence of complete LBBB and LAFB (Table 1.6).

Table 1.6

Criteria for Diagnosis of Left Ventricular Hypertrophy in Presence of Complete Left Bundle Branch Block

1. RaVL 11 mm
2. Electrical axis 40° (or S2 R1)

3. SV1 + RV5 or RV6 40 mm
4. SV2 30 and SV3 25 mm

Note: Left ventricular hypertrophy diagnosed by echocardiography when left ventricular mass is g/m2 or more.

Processes producing or leading to RV hypertrophy and enlargement

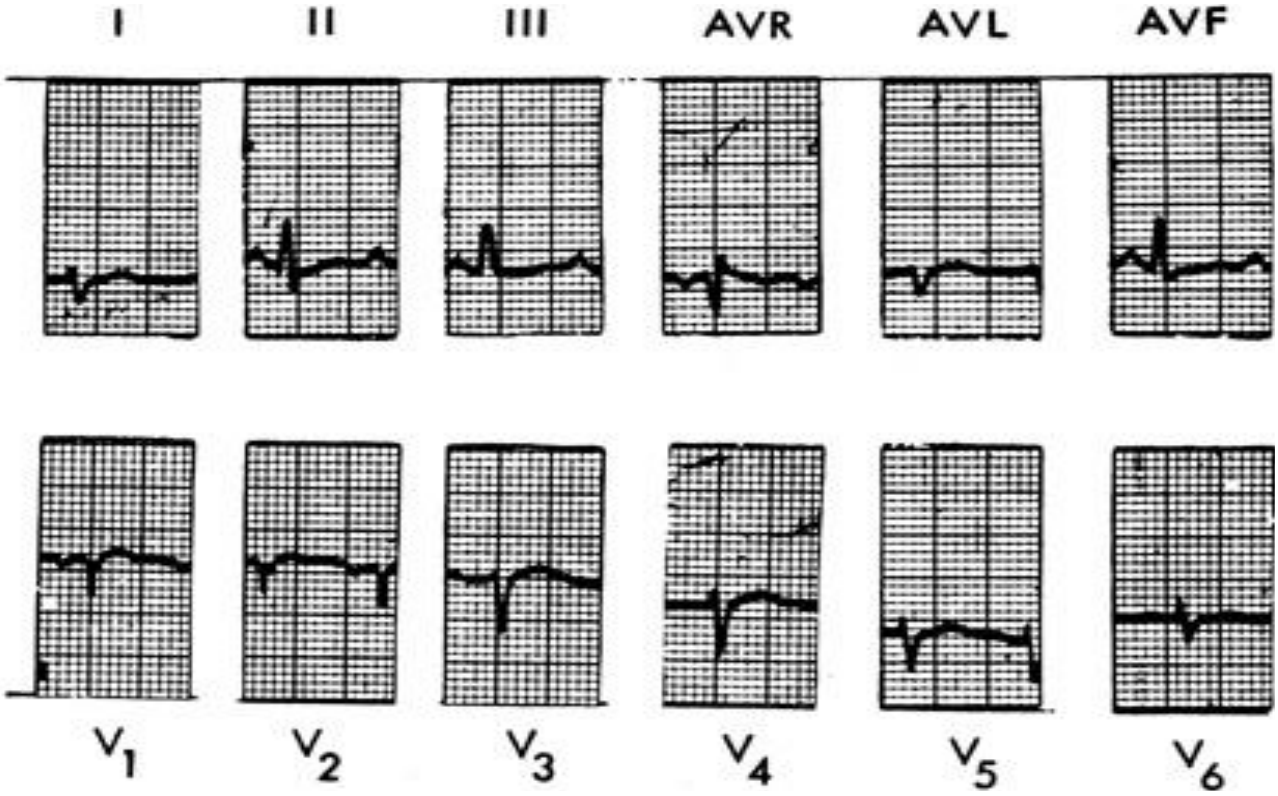
RV hypertrophy is manifest in the ECG only when the RV forces predominate over those of the left ventricle. Since the latter has, roughly, three times more mass than the former, the right ventricle may double in size (when the left ventricle is normal) or triple its weight (when there is significant LV hypertrophy) and still not result in the necessary requirements to pull the electrical forces anteriorly and to the right. For these reasons, RV hypertrophy cannot be recognized easily in adult patients. Despite these limitations, the ECG manifestations of RV hypertrophy or enlargement can be subdivided into the following main types1:

- the posterior and rightward displacement of the QRS forces associated with low voltage, as seen in patients with pulmonary emphysema,
- the incomplete RBBB pattern *with right-axis deviation* occurring in patients with chronic lung disease and some congenital cardiac malformations resulting in volume overloading of the right ventricle (Figure 1.38),
- the true posterior wall MI pattern with normal to low voltage of the R wave in V1 of mitral stenosis
- the classic RV hypertrophy and strain pattern seen in young patients with congenital heart disease (producing pressure overload) or in adult patients with high-pressure ("primary" pulmonary) hypertension.

False patterns of RV hypertrophy may occur in patients with true posterior (basal) MI, complete RBBB with LPFB, and Wolff-Parkinson-White syndrome resulting from AV conduction through left free wall or posteroseptal accessory pathways.

Figure 1.38.

Slight right-axis deviation with small rS complexes in lead I, an electrically vertical heart position, overall tendency to low voltage, and rS complexes in all chest leads in patient with pulmonary emphysema



Electrolyte imbalances

Because multiple factors can affect ventricular repolarization in diseased hearts, the finding characteristic of a specific electrolyte abnormality may be modified, and even mimicked, by various pathologic processes and the effects of certain drugs. In practice, the major problem with the ECG diagnosis of electrolyte imbalance is not the negative ECG with abnormal serum values but the production of similar changes by other conditions in patients with normal serum values.

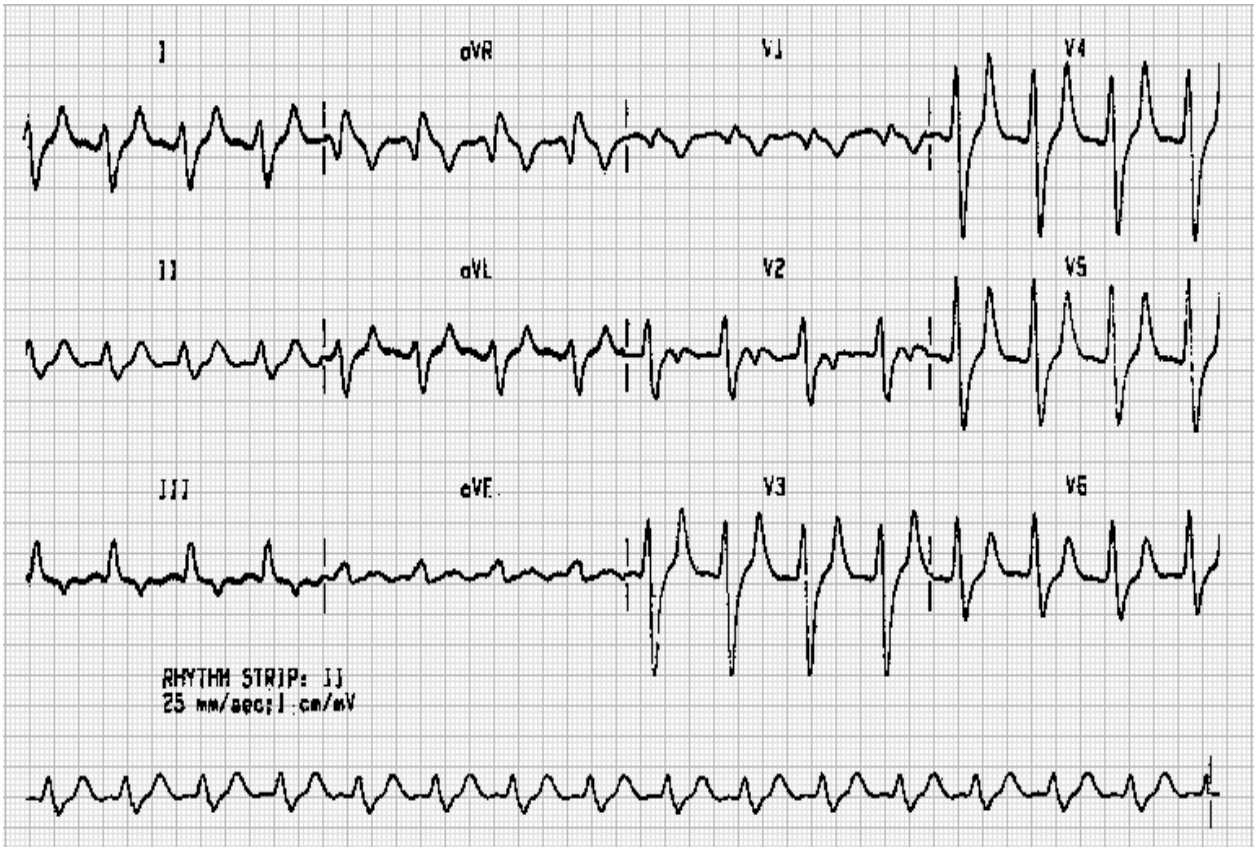
Hyperkalemia

The initial effect of acute hyperkalemia is the appearance of peaked T waves with a narrow base. The diagnosis of hyperkalemia is almost certain when the duration of the base is 0.20 s or less (with rates between 60 and 110 beats per minute). As the degree of hyperkalemia increases, the QRS complex widens, with the electrical axis usually being deviated abnormally to the left and only rarely to the right. In addi-

tion, the PR interval prolongs, and the P wave flattens until it disappears (Figure 1.39).

Figure 1.39

ECG in patient with hyperkalemia



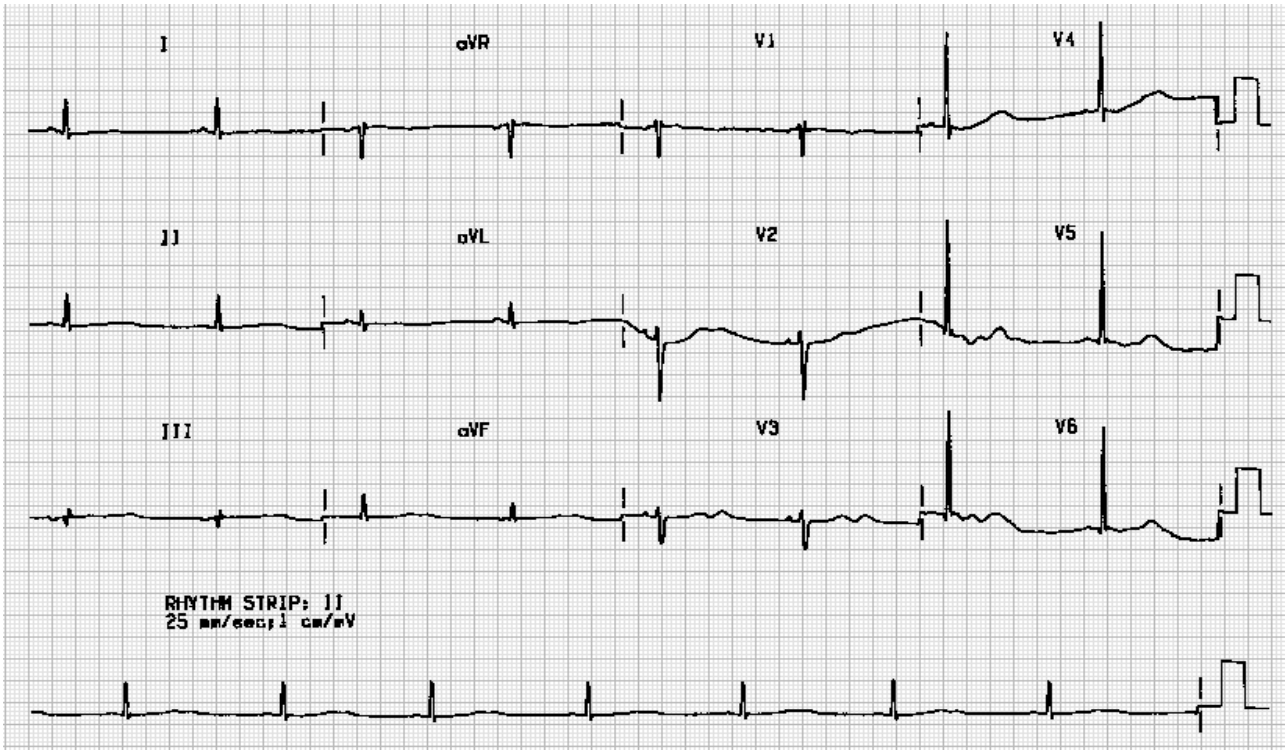
If untreated, death ensues either due to ventricular standstill or coarse, slow ventricular fibrillation. Death also can result if wide QRS complexes occurring at fast rates are diagnosed as ventricular tachycardia and the patient is treated with antiarrhythmic drugs. On the other hand, class IA, IC, and III drugs as well as large doses of tricyclic antidepressants (especially when ingested for suicidal purposes) also can produce marked QRS widening. These processes, however, do not coexist with narrow-based, peaked T waves. Rarely, hyperkalemia produces (in the absence of coronary artery disease) a degree of ST-segment elevation in the right chest leads capable of suggesting anteroseptal myocardial injury.

Hypokalemia

The abnormal and delayed repolarization that occurs in hypokalemia is best expressed as QU, rather than QT, prolongation, since at times it can be difficult to differentiate between notching of the T wave and T- and U-wave fusion (Figure 1.40).

Figure 1.40

ECG in patient with hypokalemia



On the basis of the previously mentioned M cells, these U waves are part of notched T waves, suggesting that that term be used in place of U. As the serum potassium level falls, the ST segment becomes progressively more depressed, and there is a gradual blending of the T wave into what appears to be a tall U wave. An ECG pattern similar to that of hypokalemia can be produced by some antiarrhythmic drugs, especially quinidine and, experimentally, DL-sotalol. In any case, when repolarization is greatly prolonged, ventricular arrhythmias, including the so-called torsades de pointes, can occur.

Hypomagnesemia does not produce QU prolongation unless the coexisting hypokalemia (with which it is almost invariably associated) is severe. Long-standing and very marked magnesium deficiency lowers the amplitude of the T wave and depresses the ST segment. It may be difficult to differentiate the changes produced by magnesium from those produced by potassium. For this reason, it has been stated that hypomagnesemia does not cause any changes in the ECG.

Hypermagnesemia

Similarly, in clinical tracings, the effects of hypermagnesemia on the ECG are difficult to identify because the changes are dominated by calcium. According to

some authors, administration of intravenous magnesium to patients with normal ECGs may shorten the QT interval. Other authors found no effects on ventricular refractoriness that are reflected by changes in the QT interval. Intravenous magnesium given to patients with torsades de pointes controls the arrhythmia in a high percentage of patients without changing the prolonged QT interval significantly. The calcium-blocking activity of magnesium was suggested to be one of the mechanisms responsible for this antiarrhythmic activity.

Hypercalcemia

During sinus rhythm with normal rates, the QT interval is short. In some cases, the Q-to-apex of T intervals is also short. If factors known to modify the QT interval are not present, it has been said that a reasonably accepted correlation exists between the duration of the interval and serum calcium levels. Occasionally, the ST segment disappears, and the T waves may become inverted in left and right chest leads. Digitalis also shortens the QT interval but produces its characteristic "effects" in leads where the R waves predominate. The classic upward concavity of the ST segment is seen in the left chest leads in patients with LV hypertrophy and in leads V_1 and V_2 when there is RV hypertrophy (with predominantly positive deflections in these leads).

Hypocalcemia

The typical ECG pattern of hypocalcemia consists of QT prolongation at the expense of the ST segment. The T wave is usually of normal width but can be narrow if there is coexisting (moderate) hyperkalemia. A very marked injury (with the so-called hyperacute ST-T changes) can produce a similar pattern, but in such cases the T wave, though peaked, is not as narrow based. It has been said that hypocalcemia per se does not produce T-wave inversion. When present, the latter is usually a reflection of coexisting processes such as LV hypertrophy and incomplete LBBB. An ECG pattern similar to that of hypocalcemia can be produced by some organic abnormalities of the central nervous system and by congenitally prolonged QT intervals.

QT Interval: Normal and Prolonged

The QT interval is measured from the beginning of the q wave to the end of the T wave. The latter may be difficult to define. The point at which the maximal downslope of the T wave crosses the baseline helps to identify the end of this wave. The QT interval is affected by autonomic tone and cathecolamines and has day-night differences. It varies with heart rate and sex. Several formulas have been proposed to take these variables into account and provide a corrected measurement (QTc interval). In general, the unadjusted (noncorrected), usually resting QT interval decreases from ±0.42 s at rates of 50/min to ±0.32 s at 100/min to ±0.26 s at 150/min. During exercise, the rate becomes faster; the QTc first increases until reaching, approximately, a rate of 120/min, thereafter again decreasing. Although the value of the normal QTc is open to question, it is still used in routine computer interpretations. Because the 12-lead ECG shows a normal degree of QT and QTc dispersion, indexes have been used to quantify the extent of heterogeneity in ventricular repolarization. The difference between the longest and shortest QT interval is referred to as *QT dispersion*.

Since 1990 it has been used as a prognostic marker not only in patients with prolonged QT intervals but also in those with acute MI. The upper limits of normal vary with different investigators; a value of 65 may be an acceptable compromise. Inferred from the oncoming section on spatial vectorcardiography, the fact is that a truly *spatial* QRS-T loop cannot yield *abnormal* QT dispersion, for in planar projections of this spatial loop (as well as in the standard and unipolar extremity leads of the ECG) the shortest interval occurs because the terminal forces are perpendicular to the plane or derived lead. On the other hand, if precordial leads are considered scalar leads capable of recording (as stated in a previous section) local potentials with different durations, then QT dispersion is a reality. The M-cell studies allow for the differentiation of this global "dispersion" (derived from *multiple* leads) from "local" transmural dispersion in *single* leads reflecting the time elapsing between the peak of the T wave (given by the end of the composite epicardial action potentials) and the end of the T wave (given by the end of the composite M-cell action potentials). The QT intervals are shortened with hypercalcemia, pure hyperkalemia, digoxin, and aci-

dosis. Prolongation of the QT interval may be congenital (Romano-Ward syndrome) (Figure 1.41) or acquired (amiodarone taken) and is an important marker for malignant ventricular arrhythmias. A partial list of conditions causing a prolonged QT or, in some instances, prolonged QU intervals (delayed repolarization) is given in Table 1.7.

Figure 1.41.

Prolonged QT interval on ECG in patient with Romano-Ward syndrome

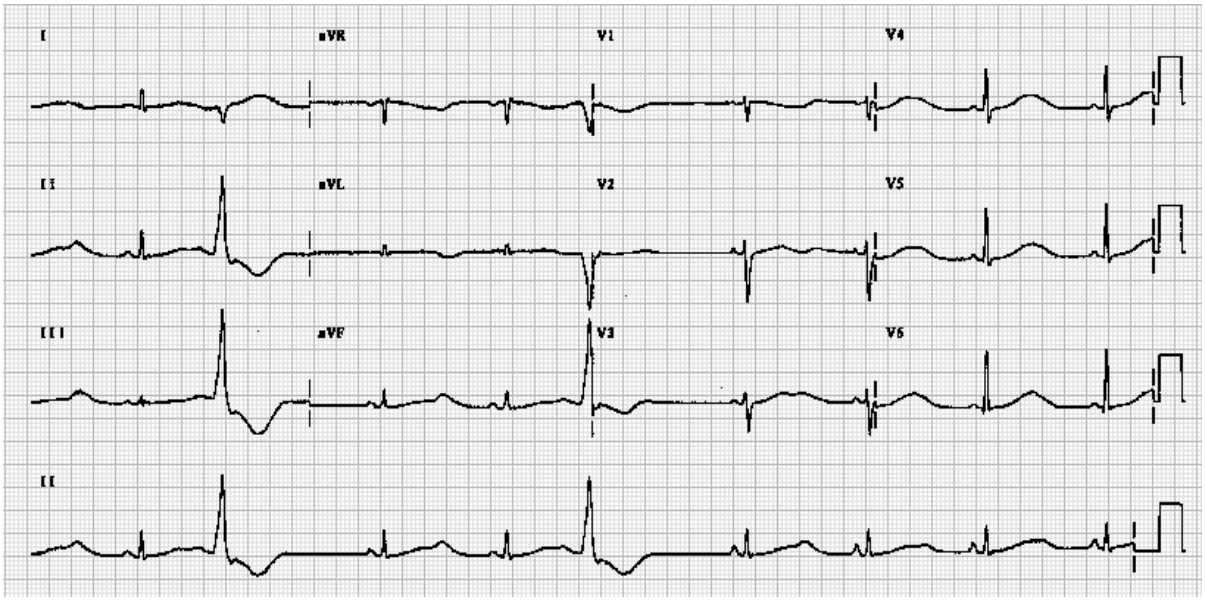


Table 1.7

Acquired QT Prolongation Usually Bradycardia-and(or) Pause-Dependent

1. Electrolyte disturbances
   a. Hypokalemia
   b. Hypocalcemia
   c. Hypomagnesemia
2. Drugs
   a. Class IA antiarrhythmic agents (quinidine, disopyramide, procainamide)
   b. Class III antiarrhythmic agents (amiodarone, sotalol)
   c. Psychotropic drugs
3. Central nervous system diseases
   a. Subarachnoid hemorrhage
   b. Ruptured berry aneurysm
   c. Cryptococcal meningitis
4. Congenital syndromes

5. Electrocardiographic ischemia

6. Arrhythmias

   a. Posttachycardia syndrome
   b. Cardiac arrest of any etiology
   c. Chronic idioventricular rhythms

7. Hypothermia

Congenital Long QT Syndrome

Various mutations in ion channel genes cause congenital long QT syndrome (QTc > 0.46 seconds). Five to 10% of gene carriers for this disorder, however, have QTc durations within normal range. Patients with the syndrome may also have marked sinus bradycardia. The T wave is often notched or biphasic, or it alternates its morphology or polarity (T-wave alternans). Prominent U waves may also be present. The extreme prolongation of the QT interval can result in pseudo 2:1 AV block when every other P wave falls during or before the preceding T wave. The long QT-3 variety seems to be caused by mutations in the SCN5A gene, which may also underlie the Brugada syndrome.

Short QT interval

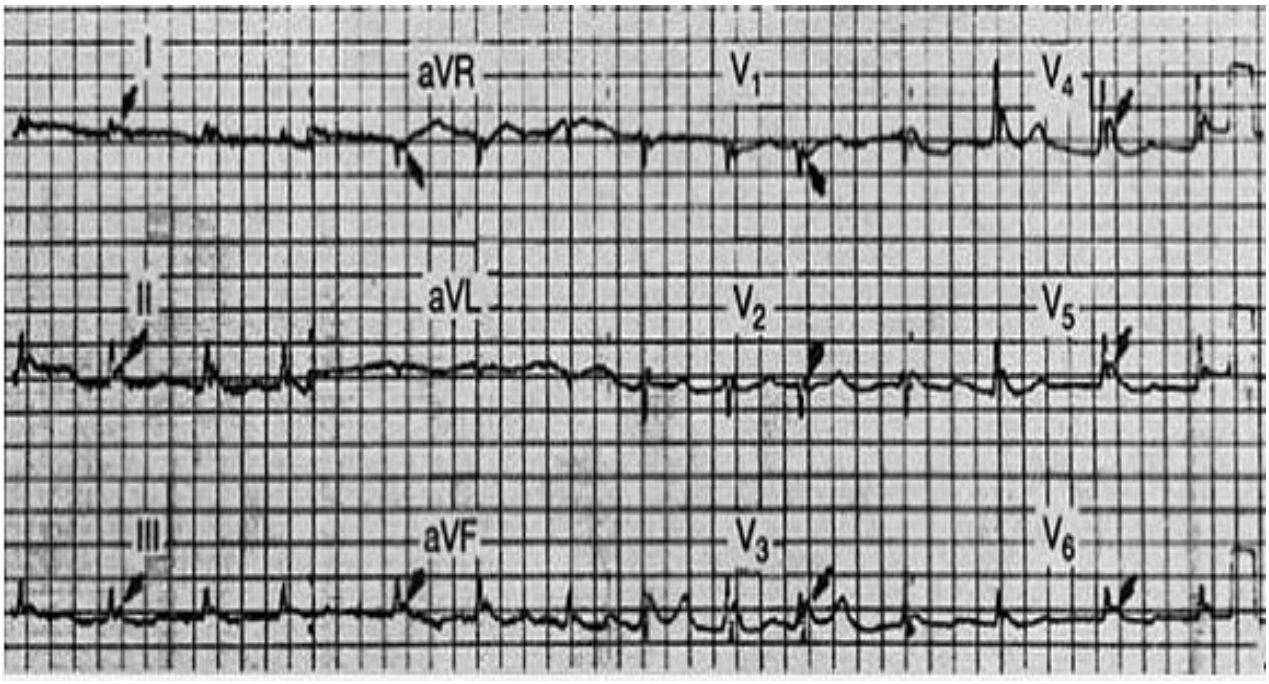
In the short QT syndrome, QTc intervals measure less than 320 milliseconds. Patients (including children) have a high incidence of ventricular tachyarrhythmias, syncope, sudden cardiac death, or atrial fibrillation. The condition may be associated with missense mutations in KCNH2 (HERG).

Hypothermia.

Characteristic ECG changes develop when the body temperature drops to approximately 30°C. The QT interval becomes prolonged. In addition, a deflection, called an *Osborn wave*, appears in a place said to be located between the end of the QRS complex and the beginning of the ST segment (Figure 1.42). This deflection has been attributed to delayed depolarization, to a current of injury, or to "early" repolarization. In leads facing the left ventricle, the deflection is positive, and its size is inversely related to body temperature. The role played by the intramyocardial M cells in its genesis has been discussed previously.

Figure 1.42

Electrocardiogram from a patient with hypothermia



Drug Effects

Therapeutic or toxic cardiac effects of various medications may cause ECG changes.

Digitalis accelerates ventricular repolarization, particularly in the subendocardium. This is first represented on the ECG by flattening of the T wave and prominent U waves with shortening of the QT interval. The most typical change, however, consists of a coved ST-segment depression. The T wave appears biphasic, with its first portion negative and merging with the ST segment. These repolarization changes do not correlate well with therapeutic or toxic blood levels of the drug. Digitalis intoxication is often manifested by arrhythmias similar to those of severe hypokalemia (i.e., atrial tachycardia with block and AV dissociation). Characteristics of digitalis-induced atrial tachycardia include atrial rate between 140 and 250 beats per minute, inferior-to-superior direction of atrial activation, and 2:1 AV block.

Propafenone and Class Ic Antiarrhythmic Drugs. Propafenone, flecainide, and encainide prolong the AH and HV intervals and the atrial and ventricular refractory periods. The QRS duration is increased. All class Ic drugs may induce ventricular arrhythmias (proarrhythmic effect). The JT interval is not prolonged.

Class III Antiarrhythmic Drugs. Dofetilide is pure class III antiarrhythmic agent that prolongs the refractory period and action potential duration. Dofetilide can also prolong the QT interval. Sotalol is a OI-blocker with class III antiarrhythmic action that prolongs the QT interval.

Transplanted Hearts. In transplant recipients, the most prevalent abnormality is incomplete or complete RBBB. The PR and QT intervals are shorter, and the precordial transitional zone is displaced to the left. The shift in the transitional zone and the conduction delay of the right bundle would indicate a clockwise rotation of the heart on its vertical axis. The increased prevalence of RBBB during follow-up, however, may be associated with mildly increased pulmonary pressures. After heart transplantation, the sudden appearance of first-degree AV block should suggest acute graft rejection

Pulmonary Abnormalities

Acute Cor Pulmonale. The ECG changes in acute cor pulmonale reflect acute pulmonary hypertension with dilation of the right chambers and perhaps myocardial ischemia. The ECG signs significantly associated with pulmonary embolism include sinus tachycardia, the classic right heart strain pattern $S_IQ_{III}T_{III}$, and atrial tachyarrhythmias. Also common are right QRS axis deviation and complete or incomplete RBBB, signs that correlate with the extent of embolization.

Pulmonary Emphysema. The overinflated lungs of pulmonary emphysema lower the diaphragm. The heart and the cardiac electrical axis become more vertical and rotate clockwise, with the QRS axis at < 90 degrees in the frontal plane. Other changes include the following: prominent P waves (>0.25 mV; indeed, a P pulmonale is a better predictor of pulmonary emphysema or low diaphragm position than of right atrial enlargement); exaggerated atrial repolarization with Ta waves producing ST-segment depression in inferior leads; decreased progression of R-wave amplitudes in precordial leads; and low voltage of the QRS complexes, especially in the left precordial leads.

Neurogenic Manifestations. Patients with acute or chronic diseases of the nervous system may show repolarization changes in the ECG. Negative T and U

waves, ST-segment changes, and QT prolongation may appear during subarachnoid hemorrhage, ischemic stroke, radical neck dissection, spinal cord trauma, electroconvulsive therapy, deep brain stimulation, and emotional stress.

Misplacement of Electrocardiographic Leads is common. A study of 11,432 ECGs detected reversals involving the left arm and foot or adjacent precordial electrodes in 2% of the recordings.

Reversal of the Right and Left Arm Cables. When the electrodes attached to the arm cables are reversed, negative P and T waves and a predominantly negative QRS complex are present. Thus, the limb leads suggest the diagnosis of dextrocardia. The precordial leads, however, show the normal progression of R wave through V_6.

Misplacement of Precordial Lead Electrodes

Variations included changes in R-wave amplitude, ST segments, Q waves, and in the transition zone. When precordial electrodes are misplaced in a high position, QS complexes or low-voltage R waves may appear, and a differential diagnosis with anterior infarction must be made. The use of device-guided lead placement improves accuracy and reproducibility in interpretation of precordial waveforms

Artifacts.

During the last few years, the number and types of instruments used for noninvasive and invasive (electrical and nonelectrical) study of cardiac functions have multiplied. Naturally, physicians and hospital administrators have concentrated their attention on them. Technicians have been more interested in working in these more lucrative services. Such factors, and others, have downgraded the importance of recording 12-lead ECGs, relegating them to less qualified personnel. Not surprisingly, the quality of technicians and of the ECG that they record has deteriorated in many centers. Optimal quality can only be achieved if the parties involved understand what is happening. The following are some of the artifacts commonly seen in current routine 12-lead ECGs. They are important because they can confound the interpreter and, worse, the computer program.

Muscle Tremor and Alternating-Current Interference. These are the most frequently encountered artifacts because some patients will continue to have disease

processes producing tremor and because the amount of electronic equipment causing interference in a hospital environment has increased.

Improper Limb-Lead Positioning. This has become more frequent after relaxation of quality control, especially in hospitals with inadequate standards for hiring technicians and with poor on-site training. Mixing up the cables from the ECG machine has gone beyond switching the right arm and left arm cables. Not frequently recognized in ECG textbooks is the incontrovertible fact that in some centers even the "sanctity" of the attachment of the right leg (ground) cable to the right leg has been violated.

Variations in Precordial-Lead Placement. This is a problem more common now than when, in 1961, Simonson noted the considerable variation in chest lead placement in the same patient by different technicians and even by the same technician in several ECGs in the same patient. Perhaps the frequency of precordial-lead misplacement is greater than that of somatic tremor.

False Variations in Voltage. In several patients, ECGs taken weeks apart showed markedly different QRS voltages. The latter were sometimes of enough magnitude to cause a pseudonormalization of a ventricular hypertrophy pattern. There had been no changes in hemodynamics, but different types of ECGs were used. A study of this problem demonstrated that electrocardiographic data had a different voltage depending on whether they were recorded and displayed on an analog electrocardiograph or on a digital electrocardiograph. Thus, if there is a statistically significant difference among ECGs, the serial comparisons must be done with the same machine. Moreover, criteria for voltage are only applicable to the type of instrument with which the data were gathered. In addition, overshooting, overdamping, and running down of the standardization battery can cause significant changes in QRS voltage and ST segments.

High-Resolution Electrocardiography and Body Surface Mapping

High-Resolution Electrocardiography. Potentials generated by the His-Purkinje system and by depressed ventricular myocardium produce a very small sig-

nal that is not detected by standard recording techniques. This finding prompted the development of special techniques:

- temporal averaging (usually referred to as signal averaging), applicable only to repetitive ECG signals;
- spatial averaging, which can record the His-Purkinje signal and late potentials on a beat-to-beat basis.

Signal averaging (the most often utilized technique) can analyze potentials in time domain, frequency domain, or a combination of both. An increased incidence of low-amplitude, high-frequency components within the QRS complex is common in patients with acute or remote myocardial infarction. Signal-averaged ECG is an interesting research tool with limited clinical applications.

Body Surface Mapping records cardiac electric events with numerous electrodes (from 16 to 200), thus adding information to that of the standard ECG. Cardiac field mapping provides details on the spatial and temporal sequence of cardiac excitation and recovery. Local intraventricular conduction disturbances, preexcitation, premature ventricular beats, and repolarization disorders can be precisely located. Visual inspection of the ECG maps does not suffice for diagnostic purposes; sophisticated statistical and deterministic models are necessary, and these requirements limit this technique's clinical usefulness.

Computer applications

It has been almost 40 years since the first attempts were made to apply computer technology to the interpretation of ECGs. Today its use is universal. In general, computer systems for true analysis of ECGs have, as their main component, a program usually having the following four basic functions:

- the measuring of ECG parameters, which includes an automatic wave-frontrecognition section and a measurement section that extracts the wave fronts, a set of values, and control,
- the interpretation of previously acquired information, responsible for the final statements generated by the program,
- the identification of various rhythms, both normal and abnormal,

- the comparison with previous ECGs to recognize significant changes.

There is a lack of standardized, universally agreed-on diagnostic terms and criteria. This problem, however, is not solely that of computers but is related to all ECG interpretations, whether performed by individuals or by machines. It has to be remembered that the program used depends on criteria imposed on it by human programmers. Physicians should insist that the program selected has to be "tuned in" with the operational environment (e.g., community hospital or teaching institution, urban center or rural areas, etc.) in which it has to perform. Once a program has been selected and is in use, it requires initial and periodic evaluation. The most practical method consists of accepting as standard constrained human observers, the constrained observers being given a set of measurements or criteria agreed on before the evaluation. Proper computerization has the following definite advantages:

- speed in providing reports with the resulting improved turnaround time,
- optimal utilization of emergency ECG services,
- reproducibility of measurements,
- improvements in quality control,
- possible decrease in physician's reading time and more consistency in interpretations,
- enhancement of the capacity to handle large volumes of ECGs,
- substantial improvement in record storage and retrieval with better comparison with previous tracings.

Administrators are usually the ones selecting equipment, and frequently they know nothing about its medical performance. They usually use standard cost-effective, not medically-effective methods. That is, the economics involved-initial investment, operational costs, payroll, overhead, and professional fees-become priorities. This is important because it was estimated that even 10 years ago more than 40 percent of all ECGs recorded in the United States were obtained by some type of automatic system. Presently, however, this figure is reaching 100 percent. Finally, em-

phasis should be placed on the obvious: All computer ECG interpretations, particularly those of rhythm disturbances, must be checked by a physician qualified to interpret ECGs and with an in depth knowledge of the program used. Decisions based on a computerized interpretation may, on occasion, lead to improper patient care. This also can have medicological implications. Of clinical importance was the report finding that computer interpretations of ECGs obtained 1 min apart were grossly different in 36 of 92 (39 percent) unselected pairs of tracings. The latter refers to only one program but nevertheless should be an impetus to designers and manufacturers to improve their product and a warning to those who rely, exclusively, on computer interpretations.

The ACC/AHA Task Force on Guidelines for Electrocardiography states: "There is no computer program that can replace the skilled physician." In conclusion, cardiology fellows in training should interpret ECGs without a printed computer interpretation rather than by having to evaluate the latter.

CHAPTER 2

RHYTHM AND CONDUCTION DISCORDERS. PRINCIPAL MECHANISMS

Foreword

Because of the increasing availability of sophisticated electrophysiologic techniques for the study of cardiac tissues both in vivo and in vitro and the ability to study arrhythmias and conduction disturbances both in experimental models and in patients, knowledge about the mechanisms of arrhythmias and conduction disturbances has increased greatly. Although much is now known, much remains to be understood. Arrhythmias are due to normal or abnormal impulse generation, abnormal impulse conduction, or a combination of simultaneous abnormalities of impulse generation and conduction. This guideline provides an overview of these mechanisms and identifies the clinical arrhythmias with which they are thought to be associated. This is followed by a much more detailed discussion of these mechanisms as they are currently understood. The detailed discussion requires that the reader have a rudimentary knowledge of the basic cellular electrophysiology of the heart, including the ionic channels and membrane currents causing the resting potential and the cardiac action potential, as well as the mechanisms for automaticity and conduction. However, much of this material is included in a detailed discussion of the mechanisms of arrhythmias, since the chapter considers how alterations in normal electrophysiology lead to abnormal cardiac rhythms.

Causes of Arrhythmias

Normal or abnormal impulse initiation

Automatic Rhythms

Normal mechanism

Cardiac cells that normally are capable of developing spontaneous diastolic (phase 4) depolarization are called *pacemaker cells*. When pacemaker cells manifest spontaneous diastolic depolarization (Figure 2.1) and thus are responsible for generating the cardiac rhythm, the rhythm is classified as an *automatic rhythm*.

Normally, the dominant pacemaker of the heart is in the sinus node, which in adults fires at a rate of 60 to 100 beats per minute. Cells capable of developing spon-

taneous diastolic depolarization (i.e., of manifesting automaticity) also are normally found in the specialized fibers in the atria, the atrioventricular (AV) junction, and the His-Purkinje system. The normal rate of impulse formation in adults by these ectopic pacemakers is 40 to 60 beats per minute in the AV junction (the AV node and His bundle). Normal rates of more distally located ectopic pacemakers are probably 20 to 40 beats per minute in the bundle branches.

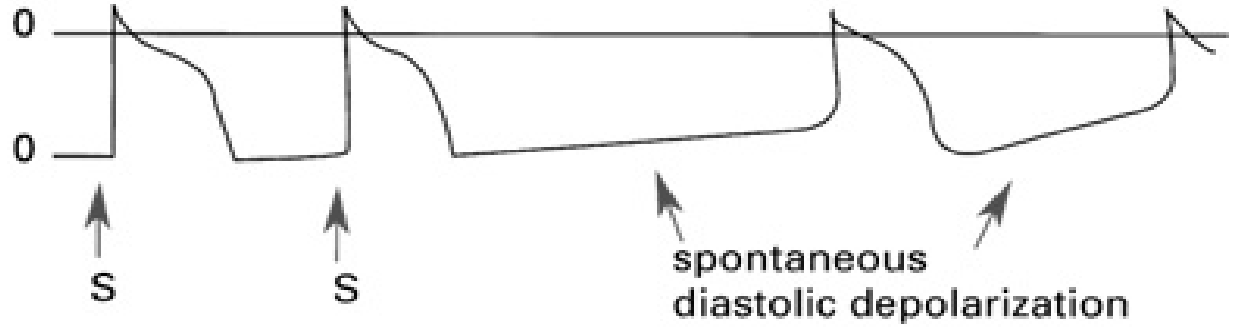
These ectopic (i.e., nonsinus) pacemakers also are called *latent* or *escape* pacemakers for two related reasons:

- The normal intrinsic rate of these pacemakers is lower than that of the dominant pacemaker, the sinus node,
- spontaneous diastolic depolarization of these latent or escape pacemakers normally is suppressed by the more rapid rate of the sinus node pacemaker through the active process of overdrive suppression.

Only when the sinus rate slows below the intrinsic rate of these ectopic pacemakers does "the next one in line" warm up and fire.

Figure 2.1

Spontaneous diastolic depolarization



Arrhythmias of the Sinus Node

An arrhythmia occurs when the sinus node pacemaker fires at a rate above 100 beats per minute (sinus tachycardia) or at a rate below 60 beats per minute (sinus bradycardia) and is still the dominant pacemaker of the heart (Table 2.1). These are called *arrhythmias resulting from normal automaticity*, since the ionic mechanism causing the pacemaker depolarization is unchanged from the normal sinus rhythm. A sinus tachycardia is usually an appropriate response to a precipitating factor (e.g., ex-

ercise, fever, hypotension), although on occasion it may be inappropriate, as in the presence of a sympathetic dysautonomia (inappropriate sinus tachycardia). By contrast, sinus bradycardia often reflects an abnormality not only of the sinus node pacemakers (they are too slow) but also of the latent or escape pacemakers (when the sinus rate slows abnormally, they do not escape). Sinus bradycardia may be due to an intrinsic abnormality of pacemaker cells, a parasympathetic dysautonomia (inappropriate sinus bradycardia), or an extrinsic factor such as suppression of automaticity by drug therapy (e.g., a beta-blocker, a $Ca2^{+}$ channel blocker, or an antiarrhythmic agent). For some patients, sinus bradycardia, particularly when it is present only at rest, may simply reflect a normal response to increased vagal tone, as in a well-trained athlete. Marked beat-to-beat variations in cycle length of the sinus rhythm, which are due virtually always to the influence of vagal tone on the pacemaker cells of the sinus node, also is considered an arrhythmia (sinus arrhythmia) even if the overall sinus rate is normal.

Table 2.1.

Types of Tachycardias and Their Selected Characteristics and Documented or Presumed Mechanism

Tachycardia	Mechanism	Origin	Rate Range, bpm	AV or VA Conduction
Sinus tachycardia	Automatic (normal)	Sinus node	≥100	1:1
Sinus nod re-entry	Re-entry	Sinus node and right atrium	110-180	1:1 or variable
Atrial fibrillation	Reentry	Atria	260-450	Variable
	Fibrillatory conduction	Pulmonary veins, SVC	?	Variable
Atrial flutter	Re-entry	Right atrium, leftatrium (infrequent)	240-350, usually 300± 20	2:1 or variable
Atrial tachycardia	Reentry	Atria	150-240	1:1, 2:1, or variable
	Automatic (normal or abnormal)	Atria	?	?
	Triggered	Atria	150-240	1:1, 2:1, or va-

	(DADs) to digitalis toxicity			riable
AV nodal reentry tachycardia	Re-entry	AV node with an atrial component	120-250, usually 150-220	1:1
AV reentry (WPW or concealed accessory AV connection)	Reentry	Circuit includes accessory AV connection, atria, AV node, His, Purkinje system, ventricles	140-250, usually 150-220	1:1
Accelerated AV junctional tachycardia	Automatic or triggered (Digitalis toxicity)	AV junction (AV node and His bundle)	61-200, usually 80-130	1:1 or variable
Accelerated idioventricular rhythm	Abnormal automaticity	Purkinje fibers	>60-?	Variable, 1:1, or AV dissociation
Ventricular tachycardia	Reentry	Ventricles	120-300, usually 140-240	AV dissociation, variable, or dissociation
	Automatic (rare) (normal or abnormal)	Ventricles	?	Variable,1:1, or AV dissociation
Bundle branch reentrant tachycardia	Reentry	Bundle branches and ventricular septum	160-250, usually 195-240	AV dissociation, variable, or 1:1
Right ventricular outflow tract	Triggered (DADs)	Right ventricular outflow tract	120-220	AV dissociation, variable, or 1:1
Torsades de pointes tachycardia	Triggered (EADs) (with re-entry)	Ventricles	>200	AV dissociation

Ectopic automatic rhythms

Arrhythmias occur when the site of the dominant pacemaker shifts to a site other than the sinus node (Table 2.1). The site of impulse initiation may shift from the sinus node to an ectopic (latent or escape) pacemaker if any of the following occur: (1) The intrinsic rate of the sinus node decreases, e.g., when pacemaker dysfunction is limited to the sinus node. (2) The intrinsic rate of the ectopic (latent or escape) pacemaker in-

creases, e.g., as a result of enhanced automaticity of latent pacemakers. During such rhythms, the sinus node is normally automatic, but overdrive suppression of the sinus node pacemaker usually occurs because the ectopic pacemaker fires at a more rapid rate. Alternatively, if the rate of the ectopic pacemaker is very fast, there may be entrance block into the sinus node, in which case exit block of the sinus impulses rather than overdrive suppression occurs. (3) The normal sinus impulse is prevented from being the dominant pacemaker of the heart because of sinus node exit block or sinoatrial block (i.e., the impulse cannot exit from the sinus node to excite the atria and subsequently the ventricles) or AV block (the impulse cannot excite the ventricles because of conduction block in the specialized AV conduction system, i.e., the AV node, His bundle, or both bundle branches). The automaticity at the ectopic pacemaker site is a result of the normal automatic mechanism; hence, these are arrhythmias caused by normal automaticity.

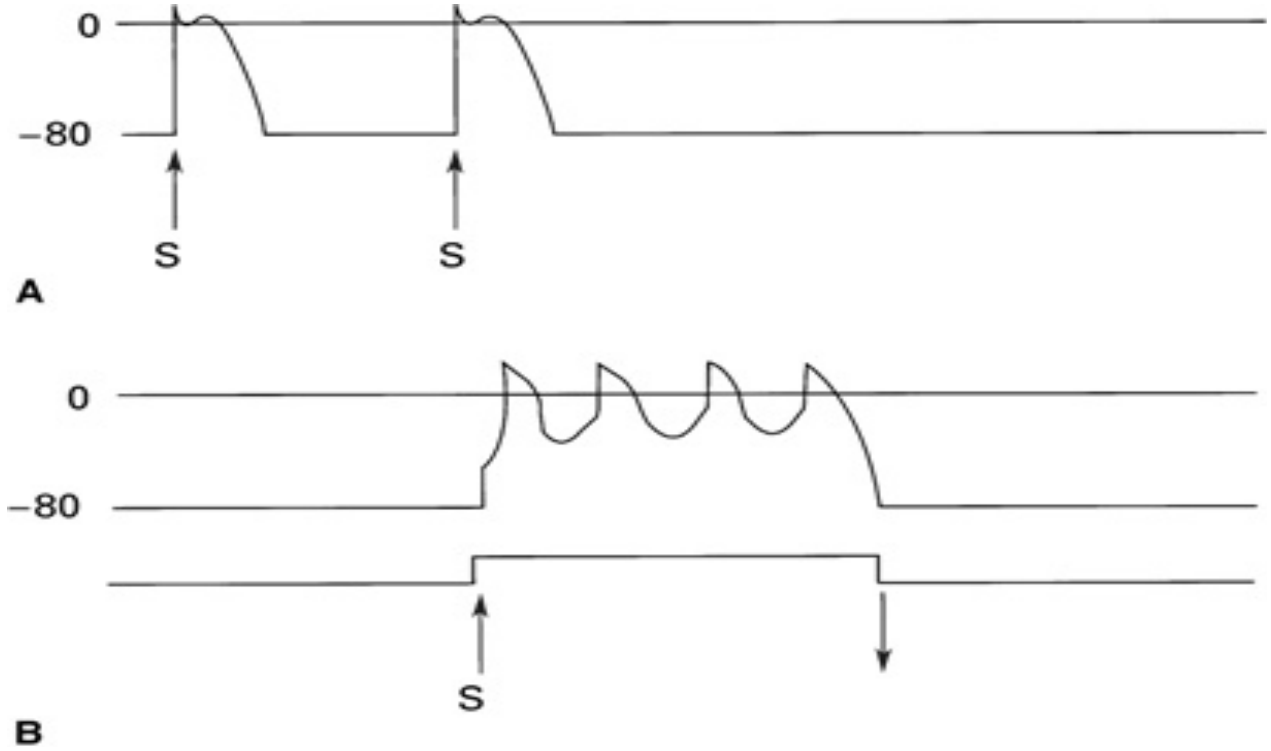
Abnormal mechanism

Typically, normal working atrial and ventricular myocardial cells do not develop automaticity. Thus, when they manifest normal transmembrane potentials, no evidence of spontaneous diastolic (phase 4) depolarization is present. Under certain conditions, however, these cardiac muscle fibers, as well as specialized atrial and ventricular fibers, can develop an abnormal type of automatic firing. This occurs when the cell is relatively depolarized so that maximum diastolic potential is reduced to levels much lower than normal, usually by intrinsic cardiac disease. When this occurs, spontaneous diastolic (phase 4) depolarization may occur (Figure 2.2). Such abnormal automaticity is caused by a pacemaker current that is different from the pacemaker current of normally automatic cells. The transmembrane action potentials associated with abnormal automaticity may be of the slow-response type; i.e., the transmembrane action potential upstroke may depend on the slow inward (L-type) $Ca2^{+}$ current because of inactivation of Na+ channels at the reduced level of membrane potential. Arrhythmias caused by abnormal automaticity will not be evident unless the rate of the abnormal focus is greater than that of the dominant automatic pacemaker (usually the sinus node) of the heart. They therefore also appear as ectopic automatic rhythms.

Accelerated idioventricular rhythms after myocardial infarction sometimes may be caused by abnormal automaticity in Purkinje's cells in the ischemic region.

Figure 2.2.

Abnormal automaticity activity of the heart muscle



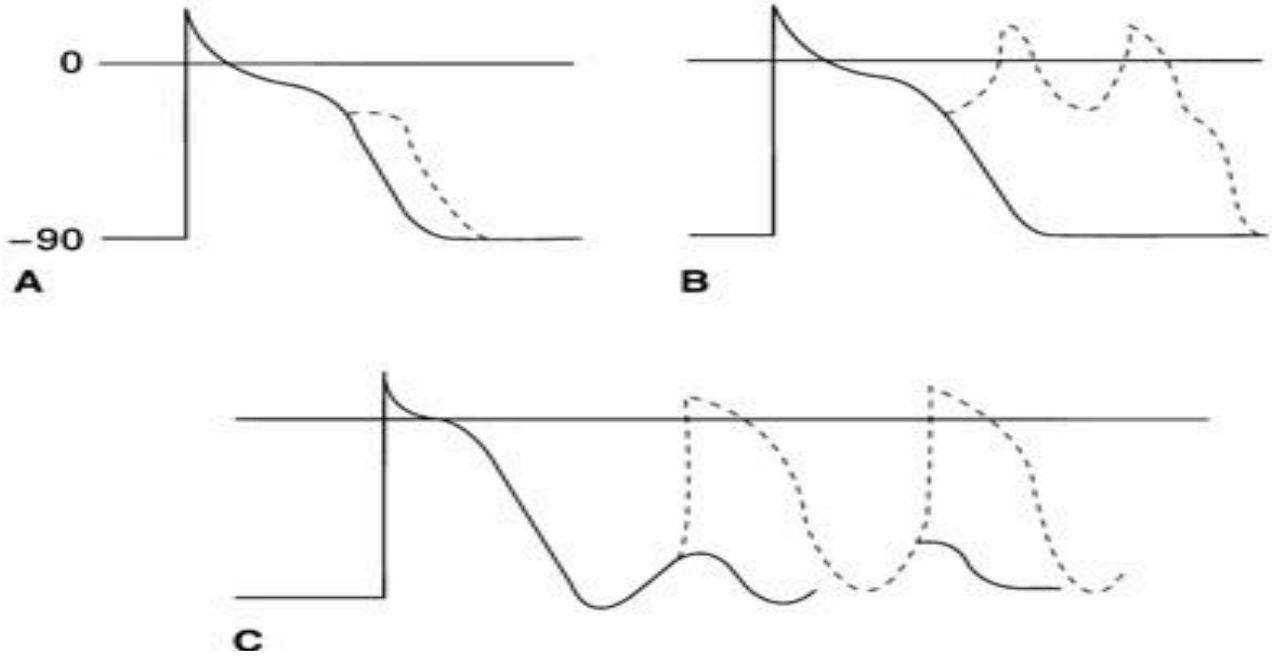
Triggered Rhythms

These arrhythmias are caused by afterdepolarizations (Table 2.1). *Early afterdepolarizations* (*EADs*) are associated with a prolongation of the duration of the action potential and occur during repolarization of a transmembrane action potential that has been initiated from a normal level of membrane potential. They appear as a shift in membrane potential in a positive direction relative to the membrane potential expected during normal repolarization (Figure 2.3). Repetitive depolarizations may originate from the low level of membrane potential that occurs during the afterdepolarization (Figure 2.3). A clinical example of a rhythm thought to be initiated by EADs is torsades de pointes. This is a polymorphic ventricular tachycardia that is associated with abnormal QT-interval prolongation (and therefore prolongation of the Purkinje fiber and ventricular muscle action potentials) caused by any of a variety of factors. This includes a toxic response to class IA or III antiarrhythmic agents or any other agents that prolong the duration of the ventricular action potential, hypokalemia, and

hypomagnesemia. It also includes torsades de pointes associated with syndromes characterized by an intrinsic prolongation of the QT interval (and therefore of the Purkinje fiber and ventricular muscle action potentials), such as the congenital long QT syndromes, which also are thought to be initiated by EADs (Table 2.1).

Figure 2.3.

Triggered activity as cause of depolarization.



Delayed after-depolarizations (*DADs*) are transient depolarizations that occur after repolarization of the transmembrane action potential (Figure 2.3). Triggered impulses occur when DADs reach the threshold potential for activation of the inward current responsible for the upstroke of the transmembrane action potential. Delayed afterdepolarizations have been recorded from atrial, ventricular, and Purkinje's cells exposed to catecholamines, digitalis, or abnormally high levels of $Ca2^{+}$ and are caused by abnormally high intracellular $Ca2^{+}$. The ionic mechanism causing DADs is the transient inward current, a current caused by oscillatory changes in intracellular $Ca2^{+}$ concentrations. Some digitalis toxic rhythms are thought to be due to delayed afterdepolarizations as well as some idiopathic ventricular tachycardias originating in the right ventricular outflow tract (Table 2.1).

Abnormal impulse conduction

Prolongation of Conduction Time of the cardiac impulse may occur anywhere in the heart. It may result from slow conduction and be generalized, as in response to a class IC antiarrhythmic agent, or the slow conduction may be localized to a portion of the heart, e.g., in a portion of the specialized AV conduction system or in ventricular myocardium injured by a myocardial infarction or by other kinds of cardiac disease. Prolongation of conduction time resulting from slow conduction also may occur as a normal response of cardiac tissue, as in prolongation of AV nodal conduction time associated with a propagated premature beat. In addition to slow conduction, prolongation of conduction time may occur when the cardiac impulse takes longer than normal to get from one place to another even though the conduction velocity of the impulse along the route is normal. An example of this is found in patients with an endocardial cushion defect in which the sinus impulse takes an abnormally long time to reach the AV node. This occurs because the location of the ostium primum defect forces the activation wavefront generated by the sinus impulse to take a longer route to reach the AV node. As is shown below, however, perhaps the most important role of prolongation of conduction time is in the genesis and maintenance of most tachycardias resulting from circus movement or reentrant excitation.

Block of Conduction the propagating impulse may occur for any number of reasons. It may block because the impulse arrives at tissue that is inexcitable either because the tissue is still in its effective refractory period after a recent depolarization or because it has an abnormally low resting potential caused by disease. Block also may occur because the strength of the propagating wave' front is insufficient to excite the tissue ahead of it despite the fact that that tissue is fully excitable (decremental conduction and block). Block also may occur because the propagating impulse encounters tissue that is intrinsically unable to conduct the cardiac impulse, e.g., scar tissue associated with a prior myocardial infarction or surgical incision. If there is conduction block of the cardiac impulse, disturbances of cardiac rhythm may occur in several different ways. If the sinus impulse fails to propagate to the right atrium (sinus node exit block or sinoatrial block), normally an ectopic (latent or escape) pacemaker will emerge and assume the role of cardiac pacemaker. If propagation of the cardiac

impulse is impaired in the specialized AV conduction system so that the ventricles are not activated at a sufficiently rapid rate, an ectopic pacemaker (latent or escape) distal to the site of block often will emerge and assume the role of cardiac pacemaker. When either sinoatrial or AV block occurs, however, an ectopic pacemaker may not emerge quickly enough and/or at a clinically adequate rate under some circumstances. Thus, a period of asystole, marked bradycardia, or both may occur. If either or both happen, the clinical problem may be quite serious and even life-threatening. Block also may occur in one of the bundle branches, causing either left or right bundle branch block. Bundle branch block per se is rarely a clinical problem of consequence except when the block occurs simultaneously in both bundle branches.

Unidirectional Block and Reentry

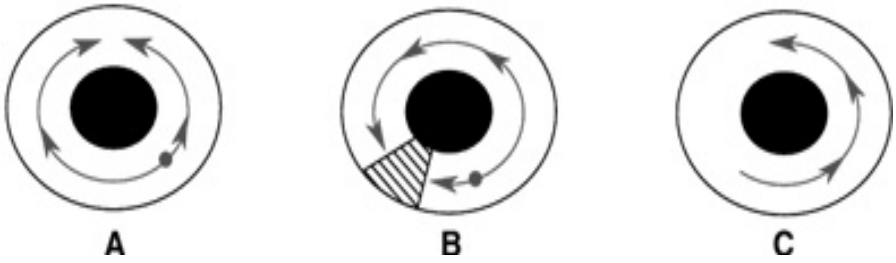
During normal sinus rhythm, the conducted impulse from the sinus node pacemaker dies out after orderly and sequential activation of the atria, the specialized AV conduction system, and the ventricles because the impulse is prevented from reactivating the myocardium by the refractoriness of the tissue that has just been activated. The heart then must wait for a new impulse from the sinus node pacemaker for each subsequent activation. The phenomenon of reentry occurs when the propagating impulse does not die out but rather continues to propagate and reactivate the heart, because the activation wave front continuously encounters excitable cardiac tissue. Most clinically important tachyarrhythmias are due to reentry (Table 2.1). For reentry to occur, several conditions must be met. First, there must be a substrate in the cardiac tissue capable of supporting reentry, i.e., a region in the heart with the appropriate electrical properties in which reentry can occur. Second, the excitation wave front must encounter unidirectional block. Third, the activation wave front must be able to circulate around a central area of block. Figure 4 illustrates a simple model of reentry in a loop of excitable tissue. The center of the loop is a hole, and this serves as a central area of block around which the reentrant wave front can circulate. If the loop of excitable tissue is stimulated at a single point, two wave' fronts of excitation circulate in the ring in opposite directions from this point (Figure 2.4A). Since the wave' fronts collide, they die out. If block of one of the circulating wave' fronts occurs (e.g., in the

shaded area), however, an excitation wave' front can circulate in only one direction around the loop; i.e., unidirectional block of the stimulated wave' front has occurred (Figure 2.4*B*). If either conduction of the nonblocked impulse around the loop is slow enough (e.g., because of a region or regions of slow conduction) or, in the presence of normal conduction, the loop is long enough so that by the time the circulating wave front has returned to its site of origin, this latter region has recovered excitability, the wave front can then re-excite (i.e., reenter) tissue it has previously excited and continue to circulate (Figure 2.4*C*). For this to occur, however, the region of block must manifest unidirectional block, i.e., block in the right-to-left direction but conduction in the left-to-right direction (Figure 2.4*C*). If the region of previous block remains unexcitable, bidirectional block at this site has prevented reentry. Since the block is unidirectional, reentry occurs. In the presence of myocardium manifesting unidirectional block and a central inexcitable area around which an excitation wave front can circulate, as long as the wavelength (the product of the conduction velocity of the circulating wave' front and the effective refractory period of the tissue of the potentially reentrant circuit) of the circulating wave front is shorter than the length of the pathway in which it is traveling, the wave front will continue to circulate. In other words, as long as myocardium in the reentrant circuit ahead of the propagating reentrant excitation wave has sufficient time to recover excitability after its prior excitation, reentry can continue. The result is classical circus movement or reentrant excitation. Thus, an area of slow conduction is not an absolute requisite for reentrant excitation to occur.

Reentry can occur at normal conduction velocities if the path length is sufficiently long. Most reentrant circuits, however, require the presence of an area of slow conduction. This is the case because in most circumstances, despite the presence of unidirectional block, the length of the potential reentrant circuit is too short, so that without the presence of an area or areas of slow conduction, the nonblocked wave' front would otherwise travel around the circuit so quickly that it would arrive at the point of origin of the wave' front before that site had recovered sufficiently to become excitable again.

Figure 2.4

Schematic representation of re-entry in a ring of excitable tissue.



Notes: A. Ring was stimulated in the area indicated by the black dot. Impulses propagated away from the point of stimulation in both directions (*arrows*) and collided; no reentry occurred.

B. The striped area was compressed while the ring was stimulated, again at the black dot. The impulse propagated around the ring in only one direction, having been blocked in the other direction by the area of compression. Then, immediately after stimulation, the compression was relieved.

C. Circulating impulse is shown returning to its point of origin and then continuing around the ring. Identical reentry would occur if the striped area in *B* were a region of permanent unidirectional conduction block with block in the right-to-left direction.

In fact, presumably for this very reason, an area or areas of slow conduction is part of the reentrant circuit for virtually all clinical reentrant rhythms. Reentrant circuits may be located almost anywhere in the heart, and they can assume many sizes and shapes. Reentry in which the circulating wave' front continuously reenters over the same stable pathway to generate the reentrant rhythm is called *ordered reentry*. The circuit may constitute a well-defined anatomic pathway, an anatomic circuit. One example is the reentrant circuit in AV reentrant tachycardia (atrium, AV node, His-Purkinje system, ventricle, accessory AV connection). Functional circuits, which depend on cellular electrophysiologic properties rather than anatomy, also can be associated with ordered reentry if the electrophysiologic properties crucial for reentry are confined to a specific location and reentry occurs only in that location. Ordered reentry also can involve a combination of anatomic and functional pathways. Examples of arrhythmias caused by ordered reentry include atrial flutter, most monomorphic ven-

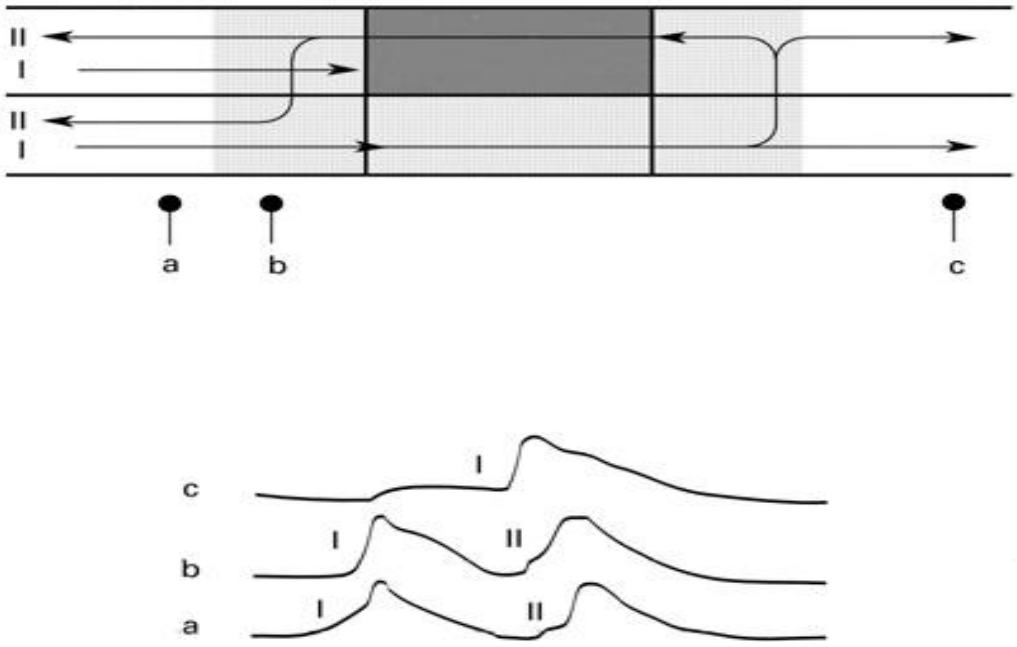
tricular tachycardias, AV nodal reentrant tachycardia, AV reentrant tachycardia involving an accessory AV connection, and sinus node reentrant tachycardia (Table 2.1). During random reentry, propagation occurs in reentrant pathways that continuously change their size and location with time. For this to occur, circuits must, at least to a significant degree, be functional. Random reentry need not depend on any special electrophysiologic abnormality in the heart, although electrophysiologic abnormalities also may lead to random reentry. Examples of random reentry include some forms of atrial and ventricular fibrillation (Table 2.1).

Reflection

The term *reflection* has been used to describe a form of reentry in a linear bundle in which two excitable regions are separated by an area of depressed conduction. During reflection, excitation occurs slowly in one direction along the bundle and is followed by continued propagation and excitation occurring in the opposite direction. One form of reflection may in fact be micro re-entry based on functional longitudinal dissociation within the depressed segment. How this may occur is diagrammed in Figure 2.5.

Figure 2.5.

Diagram of reflection based on microeentry



Notes: *Top*: Schematic representation of two adjacent myocardial fibers. The shaded region indicates an area of depressed conduction. Arrows show the pattern of activation: Arrow I is a wave' front conducting in an antegrade direction, and ar-

row II is a reflected wave' front conducting in a retrograde direction. The action potentials shown below were recorded at sites a, b, and c on the diagram.

The diagram at the top of the figure depicts two adjacent fibers in a bundle. The entire shaded area is depressed (reduced membrane potential and slow action potential upstrokes), with the darker area in the upper fiber indicating more severe depression than the lighter area in the lower fiber. Unidirectional conduction block occurs in the more severely depressed region. Arrows labeled I show the impulse entering the two fibers from the left end. Conduction of the impulse (I) blocks in the fiber at the top, in the severely depressed region, but continues in the fiber at the bottom, which is not as depressed. The impulse conducts transversely from the bottom fiber to the top fiber once it is past the region of severe depression. It then conducts retrogradely through this severely depressed region in the top bundle. Arrows labeled II show the reflected impulse returning to re-excite the left end of the bundle. Action potentials that were recorded from sites a, b, and c in the bottom fiber are shown below: action potentials labeled I were recorded as the impulse conducted from left to right; action potentials labeled II were recorded as the impulse conducted from right to left, returning to its origin. It is thought that such reentry may occur in the His bundle, one of the bundle branches or peripheral branches of Purkinje fiber bundles.

Simultaneous abnormalities of impulse generation and conduction

Parasystole

At times, an ectopic pacemaker may be connected to the remainder of the heart through tissue or tissues in which there is unidirectional block. The unidirectional block prevents the dominant rhythm, usually a sinus rhythm, from entering the region where the ectopic pacemaker is located. As a result, the ectopic pacemaker is not suppressed by the dominant rhythm of the heart. At the same time, because the block is unidirectional, impulses generated by the ectopic pacemaker can be conducted out to other regions of the heart as long as they are not refractory, causing premature beats or even a tachycardia. This kind of rhythm is called *parasystole*. Thus, parasystole is a rhythm that is due to impulse generation (presumed to be due to an ectopic pacemaker, but it could be due to any mechanism) in a protected focus. The focus is

protected because there is entrance block into the focus (owing to unidirectional block). An impulse may exit the focus and excite the heart if the impulse generated by the parasystolic focus finds tissue that is excitable, i.e., not in the effective refractory period.

Phase 4 Block

Block of an impulse may occur if the impulse arrives at a site-e.g., in the His bundle or one of the bundle branches-that is partially depolarized during spontaneous phase 4 depolarization but has not yet reached threshold. This spontaneous diastolic depolarization can depolarize the tissue sufficiently that the fast Na^+ channels are inactivated enough to cause failure of propagation.

Automaticity

It is convenient to subdivide automaticity into two kinds: normal and abnormal. Normal automaticity is found in the primary pacemaker of the heart, the sinus node, as well as in certain subsidiary or latent pacemakers that can become the pacemaker under the conditions described below. Impulse initiation is a normal property of these latent pacemakers. By contrast, abnormal automaticity, whether the result of experimental interventions or of disease, occurs in cardiac cells only when there are major abnormal changes in their transmembrane potentials, in particular in steady-state depolarization of the membrane potential. This property of abnormal automaticity is not confined to any specific latent pacemaker cell type but may occur almost anywhere in the heart.

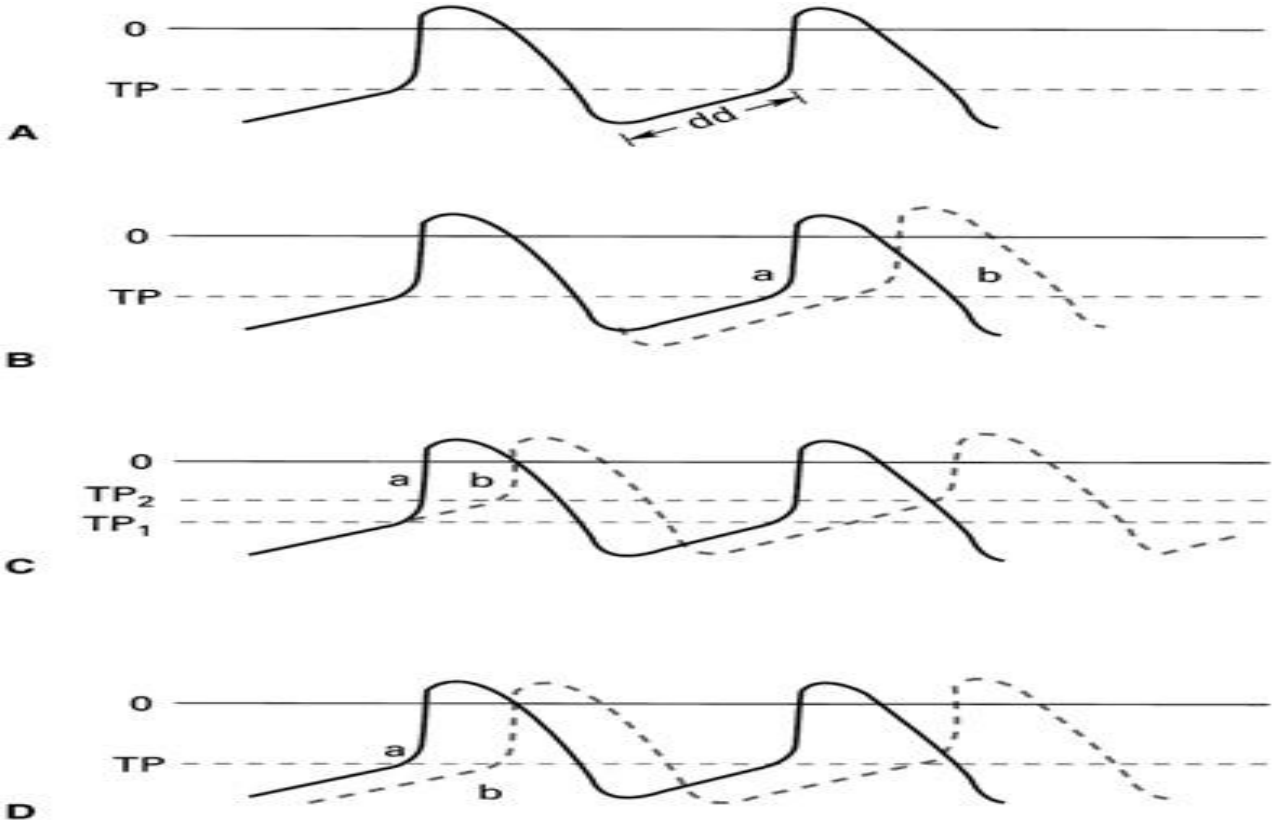
Normal Automaticity: Pacemaker Mechanisms

The normal site of impulse initiation is the sinus node. The cause of normal automaticity in the sinus node is a spontaneous decline in the transmembrane potential during diastole, referred to as the *pacemaker potential, phase 4,* or *diastolic depolarization* (the terms are interchangeable). Diastolic depolarization is the part of the sinus node membrane potential labeled dd in the top panel (*A*) of Figure 2.6. When the depolarization reaches the threshold potential (dashed line labeled TP), the upstroke of the spontaneous action potential is initiated. In the case of the sinus node this upstroke is caused mainly by an inward-directed calcium current through L-type cal-

cium channels. This fall in membrane potential during phase 4 reflects a gradual shift in the balance between inward and outward membrane currents in the direction of net inward (depolarizing) current.

Figure 2.6.

Diagrams of sinus node action potentials illustrating normal automaticity caused by spontaneous diastolic depolarization and the factors that change the rate of impulse initiation.



Notes: *A*. Typial sinus node action potential with spontaneous diastolic depolarization (dd).
B. Change in the rate when the maximum diastolic potential is shifted to a more negative level (from a to b).
C. Change in rate caused by change in threshold potential to a less negative level (from TP1 to TP2).
D. Change in rate that occurs when the slope of phase 4 depolarization is decreased (from a to b).

Studies have been done to elucidate and characterize the membrane currents that cause diastolic (phase 4) depolarization in the sinus node, using voltage clamp techniques in small tissue preparations and in single dissociated sinus node cells. The cause of the pacemaker potential is still controversial. There is some evidence that diastolic depolarization results from the turning on of an inward current, called *i*f, which is activated after repolarization of the sinus node action potential. The net in-

ward *i*f current is carried largely by Na^+. From the voltage clamp studies, it is known that the *i*f channels are inactivated at positive membrane potentials, begin to activate after hyperpolarization to around -40 mV, and are fully activated after hyperpolarization to around -100 mV. Since the maximum diastolic potential of the sinus node pacemaker cells is between -60 and -70 mV, the *i*f current is turned on during repolarization to this level, although it is not fully activated at the maximum diastolic potential.

Activation of the *i*f conductance also has a time dependency; therefore, the inward current continues to increase after complete repolarization, causing the progressive fall in the membrane potential during phase 4. Important roles for other membrane currents, including the potassium current *i*K and the T and L $Ca2^+$ currents that cause spontaneous diastolic depolarization, also have been proposed. Therefore, there may be no single pacemaker current in the sinus node; rather, a number of currents may contribute to the occurrence of automaticity.

The intrinsic rate at which sinus node pacemaker cells initiate impulses is determined by the interplay of three factors: (1) the maximum diastolic potential, (2) the threshold potential, and (3) the rate or slope of phase 4 depolarization. The third factor is related to the properties of the pacemaker current or currents. A change in any one of these factors will alter the time required for phase 4 depolarization to carry the membrane potential from its maximum diastolic level to threshold and thus alter the rate of impulse initiation.

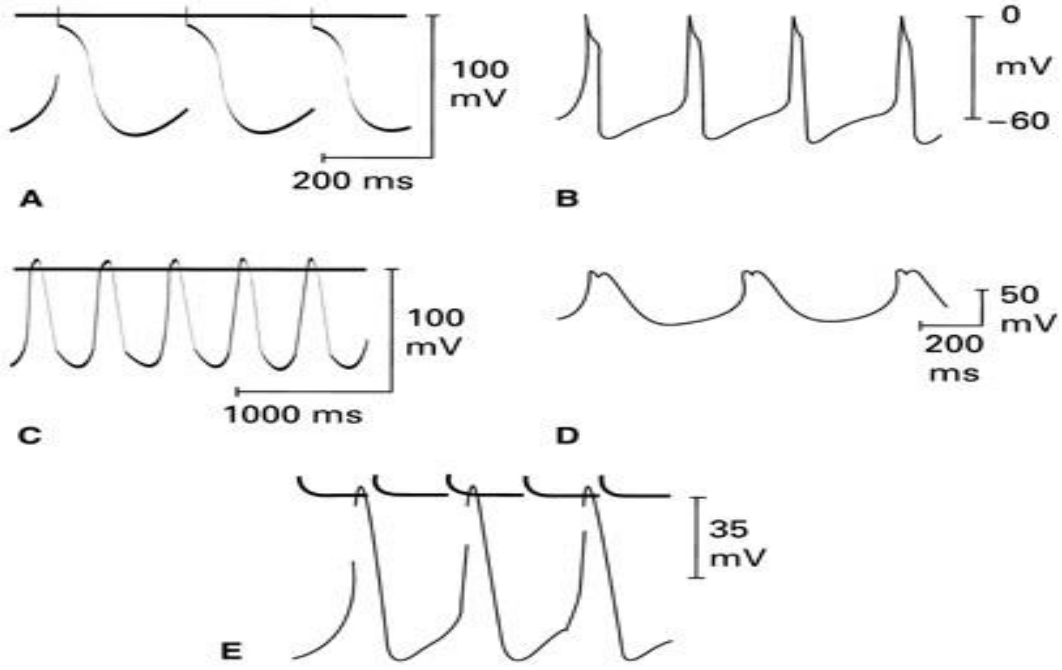
For example, if the maximum diastolic potential increases (becomes more negative) going from the solid trace to the dashed trace in Figure 6*B*, spontaneous depolarization to the threshold potential will take longer and the rate of impulse initiation will fall. Conversely, a decrease in the maximum diastolic potential will tend to increase the rate of impulse initiation (going from dashed trace to solid trace). Similarly, changes in threshold potential or changes in the slope of phase 4 depolarization will alter the rate of impulse initiation. In Figure 6*C*, a change in threshold potential from TP1 to the less negative TP2 causes spontaneous diastolic depolarization to proceed for a longer time (dashed action potential trace) before an impulse is initiated, slowing the rate. In Figure 6*D*, a decrease in the slope of spontaneous diastolic depo-

larization from a to b also results in a longer interval between action potentials (dashed trace) because of the longer time required for membrane potential to reach the threshold potential. In Figure 6*C* and Figure 6*D*, changes in the threshold potential or slope of diastolic depolarization in the opposite direction would speed up the rate. The alterations in the rate of impulse initiation in the sinus node resulting from the factors discussed above may lead to arrhythmias. These arrhythmias are often a result of the actions of the autonomic nervous system on the sinus node. Parasympathetic stimulation and the resultant release of acetylcholine hyperpolarize the membrane potential through stimulation of muscarinic receptors and the activation of a K current (Figure 12.6*B*). Acetylcholine also decreases the inward $Ca2^{+}$ current and the *i*f pacemaker current. A combination of these effects slows the rate. Sympathetic stimulation and norepinephrine release increase the slope of diastolic depolarization and therefore sinus rate by increasing L-type $Ca2^{+}$ current and increasing activation of the inward *i*f current at the completion of action potential repolarization. These effects are mediated through beta1-receptor stimulation. In addition to the sinus node, cells with pacemaking capability in the normal heart are located in some parts of the atria and ventricles, although they are not pacemakers while the sinus node is functioning normally. These are latent or subsidiary pacemakers. Since spontaneous diastolic depolarization is a normal property, the automaticity generated by these cells is classified as normal. In the atria, cells with well-polarized membrane potentials (resting potentials of around - 80 mV) and action potentials characterized by fast upstrokes, a plateau phase of repolarization, and spontaneous diastolic depolarization are located along the crista terminalis (Figure 2.7*A*). Subsidiary atrial pacemakers with somewhat lower maximum diastolic potentials (-75 to -70 mV) and prominent phase 4 depolarization are located at the junction of the inferior right atrium and the inferior vena cava, near or on the eustachian ridge (a remnant of the eustachian valve of the inferior vena cava) (Figure 2.7*B*). Other potential atrial pacemakers are at the orifice of the coronary sinus (Figure 2.7*C*) and in the atrial muscle that extends into the tricuspid and mitral valves (Fig. 2.7*D*). Action potentials of cells in the valves have slow upstrokes that probably are caused to a significant extent by L-type $Ca2^{+}$ current. In the

AV junction, AV nodal cells possess the intrinsic property of automaticity (Figure 2.7*E*), although there is still some uncertainty about the exact location of these pacemakers in the node. The intrinsic rate of the atrial pacemakers is greater than that of AV junctional pacemakers. Both atrial and AV junctional subsidiary pacemakers are under autonomic control, with the sympathetics enhancing pacemaker activity through beta1-adrenergic stimulation and the parasympathetics inhibiting pacemaker activity through muscarinic receptor stimulation. In the ventricles, latent or subsidiary pacemakers are found in the His-Purkinje system, where Purkinje fibers have the property of spontaneous diastolic depolarization. The intrinsic Purkinje fiber pacemaker rate in general is lower than the rate of atrial and AV junctional pacemakers and decreases from the His bundle to the distal Purkinje branches. The spontaneous diastolic depolarization in this region is also under similar autonomic control. As in the atria, sympathetic activation enhances automaticity, while parasympathetic activation can reduce it, mostly through inhibition of sympathetic influences.

Figure 2.7.

Transmembrane potentials recorded in isolated superfused preparations from some subsidiary pacemaker cells with the property of normal automaticity. Spontaneous diastolic depolarization that developed in the absence of overdrive suppression is shown in each panel.



Notes: *A.* Atrial fiber in the crista terminalis in the presence of isoproterenol.
B. Atrial fiber in the inferior right atrium.

C. Atrial fiber in the ostium of the coronary sinus in the presence of norepinephrine.
D. Atrial fiber in stretched mitral valve leaflet.
E. Atrioventricular nodal fiber of the rabbit heart after the AV node was separated from the atrium.

The membrane currents that cause the normal spontaneous diastolic depolarization at ectopic sites also have been studied. The most thorough analyses have been done on the pacemaker current in Purkinje's cells, using voltage clamp techniques. These studies have shown the presence of an *i*f pacemaker current, as in the sinus node. The *i*f channels are deactivated during the action potential upstroke and the initial plateau phase of repolarization but begin to activate as repolarization brings the membrane potential to levels more negative than about -60 mV. Since the activation kinetics are slow, the channels continue to activate throughout diastole, leading to an increasing net inward current carried mostly by Na+ and diastolic depolarization. Other currents are also likely to contribute to the pacemaker potential in Purkinje's cells. It is likely that the net increase in inward current during diastole that causes spontaneous diastolic depolarization in Purkinje fibers is a result of an increase in an inward current *i*f and a decrease in outward current (*iK*1 and *i*K).

Abnormal Automaticity: Pacemaker Mechanisms

Working atrial and ventricular myocardial cells do not normally have spontaneous diastolic depolarization and do not initiate spontaneous impulses even when they are not excited for long periods of time by propagating impulses. When the resting potentials of working atrial or ventricular myocardial cells are reduced sufficiently, however, spontaneous diastolic depolarization may occur and cause repetitive impulse initiation, a phenomenon called *depolarization-induced automaticity* or *abnormal automaticity*. The level of membrane potential at which abnormal automaticity occurs is often in a range between -70 and -30 mV (Figure 12.2). Likewise, cells in the Purkinje system, which are normally automatic at high levels of membrane potential, also show abnormal automaticity when the membrane potential is reduced. As was discussed before, the *i*f channels that participate in normal pacemaker activity in Purkinje fibers have a gating mechanism controlling channel opening and closing that

is dependent on the transmembrane voltage. At membrane potentials that are positive to about -60 mV, as occurs after the upstroke and during the early phases of repolarization, the channels are closed. In response to the negative potentials that occur after complete repolarization, the channels reopen, gener ating the inward pacemaker current. For this reason, when the steady-state membrane potential of Purkinje fibers is reduced to around -60 mV or less, as sometimes may occur in ischemic regions of the heart, these normal pacemaker channels are not functional and automaticity is not caused by the normal pacemaker mechanism. It can, however, be caused by an "abnormal" mechanism. The abnormal automatic rate increased as membrane potential became more positive. This is a general characteristic of abnormal automaticity in atrial and ventricular cells as well. A low level of membrane potential is not the only criterion for defining abnormal automaticity. If this were so, the automaticity of the sinus node would have to be considered abnormal. Therefore, an important distinction between abnormal and normal automaticity is that the membrane potentials of fibers showing the abnormal type of activity are reduced from their own normal level. For this reason, automaticity in the AV node or valves, where membrane potential is normally low, is not classified as abnormal automaticity. A likely cause of automaticity at depolarized membrane potentials in ventricular muscle is activation and deactivation of the delayed rectifier K current. The conductance of this K channel is activated during the normal action potential plateau, and the outward current that flows through it normally contributes to repolarization. The channel then deactivates during diastole. No significant outward current flows through this channel at normal diastolic potentials, since the resting potential lies near the reversal potential and the driving force is negligible. When the membrane potential is depolarized, however, an outward current flows through this channel, which is activated at the depolarized membrane potentials. This current hyperpolarizes the membrane potential. As the channel then deactivates at the hyperpolarized potentials, spontaneous diastolic depolarization occurs. If either Na or Ca channels have been reactivated since the preceding action potential, the spontaneous depolarization caused by K-channel deactivation may lead to an upstroke caused by current flowing through one of these channels (depending

on the level of the membrane potential). A similar mechanism may cause abnormal automaticity in partially depolarized.

Purkinje fibers.

Experiments on depolarized human atrial myocardium from dilated atria indicate that $Ca2^{+}$-dependent processes also may contribute to abnormal pacemaker activity at low membrane potentials. It was proposed that intracellular $Ca2^{+}$ released from the sarcoplasmic reticulum controls membrane permeability to an inward current during diastole, leading to spontaneous diastolic depolarization and abnormal automaticity. The mechanism may be similar to the one that causes the transient inward current responsible for DADs. An increase in intracellular $Ca2^{+}$ also is expected to cause an inward Na+ current through Na^{+}-$Ca2^{+}$exchange. In summary, therefore, several different mechanisms probably cause abnormal automaticity, including activation and deactivation of K+ currents, $Ca2^{+}$-dependent activation of an inward current, inward $Ca2^{+}$ currents, and even some contribution by the pacemaker current *i*f. It has not been determined which of these mechanisms are operative in the different pathologic conditions in which abnormal automaticity may occur. The upstrokes of the spontaneously occurring action potentials generated by abnormal automaticity may be caused by either Na^{+} or $Ca2^{+}$ inward currents or possibly a mixture of the two. In the range of diastolic potentials between approximately -70 and -50 mV, repetitive activity is dependent on extracellular Na^{+} concentration and can be decreased or abolished by the Na^{+} channel blockers lidocaine and tetrodotoxin, indicating that the Na+ inward current is involved. In a diastolic potential range of approximately -50 to -30 mV, repetitive activity depends on extracellular $Ca2^{+}$ concentration and is reduced by $Ca2^{+}$ channel blockers, Mn^{2+}, and verapamil, indicating a role for the L-type $Ca2^{+}$ inward current. The decrease in the membrane potential of cardiac cells required for abnormal automaticity to occur may be induced by a variety of factors related to cardiac disease. Although an increase in the extracellular potassium concentration can reduce membrane potential, normal or abnormal automaticity in working atrial, ventricular, and Purkinje fibers usually does not occur when [K]o is elevated because of the increase in K^{+} conductance (and hence net outward current) that results from an

increase in [K]o. This argues against abnormal automaticity being responsible for arrhythmias arising in acutely ischemic myocardium, where cells are partially depolarized by increased extracellular K^+. A decrease in [K]i, which also causes a decreased membrane potential, has been shown to occur in the Purkinje fibers that survive on the endocardial surface of infarcts, and this decrease persists for at least 24 h after the coronary occlusion. The reduction in [K]i contributes to the low membrane potential and the accompanying abnormal automaticity. Isolated preparations of diseased atrial and ventricular myocardium from human hearts superfused with Tyrode's solution show phase 4 depolarization and abnormal automaticity at membrane potentials in the range of -50 to -60 mV.70-72 It has been proposed that a decrease in membrane potassium conductance is an important cause of the low membrane potentials in the atrial fibers.

Suppression of Normal and Abnormal Automatic Subsidiary Pacemakers

During sinus rhythm in a normal heart, the intrinsic rate of impulse initiation resulting from automaticity of cells in the sinus node is higher than that of the other potentially automatic cells, and the latent pacemakers are excited by propagated impulses from the sinus node before they can depolarize spontaneously to threshold potential. Not only are latent pacemakers prevented from initiating an impulse because they are depolarized before they have a chance to fire, but the diastolic (phase 4) depolarization of the latent pacemaker cells with the property of normal automaticity is actually inhibited because they are repeatedly depolarized by the impulses from the sinus node. This inhibition can be demonstrated by suddenly stopping the sinus node, e.g., by vagal stimulation (vagal stimulation also inhibits subsidiary pacemakers in the atria and AV junction) or in the tissue bath after termination of overdrive pacing. Impulses then usually arise from a subsidiary pacemaker in the ventricular Purkinje system, but that impulse initiation generally is preceded by a long period of quiescence. Impulse initiation by the Purkinje fiber pacemaker then begins at a low rate and only gradually speeds up to a final steady rate that is, however, still slower than the original sinus rhythm. The quiescent period after abolition of the sinus rhythm reflects the inhibitory influence exerted on the subsidiary pacemaker by the dominant

sinus node pacemaker. This inhibition is called *overdrive suppression*. Similarly, the sinus node also overdrive-suppresses subsidiary atrial pacemakers. The mechanism of overdrive suppression has been characterized in microelectrode studies of isolated Purkinje fiber bundles exhibiting pacemaker activity. It is mediated mostly by enhanced activity of the Na+-K+ exchange pump that results from driving a pacemaker cell faster than its intrinsic spontaneous rate. During normal cardiac rhythm, the sinus node drives the latent pacemakers at a faster rate than their normal (intrinsic) automatic rate. As a result, the intracellular Na+ of the latent pacemakers is increased to a higher level than would be the case if the pacemakers were firing at their own intrinsic rate. This is the result of Na+ entering the cells during each action potential upstroke. The rate of activity of the Na+ pump is determined largely by the level of intracellular Na+ concentration, so that pump activity is enhanced during high rates of stimulation. The increased pump activity prevents intracellular Na+ from rising to very high levels, although there is some increase in the steady-state Na+ concentration at high rates of firing. Since the Na+ pump moves more Na+ outward than K+ inward, it generates a net outward (hyperpolarizing) current across the cell membrane. When subsidiary pacemaker cells are driven faster than their intrinsic rate by the sinus node, the enhanced outward pump current hyperpolarizes the membrane potential and suppresses spontaneous impulse initiation in these cells, which, as was described before, is dependent on the net inward current. When the dominant (overdrive) pacemaker is stopped, this suppression continues because the Na+ pump continues to generate the outward current as it reduces the intracellular Na^+ levels toward normal. The continued Na^+ pump-generated outward current is responsible for the period of quiescence, which lasts until the intracellular Na+ concentration, and hence the pump current, becomes small enough to allow subsidiary pacemaker cells to depolarize spontaneously to threshold. Intracellular Na+ concentration decreases during the quiescent period because Na^+ is constantly being pumped out of the cell and little is entering. Intracellular Na^+ and pump current continue to decline even after spontaneous firing begins because of the slow rate, causing a gradual increase in the discharge rate of the subsidiary pacemaker.

The higher the overdrive rate or the longer the duration of overdrive, the greater the enhancement of pump activity, so that the period of quiescence after the cessation of overdrive is directly related to the rate and duration of overdrive. The sinus node itself also can be overdrivesuppressed if it is driven at a rate more rapid than its intrinsic rate. Thus, there may be a quiescent period after termination of either overdrive pacing or a rapid ectopic arrhythmia before the sinus rhythm resumes. When overdrive suppression of the normal sinus node occurs, however, it is of lesser magnitude than that of subsidiary pacemakers overdriven at comparable rates. The sinus node action potential upstroke is largely dependent on slow inward current carried by Ca2+through the L-type Ca2+ channels, and far less Na+ enters the fiber during the upstroke than occurs in latent pacemaker cells such as Purkinje fibers. As a result, the activity of the Na+ pump probably is not increased to the same extent in sinus node cells after a period of overdrive; therefore, there is less overdrive suppression caused by enhanced Na+ pump current. The relative resistance of the normal sinus node to overdrive suppression may be important in enabling it to remain the dominant pacemaker even when its rhythm is perturbed transiently by external influences such as transient shifts of the pacemaker to an ectopic site. The diseased sinus node, however, may be much more easily overdrive-suppressed. There is an important distinction between the effects of the dominant sinus pacemaker on the two kinds of automaticity, as abnormal automaticity at reduced levels of membrane potential is not overdrive-suppressed to the same extent as is the normal automaticity that occurs at high levels of membrane potential. The amount of suppression of spontaneous diastolic depolarization that causes abnormal automaticity by overdrive is directly related to the level of membrane potential at which the automatic rhythm occurs. For example, Purkinje fibers that show automaticity at moderately depolarized membrane potentials of -60 to -70 mV still manifest some overdrive suppression, although less than do fibers with automaticity at -90 mV. Automaticity in Purkinje fibers with membrane potentials less than -60 mV is suppressed only slightly by overdrive, if it is suppressed at all. These differences in the effects of overdrive may be related to the reduction in the amount of Na+ entering the cell as the membrane potential decreases, as was de-

scribed for overdrive of the sinus node. At low levels of membrane potential, Na+ channels are inactivated, decreasing the fast inward Na+ current; therefore, there is a reduction in the amount of Na+ entering the cells during overdrive and the degree of stimulation of the sodium-potassium pump. In addition to overdrive suppression being of paramount importance for maintenance of normal rhythm, the characteristic response of automatic pacemakers to overdrive, as was discussed in the previous paragraphs, is often useful for identifying mechanisms of arrhythmias in the in situ heart, where arrhythmia mechanisms cannot be identified by recording transmembrane potentials because of the technical difficulties. Not all mechanisms of arrhythmogenesis respond in the same way to overdrive that automatic pacemakers do, and the differences in response sometimes can be used to distinguish among mechanisms. These differences are described in detail later in this chapter. In addition to overdrive suppression, a mechanism that may suppress subsidiary pacemakers is the electrotonic interaction between the pacemaker cells and the nonpacemaker cells in the surrounding myocardium. This mechanism may be particularly important in preventing AV nodal automaticity or automaticity in the distal Purkinje system, where the pacemaking Purkinje fibers are in contact with nonpacemaking working ventricular muscle.

Arrhythmias Caused by Automaticity

Arrhythmias caused by normal or abnormal automaticity of cardiac fibers may occur for several different reasons. Such arrhythmias may result simply from an alteration in the rate of impulse initiation by the normal sinus node pacemaker without a shift of impulse origin to a subsidiary pacemaker at an ectopic site. Sinus bradycardia and tachycardia are examples of these arrhythmias. The cellular mechanisms that can change the rate of impulse initiation in the sinus node are described in Figure 6. During alterations in sinus rate, there may be shifts of the pacemaker site within the sinus node. A shift in the site of impulse initiation to one of the regions where normal or abnormal subsidiary pacemakers are located also results in arrhythmias.

This would be expected to happen when any of the following occurs:

- the rate at which the sinus node activates subsidiary pacemaker falls considerably below the intrinsic rate of the subsidiary pacemakers,

- inhibitory electrotonic influences between nonpacemaker cells and pacemaker cells are interrupted,
- impulse initiation in subsidiary pacemakers is enhanced.

The rate at which the sinus node activates subsidiary pacemakers may be decreased in a number of situations. Impulse initiation by the sinus node may be slowed or inhibited altogether by heightened activity in the parasympathetic nervous system or as a result of sinus node disease. Alternatively, there may be block of impulse conduction from the sinus node to the atria or block of conduction from the atria to the ventricles. A latent pacemaker also may be protected from being overdriven by the sinus node if it is surrounded by a region in which impulses of sinus origin block (entrance block) before reaching the pacemaker cells. Such block, however, must be unidirectional, so that activity from the pacemaker can propagate into surrounding myocardium whenever the surrounding regions are excitable.

The protected pacemaker is said to be a *parasystolic focus*. In general, under these conditions, a protected focus of automaticity of this type can fire at its own intrinsic frequency. Electronic current flow from surrounding regions also may influence the cycle length of a protected focus, either prolonging or abbreviating it, depending on whether the surrounding activity occurs during the early or late stage of diastolic depolarization. Under any of the above conditions (sinus slowing, sinoatrial or AV block, parasystolic focus), there may be "escape" of a subsidiary pacemaker. There is a natural hierarchy of intrinsic rates of subsidiary pacemakers that have normal automaticity, with atrial pacemakers having faster intrinsic rates than do AV junctional pacemakers and AV junctional pacemakers having faster rates than do ventricular pacemakers. Once overdrive suppression is removed by sinus node inhibition, the pacemaker with the fastest rate becomes the site of impulse origin. Sometimes mechanisms responsible for the suppression of impulse initiation in the sinus node also suppress pacemaker activity in the atria. In experimental studies in which the sinus node is damaged or removed, the most prevalent atrial pacemaker site is at the junction of the inferior vena cava and the posterior wall of the right atrium. These atrial

pacemakers may cause atrial arrhythmias if the sinus node or its arterial supply is damaged.

Ectopic impulse initiation may occur in the AV junction. In fact, an AV junctional pacemaker may become the dominant rhythm in the absence of normal sinus node function. Atrioventricular junctional pacemakers may be located either in the AV node or in the His bundle. These different sites have somewhat different properties, including their intrinsic rates (faster in the AV node than in the His bundle) and responses to autonomic nerve activity (parasympathetic activity suppresses AV nodal pacemakers to a greater extent than it does His bundle pacemakers). Atrioventricular junctional rhythms may occur during AV block, since the site of block is often proximal to the AV junctional pacemaker location. If AV junctional pacemakers also are suppressed or if the site of disease causing AV block is in the His bundle or bundle branches, the subsidiary pacemaker location is in the His-Purkinje system. The His bundle at the proximal end of the specialized AV conduction system has a faster intrinsic rate than do the more distally located Purkinje fibers. The ECG during idioventricular rhythm in patients with complete heart block often is characterized by a wide, aberrant QRS complex, suggesting impulse initiation in the distal Purkinje system. In acute myocardial ischemia, particularly when it occurs in the inferior wall, parasympathetic activity may be enhanced, depressing the sinus rate, AV conduction, or both. Ectopic impulse initiation then may arise in the ventricular specialized conduction system. Any event that decreases intercellular coupling between latent subsidiary pacemaker cells and surrounding nonpacemaker cells may remove the inhibitory influence of electrotonic current flow on the latent pacemakers and allow them to fire at their intrinsic rate. Coupling may be reduced by fibrosis, which can separate myocardial fibers. For example, fibrosis in the atrial aspect of the AV junctional region that results in heart block may release nodal pacemakers from electrotonic suppression by surrounding atrial cells and permit them to become the dominant pacemakers driving the ventricles. Uncoupling also may be caused by factors that increase intracellular $Ca2^{+}$, since elevated intracellular Ca2+ levels decrease coupling between myocardial cells by decreasing the conductance of gap junction channels (*connex-*

ons). This may result, for example, from treatment with digitalis, which inhibits Na+ extrusion and thus increases $Ca2^{+}$ levels in the cell. In myocardial infarction, Purkinje fiber pacemakers may be uncoupled from damaged ventricular muscle cells, allowing the Purkinje fibers to fire at their intrinsic rates. Some inhibition of the sinus node is still necessary for the site of impulse initiation to shift to an ectopic site that is no longer inhibited because of uncoupling from surrounding cells, since, as was explained above, the intrinsic firing rate of subsidiary pacemakers is still slower than that of the sinus node. Subsidiary pacemaker activity also may be enhanced, causing impulse initiation to shift to ectopic sites even when sinus node function is normal. One cause may be enhanced sympathetic nerve activity. Norepinephrine released locally from sympathetic nerves steepens the slope of diastolic depolarization of latent pacemaker cells. and diminishes the inhibitory effects of overdrive. The increase in slope of spontaneous diastolic depolarization may result from effects of norepinephrine on the *i*f current, as was described above, as well as from an increase in inward $Ca2^{+}$ current in those cells in which this current participates in pacemaker activity. Localized effects on subsidiary pacemakers may occur in the absence of sinus node stimulation. Therefore, sympathetic stimulation may enable the membrane potential of ectopic pacemakers to reach threshold before they are activated by an impulse from the sinus node, resulting in ectopic premature impulses or automatic rhythms. There is evidence that in the subacute phase of myocardial ischemia, increased activity of the sympathetic nervous system may enhance automaticity of Purkinje fibers, enabling them to escape from sinus node domination. Enhanced subsidiary pacemaker activity also may not require sympathetic stimulation. The flow of current between partially depolarized myocardium and normally polarized latent pacemaker cells may enhance automaticity. This mechanism has been proposed to be a cause of some of the ectopic beats that arise at the borders of ischemic areas in the ventricle.

Inhibition of the electrogenic sodium-potassium pump results in a net increase in inward current during diastole because of the decrease in outward current normally generated by the pump and therefore may increase automaticity in subsidiary pacemakers sufficiently to cause arrhythmias. This may occur after adenosine triphos-

phate (ATP) is depleted during prolonged hypoxia or ischemia or in the presence of toxic amounts of digitalis. A decease in the extracellular potassium level also enhances normal automaticity, as does acute stretch. Stretch can induce rapid automatic rates in Purkinje fibers with normal maximum diastolic potentials. Stretch of the ventricles also can induce arrhythmias in an intact heart, although the site of origin of the ectopic impulses has not been localized. Stretch of the Purkinje system may occur in akinetic areas after acute ischemia or in ventricular aneurysms in hearts with healed infarcts. At normal sinus rates, there may be little overdrive suppression of pacemakers with abnormal automaticity. As a result of the lack of overdrive suppression, even transient sinus pauses or occasional long sinus cycle lengths may permit an ectopic focus with a slower rate than the sinus node to capture the heart for one or more beats. In contrast, ectopic pacemakers with normal automaticity probably would be quiescent during relatively short, transient sinus pauses because they are overdrive-suppressed. It is also possible that the depolarized level of membrane potential at which abnormal automaticity occurs may cause entrance block into the focus and prevent it from being overdriven by the sinus node even when impulses initiated in the focus could leave it (unidirectional block). This would lead to parasystole, an example of an arrhythmia caused by a combination of an abnormality of impulse conduction and initiation. All these features of abnormal automaticity are evident in the Purkinje fibers that survive in regions of transmural myocardial infarction and cause ventricular arrhythmias during the subacute phase. The firing rate of an abnormally automatic focus also might be enhanced above that of the sinus node, leading to arrhythmias in the absence of sinus node suppression or conduction block between the focus and the surrounding myocardium. The automatic rate is a direct function of the level of membrane potential: The greater the depolarization, the faster the rate. Catecholamines also increase the rate of firing caused by abnormal automaticity and therefore may contribute to a shift in the pacemaker site from the sinus node to a region with abnormal automaticity. Among the clinical arrhythmias that are likely to be caused by abnormal automaticity is accelerated idioventricular rhythm after myocardial infarction.

Triggered activity is a term used to describe impulse initiation in cardiac fibers that is dependent on afterdepolarizations.After-depolarizations are oscillations in membrane potential that follow the upstroke of an action potential. Two kinds of afterdepolarizations may cause triggered activity. One occurs early, i.e., during repolarization of the action potential (EADs), and the other is delayed until repolarization is complete or nearly complete (DADs). When either kind of afterdepolarization is large enough to reach the threshold potential for activation of a regenerative inward current, action potentials result that are referred to as "triggered." Therefore, a key characteristic of triggered activity, discriminating it from automaticity, is that for triggered activity to occur, at least one action potential must precede it (the trigger). Automatic rhythms can arise de novo in the absence of any prior electrical activity, such as after long periods of quiescence, whereas triggered activity cannot. Triggered activity will cause arrhythmias when the site of impulse initiation shifts from the sinus node to the triggered focus. For this to occur, the rate of triggered impulses should be faster than the sinus rate either transiently or persistently. This may result when firing of the sinus node is slowed or inhibited, when there is block of sinus impulses, or when the rate of triggered activity is faster than normal sinus node impulse initiation. The factors causing the shift in the site of impulse initiation should be very similar to those described in the discussion of automaticity.

Delayed Afterdepolarizations and Triggered Activity

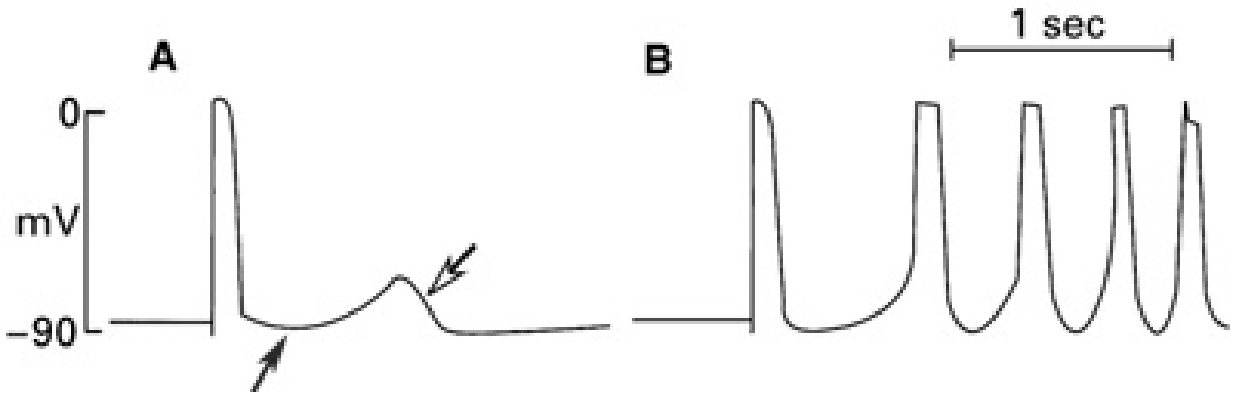
Figure 8 shows an example of a DAD recorded with a microelectrode in a superfused preparation of atrial muscle exposed to catecholamines. The DAD is an oscillation in membrane potential that occurs after repolarization of the action potential (indicated in the figure by the unfilled arrow). The DAD is caused by events occurring during the action potential that will be described below. Figure 2.8*A* also shows that a DAD may be preceded by an after-hyperpolarization, in which case the membrane potential transiently becomes more negative after the action potential than it was just before it. After-hyperpolarizations, however, do not always precede DADs. The transient nature of the DAD clearly distinguishes it from normal spontaneous diastolic

(pacemaker) depolarization, during which the membrane potential declines almost monotonically until the next action potential occure.

A second important problem is a possible difficulty in locating focal sites at which afterdepolarizations and triggered activity may be originating. Nevertheless,extracellular electrodes have been used to demonstrate what appear to be DADs occurring in the in situ heart.

Figure 2.8.

An example of a DAD (*white arrow*) recorded with a microelectrode from an atrial fiber in the canine coronary sinus. The black arrow indicates an after-hyperpolarization. *B.* The onset of triggered activity is shown.



A triggered impulse is initiated when a DAD depolarizes the membrane potential to the threshold potential for activation of the inward current responsible for the upstroke of the action potential. After-depolarizations do not always reach threshold, so that triggerable fibers sometimes may be stimulated at a regular rate without becoming rhythmically active. Probably the most important influence that causes subthreshold DADs to reach threshold is a decrease in the cycle length (an increase in the rate) at which action potentials occur. Therefore, arrhythmias triggered by DADs can be expected to be initiated by either a spontaneous or a pacing-induced increase in the heart rate. A triggered action potential also is followed by an afterdepolarization that may or may not reach threshold. When it does not reach threshold, only one triggered action impulse occurs. Quite often, the first triggered action potential is followed by a short or long "train" of additional triggered action potentials, each arising from the afterdepolarization caused by the previous action potential. The merging of the rising phase of the afterdepolarization with the upstroke of the action potential during trig-

gered activity may be smooth, and as a result, the fiber may show phase 4 depolarization that is indistinguishable from the phase 4 depolarization seen during automatic activity.

Causes of delayed afterdepolarizations and triggered activity

Delayed afterdepolarizations usually occur under a variety of conditions in which there is an increase in Ca^{2+} in the myoplasm and the sarcoplasmic reticulum above normal levels (sometimes referred to as *Ca overload*). Abnormalities in the sequestration and release of Ca^{2+} by the sarcoplasmic reticulum also may contribute to their occurrence. On depolarization of the membrane during an action potential, the intracellular free Ca^{2+} normally increases, primarily by Ca^{2+} influx through the L-type Ca^{2+} channels. Initially, this rapid rate of change of intracellular Ca^{2+} triggers Ca^{2+} release from the sarcoplasmic reticulum, causing a further rise in intracellular free Ca^{2+} and contraction. Repolarization then induces synchronous Ca^{2+} uptake by the sarcoplasmic reticulum in the cell and relaxation. If intracellular Ca^{2+} is very high or if catecholamines or cyclic adenosine monophosphate (AMP) is present, both of which enhance Ca^{2+} uptake by the sarcoplasmic reticulum, the Ca^{2+} in the sarcoplasmic reticulum may rise during repolarization to a critical level, at which time a secondary spontaneous release of $Ca^{2+}$from the sarcoplasmic reticulum occurs after the action potential and relaxation of contraction. This secondary release of Ca^{2+} generates an aftercontraction as well as the transient inward (TI) current and the afterdepolarization. The TI current is an oscillatory membrane current that is distinct from the pacemaker currents. After one or several afterdepolarizations, myoplasmic Ca^{2+} may decrease because Na^{+}-Ca^{2+} exchange extrudes Ca^{2+} from the cell, and the membrane potential stops oscillating. The exact mechanism by which the secondary rise in myoplasmic Ca^{2+} after repolarization causes the TI current is unclear. Two possibilities have been considered. The first is that the Ca^{2+}released from the sarcoplasmic reticulum after repolarization acts on the sarcolemma to increase its conductance to ions (mainly Na^{+}) that flow into the cell down a concentration gradient through membrane channels. The second mechanism proposed for the origin of the TI current is that the rise in Ca^{2+} causes the TI current through an electrogenic (rheogenic) exchange of Ca^{2+} for Na^{+}.

According to this hypothesis, the transient rise in myoplasmic Ca^{2+} released from the sarcoplasmic reticulum after the action potential is expected to result in "transport" of Ca^{2+} out of the cell across the sarcolemma by the Na^{+}-Ca^{2+} exchanger. Such an efflux is coupled to an Na+influx. If more than two Na+ ions are exchanged for each Ca^{2+} ion, a net inward current occurs. The most widely recognized cause of DAD-dependent triggered activity is digitalis toxicity. After-depolarizations caused by digitalis sometimes may reach threshold to cause triggered action potentials, particularly if the rate of stimulation is sufficiently rapid. Ventricular arrhythmias (repetitive responses) caused by digitalis in the heart in situ also can be initiated by pacing at rapid rates. As toxicity progresses, the duration of the trains of repetitive responses induced by pacing increases. It is assumed that these arrhythmias are caused by DADs. In addition, spontaneously occurring accelerated ventricular rhythms and ventricular tachycardia that occur during digitalis toxicity are likely to be caused by DADs. Cardiac glycosides cause DADs by inhibiting the Na^{+}-K^{+} pump. In toxic amounts, this effect results in a measurable increase in intracellular Na^{+}. An increase in intracellular Na+ in turn causes an increase in intracellular $Ca^{2+.}$ When intracellular Na+ is increased, the concentration-dependent driving force for Na+ across the sarcolemma is decreased, and this in turn diminishes Ca^{2+} extrusion from the cell by Na^{+}-Ca^{2+} exchange. Hence, there is a net inward Ca^{2+}movement. Catecholamines are probably the next most widely recognized cause of DADs. Delayed afterdepolarizations and triggered activity caused by catecholamines have been recorded with microelectrodes in atrial fibers of the mitral valve, atrial fibers lining the coronary sinus, atrial fibers in the inferior right atrium, and atrial fibers from hearts with cardiomyopathy. Infusion of catecholamines through a catheter into the coronary sinus in the dog causes atrial tachycardia that has all the characteristics of triggered activity; therefore, some naturally occurring atrial tachycardias caused by triggered activity probably are induced by the sympathetic nervous system. Ventricular muscle and Purkinje fibers also can develop DADs in the presence of catecholamines. Sympathetic stimulation therefore may also cause triggered ventricular arrhythmias, possibly some of the ventricular arrhythmias that accompany exercise and some ventricu-

lar arrhythmias that occur during ischemia and infarction. Catecholamines may cause DADs by increasing the slow inward L-type Ca^{2+} current through stimulation of beta-adrenergic receptors. The net effect is an increase in transsarcolemmal Ca^{2+} entry into cardiac cells. In addition to increasing the inward Ca^{2+} current, catecholamines enhance the uptake of Ca^{2+} by the sarcoplasmic reticulum, leading to increased Ca^{2+} stored in the sarcoplasmic reticulum and the subsequent release of an increased amount of Ca^{2+} from the sarcoplasmic reticulum during contraction. The increased Ca^{2+} in the sarcoplasmic reticulum induced by catecholamines also may lead to the occurrence of DADs. Delayed afterdepolarizations and triggered activity also may occur in the absence of pharmacologic agents, catecholamines, or an increase in extracellular Ca^{2+}. Triggerable fibers have been found in the upper pectinate muscles bordering the crista terminalis in the rabbit heart, branches of the sinoatrial ring bundle or transitional fibers between the ring bundle and ordinary pectinate muscle, apparently normal fibers in human atrial myocardium, human atrial fibers with very low membrane potentials (below -60 mV) and slow response action potentials, rat ventricular muscle that is hypertrophic secondary to renovascular hypertension, and ventricular myocardium from diabetic rats.

Properties of delayed afterdepolarizations

The TI current that causes DADs is maximal at around -60 mV and diminishes at more positive and more negative membrane potentials. As a result of the dependence of the TI current on the level of membrane potential, the amplitude of DADs and therefore the possibility of triggered activity are influenced by the level of membrane potential at which the action potentials occur. In the digitalis-toxic Purkinje system, there is a "window" of membrane voltage for maximum diastolic potential, which is approximately between -75 and -80 mV, at which the amplitude of DADs tend to be greatest. When DADs occur at the membrane potentials that favor a maximum amplitude, any intervention that hyperpolarizes or depolarizes the membrane tends to reduce their magnitude and suppress any rhythms the afterdepolarizations might induce. Similarly, when there are no DADs in the presence of digitalis and the membrane potential is at a voltage less than or greater than the window, interventions

that bring membrane potential into this voltage range often induce DADs. A similar dependence on membrane potential has been shown for DADs in atrial fibers of the coronary sinus and in Purkinje fibers from infarcts. Delayed after-depolarizations are influenced by the action potential duration, with longer action potential durations favoring the occurrence of DADs. When the action potential duration is longer, more Ca^{2+} is able to enter the cell. Drugs such as quinidine, which prolong action potential duration, may increase DAD amplitude,183 while drugs such as lidocaine, which shorten action potential duration, may decrease DAD amplitude. The amplitude of DADs is dependent on the number of action potentials that precede them; i.e., after a period of quiescence, the initiation of a single action potential may be followed by either no afterdepolarization or only a small one. With continued stimulation, the after-depolarizations increase in amplitude, and triggered activity eventually may occur. The amplitude of DADs and their coupling interval to the previous action potentials also are dependent on the cycle length at which action potentials are occurring, and triggered activity can be induced by a critical decrease in the drive cycle length. This is illustrated by the effects of the stimulus cycle length on the amplitude of DADs recorded from an atrial fiber in the canine coronary sinus. Digitalis-induced DADs occur either singly or as two or more "damped" oscillations after the action potential. When two or more after-depolarizations are present, their relation to the drive cycle length is complex. As drive cycle length decreases, the amplitude of the first afterdepolarization increases, reaching a peak at a cycle length of about 500 ms, and triggered activity may occur. If it does not, at shorter drive cycle lengths the magnitude of this first afterdepolarization decreases. The second DAD, however, continues to increase in magnitude as drive cycle length shortens further and eventually may reach threshold and induce triggered activity. A decrease in the length of even a single drive cycle (i.e., a premature impulse) also results in an increase in the amplitude of the DAD that follows the premature cycle.

The premature coupling interval at which triggered activity occurs is also dependent on the basic drive cycle length. As the basic drive cycle length decreases, the premature coupling interval needed to induce triggered activity increases. Decreasing

the drive cycle length, in addition to increasing amplitude, tends to decrease the coupling interval of DADs to the action potential upstroke or terminal phase of repolarization by increasing the rate of depolarization of the afterdepolarization. As a result, there is a direct relation between the drive cycle length at which triggered impulses are initiated and the coupling interval between the first triggered impulse and the last stimulated impulse that induced them; i.e., as the drive cycle length is reduced, the first triggered impulse occurs earlier with respect to the last driven action potential. This characteristic property forms the basis for one of the indirect ways in which triggered activity induced by a decrease in the drive cycle length in the whole heart sometimes is distinguishable from reentrant activity induced by a decrease in the drive cycle length, since the relationship for reentrant impulses initiated by rapid stimulation is often the opposite; i.e., as drive cycle length is reduced, the first reentrant impulse occurs later with respect to the last driven action potential because of rate-dependent conduction slowing in the reentrant pathway (described in more detail later in this chapter). The increased time during which the membrane is in the depolarized state at shorter stimulation cycle lengths or after premature impulses increases Ca^{2+} in the myoplasm and the sarcoplasmic reticulum, thus increasing the TI current responsible for the increased afterdepolarization amplitude and causing the current to reach its maximum amplitude more rapidly, decreasing the coupling interval of triggered impulses. The repetitive depolarizations can increase intracellular Ca^{2+} because of repeated activation of the inward Ca^{2+} current that flows through L-type Ca^{2+} channels.

Early Afterdepolarizations and Triggered Activity

Early afterdepolarizations are manifest as a sudden change in the time course of repolarization of an action potential such that the membrane potential does not follow the trajectory characteristic of normal repolarization but suddenly shifts in a depolarizing direction. Early afterdepolarizations may appear at the plateau level of membrane potential, which is usually more positive than -60 mV, or they may appear later, during phase 3 of repolarization. Normally, a net outward membrane current shifts the membrane potential progressively in a negative direction during repolarization of

the action potential. An EAD occurs when for some reason the current-voltage relation is altered to cause outward current during repolarization to approach or attain 0, at least transiently. Such a shift can be caused by any factors that either decrease outward current, mostly carried by K+, or increase inward current, carried by Na^+ or $Ca^{2+.}$ If the change in the current-voltage relation results in a region of net inward current during the plateau range of membrane potentials, it can lead to a secondary depolarization (a triggered action potential) during the plateau or phase 3 by activating a regenerative inward current.

The level of membrane potential at which the triggered action potentials occur determines both the rate of triggered activity and whether the triggered action potentials can propagate and excite adjacent normal regions. At the more positive membrane potentials of the plateau, the rate of triggered activity is more rapid than it is late during phase 3. Triggered action potentials occurring at the plateau level have slow upstrokes; therefore, conduction of these action potentials sometimes may block, while the faster upstrokes of triggered action potentials occurring later during phase 3 enable them to propagate more easily. The ionic current responsible for the upstrokes of the action potentials during triggered activity caused by EADs is determined by the level of membrane potential at which the action potentials occur. Triggered action potentials occurring during the plateau phase and early during phase 3, at a time when most fast Na^+channels are still inactivated, most likely have upstrokes caused by the inward L-type Ca^{2+}current. At higher membrane potentials during late phase 3 of repolarization, where there is partial reactivation of the Na^+ channels, the upstrokes are caused by the fast inward Na^+ current. Current flowing through both L-type Ca^{2+} channels and partially reactivated fast Na^+ channels may be involved over intermediate ranges of membrane potential.

Causes of early afterdepolarizations and triggered activity

Early after-depolarizations and triggered activity have been produced in experimental studies under a variety of conditions, some of which would never be expected to be associated with naturally occurring arrhythmias in the in situ heart. Most of these conditions somehow delay repolarization of the action potential by increasing

inward current or decreasing outward current during the plateau and repolarization phases. Most often, EADs occur more readily in Purkinje fibers than in ventricular or atrial muscle, although EADs can readily occur in the so-called M cells, which are ventricular muscle cells with a prominent plateau phase. Early afterdepolarizations may occur when the rate of stimulation is markedly slowed, reducing the outward current generated by the Na^+-K^+ pump, especially when K^+ in the extracellular environment is lower than normal, also reducing outward current.

Early depolarizations and triggered activity have been seen in monophasic action potentials recorded from the ventricles in dogs with cesium-induced ventricular tachycardia. Because the experimental arrhythmias caused by agents such as cesium, which are known to induce EADs, resemble torsades de pointes, it has been proposed that clinically occurring torsades de pointes sometimes may be caused by EADs. Other agents that can cause EADs and triggered activity are used therapeutically, and therefore, arrhythmias associated with their use may result from triggered activity. Antiarrhythmic drugs that prolong the duration of the action potential of Purkinje fibers or ventricular muscle (e.g., sotalol, *N*-acetylprocainamide, and quinidine) can cause EADs and triggered activity.

Arrhythmias Caused by Reentry

Requisites for reentrant excitation

Perhaps the easiest way to illustrate this is to discuss again, but in more detail, the earliest description of re-entrant excitation by Mayer in 1906 in the excitable subumbrella ring of tissue of the scyphomedusae (jellyfish). Unidirectional block must be present or the excitation wave fronts traveling around the ring will collide and extinguish each other. If the site of unidirectional block instead manifests bidirectional block, reentrant excitation will not occur because the circulating excitation wave' front will be unable to propagate through the area of block to re-excite the tissue that initially was excited. There must be a central area of block around which the reentrant excitation wave front can circulate. In this example, it is the hole in the center of the ring that clearly is inexcitable. Without a central area of block, the excitation wave front will not necessarily be conducted around the ring of excitable tissue. Rather, it

could take a shortcut, permitting the circulating excitation wave front to arrive quite early at the site where it originated. If it arrives sufficiently early, the latter tissue will still be refractory, and reentrant excitation will not be possible. But even with the presence of a central area of block and without the presence of a shortcut, the circulating wave front will manifest reentrant excitation only if the tissue it initially activated has had sufficient time to recover its excitability by the time the reentrant wave front returns. Thus, conduction of the circulating excitation wave front in the rest of the circuit must take long enough for this to happen, and there must always be a gap of excitable tissue (either fully or partially excitable) ahead of the circulating wavefront (the so-called excitable gap). In the case of the experiment by Mayer on the subumbrella ring of excitable tissue of the jellyfish, conduction velocity was constant and the length of the ring was long enough that conduction time around the ring was longer than the effective refractory period of the excitable tissue constituting the ring, permitting reentry. If the length of the ring had been critically shorter or if the conduction velocity had been critically faster, the circulating excitation wavefront would have arrived at the site of initial excitation before sufficient recovery of excitability had occurred, preventing re-excitation.

From these sorts of observations grew the concept of the wavelength of the circulating impulse. The wavelength is the product of the conduction velocity of the circulating excitation wave front and the effective refractory period of the tissue in which the excitation wave front is propagating. It quantifies how far the impulse travels relative to the duration of the refractory period. Thus, the wavelength of the reentrant excitation wave front must be shorter than the length of the pathway of the potential reentrant circuit for reentrant excitation to occur; i.e., the impulse must travel a distance during the refractory period that is less than the complete reentrant path length to give myocardium ahead of it sufficient time to recover excitability.

For virtually all clinically important reentrant arrhythmias resulting from ordered reentry, however, in the presence of uniform, normal conduction velocity along the reentrant pathway, the wavelength would be too long to permit reentrant excitation. Thus, virtually all these arrhythmias must have, and in fact do have, one or more

areas of slow conduction as a part of the reentrant circuit. The associated changes in conduction velocity (as well as associated changes in refractory periods) actually cause the wavelength to change in different parts of the circuit. However, the presence of one or more areas of slow conduction permits the average wavelength of reentrant activation to be shorter than the path length. The fact that the reentrant circuit of virtually all clinically important reentrant arrhythmias has one or more areas of slow conduction serves to emphasize the fact that the electrophysiologic properties of the cardiac tissue making up the reentrant circuit are not uniform. In fact, there may be, and usually are, variations of conduction velocity and refractoriness along the course of the reentrant circuit. An additional requisite for random reentry is the necessity of a critical mass of tissue to sustain the one or usually more simultaneously circulating reentrant excitation wavefronts.

Thus, it is essentially not possible to achieve sustained fibrillation of ventricles of very small normal mammalian hearts and equally difficult to achieve sustained fibrillation of the normal atria of humans or smaller mammals. Finally, another prerequisite for reentrant excitation to occur is often (but not always) the presence of an initiating trigger. The trigger, usually the occurrence of one or more premature beats, frequently is required because it elicits or brings to a critical state one or more of the conditions necessary to achieve reentrant excitation.

Thus, a premature impulse initiating reentry may arrive at one site in the potential reentrant circuit sufficiently early that it encounters unidirectional block because that tissue has had insufficient time to recover excitability after excitation by the prior beat. Furthermore, in the other limb of the potential reentrant circuit, the premature arrival of the excitation wave front either causes slow conduction or results in further slowing of conduction of the excitation wave front through an area of already slow conduction. The resulting increase in conduction time around this limb of the potential reentrant circuit serves to allow the region of unidirectional block in the tissue in the other limb activated initially by the premature beat to recover excitability. Thus, when the circulating excitation wave front of the premature beat arrives at these tissue sites, the excitation wave front can re-excite the tissue, thus manifesting reentrant

excitation. It should be noted that the mechanism causing the premature beat may be different from the reentrant mechanism causing the tachycardia.

Thus, the premature beat may be caused by automaticity or triggered activity. An example of the latter may be torsade de pointes, in which the initiating beat (or beats) is the result of triggered activity caused by early afterdepolarization, but the remainder of the beats in this rhythm (it is frequently nonsustained) are now thought to be due to reentry. Another example may occur during cardiac catheterization, in which the premature beat may be due to the catheter forcefully hitting the heart wall, i.e., a mechanical cause. However, the trigger to initiate reentrant excitation need not be a premature beat. The trigger to initiate reentrant excitation may be the normal sinus beat. One example is the rhythm known as permanent nonparoxysmal AV junctional reentrant tachycardia. In this example, the potential reentrant circuit contains an area of permanent unidirectional block in an antegrade direction. Moreover, the potential reentrant circuit also has a relatively stable area of very slow conduction, causing the wavelength of the propagating excitation wavefront to be shorter than the path length of the potential reentrant circuit. In this circumstance, the normal sinus beat propagates around the reentrant circuit with sufficient delay that when it arrives in a retrograde direction at the area of permanent antegrade unidirectional block, the tissue at that site has recovered excitability. Furthermore, the conduction time around the reentrant circuit is such that the excitation wavefront continually encounters excitable tissue in the direction in which it is propagating, resulting in continuous reentrant excitation and an incessant tachycardia. Another example where a premature beat is not necessary is reentrant premature ventricular beats, as in ventricular bigeminy.

Components of the reentrant circuit

The Substrate

The cardiac tissue that constitutes the substrate for reentrant excitation can be located almost anywhere in the heart. Furthermore, the reentrant circuit may be a variety of sizes and shapes and may include a number of different kinds of myocardial cells, e.g., atrial, ventricular, nodal, and Purkinje. The reentrant circuit may be an anatomic structure such as a loop of fiber bundles in the Purkinje system. The reen-

trant circuit may be a functionally rather than an anatomically defined pathway, with its existence, size, and shape determined by the electrophysiologic properties of cardiac tissues in which the reentrant wavefront circulates, as has been shown in some patients with atypical atrial flutter. Or it may be an anatomic-functional combination, as has been suggested for some intraatrial reentrant rhythms, such as atrial flutter.

The Area(s) of Slow Conduction

As has been discussed, a condition necessary for reentry is that the impulse be delayed sufficiently in the alternative pathway(s) to allow elements proximal to the site of unidirectional block to recover excitability. If reentry is to succeed, the impulse traveling around the reentrant circuit in one direction as a result of the unidirectional block must not return to this site of block before it and regions around it recover excitability. In the presence of normal conduction, sufficient time to allow recovery of excitability may occur if the alternative pathway is sufficiently long. Reentry is facilitated when conduction in all or a part of the alternative pathway is slow, since long pathways that are often not present in the heart are then not necessary. The area(s) of slow conduction may be an anatomic structure normally expected to manifest slow conduction, such as the AV node.

Thus, the AV node is the area of slow conduction in AV reentrant tachycardia (a reentrant tachycardia in which the circuit involves the atria, the AV node, the His-Purkinje system, the ventricles, and an accessory AV connection). The area of slow conduction may be in cardiac tissue that normally does not manifest slow conduction. Such an area is not present during sinus rhythm (in contrast to the AV node) but is functionally present during the tachycardia. These areas may develop as a result of premature excitation or may evolve during a rapid transitional rhythm as occurs during atrial flutter. An example of a functionally determined area of slow conduction is found in the posterior-inferior right atrium during atrial flutter in patients or in the free wall of the right atrium of the canine sterile pericarditis mode of atrial flutter. Slow conduction can be a consequence of active membrane properties determining the characteristics of inward currents depolarizing the membrane during the action

potential, or it can be a consequence of passive properties governing the flow of current between cardiac cells.

Depression of resting membrane potential

An important feature of the transmembrane action potential of atrial, ventricular, and Purkinje fibers that governs the speed of propagation is the magnitude of the inward Na^+ current flowing through the fast Na^+ channels in the sarcolemma during the upstroke. The magnitude of this current flow is reflected in the rate at which the cell depolarizes (V(r)max of phase 0) and the overshoot of the upstroke (the positive level of depolarization). The depolarization phase or upstroke of the action potential results from the opening of specific membrane channels (fast Na^+channels) through which Na^+ ions rapidly pass from the extracellular fluid into the cell. During conduction of the impulse, the inward transmembrane Na+ current flowing during the depolarization phase (phase 0) of the action potential results in the flow of axial current along the cardiac fiber through the cytoplasm and the gap junctions of the intercalated disks that connect the cardiac cells. The current flows out of the cells through the membrane ahead as resistive and capacitive current. The conduction velocity depends on both how much capacitive current flows out of the cell at unexcited sites ahead of the propagating wave front and the distance at which the capacitive current can bring membrane potential to threshold. One important factor that influences the amount of current flowing through the sarcoplasm of a muscle fiber (axial current), and therefore capacitive current, is the amount of fast inward current causing the propagating action potential. A reduction in this inward current, leading to a reduction in the rate or amplitude of depolarization during phase 0, may decrease axial current flow, slow conduction, and lead to conduction block. Such a reduction may result from inactivation of Na^+ channels. The intensity of the inward Na^+ current depends on the fraction of Na^+ channels that open when the cell is excited and the size of the Na^+ electrochemical potential gradient (relative concentration of Na^+ in the extracellular space compared with Na^+ concentration inside the cell). The fraction of Na^+ channels available for opening is determined largely by the level of membrane potential at which an action potential is initiated. The Na^+ channels are inactivated either after the upstroke

of an action potential or if the steady-state resting membrane potential is reduced. Immediately after the upstroke, cardiac fibers are inexcitable because of Na^+ channel inactivation at the positive level of membrane potential.

During repolarization, progressive removal of inactivation allows increasingly large Na+ currents to flow through the still partially inactivated Na^+ channels when the cells are excited. The inward Na^+ current, amplitude, and rate of rise of premature action potentials initiated during this relative refractory period are reduced because the Na^+ channels are only partly reactivated. The conduction velocity of these premature action potentials is low. Premature activation of the heart therefore may induce reentry because premature impulses conduct slowly in regions of the heart where the cardiac fibers are not completely repolarized (where Na^+ channels are to some extent still inactivated).

Conduction slow enough to facilitate reentry also may occur in cardiac cells with persistently low levels of resting potential (which may be between -60 and -70 mV) caused by disease. At these resting potentials, a significant percentage of the Na^+ channels are inactivated; therefore, they are unavailable for activation by a depolarizing stimulus. Also, at these resting membrane potentials, recovery from inactivation is markedly prolonged and extends beyond complete repolarization. The magnitude of the inward current during phase 0 of the action potential is reduced; consequently, both the speed and the amplitude of the upstroke are diminished, decreasing axial current flow and slowing conduction significantly. Such action potentials with upstrokes dependent on inward current flowing via partially inactivated Na^+ channels sometimes are referred to as *depressed fast responses*. Further depolarization of the resting membrane potential and further inactivation of the Na^+ channel may decrease the excitability of cardiac fibers to such an extent that they may become a site of unidirectional conduction block. Thus, in a diseased region with partially depolarized fibers, there may be some areas of slow conduction and some areas of conduction block, depending on the level of resting potential and the amount of Na^+ channels that are inactivated. This combination may cause reentry. The chance for reentry in such fibers is even greater during premature activation or during rhythms at a rapid rate

because slow conduction or the possibility of block is increased even further owing to the prolonged time for the Na^+ channels to recover from inactivation when the resting potential is partially depolarized.

After the upstroke of the normal action potential of atrial, ventricular, or Purkinje cells, membrane potential begins to return to the resting level because the Na+ channels are inactivated and the fast (depolarizing) Na^+ current ceases to flow. This return, however, is slowed by a second inward current that is smaller and slower than the fast Na^+ current and probably is carried by both Na^+ and Ca^{2+} ions. This secondary inward current flows through L-type Ca^{2+} channels that are distinct from the fast Na^+ channels. The threshold for activation of the L-type Ca^{2+} current is in the range of -30 to -40 mV, compared with about -70 mV for the fast Na^+ current. This current inactivates much more slowly than does the fast Na+ current and gradually diminishes as the cell repolarizes. It causes much of the plateau phase of the action potential. Under special conditions, this Ca^{2+} current also may underlie the occurrence of the slow conduction that causes reentrant arrhythmias. Although the fast Na+ channel may be largely inactivated at membrane potentials near -50 mV, the L-type Ca^{2+} channel is not inactivated and is still available for activation. Under certain conditions, when the resting potential is reduced to levels lower than -60 mV (as occurs when membrane conductance is very low or when catecholamines are present), this normally weak inward Ca^{2+} current may give rise to regenerative action potentials that propagate very slowly and are prone to block. The propagated action potential, which is dependent on inward Ca^{2+} current, is referred to as the *slow response*. Slow-response action potentials can occur in diseased cardiac fibers with low resting potentials, but they also occur in some normal tissue of the heart, such as cells of the sinus and AV nodes, where the maximum diastolic potential is normally about -60 mV or less. In fact, slow conduction is a normal property of both the sinus and the AV nodes. Thus, it should be of no surprise that either of these nodes may be a critical area of slow conduction in some reentrant circuits, e.g., the AV node in AV reentrant tachycardia involving an accessory AV connection.

Anisotropy

The slow conduction that facilitates the occurrence of reentry also can be caused by factors other than a decrease in inward current during the upstroke of the transmembrane action potential. An increased resistance to axial current flow, which can be expressed as *effective axial resistance* (defined as resistance to current flow in the direction of propagation) decreases the magnitude and spread of axial current of the propagating impulse among the myocardial fibers and may decrease conduction velocity. During conduction of the impulse, axial current flows from one myocardial cell to the adjacent cell through the gap junctions of the intercalated disks, which form a major source of intercellular resistance to current flow between fiber bundles. Therefore, the structure of the myocardium that governs the extent and distribution of these gap junctions has a profound influence on axial resistance and conduction. This influence can be seen in normal atrial or ventricular myocardium, although the structure is different in different regions. The atria (crista terminalis) and certain regions of the ventricles (except for the subepicardial muscle) are composed of bundles of myocardial cells that have been called *unit bundles.* Such bundles are made up of 2 to 30 cells surrounded by a connective tissue sheath. Within a unit bundle, cells are tightly connected or coupled to each other through intercalated disks that contain the gap junctions. All the cells of a unit bundle are connected to each other within the space of 30 to 50 m down the length of a strand. An individual cardiac myocyte may be connected to as many as nine other myocytes through one or more intercalated disks. These connections are mainly at the ends of the myocytes rather than along their sides, but the overlapping nature of the junctions effectively connects myocytes within a bundle in the transverse direction as well as the longitudinal direction. Therefore, as a consequence of the many intercellular connections, the myocytes in a unit bundle are activated uniformly and synchronously as an impulse propagates along the bundle. The unit bundles also are connected to each other. Unit bundles lying parallel to each other in normal atrial and ventricular muscle are connected in a lateral (transverse) direction at intervals in the range of 100 to 150 m. As a consequence of this structure, the myocardium in regions in which unit bundles occur is better coupled in the direction of the long axis of its cells and bundles (because of the

high frequency of the gap junctions within a unit bundle) than in the direction transverse to the long axis (because of the low frequency of interconnections between the unit bundles). This is reflected in a lower axial resistivity in the longitudinal direction than in the transverse direction in cardiac tissues that are composed of many unit bundles. The structure of the interconnections between muscle fibers is somewhat different in the subepicardial regions of the ventricles (and possibly other regions as well) but is still a cause of lower longitudinal axial resistance rather than transverse axial resistance. The subepicardial region is not made up of unit bundles. Each ventricular muscle cell is connected to approximately 11 to 12 other muscle cells in three dimensions. The junctions that connect the cells occur at both the ends and the sides of cells in roughly equivalent numbers; approximately half of all connections are side to side, and half are end to end.

Therefore, activation wave fronts can conduct equally well between individual cells in both the longitudinal and transverse directions because there are equal numbers of gap junctions. In the transverse direction, however, a wave front encounters more gap junctions than it does over an equivalent distance in the longitudinal direction because cell diameter is much smaller than cell length; therefore, the wave front must traverse more cells transversely. Thus, there is a greater resistance transversely than longitudinally because of the increased number of gap junctions per unit distance traveled. As was stated above, the effective axial resistivity is an important determinant of the conduction velocity; therefore, conduction through atrial and ventricular myocardium is much more rapid in the longitudinal direction, owing to the lower resistivity, than it is in the transverse direction.

Thus, cardiac muscle is anisotropic; its conduction properties vary depending on the direction in which they are measured. It has been classified anisotropy into two major subdivisions: uniform and nonuniform. Uniform anisotropy is characterized by an advancing wavefront that is smooth in all directions (longitudinal and transverse to fiber orientation), indicating relatively tight coupling between groups of fibers in all directions. Uniform anisotropy is exemplified by the conduction properties of normal septal ventricular muscle. The slow conduction in the direction transverse to the lon-

gitudinal fiber axis occurs despite action potentials with normal resting potentials and upstroke velocities and is caused by the higher transverse axial resistance. Associated with the differences in conduction velocity that are based on the direction of propagation, however, are unexpected changes in the action potentials. In uniformly anisotropic tissue, the extracellular unipolar waveform has a large-amplitude, smooth biphasic, positivenegative morphology during propagation in the fast longitudinal direction and a low-amplitude, smooth triphasic morphology in the transverse direction. The initial negativity of the electrogram in the transverse direction is a reflection of distant activity rapidly propagating along the longitudinal axis.

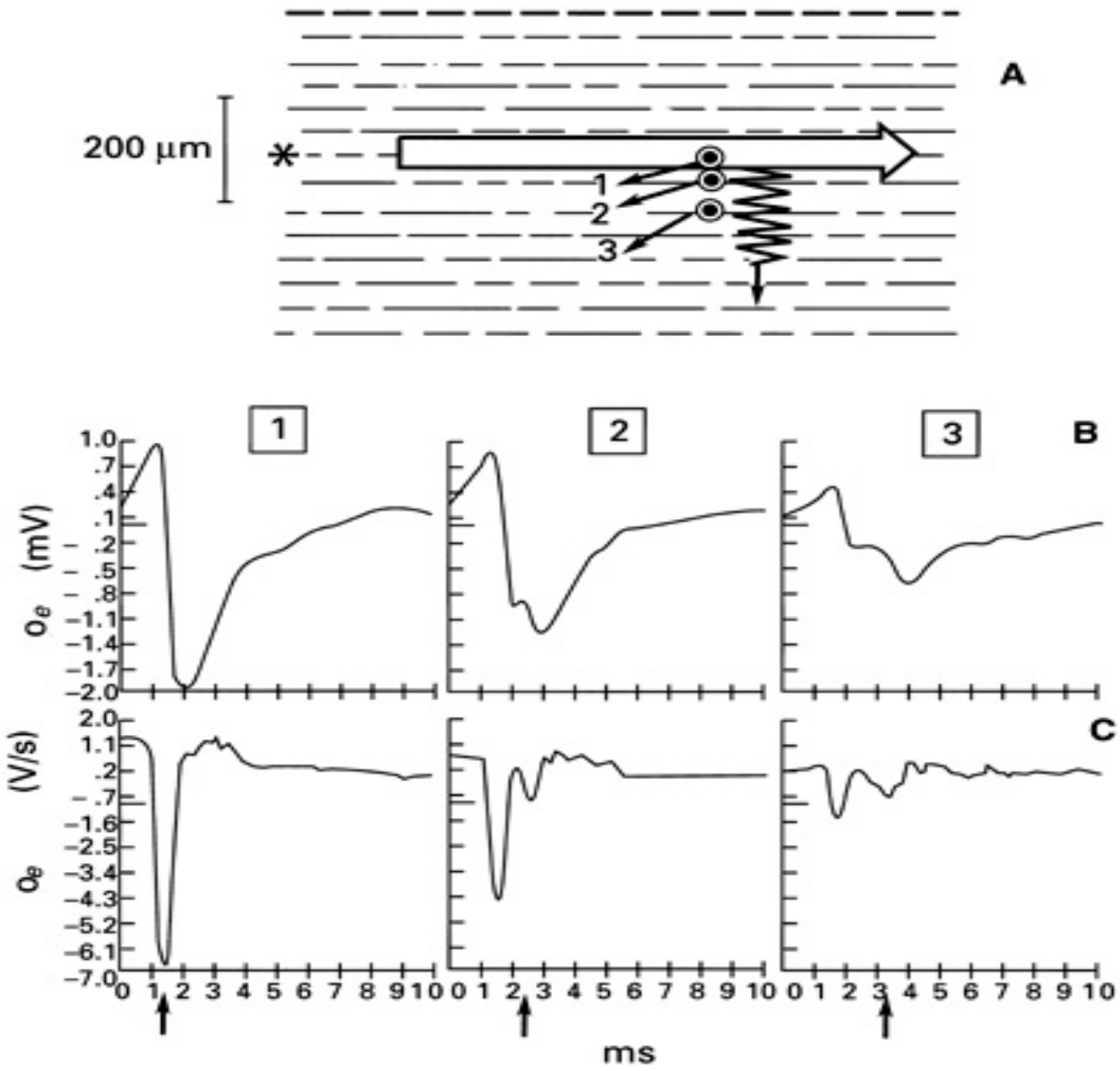
Nonuniform anisotropy has been defined as tight electrical coupling between cells in the longitudinal direction but recurrent areas in the transverse direction in which side-to-side electrical coupling of adjacent groups of parallel fibers is absent. Therefore, propagation of normal action potentials transverse to the long axis is interrupted so that adjacent bundles are excited in a markedly irregular sequence (*zigzag conduction*). In nonuniformly anisotropic muscle, there also may be an abrupt transition in conduction velocity from the fast longitudinal direction to the slow transverse direction, unlike the case with uniform anisotropic muscle, in which intermediate velocities occur between the two directions. This pattern of excitation in nonuniform anisotropic atrial pectinate bundles from older patients is diagrammed in Figure 2.9.

The white arrow on the outline of the preparation indicates the narrow region of fast conduction down the long axis of the fibers when the bundle was excited at the asterisk. The zigzag arrow indicates the irregular course of excitation across the fibers, which occurred all along the length of the zone of fast conduction.

Conduction in the transverse direction in these nonuniformly anisotropic bundles was nearly as slow at the slowest conduction associated with membrane depolarization and slowresponse action potentials. As in uniform anisotropy, the upstroke velocity of the action potential is more rapid in the slow direction transverse to the long axis of the fibers than in the fast direction parallel to the long axis.

Figure 2.9

Diagram of a nonuniform anisotropic atrial muscle bundle with the long axis of the myocardial fibers indicated by the dashed lines.



Notes:

A. The bundle was stimulated at the asterisk. Propagation of the longitudinal wavefront is shown by the large white arrow. Transverse propagation occurred as diagrammed by the zigzag arrow.

B. Electrograms recorded from sites 1, 2, and 3 on the diagram.

C. The first derivative of these electrograms is shown

The morphologic basis for the nonuniform anisotropic properties in human atrial muscle is that the fascicles of muscle bundles are separated in the transverse direction by fibrous tissue that proliferates with aging to form longitudinally oriented insulating boundaries. Intercellular connections cannot occur where the cardiac fibers are

separated by connective tissue septa and there is uncoupling between parallel-oriented groups of fibers. Part of the reduction of the conduction velocity in this transverse direction may be a result of the tortuous path length necessary for the wavef ront to propagate transversely from one bundle to another because of these septa, accounting for the zigzag activation pattern. Similar connective tissue septa cause nonuniform anisotropy in other normal cardiac tissues, such as the crista terminalis and the interatrial band in adult atria or ventricular papillary muscle, as well as pathologic situations such as chronic ischemia or a healing myocardial infarction, in which fibrosis in the myocardium occurs.

In addition to the structural features of the cellular interconnections influencing axial current flow and conduction as expressed in the anisotropic properties of cardiac muscle, the intercellular resistance may increase because of an increase in gap junctional resistance that results from a decrease in the conductance of the junctions, i.e., a decrease in the ease with which the ions that carry axial current move through the junctions.

Unidirectional Block

Unidirectional block occurs when an impulse cannot conduct in one direction along a bundle of cardiac fibers but can conduct in the opposite direction. This condition is necessary for the occurrence of classical reentrant rhythms. Thus, unidirectional block in part of the circuit leaves a return pathway through which the impulse conducts to reenter previously excited areas. A number of mechanisms, involving both active and passive electrical properties of cardiac cells, may cause unidirectional block.

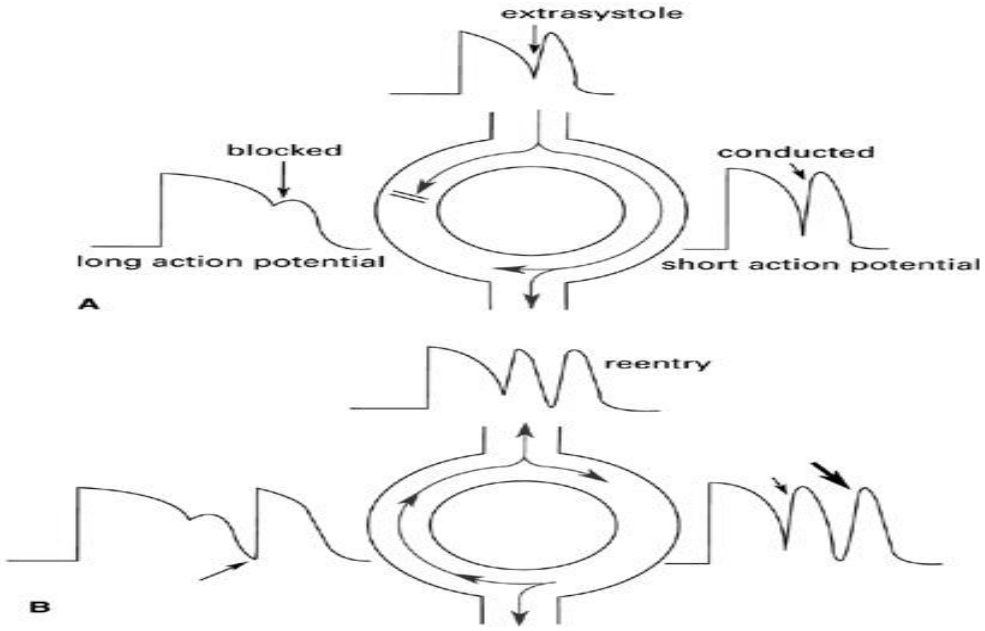
Regional differences in recovery of excitability

One cause of unidirectional block that allows the initiation of reentry is regional differences in recovery of excitability. When differences in the duration of the effective refractory period occur in adjacent areas, conduction of an appropriately timed premature impulse may be blocked in the region with the longest refractory period, which then becomes a site of unidirectional block, while conduction continues through regions with a shorter refractory period. Figure 2.10 is a schematic represen-

tation of the initiation and continuation of circus movement in an anatomically defined circuit, with differences in effective refractory period duration resulting from differences in the time course of action potential repolarization being the cause of unidirectional block in one of the pathways.

Figure 2.10.

Diagram of reentry caused by dispersion in refractory periods. A ring of cardiac tissue is shown, and the pattern of conduction is indicated by the arrows. Action potentials with different durations located in different regions of the ring are diagrammed.



The action potentials in various parts of the circuit are shown. In the upper panel (*A*), conduction of a premature impulse (extrasystole), which either can be induced by electrical stimulation or may occur "spontaneously," is blocked in the pathway with the long action potential duration and therefore long effective refractory period (to the left), referred to as the *blocked pathway*. The premature impulse, however, conducts in the other pathway with shorter action potential durations and refractory periods (to the right). This pattern of activation is indicated by the arrows. For block to occur, the premature impulse also must arise in a region with a short effective refractory period so that it occurs before repolarization of the action potentials in the left pathway occurs. In the lower panel (*B*), which shows the continuation of these events, the blocked pathway is invaded retrogradely by the impulse conducting from the right, thus causing the second action potential (arrow at the left). The proximal region

where the premature impulse originated is then reexcited (reentry) as the impulse once again enters the right pathway and continues around the reentrant circuit, causing another action potential in the right pathway (large arrow). For successful reexcitation to occur in the region where the premature impulse was initiated, elements in the circuit at the region of block and proximal to it (toward the site of origin) must have regained their excitability by the time the cardiac impulse arrives there. Continuation of reentry induced by a premature impulse also is facilitated because the duration of the effective refractory period associated with conduction of the premature impulse is shortened. Therefore, on the next excursion of the reentrant impulse around the circuit, conduction occurs in a circuit with a shorter effective refractory period. Finally, the conduction velocity of premature impulses may be decreased, shortening the wavelength and facilitating successful excitation of the region proximal to the unidirectional block.

Therefore, unidirectional block caused by regional differences in excitability is actually a result of transient block. Block occurs in the antegrade direction in the left pathway while conduction is successful in the retrograde direction. This kind of unidirectional block can cause the initiation of reentry not only in anatomic circuits, as shown in Figure 10, but also in functional circuits. For reentrant arrhythmias to arise because of regional differences in effective refractory periods, a premature impulse that initiates reentry is as necessary a requirement as are the conditions allowing the perpetuation of reentrant activation. Thus, both a "trigger" (the premature impulse) and a "substrate" (the reentrant circuit) are needed. The mechanism causing the premature impulse may be quite different from the arrhythmia it initiates. It may arise spontaneously by automaticity or result from triggered activity. The premature impulse also may be induced by an electrical stimulus during a programmed stimulation protocol. The degree of nonuniformity in effective refractory period duration necessary for a properly timed premature stimulus to cause unidirectional block may be quite small. This degree of nonuniformity often is referred to as the *dispersion in the refractory periods* or *dispersion in recovery of excitability,* meaning the difference between the shortest and longest refractory periods.

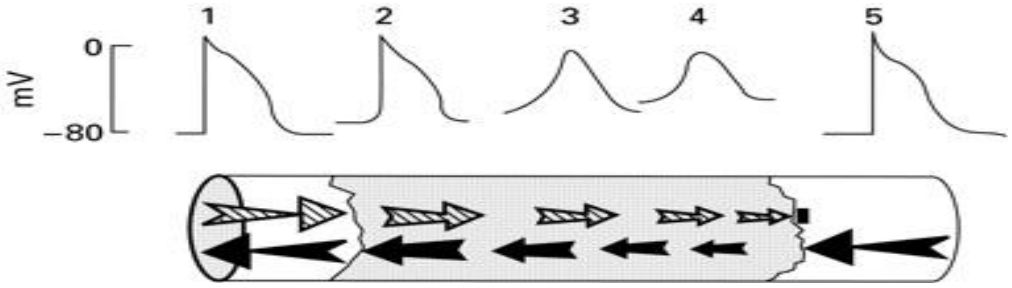
When stimuli were delivered in the region with the shortest refractory period at the border of two areas with different refractory periods in atrial tissue, the minimal difference in effective refractory period needed to cause block of an appropriately timed stimulated premature impulse was between 11 and 16 ms, well within the normal physiologic range of variation of effective refractory period durations. A properly timed single premature stimulus can initiate reentry in the atria because the differences in refractory period may cause unidirectional block. In the ventricles, where refractory periods are much longer than they are in the atria, the physiologic differences between the longest and shortest refractory period durations is on the order of 40 ms. Unlike the case in the atria, dispersion of refractory periods in normal ventricles is not sufficiently large to allow initiation of reentry by premature impulses.

Asymmetric depression of excitability

Unidirectional conduction block in a reentrant circuit also can be persistent and independent of premature activation. Persistent unidirectional block often is associated with depression of the transmembrane potentials and excitability of cardiac fibers. There are several possible mechanisms for the persistent unidirectional block in a region where action potentials are depressed. One mechanism is asymmetric depression of excitability. This asymmetric depression may occur because of asymmetric distribution of a pathologic event. As a simple example, the action potential upstrokes in a bundle of fibers may be diminished as a result of a reduction of perfusion after coronary occlusion, but the depression of the upstroke may be more severe toward one end of the bundle than toward the other. This situation is diagrammed in Figure 2.11. A propagating impulse consisting of an action potential with a normal upstroke velocity (site 1) enters the poorly perfused region (stippled in the diagram) and propagates through this region with decrement (from left to right or from site 1 to 4); i.e., as it conducts from the less depressed end (1) to the more severely depressed end (4), the action potential upstroke velocity and amplitude progressively decrease, as does the axial current flowing toward cells that will be excited by the upstroke (as indicated by the decreasing size of the striped arrows). When the impulse arrives at the opposite end of the depressed segment of the bundle where there is suddenly a

normally perfused bundle with normal action potentials (between action potentials 4 and 5), the action potential amplitude is markedly reduced and the weak axial current from site 4 is not sufficient to depolarize the normal membrane to threshold at site 5. Conduction therefore blocks in the left-to-right direction even though the normally perfused region is excitable. Conduction in the opposite direction (from right to left), however, still may succeed. The large axial current generated by the normal action potential at site 5 can flow for a considerable distance through the depressed region and may depolarize to threshold fibers at some distance from the most severely depressed region (perhaps as far as site 3). These cells in turn may be able to excite adjacent fibers in the direction of propagation (from right to left), and as a result, the impulse successfully propagates from site 3 to site 1, as indicated by the black arrows.

Figure 2.11.
Asymmetric depression of excitability as a mechanism for unidirectional conduction block in a bundle of cardiac muscle fibers.



Note: the action potentials shown above were recorded from sites on the fiber bundle. The shaded part of the bundle is depressed. Conduction from left to right along the bundle is indicated by the striped arrows, conduction from right to left by the black arrows.

Geometric factors causing unidirectional block

Geometric factors related to tissue architecture also may influence impulse conduction and under certain conditions lead to unidirectional block. An impulse can conduct rapidly in either direction along the length of a bundle of atrial, ventricular, or Purkinje fibers with normal electrophysiologic properties. There is usually some asymmetry in the conduction velocity, however, meaning that conduction in one di-

rection may take slightly longer than it does in the other direction. This is usually of no physiologic significance.

The asymmetry of conduction can result from several factors. Bundles of cardiac muscle are composed of interconnecting myocardial fibers with different diameters packed in a connective tissue matrix. These bundles branch frequently (although the individual myocardial fibers do not branch). An impulse conducting in one direction encounters a different sequence of changes in fiber diameter, branching, and frequency and distribution of gap junctions than it does when traveling in the opposite direction. The configuration of pathways in each direction is not the same. These structural features influence conduction by affecting the axial currents that flow ahead of the propagating wave front.

The results of theoretical analyses indicate that the conduction velocity of an impulse passing abruptly from a fiber of small diameter to one of large diameter transiently slows at the junction because the larger cable results in a larger sink for the longitudinal axial current (there is more membrane for this current to depolarize to threshold if conduction of the impulse is to continue). A similar slowing occurs when an impulse conducts into a region where there is an abrupt increase in branching of the myocardial syncytium; conduction transiently slows because of the larger current sink provided by the increased membrane area that must be depolarized.

In the opposite direction, it can be predicted that conduction will speed transiently as the impulse moves from a larger cable to a smaller cable because the small sink for axial current results in more rapid depolarization of the membrane to threshold. Theoretically, if there is a large enough difference in the diameter of the two cables, an impulse conducting from the small cable to the large cable should block at the junction, while conduction in the opposite direction (from large cable to small cable) is maintained.

Anisotropy also can result in unidirectional block at sites of muscle bundle branching or at the junction of muscle bundles. When a wave front propagating in a bundle of parallel fibers enters a branch formed at an acute angle, the direction of propagation is altered quickly from longitudinal to transverse, causing an abrupt in-

crease in the effective axial resistance in the direction of propagation and a slowing of conduction velocity. If the inward current also is reduced by partial depolarization, as occurs after premature stimulation or elevation of extracellular K+, conduction block may occur.

Alterations in Refractory Period

Alterations in the effective refractory period may contribute to the occurrence of reentry. A decrease in the effective refractory period decreases the wavelength of the reentrant impulse and therefore the necessary size of the reentrant circuit. If the refractory period is decreased, the degree of slow conduction needed for successful reentry is diminished. The effective refractory period of cardiac fibers in a reentrant circuit may be decreased during rapid tachycardias because of rate-dependent shortening of the action potential duration. If the effective refractory period is decreased sufficiently, more than one reentrant circuit can exist at a time in some regions. The effective refractory period of atrial muscle, for example, is decreased by the acetylcholine released during vagal stimulation. As a result, reentry in atrial muscle causing atrial fibrillation is more easily induced during vagal stimulation. Several reentrant circuits exist simultaneously during this arrhythmia. Action potential duration and effective refractory period are decreased in the ventricle during reperfusion after brief periods of ischemia or in some of the ventricular muscle cells in chronically ischemic areas, probably contributing to the occurrence of reentry.

The Central Area of Block

The central area of block around which the reentrant wavefront circulates may be anatomic, functional, or a combination of the two. Anatomic block is the result of a nonconductive medium in the center of the circuit. An example of an anatomically determined central area of block is in the tricuspid ring reentrant circuit found in a canine model of atrial flutter and perhaps present in a clinical counterpart, the atrial flutter found commonly in patients who have previously had a Mustard procedure to repair transposition of the great vessels. The animal model depends critically on large incisions made in the right atrial free wall, which in fact are similar to those made by

the surgeon during the Mustard procedure. Functional block at the center of a circuit occurs when there is block of impulses in otherwise excitable cardiac muscle.

The central area of functional block develops during the initiation of the reentrant circuit by the formation of a line of block that most likely is due to refractoriness. When the reentrant circuit forms, the line of block then is sustained by centripetal activation from the circulating reentrant wave front, which by repeatedly bombarding the central area of block maintains the state of refractoriness of this region. A combination of an anatomic and a functional central area of block in the reentrant circuit has been described in some models of atrial flutter (e.g., the orifice of one or both of the cavae and an area of functional block continuous with or adjacent to either or both of the caval orifices).

The Excitable Gap in a reentrant circuit is the region of excitable myocardium that immediately precedes the head of the reentrant wavefront and moves around the circuit in advance of the reentrant wavefront. The occurrence of a gap is dependent on the recovery of excitability of the myocardium from its previous excitation by the reentrant wavefront. There are two different measurements of the excitable gap. One is the spatial gap, which is the distance in the circuit ahead of the wavefront that is excitable. The spatial gap may be composed of either partially excitable or fully excitable myocardium, depending on the time interval between successive excitations of the circuit. The size of the spatial gap changes in different parts of the circuit as the wavelength of the reentrant impulse changes because of changes in conduction velocity, refractory periods, or both, as was described previously.

The second measurement of the excitable gap is the temporal excitable gap. This is the time period during the cardiac cycle in which a stimulus can excite the region ahead of the reentrant wave front. In regard to the spatial gap, the temporal gap in different parts of the reentrant circuit also can have both partially excitable and fully excitable components and varies in different parts of the circuit because of the changes in the wavelength. The characteristics of the excitable gap may be quite different in reentrant circuits caused by different mechanisms. For example, some anatomically determined circuits have been shown to have large excitable gaps with a fully excita-

ble component, although even in anatomically determined circuits, the gap may be only partially excitable. By comparison, functional reentrant circuits caused by the leading circle mechanism have very small gaps that are only partially excitable, although parts of some functionally determined reentrant circuits may have a small fully excitable gap during part of the reentrant cycle.

Types of reentry

It was indicated previously that there are two types of reentry: ordered and random. The reentrant circuits can be anatomically determined, functionally determined, or both. In anatomically determined circuits, the pathway is fixed and the characteristics of the reentrant circuit are determined by the characteristics of the anatomic components of the circuit. Anatomic circuits therefore are associated with ordered reentry. Perhaps the best example is AV reentrant tachycardia, in which the reentrant circuit is composed of atrium, the AV node, the His-Purkinje system, the ventricle, and an accessory AV connection.

In functionally determined circuits, the pathway is formed because of the electrophysiologic properties of the cardiac cells, not by a predetermined anatomic pathway. Functional circuits can be associated with ordered or random reentry. Mechanisms for functionally determined reentrant circuits include the leading circle type of reentry, anisotropic reentry, and spiral wave re-entry.

It has been identified that an initiation of re-entry was made possible by the different refractory periods of atrial fibers in close proximity to one another. The premature impulse that initiated reentry blocked in fibers with long refractory periods and conducted in fibers with shorter refractory periods, eventually returning to the initial region of block after excitability recovered there. The impulse then continued to circulate around a central area that was kept refractory because it was bombarded constantly by impulses propagating toward it from all sides of the circuit. This central area provides a functional obstacle that prevents excitation from propagating across the fulcrum of the circuit. No anatomic obstacles or anatomically defined conducting pathways are present in the leading circle, and the reentrant circuit is completely defined by the electrophysiologic properties of the tissue involved. The circumference

of the leading circle around a functional obstacle may be as little as 6 to 8 mm and represents a pathway in which the efficacy of stimulation of the circulating wave front is just sufficient to excite the tissue ahead, which is still in its relative refractory phase. Conduction through the functional reentrant circuit is slowed, therefore, because impulses are propagating in partially refractory tissue (a partially excitable gap). Some of the reentrant excitation that has been mapped in the atria of canine models of atrial flutter may be caused by the leading circle mechanism. The reentrant circuit remains in the same place during the flutter and therefore is ordered reentry. Functional reentrant circuits of the leading circle type also may change their size and location; if they do, they fall under the general category of random reentry. This may occur when leading circle reentry causes fibrillation.

Anisotropy can cause conduction slow enough to result in reentry in small anatomic circuits. Reentrant circuits caused by anisotropy also can occur without well-defined anatomic pathways and may be classified as functional. Unlike the functional characteristic that leads to the leading circle type of reentry (local differences in membrane properties causing a difference in effective refractory periods in adjacent areas), in functional reentry caused by anisotropy, the functional characteristic that is important is the difference in effective axial resistance to impulse propagation dependent on fiber direction. This mechanism has been classified as *anisotropic reentry*. In its pure form, both the unidirectional conduction block and slow conduction in the reentrant circuit result from anisotropic, discontinuous propagation, and there is no need for variations in membrane properties such as regional differences in effective refractory periods or depression of the resting and action potentials.

On the basis of the longitudinal and transverse conduction velocities of premature impulses in nonuniform anisotropic muscle and of measurements of refractory periods in these experiments. Furthermore, anisotropic circuits are elliptical or rectangular because of the directional differences in conduction velocities with the long axis of the ellipse in the fast, longitudinal direction. Circuits with this shape can have a smaller dimension than do circular circuits such as the leading circle. Anisotropic reentrant circuits usually remain in a fixed position to cause ordered reentry. The de-

gree of anisotropy (ratio of longitudinal to transverse conduction velocity) varies in different regions of the heart, and the circuit can reside only in a region where the conduction transverse to the longitudinal axis is sufficiently slow to allow reentry. Stability of anisotropic reentrant circuits also is assisted by the presence of an excitable gap that does not occur in the leading circle functional circuit. The excitable gap is caused by the sudden slowing of conduction velocity and a decrease in the wavelength of excitation as the reentrant impulse turns the corner from the fast longitudinal direction to the slow transverse direction and from the slow transverse direction to the fast longitudinal direction. Another type of functional reentrant excitation, called spiral waves, does not require any inhomogeneities of refractory periods as in leading circle reentry, inhomogeneities in conduction properties as in aniostropic reentry, or a central obstacle, whether functional or anatomic. Spiral waves originally were initiated in computer models of homogeneous elements or in various kinds of homogeneous excitable media (properties do not vary throughout the media), an example of which is molecular diffusion in a chemical system. Under appropriate circumstances, a pulse in two-dimensional, homogeneous, excitable media can be made to circulate as a rotor with a wavelength that is proportional to the square root of the diffusion coefficient of the media. Preexisting functional heterogeneities in conduction (or diffusion) properties or refractoriness (time course of recovery of excitability) are not prerequisites for the initiation of spiral waves in excitable media. The heterogeneity that allows initiation can result from a previous excitation wave and the pattern of recovery from that wave. When heterogeneities in recovery exist, the application of a second stimulus over a large geometric area to initiate a second excitation wave only excites a region where there has been sufficient time for recovery from the previous excitation, not regions that have not yet recovered. An excitation wave is elicited at the excitable site that is in the form of a rotor because the wave cannot move in the direction of the wake of the previous wave but only in the opposite direction, moving into adjacent regions as they in turn recover. The inner tip of the wave front circulates around a disk of quiescent medium instead of a region of conduction block. The size of this disk expands as the medium is made less excitable. The rotor, by definition,

has a marked curvature, and this curvature slows down its propagation. A similar pattern of excitation can be induced in cardiac muscle. In the case of a curved depolarization wave front (rotor) in excitable tissue such as cardiac muscle, slow conduction results from an increased electrical load; e.g., not only must a curved wave front depolarize cells in front of it in the direction of propagation, but current also flows to cells on its sides. The slow activation by a rotor is not dependent on conduction in relatively refractory myocardium; therefore, there is an excitable gap despite the functional nature of reentry. The location of the rotor can occur anywhere the second stimulated excitation encounters the wake of the first excitation with the appropriate characteristics. Reentrant excitation that occurs during the initiation of ventricular fibrillation by strong electrical shocks has characteristics consistent with spiral waves or rotors. These small circulating rotors are not stable and meet the criteria of random reentry. Spiral waves also may cause other kinds of arrhythmias. Even though nonuniform dispersions of refractoriness or anisotropy are not necessary for the initiation of reentrant excitation caused by rotors in excitable media, the myocardium, even when normal, is never homogeneous and the heterogeneities may modify the characteristics of the spiral waves.

Methods to Identify Mechanisms of Arrhythmias

Cardiac pacing to determine arrhythmogenic mechanisms

The mechanism of an arrhythmia in the in situ heart sometimes can be deduced from the response of the arrhythmia to cardiac pacing. Knowledge about the response of the different arrhythmogenic mechanisms to pacing is based largely on studies in which the effects of electrical stimulation were determined on transmembrane action potentials recorded with microelectrodes in isolated and superfused cardiac tissues. Critical to the ability to use the response to electrical stimulation to determine arrhythmia mechanisms is the requirement that the stimulated impulse(s) reach the site of origin of the arrhythmia. There are many reasons why this may not happen. The stimulated impulse(s) may not reach the site at which the arrhythmia arises because of the electrophysiologic properties of the intervening tissue between the stimulus site and the site of arrhythmia origin. An intervening region of prolonged refractoriness or

depressed conduction may cause stimulated impulses to block before they reach the site of origin. If conduction time from the stimulation site to the site of arrhythmia origin is prolonged for any reason, impulses generated in the arrhythmogenic focus also may be able to leave that focus and depolarize large regions of myocardium around it, preventing the stimulated impulse from reaching the site of arrhythmia origin. Even when the stimulation site is close to the site of arrhythmia origin, areas of depressed conduction may prevent the stimulated impulses from reaching the arrhythmogenic cells.

Two basic patterns of stimulation generally are used to study the mechanisms of arrhythmias:

- overdrive pacing (pacing at a rate or rates faster than the spontaneous rate of the arrhythmia)
- introduction of a premature beat or beats by using programmed stimulation.

With either technique, the effects of the stimulated impulses on the spontaneous rhythm are observed. Overdrive pacing generally is used during the arrhythmia to determine whether the overdrive can terminate it or, if it does not, to determine the effect of the overdrive on characteristics of the arrhythmia. Overdrive pacing sometimes is used during sinus rhythm to determine whether the period of stimulation can induce an arrhythmia that previously has occurred spontaneously. The introduction of a premature beat or beats at selected intervals during electrical diastole by programmed stimulation of the heart can be performed either during the spontaneous arrhythmia to test the effects of the premature beats or during sinus rhythm or fixed-rate pacing to see if the arrhythmia can be induced.

Effects of electrical stimulation on arrhythmias caused by automaticity

The prior discussion of automaticity as an arrhythmogenic mechanism included a consideration of how the sinus node pacemaker and electrical stimulation (pacing) influence subsidiary pacemakers with different automatic mechanisms. Overdrive either by the sinus node or by electrical stimuli exerts an inhibitory effect on the normal automatic mechanism of subsidiary or latent pacemakers (overdrive suppression) that is primarily the result of enhanced Na+-K+ pump activity but has fewer inhibitory ef-

fects on the abnormal automatic mechanism of subsidiary pacemakers. These known effects of overdrive on pacemaker mechanisms are sometimes useful in distinguishing automatic arrhythmias from arrhythmias caused by reentry or triggered activity in the in situ heart. The effects of overdrive pacing also can be of use in distinguishing arrhythmias caused by normal automaticity from those caused by abnormal automaticity. From the results of experimental studies, it can be assumed that arrhythmias caused by normal automaticity in the in situ heart cannot be initiated by overdrive pacing. Arrhythmias caused by normal automaticity can be suppressed transiently but cannot be terminated by overdrive pacing. Microelectrode studies on isolated superfused pacemaker tissues indicate that when overdrive pacing is applied during an ongoing arrhythmia caused by normal automaticity, the arrhythmia is expected to be suppressed transiently immediately after the overdrive pacing is stopped. This is manifest by a transient pause after overdrive and should be followed by a gradual speeding up of the rhythm (so-called warm-up) until the original rate of the automatic rhythm is resumed. The duration of the transient pause and the time required for resumption of the original rate are expected to be directly related to the rate and duration of the overdrive. This behavior is mainly the result of the increased activity of the Na+-K+ pump, which is dependent both on the rate and on the duration of stimulation. This characteristic behavior of normally automatic pacemakers has been demonstrated in some clinical and experimental electrophysiologic studies of both atrial and ventricular tachycardias.

Like normal automaticity, arrhythmias caused by abnormal automaticity can be neither initiated nor terminated by overdrive pacing. By contrast, arrhythmias caused by abnormal automaticity should not be suppressed by overdrive pacing unless the overdrive period is long and the rate of overdrive is fast. The difficulty in suppressing such arrhythmias stems from the lesser amount of Na+ entering the cells during the upstroke of the action potential and therefore less intense Na+pump stimulation by overdrive. Short periods of overdrive can even result in a transient speeding of the rate of impulse generation (overdrive acceleration). Accelerated idioventricular tachycardia in myocardial infarction is not easily overdrivesuppressed and therefore

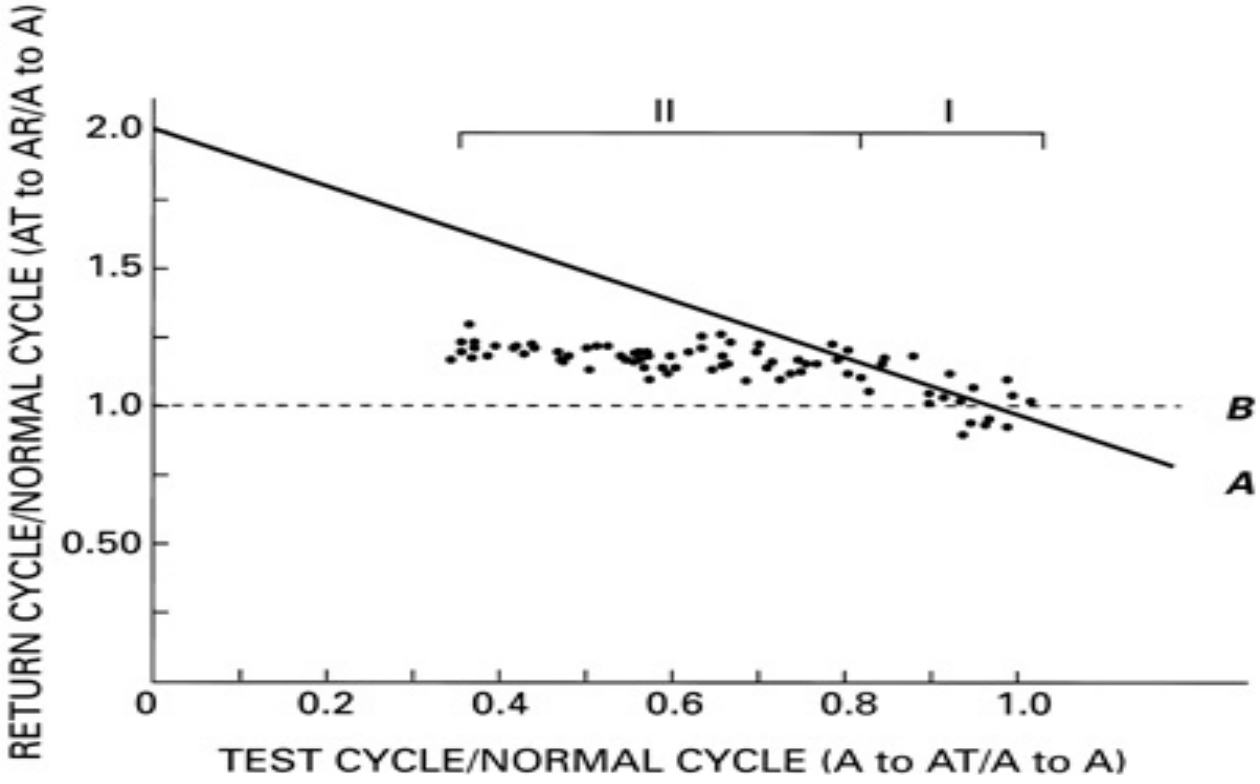
may be caused by abnormal automaticity. The response of automatic arrhythmias to premature stimulation also is sometimes useful in distinguishing automaticity from other arrhythmogenic mechanisms. Of major importance, automatic rhythms caused by either normal or abnormal automaticity can be neither initiated nor terminated by premature stimuli, in contrast to reentry and triggered activity.

Premature impulses induced at different times during diastole may transiently perturb an automatic rhythm for a few cycles. The characteristics of the perturbation sometimes may distinguish automaticity from other arrhythmogenic mechanisms. The response of normal and abnormal automaticity to premature stimulation may be somewhat similar. The characteristic response of an automatic pacemaker to premature stimulation is best exemplified by the response of the sinus node to atrial premature stimulation. Premature impulses delivered late in the cycle length are followed by a compensatory pause and fall on this line (as the test cycle shortens, the return cycle lengthens in a reciprocal manner) because the premature impulses collide with the impulse emanating from the sinus node pacemaker without reaching and resetting the pacemaker. Therefore, the pacemaker discharge that follows the premature impulse occurs exactly on time. As the premature coupling interval is decreased, a point is reached in the basic cycle where the premature impulse reaches the pacemaker before it has depolarized spontaneously to threshold and depolarizes it early. The pacemaker is reset. When this occurs, the postextrasystolic cycle (which is a result of the stimulated or reset pacemaker cells spontaneously depolarizing to threshold) is less than compensatory and the points fall below the line of identity. For the most part, the postextrasystolic cycle length is expected to be equal to the unperturbed spontaneous cycle length. The dashed line (*B*) on the graph in Figure 2.12 indicates the cycle length of the basic rhythm, and so the return cycle length relative to the basic cycle length can be seen to be somewhat longer in this study. The prolonged return cycle has been proposed to result from slowed conduction of both the premature impulse into the pacemaker site and the pacemaker impulse out of this site. It also may result, at least partly, from depression of the rate of spontaneous diastolic depolarization. Further shortening of the premature coupling interval to midcycle results in points pa-

rallel to the dashed line and possibly slightly above it; this indicates no change in the postextrasystolic cycle length over a wide range of coupling intervals. Finally, conduction of very early premature impulses may block before reaching the pacemaker, and the next pacemaker discharge will again occur on time and be compensatory. Of course, this relationship might be upset by changes in conduction of impulses into and out of the pacemaker site. This relation between premature and return cycle length found in studies of sinus rhythm also has been shown in studies on some ectopic tachycardias and, when found, indicates that the tachycardias are likely to be caused by automaticity.

Figure 2.12.

Return cycles as a function of premature stimulated cycles during premature atrial stimulation in a patient in sinus rhythm.



Notes: the graph depicts the relation of the normalized return cycle to the degree of prematurity of the test cycle, which also is normalized. Points falling on line *A* represent nonreset of the sinus pacemaker (fully compensatory pause) and are in zone I. Premature stimulated atrial beats introduced earlier in atrial diastole fall in zone II. Line *B*, projected from the *y* axis, is a reference line indicating the spontaneous sinus cycle length. The distance the zone II points (reset points) are above line *B* is interpreted to indicate conduction time into and out of the sinus

node, assuming the sinus node pacemaker cycle length immediately after the stimulated premature atrial beat is identical to the preceding sinus node pacemaker cycle length.

Ectopic pacemakers also may exist in an extensive region of slow conduction, much as the pacemaker in the sinus node does, and conduction delays into and out of the pacemaker site may influence to some extent the relationship between the return cycle and the premature cycle. Conduction delays may cause some prolongation of the return cycle. When this relationship is seen, however, it is probably indicative of automaticity (either normal or abnormal), since triggered activity and reentry are expected to show a different behavior. In addition to the atrial arrhythmias discussed here, some ventricular arrhythmias are likely to be caused by automaticity. Idioventricular rhythms in patients with complete heart block respond in the manner shown in microelectrode studies of slowly beating Purkinje fibers; the postextrasystolic cycle that follows late premature impulses is longer than the cycle length of the basic rhythm but less than compensatory, while it is shorter than the basic cycle length that follows early premature impulses (and obviously less than compensatory). Some exercise-provoked ventricular tachycardias also may be caused by normal automaticity. By contrast, there is some evidence that accelerated idioventricular rhythms in the clinical setting of myocardial infarction may be caused by abnormal automaticity.

Effects of electrical stimulation of reentrant excitation

A hallmark feature of a reentrant rhythm is that it usually can be induced and terminated by electrical stimuli (overdrive pacing, introduction of premature stimuli, or both), unlike automaticity. Initially it was thought sufficient to show that an arrhythmia could be initiated or terminated by overdrive pacing or programmed stimulation to demonstrate a reentrant mechanism. That was the case because until the 1970s the only other mechanism that was widely considered a cause of arrhythmias was automaticity, and automatic rhythms can be neither initiated nor terminated by pacing. After the 1970s, when the concept of after-depolarizationinduced arrhythmias was revived and expanded, these criteria alone were no longer sufficient, because triggered activity caused by DADs also can be initiated and terminated by pacing. The

induction of arrhythmias by overdrive pacing or the introduction of a premature beat or beats can be used as an indicator of a reentrant mechanism if other characteristics are also present that eliminate the probability of triggered activity that is dependent on DADs. The ability to demonstrate directly that the induction of an arrhythmia is related to a critical amount of slow conduction in the region where the arrhythmia originates adds credence to the interpretation that the arrhythmia is caused by reentry. The sudden large increase in the A-H interval associated with pacing induction of AV nodal reentrant tachycardia is one example. The induction of triggered activity caused by DADs is not dependent on slowed conduction and should not show this relationship. Also, when a tachycardia is initiated by the introduction of a premature beat over a wide range of coupling intervals, there may be an inverse relation between the coupling interval of the premature impulse and the interval from the premature impulse to the first impulse of tachycardia. As the premature impulse occurs earlier in the cycle, its conduction through the reentrant pathway is slower, causing the return cycle to prolong. This too is not found with the induction of triggered activity resulting from DADs. Failure to initiate an arrhythmia by stimulated impulses does not per se eliminate reentry as a mechanism for the arrhythmia. Another feature of reentrant arrhythmias is that they can be terminated by overdrive pacing or premature stimulation. This is not specific for reentry, since triggered activity caused by DADs also can be terminated. As with initiation, termination by overdrive pacing requires a critical rate and duration of the stimulation train, while termination with stimulated premature impulses requires a critical coupling interval between the premature impulse and the previous impulse of the tachyarrhythmia. Failure to terminate an arrhythmia by stimulated impulses does not by itself eliminate reentry as a mechanism for the arrhythmia. Termination of reentry requires that the stimulated impulse enter the reentrant circuit to cause the block of the reentrant wave front, and this usually requires that the circuit have a fairly large excitable gap. Some reentrant circuits, particularly if they are caused by the leading circle mechanism of reentry, may not have a gap of excitability large enough to allow a premature impulse to penetrate readily into the

circuits. If a tachycardia is very rapid, the excitable gap also may be very small, again preventing ready entry into the circuit by stimulated impulses.

Entrainment

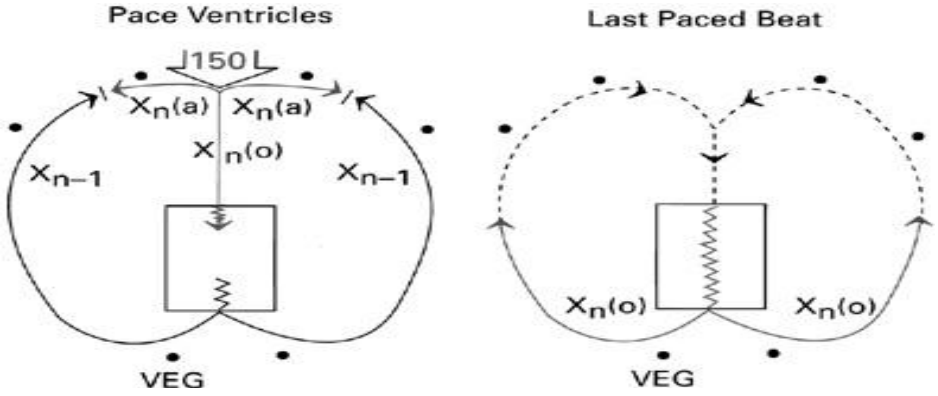
In this context, the demonstration of transient entrainment of a tachycardia with or without its subsequent interruption is a relatively easy and reliable way to identify reentry as the mechanism of a tachyarrhythmia. Transient entrainment of a tachycardia was first described in 1977 during rapid pacing to interrupt type I atrial flutter. At that time, although transient entrainment was not well understood, it was recognized as representing an increase in the rate of the tachycardia to the faster pacing rate, with resumption of the intrinsic rate of the tachycardia occuring upon either abrupt cessation of pacing or slowing of the pacing rate below the intrinsic rate of the tachycardia. On the basis of a series of clinical studies during rapid pacing of atrial flutter, ventricular tachycardia, AV reentrant tachycardia involving an accessory connection, AV nodal reentrant tachycardia, and intraatrial reentrant tachycardia, it was proposed that transient entrainment represents capture of a reentrant circuit by wave fronts generated by the pacing impulse without causing interruption of the tachycardia. This was confirmed during studies of transient entrainment in animal models of ventricular tachycardia and atrial flutter that utilized multiplexing techniques to record simultaneously from large numbers of electrodes in direct contact with cardiac tissue.

During transient entrainment of a reentrant tachycardia, the wave front from each pacing impulse enters into the excitable gap of the reentrant circuit. Once there, it travels in two directions:

- antidromically, i.e., in the opposite direction of the circulating reentrant wave front of the spontaneous tachycardia, where it collides with the orthodromic wave front of the preceding beat,
- orthodromically, i.e., in the same direction as the circulating reentrant wavefront of the spontaneous tachycardia, thus both continuing the tachycardia and resetting it to the pacing rate.

This explanation is universal for transient entrainment of any tachycardia resulting from reentry with an excitable gap and is diagrammatically illustrated in Figure 2.13.

Figure 2.13
Diagrammatic representation of the first entrainment criterion during termination of ventricular pacing



The left panel of the figure is a diagrammatic representation of the reentrant circuit during a ventricular tachycardia (VT) at an assumed rate of 150 beats per minute. The *X*s represent the orthodromic wave fronts of the reentrant rhythm. The arrows indicate the direction of spread of the impulse, the box represents an area of slow conduction in the reentrant circuit, the serpentine line indicates slow conduction of the impulse in this latter area, and the dots represent recording sites along the course of the double arc of reentry from which ventricular electrograms (VEGs) are recorded. The middle panel is a diagrammatic representation of the introduction of the first pacing impulse ($X + 1$) during ventricular pacing at a rate of 150 beats per minute during the VT. The antidromic (anti) wave fronts ($X + 1$) collide with the orthodromic wavefronts from the previous reentrant beat (X), resulting in fusion of ventricular activation. The orthodromic wavefront (ortho) from the pacing impulse ($X + 1$) continues the VT, resetting it to the pacing rate. The right panel of the figure shows a diagrammatic representation of the introduction of the second pacing impulse ($X + 2$) during ventricular pacing at a rate of 150 beats per minute during the VT. The antidromic wavefronts ($X + 2$) collide with the orthodromic wavefronts from the previous paced beat ($X + 1$), again resulting in ventricular fusion. Once again, the orthodromic wavefront ($X + 2$) from the pacing impulse continues the VT, resetting it to the pacing rate.

Criteria to establish transient entrainment

Four criteria have been established, any one of which, if demonstrated, establishes the presence of transient entrainment and thus the presence of a reentrant rhythm with an excitable gap.

1. The demonstration of constant fusion beats in the ECG during the period of rapid pacing at a constant rate except for the last captured beat, which is entrained but not fused (i.e., the last entrained beat demonstrates the ECG morphology of the spontaneous tachycardia)
2. The demonstration of constant fusion beats in the ECG during rapid pacing at any constant rate but different degrees of constant fusion at different rapid rates, i.e., progressive fusion
3. Interruption of the tachycardia associated with localized conduction block to a site(s) for one beat, followed by subsequent activation of that site(s) from a different direction, which manifests itself by a change in morphology of the electrogram at the blocked site(s) and with a shorter conduction time
4. A change in conduction time to and electrogram morphology at one recording site when pacing from another site at two different constant pacing rates, each of which is faster than the spontaneous rate of the tachycardia but fails to interrupt it.

Thus, no fusion of ventricular activation occurs despite the presence of transient entrainment. This last entrained beat travels around the reentrant circuit, continuing the tachycardia.

Concealed entrainment

While the ability to demonstrate transient entrainment of a tachycardia provides an important and powerful tool for the identification and study of reentrant tachyarrhythmias, a limitation is that it is not always possible to demonstrate any of the transient entrainment criteria despite the fact that rapid pacing may indeed have entrained and even interrupted the tachycardia. This phenomenon, called *concealed entrainment*, can result when pacing is performed from a site that is orthodromically distal to the area of slow conduction in the reentry circuit, when pacing is done from a site that is rather distant from the reentrant circuit, or when pacing is done from an area of

slow conduction in the reentrant circuit. To label a response of a tachycardia to rapid pacing as concealed entrainment, except in the example of pacing from an area of slow conduction in the reentry circuit, one also must show that transient entrainment can be demonstrated when pacing is from another site. Thus, it is clear that unless one is able to pace from an appropriate site, a reentrant circuit with an excitable gap may be present, but entrainment, though present, will not be demonstrable.

Resetting

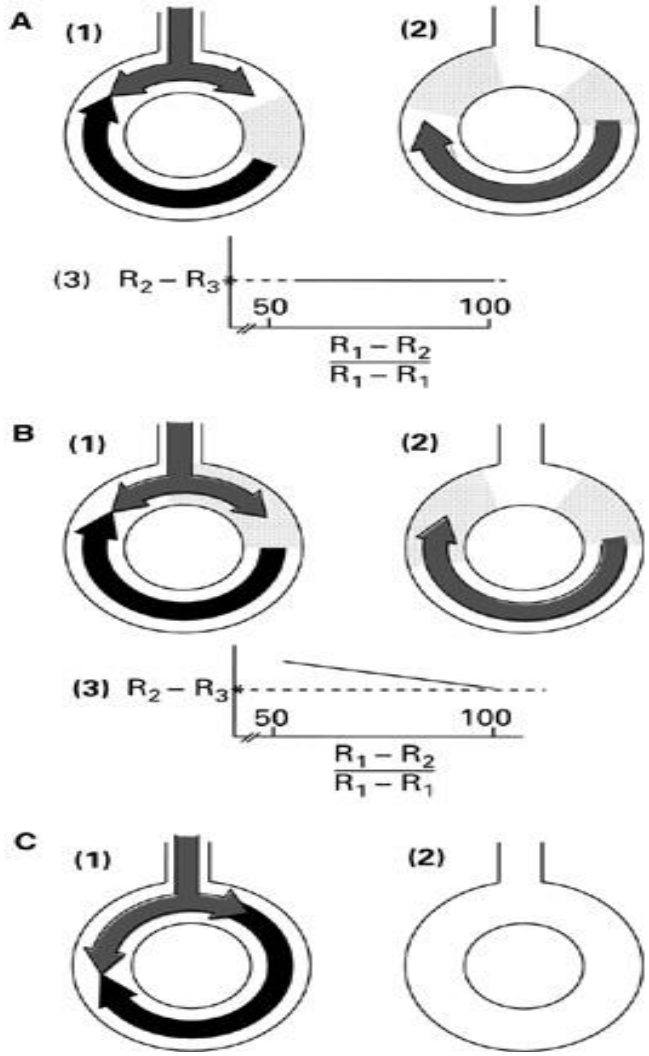
The response of an arrhythmia to a prematurely stimulated impulse that does not terminate the arrhythmia still may provide information useful for determining the mechanism of the arrhythmia. Information on the effects of stimulated premature impulses on reentry comes from studies on experimental preparations of isolated tissues or hearts in which reentrant excitation has been mapped. Other predictions concerning the effects of premature impulses on reentry are based mainly on theoretical considerations using a model of a reentrant circuit with a fixed pathway in which the circuit cannot change its dimensions and in which there is an excitable gap. Such circuits may have a single entrance and exit pathway leading into and out of the circuit, as illustrated in Figure 2.14, or the entrance and exit pathways may be separate. These characteristics will influence the characteristics of the resetting response as seen on the ECG.

The theoretically possible responses of a tachycardia caused by reentrant excitation to premature stimulation are explained in the diagram in Figure 2.14. An anatomic circuit with fixed dimensions and a single entrance pathway is diagrammed. In this diagram, the entrance pathway also serves as an exit pathway for the reentrant wavefront to enter surrounding myocardium, but other models may have separate entrance and exit pathways. The black arrow in the reentrant circuit represents the reentrant impulse, with the arrow point being the crest of the depolarizing wave and the end of the arrow being the tail. The length of the arrow is the absolutely refractory part of the circuit, the dotted area that trails it is the relatively refractory part, and the clear region is the fully excitable gap (in some instances there may be no fully excitable

gap in the reentrant circuit). The transit time of the reentrant impulse around the circuit determines one cycle length of the tachycardia (the R1-R1 interval).

Figure 2.14

Effects of premature impulses on reentrant circuit with an excitable gap.



Notes. In each panel, diagrams are shown of an anatomic circuit with a single entrance route from above. In *A*(1), *B*(1), and *C*(1), black arrows in the circuit represent the reentrant impulse causing tachycardia. The length of the arrow is the wavelength of the impulse and shows the part of the circuit that is completely refractory, The part of the circuit that is stippled is relatively refractory, and the part of the circuit that is clear is completely excitable (the fully excitable gap). Black arrows entering the circuit from above represent a prematurely stimulated impulse initiated outside the circuit. *A*(2) and *B*(2) show conduction of the premature impulse in the circuit. Graphs show the expected relation between the return (premature impulse) cycle length (R2-R3) and the premature coupling interval (R1-R2/R1-R1) for premature impulses conducting in the fully excitable gap *A*(3) and in the relatively refractory tissue of a partially excitable gap *B*(3).

In summary, the stable tachycardia cycle length (R1-R1) is determined by the time it takes the reentrant wavefront to travel one complete revolution around the circuit and reach an exit pathway to the ventricles. When such a circuit is the cause of a tachycardia, premature depolarizations delivered late in the cycle length often are followed by a postextrasystolic pause that is compensatory for the same reason described for automatic tachycardias; i.e., the stimulated impulse may not be able to reach the reentrant circuit, possibly as a result of collision between the stimulated impulse and the impulse coming from the circuit. The next tachycardia impulse then comes precisely on time. In this case, the tachycardia is not reset since the sum of the premature cycle length and the return cycle length is equal to two successive premature cycle lengths. Over the range of premature coupling intervals that do not reset the tachycardia, the relation between the premature coupling interval and the following (return) cycle falls along the line of identity.

Effects of electrical stimulation on arrhythmias caused by triggered activity

Arrhythmias Caused by Delayed Afterdepolarizations

The amplitude of DADs increases with a decrease in the cycle length at which the action potentials occur until the afterdepolarizations reach threshold to cause the triggered activity. Therefore, triggered arrhythmias caused by DADs in the in situ heart should be initiated by either overdrive pacing or programmed premature stimulation. Since automatic arrhythmias are not initiated by pacing, they should be distinguished readily from triggered arrhythmias caused by DADs. Reentrant arrhythmias also can be induced by the same stimulation protocols, however, and so whether there are any other characteristics during arrhythmia induction by pacing that might distinguish between triggered activity and reentry is important. An attempt to distinguish between the two mechanisms is further complicated by the fact that triggered activity caused by DADs may be due to different causes, e.g., digitalis and catecholamines, each with somewhat different characteristics. The following guidelines have been proposed to assist in distinguishing DAD-induced triggered activity from other causes of arrhythmias. The guidelines are based on the characteristics of triggered activity determined from in vitro studies with microelectrodes. Triggered activity caused by

DADs has been more easily induced by rapid pacing or by several successive premature stimuli than by a single premature stimulus in studies of isolated tissue preparations.

This characteristic, which should be expected to occur in the in situ human heart, probably is explained by the fact that rapid pacing or the introduction of a number of premature stimuli is more effective than a single premature stimulus in increasing intracellular Ca+ levels. The Ca+ levels control the after-depolarization amplitude. Also, arrhythmias caused by triggered activity should be more easily induced by premature stimuli superimposed on a rapid drive rate than on a slow one because during rapid pacing, the after-depolarization amplitude is larger and the membrane potential at the peak of the after-polarization is closer to threshold. In contrast, ordered reentrant rhythms in humans (with the exception of atrial flutter) seem to be more easily and reproducibly induced by premature impulses than by rapid pacing, although several premature impulses in succession sometimes are necessary. One reason for this may be that premature impulses block more effectively in areas with long refractory periods than do impulses during rapid pacing because rapid pacing can shorten refractory period duration. This, of course, is important because block is a prerequisite for the initiation of reentry. Both extrasystoles and the first beat of a tachycardia, when caused by DAD-dependent triggered activity initiated by pacing, are predicted to occur late in the cardiac cycle. This proposal is based on experimental data from studies of isolated tissue that show that DADs rarely reach their peak amplitude at less than 50 percent of the cardiac cycle when the drive cycle length is shorter than 1000 ms. In contrast, reentrant beats often occur early in the cycle. One would expect a direct relationship between the pacing cycle length that induces triggered activity resulting from DADs and the coupling interval from the last stimulated impulse to the first beat of the induced tachycardia. As the pacing cycle length decreases, the coupling interval from the last stimulated impulse to the first impulse of tachycardia should decrease because at short cycle lengths, the coupling interval of the after-depolarizations to the proceeding action potential decreases. A direct relationship between pacing cycle length and the coupling interval of the first impulse of

the tachycardia has been shown to occur in arrhythmias caused by digitalis toxicity. This relationship sometimes may be complicated by the presence of two after-depolarizations and the possibility of a triggered impulse arising from either one. No comparable data are available from pacing studies on digitalis-toxic human hearts. The direct relation also has been shown in some cases of idiopathic ventricular tachycardia believed to be caused by triggered activity. A direct relation like this is not expected during the initiation of reentrant arrhythmias. Failure to show the direct relation, however, cannot be taken as proof that the arrhythmia is not caused by triggered activity, since slow conduction into or out of the triggerable focus can distort it. In microelectrode studies, during the initiation of triggered activity with premature stimuli, no significant effects of the premature stimulus coupling interval were observed on the relation (coupling interval) of the first triggered impulse to the premature stimulus. On the basis of these data, it is expected that during the initiation of arrhythmias caused by triggered activity in situ with programmed premature stimulation, the coupling interval of the first beat of tachycardia should remain relatively constant over a range of coupling intervals of introduced premature impulses. The response to premature stimulation is also contrary to that expected during the initiation of reentrant arrhythmias, where an inverse relation is expected between the premature stimulus coupling interval and the coupling interval between the premature impulse and the first impulse of tachycardia.

Triggered arrhythmias, unlike automatic arrhythmias but like reentrant arrhythmias, are predicted to be terminated by cardiac pacing. Single premature impulses may terminate triggered arrhythmias, but on the basis of the results of microelectrode studies, termination should be infrequent and not usually reproducible at the same critical premature cycle length. In contrast, single premature impulses often terminate reentrant arrhythmias in a reproducible manner and over a consistent range of premature cycle length in any single individual as long as the reentrant circuit has an excitable gap. Therefore, an arrhythmia that is terminated readily by a single prematurely stimulated impulse is more likely to be caused by reentry than by triggered activity. The effects of premature impulses that do not terminate sustained triggered activity

also have been determined. The response is almost identical to that of automaticity. The return cycle length remains fairly constant over a wide range of premature coupling intervals and is nearly the same as the cycle length of the basic triggered rhythm (less than compensatory). By contrast, overdrive pacing should terminate triggered arrhythmias caused by afterdepolarizations. This termination requires a critical rate and duration of overdrive, just as it does with reentry. Overdrive stimulation may cause acceleration of triggered arrhythmias followed by gradual slowing and termination, or rapid overdrive may cause abrupt termination. Although reentrant rhythms may be accelerated by overdrive pacing, a gradual slowing of the rate before termination is not expected. Overdrive pacing that does not terminate triggered activity, as occurs when the cycle length of the overdrive is too long or when the duration of trains of stimuli are too short, does not entrain the arrhythmia either. In fact, none of the characteristics of entrainment are expected during overdrive pacing of triggered activity caused by DADs. It therefore is apparent that although the response of triggered arrhythmias caused by DADs to stimulation can be predicted from experimental studies, there is no single feature that would positively allow a triggered rhythm to be distinguished from reentry except entrainment. Since the characteristics of initiation and termination of triggered rhythms by stimulation are very different from the characteristics of automatic rhythms, it should be easier to distinguish between these mechanisms by using pacing techniques. This differentiation may be made more difficult when an arrhythmia is persistent and the initiation cannot be studied. Also, entrance block of stimulated impulses into arrhythmogenic foci, whether automatic, triggered, or reentrant, may negate the use of pacing techniques to distinguish between these mechanisms. The characteristics of some clinical arrhythmias occasionally conform to those expected of DAD-dependent triggered activity.

In addition to digitalis toxicity, an example is some cases of exercise-induced ventricular tachycardia in patients with no structural heart disease. This tachycardia, which occurs spontaneously during exertion, sometimes can be initiated by overdrive pacing or programmed premature stimulation. An isoproterenol infusion during stimulation may be required for successful initiation. It has been proposed that these ta-

chycardias are caused by a catecholamine-induced increase in cyclic AMP, which is known to cause DADs. Evidence supporting this hypothesis is provided by the termination of tachycardias by intravenous injection of adenosine, which antagonizes the electrophysiologic effects of catecholamines mediated through the adenylate cyclase-cyclic AMP system. It has been proposed that some forms of ventricular tachycardia associated with the congenital long QT syndrome and dependent on adrenergic stimulation result from triggered activity caused by DADs.

Arrhythmias Caused by Early Afterdepolarizations (EADs) should not be inducible by overdrive pacing, similar to automatic arrhythmias and unlike arrhythmias caused by DADs or reentry. Similarly, triggered activity dependent on EADs is not expected immediately to follow the short cycle length of one or several prematurely stimulated impulses. As has been shown in experimental studies, the appearance of EAD-induced triggered activity is facilitated by long cycle lengths. Therefore, this kind of triggered activity should be initiated by slowing the basic heart rate. Of course, if an increase in heart rate caused by pacing resulted in entrance block into a focus where EADs occur, the block could cause a prolongation of the cycle length in that focus that might result in triggered activity. Prematurely stimulated impulses also may initiate triggered activity if there is a long compensatory pause after the stimulated impulse. The long cycle might trigger an arrhythmia that would follow it. In the absence of such entrance block, bursts of tachycardia caused by EADs should occur more frequently when the heart rate is slowed, and pacing the heart at rates faster than the basic underlying rhythm is predicted to cause disappearance of the period of tachycardia. Increasing the basic heart rate shortens action potential duration and thereby suppresses EADs. When the pacing is stopped, arrhythmias should reappear, as the action potential returns to its original duration. The reappearance of the arrhythmias may not be immediate, however, since it requires some time for the action potential duration to lengthen owing to the enhanced pump current that follows a period of rapid stimulation. Many of these characteristics have been shown to apply to the experimental triggered arrhythmias caused by cesium in the in situ canine heart and have been demonstrated in some cases of torsades de pointes in human patients. Ac-

quired forms of the syndrome (e.g., prolonged QT and torsades de pointes by quinidine) exhibit all the features expected of triggered activity caused by EADs, whereas other forms (e.g., congenital) may not be due to this mechanism. Torsades de pointes invariably occurs after a preceding long R-R interval, is unlikely to be initiated by programmed stimulation, and can be prevented from occurring by pacing the heart at a rapid rate. Parenthetically, it has been suggested that such rhythms are initiated by EADs but maintained by reentrant excitation. In contrast, triggered arrhythmias caused by DADs may become more frequent as heart rate increases,327 and the effect of increasing the heart rate on extrasystoles caused by reentry is variable; i.e., reentry may be exacerbated or may stop. There may be some difficulty in distinguishing EAD-dependent triggered arrhythmias from automatic arrhythmias only on the basis of their response to electrical stimulation, however, since the occurrence of automatic arrhythmias is facilitated by slow heart rates and increasing the basic heart rate by overdrive pacing may cause disappearance of automatic arrhythmias during the periods of pacing. The ECG characteristics of arrhythmias caused by triggered activity resulting from EADs and by automaticity may be of additional help. The triggered rhythms are more likely to occur in bursts or salvos of different lengths, with the first few cycle lengths of a burst decreasing progressively and the last few cycle lengths increasing progressively. Triggered arrhythmias caused by EADs not only may occur in bursts but also may be sustained. When sustained, their response to single premature stimuli or overdrive pacing can be predicted on the basis of the results of in vitro studies. Some arrhythmias may be terminated by premature stimuli, but this should be a relatively rare occurrence. The effects of premature stimulated impulses that do not terminate the arrhythmia are expected to be the same as their effects on automatic impulse initiation. Some arrhythmias also may be terminated by overdrive pacing, but termination should not be the usual effect. When termination occurs, it is expected to follow the overdrive immediately, whereas termination of triggered activity caused by DADs sometimes may be preceded by up to 10 triggered "afterbeats." When termination does not occur, overdrive is not expected to cause any significant effect on the rhythm; the response should be more like that of an arrhyth-

mia caused by abnormal automaticity than one caused by normal automaticity, which is readily overdrive-suppressed. Because of this variability of response, stimulation during a sustained tachycardia caused by EADs is not much help in determining the mechanism.

Therefore, as in the triggered arrhythmias caused by DADs, there is no single feature in the response to cardiac pacing that would positively enable EAD-induced triggered rhythms to be distinguished from other arrhythmogenic mechanisms. Early afterdepolarization-induced nonsustained arrhythmias usually can be differentiated from rhythms induced by DADs or automaticity at high membrane potentials and sometimes from reentry by pacing, but the response of sustained triggered activity to pacing is often indistinguishable from abnormal automaticity at low membrane potentials.

Summary of effects of electrical stimulation

Despite the fact that there are exceptions and inconsistencies to virtually all the rules that can be proposed to distinguish among the different arrhythmogenic mechanisms using pacing techniques, determining the effects of electrical stimulation is quite useful. The following is a summary of the most important points: (1) Initiation of a tachycardia by stimulation indicates that the arrhythmia is caused by reentry or delayed after-depolarization-induced triggered activity. Other characteristics of initiation are then useful in distinguishing between the two. Other mechanisms of arrhythmias-such as automaticity and triggered activity caused by early after-depolarizations are eliminated when a tachycardia is induced by cardiac pacing. (2) Termination of a tachycardia by overdrive pacing or premature stimulation is expected of reentry or triggered activity caused by delayed after-depolarizations but not of automaticity and early after-depolarization-dependent triggered activity. Overdrive suppression is expected of arrhythmias caused by normal automaticity, and overdrive acceleration may occur with arrhythmias caused by abnormal automaticity. (3) Demonstration of entrainment of a tachycardia during overdrive pacing is indicative of a reentrant mechanism and is not expected of other mechanisms. (4) The response to premature stimulation is different during arrhythmias caused by automaticity and those caused by

reentry. During automatic arrhythmias, the return cycle length should not increase as the premature coupling interval decreases. The return cycle should be less than compensatory. During reentrant arrhythmias, the return cycle length should increase as the premature impulse occurs earlier in the dominant cycle. The increase sometimes may begin to occur with late coupled premature impulses or may not occur until premature impulses are early coupled. The return cycle length is often less than compensatory.

CHAPTER 3
RHYTHM AND CONDUCTION DISCORDERS. CONTEMPORARY MANAGEMENT

Foreword

Arrhythmias can occur in individuals with or without cardiac disorders. There is a great deal of overlap between clinical presentations and severity and type of heart disease. The prognosis and management are individualized according to symptom burden and severity of underlying heart disease in addition to the clinical presentation.

Assessment of Cardiac Arrhythmias

The diagnosis and management of cardiac arrhythmias and conduction disturbances require the coordination of electrocardiographic (ECG) analysis of the rhythm disturbance, assessment of the clinical setting, and identification of an end point and method of therapy. ECG recognition of arrhythmias requires an organized system of analysis of atrial and ventricular myocardial activation and deduction of atrioventricular (AV) conduction patterns. Forms of arrhythmias are separated into those that cause limited symptoms but may trigger symptomatic sustained arrhythmias under appropriate conditions (e.g., premature atrial or ventricular impulses) and those that are sustained symptomatic and/or potentially fatal arrhythmias [e.g., supraventricular tachycardias (SVTs), ventricular tachycardias (VTs), ventricular fibrillation (VF), or bradycardias] (Table 3.1)

Table 3.1

Assessment of Cardiac Arrhythmias

Forms of cardiac arrhythmias

- Ambient or triggering arrhythmias (e.g., premature atrial or ventricular impulses)
- Sustained or potentially lethal arrhythmias (e.g., supraventricular or ventricular tachycardias, ventricular fibrillation, sustained bradyarrhythmias)

Clinical settings in which arrhythmias occur

- Acute, transient (e.g., acute ischemic events, metabolic disturbances)

- Chronic, persistent, recurrent (e.g., chronic ischemic heart disease, cardiomyopathy, anatomic or physiologic substrate for paroxysmal supraventricular tachycardia, chronic conducting system disease)

End points of management

- Antiarrhythmia (suppress ambient or triggering arrhythmias)
- Antitachycardia or antifibrillatory (prevent or revert tachycardias or fibrillation)

Heart rate support (prevent symptomatic bradycardias)

Clinical settings are broadly divided into those that are acute or transient, such as acute ischemia, the acute phase of myocardial infarction, electrolyte disturbances, or proarrhythmic effects of antiarrhythmic drugs, and those that provide a persistent substrate for arrhythmias, such as chronic ischemic heart disease, cardiomyopathies, and anatomic and physiologic substrates for the various paroxysmal supraventricular tachyarrhythmias. Analogous to the concept of "triggering" and "sustained" arrhythmias, transient ischemia and hemodynamic disturbances may be viewed as triggering events and chronic ischemic heart disease and the hypertrophied or myopathic heart as sustaining substrates. The goals, or end points, of therapy of cardiac arrhythmias are dependent on the forms, clinical settings, and mechanisms of arrhythmia. Broadly, goals of treatment may be antiarrhythmic (targeted to the suppression of ambient or triggering arrhythmias or events) or antitachycardiac, antifibrillatory, or heart rate supporting (in which the goal is prevention or reversion of sustained arrhythmias), whether the arrhythmias are well tolerated, symptomatic, or life-threatening.

Principles of cardiac rhythm analysis

The Standard Electrocardiogram

The standard 12-lead ECG and rhythm strips provide a direct and easily accessible method for diagnosing disturbances of cardiac rhythm. The simultaneous-lead rhythm strip accompanying the 12-lead ECG on many current ECG machines, plus the option of recording longer multilead rhythm strips, will yield sufficient information for a prompt and accurate diagnosis of most cardiac rhythm disturbances. For many arrhythmias, analysis requires only the recognition of P-wave and QRS mor-

phology, their relative timing, and their vectors. Simple inspection of the tracing, with caliper-assisted measurements, may be sufficient; but the analysis of more complex arrhythmias is facilitated by the use of ladder diagrams. First used extensively by Sir Thomas Lewis, they are also referred to as Lewis lines. The ladders are usually constructed with three tiers-A, AV, and V-but additional tiers may be helpful in depicting events related to sinoatrial (SA) conduction or ventricular ectopic rhythms. The A and V tiers are used to depict activation of atrial and ventricular muscle, respectively. The middle tier (AV) is used to infer conduction characteristics in the AV junction. Since atrial and ventricular activation are the only direct registrations of cardiac electrical activity on the standard ECG, they are diagrammed first. The A line is drawn from the beginning of the P wave and the V line from the beginning of the QRS. Time is indicated by the slope of the line, and the site within a tier in which impulse propagation begins (upper, middle, or lower) shows the direction the impulse is traveling. The site of origin may be represented by a black dot. A blocked impulse is indicated by a short bar at a right angle to the line indicating direction of conduction, and aberrant intraventricular conduction is shown as a pair of slightly divergent lines.

Special Leads

When the standard ECG does not provide sufficient information to establish a diagnosis, usually due to inability to identify P waves, special lead systems may be used. The simplest is the Lewis lead configuration, in which the right and left arm electrodes are deployed as a bipolar lead to the right of the sternum in a superior-inferior orientation. A bipolar esophageal lead can record left atrial activity, and an intraatrial electrode catheter can record atrial activity from within the right atrium. For both techniques, it is necessary to have at least one standard surface ECG lead recorded simultaneously with the special lead. Continuous Monitor Recordings Continuous monitoring of cardiac rhythm may be performed in hospital in special care units or in the ambulatory patient using various types of portable recording devices. Some systems provide the capability for simultaneous multilead recordings that improve diagnostic yield considerably. Long-term storage capabilities for inpatient

monitoring permit off-line analysis of complex rhythm disturbances if the physician is not available at the time the arrhythmia occurs. The two most popular leads for use in bedside monitoring are lead II and MCL-I, the latter providing a pattern similar to V_1.

For infrequently occurring arrhythmias, a number of event recorders are now available. They allow the patient to activate the device when an event occurs, providing internal storage that can be transmitted by telephone to a central station for later review. Transtelephonic transmitters also can be used in real time for more persistent or frequent events. Finally, a small subcutaneous implantable recorder is available for patients with infrequent arrhythmias that warrant an aggressive documentation attempt. The device may be explanted after a diagnosis is established.

Exercise Testing for Cardiac Arrhythmias

Treadmill stress testing may be used to initiate an evanescent arrhythmia, document an exercise relationship to its onset, and evaluate both efficacy and adverse responses to therapy. The standard treadmill is used, and thallium or echocardiographic imaging is not necessary unless an ischemic basis correlating with the onset of arrhythmia is suspected. The procedure is especially useful for eliciting and evaluating therapy of exercise-induced ventricular arrhythmias, for distinguishing autonomic from structural disease mechanisms of sinus or AV node dysfunction, and for evaluating adverse effects of drug therapy, such as rate-dependent proarrhythmic effects, as may occur with strong Na^+-channel blockers, such as flecainide. Exercise testing may also provide some general insights into the refractory period of an accessory pathway in Wolff-Parkinson-White (WPW) syndrome. Abrupt disappearance of the delta wave during exercise induced increase in heart rate suggests encroachment on the refractory period, while gradual disappearance may simply be due to enhanced AV nodal conduction.

Signal-Averaged Electrocardiography, Heart Rate Variability, and Baroreceptor Sensitivity

Signal-averaged electrocardiography, heart rate variability, and baroreceptor sensitivity provide information on mortality risk and the probability of life-

threatening arrhythmias, whether used separately or combined with other estimates of risk [e.g., premature ventricular contractions (PVCs) and nonsustained VT on 24-h ambulatory monitoring and ejection fraction (EF) measurements]. They have been applied most intensively after myocardial infarction.

Signal-averaged electrocardiography employs amplification of low-amplitude signals occurring after the termination of the standard electrocardiographic QRS complex, as recorded by high-amplification techniques. The low-amplitude signals are repetitive electrical events caused by a delayed activation sequence of part or parts of the ventricular muscle mass. Their repetitive timing allows them to be amplified during signal averaging, while random noise is being canceled out. The resultant signal is a high-gain, high frequency QRS complex, followed by low-amplitude signals representing the late potentials. The terminal delayed activation pattern represents a pathophysiologic marker for susceptibility to ventricular arrhythmias. It results from fragmented activation in an area of delayed conduction, which is a well established substrate for reentrant arrhythmias. The characteristics of an abnormal signal-averaged ECG include

- a prolonged filtered QRS complex (115 ms) with a normal duration of the standard QRS complex,
- the terminal portion of the filtered QRS complex less than 40 V for 39 ms,
- less than 20 V of amplitude during the last 40 ms of the filtered QRS complex.

At least two of the three criteria must be abnormal to consider the tracing abnormal, and many would require all three to be abnormal. Residual high-frequency noise content must be less than 1 V with a 25-Hz high-pass cutoff Signal-averaged electrocardiography is most useful for demonstrating presence and absence of risk for ventricular arrhythmias and sudden death after myocardial infarction. It is most powerful as a negative predictor of risk, in that a normal signal-averaged ECG after healing of myocardial infarction identifies a greater than 97 percent probability of remaining free of ventricular arrhythmias. The positive predictive accuracy is less powerful and is heavily influenced by other variables, such as EF and ambient ventricular arrhythmias. Signal-averaged electrocardiography alone has a positive predic-

tive value in the range of 20 percent, and combined with a low EF and ambient arrhythmias, the risk may be as high as 50 percent in some subgroups.

Heart rate variability studies provide estimates of sympathetic and parasympathetic balance. Blunting of the normal patterns of variability of sinus rate over time in subgroups of myocardial infarction and cardiac arrest survivors appears to increase the risk of life-threatening events. As is the case for signal-averaged electrocardiography, the test is used primarily for prognostic information rather than as a therapeutic guide. Baroreceptor sensitivity estimates the relationship between phenylephrine-induced blood pressure increase and concomitant fall in heart rate as an indication of parasympathetic responsiveness to the pure adrenergic stimulus. Following a myocardial infarction, a blunted baroreceptor sensitivity predicts an increased risk of VT and death. A recent large study also demonstrated its power for predicting adverse outcome following a myocardial infarction, which was further enhanced when combined with other risk variables, such as low EF and ambient arrhythmias.

Intracardiac Electrocardiography and Programmed Electrophysiologic Studies

Intracardiac electrocardiography and programmed electrophysiologic studies can be used to diagnose many disturbances in rhythm and conduction for which surface electrocardiography is insufficient. Intracardiac electrophysiologic studies are also used to define appropriate therapy and to test the results of therapy for various forms of supraventricular and ventricular arrhythmias. The use of multicatheter electrode systems, providing simultaneous recordings from many intracardiac sites, allows mapping of the sequence of excitation in the atria, AV junction, and ventricle. Intracardiac mapping procedures permit the identification of sites of accessory pathways, mechanisms of ventricular tachyarrhythmias, and the reentrant circuits or sites of origin of supraventricular tachyarrhythmias. Such techniques provide the basis for electrocardiographically guided therapy, such as radiofrequency (RF) ablation. In addition, the distinction between AV block above and below the level of the bundle of His and between true AV block and pseudo-AV block caused by concealed extrasystoles is

Endocardial Catheter Mapping and Intraoperative Multiarray Epicardial Mapping

Techniques for mapping pathways and sites of origin for both ventricular and supraventricular tachyarrhythmias, originally developed for intraoperative mapping during antiarrhythmic surgery, have found broad application in catheter-based procedures. Greatly improved catheter-ablation techniques for many arrhythmias, in conjunction with the development of sophisticated computer-based recording, storage, and retrieval systems, have limited the role of intraoperative mapping and interventions with the expansion of catheter techniques. The new mapping systems allow simultaneous recordings from many points, generating on-line maps of activation during a procedure. This technology allows the clinical electrophysiologist to identify target areas for delivery of RF energy during an ablation procedure. Computer-generated maps are now also available for ventricular arrhythmias.

Overview of management strategies

Strategies for the prevention and management of cardiac arrhythmias are based on an understanding of the mechanisms of specific arrhythmias (Table 3.2), in conjunction with systemic and cardiac factors that can be modified to influence predisposition to arrhythmias, and the range of indications for pharmacologic therapy and nonpharmacologic interventions. Many patients are managed with multiple interventions, one therapeutic mode being complementary to another.

Table 3.2

Summary of Approaches to Arrhythmia Management

General systemic interventions
- Respiratory support
- Hemodynamic support
- Metabolic and electrolyte control
- Neurophysiologic control

Electropharmacologic therapy
- Control triggering events
  - Suppress triggering arrhythmias
  - Prevent or reverse arrhythmogenic factors (e.g., anti-ischemic therapy, or electrolyte replacement)
- Control sustained arrhythmias

- Acute interventions
- Chronic prevention
- Control ventricular rate

Catheter ablation procedures

- Supraventricular tachycardias
  - AV nodal reentry
  - WPW syndrome
  - AV node ablation in atrial fibrillation
  - Atrial flutter
  - Atrial fibrillation, focal mechanismsa
  - Atrial, sinus node, and AV junctional tachycardias
- Ventricular tachycardias

Surgical intervention

- Antiarrhythmic surgery
- Anomalous pathwaysa
- Aneurysmectomy, endocardial resectiona
- Cryoablation
- Maze procedure for atrial fibrillationa
- Anti-ischemic surgery
- Structural heart disease surgery

Electronic device

- Acute applications
- Cardioversion
- Defibrillation
- Temporary pacemakers
- Long-term applications
- Permanent pacemakers
- Implantable cardioverter defibrillators

A complete management plan for any arrhythmia must coordinate three spheres of information:

- underlying structural etiology (coronary heart disease, cardiomyopathy, WPW syndrome, etc.);
- transient triggering factors that interact with the underlying structural abnormality (e.g., transient ischemia and hemodynamic, electrolyte, metabolic, and respiratory abnormalities),
- individual patients' preferences and decisions regarding pharmacologic versus interventional approaches.

The identification of contributing factors, which interact with underlying etiology as the proximate causes of an arrhythmia, is inherent to any treatment plan. Contributing factors may be systemic or cardiac. The major systemic abnormalities include hemodynamic dysfunction, hypoxia, acidosis, electrolyte disturbances, toxic or

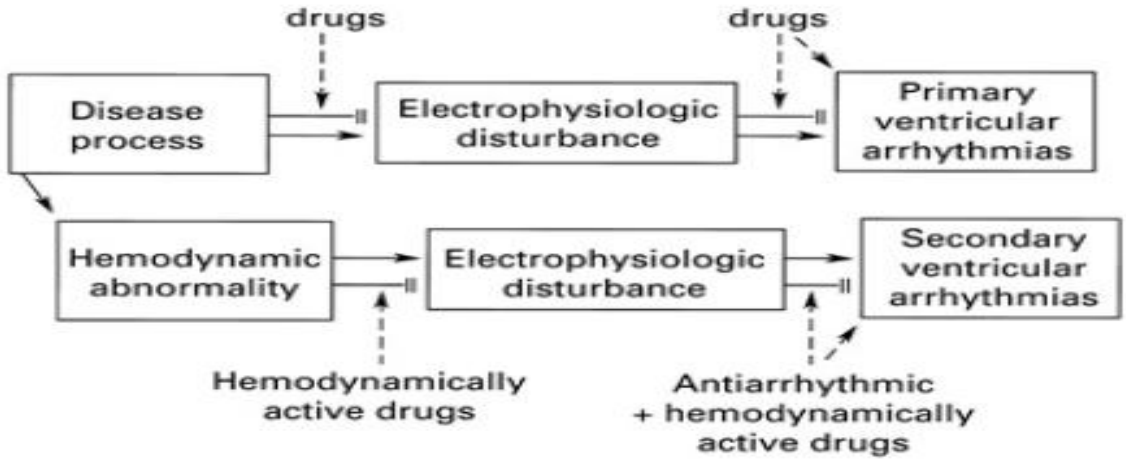
proarrhythmic drug effects, and endocrine abnormalities. Central nervous system factors, including fluctuations in autonomic tone, may cause or aggravate specific arrhythmias. Prompt reversal of serious arrhythmias may follow control of these disturbances.

Primary and secondary arrhythmias must be distinguished for both management and prognosis. Medical writings contain conflicting definitions of the term *primary arrhythmia*, which must be clarified for interpretation of investigative data. Historically, a primary arrhythmia was first described as one that resulted from an electrophysiologic disturbance caused by a disease process, in the absence of a significant change in hemodynamic function. An arrhythmia that resulted from an electrical disturbance caused or perpetuated by hemodynamic deterioration or metabolic abnormalities was defined as a secondary arrhythmia (Figure 3.1).

In the former, antiarrhythmic drugs alone may be useful, while a secondary arrhythmia requires the concomitant use of hemodynamically active drugs to support the failing circulation.

Figure 3.1

Primary and secondary arrhythmias



In secondary arrhythmias, antiarrhythmic and hemodynamically active drugs have complementary roles. Subsequent uses of the term *primary arrhythmia* were an arrhythmia that was the first clinical manifestation of disease, such as cardiac arrest due to ventricular fibrillation in coronary heart disease, or an arrhythmia in the absence of structural disease. To avoid confusion, the term primary must be carefully defined with each use.

Direct cardiac interventions for control of arrhythmias include pharmacologic approaches, ablation of specific foci involved in arrhythmogenesis, antiarrhythmic surgical approaches, and implantable devices designed to control tachyarrhythmic events or to prevent symptomatic bradyarrhythmias. Antiarrhythmic drugs may be classified into groups using the modified Vaughn Williams system, which categorizes them on the basis of electropharmacologic and electrophysiologic properties (Table 3.3). This classification is useful and practical for the clinician but has shortcomings. These include difficulty categorizing new drugs, exclusion of some drugs with obvious antiarrhythmic properties (e.g., adenosine), and inability to correlate drug class with specific effects as antiarrhythmic agents. Another classification system, the Sicilian gambit, was developed for the purpose of providing deeper insight into drug effects, therapeutic targets, mechanisms of action, and responses. While it is too complex for use as a practical clinical tool, it provides an excellent teaching method for understanding applied pharmacology.

Table 3.3

Modified Vaughn Williams Classification of Drugs Approved for Antiarrhythmic Uses

Examples	Depolarization	Repolarization
Class I: Membrane-active drugs		
IA Quinidine (Quinaglute, Quinidex, Cardioquin) Procainamide (Pronestyl, Procan SR) Disopyramide (Norpace) Moricizine (Ethmozine)	Moderate depression of Na+ current; intermediate kinetics	Prolonged
IB Lidocaine (Xylocaine) Tocainide (Tonocard) Mexiletine (Mexitil) Phenytoin (Dilantin)	Limited depression of Na+ current; rapid kinetics	No effect or shortened
IC Flecainide (Tambocor) Propafenone (Rhythmol)	Marked depression of Na+ current; slow kinetics	Minimal effect
Class II: Beta-adrenoceptor blocking drugs		
Propranolol (Inderal) Esmolol (Brevibloc) Acebutolol (Sectral)		
Class III: Drugs that prolong repolarization		
Amiodarone (Cordarone) Bretylium tosylate (Bretylol)		Prolonged

Sotalol (Betapace; Betapace AF) Ibutilide (Corvert) Dofetilide (Tikosyn)		
Class IV: Ca2+-entry blocking drugs		
Verapamil (Isoptin, Calan) Diltiazem (Cardizem)		
Unclassified in this system		
Digoxin (Lanoxin) Adenosine (Adenocard)		

Management of sinus tachycardia

Sinus tachycardia, except when it is an appropriate response to acute physical or emotional stress, is usually categorized as persistent and is easily recognized. Its management almost always depends on control of exogenous or endogenous systemic factors or of an underlying cardiac disease. Its differentiation from other SVTs at rates of 150 or more a minute may be achieved with carotid sinus massage. Specific therapy is rarely required. When it is required, beta-adrenergic blockade will often achieve at least partial control. In uncomplicated acute myocardial infarction, the sinus rate may be controlled with small doses of propranolol (10 to 20 mg every 6 h). Persistent sinus tachycardia occurs in thyrotoxicosis, and higher doses of propranolol may be required for its control. Sinus tachycardia during heart failure or hypovolemic states will respond promptly to improving hemodynamic status. The chronic or intermittent form of nonparoxysmal inappropriate sinus tachycardia, when symptomatic or associated with tachycardia-induced heart failure, may require RF energy modification or ablation of the sinus node area if it is not controllable by drug therapy.

Management of premature atrial contractions

PACs usually do not require treatment, especially when they occur in normal individuals or when due to systemic influences or minor cardiac abnormalities such as mitral valve prolapse and acute viral pericarditis. When PACs may be the triggering events for sustained arrhythmias, their management may become important. Generally, SVT due to AV nodal reentry or the WPW syndrome, paroxysmal atrial fibrillation, or the rare instances of induction of sustained ventricular arrhythmia by supraventricular impulses are best managed by therapy targeted to the prevention of the

sustained arrhythmias, but occasionally suppression of triggering PACs is helpful. In recent years, repetitive focal PACs and atrial tachycardia on ambulatory monitor recordings from patients prone to atrial fibrillation have been identified as RF ablation targets during studies in the electrophysiology laboratory. In some patients, these forms of PACs appear to act not only as triggers, but also as drivers, of atrial fibrillation episodes. Annoying palpitations are a common symptom of PACs in patients who have either no underlying heart disease or mitral valve prolapse. Reassuring the patient of the benign nature of the arrhythmia may suffice, and no therapy is necessary other than removal of inciting factors, such as cigarettes, coffee, alcohol, and excessive fatigue. When the palpitations are sufficiently bothersome to affect on the quality of life, an intervention must be considered. A low dose of a beta-adrenergic blocking agent is preferred to more aggressive (and more dangerous) membraneactive antiarrhythmic agents. Digitalis has been tried, but no systematic studies of its efficacy have been reported.

When it is necessary to treat PACs because of intolerable palpitations, conventional antiarrhythmic agents may be effective. Depending upon tolerance and side effects, any of the membrane-active drugs or adrenoceptor-blocking agents may be considered. Few data are available on the efficacy of antiarrhythmic drug therapy for PACs, but clinical experience suggests that it may be effective, particularly in the absence of structural cardiac or pulmonary disease. Antiarrhythmic drugs have not been approved for this indication in the United States, and the threshold for their use for a troublesome but benign arrhythmia is high. Class IC drugs should be avoided for this indication in patients with even the remote possibility of coronary artery disease because of the adverse outcome. Atrial distention in heart failure may induce PACs; they usually disappear as hemodynamics improve and antiarrhythmic drugs are avoided.

The reentrant paroxysmal supraventricular tachycardias

PSVT may be due to AV nodal reentry, the WPW syndrome, or intraatrial or sinoatrial re-entry. Most of the interventions for SVT listed in Table 3.4 are applicable to these arrhythmias.

Management of PSVT due to AV nodal reentry

PSVT due to AV nodal reentry is a benign disturbance requiring intervention primarily for the patient's comfort and sense of well-being. When it coexists with other disease processes in which the tachyarrhythmia is poorly tolerated, such as ischemic heart disease or mitral stenosis, it may have more serious implications. Occasionally, the rate is rapid enough to cause near-syncope or syncope in otherwise normal individuals, although such rates are more common in PSVT due to WPW.

Table 3.4

Management of Paroxysmal Supraventricular Tachycardias

Interventions	Acute	Long-Term
Physiologic interventions	Rest, sedation, Valsalva maneuver, carotid sinus massage	Self-administered, Valsalva maneuver, carotid sinus massage, avoidance of inciting factors
Pharmacologic therapy	Drugs with direct effect on AV nodal or accessory pathway	Drugs that alter properties of AV node or accessory pathways
	Drugs that control ventricular rate	Drugs that control ventricular rate
Catheter ablation and surgical techniques	-	Ablation of reentrant pathway Modification of AV node
Electronic devices	Temporary pacing Cardioversion	Permanent pacemaker

Rest, sedation, and vagotonic maneuvers are simple means of reverting acute episodes, and patients can be taught self-administered vagotonic maneuvers for recurrences. Patients should be advised to avoid inciting factors, such as smoking, alcohol, extreme fatigue, and stress. Many of the effective pharmacologic interventions for acute episodes used in the past have given way to new drug therapy. Infusions of sympathomimetic drugs (e.g., phenylephrine or methoxamine), parasympathomimetic drugs (e.g., edrophonium or neostigmine), and digoxin have been supplanted by intravenous adenosine, Ca^{2+}-entry blockers, or beta-adrenergic blockers for managing the acute episodes. Adenosine, 6 mg given intravenously, followed by one or two 12-mg boluses if necessary, is effective and safe for acute treatment. Because of its very short duration of action and lack of the negative inotropic effects of Ca^{2+}-entry blockers, it is now preferred to other acute pharmacologic therapies, especially when man-

aging a patient with concomitant structural heart disease. A 5-mg bolus of verapamil, followed by one or two additional 5-mg boluses 10 min apart if the initial dose does not convert the arrhythmia, has been an effective regimen in up to 90 percent of patients with PSVT due to AV node reentry. However, it must not be used for an unknown wide QRS tachycardia because of risk of adverse effects when used in patients who have VT. Intravenous diltiazem is also effective. Initial treatment consists of a bolus of 0.25 mg/kg body weight administered over 2 min. If the response is inadequate, a repeat bolus of 0.35 mg/kg over 2 min is administered 15 min later. Intravenous digoxin, 0.5 mg infused over 10 min and repeated if necessary, may convert the arrhythmia. An additional 0.25 mg every 4 h to a maximum dose of 1.5 mg in 24 h may be used. A slow infusion of propranolol may be used; 1 mg/min is given to a total dose of 5 to 10 mg or a significant fall in blood pressure. The class IA antiarrhythmic agents, which appear to depress conduction in the fast pathway, may be tried if other drugs fail, a strategy that is rarely needed. Several special points must be remembered. When the QRS complex is wide and VT is mistakenly diagnosed as SVT with aberrant conduction, intravenous verapamil frequently causes a clinically significant fall in blood pressure and potentially lethal events. Unless it is known with certainty that a wide QRS tachycardia is due to aberrant intraventricular conduction or preexisting bundle-branch block, verapamil should not be used. Similarly, in patients with coexisting hemodynamically significant underlying heart disease, intravenous propranolol must be used with caution, if at all. For those few patients in whom the clinical setting demands an immediate return to a normal sinus mechanism, DC cardioversion can be employed. A low-energy shock (10 to 50 W·s) may be sufficient; larger energies are used if necessary. If DC cardioversion should be avoided, pacing the right atrium or ventricle via a temporary pacing catheter is usually successful.

Long-term prevention of recurrent PSVT due to AV nodal reentry may be achieved with pharmacologic therapy or catheter ablation. Surgical techniques and electronic devices have been used in the past but are now obsolete. Patients who have infrequent, well-tolerated episodes that are short-lived and/or respond to self-administered physiologic maneuvers may require no long-term interventions. In

many others, pharmacologic therapy is sufficient. Most patients have reduced numbers and severity of attacks with simple medications such as propranolol, verapamil, or digoxin. These drugs act by altering conduction velocities and refractory periods in the AV nodal pathways, disrupting the delicate balance required for initiation or maintenance of sustained arrhythmias. Membrane-active antiarrhythmic drugs may prevent recurrences, both by suppressing triggering premature impulses and by depressing conduction in the anterograde (fast) pathway of the AV nodal re-entrant circuit. However, the risk of potentially serious proarrhythmic responses, combined with other troublesome side effects, limits their use for these arrhythmias. RF catheter ablation is safe and very effective for PSVT due to AV nodal reentrant tachycardia. It has therefore emerged as the treatment of choice for patients with frequent arrhythmic episodes and/or poor tolerance of drugs. It is also the preferred option for pharmacologically controllable AV nodal reentrant tachycardia among patients who want to avoid pharmacologic side effects. Among women who have a history of clustering of episodes of AV nodal reentrant tachycardia when perimenstrual, RF ablation procedures should be scheduled when they are premenstrual, in order to maximize the chance of inducing the target arrhythmia during the procedure.

Management of PSVT due to WPW syndrome

This form of reentrant SVT is amenable to a broad range of interventions. Careful attention to the details of therapy is required because a subgroup of patients is at risk for potentially lethal arrhythmias due to very rapid conduction across the AP during atrial flutter or fibrillation. This concern influences the pharmacologic approaches to PSVT in the WPW syndrome, since drugs have different effects on APs and the AV node and because reciprocating PSVT may convert to atrial flutter or fibrillation. Physiologic interventions and vagomimetic drugs can be used safely during acute episodes of reciprocating tachycardia. In addition, adenosine, verapamil diltiazem, propranolol, and membrane-active antiarrhythmic agents, such as procainamide, quinidine, or disopyramide, may be used to convert acute reentrant tachycardias. Verapamil and lidocaine may accelerate the ventricular rate during atrial flutter or fibrillation in the WPW syndrome, however, and should be avoided if atrial fibrillation is

present or if the patient has previously demonstrated alternation between atrial fibrillation and reciprocating tachycardia. Digoxin must be avoided in patients with WPW because it may shorten the refractory period of the AP46 as well as atrial muscle. Should this occur in the presence of unrecognized atrial flutter or fibrillation or with the conversion of a reciprocating tachycardia to atrial fibrillation, the patient could develop a life-threatening tachyarrhythmia due to rapid AP conduction. Whenever there is doubt, therapy should be limited to those drugs that will depress conduction in the AP or prolong its refractory period, such as the membrane-active antiarrhythmic agents (e.g., intravenous procainamide), or to agents, such as adenosine, that usually have no effect on an AP. Electrical cardioversion should be used if other means have failed or as initial therapy if the patient has extremely rapid rates causing hemodynamic intolerance of the tachycardia.

The approach to long-term management of patients with WPW syndrome is determined by the physiologic characteristics of the bypass tract and the frequency, duration, and symptoms of arrhythmias. Two primary approaches to therapy are available: drugs and catheter ablation. The latter, using an RF energy source, is the preferred method for treatment of patients with tachycardias symptomatic enough to limit their quality of life (e.g., near-syncope or syncope) or with symptomatic life-threatening arrhythmias in WPW (e.g, atrial fibrillation with short refractory period bypass tract). Surgery is a rarely used secondary approach, reserved for the occasional patients requiring treatment and not amenable to catheter ablation or pharmacologic therapy and for some who require surgery for other causes as well. Although intracardiac electrophysiologic studies provide information on drug efficacy and pharmacologic effects on the bypass tract, this invasive procedure is seldom performed for this purpose any longer. Patients who demonstrate a good clinical response to therapy, measured in terms of reduced frequency or rate of tachyarrhythmic episodes, can be managed noninvasively; patients with an intermittent delta wave and no clinical arrhythmia need no therapy. On the other hand, patients who have frequent or poorly tolerated tachyarrhythmias, those who are prone to episodes of atrial flutter or fibrillation (particularly if they develop wide QRS complexes during their tachyarrhyth-

mias, suggesting bypass tract conduction), or those who have a family history of WPW and sudden death should be evaluated by electrophysiologic testing. In such patients, catheter ablation using RF energy is the intervention of choice when available in an experienced laboratory and accepted by the patient. In the event of failure of the technique to interrupt the tract or tracts, surgical interventions may be considered, but the threshold for surgical intervention is higher. Among those with symptomatic or life-threatening arrhythmias for whom RF ablation is not available, accepted, or feasible, a clear-cut response to antiarrhythmic therapy is mandated. Among the antiarrhythmic agents, the class IA, IC, and III drugs may be useful. Not all drugs in these categories are approved for this indication in the United States, but efficacy studies are impressive. Because of its side-effect profile, the threshold for use of amiodarone has been higher, despite good efficacy. PSVT also occurs in patients with *concealed* WPW syndrome, a condition in which the bypass tract is incapable of conducting in the antegrade direction. Thus, there is no delta wave during sinus rhythm, but intact retrograde conduction permits completion of reciprocating tachycardia circuits. The diagnosis is suggested by longer RP intervals on the ECG during tachycardia than occur in AV nodal reentry and can be established by electrophysiologic testing. Management is similar to that for other WPW syndrome patients. However, even though atrial fibrillation may occur, there is no concern about risk of degenerating to ventricular fibrillation. In such patients, the ventricular rate is controlled by normal AV nodal properties, since the AP cannot provide antegrade conduction.

Management of Ectopic Atrial Tachycardias

Treatment is dictated by identification and reversal of inciting factors, by ablation of a defined focal source when identifiable, and by control of the heart rate when necessary. Temporary pacing is required infrequently. More commonly, the problem is one of a rapid ventricular rate. Attempts to control the ectopic atrial arrhythmias with membrane-active antiarrhythmic drugs have not been generally successful. (Beta-adrenergic blocking agents or Ca2+-entry blocking agents may be successful in controlling the arrhythmia in some patients, but a uniformly beneficial response should not be expected. Electrical cardioversion is not indicated because it is usually

unsuccessful. The mainstay of therapy remains the removal or reversal of inciting factors. If a controllable inciting factor cannot be identified or reversed, antiarrhythmic drugs may be tried. In addition, catheter ablation techniques may have a short-term success rate of as much as 80 percent among those whose arrhythmia has a structural basis. It is not useful for metabolic or toxic causes and is very limited for those having multiple foci of origin.

Management of Paroxysmal Atrial Flutter

Treatment of acute paroxysmal atrial flutter differs from the treatment of PSVT due to AV nodal reentry or AV reciprocating mechanisms. Carotid sinus massage will not interrupt atrial flutter but transiently slows the ventricular rate by impairing AV nodal conduction. The pharmacologic treatment of atrial flutter may be directed to reversion to a sinus mechanism or to control of the ventricular rate. The usual ventricular rate of 150 impulses per minute (±10 impulses per minute) may be well tolerated in the absence of myocardial dysfunction, symptomatic coronary artery disease, or mitral stenosis. The ventricular rate should be slowed with digitalis before antiarrhythmics are instituted to convert the atrial arrhythmia to avoid very rapid rates associated with drug-induced 1:1 AV conduction. Control of the heart rate during the paroxysm may also be achieved with Ca^{2+}-entry blocking agents. Verapamil has been studied in detail, and intravenous diltiazem is also successful. When the ventricular rate is poorly tolerated due to effects on hemodynamics or coronary blood flow, electrical cardioversion is used as initial treatment. An attempt using 10 to 50 J may be successful; higher energies are often necessary. Membrane-active antiarrhythmic agents are used to convert flutter to sinus rhythm, but efficacy is unpredictable. Historically, quinidine has been the initial drug of choice, but the other class IA antiarrhythmic agents may be equally effective. Conventional dosing schedules are now used, in contrast to the highly toxic aggressive quinidine protocols of the past. The class IC drugs (e.g., flecainide or propafenone) may also be effective for pharmacologic reversion of atrial flutter, although they slow intraatrial conduction without lengthening refractory periods. This drug effect may result in slowing atrial flutter from 300 per minute to less than 240 per minute, allowing 1:1 conduction to the ven-

tricles at rates as high as 220 to 240 per minute. Because of the concomitant rate-dependent effect on ventricular conduction velocity, the slowed atrial rate with 1:1 conduction may generate wide QRS complexes mimicking ventricular tachycardia. Ibutelide, an intravenous drug with class III effects, is also effective for acute treatment of atrial flutter. Its major concern is the short-term risk of "torsades de pointes", which necessitates monitoring for several hours after administration. Failing conversion or achieving an acceptable rate with drugs, elective DC cardioversion is usually successful. If cardioversion is contraindicated or fails, an attempt to entrain the atrium with rapid atrial pacing may result in conversion to sinus rhythm. Occasionally, rapid pacing may convert atrial flutter to atrial fibrillation, which will have a slower ventricular response. Pharmacologic management for recurrences of the paroxysmal form of atrial flutter includes long-term use of antiarrhythmic therapy to prevent the arrhythmia and the use of AV nodal blocking agents to control heart rate during recurrences. For the former, the class IA antiarrhythmic agents, especially quinidine, have been used with variable success. Class IC and class III drugs are potentially useful, but the concern with the mechanism of action of class IC drugs in atrial flutter cited above limits their use. Control of ventricular rate is best achieved with digitalis because of safety and efficacy considerations. Long-term oral use of verapamil for control of rate in recurrent atrial flutter is less predictably effective than intravenous use to slow the rate during a paroxysm. Beta-adrenergic blocking agents have been used, and if the drugs are well tolerated, the dose can be titrated to clinical beta-blocking efficacy by heart rate and blood pressure criteria. Subsequent observations of ventricular rates during recurrences will establish efficacy. There is no known excess incidence of embolic events during paroxysmal atrial flutter or during its reversion. Anticoagulants are not used before, during, or after reversion. In recent years, RF catheter ablation procedures have been used with increasing frequency for patients with atrial flutter, especially for patients with frequent symptomatic episodes of atrial flutter or those resistant to drug therapy. A linear RF ablation lesion across the subeustachian isthmus, between the tricuspid valve annulus and the inferior vena cava, interrupts the reentrant pathway responsible for type I flutter. The procedure

has a high probability of permanent clinical success, avoiding the need for long-term pharmacologic therapy among these patients.

Management of Persistent Atrial Flutter

Atrial flutter may occur in a persistent form secondary to noncardiac factors, such as thyrotoxicosis or pulmonary embolism, although it is most common in the presence of chronic heart disease. Persistent or chronic atrial flutter occurs, but not commonly, in otherwise normal persons. Patients subject to recurrent episodes of persistent atrial flutter can be maintained on long-term antiarrhythmic therapy. However, RF ablation has emerged as the therapy of choice for symptomatic patients in this category. Recurrence of atrial flutter after an RF ablation procedure occurs in approximately 15 percent and is usually due to gaps in the linear lesion across the isthmus, maintaining continuity of conduction in the reentrant pathway. These gaps can often be identified and sealed during a repeat RF ablation procedure. If RF ablation fails or is not desired by the patient, therapeutic approaches during recurrences include additional antiarrhythmic agents for reverting atrial flutter and agents that will control the ventricular rate. Acute antiarrhythmic therapy may include intravenous procainamide or ibutilide or orally administered drugs that prolong refractoriness (e.g., sotolol). Electrical reversion, however, may still be required.

Management of Chronic Atrial Flutter

Some patients will remain in chronic atrial flutter despite aggressive antiarrhythmic or interventional therapy, and flutter may recur predictably shortly after DC cardioversion. This usually occurs in the setting of advanced heart disease, may occur as the forerunner of chronic atrial fibrillation, and appears to be especially frequent with the variants of flutter, such as type II atrial flutter. It may occur rarely in otherwise normal persons and more commonly in association with other SVTs, such as WPW and AV nodal reentry. If the ventricular rate is adequately controlled and the patient is asymptomatic, chronic atrial flutter need not be treated aggressively. In these cases, there is little justification for the use of complex antiarrhythmic drug regimens with adverse side-effect profiles. Rather, catheter ablation procedures can be used, especially for type I flutter, where the success rate is high. Surgical ablation of

atrial flutter is feasible but is used only in rare circumstances, usually in conjunction with surgery being performed for another primary indication.

Control of ventricular rate is the major issue for management. AV nodal blocking agents, such as digoxin, beta-adrenergic blockers, and Ca^{2+}-entry blockers, may be tried. The major problem is the tendency for AV conduction to respond to pharmacologic control in step patterns. The patient who is well controlled with 4:1 conduction at a ventricular rate of 75 per minute may abruptly increase to 150 per minute under conditions of stress, which enhance AV nodal conduction. In patients with enhanced AV nodal conduction and atrial flutter, it may be difficult to slow the rate below 150 per minute pharmacologically. Verapamil appears to be more effective than digoxin for the AV node with enhanced conduction but is not uniformly effective. Rarely, catheter ablation for AV node modification or interruption, with pacemaker implantation, is used for heart rate control in patients who are resistant to or intolerant of AV nodal blocking drugs and who have failed ablation attempts to interrupt the flutter pathway. In the past, long-term anticoagulation was not generally recommended for patients with chronic atrial flutter. However, the potential risk of thromboembolism in atrial flutter has been reevaluated, and it is now recommended to follow the guidelines of anticoagulation for atrial fibrillation in patients with atrial flutter. Although the precise risk of stroke associated with atrial flutter has not been yet established by a large prospective clinical trial, the retrospective observations cited suggest an incidence of stroke similar to that expected in chronic atrial fibrillation. There is transesophageal echocardiographic evidence of atrial clot formation and spontaneous contrast in these patients. Finally, it is clinically difficult to ensure that a patient with atrial flutter will not have occasional periods of atrial fibrillation.

Management of Recurrent Episodes of Paroxysmal Atrial Fibrillation

Paroxysms of atrial fibrillation lasting less than 48 h in the absence of underlying heart disease are usually managed conservatively. Rest, mild sedation with 5 to 10 mg of diazepam, and Ca^{2+}-entry blockers, beta-adrenergic blockers, or digitalis for control of the ventricular rate constitute an accepted approach. After the first episode, patients who have lone atrial fibrillation can be reassured in respect to the absence of

underlying organic heart disease and guided to avoid precipitating factors. In the presence of heart disease, particularly when the hemodynamic circumstances require either the mechanical benefit of atrial systole or a properly controlled ventricular rate for adequate diastolic filling, immediate reversion to sinus rhythm or slowing of the ventricular rate may be mandatory. The presence of clinical signs of heart failure requires immediate cardioversion to achieve either or both of these goals.

If the patient is tachycardic but clinically stable, pharmacologic approaches to control the rate (digitalis or intravenous verapamil or diltiazem) may be attempted. The overall probability of spontaneous conversion of paroxysmal atrial fibrillation within 24 h is approximately 50 percent. However, a number of antiarrhythmic drug strategies have been used to achieve earlier reversion or increase the reversion rate without electrical cardioversion. Intravenous procainamide and ibutilide have been used for pharmacologic reversion of acute paroxysms. The latter must be used with caution because it may prolong the QT interval acutely, with the short-term risk of torsades de pointes. Intravenous formulations of the class IC drugs flecainide and propafenone have also been used successfully for treatment of acute atrial fibrillation. Oral bolus therapy using flecainide (300 mg dose) or propafenone (600 mg) in a single dose has been used, although it is not clear whether it provides more or simply earlier conversions than in control subjects. Long-term pharmacologic therapy in the absence of underlying heart disease or in the presence of trivial abnormalities is intended to reduce or eliminate recurrent episodes and to control ventricular rate during recurrences, should they occur. Digitalis, beta-adrenergic blockers, or Ca^{2+} entry blockers are used for rate control as described for atrial flutter. Digitalis controls ventricular rate at rest, although it appears less effective for limiting effort-induced increases in ventricular rate during atrial fibrillation.

Prevention of episodes of atrial fibrillation may be achieved with class IA, IC, or III antiarrhythmic drugs. If episodes are clinically benign and infrequent, the threshold for such treatment is higher than if they are more frequent and symptomatic. Efficacy is uneven and proarrhythmic or toxic side effects are of concern. During short paroxysms of atrial fibrillation (up to 48 h), anticoagulation is not required prior

to reversion; long-term anticoagulation is not necessary for patients subject to brief paroxysmal attacks.

Management of Persistent Atrial Fibrillation

The decision to intervene in longer episodes of atrial fibrillation is based on the balance between hemodynamic tolerance and the likelihood of being able to control future episodes. Because of the demonstrated effects of "electrical remodeling" of atrial myocytes during persistent atrial fibrillation, which favors persistence of the arrhythmia and resistance to reversion, there is a tendency toward a more aggressive approach to early reversion. Many patients with organic heart disease have intermittent episodes of persistent atrial fibrillation prior to establishing chronic atrial fibrillation. Among these patients, antiarrhythmic efficacy for control of recurrences is unpredictable. Prediction of the ability to control ventricular rate by AV nodal blocking agents is better but still imperfect. When a patient has had multiple recurrences of persistent atrial fibrillation despite trials of several antiarrhythmic agents and the arrhythmia is well tolerated hemodynamically, many clinicians avoid repeated electrical cardioversions, especially in the presence of advanced heart disease. If elective cardioversion is to be attempted, 3 weeks of anticoagulation should precede the procedure to reduce embolic risk. A more expeditious alternative strategy is to perform a transesophageal echocardiogram to rule out the presence of atrial thrombi. If results are negative, heparin can be started and chemical or electrical cardioversion performed. However, there remains some debate about the efficacy of this strategy. If cardioversion is not attempted and the patient has recurrent episodes of atrial fibrillation lasting 48 to 72 h, long-term anticoagulant with warfarin is indicated. If the patient is without structural disease, is less than 60 years of age, and has a normal echocardiogram and no prior history of embolism, long-term warfarin therapy is unnecessary.

In the presence of advanced or progressive cardiac disease, atrial fibrillation is likely to revert and recur intermittently until the condition evolves into chronic atrial fibrillation. When this occurs, the best therapeutic approach may be control of ventricular rate during recurrences. Membraneactive antiarrhythmic agents are often used in an attempt to limit the number of recurrences, but efficacy is unpredictable, and

risk of side effects is high. The flecainide data suggest efficacy, especially for patients with good LV function and those free of underlying coronary artery disease. Class III antiarrhythmic drugs, including sotalol, amiodarone, dofetilide, and azemilide, are also effective.

Management of Chronic (Permanent) Atrial Fibrillation

The ventricular rate in chronic atrial fibrillation is usually more predictably controlled than in recurrent episodes of paroxysmal or persistent atrial fibrillation. Pharmacologic or electrical cardioversion in patients with advanced heart disease and atrial enlargement is attempted in the hope of achieving a hemodynamic benefit, but the probability of maintaining sinus rhythm is low. Until more data are available, the choice between attempting to restore sinus rhythm and simply controlling heart rate (with anticoagulation) is a matter for individual clinical judgment. Among patients with advanced heart disease who have been electrically cardioverted while taking antiarrhythmic drug therapy, approximately one-third will revert to atrial fibrillation within 1 week and two-thirds within 12 months. If the rhythm reverts to chronic atrial fibrillation shortly after cardioversion, the probability of long-term maintenance of sinus rhythm by additional pharmacologic approaches is very low. The ventricular rate is then controlled as outlined above. Pharmacologic control of ventricular rate may be problematic in recurrent episodes of both persistent and chronic atrial fibrillation. Under both circumstances, catheter modification of the AV junction or complete interruption (catheter ablation) of the AV junction with permanent pacing may provide heart rate control. Other nonpharmacologic strategies for control of atrial fibrillation include surgical procedures designed to establish sinus node control of the ventricular rate and rhythm, implantable device therapy, and catheter ablation procedures. Among the surgical approaches, the "corridor" procedure establishes a pathway from sinus node to AV node, while the MAZE procedure interrupts pathways necessary for maintaining fibrillation and reestablishes both rate control and mechanical function. The MAZE technique has been used both as primary surgery and as an added procedure for patients undergoing cardiac surgery for other reasons. An implantable atrial defibrillator has been developed for use in patients with chronic recur-

rent atrial fibrillation. It appears to have only limited applicability as a stand-alone device, but integration of the technology within the platform of conventional implantable cardioverter defibrillators (ICDs) may be useful for patients with paroxysmal atrial fibrillation at risk for life-threatening ventricular arrythmias. Another device strategy being evaluated is the use of dualsite atrial pacing in an attempt to resynchronize atrial depolarization and avoid dispersion of atrial refractoriness. Catheter ablation techniques for preventing atrial fibrillation (i.e., catheter-based MAZE procedure or ablation of focal triggering sites for atrial fibrillation) are currently being evaluated. The ultimate role for these approaches in the management of patients with recurrent or chronic atrial fibrillation remains to be determined.

Management of patient with different forms of atrial fibrillation is presented in Figure 3.2, 3.3, 3.4 and 3.5.

Figure 3.2

Management of patient with newly diagnosed atrial fibrillation

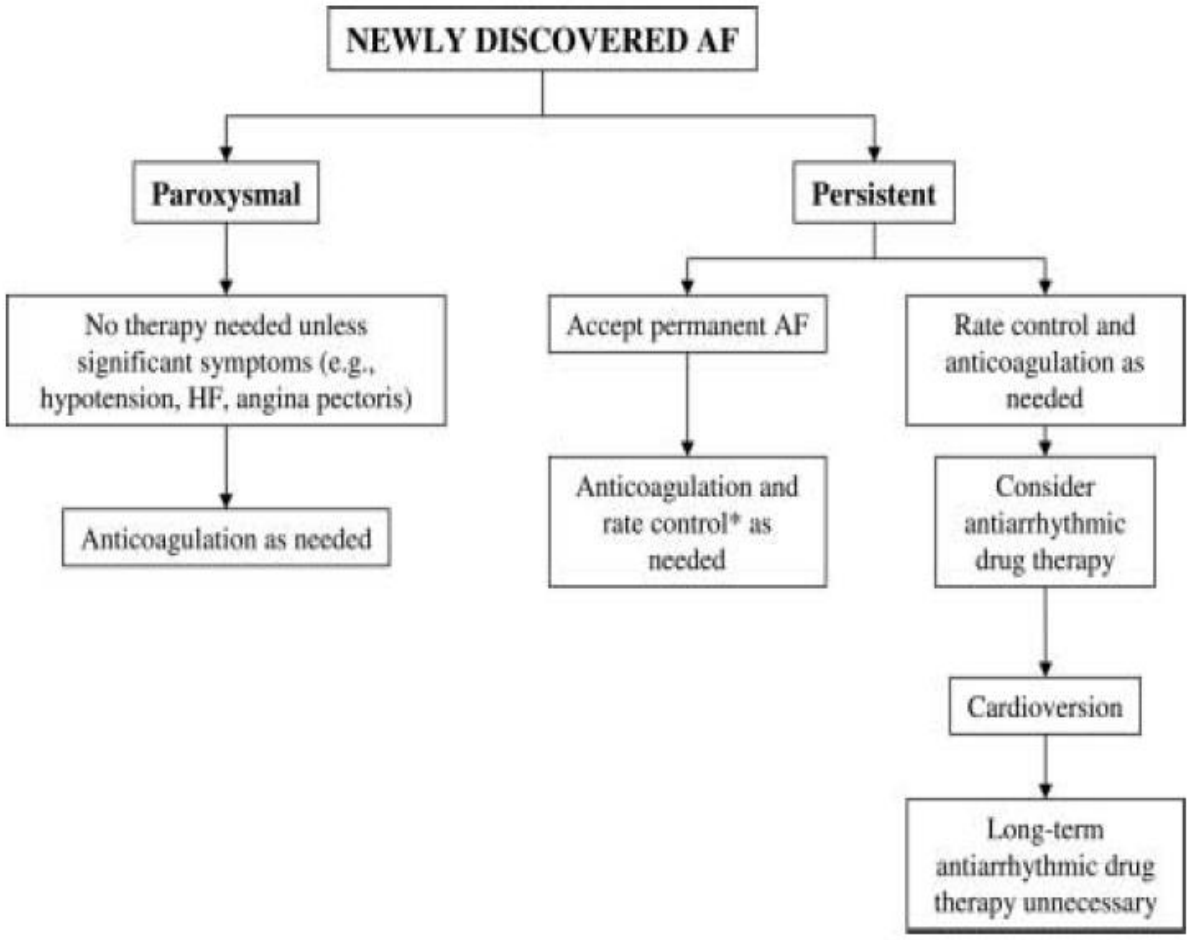


Figure 3.3.

Management of patient with recurrent paroxismal atrial fibrillation

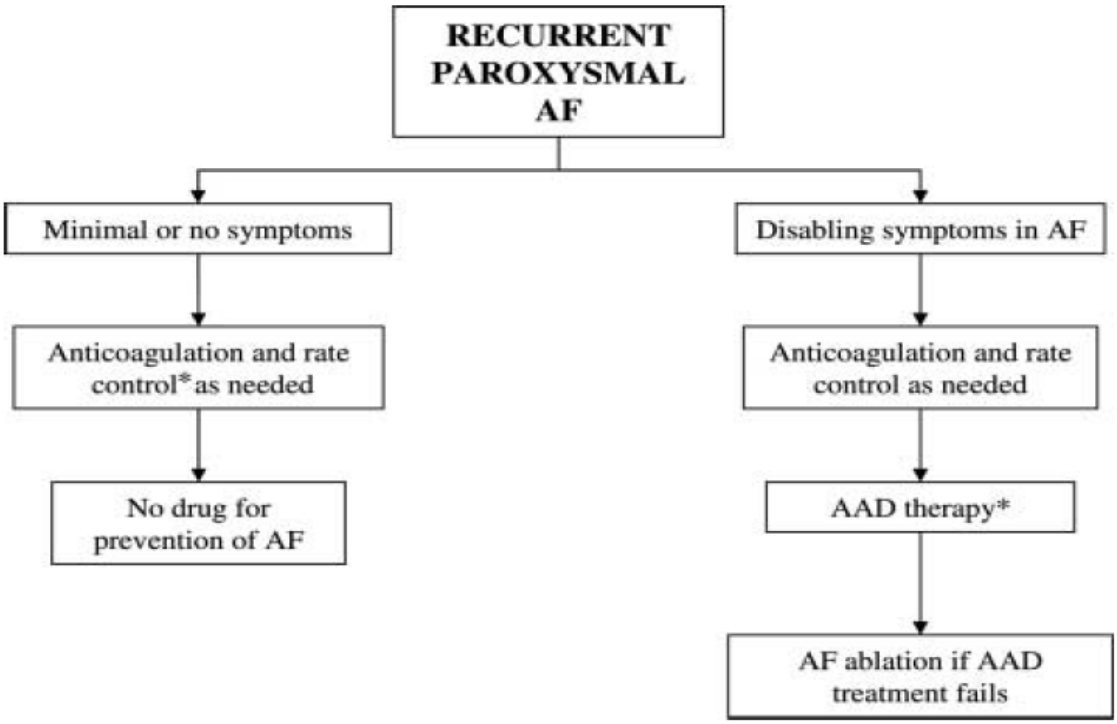


Figure 3.4.

Maintenance of sinus rhythm management of patient with atrial fibrillation

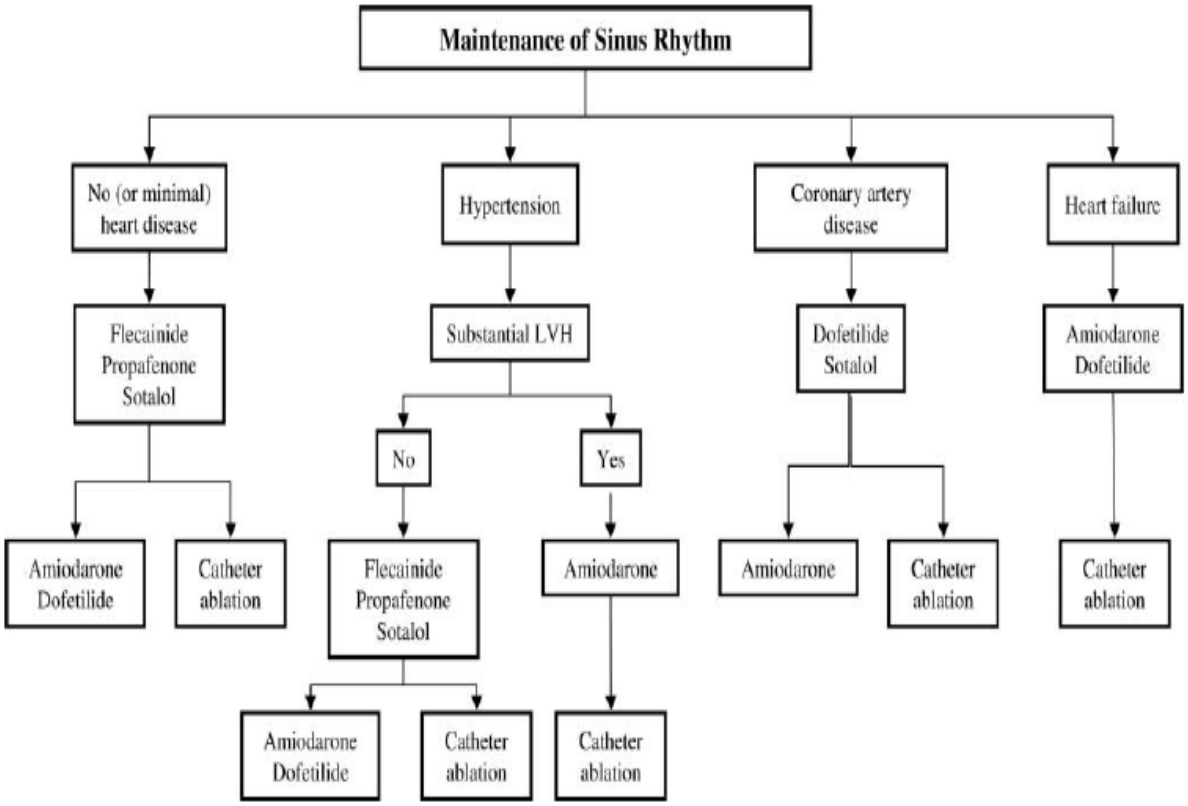
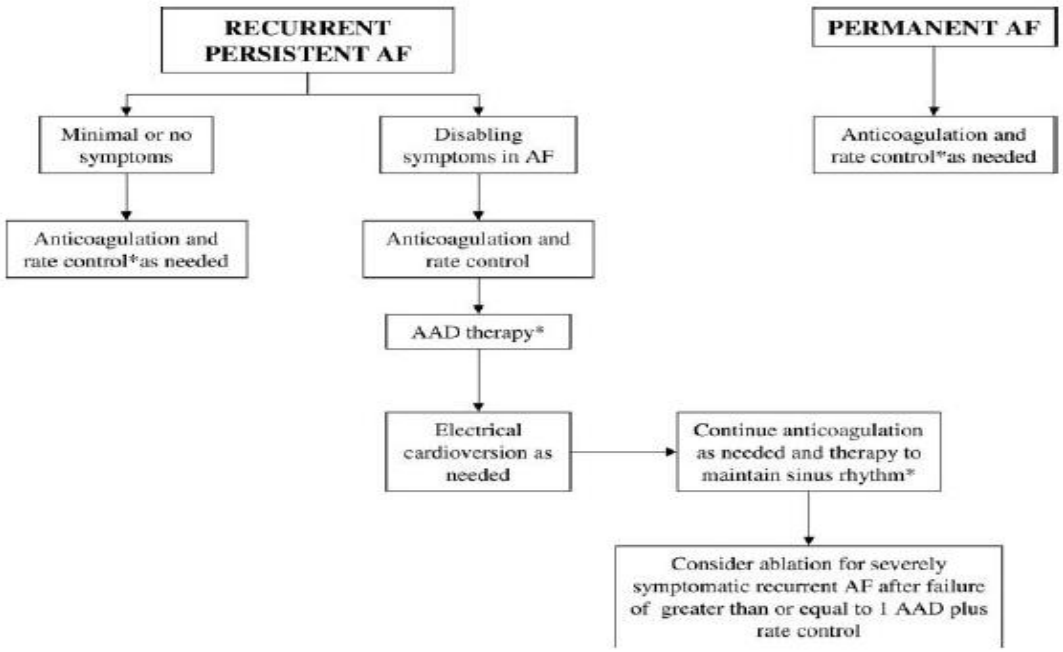


Figure 3.5

Management of patient with recurrent persistent and permanent forms of atrial fibrillation



Anticoagulation of Patients with Atrial Fibrillation

Patients with atrial fibrillation have a greater than fivefold increase in risk of stroke compared to control populations without atrial fibrillation. In addition, there are specific high-risk subgroups. Among patients with rheumatic heart disease, the risk exceeds by up to 17 times that of a control group. Other subgroups at high risk include patients with dilated cardiomyopathy, dilated left atrium of any cause, atrial fibrillation of recent onset, and a history of prior embolism. Patients with atrial fibrillation and LVH are also at increased risk, as are thyrotoxic patients. It is generally agreed, however, that patients older than 60 years with lone atrial fibrillation are at risk and should be anticoagulated with warfarin. As a group, the nonrheumatic disease states associated with atrial fibrillation tend to have excess risks in the range of five- to six-fold, according to various studies. Absolute risks differ little among the various rheumatic and nonrheumatic etiologies, however, with event rates in the range of 4 to 6 percent for each, except for lone atrial fibrillation, which has a considerably lower rate. The risk of embolic events tends to cluster around changes in rhythm, the highest incidence occurring within the first year after onset of chronic atrial fibrillation and a concentrated 1 to 2 percent risk occurring in the first days af-

ter restoration of sinus rhythm, whether by pharmacologic strategies or DC cardioversion.

The issue of anticoagulation in atrial fibrillation hinges on a balance between efficacy of preventing embolic events and risk of bleeding. Indicators of increased risk of embolic events, in addition to the general presence of structural heart isease, include previous stroke or transient ischemic attack, hypertension, heart failure, prosthetic heart valves, and hyperthyroidism. Age and female gender (particularly elderly women) also identify increased risk. Efficacy and risk both relate well to the level of anticoagulation with warfarin. Measured as the now-standard international normalized ratio (INR), benefit is optimal at or above an INR of 2.0, while bleeding risk increases above an INR of 3.5 to 4.0.143 Until recently, most of the data on efficacy of anticoagulation for reducing incidence of embolic events in atrial fibrillation were from poorly controlled or uncontrolled studies, and there was no consensus based on the available data. The available combination of risk data and retrospective or uncontrolled efficacy data tended to result in the practice of using long-term anticoagulation for patients with a rheumatic etiology and for those with advanced structural diseases associated with atrial fibrillation. Such patients included those with coronary artery disease and a prior embolism, idiopathic dilated cardiomyopathy, and prosthetic cardiac valves. More recent data have reaffirmed that warfarin is superior to aspirin and provided additional insight into effective warfarin dose ranges. In patients at high risk for embolic events, fixed low-dose warfarin (0.5 to 3.0 mg/day; INR = 1.2 to 1.5) plus aspirin (325 mg/day) was inferior to conventional dose adjusted warfarin (INR target = 2.0 to 3.0). Indications for anticoagulation prior to elective cardioversion have not undergone the same scrutiny for efficacy as has now been provided for intermittent and chronic atrial fibrillation. Nonetheless, there is enough information available to warrant the routine use of anticoagulation prior to elective cardioversion of recent onset (more than 48 to 72 h), persistent atrial fibrillation or chronic atrial fibrillation, particularly when associated with an enlarged left atrium or other structural diseases regardless of etiology. Anticoagulation with warfarin is started 3 to 4 weeks before elective cardioversion and is maintained for 3 to 4 weeks subsequently. If

there is concern about the ability of a patient to recognize a recurrence of atrial fibrillation, it may be warranted to maintain anticoagulation indefinitely, particularly if the patient has advanced structural heart disease.

The risk-benefit data are less clear for anticoagulation prior to elective cardioversion of atrial fibrillation of short duration (less than or equal to 48 h), particularly lone atrial fibrillation or when associated with minimal structural disease and normal atrial dimensions. The potential efficacy of anticoagulation must be weighed against its risk. Patients receiving anticoagulants retain a risk of embolization ranging from 1 to greater than 3 percent per year, depending upon disease states. Furthermore, there is a significant incidence of life-threatening bleeding or major events requiring transfusion among patients on long-term anticoagulation. Lower warfarin dosing than used previously, titrated to an INR of 2.0 to 3.0, may be one reason for the reduction of bleeding risk with warfarin use. Since the risk of bleeding is increased significantly with an INR of 5.0, the inability to control the prothrombin time, including the inability of the patient to comply with the prescribed dosages, must be considered relative contraindications. The major complication of intracranial bleeding may have an incidence of 1 to 2 percent per treatment-year. The physician must balance accepted indications and risks in judging whether to use anticoagulation in individual patients. In most circumstances now, however, one should err on the side of use rather than avoidance if the risk-benefit relationship is not clear, assuming the INR is assiduously maintained between 2.0 and 3.0 in candidates at higher risk for bleeding complications.

Management of premature ventricular contractions

Management of PVCs in the Absence of Significant Structural Heart Disease PVCs occur in many healthy individuals. In the absence of heart disease, there is little or no increased risk, and the risk-benefit ratio of antiarrhythmic therapy does not support a need for routine treatment. For the patient who complains of disturbing or disabling palpitations due to PVCs, however, the clinician may have to treat for symptom relief. Reassurance and avoidance of potentially aggravating factors (e.g., tobacco, coffee, caffeine-containing soft drinks, environmental stress, or stimulants) should be tried before pharmacologic therapy. For the latter, mild anxiolytic drugs or

beta-adrenergic blockers (which may sedate, reduce PVC frequency, and decrease the strength of postextrasystolic impulses causing the perception of palpitations) are preferred. When used for this purpose, low doses of beta-adrenergic blockers are often sufficient. The end point, relief of symptoms, may not necessarily be accompanied by significantly reduced PVC frequency. The frequency of PVCs may be modulated by underlying heart rate, and thus manipulations of sympathetic and parasympathetic balance may be useful. Because of their side-effect profiles, class I antiarrhythmic agents are rarely indicated in this clinical setting, and the class III agent amiodarone is unnecessarily potent. PVCs are often more prominent with pregnancy and premenstrually and increase in frequency with age.

Management of PVCs in Acute Syndromes

PVCs are nearly ubiquitous in acute myocardial infarction, but the threshold for treatment remains unsettled. The original concept of "warning arrhythmias" published by Lown et al. remains an indication for aggressive treatment, even though the predictive value of such warning arrhythmias remains unsubstantiated. The concept of routine treatment of all patients with acute infarctions with lidocaine to prevent PVCs as well as VT or VF is no longer applied, having yielded to a threshold for treatment at various frequencies of manifest PVCs. Suppression of PVCs in acute myocardial infarction is usually accomplished with intravenous lidocaine (a bolus of 50 to 100 mg followed by a continuous infusion of 2 to 4 mg/min), with intravenous procainamide as a second choice (100 mg every 5 min to a total dose of 500 to 750 mg, followed by an infusion of 1 to 4 mg/min). Both drugs have significant side effects, especially with improper dosing. Furthermore, these drugs have not been shown to change hospital mortality rates for patients for whom prompt medical attention and electrical defibrillation are available. Lidocaine levels and binding both increase during the course of acute myocardial infarction, theoretically rendering free drug levels stable. The practice of tapering the lidocaine infusion to avoid toxicity is not appropriate if free drug concentration represents active drug and does not rise. A number of other acute cardiac states are associated with the emergence of PVCs. For example, PVCs may emerge during and immediately after transient myocardial ischemia and

are accompanied by a risk for sustained VT or VF. The primary intervention for controlling PVCs in these settings is the reversal of ischemia. On first contact, however, intravenous lidocaine or procainamide should be administered to suppress the arrhythmias. Clinical circumstances characterized by myocardial reperfusion-such as Prinzmetal's angina, thrombolysis in AMI, or balloon deflation during percutaneous transluminal coronary angioplasty (PTCA)-may cause reperfusion-induced arrhythmias. The arrhythmias generated include PVCs and accelerated ventricular rhythms (e.g., postthrombolysis or PTCA) or nonsustained VT (often polymorphic) after reversal of coronary spasm. These arrhythmias are usually transient and self-limiting but may evolve into sustained VT or VF. Although there are theoretical and experimental reasons to suspect that Ca^{2+}-mediated electrophysiologic disturbances occur during reperfusion, intravenous lidocaine is currently used to treat reperfusion-induced arrhythmias. It is used in the same dose and with the same infusion techniques as in acute myocardial infarction. Severe heart failure and acute pulmonary edema are commonly accompanied by frequent and advanced forms of PVCs; as in acute myocardial infarction with low-output states, the PVCs are considered secondary to the hemodynamic abnormality. The use of antiarrhythmic agents while the hemodynamic status is being stabilized is appropriate but may have only limited success until adequate hemodynamic control is achieved. Acute and subacute myocarditis and pericarditis are commonly accompanied by PVCs, and sustained VT or VF may occur infrequently, even in the absence of significant myocardial dysfunction. Frequent PVCs and salvos or nonsustained VT are usually treated until the carditis has resolved. In those patients who have not had sustained VT or VF conventional antiarrhythmic agents are given orally and titrated to suppression of the PVCs if possible, or at least to achieve suppression of repetitive forms. Antiarrhythmic therapy is continued for a minimum of 2 months, and then the patient is taken off antiarrhythmic drugs while still being monitored. If advanced forms do not reappear, the drug is not restarted; if they do reappear, treatment is continued for another 2 to 3 months, after which the same procedure is carried out. Myocarditis that has not evolved into a cardiomyopathic state is only rarely followed by frequent or complex forms of PVCs

beyond 6 months. Virtually all other acute cardiac syndromes and many acute systemic disorders may be associated with PVCs that will abate with reso
lution of the initiating abnormality.

Management of Chronic PVCs in the Presence of Cardiac Disease

Chronic PVCs carry a different connotation in patients with established heart disease than in those free of disease. Sudden and total death rates are increased in patients who have frequent or repetitive PVCs in the major categories of chronic cardiac disease in the United States, including chronic ischemic heart disease, hypertensive heart disease, and the cardiomyopathies. When frequent PVCs and/or salvos or runs of nonsustained VT are accompanied by a reduced EF, both the arrhythmia and the EF contribute to risk, and the rate of sudden death is increased. Management of frequent and repetitive forms of chronic PVCs after myocardial infarction has changed dramatically since the results of the CAST study were published. Previous studies as well as CAST itself had demonstrated that PVC suppression was feasible in these patients, but CAST clearly demonstrated a significant excess risk of sudden cardiovascular death among the treatment groups receiving the two class IC agents (flecainide and encainide) evaluated in the study. CAST II, the continuation of the study with moricizine, the one drug that had not crossed a boundary of significance during CAST I, demonstrated neither benefit nor adverse effect, showing only an early classic proarrhythmic mortality risk, which did not influence long-term outcome. Meta-analyses of data derived from previous smaller randomized studies, as well as the subsequent (SWORD) study, testing the effect of antiarrhythmic drugs on mortality rates after myocardial infarction, also suggested an adverse effect of most antiarrhythmic drugs when used in postmyocardial infarction patients. Accordingly, the drugs used in CAST are now contraindicated following myocardial infarction in patients with asymptomatic or mildly symptomatic PVCs, and there is a trend away from the use of any membrane-active antiarrhythmic agent in such patients. Recent large randomized, placebo-controlled trials testing the possible benefit of amiodarone in postmyocardial infarction patients (EMIAT and CAMIAT) demonstrated no benefit on total mortality rates. Beta-adrenoceptor blocking agents, however, have a sub-

stantial beneficial effect on long-term outcome in the postmyocardial infarction patient as well as improving total mortality rates in the subgroups of the amiodarone postmyocardial infarction trials in whom beta-adrenoceptor-blocking agents were used with amiodarone. In addition, beta-adrenoceptor-blocking agents are effective in suppressing repetitive forms of PVCs in many patients. Beta blockers, therefore, have evolved as the drugs of choice following myocardial infarction in patients with mildly symptomatic PVCs. While no properly randomized study directed to a sudden and total death outcome as a result of PVC suppression using beta-adrenoceptor-blocking agents has been reported, the existing randomized data on mortality rates in patients following myocardial infarction in general demonstrates beneficial effects.

In patients with *symptomatic* PVCs (e.g., palpitations or repetitive beats) following myocardial infarction, especially when accompanied by a low EF, management becomes more difficult. Such patients have a higher mortality rate, and it is not known whether the CAST data should be extrapolated to this population. Because of CAST, class IC agents are avoided in these patients, but clinicians may use other antiarrhythmic drugs if they are well tolerated and no adverse effects are observed. However, the threshold for initiation of therapy is generally higher than it was prior to CAST. Even if the EF is depressed, beta-adrenergic blocking agents should be tried initially. If they are effective and well tolerated, they are the preferred treatment.

Class III (e.g., sotalol and amiodarone) and perhaps class IA drugs also appear to be safe and may be used if treatment is necessary. Chronic PVCs are very common in patients with advanced idiopathic dilated cardiomyopathy and in patients with hypertrophic cardiomyopathy, and both groups have a major risk of arrhythmic sudden death. In some reports, more than 90 percent of patients with dilated cardiomyopathy have frequent PVCs, and over 50 percent have salvos or nonsustained VT. Efficacy of antiarrhythmic therapy for both suppression of chronic PVCs and prevention of VT and VF is unclear and perhaps is quite limited in these patients. Treatment is controversial. It is not known whether the CAST data can be extrapolated to this group or whether there is any mortality benefit from the use of antiarrhythmic drugs among these patients. When treatment is prescribed, the patient should be hospitalized for in-

itiation of antiarrhythmic therapy because of proarrhythmic risk in cardiomyopathy. Secondary ventricular arrhythmias in patients who have chronic heart failure may respond to control of heart failure. In one carefully designed study, treatment with an angiotensin-converting enzyme inhibitor had a very favorable effect on both parameters of heart failure and ventricular ectopy. When antiarrhythmic drugs are to be used, the selection of a drug or a combination of drugs for high-risk patients with chronic PVCs is complex. The class IA drugs are moderately effective but have a high incidence of allergic reactions (e.g., procainamide) and poorly tolerated side effects (e.g., quinidine causing thrombocytopenia). They may also produce significant further myocardial depression in patients with an already reduced EF (e.g., disopyramide). Moricizine appears to be better tolerated, but all have significant risks of proarrhythmic effects, although many of these events are not life-threatening. Among the class IB agents (e.g., tocainide and mexiletine), efficacy might be good in some patients and the proarrhythmic incidence is lower, but there is a high incidence of uncomfortable side effects. The currently available IC agents (flecainide and propafenone) are very effective for reducing ventricular ectopy and are well tolerated in patients with normal or only minimally depressed LV function. Their use is not indicated for patients with ischemic heart disease because of the adverse outcome observed in CAST and is limited more generally by the fact that the incidence of proarrhythmic effects and myocardial depression is highest in the subgroup at greatest need for the intervention: those with repetitive forms and impaired LV function. It is not yet known, however, whether the higher absolute risk of adverse effects in patients with abnormal LV function is balanced by a benefit in this higher-risk group. Specifically, the long-term effects of the class I agents on death rates in groups of patients other than the lower-risk category enrolled in CAST are unknown at present.

There are differences in adverse proarrhythmic effects among the various drug groups. Class IA drugs are predominantly associated with classical proarrhythmia. Class III drugs have the same pattern of proarrhythmia, perhaps with a lower incidence of torsades de pointes for amiodarone. Sotalol demonstrates a dose-dependent incidence of torsades de pointes, in contrast to the idiosyncratic pattern for the class

IA drugs. The common denominator between class IA and class III drugs, which likely contributes to this concordant proarrhythmic pattern, is moderate to marked prolongation of repolarization, as reflected in QT interval prolongation. In contrast, the class IC drugs, which have minimal effect on repolarization, have a low rate of classic proarrhythmia: torsades de pointes. They may, however, worsen clinical arrhythmias or generate a new rapid sinusoidal sustained VT. In addition, the excess death rate in CAST, attributed to proarrhythmia, extended over the entire period of drug exposure rather than being close in time to the start of treatment. A possible explanation for this pattern is a tendency for the class IC drugs to interact with sporadic intercurrent events, such as transient ischemia or LV dysfunction. Such an explanation is consistent with disturbed conduction patterns (depolarization) contributing to proarrhythmia rather than repolarization abnormalities. It is also consistent with the observation in CAST that increased risk of mortality in the flecainide and encainide arms was accompanied by a decreased incidence of nonfatal ischemic events compared to their placebo groups. Combining drug classes has been found to be effective by some, although carefully controlled studies are limited; combinations such as a class IA and a class IB drug may be tried. The class II drugs, beta-adrenergic blocking agents, have been mentioned earlier, and many consider them the first choice of therapy even if the EF is reduced. They may be used in combination with class I drugs in some patients. Class III drugs have been approved only for use in life-threatening arrhythmias, although amiodarone and sotalol are both appropriate for selected patients with symptomatic runs of nonsustained VT and advanced LV dysfunction. The available data on amiodarone is promising for patients with life-threatening arrhythmias, but the specific benefit for patients with PVCs and nonsustained VT in the presence of advanced heart disease is unclear. In the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (CHF-STAT) study, which randomized ischemic and nonischemic myopathies and PVCs to amiodarone and placebo, no mortality benefit was observed. Another study, GESICA, which randomized cardiomyopathic patients to the same drug versus placebo, however, showed a survival benefit for the amiodarone-treated group. PVC stratification was not carried out in the

latter. In both studies, amiodarone-treated patients with nonischemic cardiomyopathies tended to respond more favorably to the drug than those with ischemic cardiomyopathies. The class IV drugs, Ca^{2+}-entry blockers, have no role in the treatment of chronic PVCs. With any of these drugs or drug combinations, attention to underlying heart disease and systemic factors is necessary. Treatment for limiting the frequency of episodes of transient ischemia, maximizing LV function, maintaining electrolyte balance, and controlling blood pressure all may act in concert with antiarrhythmic agents to limit the risk of cardiac morbidity and mortality in patients with chronic PVCs. The end point of treatment of patients who have structural heart disease and high-risk forms and frequency of chronic PVCs is not at all clear. The pharmacodynamics of PVC suppression differ from those of VT prevention, and quantitative PVC suppression is difficult to achieve. Suppression of advanced forms of PVCs (e.g., couplets, salvos, and nonsustained VT) is sometimes achieved, even if quantitative PVC suppression fails. General guidelines have included suppression of 70 to 80 percent of total PVCs on a 24-h ambulatory monitor and complete (or nearly complete) suppression of repetitive forms. An ongoing trial, MADIT II, is designed to determine whether mortality rates can be improved by ICDs in postmyocardial infarction patients with PVCs and ejection fractions of 30 percent or less.

Acute management of sustained monomorphic ventricular tachycardia

Sustained monomorphic VT may occur in acute or chronic ischemic heart disease syndromes, in idiopathic dilated or hypertrophic cardiomyopathy, and, less frequently, in inflammatory or infiltrative disease states. It occurs occasionally as a primary electrical disturbance. Management depends upon the clinical setting and the clinical characteristics of the tachycardia. In acute myocardial infarction, sustained VT occurs most commonly within 24 h of the onset. Although degeneration into VF is uncommon, sustained VT carries that risk and must be treated aggressively. If the patient is clinically stable and the arrhythmia electrically stable, a 75- to 100-mg bolus of intravenous lidocaine, followed by a continuous infusion of 1 to 4 mg/min, may be tried. The infusion dose depends upon the patient's age, size, and general clinical status. In heart failure and low-output states, the dose should be reduced. If the

VT does not revert immediately or if the patient is hypotensive, immediate DC cardioversion is required. Following cardioversion, intravenous lidocaine is continued to prevent recurrences. If VT recurs with lidocaine, 100-mg boluses of procainamide are infused at 5-min intervals to a total loading dose of 500 to 1000 mg, followed by a constant infusion of 2 to 4 mg/min. If breakthroughs occur on both drugs, the next drug of choice is intravenous amiodarone or bretylium tosylate. Amiodarone, currently the preferred therapy for this indication, is administered intravenously with a loading dose of 150 mg infused over 10 min, followed by a continuous infusion of 1 mg/min for 6 h and then a maintenance infusion at a rate of 0.5 mg/min. Bretylium, less commonly used than in the past, is administered as a loading dose of 5 mg/kg intravenously infused over 15 min, repeated if necessary, and followed by a 0.5- to 2.0-mg/min infusion. Total dose should not exceed 25 mg/kg per 24 h. Antiarrhythmic therapy may be stopped after 48 to 72 h, since the risk of recurrence is small at that point. Sustained VT during the acute phase of transmural myocardial infarction is due to transient factors and does not predict later recurrent arrhythmias.

A second category of sustained VT related to acute myocardial infarction is that which occurs during the convalescent period. It is unrelated pathophysiologically to the VT that occurs early and has much more serious long-term implications. It is most common in patients with large anterior wall myocardial infarction. Management of the acute event requires intravenous antiarrhythmic drugs and/or cardioversion, using an algorithm similar to that described for acute-phase VT. There is, however, a very high death rate during follow-up of these patients, in part related to the size of the infarct. Sustained VT in patients beyond the convalescent phase of myocardial infarction (6 to 8 weeks) has a somewhat less ominous prognosis than does convalescent-phase VT but is still considered life-threatening and requires special interventions.

Sustained VT may complicate other acute or transient cardiac syndromes, including ischemia-reperfusion sequences associated with coronary spasm or thrombolysis early after the onset of myocardial infarction, heart failure, acute myocarditis, and almost any toxic or metabolic disturbance of sufficient severity. Therapeutic approaches include both conventional arrhythmia treatment, as described above for sus-

tained VT in acute myocardial infarction, and careful attention to underlying predisposing factors.

Long-term management of ventricular tachycardia in chronic ischemicheart disease

The long-term management of recurrent VT in patients with chronic ischemic heart disease has evolved into a complex clinical exercise. Prevention of recurrences is related to successful management of the underlying precipitating factors, such as ischemia and hemodynamic status, as well as to specific antiarrhythmic approaches.

Four general approaches to antiarrhythmic therapy are available:

- antiarrhythmic therapy guided by invasive electrophysiologic testing or by ambulatory monitoring or exercise testing,
- surgical procedures designed to excise or cryoablate reentrant pathways or automatic foci,
- catheter ablation procedures,
- ICDs.

The relative proportion of patients managed by each of these four techniques has changed in recent years, with fewer and more selective surgical approaches, fewer antiarrhythmic drug trials, and broader use of ICD therapy. The use of catheter ablation techniques for VT in chronic ischemic heart disease is largely palliative, often employed as adjunctive therapy with other primary approaches. As technology improves, however, it may develop broader applications.

Pharmacologic Management

Invasive electrophysiologic testing to guide pharmacologic therapy in patients with recurrent monomorphic sustained VT due to ischemic heart disease has yielded, in large part, to empiric antiarrhythmic therapy (primarily amiodarone), ICD implantation, and catheter ablation. At one time the index for the initial treatment strategy for such patients, the initial study free of antiarrhythmic drugs required to demonstrate inducibility of the clinical VT and its characteristics at baseline, is now largely used for risk stratification. Several clinical trials have demonstrated that inducibility predicts risk along with better outcomes with ICD therapy than with drug therapy in high-risk patients. It is also useful in conjuction with ablation or surgical procedures.

Although there have been controversies about the validity of different protocols for programmed electrical stimulation in patients who have clinical sustained ventricular arrhythmias, up to 95 percent of inducible sustained monomorphic VTs can be induced by right ventricular stimulation, using up to two drive cycle lengths between 600 and 400 ms from two right ventricular locations (apex and outflow tract) with up to three extrastimuli. In at least 80 percent of patients with chronic ischemic heart disease and recurrent monomorphic sustained VT, the clinical tachyarrhythmias can be induced during a baseline study free of antiarrhythmic agents. The subsequent identification of a drug regimen that will prevent reinduction into the same sustained monomorphic VT is associated with a reduction of risk of recurrent VT at 1 year of follow-up. The risk appears to decrease from 30 to 40 percent if VT remains inducible on therapy to 10 to 15 percent if therapy results in noninducibility. The results of acute intravenous testing of a drug should not be extrapolated to long-term oral therapy without retesting on the oral regimen, because intravenous regimens do not predict responses on oral drugs. In addition, a drug capable of preventing induction of a VT previously induced during baseline testing can be identified in only a minority of patients (approximately 20 to 35 percent in various studies). Moreover, the success rate for membraneactive drugs is considerably lower if multiple monomorphic VTs are induced at baseline. Left ventricular EF strongly influences probability of recurrence. Among cardiac arrest survivors, an EF of 30 percent or less predicts a mortality rate approximately twice as high as for patients in the same category with EFs above 30 percent. A similar relationship likely exists for patients who present clinically with sustained VT. Unfortunately, all statements about the potential benefit of therapy guided by programmed electrical stimulation are based upon comparisons of groups who did (responders) or did not (nonresponders) convert from an inducible status to a noninducible status as a result of the therapy. Patients who have a partial response to a drug regimen (i.e., induced runs of 6 or more but fewer than 15 impulses) also appear to have a lower risk of recurrent VT. Many electrophysiologists currently will accept induced runs of less than 10 impulses on therapy as a satisfactory end point, and almost all will accept less than 6. Any change in therapy established by invasive

electrophysiologic testing because of drug intolerance or clinical failure should be evaluated by repeat testing. Finally, it has been demonstrated that patients who had nonsustained VT on ambulatory monitoring with inducible VT at baseline study and failed antiarrhythmic drug therapy during repeat study had better long-term survival rates if they received ICDs than if they received drug therapy. It is important to note that patients who received ICDs based on failed electrophysiologic testing-considered a high-risk group-did even better than those who had a successful electrophysiologic study on drug therapy.

Noninvasive management strategies for VT require identification of frequent (i.e., 10 to 30 PVCs per hour in various studies) and/or repetitive PVC forms (i.e., salvos or nonsustained VT) at baseline monitoring or VT induced during exercise testing. Reduction of PVC frequency (80 percent or more suppression) and abolition of complex forms has been used as the index of a successful end point. This approach has been reported to be successful in some studies, even among patients who have failed to achieve a successful end point by invasive electrophysiologic testing. Unfortunately, the *residual risk* among many patient groups with successful noninvasive or invasive end points is still very high. Thus, because of the *relative* benefit of ICDs in several patient groups compared to empiric amiodarone, many clinicians now prefer implantable devices for both primary and secondary prevention of life-threatening arrhythmias in these high-risk patients.

Surgical Therapy

Patients who have recurrent sustained monomorphic VT associated with prior myocardial infarction and inducibility into a hemodynamically stable tachycardia were uniformly considered for antiarrhythmic surgery until recent years. The indication was reinforced by the presence of discrete ventricular aneurysms and bypassable coronary artery lesions. With the development of ICDs capable of flexible antitachycardia pacing programs, many patients who were formerly surgical candidates are now receiving ICDs. However, surgery is still recommended, in the absence of contraindications, for a small number of such patients, particularly if they require revascularization surgery as well or their tachycardias are not easily pace-terminated dur-

ing induction studies. Patients without discrete aneurysms who have large dyskinetic areas may have sites of origin of VT mapped in the cardiac electrophysiology laboratory and operating room if they are inducible into stable monomorphic tachycardias. Mapping allows the identification of areas that may be attacked by endocardial resection or surgical cryoablation. Mapguided surgical procedures employing resection, cryoablation, and revascularization have markedly improved the clinical outcome of surgically treated patients. Overall surgical results have also benefited from the preferred use of ICDs in patients previously referred for surgery out of desperation. Coronary bypass surgery may be used as primary therapy for patients who have recurrent VT initiated by transient ischemic episodes. It is also a valuable adjunct to antiarrhythmic surgery.

Catheter Ablation Procedures for Ventricular Tachyarrhythmias

The combination of LV endocardial mapping by catheter techniques and RF energy delivery systems provides the capability for catheter ablation therapy of sustained, hemodynamically stable VTs. While these techniques are currently limited to only a small fraction of patients as primary therapy, they are useful as an adjunct to ICD therapy. Improvements of mapping techniques capable of storage and recall of spatial activation maps and improved energy delivery systems will enhance the use of catheter ablation as primary therapy and as more effective ancillary therapy in the future.

Implantable Defibrillators

As a result of the outcomes of several large clinical trials and advances in technology that resulted in a significant decrease in device size and range of functions, the role of ICD therapy for patients with ventricular tachyarrhythmias has expanded dramatically in recent years. It is no longer necessary or desirable to test a long sequence of antiarrhythmic drugs in patients with sustained monomorphic VT. For those subgroups among whom ICDs have not been demonstrated to be superior to drug therapy (e.g., those with EFs greater than 40 percent), failure of no more than one or two drugs during electrophysiologic study is generally considered an indication for ICD therapy. Their use is amplified by such enrichments as antitachycardia pacing, allowing effective programmable tiered-therapy algorithms, back-up bra-

dyarrhythmia pacing (including dual-chamber pacing in some devices), and electrogram storage for retrieving and analyzing events. Patients who present with clinical VT and have inducible, hemodynamically *unstable* VT associated with ischemia before surgery should receive an ICD after revascularization surgery if they remain inducible into VT. The routine use of an ICD after antiarrhythmic surgery, even if successful by postsurgical programmed stimulation study, has been advocated but has gained only limited acceptance.

ICDs are indicated for patients with recurrent or unstable VT whose arrhythmias cannot be controlled medically or surgically or who belongs to subgroups that have been demonstrated to benefit specifically from device therapy. Antitachycardia pacing capabilities and programmable tiered therapy have expanded the scope of ICD therapy for recurrent sustained VT. The availability of antitachycardia pacing obviates the need for antiarrhythmic surgery in many patients who had been considered surgical candidates on the basis of anatomy and physiology in the past

Long-term management of ventricular tachycardia in Nonischemic Heart Disease

Sustained VT in patients with idiopathic dilated cardiomyopathy, dilated cardiomyopathies due to specific etiologies, or hypertrophic cardiomyopathies carries a poor prognosis. Management approaches differ from those used for patients with ischemic heart disease. Invasive electrophysiologic testing, to identify risk or guide therapry is less predictably useful in the small fraction of patients with dilated cardiomyopathy who have clinical sustained monomorphic VT than it is in coronary heart disease patients. In a subgroup of these patients, however, sustained VT is due to bundle-branch reentry, which can be cured by catheter ablation of the right bundle branch. Electrophysiologically guided management does not appear useful in idiopathic dilated cardiomyopathy patients who have survived out-of-hospital VF or have clinical nonsustained VT. There is almost no role for surgical therapy in these patients at present, but the ICD is an appropriate means of management. The device appears effective for reverting potentially fatal arrhythmias in patients who have cardiomyopathy, but the long-term outcome may be dominated by LV function. The evaluation of ICD therapy in these patients has been confounded by the observation

that, in some (perhaps a substantial fraction) of these patients, sudden death is caused by the bradyarrhythmic asystole-pulseless electrical activity complex, which would not benefit from any form of antiarrhythmic therapy. The availability of ICD with electrogram storage capability should begin to clarify the magnitude of this problem. Ultimately, identification of groups at risk for specific mechanisms will help define the best therapy, but such data are currently lacking. Sustained VT is also a late consequence and poor prognostic sign in patients with hypertrophic cardiomyopathy. In this setting, the use of electrophysiologic testing has been limited because of unvalidated concerns about the ability to cardiovert the severely hypertrophied and obstructed ventricle, and there is no uniform opinion regarding the best approach to management of these patients, other than the accepted need for therapy. The recent trend toward ICD therapy, rather than pharmacologic therapy, particularly among higher-risk subgroups, has now received support from multicenter observational data suggesting ICD benefit. Preoperative electrophysiologic testing is generally avoided in patients with severe aortic stenosis who have survived sustained VT or VF.

Management of acquired long QT interval syndrome

Treatment is directed at the underlying cause, or causes, with careful attention to electrolyte and metabolic disturbances and to identifying and reversing or removing iatrogenic factors. Although electrical cardioversion may interrupt torsades de pointes, the arrhythmia frequently recurs as long as the offending influence is present. In addition, many runs are nonsustained. Intravenous magnesium sulfate is often effective, especially when “torsades de pointes” is due to quinidine. It may be given in a dose of 2 g over 2 min followed by an infusion of 2 to 20 mg/min. Although $Mg2^{+}$ will effectively control the arrhythmia, it will not reduce the duration of the QT interval. That must await clearance of the offending agent. Overdrive atrial or ventricular pacing to induce rate-related QT shortening may also be required. Acceleration of the underlying heart rate with isoproterenol infusion to shorten the acquired QT interval prolongation may be effective but should be avoided in patients with symptomatic ischemic heart disease, if possible. Lidocaine also may be beneficial, as may other class IB drugs. These drugs tend to shorten the QT interval in normal myocardium.

Class IA and class III antiarrhythmic agents should be avoided, since they prolong the QT interval.

Management of ventricular flutter and ventricular fibrillation

There are two major goals of therapy: immediate life support and resuscitation and long-term prevention of recurrences. Basic life support with standard cardiopulmonary resuscitation is used until emergency defibrillation at 200 J or more can be carried out. After three unsuccessful shocks at energies up to 360 J, 1 mg of epinephrine should be administered by intravenous push and defibrillation attempted again.

Early defibrillation is essential to survival. Resistance of defibrillation may occur due to the patient's size, improper paddle placement, improper use of conducting media, acidosis, hypoxemia, or electrolyte disturbances. Some antiarrhythmic drugs may raise the defibrillation threshold. Energy thresholds for defibrillation may be decreased by administration of bretylium, lidocaine, or epinephrine, the latter especially when the fibrillatory waveform is fine. Immediate steps to improve metabolic and electrolyte disturbances are required, paramount of which is to establish an airway, followed by techniques to support ventilation. In rare instances, "spontaneous" reversion of VF or "medical" defibrillation with bretylium has been reported. A physiologic or pharmacologic increase in catecholamines has been postulated as the underlying mechanism.

After successful defibrillation, careful attention to the total clinical status of the patient and prophylactic antiarrhythmic drugs are required. Intravenous therapy with lidocaine is commonly used initially. For recurrent and resistant cases, intravenous procainamide or amiodarone can be administered intravenously, the latter having replaced bretylium tosylate in order of priority and urgency. In addition to oxygenation and improving the metabolic milieu, aggressive steps to identify and treat or prevent recurrent ischemia or heart failure are necessary, since they may act as pathophysiologic triggers for recurrences. In the in-hospital setting, early recognition and aggressive treatment of VT may prevent VF. In the patient with acute myocardial infarction, early VF (48 h), as with early VT, is not associated with an independent influence on posthospital mortality risk and does not justify long-term antiarrhythmic therapy. When VF occurs as a convalescent-phase complication of acute myocardial

infarction, however, aggressive long-term antiarrhythmic management is indicated. The vast majority of patients who have VT or VF in the convalescent phase after acute myocardial infarction (3 days to 8 weeks) will have inducible ventricular arrhythmias at baseline electrophysiologic study. Among survivors of out-of-hospital VF not caused by acute myocardial infarction, control of ischemia and heart failure is essential. The clinical context is evaluated in terms of the interaction between structural abnormalities (e.g., coronary heart disease, myopathy, hypertrophy, or anatomic electrical abnormalities) and functional states (e.g., ischemia-reperfusion, or systemic factors, including congestive heart failure, metabolic and electrolyte disturbances, neurophysiologic interactions, and toxic effects). For long-term estimate of the risk of arrhythmic death, invasive electrophysiologic testing of pharmacologic efficacy is one accepted approach. Only about 33 to 40 percent of survivors, however, will be inducible into a reproducibly inducible ventricular tachyarrhythmia at baseline. A similar fraction will be inducible into nonsustained VT or VF, and 20 to 30 percent are noninducible. The subgroup whose unexpected VF is related to transient ischemia, in contrast to an underlying structural basis, is less likely to be inducible at baseline. With high-risk forms of arrhythmias on ambulatory monitoring or exercise testing but without inducible arrhythmia at baseline by invasive testing, drug therapy can be guided by suppression of these spontaneous arrhythmias by noninvasive techniques as long as the EF is greater than 40 percent. For such patients with lower EFs, the use of ICDs is emerging as the preferred treatment. Usefulness of long-term drug therapy is limited by the fact that no more than 20 to 30 percent of the patients with inducible arrhythmias will have a drug identified that will prevent inducibility. Whether amiodarone will have equivalent (or greater) benefit remains to be determined. Patients who have recurrences despite drug therapy predicted to be effective during testing, those in whom an end point of therapy cannot be established, or those in whom the risk of recurrence remains high because underlying precipitating factors cannot be adequately controlled should receive ICDs. The development of programmable devices with diagnostic electrogram storage capability and transvenous lead systems is expanding the set of circumstances in which ICDs are preferred therapy.

Moreover, for secondary prevention of recurrent cardiac arrest, the relative benefit of ICDs now has been shown to be greater than that of empiric amiodarone (and likely other drugs), measured as total mortality during long-term follow-up.

Management of Sinus Bradyarrhythmias

Treatment of patients who have asymptomatic bradycardia is often unnecessary. In the symptomatic patient, elimination of reversible aggravating factors is an essential step in management. When this is ineffective or negative chronotropic agents are essential to overall patient management, permanent pacing may be needed. A similar approach is taken for patients with sinus pauses, sinus arrest, or SA exit block, which may be associated with myocardial infarction, myocarditis, sinus node fibrosis, digitalis excess, or excess vagal tone. In the patient with symptomatic hypersensitive carotid sinus syndrome, medical treatment is usually inadequate. Permanent ventricular or dual-chamber pacing is usually effective but occasionally may not relieve symptoms because of a coexisting vasodepressor reflex.

The complex of neurocardiogenic syncope, or neurally mediated vasodepressor syncope, has combined manifestations of sinus bradycardia and vasodepressor responses. It is revealed by the response to head-up tilt testing and is due to an abnormal reflex, the afferent limb of which originates in the LV wall. The efferent limb is parasympathetic, causing both decreases in peripheral vascular tone, leading to hypotension, and sinus node depression, leading to sinus bradycardia or a junctional escape rhythm. In the majority of patients, the vasodepressor component dominates, limiting the effectiveness of pacing therapy. However, among the subgroup of patients in whom the cardioinhibitory component predominates, cardiac pacing featuring "rate-drop response" or a similar algorithm appears to be effective. Among pharmacologic agents, beta-adrenergic blockers have been most useful, presumably by the mechanism of blocking the sympathetically mediated afferent limb of the reflex

Management of atrioventricular block

First-Degree Heart Block. Isolated first-degree AV block is asymptomatic and is not an indication for temporary or permanent pacing. However, one possible exception is a subgroup of patients with marked first-degree AV block (greater than 300 ms)

associated with LV dysfunction and symptoms of congestive heart failure in whom a shorter AV interval caused by sequential AV pacing results in hemodynamic improvement.

Second-Degree Heart Block. Mobitz type I AV block, or the Wenckebach phenomenon, is usually associated with an adequate ventricular rate and is rarely symptomatic. It occurs in highly trained athletes and is a normal response to rapid atrial pacing. In most patients who have the Wenckebach phenomenon secondary to AV nodal disease, routine prophylactic pacing is not advised, since it is minimally symptomatic (if at all) and tends not to progress. Rarely, the effective ventricular rate is slow and patients are symptomatic, requiring pacing if vagolytic maneuvers are ineffective. The prognosis in patients who have underlying organic heart disease is determined by the extent of the underlying disease, not the Mobitz type I block.

Second-degree heart block is common in the acute phase of inferior wall myocardial infarction and rarely requires temporary pacing in this setting. Reversion is usually prompt-measured in hours to days. Mobitz type II block is less common but implies more significant disease in the conduction system. The site of block is almost always below the AV node and usually below the bundle of His. Therefore, slower escape rhythms and risk of progression to complete heart block are of concern. It is almost always associated with a defined disease process. Permanent pacing is indicated, except where Mobitz type II block is induced by rapid artificial pacing. The purpose of pacing is primarily to protect against symptomatic events, such as syncope, and thus to protect the patient from injuring him- or herself or others.

Available data do not suggest that pacemakers will prolong the life of patients with Mobitz type II block. A special circumstance involves 2:1 AV block in which the underlying mechanism and site of block remain obscure. The decision to treat is inferred from the clinical setting. Wide QRS complexes, sudden onset of periods of block, and inadequate escape rates favor type II block, whereas narrow complexes and coincident episodes of typical type I block favor Wenckebach block.

Another variant pattern is multilevel block in the AV junction. This commonly occurs during atrial tachycardias and may be functional, pharmacologic, or pathologic. The pattern of multilevel block during atrial tachycardia may be deceiving. This

pattern is a basic 2:1 pattern with Wenckebach conduction patterns of the impulses that conduct through the area of 2:1, and it produces group beating of the ventricles. This may result in relatively slow ventricular rates, but the primary problem is the atrial arrhythmias with physiologic or insignificant pathologic responses at the level of the AV node. His-bundle electrograms may be diagnostic, but such invasive studies are indicated only when needed for a therapeutic decision.

Paroxysmal AV Block. Runs of consecutive atrial impulses that fail to conduct to the ventricles may last for up to 10 to 20 s and may be associated with syncope. Unless a clearly defined, reversible cause is identified, permanent pacing is required. Bradycardia-dependent AV block, or phase 4 block, usually affects patients with underlying conduction system disease. It is characterized by spontaneous phase 4 depolarization of tissue in the His-Purkinje system. The partially depolarized tissue impairs ventricular conduction of propagating impulses of sinus origin, most commonly affecting the conduction in the left bundle-branch system (bradycardia dependent left bundle-branch block). Block by this mechanism at a more proximal site in the conducting system may result in complete heart block, not responsive to atropine or isoproterenol, but only to cardiac pacing. A precordial thump may produce a PVC able to depolarize and reset the ventricle including the site of automatic activity, thereby allowing resumption AV conduction down the distal conducting system.

Complete AV Block. Complete heart block may be acute in onset or slowly progressive and chronic; it may produce abrupt, clinically significant symptoms or may remain asymptomatic and be discovered incidentally. When acute and symptomatic, evaluation and rate support are urgently needed. Pharmacologic intervention with atropine or isoproterenol is usually most readily available. The latter should be avoided in the presence of ischemic heart disease, and external pacing instituted if needed. Reliable rate control is achieved by ventricular or dual-chamber temporary cardiac pacing. Permanent pacing is indicated unless those factors responsible for the heart block are reversible or when transient complete block complicates an acute inferior wall myocardial infarction. Since the advent of thrombolytic therapy and primary angioplasty in acute myocardial infarction, the incidence of complete heart

block in myocardial infarction has decreased. However, in acute anterior wall infarction, the prognosis remains grave, even after permanent pacemaker implantation. Isolated congenital AV block usually occurs at the level of the AV node and is accompanied by an adequate junctional escape rate. Although it is often well tolerated in the young, adult patients ultimately may develop symptoms of exercise intolerance, and thus permanent pacemaker implantation is a commonly used management strategy. When AV block coexists with other congenital structural abnormalities, the risk of symptoms with congenital AV block is higher, and pacemakers are more clearly indicated. There are specific guidelines for pacemaker implantation in the pediatric population.

Atrioventricular Dissociation. AV dissociation is not synonymous with AV block but occurs in conjunction with block as well as in its absence. It implies an abnormality of intrinsic pacemaker activity that may be slowing of normal pacemaker activity (*default*), acceleration of a normally subordinate or latent pacemaker (*usurpation*), AV block, or a combination of these phenomena.

Management. Treatment, when needed, is directed toward the underlying cause. It is important to evaluate whether symptoms are present and whether they are due to a rapid or slow rate. Suppression of tachyarrhythmias, such as AV dissociation in VT, is the primary goal when symptoms are related primarily to the tachyarrhythmia and an intact intrinsic or artificial pacemaker is present. Intermittent ventricular ectopy may be an escape phenomenon in an otherwise asymptomatic patient who has an underlying persistent bradycardia. In such cases, rate support with pacing is indicated to relieve bradycardia symptoms, and the escape ventricular ectopy will resolve secondarily. If initial therapy is targeted to a tachycardia in the presence of an underlying bradycardia, symptoms may worsen due to drug suppression of lower intrinsic pacemaker sites.

Indications For Pacing. Pacing is indicated for symptomatic bradyarrhythmias that have no identifiable reversible cardiac or noncardiac cause. Prophylactic pacing to prevent death or the onset of life-threatening symptoms is controversial, since increased risk of death is more likely related to the severity of underlying organic heart disease. The mortality benefits of pacing, though theoretically sound, often lack ri-

gorous proof of effectiveness. Less controversial is the use of permanent pacing for morbidity benefit, namely, to reduce symptomatic bradyarrhythmic events and their consequences. Temporary pacing is indicated for AV block associated with acute anterior wall infarction if the heart rate is excessively slow and/or associated with rate-dependent hypotension, and if there is a newly acquired left or right bundle-branch block accompanied by hemiblock. The availability of external pacing techniques has tended to relax the sense of urgency for prophylactic pacing catheters in these settings. New left bundle-branch block or preexisting right or left bundle-branch block is managed with less immediate urgency and often does not require pacing. Permanent pacing is often recommended for those with acute anterior wall infarction who have had transient complete heart block. The change in long-term survival, however, is not well documented. Temporary pacing can often be avoided in AV block associated with inferior infarction, since block is often related to ischemia or parasympathetic reflexes, is usually asymptomatic, and reverses with time. If hypotension occurs in inferior infarction that is not due to hypovolemia or right ventricular infarct, temporary pacing for severe sinus bradycardia or higher grades of AV block is often used. Permanent pacing after AV block in inferior infarction is required only very rarely.

Permanent prophylactic pacing in bifascicular block without symptoms of transient AV block is not routinely recommended. In patients at high risk for complete heart block (e.g., Kearns-Sayre syndrome) or recurrent neurologic symptoms associated with advanced HV prolongation (e.g., HV longer than 70 to 80 ms), however, prophylactic pacing may be of benefit.

In summary, treatment strategy of rhythm and conduction disorders depend on their forms and should be provided as more aggressively with continued monitoring of clinical condition.

SQUEEZE FOR RESTING ECG

1. What kinds of limitations of the Current 12-Lead ECG System in adults?
   a. limitations of the Current 12-Lead System
   b. the remaining activation forces cancel each other
   c. the normal right ventricle has no ECG representation because its forces are obscured by the dipoles generated in the massive LV
   d. poor orthogonality and redundancy
   e. all answeres are correct
2. What kinds of features are belonged for P Wave?
   a. P wave represents the activation in the right and left atrium
   b. The normal P wave is rounded and upright in leads I and II and from V_2 to V_6.
   c. The P-wave axis is approximately 60 degrees
   d. The right atrium faces lead V_1, in which the initial portion of the P wave appears positive while its terminal part appears negative
   e. all answeres are correct
3. What kinds of features are belonged for PR Interval?
   a. PR Interval is a time from onset of the P wave to onset of the QRS complex
   b. PR Interval is a time between the onset of atrial depolarization in the myocardium adjacent to the sinus node and the onset of ventricular depolarization in the myocardium adjacent to the Purkinje network
   c. The normal PR interval measures 0.12 to 0.22 second
   d. A major portion of it is inscribed during the slow conduction through the AV node
   e. all answeres are correct
4. What kinds of features are belonged for QRS complex?
   a. The QRS complex represents ventricular activation
   b. The QRS complex measures 0.07 to 0.10 second and increases with the subject's height
   c. The QRS complex is measured from the beginning of the first appearing Q or R wave to the end of the last appearing R, S
   d. The onset of the QRS complex is not recorded simultaneously in all ECG leads
   e. all answeres are correct
5. What kinds of features are belonged for R Waves?
   a. R wave is the first positive wave of the QRS complex regardless of whether it is preceded by a Q wave
   b. The second activation vector results in an R wave in leads II and III, and the third vector produces an R wave in leads I, II, III, aVL, aVF, V_5, and V_6.
   c. The precordial leads provide a panoramic view of the cardiac electrical activity progressing from the right ventricle to the thicker LV
   d. R wave increases its amplitude and duration from V_1 to V_4 or V_5
   e. all answeres are correct
6. What kinds of features are belonged for S Waves?
   a. S wave is a negative deflection following an R wave.
   b. the third vector produces an S wave in leads aVr, V_1, V_2, V_3, and V_4
   c. the S wave in the precordial leads is large in V_1, larger in V_2, and then progressively smaller from V_3 through V_6

d. The last vector, directed superiorly and posteriorly, may result in a terminal S wave in leads I, V_5, and V_6.
e. all answeres are correct

7. What kinds of features are belonged for normal QRS axis in adults?
   a. -30 and + 90 degrees.
   b. 0 and + 90 degrees
   c. + 30 and + 90 degrees
   d. + 30 and + 60 degrees
   e. 0 and + 60 degrees
8. What kinds of features are belonged for sinus rhythm in adults?
   a. P wave is before QRS ccomplex
   b. P wave is obligatory upright in I and avF leads
   c. Heart rate is less than 100 beat per minute
   d. Cardiac rhythm is regular
   e. all answeres are correct
9. What kinds of features are belonged for ST segment in healthy adults?
   a. the ST segment represents the time period in which the ventricular myocardium remains depolarized
   b. a term ST segment is used whether the QRS complex ends in an R wave or in an S wave.
   c. the ST segment forms a nearly 90-degree angle and then proceeds horizontally until it curves gently into the T wave
   d. The ST-segment length and appearance are influenced by factors that alter the duration of ventricular activation
   e. all answeres are correct

SQUEEZE FOR CARDIAC RHYTHM AND CONDUCTION DISCORDERS

1. What kinds of features are belonged for junctional rhythm?
   a. no P wave in front of the QRS
   b. the QRS is narrow <80 msecond
   c. junctional rhythm is slower than the expected sinus rate
   d. Intermittent junctional rhythm can be normal
   e. all answeres are correct
2. What kinds of features are belonged for junctional rhythm?
   a. no P wave in front of the QRS
   b. the QRS is narrow <80 msecond
   c. junctional rhythm is slower than the expected sinus rate
   d. Intermittent junctional rhythm can be normal
   e. all answeres are correct
3. Determine optimal treatment strategy for polymorphic ventricular tachyarrhythmia with elongation of QT interval:
   a. Intravenous introduction of amiodaron
   b. Cancellation of medication that caused elongation of QT
   c. Correction of electrolytes' balance
   d. Intravenous introduction of magnesium sulfate
   e. Cardio stimulation to increase the heart rate

4. Determine a figure of ECG recorded from a body surface at pacing with location of one of electrod in the left ventricle:
    a. Complet left bundle-branch block
    b. Total right bundle-branch block plus left anterior hemiblock
    c. Normal ECG
    d. Complit right bundle-branch block
    e. Complit right bundle-branch block plus left posterior hemiblock
5. Determine a figure of Brugada syndrome
    a. Complet right bundle-branch block and coved ST-segment elevation in right precordial or inferior leads
    b. Complet right bundle-branch block and left anterior hemiblock
    c. Complet left bundle-branch block and coved ST-segment elevation in right precordial or inferior leads
    d. Complit right bundle-branch block
    e. Complit right bundle-branch block plus left posterior hemiblock
6. Determine a figure of ventricular tachycardia
    a. The tachycardia is regular at a rate of 160 beat per menute
    b. wide QRS complex
    c. vector of the QRS-T complexes are obligatory alternates
    d. the polymorphic ventricular tachycardias generally do not persist as long as the monomorphic ventricular tachycardias, either spontaneously reverting to a normal rhythm
    e. all answeres are correct
7. Determine a figure of atrial flutter
    a. Atrial flutter is a rapid, regular atrial tachyarrhythmia
    b. Average of heart rate is 280-450 bpm
    c. P waves are absent, RR intervals can be irregular
    d. F waves are present
    e. all answeres are correct
8. Determine a figure of atrial fibrillation
    a. Atrial flutter is a rapid, chaotic atrial tachyarrhythmia
    b. Average of heart rate is 450-600 bpm
    c. P waves are absent, RR intervals are irregular
    d. f waves are present
    e. all answeres are correct
9. Determine specific forms of ventricular tachycardia
    a. Salvo
    b. Sustained
    c. Nonsustained
    d. uniform
    e. all answeres are correct
10. Determine a figure of supraventricular tachycardia
    a. P waves and QRS complexes are dissociated from one another
    b. Uniform QRS complexes
    c. AV dissociation is present

d. Average of heart rate is 140-280 bpm
e. all answeres are correct

References.

1. Bansal A, Joshi R. Portable out-of-hospital electrocardiography: A review of current technologies. J Arrhythm. 2018; 34(2): 129-138.
2. Caforio ALP, Malipiero G, Marcolongo R, Iliceto S. Myocarditis: A Clinical Overview. Curr Cardiol Rep. 2017;19(7):63
3. Casella M, Dello Russo A, Vettor G, Lumia G, Catto V, Sommariva E, Ribatti V, Biagioli V, Tundo F, Carbucicchio C, Di Biase L, Natale A, Tondo C. Electroanatomical mapping systems and intracardiac echo integration for guided endomyocardial biopsy. Expert Rev Med Devices. 2017; 14(8):609-619.
4. Cheung CC, Constantine M, Ahmadi A, Shiau C, Chen LYC. Eosinophilic Myocarditis. Am J Med Sci. 2017; 354(5): 486-492.
5. Farzad A, Schussler JM. Acute Myopericardial Syndromes. Cardiol Clin. 2018; 36(1):103-114.
6. Feigenbaum's Echocardiography, 6th Edition / Feigenbaum H., Armstrong W.F., Ryan Th. (2005) Lippincott Willians & Wilkins.
7. Geske JB, Ommen SR, Gersh BJ. Hypertrophic Cardiomyopathy: Clinical Update. JACC Heart Fail. 2018. pii: S2213-1779(18)30152-5. doi: 10.1016/j.jchf.2018.02.010.
8. Honarbakhsh S, Hunter L, Chow A, Hunter RJ. Bradyarrhythmias and pacemakers. BMJ. 2018; 360: k642.
9. Jones WM, Napier L. Rhythm, Atrioventricular Block, Second-Degree. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan-2018 Jan 7.
10. Jordaens L. A clinical approach to arrhythmias revisited in 2018: From ECG over noninvasive and invasive electrophysiology to advanced imaging. Neth Heart J. 2018; 26(4):182-189.
11. Kelder JC, Cramer MJ, Van WJ, et al. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. Circulation. 2011; 124:2865-73.
12. Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, Kapur NK, Kociol RD, Lewis EF, Mehra MR, Pagani FD, Raval AN, Ward C; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; and Council on Cardiovascular Surgery and Anesthesia. Evaluation and Management of Right-Sided Heart Failure: A Scientific Statement From the American Heart Association. Circulation. 2018. pii: CIR.0000000000000560. doi: 10.1161/CIR.0000000000000560.
13. Kundu A, Vaze A, Sardar P, Nagy A, Aronow WS, Botkin NF. Variant Angina and Aborted Sudden Cardiac Death. Curr Cardiol Rep. 2018; 20(4): 26.
14. Lerman BB, Cheung JW, Ip JE, Liu CF, Thomas G, Markowitz SM. Mechanistic subtypes of focal right ventricular tachycardia. J Cardiovasc Electrophysiol. 2018. doi: 10.1111/jce.13505.
15. McKenna WJ, Maron BJ, Thiene G. Classification, Epidemiology, and Global Burden of Cardiomyopathies. Circ Res. 2017; 121(7):722-730.