# 11 - 250 Principles of Clinical Cardiac Electrophysiology

## 250 Principles of Clinical Cardiac Electrophysiology

PART 6 Disorders of the Cardiovascular System FIGURE 249-8 Fractional flow reserve. The fractional flow reserve is measured using a coronary pressure-sensor guidewire that measures the ratio of the pressure in the coronary artery distal to the stenosis (Pd, green) divided by the pressure in the artery proximal to the stenosis (Pa, red) at maximal hyperemia following the injection of adenosine. A fractional flow reserve of <0.80 indicates that revascularization would be beneficial. ■ ■FURTHER READING Bangalore S et al: Evidence-based practices in the cardiac catheter ization laboratory. Circulation 144:e107, 2021. Moscucci M (ed): Grossman & Baim's Cardiac Catheterization, Angiography, and Intervention, 9th ed. Philadelphia, Lippincott Williams & Wilkins, 2020. Nishimura R et al: Hemodynamics in the cardiac catheterization laboratory of the 21st century. Circulation 125:2138, 2012. Räber L et al: Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. Eur Heart J 39:3281, 2018. Samuels BA et al: Comprehensive management of angina with nonobstructive coronary artery disease (ANOCA), Part 1 defini tion, patient population, and diagnosis. J Am Coll Cardiol 82:1245, 2023. Principles of Clinical Cardiac Electrophysiology William H. Sauer, Bruce A. Koplan, Paul C. Zei

HISTORICAL PERSPECTIVE Clinical cardiac electrophysiology is the subspecialty of cardiology that focuses on the study and management of heart rhythm disorders. The development of the modern surface electrocardiogram (ECG) by Willem Einthoven more than 100 years ago enabled an understanding of the relationship between cardiac electrical potentials, mechanical cardiac function, and pathophysiology of cardiac arrhythmias. In the mid-twentieth century, the recording of cellular membrane currents enabled the understanding that the surface ECG represents the sum of cellular cardiac electrical activity. An understanding of cellular electro physiology also ushered in the development of antiarrhythmic drugs utilized by cardiac electrophysiologists. The modern era of clinical cardiac electrophysiology began with the first recordings of human intracardiac electrograms in the 1960s. Ini tially, invasive electrophysiology studies were limited to diagnostic tools. This included serial electrophysiologic testing to evaluate arrhythmia mechanisms and evaluate arrhythmia suppression by antiarrhythmic drugs, and programmed stimulation of the ventricle for risk stratifica tion of sudden cardiac death. In the 1960s and 1970s, cardiac surgery was the only available invasive treatment for cardiac arrhythmias. The subsequent development of

radiofrequency catheter ablation in the 1980s ushered in the era of interventional cardiac electrophysiology. In addition, with the development of implanted cardiac rhythm manage ment devices including pacemakers and defibrillators, clinical cardiac electrophysiology became a distinct medical subspecialty. Developments in catheter ablation techniques, cardiac resynchronization and conduc tion system pacing, subcutaneous defibrillator implantation, leadless pacemaker implantation, left atrial appendage closure, and laser-assisted lead extraction have broadened the procedural aspects of the specialty over the past 30 years; however, the principles of arrhythmia patient management have remained the same. CELLULAR ELECTROPHYSIOLOGY The cardiac action potential (AP) drives the electrophysiologic behav ior of all cardiac myocytes. The AP is characterized morphologically by five distinct phases, termed phases 0–4, as shown in Fig. 250-1. Moreover, as ventricular electrophysiologic activity accounts for the QRS and T complexes of the surface ECG, each AP phase in ventricular tissues corresponds to distinct phases in the surface ECG: Phase 0, the rapid upstroke, corresponds to the QRS deflection; phases 1–2 account for the ST segment; phase 3 accounts for the T wave; while phase 4 corresponds to the segment between the end of the T wave and the sub sequent QRS deflection. In addition, the P wave corresponds to atrial depolarization, while the PR interval corresponds to the time between Section 3 Disorders of Rhythm

Ventricular AP Current GENE (Protein) INa INa SCN5A (Nav1.5) Depolarizing Repolarizing ICa-L ICa-L CACNA1C (Cav1.2) INCX SLC8A1 (NCX1.1)

Voltage 0 1

Time

IK1 IK1 KCNJ2 (Kir2.1) Ito Ito KCND3/KCNIP2 (Kv4.3/KChIP2) IKr IKr KCNH2/KCNE2 (HERG/MiRP-1) IKs IKs KCNQ1/KCNE1 (KVLQT1/minK) IKur KCNA5 (Kvt.5) A FIGURE 250-1 A. Cellular atrial and ventricular action potentials. Phases 0–4 are the rapid upstroke, early repolarization, plateau, late repolarization, and diastole, respectively. The ionic currents and their respective genes are shown above and below the action potentials. The currents that underlie the action potentials vary in atrial and ventricular myocytes. Potassium current (IK1) is the principal current during phase 4 and determines the resting membrane potential of the myocyte. Sodium current generates the upstroke of the action potential (phase 0); activation of Ito with inactivation of the Na current inscribes early repolarization (phase 1). The plateau (phase 2) is

generated by a balance of repolarizing potassium currents and depolarizing calcium current. Inactivation of the calcium current with persistent activation of potassium currents (predominantly IKr and IKs) causes phase 3 repolarization. Currents that result in membrane depolarization are grouped at the top of the figure above the action potentials, while repolarizing currents are shown below the action potentials. B. A surface electrocardiogram (ECG) representation of sinus rhythm is shown with respective intracardiac action potentials that are active during each phase of the ECG. Each cardiac conduction region’s action potential is shown in the upper portion of the panel, with colors reflected in the ECG segment shown in the lower portion of the panel. Note that during the P wave, atrial depolarization is active. During the PR interval, the atrioventricular (AV) nodal, His, bundle branches, and Purkinje fibers are active (in sequence), although these action potentials are not discernible on the surface ECG. During the QRS interval, ventricular action potentials are

active, with the QRS morphology most reflective of the sequence of ventricular tissue action potential activation. The ST segment is predominantly determined by the plateau phase 2 of the ventricular action potential. The T wave is determined largely by ventricular repolarization (phase 3), while the isoelectric segment is the result of the electrically neutral phase 4 of the ventricular action potential. the initiation of atrial depolarization to the initiation of ventricular depolarization, comprised (typically) for the most part by the conduc tion time through the atrioventricular (AV) node. AP morphologies are the result of the precise and carefully timed sequences of opening, closing, and inactivation of an array of membrane ion channels in response to cellular membrane potential changes, ligands that bind to the ion channel complex, or membrane stretch in a timedependent fashion. The open ion channel allows flux of specific charged ions through a central pore, resulting in electrical (ionic) currents that drive the AP. The activity of different subsets of ion channels drives the different phases of the AP. Specific ionic currents that flux through an open channel are driven by the electrochemical gradient of that particular ion across the membrane, which in turn are driven by ion pumps or transport ers/exchangers, which in turn are catalyzed by ATP (Fig. 250-2). Ion channels are complex, multi-subunit transmembrane glycopro teins that contain a central pore that is selective for particular ionic spe cies (selectivity); a “gating” apparatus that regulates the opening, closing, and inactivation apparatus; and often one or more regulatory subunits. Most channels gate in response to changes in membrane potential, a spe cific ligand, or mechanical deformation. The molecular underpinnings of these specific functional properties of channels have become well understood through decades of basic electrophysiologic study using the tools of voltage clamp and patch clamp techniques, and more recently, molecular, genetic, and structural/crystallographic techniques. The structural makeup of most ion channels contains several com mon motifs. All channels form a central conducting pore, with ionic selectivity determined by specific amino acids that line the central pore. The central pore of most channels is formed by the P domain, a series of hydrophilic amino acid residues, with one of several structural variants: four separate homologous alpha subunits, each with homolo gous P domains (voltage-gated K channels); a single alpha subunit with four internally homologous P domains (voltage-gated Na or Ca channels); or two internally homologous P domains from two separate subunits (most ligand-gated K channels). A series of one or

Atrial AP CHAPTER 250 SA node Atrial myocardium AV node Voltage His bundle Time Principles of Clinical Cardiac Electrophysiology Bundle branches Purkinje fibers Myocardium P QRS T B more transmembrane segments surrounds the central pore. In voltagegated channels, the fourth of six segments, the S4 segment, contains a series of charged amino acid residues that functions as a voltage sensor, responding to changes in membrane potential by facilitating protein conformational changes that result in channel opening or closing (gat ing). In ligand-activated channels, the binding of a ligand (transmitters, molecules, or other ions) results in channel opening or closing, while deformations in membrane shape determine gating in stretch-activated channels. In addition, in many ion channels, a complex of auxiliary proteins is associated with the primary alpha subunit; most auxiliary subunits appear to facilitate regulation of ion channel expression and activity. A distinct type of transmembrane protein complex is the gap junction complex. A large multimeric complex of connexin subunits forms a large, nonselective pore that spans and thereby connects adja cent myocytes. This allows free flux of ions between adjacent myocytes, facilitating impulse propagation across myocardial tissues. Due to the physiologic gradient of their respective ions across the cell membrane, Na and Ca channels account for most inward, or depo larizing, currents in cardiac myocytes, and these channels respond to membrane depolarization with rapid opening,

relatively rapid closing, and inactivation. Na and Ca currents therefore drive phase 0 depolar ization of the AP. Potassium channels, on the other hand, account for most of the repolarizing currents seen in cardiac myocytes. Relatively slow K channel opening, as well as Na and Ca channel closing and inactivation, drives the plateau of phases 1–2 as well as the repolarizing phase 3 of the AP. Mutations in K channel subtypes are causative of many inherited channelopathies. Mutations that either inherently delay the closing or inactivation of K channels result in prolongation of the QT interval, leading to many forms of inherited long QT syndrome. The morphologic and functional properties of APs vary across different regions of the heart. These variations are the result of varia tions in the active ionic currents during each phase of the AP, which in turn reflects regional variation in ion channel expression. In atrial and ventricular myocytes, Na currents dominate the rapid upstroke

K channels N α Subunits β Subunits PART 6 Disorders of the Cardiovascular System C N C X4 Extracellular K+ N Intracellular Pore segments Na channels N N + + + + + + + + + + + + + β1 C P C C N P P P P P Inactivation LA binding Ca channels α2 S S γ δ α1 β FIGURE 250-2 Topology and subunit composition of the voltage-dependent ion channels. Potassium channels are formed by the tetramerization of α or pore-forming subunits and one or more β subunits; only single β subunits are shown for clarity. Sodium and calcium channels are composed of α subunits with four homologous domains and one or more ancillary subunits. In all channel types, the loop of protein between the fifth and sixth membrane-spanning repeat in each subunit or domain forms the ion-selective pore. In the case of the sodium channel, the channel is a target for phosphorylation, the linker between the third and fourth homologous domain is critical to inactivation, and the sixth membrane-spanning repeat in the fourth domain is important in local anesthetic antiarrhythmic drug binding. The Ca channel is a multi-subunit protein complex with the α1 subunit containing the pore and major drug-binding domain. (phase 1) of the AP, while in nodal tissues, Ca currents, which activate more slowly, dominate phase 1. Hence, for instance, drugs that bind and block the cardiac Na channel demonstrate efficacy in treating tachyarrhythmias arising from the atria and ventricles, whereas Ca channel blocking agents demonstrate efficacy at nodal tissues. During

the pre-depolarizing phase 4 of the AP, ionic currents remain relatively quiescent in atrial and ventricular myo cytes as they await local depolarization that triggers the next AP. In contrast, in sinus nodal tissues, which possess the property of automaticity, or intrinsic rhythmic depo larization, there is gradual depolarization observed dur ing phase 4, until a threshold is reached that initiates the next AP. In these nodal tissues, this depolarizing phase 4 current is generated by a semiselective Na/Ca channel, termed the “funny current” or If, which is the target for the medication ivabradine. NORMAL CARDIAC IMPULSE PROPAGATION The normal cardiac impulse initiates and travels through specialized conduction fibers, often referred to as the cardiac conduction system. Each impulse is initiated in the sinoatrial (SA) node, located at the lateral junction between the superior vena cava (SVC) and right atrium (RA). SA nodal tissues exhibit automaticity, such that a reliable, rhythmic impulse emanates from the SA node. The SA node (along with the AV node) is richly inner vated by autonomic fibers, allowing precise and dynamic control of heart rate and overall function by the central nervous system. The normal impulse then travels across the RA then the LA across preferential conduction path ways, initiating atrial systole. Once the impulse reaches the AV node, conduction occurs in a relatively slow time frame through the AV nodal tissues. This conduction time not only serves to provide physiologic AV synchrony but also is reflected in the surface ECG as the PR interval, or time between the atrial inscription and the

subsequent ventricular, or QRS, complex. In normal hearts, the AV node serves as the only electrical connection between atria and ventricles. Both the SA and AV nodes respond exquisitely to autonomic input; for instance, with exercise and increased adrenergic tone, the PR interval physiolog ically shortens. After the AV node, the impulse travels through a network of specialized conduction fibers: the bundle of His divides into a right and left bundle branch, which transmit conduction to the right and left ventricles, respectively. The left bundle then divides further into the left anterior and posterior fascicles. The fascicles then further divide into a network of Purkinje fibers. The conduction velocity of electrical impulses is much higher in Purkinje fibers (2–3 m/s) than in myocardial cells (0.3–0.4 m/s). Different connexins in gap junctions of Purkinje networks are partially responsible for more rapid conduction. This network of conductive Purkinje fibers is located endocardially and serves to rapidly transmit depolarization throughout the ventricles, such that myocardial depolarization, and hence mechanical contraction, occur rapidly and in a coordinated, synchro nized fashion, optimizing mechanical contraction of the ventricles. Repolarization of the ventricular myocardium, on the other hand, occurs relatively slowly and progresses from the epicardial surface back toward the endocar dium. Hence, the T wave inscription in most ECG leads is concordant with the QRS complex. β2 MECHANISMS OF CARDIAC ARRHYTHMIAS Cardiac arrhythmias are the manifestation of abnormalities in the initiation and/or propagation of the cardiac electrical impulse. Bradyarrhythmias result most commonly from abnormalities in the specialized conduction tissues. Abnormal function of the SA node may result in pathologic sinus bradycardia; AV node disease may result in conduction block; pathology in the His-Purkinje system may result in conduction block as well. Tachyarrhythmias may arise from not only

TABLE 250-1 Overview of the Mechanisms of Cardiac Tachyarrhythmias TACHYARRHYTHMIA CATEGORY MECHANISM PROTOTYPICAL ARRHYTHMIAS Abnormal automaticity Enhanced (acceleration of phase 4 repolarization) Idiopathic VT; AT Suppressed (absent or decelerated phase 4 repolarization) Sinus node dysfunction Triggered activity EADs TdP in long QT syndrome, PVCs DADs Reperfusion PVCs/ VT, AT and VT with digitalis toxicity Reentry (1) Anatomic or functional confinement of a circuit (i.e., scar, accessory pathway); (2) unidirectional block after a premature impulse; (3) wave of excitation that travels in a single direction returning to its point of origin AVNRT, AVRT, atrial flutter, scarrelated VT Abbreviations: AT, atrial tachycardia; AVRT, atrioventricular reentry tachycardia; AVNRT, atrioventricular nodal reentry tachycardia; DADs, delayed afterdepolarizations; EADs, early afterdepolarizations; PVC, premature ventricular contraction; TdP, torsades des pointes; VT, ventricular tachycardia. nearly every location within the conduction tissues, but also within atrial or ventricular tissues. Tachyarrhythmias are typically classified by mechanism: enhanced automaticity refers to abnormal spontaneous depolarization, which can occur along the conduction system, the atria, or ventricles; triggered arrhythmias result from abnormal afterdepo larizations that occur in either phase 2/3 (early afterdepolarizations) or phase 4 (delayed afterdepolarizations) of the AP; reentry results from cir cus movement of an electrical impulse (see Table 250-1 and Fig. 250-3). ■ ■ENHANCED AUTOMATICITY Automaticity, defined as spontaneous depolarizations occurring dur ing phase 4 of the AP, is a normal property of several myocardial tis sues, including the SA node, AV node, and the His-Purkinje system. The automaticity of the SA node triggers the normal cardiac impulse. When the automaticity of a more proximal conduction system tissue Abnormal automaticity Reentry Triggered activity Early afterdepolarizations Triggered activity Delayed afterdepolarizations FIGURE 250-3 Schematic action potentials with early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs).

is unreliable or slow, the automaticity of a more distal aspect of the conduction system may result in an “escape rhythm” that may maintain cardiac output. Automaticity in these tissues results from phase 4 depo larization of cellular membranes driven by several ionic currents. In the SA node, the nonselective Na/Ca If current drives this depolarization, while in other tissues, K currents, Ca currents, or even the Na/Ca and ATP-driven Na/K exchangers contribute.

CHAPTER 250 The rate of depolarization during phase 4 drives the frequency of APs and hence automaticity rate of these tissues. In nodal tissues, this rate of depolarization is highly regulated by the autonomic system. Parasympathetic input results in local acetylcholine (ACh) release, which then binds the IKACh potassium channel complex (specifically via a G protein–mediated mechanism). The opening of IKACh channels, resulting in K efflux, hyperpolarizes these cells, resulting in slow ing of phase 4 depolarization, thereby slowing the automaticity rate. Sympathetic input, via catecholamines, activates both alpha- and betaadrenergic receptors. Beta-1 adrenergic stimulation results in activation of L-type Ca channels, Ca influx, and as a result, enhanced depolarization rates during phase 4, and increased automaticity rates. The normal range of SA automaticity rates is between 30 and 220 beats/min, corresponding to the normal range of rates during sinus rhythm. The sinus rate at any instant is therefore a dynamic balance between sympathetic and para sympathetic input, with the latter dominating in the restful state. The intrinsic heart rate (IHR) is defined as the “native” automaticity rate of the SA node, absent any autonomic input. Principles of Clinical Cardiac Electrophysiology Abnormally enhanced automaticity may occur at any site that exhibits automaticity, including the SA node, AV node, or His-Purkinje system, resulting in pathologic tachycardia. In addition, in pathologic states, other stereotyped regions in the heart may exhibit enhanced automaticity, including the pulmonary veins, coronary sinus superior vena cava, and ventricular outflow tracts. Injury to myocardium, whether through ischemia or other mechanisms, may alter its cel lular membrane properties, resulting in automaticity in these tissues. For instance, the border zones of infarcted ventricular myocardium, or rapidly reperfused ischemic myocardium, often exhibit automatic arrhythmias including premature ventricular contractions (PVCs) or automatic idioventricular rhythms (AIVR). Abnormal automaticity in the pulmonary veins is believed to underpin the triggers that drive paroxysmal atrial fibrillation, while automaticity elsewhere in the atria drives atrial tachycardias. ■ ■AFTERDEPOLARIZATIONS AND TRIGGERED ARRHYTHMIAS Afterdepolarizations and triggered arrhythmias refer to abnormal depolarizations that occur in the late phases of the AP (afterdepolar izations) that can initiate sustained arrhythmias. Early afterdepolariza tions (EADs) occur typically during phases 2–3 of the AP and may be facilitated by intracellular Ca loading. When the QT interval prolongs, typically in a heterogeneous fashion across the ventricles, EADs may trigger wavefronts of abnormal depolarizations, resulting in torsades des pointes (TdP), a nonsustained or sustained ventricular arrhythmia that may result in cardiac arrest. Medications that prolong QT inter val, as well as other QT-prolonging factors including hypokalemia, hypomagnesemia, and bradycardia, predispose the ventricles to EADs, leading to TdP. Electrical remodeling in cardiomyopathies may also predispose to QT prolongation and risk of EADs and TdP. Delayed afterdepolarizations (DADs) are abnormal depolarizations occurring in phase 4 of the AP. The mechanism underlying DADs is increased intracellular Ca, which then enhances repetitive depolariza tions during the late phases of the AP. As a result, repetitive depolariza tions ensue, including the well-described phenomenon of bidirectional ventricular tachycardia (VT). Digitalis glycoside toxicity, ischemia, and catecholamines are the most commonly described causes for DADs. ■ ■REENTRY Reentry refers to the circus movement of a wavefront of electri cal activation.

Reentry can occur around a fixed anatomic barrier, referred to as anatomic reentry, or around a functionally blocked or

refractory barrier or anchor, termed functional reentry. Initiation and maintenance of a reentrant arrhythmia require (1) unidirec tional block, where the electrical wavefront can only propagate in one direction, and (2) slow conduction, a zone within the reentrant circuit where conduction is relatively slow, allowing the remainder of the circuit to repolarize and recover from refractoriness (the inability to reexcite).

PART 6 Disorders of the Cardiovascular System The more common form of reentry is anatomic, which requires a defined electrical/anatomic circuit with a pathway around a fixed barrier. A wavefront of depolarization encounters a barrier to con duction that allows propagation in only one direction (unidirectional block), forcing activation preferentially along one limb or pathway. Due to slow conduction, the depolarization wavefront travels through the remaining circuit and continually encounters tissues that have recovered from refractoriness and are hence excitable. This results in perpetual circus movement. Moreover, if the total length of the cir cuit exceeds a distance determined by the product of the conduction velocity (theta) of the tissue and the refractory period (duration) of that tissue (tr), referred to as the wavelength of tachycardia (lambda = theta × tr), an excitable gap, where tissue is recovered from refrac tory and able to depolarize, is created, allowing reentry. Reentry is the mechanism for several clinically important and common cardiac arrhythmias, including atrial flutter, AV nodal reentry, AV recip rocating tachycardia utilizing an accessory pathway, and scar-based reentrant VT. When reentry occurs in the absence of a fixed anatomic bar rier, it is termed functional reentry. A nidus of partially refractory tissue anchors the depolarization wavefront, resulting in a circular or rotational reentrant wavefront. In this case, the reentrant circuit or activity tends to be less stable than that from anatomic reentry, resulting in variations in depolarization rate and propensity to easily terminate and/or reinitiate. There is evidence that functional reen try is the underlying mechanism for perpetuation and maintenance of both atrial fibrillation (AF) and ventricular fibrillation (VF). In both of these apparently chaotic and disorganized arrhythmias, mul tiple wavefronts resulting from multiple functional reentrant circuits appear to drive arrhythmia in many, if not most, instances. Underlying pathology of the myocardium resulting in heterogeneous electrophysi ologic properties, altered activation, and repolarization properties pre dispose myocardial tissues to initiation and propagation of functional reentry-based arrhythmias. In addition to intrinsic alterations in cellular membrane electro physiologic properties that underpin most arrhythmias, extrinsic factors may precipitate other architectural and tissue changes that contribute to proarrhythmia. Ischemia and infarct may create regions of heterogeneous fibrosis, resulting in islands of scar surrounded by injured tissue. This creates the anatomic substrate that can sustain ana tomic reentry, which underlies scar-based VT, as well as many macroreentrant atrial arrhythmias. Peri-infarct border zones often contain injured myocardium as well, and the resultant alterations in cellular membrane properties may promote enhanced automaticity or trig gered arrhythmias. Chronic ischemia also results in downregulation of connexin proteins and gap junctions, resulting in slowed impulse prop agation, which is one of the factors required for reentrant arrhythmias. Alterations in ion channel function, either through inherited mutations or through drug effect, can promote arrhythmias. QT prolongation can occur when the closing of potassium channels that should hyperpolar ize cells is delayed or slowed, or when the closing or inactivation of Na channels is impaired. ■ ■UNDERPINNINGS OF THE TREATMENT OF ARRHYTHMIAS Pharmacologic therapies for arrhythmias are directed toward the

specific underlying mechanism. For enhanced automaticity-based arrhythmia, medications that target phase 4 depolarization, including Ca channel blockers, beta-adrenergic blockers (via indirect action on adrenergic input), or ivabradine may be used. For triggered activitybased arrhythmia, correcting the precipitating factor is most effective. This includes, among other therapies, removal of digitalis glycosides

from the body, discontinuation of QT-prolonging medications, or even increasing heart rate, thereby shortening QT interval. For reen trant arrhythmia, medications that increase the refractory period, in particular K channel blocking agents, will increase the wavelength of conduction beyond the circuit length of tachycardia, resulting in the inability to sustain reentry. Medications that slow conduction velocity may have the paradoxical effect of promoting reentrant arrhythmias due to the creation of a larger excitable gap. This explains much of the proarrhythmic effect of many antiarrhythmic medications. Therefore, for these agents, which typically include Na channel blockers, sufficient dosing is required to slow conduction velocity to the point of extin guishing meaningful arrhythmia circuit conduction. A major aspect of clinical cardiac electrophysiology that has evolved over several decades is the ability to disrupt arrhythmic substrates through catheter-based (or rarely surgical) myocardial ablation. For automaticity-based arrhythmias, precise localization and elimination or isolation through ablation of the site of focal automaticity is effective in eliminating arrhythmia. For anatomically bound reentrant arrhythmias, interruption of the reentrant circuit with a series of ablation lesions is effective. In contrast, given the lack of a fixed anatomic circuit, and perhaps also due to the pres ence of multiple, often migratory, circuits, it appears that mechanical disruption, typically through catheter-based ablation, of identified sites of functional reentry appears to be ineffective in eliminating arrhythmia. CARE OF THE ARRHYTHMIA PATIENT ■ ■EVALUATION AND DIAGNOSIS The evaluation of a patient with suspected arrhythmia begins with a directed history and physical examination, which must include an ECG. The history and examination should focus on determining the nature of symptoms attributable to the arrhythmia itself and clues to potential underlying cardiac, medical, or metabolic conditions that may predispose to specific arrhythmias, and hence direct further stud ies and evaluations, ultimately directing appropriate therapy, prognosis, and counseling. Family history may also provide clues toward possible inherited arrhythmia syndromes. Symptoms attributable to arrhythmia can vary from a vague sensation of fatigue, chest pain, dyspnea, or lightheadedness to more specific sensations of rapid, slow, or irregular heart rate. Premature contractions, whether atrial or ventricular, may be sensed as extra beats, or if these extrasystoles result in diminished stroke volume for that particular beat, a sensation of a missed beat. Second, the hemodynamic sequelae of impaired cardiac output may result in symptoms, from presyncope to frank syncope, dyspnea, chest discomfort, or generalized weakness. Importantly, as the cadence and duration of arrhythmia episodes are highly variable, the temporal man ifestations of arrhythmia symptoms may vary significantly. Sporadic episodes of arrhythmia will result in intermittent symptoms, including syncope if hemodynamic compromise is significant; protracted epi sodes of arrhythmia may cause persistent symptoms. In patients with underlying compromise in cardiac function, most typically in patients with structural heart disease, arrhythmia leading to diminished cardiac output may trigger or exacerbate symptoms associated with the under lying condition such as angina, congestive heart failure, or hypoxiaassociated symptoms. Inciting factors or associations may also provide clues to the diag nosis. Arrhythmias associated with activities that increase adrenergic tone, such as exercise, stimulant intake, or emotional stress, may suggest not only tachyarrhythmias but also automaticity-triggered arrhythmias. However, keep in mind that

exceptions will occur. Medi cation use may be highly suggestive of an etiology: use of Ca channel blockers or beta blockers may suggest bradycardia exacerbated by these medications. Medications known to potentially prolong QT interval may suggest a malignant ventricular arrhythmia, specifically TdP. Eliciting a thorough family history, not only for known arrhythmia diagnoses, but of unexplained sudden death, may point toward a heri table syndrome. Demographic factors may point toward or away from certain diagnoses. For instance, AF rarely occurs in children and young

adults, save rare familial forms, or AF associated with structural heart disease; a strong male predominance, as well as a higher prevalence in certain ethnic populations such as Southeast Asians, is seen in Brugada syndrome; inappropriate sinus tachycardia is nearly exclusively a con dition affecting young women; degenerative conduction system disease leading to symptomatic bradycardia is most commonly a condition seen in older patients. Arrhythmias may run the gamut from benign to malignant, lifethreatening etiologies. Therefore, an important aspect of the evalu ation of suspected arrhythmia is to discern patient prognosis, which then informs treatment. Arrhythmias that result in more significant hemodynamic compromise, and therefore more profound symptoms, tend to correlate with more malignant disease. In turn, the higher the suspicion for a malignant arrhythmia, the more aggressive the evalu ation will likely be. Loss of consciousness, which may be the result of cardiac arrhythmia but also other etiologies that may be more benign, presents a particularly challenging yet common diagnostic dilemma. Therefore, careful thought into the appropriate evaluation for a patient with syncope is critical. In general, the presence of underlying struc tural abnormality of ventricular myocardium favors more malignant arrhythmias, both due to the increased risk of lethal ventricular arrhythmias and to potential inability to hemodynamically tolerate any particular arrhythmia. A careful history of circumstances, symptoms, and associated findings during the syncopal episode(s) can be very helpful in formulating a differential diagnosis. The ECG is the cornerstone and most important diagnostic test that should be performed on every patient with suspected arrhythmia. A 12-lead resting ECG may offer clues to the diagnosis. Most simply, if active arrhythmia is captured on the ECG, a definitive diagnosis can be made. In addition, evidence suggesting underlying cardiac disease, such as prior myocardial infarction, left ventricular hypertrophy and possible hypertrophic cardiomyopathy, atrial disease, or baseline conduction system disease, may suggest a diagnosis. A subset of condi tions that predispose to arrhythmia, both inherited or acquired, may be discerned as well, including ventricular preexcitation, prolonged or shortened QT interval, or ECG findings suggestive of specific inherited conditions such as Brugada syndrome or right ventricular cardiomyopathy. However, the ECG typically records only 6 s of cardiac electrical activity, and therefore more intermittent and transient arrhythmias, particularly those not typically associated with abnormalities on the resting ECG, may not be seen. Many arrhythmias, including forms of both supraventricular tachycardia (SVT) and VT, can only be diag nosed definitively if an ECG is performed during active arrhythmia and/or symptoms from arrhythmia or, alternatively, provoked in the electrophysiology laboratory. Therefore, various forms of ambulatory monitoring may be performed to attempt to capture ECG activity during active arrhythmia. A growing variety of monitoring options are available; the most appropriate option should be primarily guided by the cadence of suspected arrhythmia episodes. For instance, if daily symptoms occur, a 24- or 48-h continuous Holter monitor is appropri ate. On the other hand, a patient-activated event recorder is inappro priate in a patient with syncope, as the arrhythmic event will likely have passed once the patient reawakens. Attempts at provoking arrhythmia may be warranted in the appro priate circumstances. An ECG-monitored treadmill test may elicit exercise-induced arrhythmias, or if long QT is suspected, a QT interval that fails to

shorten appropriately with increased heart rate may be helpful. Pharmacologic provocation may be indicated for certain sus pected diagnoses, such as Brugada syndrome. Judicious and appropri ate use of carotid sinus massage or other means to enhance vagal tone may be helpful to diagnose carotid hypersensitivity or overall vagally mediated syncope. Tilt table testing (TTT) involves having a patient strapped to a tiltable table. While monitoring heart rate and blood pressure, the patient is moved from a supine to upright position. In patients with suspected autonomic dysfunction–mediated syncope or presyncope, this provocation may elicit a paradoxical vagal response, resulting in bradycardia and/or sinus pauses as well as hypotension, and perhaps

frank syncope. However, given the significant lack of both sensitivity and specificity, the current role of TTT is unclear, and it is seldom indicated after a careful history elucidates a neurally mediated cause for syncope.

Invasive electrophysiologic (EP) testing is the most useful diag nostic modality for many arrhythmias. Catheter-based recordings of intracardiac electrograms, with or without provocative pacing or pharmacologic maneuvers, may elicit the clinical arrhythmia. This will, in turn, help to define the mechanism of arrhythmia. However, one must keep in mind that for certain arrhythmia mechanisms, such as automaticity-driven tachycardia, EP study may fail to elicit arrhythmia due to the often transient and multifactorial nature of initiation of these arrhythmias. The nature of arrhythmia elicited will aid in determination of the patient’s prognosis. In a typical EP study, catheters are placed within the heart via femoral venous access. Baseline conduction properties are measured. Provocative maneuvers including electrical pacing maneuvers, programmed stimulation, and pharmacologic provocation are performed. In the modern era, the vast majority of invasive EP studies are performed in conjunction with planned catheter ablation, although programmed ventricular stimula tion for risk stratification of sudden death may still be utilized. EP study during catheter ablation is performed to confirm the diagnosis, localize appropriate ablation targets, and evaluate the efficacy of abla tion performed during the procedure. CHAPTER 250 Principles of Clinical Cardiac Electrophysiology Depending on the suspected arrhythmia diagnosis, further testing may be indicated. If structural heart disease is suspected, echocar diography is most often the best next test, as it can assess for underly ing structural disease, evaluate left ventricular function, and assess atrial dimensions and mitral valve function if AF is suspected, both of which are fair prognostic indicators. In patients in whom underlying coronary artery disease is suspected, an evaluation for coronary isch emia is indicated. Further evaluation for underlying structural heart disease will be directed based on the differential diagnosis. Cardiac computed tomography provides broad diagnostic utility, depending on the scanning protocol, including evaluation for ischemia, ven tricular scar, anatomic evidence of coronary artery disease, congeni tal anomalies, and left atrial anatomy. Cardiac magnetic resonance imaging provides significant resolution of soft-tissue characteristics and may be used to assess for ischemia, infarct, cardiomyopathy, or infiltrative disease. Cardiac positron emission tomography can also discern underlying ischemia, as well as metabolic/inflammatory/ infiltrative conditions. TREATMENT Cardiac Arrhythmias ANTIARRHYTHMIC DRUG THERAPY The effects of pharmacologic agents on cardiac electrophysio logic properties are often complex and, in some instances, remain incompletely understood. The complexity is the result of complex pharmacodynamics and pharmacokinetics, in particular significant cross-reactivity of certain drugs across different targets as well as variable effects on drug targets across drugs within the same category. There are regional differences in drug effect within the myocardium, and interpatient variations in drug metabolism play important

roles. This has, in part, led to many instances of harm that have come from the adverse effects of many agents used over the years. In fact, many antiarrhythmic agents currently in use carry significant risks of side effects, some of which may be significant and even lethal. Therefore, judicious use of antiarrhythmic medi cations by those with appropriate knowledge base and experience is warranted. The practical result of the narrow therapeutic index of this class of medications has rendered their use increasingly as ancillary options (Table 250-2). The traditional nomenclature of antiarrhythmic drugs (AADs) is known as the Vaughan-Williams classification schema. In this schema, there are four classes (I–IV; Table 250-2). Class I AADs primarily target the Na channel, class II agents target the

PART 6 Disorders of the Cardiovascular System beta-adrenergic receptor, class III agents target potassium channels, and class IV agents target Ca channels. Class I agents are further subdivided into three subclasses based on the kinetics of drug to Na channel interactions. Class IA agents, including procainamide and quinidine, possess intermediate binding kinetics and potency. Class IB agents, including lidocaine and mexiletine, possess rapid binding kinetics and relatively low potency. Class IC agents (flecainide, propafenone) possess slow kinetics and high potency. Class II agents consist entirely of beta-adrenergic blocking agents. Class III agents (sotalol, dofetilide, ibutilide) specifically target the Kv11.1 potassium channel (encoded by the KCNH2 gene) and risk prolon gation of the QT interval through these effects on phases 2/3 of the AP and hence ventricular repolarization. Class IV agents are cardi oselective Ca channel blockers including verapamil and diltiazem. This classification has significant limitations, however. Many AADs interact with multiple ion channels, and as a result, many exhibit behavior consistent with multiple classes. Amiodarone, in particu lar, exhibits properties of all AAD classes. Adenosine, with primary antiarrhythmic effects as an acute and transient, intravenously administered AV nodal blocking agent, as well as digitalis glycoside, which blocks the Na+/K+ pump, which in turn inhibits the Na+/Ca++ exchanger, resulting in antiarrhythmic effect, do not neatly fit into this classification schema. CATHETER ABLATION The rationale that underlies catheter ablation for cardiac arrhyth mia is that an anatomic substrate can be identified and localized, and disruption or isolation of that substrate will eliminate the cardiac arrhythmia. For automaticity-driven arrhythmias, a focal source of automaticity is identified, localized, and ablated. For anatomic reentrant arrhythmias, a critical zone of slow conduc tion that sustains arrhythmia and can be reasonably targeted is ablated. Moreover, the ablation target must be in a location deemed at acceptable risk of not damaging critical structures such as the native conduction system, coronary arteries, or extracardiac structures including the esophagus and phrenic nerve. Advances in electroanatomic mapping, a technology that uses alterations in electrical impedance and a magnetic field as measured by an intra cardiac mapping catheter, have allowed for real-time reconstruc tion of cardiac chambers and identification of arrhythmogenic tissue to be targeted for ablation while safely avoiding nontargeted critical structures. Intracardiac echocardiography has also been used to enhance the safety and efficacy of invasive electrophysi ologic procedures with real-time visualization of cardiac structures (Fig. 250-4). In the 1950s–1960s, as the underlying anatomic substrates for arrhythmias became better understood, open surgical disruption of arrhythmia circuits was the only available interventional and cura tive therapy for many arrhythmias. Surgical ligation of accessory pathways or resection of ischemic VT substrates was performed at specialized surgical centers. The first attempts at clinical catheter ablation utilized direct current (DC) electrical energy. This resulted in a high-voltage pulse of electrical energy that would ablate cardiac tissue, but with a difficult-to-control scope, often leading to sig nificant complications. Radiofrequency (RF) energy was adapted to catheter-based cardiac ablation in the 1980s. RF alternating electri cal current (300–550 kHz)

delivered through a catheter tip results in local tissue heating and permanent injury, rendering the targeted tissue electrically inert. This type of ablation is similar to the tech nology used in electrosurgical techniques using a Bovie electro cautery device. For >35 years, RF delivery via catheters has been iteratively optimized such that it has become the most common and mainstay energy source for catheter ablation. Catheter ablation is indicated for a wide variety of clinical arrhythmias, including SVT, accessory pathways, atrial flutter, AF, PVCs, and VT. Alternative TABLE 250-2 Antiarrhythmic Drug Actions DRUG CLASS ACTIONS OTHER ACTIONS/COMMON SIDE EFFECTS I II III IV Quinidine ++ ++ Anticholinergic Flecainide +++ + Can promote reentrant arrhythmias (atrial flutter, ventricular tachycardia) Propafenone ++ + Mild beta-blocker effect Amiodarone ++ ++ +++ + Multiorgan toxicity with long-term use Sotalol ++ +++ Prominent beta-blocker effect Dofetilide +++ Prolongation of QT at slower heart rates Dronedarone + + + + Mild effect Ibutilide +++ Used only for acute cardioversion Ranolazine ++ ++ Late sodium channel blockade Lidocaine ++ Used for reperfusion arrhythmias A B FIGURE 250-4 Catheter ablation of cardiac arrhythmias. A. A schematic of the catheter system and generator in a patient undergoing radiofrequency catheter ablation (RFCA); the circuit involves the catheter in the heart and a dispersive patch placed on the body surface (usually the back). The inset shows a diagram of the heart with a series of intracardiac catheters placed via the inferior vena cava (IVC), typically through femoral venous access. Catheters are located at the high right atrium, His bundle location, right ventricular (RV) apex, and through a transseptal puncture within the left atrium. B. Images from an electroanatomic mapping system are shown during mapping and ablation of typical cavo-tricuspid isthmus-dependent atrial flutter. This system allows three-dimensional real-time localization and annotation of catheter position and cardiac anatomy to guide mapping and ablation. In this instance, two projections of the map are shown at the top of the right atrium (RA), a right anterior oblique (RAO) and left anterior oblique (LAO) caudal view. Annotations of ablation lesion delivery are shown as red dots. In the left lower aspect of this panel, a simultaneous image from intracardiac echocardiography (ICE) is shown of the RA, with the ablation catheter in view in all three images. In the lower right aspect of this panel, surface electrocardiogram and intracardiac electrograms acquired in real time are shown.

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