NASPE 25TH ANNIVERSARY SERIES

Mechanisms of Clinical Arrhythmias

DOUGLAS P. ZIPES, M.D.

From the Krannert Institute of Cardiology, Indiana University School of Medicine and the Roudebush Veterans Administration Medical Center, Indianapolis, Indiana, USA

Introduction

The mechanisms responsible for cardiac arrhythmias are generally divided into categories of disorders of impulse formation, disorders of impulse conduction, or combinations of both.[1] Using the features of entrainment (see later), arrhythmias caused by macroreentrant circuits can be identified. It is important to realize, however, that our present diagnostic tools do not permit unequivocal determination of the electrophysiologic mechanisms responsible for many clinically occurring arrhythmias, or their ionic bases. This is especially true for ventricular arrhythmias. It may be very difficult to separate reentry, particularly microreentry, from automaticity. In addition, an episode of tachycardia caused by one mechanism can precipitate a tachycardia perpetuated by a different mechanism. For example, an initiating tachycardia or premature complex caused by abnormal automaticity can precipitate an episode of tachycardia sustained by reentry. Initiation or termination of tachycardias by pacing stimuli, response to overdrive pacing, the demonstration of electrical activity bridging diastole, fixed coupling, and a variety of other clinically used techniques do not provide absolute proof of mechanisms.

Disorders of Impulse Formation

Inappropriate discharge rate of the normal pacemaker, the sinus node, or discharge from an ectopic pacemaker characterizes disorders in this category. Pacemaker discharge from ectopic sites, often called *latent* or *subsidiary pacemakers,* can occur in fibers located in several parts of the atria, the coronary sinus and pulmonary veins, the AV valves, portions of the AV junction, and the His-Purkinje system, or in ventricular muscle, right and left ventricular outflow tracts, and valves. Ordinarily kept from reaching the level of threshold potential because of overdrive suppression by the more rapidly firing sinus node or electrotonic depression from contiguous fibers, ectopic pacemaker activity at one of these latent sites can become manifest when the sinus nodal discharge rate slows or block occurs at some level between the sinus node and the ectopic pacemaker site to permit *escape* of the latent pacemaker at the latter's normal discharge rate.

Alternatively, the discharge rate of the latent pacemaker can speed inappropriately and usurp control of cardiac rhythm from the sinus node, which has been discharging at a normal rate. Such disorders of impulse formation can be due to speeding or slowing of a *normal* pacemaker mechanism but occurs inappropriately fast or slow, or due to an ionically *abnormal* pacemaker mechanism. Present clinical tools do not permit differentiation between the two mechanisms, which, conceivably, could be important for future drug selection.

A patient with persistent sinus tachycardia at rest or sinus bradycardia during exertion exhibits inappropriate sinus nodal discharge rates, but the ionic mechanisms responsible for sinus nodal discharge may still be normal. When a patient experiences ventricular tachycardia in the setting of structural heart disease, ionic mechanisms not normally involved in formation of spontaneous impulses for this fiber type may be operative.

Abnormal Automaticity

Abnormal automaticity has been found in Purkinje fibers removed from dogs subjected to myocardial infarction, in rat myocardium damaged by epinephrine, in human atrial samples, in ventricular myocardial specimens from patients undergoing aneurysmectomy and endocardial resection for recurrent ventricular tachyarrhythmias, and during current passage that reduces diastolic potential. It is possible that partial depolarization and failure to reach normal maximal diastolic potential can induce automatic discharge in most, if not all, cardiac fibers. Although this type of spontaneous automatic activity has been found in human atrial and ventricular fibers, its relationship to the genesis of clinical arrhythmias has not been established.

Rhythms resulting from automaticity may be slow atrial, junctional, or ventricular escape rhythms, certain types of atrial tachycardias (such as those produced by digitalis or perhaps those coming from the pulmonary veins), accelerated junctional (nonparoxysmal junctional tachycardia) and idioventricular rhythms, and parasystole. Because the maximum rate that can be achieved by adrenergic stimulation of normal automaticity is generally <200 beats/min, it is likely that episodes of faster tachycardia are not due to enhanced normal automaticity.

Triggered Activity

Automaticity is the property of a fiber to initiate an impulse *spontaneously,* without the need for prior stimulation;

Supported in part by the Herman C. Krannert Fund and by Grant HL52323 from the National Heart, Lung, and Blood Institute of the National Institutes of health.

This manuscript was processed by a guest editor.

J Cardiovasc Electrophysiol, Vol. 14, pp. 902-912, August 2003.

Address for correspondence: Douglas P. Zipes, M.D., Krannert Institute of Cardiology, 1800 N. Capitol, Suite E475, Indianapolis, IN 46202. Fax: 317-962-0568.

electrical quiescence does not occur. *Triggered activity* is pacemaker activity that results *consequent* to a preceding impulse or series of impulses, without which electrical quiescence occurs. Triggered activity is not caused by an automatic self-generating mechanism but by afterdepolarizations, which are depolarizing oscillations in membrane voltage induced by one or more preceding action potentials. Thus, the term *triggered automaticity* is contradictory. These depolarizations can occur before full repolarization of the fiber and are termed *early afterdepolarizations* (EADs).[2] They arise from a reduced level of membrane potential during phases 2 (type 1) and 3 (type 2) of the cardiac action potential (Fig. 1). *Late* or *delayed afterdepolarizations* (DADs) result when they occur after completion of repolarization (phase 4), generally at a more negative membrane potential than that from which EADs arise (Fig. 2). All afterdepolarizations may not reach threshold potential, but if they do, they can trigger another afterdepolarization and thus self-perpetuate.

Early afterdepolarizations

A variety of interventions, each of which increases intracellular positivity, can cause EADs. The L-type calcium channel may be important, perhaps signaled by calmodulin kinase II.[3] Activators of ATP-dependent potassium channels, such as pinacidil and cromakalim, can eliminate EADs. EADs may be responsible for the lengthened repolarization time and ventricular tachyarrhythmias in several clinical situations, such as the acquired and congenital forms of the long QT syndrome. In patients with the long QT syndrome, T wave morphology often is abnormal, and the corrected QT interval (QTc) is prolonged. Patients with the heritable long QT syndrome have either potassium channel defects (LQT1 due to mutations in *KvLQT1* that encodes I_{Ks}, and LQT2 due to mutations in *HERG* that encodes I_{Kr}) or sodium channel–linked defects (LQT3 due to mutations in *SCN5A* that encodes the sodium channel) and, consequently, an abnormally prolonged cardiac action potential duration. (LQT4 is due to abnormalities in ankyrin-B, LQT5 due to mutations in *KCNE1,* and LQT6 due to mutations in MiRP1.[4,5])

The genesis of ventricular tachyarrhythmias in the long QT syndrome still is not clear.[6] Experimental observations suggest an important role of transmural heterogeneity of repolarization. Multiple studies in isolated ventricular myocytes or in tissue preparations have demonstrated spatial dispersion of repolarization along the transmural axes of the left and right ventricular free wall. A prominent spike and dome is apparent in myocytes from the epicardium and the mid-ventricle (M cell region), but not in myocytes from the endocardium. Action potential prolongation is considerably more pronounced in cells isolated from the M region (Fig. 3). The ionic basis for electrophysiologic distinctions among epicardial, mid-myocardial, and endocardial myocytes is a large gradient in both the density- and rate-dependent properties of the transient outward K^+ current and a smaller density of the slow component of the delayed rectifier K^+ current I_{Ks} in mid-myocardial cells than in myocytes of endocardial and epicardial origin.[7]

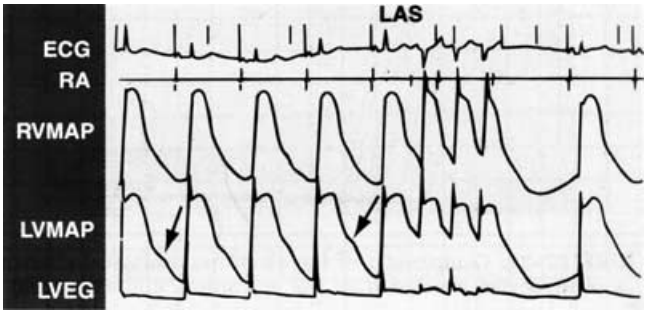

Figure 1. *After cesium administration during left ansae subclaviae stimulation (LAS), early afterdepolarizations increase in amplitude (arrows) and culminate in a short run of nonsustained ventricular tachycardia. LVEG = left ventricular electrogram; LVMAP = left ventricular monophasic action potential recording; RVMAP = right ventricular monophasic action potential recording. Time lines represent 1 second. (From Ben-David J, Zipes DP: Differential response to right and left stellate stimulation of early afterdepolarizations and ventricular tachycardia in the dog. Circ Res 1988;78:1241. By permission of the American Heart Association.)*

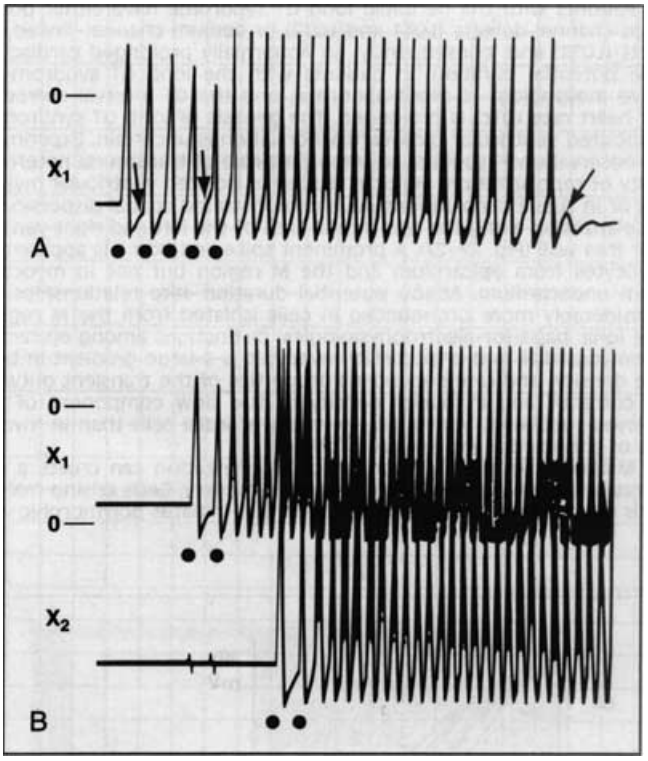

Figure 2. *Triggered sustained rhythmic activity and delayed afterdepolarizations in diseased human ventricle. A: Spontaneous activity triggered by a series of driven action potentials (indicated by the dots) at recording site X_1. Note the gradual increase in the size of the delayed afterdepolarizations (arrows) until the afterdepolarizations reach threshold and maintain sustained rhythmic activity after cessation of pacing. The sustained rhythmic activity finally terminates when the last afterdepolarization fails to reach threshold (arrow). B: Initiation of triggered activity by intracellular current injection (indicated by the dots beneath the respective action potential recordings) at sites X_1 and X_2, which lie along the same trabecula. Although sites X_1 and X_2 were only about 4 mm apart, triggered sustained rhythmic activity from one site did not propagate to the other site, thus indicating complete dissociation between these two sites. For current pulses, cycle length = 2,000 msec; pulse duration = 10 msec; pulse intensity = 200 nA. Vertical calibration: 50 mV; horizontal calibration: 10 seconds. (Reprinted from American Journal of Cardiology, Vol. 51, Gilmour RF Jr, Heger JJ, Prystowsky E, Zipes DP: Cellular electrophysiological abnormalities of diseased human ventricular myocardium, p. 136, Copyright 1983, with permission from Excerpta Medica Inc.)*

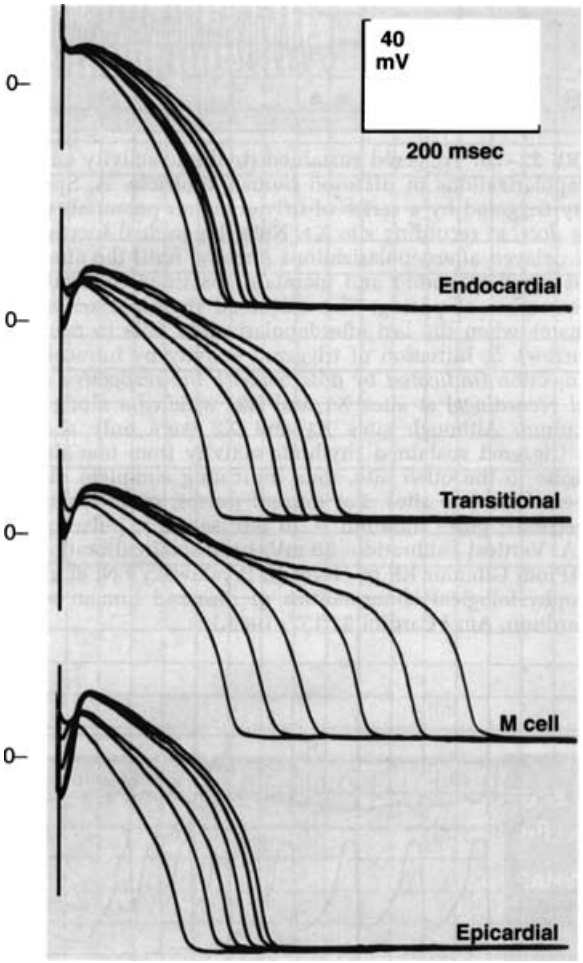

Figure 3. *Comparison of the electrophysiologic characteristics of myocytes isolated from the epicardial, mid-myocardial (M cell), and endocardial regions of the canine left ventricular free wall. Each panel shows superimposed action potentials recorded at basic cycle lengths of 300 to 8,000 msec. An increase in basic cycle length leads to progressive accentuation of the spike-and-dome configuration of the action potential in epicardial and mid-myocardial cells. In cells from the M region, but not in those from the epicardial and endocardial regions, deceleration causes remarkable prolongation in action potential duration (APD). Thus, a much steeper APD-rate relationship is observed in myocytes from the M region. (From Liu DW, Antzelevitch C: Characteristics of the delayed rectifier current (I_{Kr} and I_{Ks}) in canine ventricular epicardial, midmyocardial, and endocardial myocytes. Circ Res 1995;78:351. By permission of the American Heart Association.)*

Marked transmural dispersion of repolarization can create a vulnerable window for the development of reentry. EADs arising from M cells may underlie the premature complex that initiates (or perpetuates) the characteristic polymorphic ventricular tachycardia, torsades de pointes, in patients with the long QT syndrome. Sympathetic stimulation, primarily left, could periodically increase the EAD amplitude to provoke ventricular tachyarrhythmias. Alpha-adrenoceptor stimulation also increases the amplitude of cesium-induced EADs and the prevalence of ventricular tachyarrhythmias in dogs, both of which are suppressed by magnesium. Short coupling intervals and rapid rates suppress EADs.

Patients can develop the acquired long QT syndrome and torsades de pointes from a host of drugs that affect repolarization. It is possible that multiple drugs can cause summating effects to provoke EADs and torsades de pointes in patients. EADs recently have been implicated as a cause of focal tachycardias in pulmonary veins.[8]

Delayed afterdepolarizations

DADs appear to be caused by a transient inward current (I_{ti}) that is small or absent under normal physiologic conditions. When intracellular Ca^{2+} overload occurs, spontaneous release of Ca^{2+} from the sarcoplasmic reticulum can activate Cl^- currents or the Na/Ca exchanger and result in transient inward currents and brief membrane depolarizations. Compounds that reduce the sarcoplasmic Ca^{2+} load (L-type Ca^{2+} channel antagonists, beta-adrenergic receptor blocker) or inhibit sarcoplasmic Ca^{2+} release (thapsigargin, ryanodine, cyclopiazonic acid) suppress DADs. Inhibitors of calmodulin kinase eliminated I_{ti} carried by inward $I_{Na/Ca}$ in isolated rabbit ventricular myocytes, thus indicating that activation of this enzyme appears to play an important role in cardiac arrhythmogenesis.[3] In addition, drugs that reduce I_{Na} also reduce $[Na^+]_{ti}$, relieve Ca^{2+} overload, and can abolish DADs.

DADs and triggered activity have been demonstrated in Purkinje fibers, specialized atrial fibers and ventricular muscle fibers exposed to digitalis preparations, normal Purkinje fibers exposed to Na-free superfusates from the endocardium of the intact heart, ventricular myocardial cells, and endocardial preparations after a myocardial infarction. When fibers in rabbit, canine, simian, and human mitral valves and in the canine tricuspid valve and coronary sinus are superfused with norepinephrine, they exhibit the capacity for sustained triggered rhythmic activity.

Triggered activity caused by DADs also has been noted in diseased human atrial and ventricular fibers studied in vitro. Left stellate ganglion stimulation can elicit DADs in canine ventricles. In vivo, atrial and ventricular arrhythmias apparently caused by triggered activity have been reported in the dog and possibly in humans. It is tempting to ascribe certain clinical arrhythmias to DADs, such as some arrhythmias precipitated by digitalis. The accelerated idioventricular rhythm 1 day after experimental canine myocardial infarction may be due to DADs, and some evidence suggests that certain ventricular tachycardias, such as those arising in the right ventricular outflow tract, may be due to DADs, whereas other data suggest that EADs are responsible. Some left ventricular fascicular tachycardias may be due to triggered activity and others to reentry. DADs have been found in single cardiomyocytes isolated from pulmonary veins[8] and may be responsible for some types of atrial fibrillation (AF).

Short coupling intervals or pacing at rates more rapid than the triggered activity rate (overdrive pacing) in general increase the amplitude and shorten the cycle length of the DAD following cessation of pacing (overdrive acceleration) rather than suppressing and delaying the escape rate of the afterdepolarization, as in normal automatic mechanisms. Premature stimulation exerts a similar effect; the shorter the premature interval, the larger the amplitude and shorter the escape interval of the triggered event. The clinical implication of these observations might be that tachyarrhythmias caused by DAD-triggered activity may not be suppressed easily or, indeed, may be precipitated by rapid rates, either spontaneous (such as a sinus tachycardia) or pacing induced. Finally, because a single premature stimulus can both initiate and

terminate triggered activity, differentiation from reentry can be difficult.

A group of probable nonreentrant ventricular tachycardias occurring in the absence of structural heart disease can be initiated and terminated by programmed stimulation. They are catecholamine dependent and are terminated by the Valsalva maneuver, adenosine, and verapamil. These ventricular tachycardias are generally, but not exclusively, located in the right ventricular outflow tract and may be due to triggered activity, possibly DADs that are cAMP dependent. EADs have been recorded in this tachycardia. Triggered activity may cause some atrial tachycardias and AF.

Disorders of Impulse Conduction

Block

Conduction delay and block can result in bradyarrhythmias or tachyarrhythmias, the former when the propagating impulse is blocked and is followed by asystole or a slow escape rhythm, and the latter when the delay and block produce reentrant excitation (see later). Various factors involving both active and passive membrane properties determine the conduction velocity of an impulse and whether conduction is successful. Among these factors are the stimulating efficacy of the propagating impulse, which is related to the amplitude and rate of rise of phase 0, the excitability of the tissue into which the impulse is conducted, and the geometry of the tissue.

Diastolic depolarization has been suggested as a cause of conduction block at slow rates, so-called *bradycardia-* or *deceleration-dependent block.* Yet excitability *increases* as the membrane depolarizes until about −70 mV, despite a reduction in action potential amplitude and V_{max}. A more probable explanation of deceleration-dependent block is the reduction in action potential amplitude and excitability at long diastolic intervals. Rapid pacing can produce overdrive suppression of conduction, with a similar mechanism related to the depression of action potential amplitude and excitability.

More commonly, impulses are blocked at *tachycardia rates* or *short cycle lengths* as a result of incomplete recovery of refractoriness caused by incomplete time- or voltage-dependent recovery of excitability. Such incomplete recovery is the usual mechanism responsible for a nonconducted premature P wave or one that conducts with a functional bundle branch block.

The term *decremental conduction* is used commonly in the clinical literature but often is misapplied to describe any Wenckebach-like conduction block, i.e., responses similar to block in the AV node during which progressive conduction delay precedes the nonconducted impulse. Correctly used, *decremental conduction* refers to a situation in which the properties of the fiber change along its length so that the action potential loses its efficacy as a stimulus to excite the fiber ahead of it. Thus, the stimulating efficacy of the propagating action potential diminishes progressively, possibly as a result of its decreasing amplitude and V_{max}.

Reentry

Electrical activity during each normal cardiac cycle begins in the sinus node and continues until the entire heart has been activated. Each cell becomes activated in turn, and the cardiac impulse dies out when all fibers have been discharged and are completely refractory. If, however, a group of fibers not activated during the initial wave of depolarization recovers excitability in time to be discharged before the impulse dies out, they may serve as a link to reexcite areas that were just discharged and have now recovered from the initial depolarization. Such a process is given various names, all meaning approximately the same thing: reentry, reentrant excitation, circus movement, reciprocal or echo beat, or reciprocating tachycardia.

A key feature of a tachycardia due to reentry is the property of entrainment.[9] If the rate of the tachycardia can be increased to a faster rate by pacing, with resumption of the intrinsic rate of the tachycardia when pacing is stopped, the presence of reentry can be established. Entrainment represents capture or continuous resetting of the reentrant circuit of the tachycardia by the pacing-induced activation. Each pacing stimulus creates a wavefront that travels in an anterograde direction (orthodromic) and resets the tachycardia to the pacing rate. A wavefront propagating retrogradely in the opposite direction (antidromic) collides with the orthodromic wavefront of the previous beat (Fig. 4). These wavefront interactions create ECG and electrophysiologic features that can be explained best by reentry. Therefore, the criteria of entrainment can be used to establish the reentrant mechanism of a clinical tachycardia and form the basis for localizing the pathway traveled by the tachycardia wavefront. Such localization is essential for ablation therapy. Further, characteristics of the entrainment can establish whether the pacing site is within or outside the reentrant circuit.[10]

Anatomic reentry

The earliest studies on reentry used models that had anatomically defined separate pathways in which it could be shown that they had (1) an area of unidirectional block, (2) recirculation of the impulse to its point of origin, and (3) elimination of the arrhythmia by cutting the pathway. In models with anatomically defined pathways, because the two (or more) pathways have different electrophysiologic properties, e.g., a refractory period longer in one pathway than the other, the impulse (1) is blocked in one pathway (site A in Fig. 4) and (2) propagates slowly in the adjacent pathway (serpentine arrow, D to C, Fig. 4). If conduction in this alternative route is sufficiently depressed, the slowly propagating impulse excites tissue beyond the blocked pathway (horizontal lined area in Fig. 4) and returns in a reversed direction along the pathway initially blocked (B to A in Fig. 4) to (3) reexcite tissue proximal to the site of block (A to D in Fig. 4). A clinical arrhythmia caused by anatomic reentry is most likely to have a monomorphic contour.

For reentry of this type to occur, the time for conduction within the depressed but unblocked area and for excitation of the distal segments must exceed the refractory period of the initially blocked pathway (A in Fig. 4) and the tissue proximal to the site of block (D in Fig. 4). Stated another way, continuous reentry requires the anatomic length of the circuit traveled to equal or exceed the reentrant wavelength. The latter is equal to the mean conduction velocity of the impulse multiplied by the longest refractory period of the elements in the circuit. Both values can be different at different points along the reentrant pathway; thus, the wavelength value (and concept) is somewhat contrived.

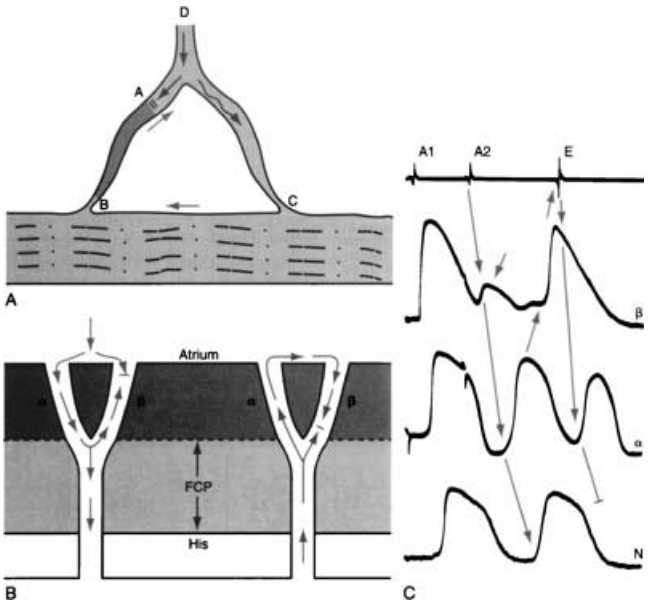

Figure 4. *A: Diagram of reentry by Schmitt and Erlanger published in 1928. A Purkinje fiber (D) divides into two pathways (B and C), both of which join ventricular muscle. It is assumed that the original impulse travels down D, is blocked in its anterograde direction at site A (arrow followed by a double bar), but continues slowly down C (serpentine arrow) to excite ventricular muscle. The impulse then reenters the Purkinje twig at B and retrogradely excites A and D. If the impulse continues to propagate through D to the ventricular myocardium and elicits ventricular depolarization, a reentrant ventricular extrasystole results. Continued reentry of this type would produce ventricular tachycardia. B: Schematic representation of intranodal dissociation responsible for an atrial echo (left panel). A premature atrial response fails to penetrate the beta pathway, which exhibits a unidirectional block, but propagates anterogradely through the alpha pathway. Once the final common pathway (FCP) is engaged, the impulse may return to the atrium via the now-recovered beta pathway to produce an atrial echo. The right panel illustrates the pattern of propagation during generation of a ventricular echo. A premature response in the His bundle traverses the FCP, encounters a refractory beta pathway (unidirectional block), reaches the atrium over the alpha pathway, and returns through a now-recovered beta pathway to produce a ventricular echo. C: Actual recordings from the atrium (top tracing), with cells impaled in the beta region (second tracing), alpha region (third tracing), and N portion of the AV node (bottom tracing) in an isolated rabbit preparation. The basic response to A_1 activated both alpha and beta pathways and the N cell (first tier of action potentials). The premature atrial response A_2 caused only a local response in the beta cell (heavy arrow), was delayed in transmission to the alpha cell, and was further delayed in propagation to the N cell. Following the alpha response, a retrograde spontaneous response occurred in the beta cell and propagated to the atrium (E). This atrial response represents an atrial echo. The echo returned to stimulate the alpha cell but was not propagated to the N cell. It is important that although intranodal reentry has been shown to occur within the rabbit AV node, AV nodal reentry in humans probably occurs over extranodal pathways. (From Mendez C, Moe GK: Demonstrations of a dual AV nodal conduction system in the isolated rabbit heart. Circ Res 1966;19:378. By with permission of the American Heart Association.)*

The length of the pathway is fixed and determined by the anatomy. Conditions that depress conduction velocity or abbreviate the refractory period will promote the development of reentry in this model, whereas prolonging refractoriness and speeding conduction velocity can hinder it. For example, if conduction velocity (0.30 m/sec) and refractoriness (350 m/sec) for ventricular muscle were normal, a pathway of 105 mm (0.30 msec $\times$ 0.35 sec) would be necessary for reentry to occur. However, under certain conditions, conduction velocity in ventricular muscle and Purkinje fibers can be very slow (0.03 m/sec), and if refractoriness is not greatly prolonged (600 msec), a pathway of only 18 mm (0.03 m/sec $\times$ 0.60 sec) may be necessary. Such reentry frequently exhibits an excitable gap, i.e., a time interval between the end of refractoriness from one cycle and the beginning of depolarization in the next, when tissue in the circuit is excitable. This condition results because the wavelength of the reentrant circuit is less than the pathway length. Electrical stimulation during this time period can invade the reentrant circuit and reset its timing or terminate the tachycardia.

In reentrant circuits with an excitable gap, conduction velocity determines the revolution time of the impulse around the circuit and, hence, the rate of the tachycardia. Prolongation of refractoriness, unless it is sufficient to eliminate the excitable gap and make the impulse propagate in relatively refractory tissue, will not influence the revolution time around the circuit or the rate of the tachycardia. Anatomic reentry occurs in patients with the Wolff-Parkinson-White syndrome, AV nodal reentry, some atrial flutters, and some ventricular tachycardias.

Functional reentry

Functional reentry lacks confining anatomic boundaries and can occur in contiguous fibers that exhibit functionally different electrophysiologic properties caused by local differences in transmembrane action potential (Fig. 5). Dispersion of excitability and/or refractoriness, as well as anisotropic distributions of intercellular resistance, permits initiation and maintenance of reentry. A clinical arrhythmia caused by functional reentry is most likely to be polymorphic because of changing or drifting circuits.

Leading circle reentry, perhaps important in AF, is a form of functional reentrant excitation during which the reentrant circuit propagates around a functionally refractory core and follows a course along fibers that have a shorter refractory period so that the impulse is blocked in one direction in fibers with a longer refractory period.[11] The pathway length of a functional circuit is determined by the smallest circuit in which the leading wavefront is just able to excite tissue ahead that is still relatively refractory. If these parameters change, the size of the circuit also may change and alter the rate of the tachycardia. Shorter wavelengths may predispose to fibrillation. No, or a very short, excitable gap exists, and the duration of the refractory period of the tissue in the circuit primarily determines the cycle length of the tachycardia because the stimulating efficacy of the head of the next impulse is just sufficient to excite the relatively refractory tissue in the wake of the preceding impulse. Propagating impulses originating outside the circuit cannot easily enter the circuit to reset, entrain, or terminate the reentry.

Theoretically, drugs that prolong refractoriness and do not delay conduction would slow a tachycardia due to the leading circle mechanism and not affect tachycardia with an excitable gap until the prolongation of refractoriness exceeded the duration of the excitable gap. Drugs that primarily slow conduction would have major effects on tachycardia with an excitable gap and not on tachycardias resulting from the leading circle concept. Mixed circuits with both anatomic and functional pathways obfuscate these differences.

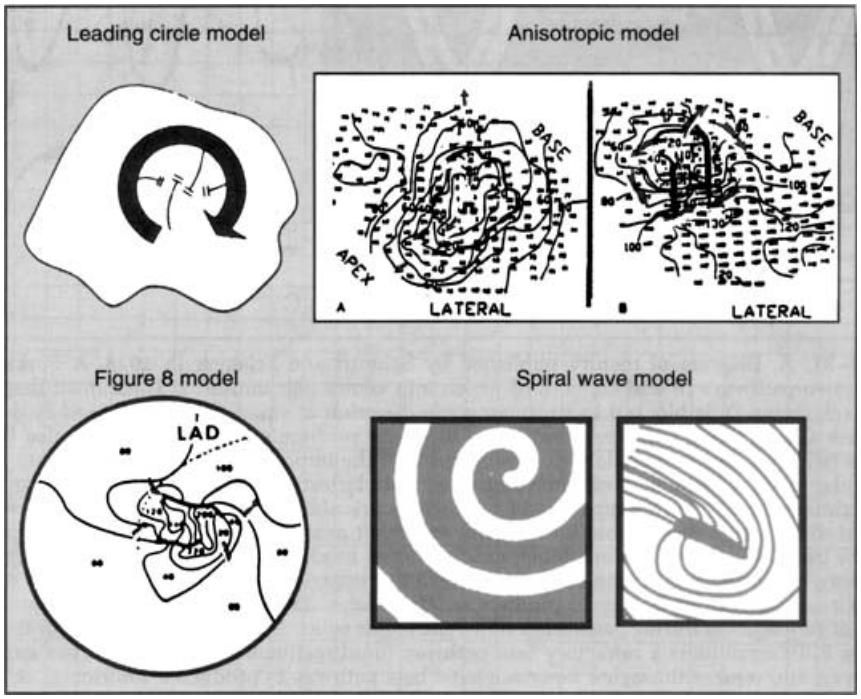

Figure 5. *Functional models of reentry. Top left: Leading circle model. Diagrammatic representation of the leading circle model of reentry in isolated left atrium of the rabbit. The central area is activated by converging centripetal wavelets. (From Allessie MA, Bonke FIM, Schopman FJG: Circus movement in rabbit atrial muscle as a mechanism of tachycardia: III. The "leading circle" concept: New model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ Res 1977;41:9. By permission of the American Heart Association.) Bottom left: Figure-of-eight model. Activation map (in 20-msec isochrones) of a figure-of-eight circuit in the surviving epicardial layer of a dog 4 days after ligation of the left anterior descending coronary artery (LAD). The circuit consists of clockwise and counterclockwise wavefronts around two functional arcs of block that coalesce into a central common front that usually represents the slow zone of the circuit. (Reprinted from El-Sherif N: The figure 8 model of reentrant excitation in the canine post-infarction heart. In Zipes DP, Jalife J, eds: Cardiac Electrophysiology and Arrhythmias. p. 363, Copyright 1985, with permission of Elsevier.) Top right: Anisotropic model showing stimulation from the center of a multiple electrode array (at the pulse symbol, A) on the epicardial border zone of a 4-day-old canine infarct producing an elliptical pattern of activation characteristic of conduction in an anisotropic medium. Arrows indicate the direction of the fast axes of conduction and longitudinal orientation of the myocardial fibers. B: Activation map of a reentrant circuit on the epicardial border obtained with the same electrode array during sustained ventricular tachycardia in the same heart. Arrows indicate the sequence of isochrones and thus the direction of movement of activation. (Reproduced with permission from Wit AL, Janse MJJ: The Ventricular Arrhythmias of Ischemia and Infarction: Electrophysiological Mechanisms. Mt. Kisco, NY: Futura Publishing Company, 1992.) Bottom right: Spiral wave model. Activation map of spiral wave activity in a thin slice of isolated ventricular muscle from a sheep heart (right panel). Isochrone lines were drawn from raw data by overlaying transparent paper on snapshots of video images during spiral wave activity (left panel, not from the same experiment). Each line represents consecutive positions of the activation front recorded every 16 msec. (Reproduced with permission from Brugada J, Boersma L, Kirchhof C, Zetelaki Z, Abdollah H, Konings K, Allessie M: Sustained monomorphic ventricular tachycardia: A single electrocardiographic expression of different patterns of reentry. Pacing Clin Electrophysiol 1991;14:1943-1946.)*

Anisotropic reentry

Anisotropic reentry is due to the structural features normally present in all hearts, which are responsible for variations in conduction velocity and the time course of repolarization. These include features such as the concentration of gap junctions at the ends rather than on the side of cells, which can result in block and slowed conduction with subsequent reentry. Even in normal cardiac tissue exhibiting normal transmembrane potentials and uniform refractory periods, conduction can be blocked in the direction *parallel* to the long axis of fiber orientation, propagate slowly in the direction *transverse* to the long axis of fiber orientation, and reenter the area of block. Spatial differences in refractoriness may not be necessary for reentry to occur. Such anisotropic reentry has been shown in atrial and ventricular muscle and may be responsible for ventricular tachycardia in epicardial muscle surviving myocardial infarction[12] (Fig. 6). An excitable gap may be present.

Figure-of-eight reentry

Figure-of-eight reentry consists of clockwise and counterclockwise wavefronts around two functional arcs of block that coalesce into a central common path usually representing the slow zone of the circuit. Such reentry has been shown in both atrial and ventricular muscle, and it may be important in infarcted myocardium.[13]

Spiral wave reentry

Spiral waves of excitation have been demonstrated in cardiac muscle and represent a two-dimensional form of reentry, which, in three dimensions, may be represented by scroll waves. Spiral waves may be stationary when the shape, size, and location of the arc remain unchanged throughout the episode, drifting when the arc migrates away from its site of origin or anchoring when the drifting core becomes anchored to some small obstacle, such as a blood vessel. One

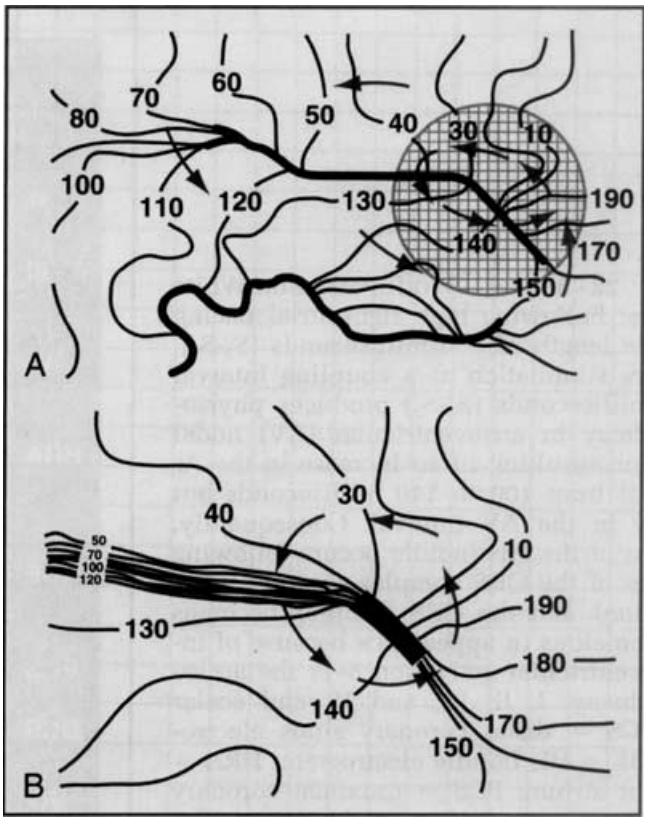

Figure 6. *Model of anisotropic reentry in the epicardial border zone. A: Activation map of the single reentrant circuit. The large arrows point out the general activation pattern; activation appears to occur around a long line of block. However, parallel isochrones adjacent to the line (isochrones 130 and 140) suggest that activation also is occurring across the line and thereby results in the smaller circuit shown by the small arrows. B: Same circuit shown enlarged. Rapid activation occurs parallel to the long axis of the fiber orientation (isochrones 10 to 40 and at 130 to 150), whereas very slow activation (closely bunched isochrones 50 to 100) occurs transverse to fiber orientation in the circuit. The dark black rectangle is an area of either functional or anatomic block that forms the fulcrum of the circuit. (Reproduced with permission from Wit AL, Dillon SM: Anisotropic reentry. In Zipes DP, Jalife J, eds: Cardiac Electrophysiology: From Cell to Bedside. Philadelphia: WB Saunders, 1990.)*

can speculate that a stationary spiral wave could be responsible for a monomorphic tachycardia, a drifting spiral wave responsible for rhythm with changing contours such as torsades de pointes, and an anchoring spiral wave responsible for the transition from a polymorphic to a monomorphic tachycardia. A single rapidly moving rotor or a small number of coexisting, but short-lived, rotors can give rise to ECG patterns of activity indistinguishable from ventricular fibrillation (VF). The rotors can drift and interact with each other and with boundaries in the heart and result in annihilation and/or formation of new, but short-lived, rotors. Maintenance of fibrillation, both in the atria and ventricles, may depend on the periodic activity of rotors that give rise to spiraling wavefronts. Complex patterns of block can result as the rotors propagate, producing fibrillatory patterns on the ECG.[14,15]

Reflection

Reflection can be considered a special subclass of reentry. As in reentry, an area of conduction delay is required, and the total time for the impulse to leave and return to its site of origin must exceed the refractory period of the proximal segment. Reflection differs from reentry in that the impulse does not require a circuit but appears to travel along the *same* pathway in both directions.

Clinical Tachycardias Caused by Reentry

Reentry probably is the cause of many, perhaps most, tachyarrhythmias, including various kinds of supraventricular and ventricular tachycardias, flutter, and fibrillation. However, in complex preparations, such as large pieces of tissue in vitro or the intact heart, it becomes much more difficult to unequivocally prove that reentry exists.

Sinus nodal reentry

The sinus node shares with the AV node electrophysiologic features such as the potential for *dissociation of conduction,* i.e., an impulse can conduct in some nodal fibers but not in others, thereby permitting reentry to occur. The reentrant circuit can be located entirely within the sinus node or involve both the sinus node and atrium. Supraventricular tachycardias caused by sinus nodal reentry generally are less symptomatic than other supraventricular tachycardias because of slower rates. Modification of the sinus node by ablation can be necessary in an occasional refractory tachycardia.

Atrial flutter

Reentry is the most likely cause of the usual form of atrial flutter, with the reentrant circuit confined to the right atrium. It usually travels counterclockwise, in a caudocranial direction in the interatrial septum and in a craniocaudal direction in the right atrial free wall.[16] An area of slow conduction is present in the posterolateral to posteromedial inferior area of the right atrium, with a central area of block that can include an anatomic (inferior vena cava) and functional component. It is possible that several different reentrant circuits exist in patients with atrial flutter. However, this area of slow conduction is rather constant and represents the site of successful ablation of atrial flutter. Ablation results are consistent with a macroreentrant circuit.

Atrial fibrillation

According to Moe's multiple wavelet hypothesis, AF is characterized by fragmentation of the wavefront into multiple daughter wavelets that wander randomly throughout the atrium and give rise to new wavelets that collide with each other and are mutually annihilated or give rise to new wavelets in a perpetual activity. However, the apparent randomness of the irregular electrical activity during AF has been disputed recently on the basis of both statistical methods and experimental studies showing that the cycle length of the source in the left atrium determines the dominant peak in the frequency spectra. The underlying periodicity may stem from a repetitive focal discharge propagated from an individual pulmonary vein to the remainder of the atrium as fibrillating waves.[14]

Electrical remodeling of the atria may be important for maintenance of AF. Prolonged rapid atrial rates causes electrophysiologic alterations of the atria, including shortening and loss of the physiologic rate adaptation of refractoriness and decrease in conduction velocity. Because abbreviation of the atrial refractory period is disproportionally larger than

the reduction of conduction velocity, the wavelength of the reentrant wavelets shortens and thereby promotes reentrant activity. The ionic basis of shortening of the refractory period and slowing of conduction may be a significant reduction in the density of both the L-type Ca^{2+} current and the fast Na^{+} current. The electrophysiologic changes are paralleled by similar decreases in mRNA levels of Ca^{2+} and Na^{+} channel genes, which suggests alterations in gene expression as the underlying molecular mechanisms of atrial electrical remodeling. Changes in the density and/or spatial distribution of various connexin types may also cause alterations in atrial impulse propagation. Autonomic remodeling also appears to play a key role in both triggering and maintaining AF. Heterogeneous sympathetic denervation of the atria favors the development of sustained AF.[15]

Atrial reentry

Reentry within the atrium, unrelated to the sinus node, can be a cause of supraventricular tachycardia in humans. Atrial tachycardias have been shown to be due to reentry, automaticity, EADs, and DADs, causing triggered activity. Distinguishing atrial tachycardia caused by automaticity from atrial tachycardia sustained by reentry over quite small areas, i.e., microreentry of the leading circle type, is difficult.

AV nodal reentry

Longitudinal dissociation of the AV node into two or more pathways has been demonstrated in the isolated rabbit AV node, where cells in the upper portion of the AV node can be dissociated during propagation of premature stimuli so that one group of cells, called *alpha,* can discharge in response to a premature stimulus at a time when another group of cells, called *beta,* fails to discharge. The impulse can then turn around (without needing to activate the His bundle) to reexcite the beta group of cells and produce an atrial echo (Fig. 4B) or sustained tachycardia.[17]

The presence of dual AV nodal pathways has been supported by the finding that an impulse traveling from the ventricle to the atrium, if timed properly, can reach the atrium at the same time that another impulse is traveling from the atrium to the ventricle. For this event to occur, the impulses traveling in opposite directions without colliding must be conducting in different AV nodal pathways. In addition, catheter ablation of either the slow or fast pathway eliminates AV nodal reentrant tachycardia (AVNRT), with preservation of AV nodal conduction. Another convincing fact is the finding of two ventricular responses to a single atrial depolarization or two atrial responses to a single ventricular depolarization, as a result of simultaneous transmission over both the slow and fast AV nodal pathways.

Usually AVNRT begins when a premature atrial response blocks anterogradely in one AV nodal pathway that conducts more rapidly (fast pathway, or beta pathway in Fig. 4B) but has a longer refractory period than a second pathway (slow pathway, or alpha pathway in Fig. 4B). The premature atrial response travels to the ventricle over the slow (alpha) pathway, thereby prolonging the A-H interval, and returns back to the atrium over the fast (beta) pathway with a short H-A interval, so-called slow-fast AVNRT. Less commonly, the slow pathway has a long refractory period, and the premature atrial response can block anterogradely in the slow pathway and travel in the fast pathway by using the slow pathway retrogradely, so-called fast-slow AVNRT. Finally, some patients can have anterograde conduction over transitional fibers and retrograde conduction over slowly conducting AV nodal fibers, so-called slow-slow AVNRT.[17] Some patients may have more than two pathways. The results of radiofrequency catheter ablation, surgery, and experimental studies leave little doubt that, in the majority of patients, the fast and slow pathways have their origins well outside the limits of the compact portion of the AV node and, at the point that they are interrupted, are composed of ordinary working atrial myocardium. The slow and fast pathways are likely to be atrionodal approaches or connections rather than discrete intranodal pathways. Although it is clear that activation of the ventricle is not necessary for AVNRT and activation of His bundle may also not required in some patients, the necessary role of atrial participation in the reentrant circuit is still debated, and it probably is true that some patients have AVNRT confined to reentry within the AV node.

During the common form of AV nodal reentry, anterograde conduction occurs over a posteroinferior atrial approach, or "slow" pathway, whose upper end is posteroinferior to the AV node, toward the coronary sinus orifice. Radiofrequency lesions in this area eliminate AV nodal reentry by selectively affecting conduction over the slow pathway. The lower end of this pathway enters the compact portion of the AV node, where the impulse is able to "turn around" and retrogradely enter the "fast" or anterosuperior atrial approach, whose upper end inserts at the apex of the Koch triangle near the His bundle. This pathway can also be selectively ablated. During sinus rhythm, anterograde conduction probably occurs over the anterosuperior atrial approaches.

Preexcitation syndrome

In most patients who have reciprocating tachycardias associated with the Wolff-Parkinson-White syndrome, the accessory pathway conducts more rapidly than does the normal AV node but takes a longer time to recover excitability, i.e., the anterograde refractory period of the accessory pathway exceeds that of the AV node at long cycles. Consequently, a premature atrial complex that occurs sufficiently early is blocked anterogradely in the accessory pathway and continues to the ventricle over the normal AV node and His bundle. After the ventricles have been excited, the impulse is able to enter the accessory pathway retrogradely and return to the atrium. A continuous conduction loop of this kind establishes the circuit for the tachycardia. The usual (orthodromic) activation wave during such a reciprocating tachycardia in a patient with an accessory pathway occurs anterogradely over the normal AV node–His-Purkinje system and retrogradely over the accessory pathway, which results in a normal QRS complex.

Because the circuit requires both atria and ventricles, the term *supraventricular tachycardia* is not precisely correct, and the tachycardia is more accurately called *atrioventricular reciprocating tachycardia* (AVRT). The reentrant loop can be interrupted by ablation of the normal AV node–His bundle pathway *or* the accessory pathway. Occasionally, the activation wave travels in a reverse (antidromic) direction to the ventricles over the accessory pathway and to the atria retrogradely up the AV node. Two accessory pathways can form the circuit in some patients with antidromic AVRT. In some patients, the accessory pathway may be capable of only

retrograde conduction ("concealed"), but the circuit and mechanism of AVRT remain the same. Less commonly, the accessory pathway may conduct only anterogradely. Patients can have AF as well as AVRT, with conduction over either the AV node and/or the accessory pathway.

Unusual accessory pathways with AV nodal-like electrophysiologic properties, i.e., nodofascicular or nodoventricular fibers, can constitute the circuit for reciprocating tachycardias in patients who have some form of the Wolff-Parkinson-White syndrome. Tachycardia in patients with nodoventricular fibers can be due to reentry in which these fibers are used as the anterograde pathway and the His-Purkinje fibers and a portion of the AV node are used retrogradely.

Ventricular tachycardia

Many animal and clinical studies have supported reentry in the ventricle, both anatomic and functional, as a cause of sustained ventricular tachycardia. Reentry in ventricular muscle, with or without contribution from specialized tissue, is responsible for many or most ventricular tachycardias in patients with ischemic heart disease (Fig. 7). The area of microreentry can be quite small; less commonly, a macroreentry is found around the infarct scar. Surviving myocardial tissue separated by connective tissue provides serpentine routes of activation traversing infarcted areas that can establish reentrant pathways. Bundle branch reentry also can cause sustained ventricular tachycardia, particularly in patients with dilated cardiomyopathy.

Both figure-of-eight and single-circle reentrant loops have been described as circulating around an area of functional block in a manner consistent with the leading circle hypothesis, or conducting slowly across an apparent area of block created by anisotropy or scar. When intramural myocardium survives, it may form part of the reentrant loop. Structural discontinuities that separate muscle bundles, e.g., as a result of naturally occurring myocardial fiber orientation and anisotropic conduction, as well as collagen matrices formed from the fibrosis after a myocardial infarction, establish the basis for slowed conduction, fragmented electrograms, and continuous electrical activity that can lead to reentry. After the infarction, action potential recordings from surviving cells return to normal, which suggests that depressed activity in these cells does not account for the slowed conduction. However, ventricular myocardium resected from humans with recurrent ventricular tachycardia demonstrates abnormal action potentials, thus suggesting that causes of depressed conduction in humans may be multifactorial. During acute ischemia, a variety of factors, including elevated $[K]_o$ and reduced pH, combine to create depressed action potentials in ischemic cells that retard conduction and can lead to reentry.

In some instances of ventricular tachycardia related to coronary artery disease, but especially in patients without coronary artery disease, nonreentrant mechanisms are important causes of ventricular tachycardias. In many patients, however, the mechanism of the ventricular tachycardia remains unknown.

Prolonged rapid ventricular rates reproducibly cause action potential *prolongation* in a variety of species, similar to what has been observed in cells isolated from human hearts with dilated cardiomyopathy. The ionic basis for these repolarization abnormalities varies among species, but a reduction in the density of L-type Ca^{2+} currents and down-regulation and up-regulation of I_{to} and $I_{Na/Ca}$, respectively, appear to be involved. A change in ventricular rate, even of short duration, can cause lasting changes in cardiac electrophysiology. Transient superimposition of a fast ventricular rate on a slow rate was found to lengthen the QT interval and refractoriness for hours and to facilitate induction of torsades de pointes. Action potential prolongation was still present in cells isolated from hearts subjected to transient tachycardia and resulted from a reduction in I_{to} and enhanced $I_{Ca,L}$.[18]

Ventricular fibrillation

Substantial experimental support has accumulated in favor of the concept that the onset of VF involves the disintegration of a single spiral wave into many self-perpetuating waves. It has been proposed that the breakup of spiral waves is precipitated by oscillations of action potential duration that are of sufficiently large amplitude to cause conduction block along the spiral wavefront.

Experimental support for this idea comes from most studies demonstrating that if action potential duration restitution (which relates action potential duration to the preceding dias-

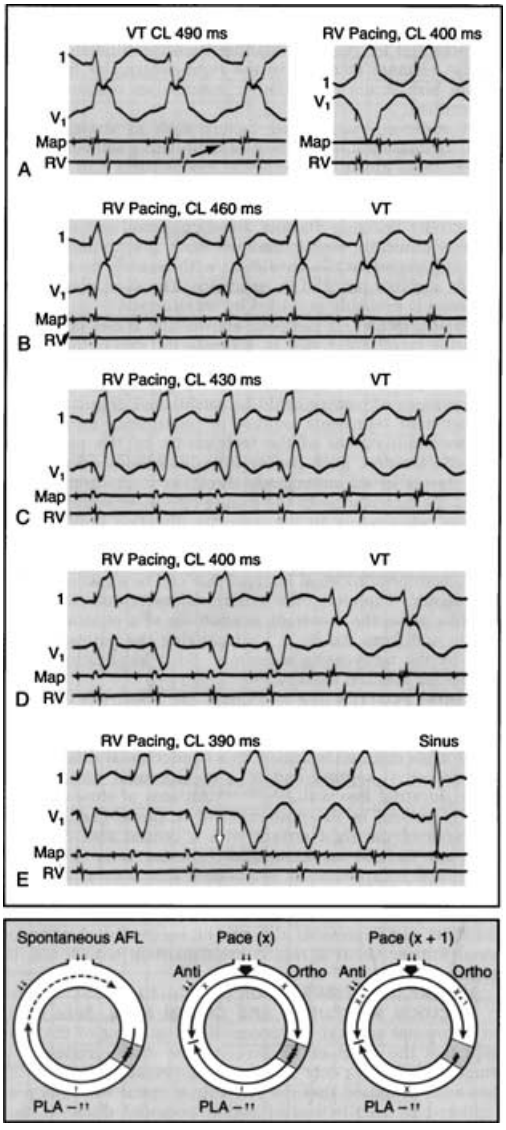

Figure 7.

tolic interval) contains a region of slope >1, action potential duration alternans is possible and can lead to the formation of reentrant waves. Reduction of the slope of the restitution relationship can prevent the induction of VF, thus indicating that the kinetics of electrical restitution appears to be a key determinant of VF.[19] The mass of the tissue appears to be another important factor in the development of fibrillation.[20] It was shown in an isolated swine model that tissue mass reduction resulted in the termination of VF when a critical mass (19 g) was reached.[21] In humans, this value appears to be much greater (>111 g).[22] Similarly, partitioning the atrium into small segments prevents AF, a concept that has led to corrective surgical and ablation procedures.[23]

The cardiac response to electrical stimulation depends on the strength and timing of the stimulus relative to cardiac recovery (coupling interval). A vulnerable zone is present during which a stimulus with appropriate strength can induce VF. When the heart is beating spontaneously (e.g., during sinus rhythm), the timing of the vulnerable period corresponds to the T wave on the surface ECG or, more precisely, to the latter part of its upslope and its peak. The strength of a stimulus cannot be either too low or too high. There is a lower limit of stimulus strength that can induce VF, as well as an upper limit of vulnerability, defined as a current strength at or above which VF cannot be induced.[24]

Propagated graded responses may underlie the mechanisms of ventricular vulnerability to a single premature stimulus. A stimulus delivered during incomplete recovery evokes a gradual response that propagates slowly to neighboring recovered cells and, if its amplitude is large enough, can induce an all-or-none response. This all-or-none response spreads in all directions except into regions near the site of the stimulus because of a graded response-induced increase in effective refractory period at the latter site, which results in unidirectional block and reentry (propagated graded-response hypothesis of ventricular vulnerability). When the extrastimulus strength increases and thus the magnitude of gradual responses increases beyond a critical level, the increase in refractoriness at the site of the stimulus becomes so long that the unidirectional block becomes bidirectional and prevents the formation of reentry (upper limit of vulnerability).

Brugada syndrome

A reentrant mechanism has been implicated in the genesis of ventricular tachycardia/fibrillation associated with the inheritable Brugada syndrome, which is characterized by ST segment elevation (unrelated to ischemia, electrolyte abnormalities, or structural heart disease) in the right precordial (V_1–V_3) ECG leads, often but not always accompanied by an apparent right bundle branch block. The Brugada syndrome is a congenital ion channel disorder with mutations in the cardiac sodium channel gene *SCN5A*. The gene defect results in either acceleration of recovery of the sodium channel from inactivation or a nonfunctional sodium channel. Inhibition of the sodium channel current causes heterogeneous loss of the action potential dome (plateau) in the right ventricular epicardium, which leads to propagation of the dome from sites at which it is maintained to sites at which it is lost. This causes local reexcitation via a phase 2 reentrant mechanism.[25]

Conclusion

In the 25 years of NASPE's existence, some of us have had the thrill of participating not only in its growth but also in the growth of the specialty it represents. Such an opportunity is rare in medicine. Beginning in the late 1960s, with the advent of invasive electrophysiologic studies, we learned much about the mechanisms responsible for clinical cardiac arrhythmias, as well as the sites/pathways involved. However, until the advent of surgery and then catheter ablation, there was relatively little we could do with that information. These two modalities provided the tools to implement what we had learned, and the rest, as can be said, "is history." But those of us with enough gray hair still remember the dose of phenylephrine used to elevate the blood pressure and produce a reflex vagal response to terminate a

←

Figure 7. *Top panel: Illustrated criteria for entrainment exemplified in a case of postinfarct ventricular tachycardia (VT). A, left panel: Two ECG leads of a VT and intracardiac recordings from a mapping catheter (Map) at a left ventricular site critical for VT continuation, as well as from the right ventricular apex (RV). Note the diastolic potential (dark arrow) during VT. Recordings are similarly arranged in all subsequent panels. A, right panel: RV pacing in the setting of sinus rhythm. B: RV pacing at a cycle length (CL) slightly shorter than VT produces a QRS complex that is a blend between fully VT and fully paced ("fusion") complexes. All recordings are accelerated to the paced CL, and, after pacing ceases, the same VT resumes. Each fused QRS complex is identical and the last beat is entrained, but surface fusion is absent. C,D: Same phenomena, but at shorter paced CL. Note that the fused QRS complex appears more similar to pacing than it does to VT as the pacing CL shortens. B through D thus illustrate a progressive degree of ECG fusion. The Map recording of B through D also shows a progression of fusion, with both the morphology and timing of a portion of the electrogram changing with faster pacing. E: Finally, a still shorter paced CL results in a sudden change in both the Map electrogram (block in the small diastolic potential, white arrow) and the surface ECG, which is now fully paced. When pacing ceases, VT has been interrupted. (Reprinted from Journal of the American College of Cardiology, Volume 34, Zipes DP: A century of cardiac arrhythmia: In search of Jason's Golden Fleece. Pages 959-965, Copyright 1999, with permission from American College of Cardiology Foundation). Bottom panel: Diagrammatic representation of the reentrant circuit during spontaneous atrial flutter (AFL) and during transient entrainment of the AFL. Left: The reentrant circuit during spontaneous type I AFL. f = circulating wavefront of the AFL. Center: Introduction of the first pacing impulse (X) during rapid pacing from a high atrial site during AFL. The large arrow indicates entry of the pacing impulse into the reentrant circuit, whereupon it is conducted orthodromically (Ortho) and antidromically (Anti). The antidromic wavefront of the pacing impulse (X) collides with the previous beat, in this case the circulating wavefront of the spontaneous AFL (f), which results in an atrial fusion beat and, in effect, terminates the AFL. However, the orthodromic wavefront from the pacing impulse (X) continues the tachycardia and resets it to the pacing rate. Right: Introduction of the next pacing impulse (X + 1) during rapid pacing from the same high atrial site. The large arrow again indicates the entry of the pacing impulse into reentrant circuit, whereupon it is conducted orthodromically and antidromically. Once again, the antidromic wavefront from the pacing impulse (X + 1) collides with the orthodromic wavefront of the previous beat. In this case, it is the orthodromic wavefront of the previous paced beat (X), and an atrial fusion beat results. The orthodromic wavefront from the pacing impulse (X + 1) continues the tachycardia and resets it to the pacing rate. In all three parts, arrows indicate the direction of spread of the impulses; the serpentine line indicates slow conduction through a presumed area of slow conduction (stippled region) in the reentrant circuit, and the dots with tails indicate bipolar electrodes at the high atrial pacing site, the poster inferior portion of the left atrium (PLA), and another atrial site. (Reproduced with permission from Waldo AL: Atrial flutter. Entrainment characteristics. J Cardiovasc Electrophysiol 1997;8:337-352.)*

supraventricular tachycardia; or the dose of edrophonium to do the same; or the doses of the multiple digitalis preparations, including digitalis leaf, digitoxin, acetyl strophanthidin, cedilanid, as well as digoxin; or the escalating doses of quinidine to terminate AF; and so on.

It has been an exhilarating ride, but it is not over, not with 450,000 sudden cardiac deaths annually and inadequate screening approaches, and not with new antiarrhythmic drugs that are made to block a single ion channel. There exists incredible heterogeneity in the *normal* heart, never mind the *diseased* one, making it unlikely that drugs with such focused actions will *uniformly* affect the electrophysiologically diverse substrate and prevent an arrhythmia. We have searched in vain for Jason's Golden Fleece,[26] to be able to wed the tachycardia's mechanism to the drug's action. Despite the lack of success,[27] effective drugs would be preferable in many clinical circumstances, such as control of AF. Until that time, however, nonpharmacologic approaches continue to gain favor.

So there is much left to do. In the keynote address that I gave at the first NASPE scientific sessions in Houston, Texas, on March 13, 1980, I said that, ". . .with the growth of pacing, it is likely, in the not too distant future, that the pacing field will become a well-recognized subspecialty."[28] That and more have been achieved, but to paraphrase Robert Frost, we have miles to go before we sleep.

References

1. Hoffman BF: Cardiac arrhythmias: What do we need to know about basic mechanisms? J Cardiovasc Electrophysiol 1999;10:414-416.
2. Satoh T, Zipes DP: Cesium-induced atrial tachycardia degenerating into atrial fibrillation. Atrial torsades de pointes? J Cardiovasc Electrophysiol 1998;9:970-975.
3. Anderson ME: Calmodulin and the philosopher's stone: Changing Ca^{2+} into arrhythmias. J Cardiovasc Electrophysiol 2002;13:195-197.
4. Schwartz PJ, Priori SG: Long QT syndrome: Genotype-phenotype correlations. In Zipes DP, Jalife J, eds: *Cardiac Electrophysiology: From Cell to Bedside*. Fourth Edition. (In press).
5. Moss A: Long QT syndrome: Therapeutic considerations. In Zipes DP, Jalife J, eds: *Cardiac Electrophysiology: From Cell to Bedside*. Fourth Edition. (In press).
6. El-Sherif N: Mechanism of ventricular arrhythmias in the long QT syndrome: On hermeneutics. J Cardiovasc Electrophysiol 2001;12:973-976.
7. Burashnikov A, Antzelevitch C: Prominent I(Ks) in epicardium and endocardium contributes to development of transmural dispersion of repolarization but protects against development of early afterdepolarizations. J Cardiovasc Electrophysiol 1997;8:337-352.
8. Chen YJ, Chen SA, Chen YC, Yeh HI, Chan P, Chang MS, Lin CI: Effects of rapid atrial pacing on the arrhythmogenic activity of single cardiomyocytes from pulmonary veins: Implication in initiation of atrial fibrillation. Circulation 2001;104:2849-2854.
9. Waldo AL: Atrial flutter: Entrainment characteristics. J Cardiovasc Electrophysiol 1997;8:357-352.
10. Soejima K, Stevenson WG, Maisel WH, Delacretaz E, Brunckhorst CB, Ellison KE, Friedman PL: The + 1 difference: A new measure for entrainment mapping. J Am Coll Cardiol 2001;37:1386-1394.
11. Allessie MA, Bonke FI, Schopman FJ: Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The "leading circle" concept: A new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ Res 1976;39:168-177.
12. Spach MS, Josephson ME: Initiating reentry: The role of nonuniform anisotropy in small circuits. J Cardiovasc Electrophysiol 1994;5:182-209.
13. Boersma L, Zetelaki Z, Brugada J, Allessie M: Polymorphic reentrant ventricular tachycardia in the isolated rabbit heart studied by high density mapping. Circulation 2002;105:2053-2061.
14. Jalife J: Rotors and spiral waves in atrial fibrillation. J Cardiovasc Electrophysiol 2003;14:776-780.
15. Nattel S: New ideas about atrial fibrillation 50 years on. Nature 2002;90:1173-1180.
16. Saoudi N, Cosio F, Waldo A, Chen SA, Iesaka Y, Lesh M, Saksena S, Salerno J, Schoels W: Classification of atrial flutter and regular atrial tachycardia according to electrophysiologic mechanism and anatomic bases: A statement from a joint expert group from the Working Group of Arrhythmias of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. J Cardiovasc Electrophysiol 2001;12:852-866.
17. Wu J, Zipes DP: Mechanisms underlying atrioventricular nodal conduction and the reentrant circuit of atrioventricular nodal reentrant tachycardia using optical mapping. J Cardiovasc Electrophysiol 2002;13:831-834.
18. Rubart M, Lopshire JC, Fineberg NS, Zipes DP: Changes in left ventricular repolarization and ion channel currents following a transient rate increase superimposed on bradycardia in anesthetized dogs. J Cardiovasc Electrophysiol 2000;11:652-664.
19. Weiss JN, Chen PS, Qu Z, Karagueuzian HS, Lin SF, Garfinkel A: Electrical restitution and cardiac fibrillation. J Cardiovasc Electrophysiol 2002;13:292-295.
20. Zipes DP, Fischer J, King RM, Nicoll A deB, Jolly WW: Termination of ventricular fibrillation in dogs by depolarizing a critical amount of myocardium. Am J Cardiol 1975;36:37-44.
21. Kim YH, Garfinkel A, Ikeda T, Wu TJ, Athill CA, Weiss JN, Karagueuzian HS, Chen PS: Spatiotemporal complexity of ventricular fibrillation revealed by tissue mass reduction in isolated swine right ventricle. Further evidence for the quasiperiodic route to chaos hypothesis. J Clin Invest 1997;100:2486-2500.
22. Wu TJ, Yashima M, Doshi R, Kim YH, Athill CA, Ong JJ, Czer L, Tento A, Blanche C, Kass RM, Garfinkel A, Weiss JN, Fishbein MC, Karagueuzian HS, Chen PS: Relation between cellular repolarization characteristics and critical mass for human ventricular fibrillation. J Cardiovasc Electrophysiol 1999;10:1077-1086.
23. Page PL: Surgery for cardiac arrhythmias. In Zipes DP, Jalife J, eds: *Cardiac Electrophysiology: From Cell to Bedside*. Fourth Edition. (In press).
24. Chattipakorn N, Fontuhi PC, Zheng X, Ideker RE: Left ventricular apex ablation decreases the upper limit of vulnerability. Circulation 2000;101:2458-2460.
25. Antzelevitch C: The Brugada syndrome: Ionic basis and arrhythmia mechanisms. J Cardiovasc Electrophysiol 2001;12:268-271.
26. Zipes DP: A century of cardiac arrhythmias: In search of Jason's Golden Fleece. J Am Coll Cardiol 1999;34:959-965.
27. Sicilian Gambit. The search for novel antiarrhythmic strategies. Eur Heart J 1998;19:1178-1196; Jpn Circ J 1998;62:633-648.
28. Zipes DP: Pacing 1980. Keynote address for the first meeting of the North American Society for Pacing and Electrophysiology. Pacing Clin Electrophysiol 1981;4:182-192.