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PLENARY LECTURE

Cardiac Electrophysiology: Promises and Contributions

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Introduction

Patient J.D. is a 53 year old man who was recovering uneventfully in a coronary care unit 5 days after having an acute inferior myocardial infarction. Fifteen *seconds* after being told that his mother died, J.D. developed ventricular fibrillation (Fig. 1).

In this presentation, I discuss concepts that relate to the onset of ventricular tachyarrhythmia in patients like J.D. I do this by reviewing some of the clinically relevant contributions made by cardiac electrophysiology and the promises that the future offers in understanding and treating patients with cardiac arrhythmias. Selected aspects of four areas will be discussed: pathogenesis, treatment, prognosis and future directions.

Pathogenesis of Cardiac Arrhythmias

Mechanisms responsible for cardiac arrhythmias are generally divided into three major categories: disorders of impulse formation, disorders of impulse conduction and combinations of both causes (Table 1) (1–5). The classification is limited and contains some inconsistencies. For example, reentry is not actually a mechanism, but rather is a pathway traveled by the cardiac impulse. The mechanism is really a circus movement of excitation (2). Abnormalities in cell to cell coupling and excitability (6), effects of anisotrophy (7) and other factors are lumped under single, simple headings. Nevertheless, it serves as a useful framework in which to discuss arrhythmogenesis.

Disorders of Impulse Formation

Automaticity, triggered activity and afterdepolarizations. Normal automaticity relates to the normal diastolic depolarization of pacemakers found in the normal sinus node, Purkinje fibers and some other areas in the heart. Abnormal automaticity may occur in many of these fibers subjected to the effects of ischemia, drugs or other interventions. Both normal and abnormal forms of automaticity can generate arrhythmias (1–5,8).

Triggered activity. This concept has been emphasized recently (3), though it is not new (9). It refers to a transient membrane oscillation triggered by cardiac depolarization. When this oscillation occurs early, before repolarization is completed, it is called an early afterdepolarization; when it occurs late, after repolarization is completed, it is called a delayed afterdepolarization (3). Slow heart rates generally increase the amplitude of early afterdepolarizations, whereas fast heart rates, within limits, increase the amplitude of delayed afterdepolarizations. In this example of a transmembrane cardiac action potential recording (Fig. 2), depolarization during the upstroke of the cardiac action potential (arrow) corresponds to the QRS complex in the scalar electrocardiogram (ECG) (10). During repolarization, when the T wave would be present, additional depolarizations occur (arrowheads). These early afterdepolarizations, produced in this example by superfusing an isolated Purkinje fiber with cesium, can prolong repolarization (lengthen the QT interval in the scalar ECG) and can give rise to premature complexes or tachycardia (Table 1) (11–14).

Afterdepolarizations. Early afterdepolarizations result from a reduced repolarizing current in comparison with the depolarizing current. This may be caused by a reduced outward current, an increased inward current or both (3). Because interventions that act through different mechanisms can abolish early afterdepolarizations (such as the calcium channel blockers, verapamil, D-600 and nitrendipine [15]; the sodium channel blockers like tetrodotoxin and lidocaine [16] and increasing rate or increasing external potassium [K^+]) and because a variety of substances can induce early afterdepolarizations (such as quinidine [16] and related drugs [3], a sea anemone polypeptide [17], calcium current agonists [18], acidosis [19], low extracellular K^+ concentration [20], hypoxia and catecholamines), a diversity of currents have been suggested as causes. These include a calcium current through L-type calcium channels (18), the sodium "window" or slowly inactivating current (21), sodium channel exchange mechanisms (22), the transient inward current

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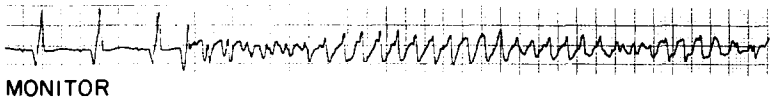


Figure 1. Monitor recording from patient J.D., showing the onset of ventricular fibrillation.

activated by elevated intracellular calcium (23) intracellular potassium accumulation (21) and the I_{x1} current (24).

Cesium blocks inward-rectifying potassium currents and delays repolarization (25). However, the ionic basis of cesium-induced early afterdepolarizations is still unclear. Some early afterdepolarizations may be due to electrotonic membrane events (11). A calcium current through L-type calcium channels may be involved (18,26). Cesium produces early afterdepolarizations in canine cardiac Purkinje fibers (10,12) and in the intact heart (10,11). The latter exhibits similarities to both the acquired and the idiopathic (congenital) long QT syndromes (see below). Magnesium suppresses these early afterdepolarizations and associated ventricular tachyarrhythmias (10,27), possibly by blocking the calcium current (28), whereas ansae subclaviae stimulation and norepinephrine infusion stimulates them.

Alpha-1 adrenoceptor stimulation, by provoking intracellular calcium accumulation, has been implicated in the genesis of ventricular arrhythmias associated with ischemia (29). Alpha-1 adrenoceptor stimulation has also been shown

Table 1. Mechanisms of Arrhythmogenesis

I. Disorders of impulse formation
  A. Automaticity
    1. Normal automaticity
      a. Experimental examples—normal in vivo or in vitro sinus node, Purkinje fibers, others
      b. Clinical examples—sinus tachycardia or bradycardia inappropriate for the clinical situation, possibly ventricular parasystole
    2. Abnormal automaticity
      a. Experimental example—depolarization-induced automaticity in Purkinje fibers or ventricular muscle
      b.Clinical example—possibly accelerated ventricular rhythms after myocardial infarction
  B. Triggered activity
    1. Early afterdepolarizations (EADs)
      a. Experimental example—EADs produced by barium, hypoxia, high concentrations of catecholamines, drugs such as sotalol, N-acetylprocainamide, cesium
      b. Clinical examples—possibly acquired long QT syndrome and associated ventricular arrhythmias
    2. Delayed afterdepolarizations (DADs)
      a. Experimental example—DADs produced in Purkinje fibers by digitalis
      b. Clinical example—possibly some digitalis-induced arrhythmias
II. Disorders of impulse conduction
  A. Block
    1. Bidirectional or unidirectional without reentry
      a. Experimental example—SA node, AV node, bundle branch, Purkinje muscle, others
      b. Clinical example—SA node, AV node bundle branch, others
    2. Unidirectional block with reentry
      a. Experimental examples—AV node, Purkinje muscle junction, infarcted myocardium, others
      b. Clinical examples—reciprocating tachycardia in WPW syndrome, AV nodal reentry, VT due to bundle branch reentry, others
    3. Reflection
      a. Experimental example—Purkinje fiber with area of inexcitability
      b. Clinical example—unknown
III. Combined disorders
  A. Interactions between autonomic foci
    1. Experimental examples—depolarizing or hyperpolarizing subthreshold stimuli speed or slow automatic discharge rate
    2. Clinical example—modulated parasystole
  B. Interactions between automaticity and conduction
    1. Experimental examples—deceleration-dependent block, overdrive suppression of conduction, entrance and exit block
    2. Clinical examples—similar to experimental examples

AV = atrioventricular; SA = sinoatrial; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White syndrome. Reproduced with permission from Zipes (176).

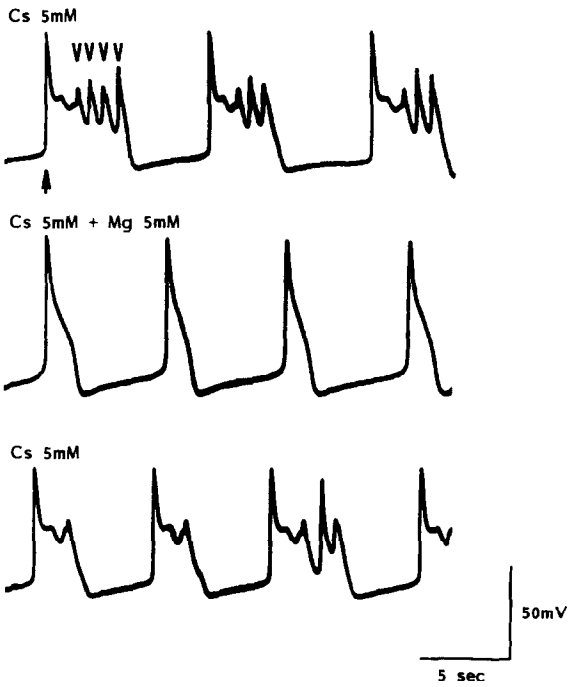


Figure 2. Transmembrane potential recordings showing the effect of magnesium chloride on early afterdepolarizations induced by cesium in a spontaneously discharging canine cardiac Purkinje fiber. **Top,** Several repetitive early afterdepolarizations were induced by 5 m*M* cesium (Cs) in 2.7 potassium chloride Tyrode's solution. **Middle,** Five minutes after superfusion with 5 m*M* magnesium chloride added to the cesium-low potassium Tyrode's solution, early afterdepolarizations were abolished. **Bottom,** Four minutes after washout of magnesium chloride and resumption of superfusion with cesium-low potassium Tyrode's solution, early afterdepolarizations recurred. Reproduced with permission from the American Heart Association, Inc. (10).

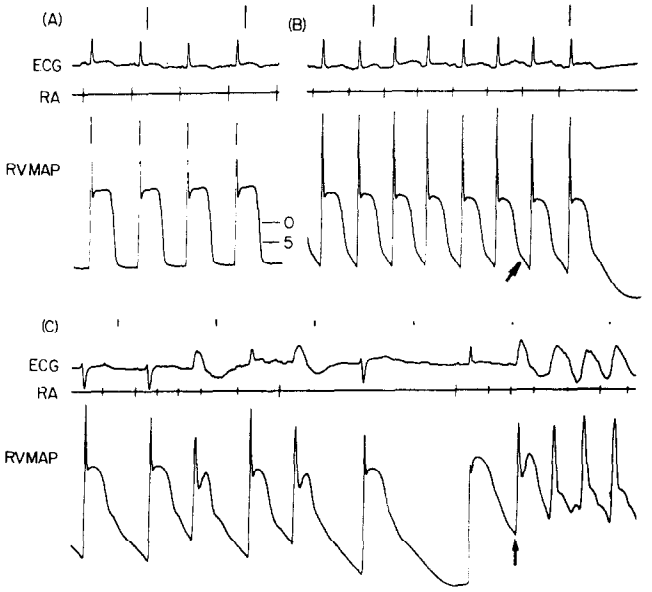


Figure 3. Recording of monophasic action potential from the right ventricle (RVMAP) along with electrocardiographic (ECG) lead II and right atrial electrogram (RA). **Panel A,** Control. No early afterdepolarization present. **Panel B,** Immediately after administration of cesium (intravenously). Early afterdepolarization is indicated by the **arrow**. **Panel C,** After continued administration of cesium, premature ventricular complexes and ventricular tachycardia result. Note the large early afterdepolarization occurring after a pause in the cycle (**arrow**).

to produce delayed afterdepolarizations in Purkinje fibers removed from cats with previous myocardial infarction, but not in normal feline Purkinje fibers unless the extracellular calcium concentration is raised (30). Alpha-1 adrenoceptor stimulation leads to an increase in cytosolic free calcium (31), which could increase the net inward current. This would magnify the amplitude of early afterdepolarizations and exacerbate the prevalence of ventricular tachyarrhythmias related to them. Alpha-1 adrenoceptor blockade might be expected to exert opposite effects (32).

Long QT syndromes. Just as the Wolff-Parkinson-White syndrome serves the clinical electrophysiologist as the Rosetta stone of reentry, so may the long QT syndrome be the Rosetta stone for an entirely different class of arrhythmias. In patients with acquired and idiopathic (congenital) long QT syndromes (33,34), early afterdepolarizations may be responsible for the prolonged repolarization and the associated ventricular arrhythmias such as torsade de pointes (14,35). The example illustrated in Figure 3 was recorded in an intact dog with use of a special catheter electrode that produces a monophasic action potential (36) resembling the intracellular recording in Figure 2. Early afterdepolarizations (Fig. 3, arrow) develop shortly after cesium injection. Early afterdepolarizations can occur at a reduced (Fig. 2) or a more negative (Fig. 3) membrane potential. When sufficient cesium is administered, ventricular tachyarrhythmias similar to torsade de pointes result. Note the long-short cycle length in Figure 3 before the onset of the ventricular tachycardia (Fig. 4). Magnesium has been reported to suppress torsade de pointes in patients with the acquired long QT syndrome due to quinidine and other antiarrhythmic agents (37). It also suppresses cesium-induced early afterdepolarizations (Fig. 2) (10,27) and ventricular tachyarrhythmias in the dog (10).

Idiopathic long QT syndrome: role of left stellate stimulation. In patients with the idiopathic long QT syndrome, left stellate stimulation, possibly due to sympathetic imbalance, has been postulated as a possible cause of ventricular arrhythmias (38). This animal model produced by cesium administration simulated many aspects of the acquired and idiopathic long QT syndromes and provided the opportunity to test this hypothesis. We found that dogs treated with cesium had larger amplitude early afterdepolarizations and a greater prevalence of ventricular tachycardia during left stellate stimulation compared with right stellate stimulation (Fig. 5) (39). Left sympathetic stimulation may be arrhyth-

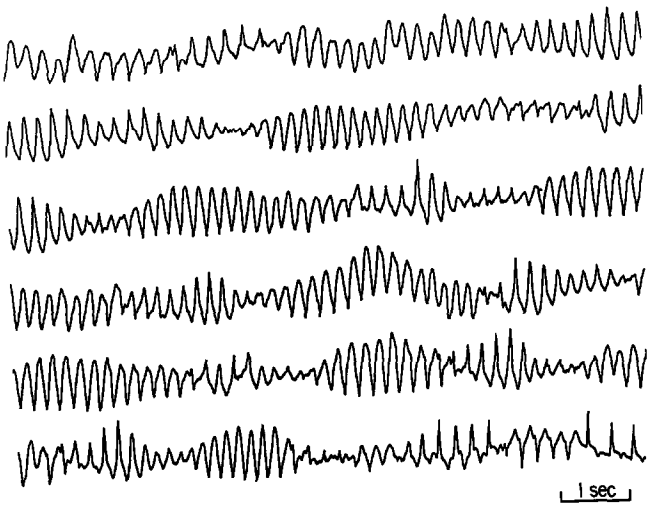


Figure 4. Polymorphic ventricular tachycardia resembling torsade de pointes. The ventricular tachycardia shown during its onset in Figure 3 continues as polymorphic ventricular tachycardia resembling torsade de pointes. Finally, it terminates at the end of the continuous recording of electrocardiographic lead II. Reproduced with permission from the American Heart Association, Inc. (175).

mogenic because it exerts a quantitatively greater adrenergic influence on the ventricles, particularly the left ventricle, than does the right stellate ganglion. We postulate that left sympathetic stimulation, which results in a larger ventricular mass being affected by more norepinephrine being released, rather than qualitative differences between the stellate ganglia or right-left stellate imbalance, may be the basis for the arrhythmogenic potential of the left stellate ganglion. It also may account for the beneficial effects of surgical interruption of the left stellate ganglion.

One can hypothesize that patients with the idiopathic long QT syndrome have a primary *myocardial membrane defect* manifested during repolarization (for example, involving an outward repolarizing potassium current or an inward calcium current) that creates early afterdepolarizations and the long QT interval. Autonomic imbalance is not necessary. Sympathetic stimulation, primarily left, could periodically increase the amplitude of the early afterdepolarizations to reach threshold and produce ventricular tachyarrhythmias. The fact that left stellate ganglion interruption reduces the incidence of syncope and sudden death in some patients with the idiopathic long QT syndrome in whom beta-adrenoceptor blocking drugs are ineffective (40) underscores the potential importance of alpha-adrenoceptor stimulation of early afterdepolarizations (32). In patients with the long QT syndrome after surgery, the long QT interval generally does not shorten, although ventricular tachyarrhythmias cease, possibly because early afterdepolarizations are still present, though subthreshold. Left stellate ganglion interruption has also been shown to reduce sudden death in patients after anterior myocardial infarction (41) and, thus, its stimulation may be arrhythmogenic during ischemia in patients like J.D. (Fig. 1).

Causes of delayed afterdepolarizations. Delayed afterdepolarizations have been reported (42–44) experimentally in

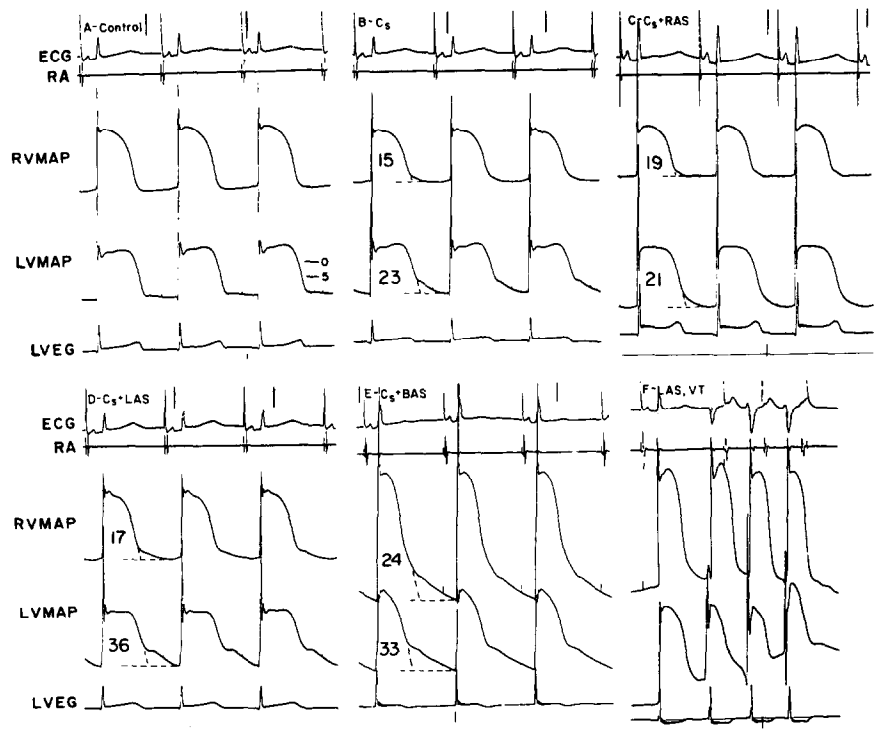


Figure 5. Differential response of early afterdepolarizations during each intervention in the same dog. **Panel A** was recorded during control; no early afterdepolarizations or any voltage deflections exist during phase 3 or 4. One minute after cesium injection, **panels B, C, D and E** were recorded during cesium alone (**panel B**) or with right (RAS) (**panel C**), left (LAS) (**panel D**) and bilateral (BAS) (**panel E**) ansae subclaviae stimulation. The numbers within the monophasic action potential (MAP) recordings represent the early afterdepolarization amplitude as a percentage of the monophasic action potential amplitude. **Panel F** shows the effect of left stellate stimulation (LAS) on the same dog 25 s after **panel D** was recorded; after an atrial paced beat, a short run of nonsustained ventricular tachycardia (VT) occurred. Note the decreased amplitude of the early afterdepolarization in the right ventricle (RV) compared with the high take-off potential of the early afterdepolarization in the left ventricle (LV), initiating the ventricular tachycardia. LVMAP = left ventricular monophasic action potential recording; −0, −5 indicate 0 to 5 mV. LVEG = left ventricular electrogram; other abbreviations as in Figure 3. Reproduced with permission of the American Heart Association, Inc. (39).

several settings, such as in digitalis-treated hearts, during catecholamine stimulation of the coronary sinus, sympathetic neural stimulation and 24 h after myocardial infarction in dogs (Table 1). Digitalis poisons sodium-potassium adenosine triphosphate, which leads to an increase in intracellular sodium that then exchanges for calcium. The elevated intracellular calcium concentration causes more calcium to be released from the sarcoplasmic reticulum (calcium-initiated calcium release), which triggers a transient inward current carried by sodium that causes the delayed afterdepolarizations (45). Delayed afterdepolarizations may be responsible for some of the clinical arrhythmias that are found in situations resembling the experimental conditions in which they have been produced (for example, arrhythmias due to digitalis or occurring after myocardial infarction). Delayed afterdepolarizations could be recorded in endocardium resected from a patient with recurrent episodes of ventricular tachycardia due to coronary artery disease (Fig. 6) (46). In this example, during initial electrical stimulation (filled circles), the preparation developed a gradual increase in the amplitude of the delayed afterdepolarizations (arrows). The depolarization phase of the action potential is not clearly seen because of the rapid upstroke, whereas repolarization is obvious. After cessation of stimulation (last filled circle), a large delayed afterdepolarization results and triggers the sustained short run of spontaneous action potentials, probably comparable with ventricular tachycardia in an intact heart. A subthreshold delayed afterdepolarization (arrow) terminates the burst. Accelerated atrioventricular (AV) junctional escape complexes may be due to delayed afterdepolarizations (47).

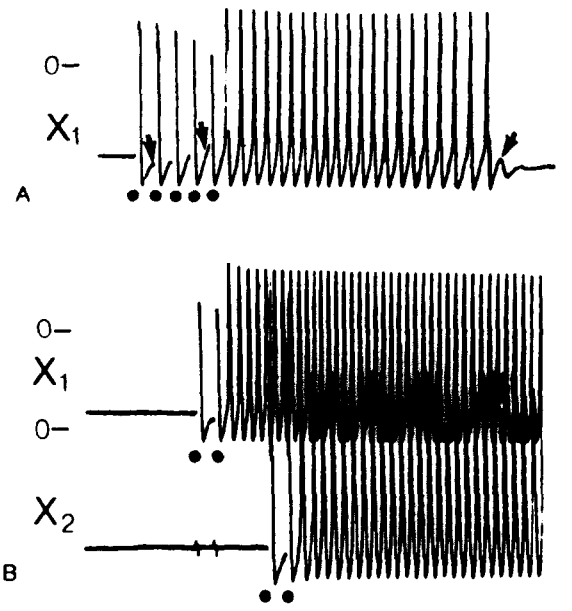


Figure 6. Triggered sustained rhythmic activity and delayed afterdepolarizations in diseased human ventricle. **A,** Spontaneous activity triggered by a series of driven action potentials (**dots**) at recording site X_1. Note the gradual increase in the size of the delayed afterdepolarizations (**arrows**) until the afterdepolarization reaches threshold and maintains sustained rhythmic activity after cessation of pacing. The sustained rhythmic activity finally terminates when the last afterdepolarization fails to reach threshold (**third arrow**). **B,** Initiation of triggered activity by intracellular current injection (**dots** beneath the respective action potential recordings) at sites X_1 and X_2, which lie along the same trabeculum. 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, indicating complete dissociation between these two sites. For current pulses, cycle length = 2,000 ms; pulse duration = 10 ms; pulse intensity = 200 na. Vertical calibration: 50 mV; horizontal calibration: 10 s. Reproduced with permission from Gilmour et al. (46).

Disorders of Impulse Conduction

Reentrant tachyarrhythmias. The presence of unidirectional block is the basis for reentry and has been demonstrated experimentally in many preparations, including AV nodel tissue, ischemic/infarcted ventricular muscle, the bundle branches (49), Purkinje-muscle junctions and at other cardiac sites (49–52). Determinants of conduction patterns that produce reentry are multiple and complex, including changes in cellular excitability and cell to cell coupling (6), anisotropic propagation (7) and rate of rise of action potential depolarization. Calcium concentration (53), pH (54) and autonomic influences (55) affect cell to cell coupling, which in turn modulates conduction.

Reentry can occur over anatomically or functionally defined pathways and is basically of three types: 1) reentrant circuits created by separate anatomic pathways, such as in the Wolff-Parkinson-White syndrome (56,57); 2) functionally determined reentrant circuits without an anatomic obstacle (leading circle reentry), such as in some forms of intraatrial reentry (51); and 3) anisotropic reentry, recently described in ventricular muscle (58). Anisotropic reentry is also functional and is dependent on myocardial geometry. Conduction of the cardiac impulse on a microscopic level is discontinuous as a result of recurrent changes in resistance to propagation. Conduction is several times faster in a directional parallel to the long axis of the fiber compared with a transverse direction because of better cell to cell coupling longitudinally (7). However, the safety factor for conduction is lower in a longitudinal compared with a transverse direction (that is, conduction block occurring after premature stimulation is more likely to occur longitudinally than transversely). Slow transverse activation can provide the necessary time for recovery of excitability in previously blocked fibers to permit reentry (58). Anistropy can be uniform (when fibers are all parallel to each other) or nonuniform (when barriers such as nonconductile connective tissue are interposed). Nonuniform anisotropy might be particularly conducive to the development of reentry because of inhomogeneous activation.

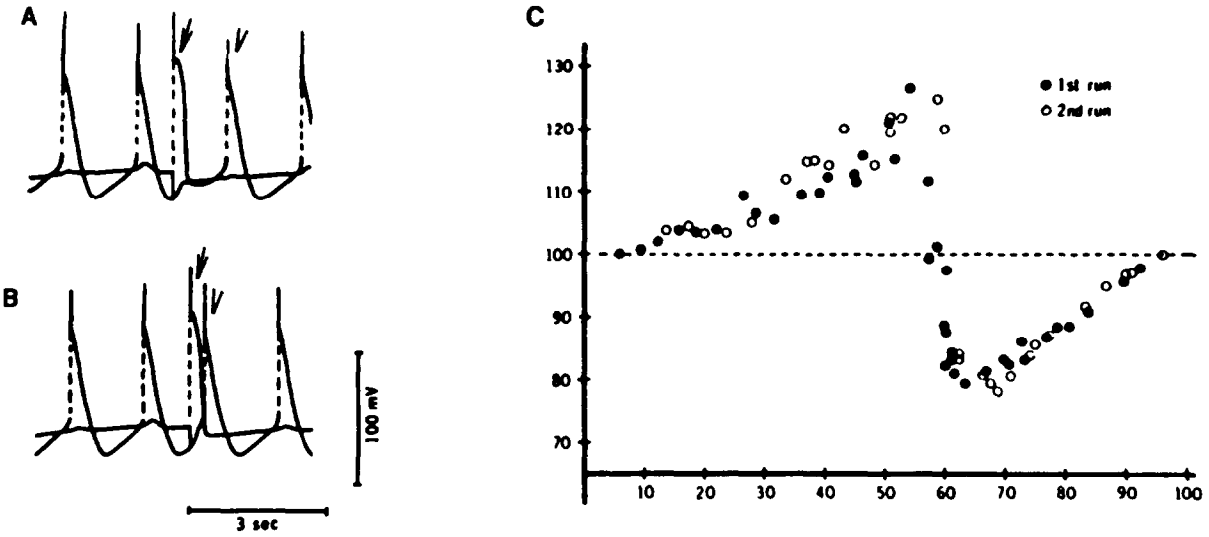


Figure 7. Phase-dependent acceleration and delay of Purkinje fiber automaticity induced by subthreshold depolarizations. The Purkinje fiber was separated into two segments by an inexcitable segment so that stimulation of one side produced action potentials that blocked at the inexcitable middle segment. However, the middle segment acted as a conduit for passive flow of current from right and left segments. Thus, action potentials in one (right) segment generated an electrotonic potential that produced subthreshold depolarizations in the other (left) segment. **A,** Action potentials were recorded from the right (**upper recording**) and left (**lower recording**) segments of the fiber. The control spontaneous cycle length of the left segment was 1,500 ms. Stimulation of the right segment of the fiber (**arrow**) 800 ms after the left segment had discharged spontaneously produced a subthreshold depolarization in the left segment and prolonged the cycle length of the next spontaneous discharge (**arrowhead**) to 1,850 ms (a 23% increase). **B,** Stimulation of the right segment (**arrow**) 1,000 ms after the left had discharged spontaneously shortened the spontaneous cycle length (**arrowhead**) to 1,230 ms (an 18% decrease). **C,** Complete phase-response curves for the experiment shown in **A** and **B**. Two different runs are shown. **Ordinate**: Percent increase or decrease in the spontaneous cycle length of the left segment (control cycle length = 100%). **Abscissa**: percent of the control left segment spontaneous cycle length at which the cycle length was stimulated. The spontaneous cycle length was maximally prolonged (by 26%) or shortened (by 20%) by subthreshold depolarizations that entered the left segment after approximately 50 and 60% of the cycle had elapsed, respectively. Reproduced with permission from the American Heart Association (Jalife J, Moe GK. Circ Res 1976;39:801–12).

Reflection (50) is a form of reentry occurring in a one-dimensional structure. The impulse travels back and forth over the same pathway. Clinical arrhythmias due to reflection have not yet been definitely identified.

Most would agree that the tachyarrhythmia definitely due to reentry in humans is the AV reentrant tachycardia in patients with the Wolff-Parkinson-White syndrome (56). Interruption of this tachycardia by surgical dissection at widely separated points in the reentrant loop (that is, at the AV node-His bundle or the accessory pathway) provides compelling evidence to support a reentrant mechanism. Similarly, clinical and laboratory data (57) point to AV node reentrant tachycardia as the tachycardia next most likely to be due to reentry. Although many, if not most, atrial and ventricular tachycardias (58), flutter and fibrillation are due to reentry, normal or abnormal forms of automaticity or triggered activity may also be responsible. Therefore, one cannot generalize about the mechanism responsible for an entire group of arrhythmias such as ventricular tachycardia.

Reentry and mechanisms of clinical arrhythmias. At times, both reentrant and nonreentrant mechanisms may operate simultaneously, as shown recently (59) in the cat heart after coronary occlusion. Studies based on entrainment criteria (60), analysis of sites of slow conduction and the abolition of tachycardia by relatively discrete ablative shocks (61) offer strong but circumstantial evidence for reentry as a cause of many clinical arrhythmias. Conclusions about mechanisms of arrhythmias derived from interpretations of the scalar ECG or even from intracardiac catheter electrode recordings, response of the arrhythmia to drugs assumed to exert selective actions on automaticity or conduction and to electrical stimulation must be made cautiously. When one is investigating an arrhythmia originating in a small reentrant island lost in a large sea of myocardium, accurate charting becomes very difficult.

Combined Disorders of Impulse Formation and Conduction

Parasystole. The last category of mechanisms deals with interactions between automatic foci and conduction. On the basis of experimental and clinical data, an arrhythmia explained by such interactions is modulated parasystole. Jalife and Michaels (62) have developed phase-response curves for

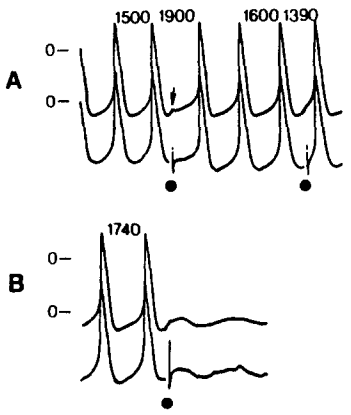


Figure 8. Modulation of pacemaker activity by subthreshold current pulses in diseased human ventricle. **A,** Two recording sites along the same trabeculum in a spontaneously active preparation. Intervals are in milliseconds. Injection of a subthreshold current pulse through the lower microelectrode (**dot**) early in the spontaneous cycle (about 680 ms after initiation of the rapid portion of the preceding action potential upstroke) produced a subthreshold depolarization in the upper recording (**arrow**) and delayed the next spontaneous discharge by 400 to 1,900 ms. This response would fall in the first half of the curve indicated in Figure 7. A current pulse delivered later in the spontaneous cycle (950 ms after the preceding upstroke) accelerated the next discharge by 210 to 1,390 ms, relative to the previous two action potentials. The response to this current injection falls in the second half of the graph depicted in Figure 7. **B,** A stimulus (**dot**) at a precise interval in the cardiac cycle (called the singular point [in this example, 930 ms after the preceding action potential upstroke]) abolished pacemaker activity. Reproduced with permission from the *American Journal of Cardiology* (46).

such parasystolic pacemakers (Fig. 7), which can be applied to automatic activity in human ventricular myocardium (Fig. 8) and to clinical examples of parasystole (Fig. 9). Classically, parasystole has been likened to the function of a fixed rate, asynchronously discharging pacemaker; its timing is not altered by the dominant rhythm, it produces depolarization when the myocardium is excitable and the intervals between discharges are multiples of a basic interval. Complete entrance block, constant or intermittent, insulates and protects the parasystolic focus from surrounding electrical events and accounts for such behavior. Occasionally, the focus may exhibit exit block, during which it may fail to depolarize excitable myocardium.

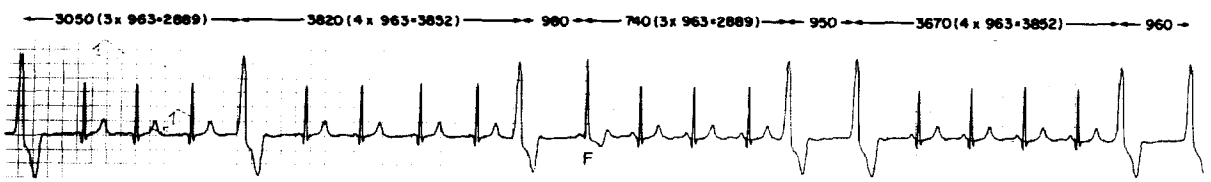
Figure 9. Ventricular parasystole. Measured intervals between premature ventricular complexes (indicated in milliseconds). Numbers in parentheses indicate multiples of a basic cycle length determined as the mean interval between parasystolic discharges. F = fusion beat.

Data from recent experiments (62) indicate that these "rules" should be modified. The discharge rate of an isolated "protected" focus can be modulated by electrotonic interactions with the dominant rhythm across an area of depressed excitability, so that the dominant cardiac rhythm (usually sinus) may speed or slow the parasystolic discharge rate (63,64). Brief subthreshold depolarizations induced during the first half of the cardiac cycle of a spontaneously discharging pacemaker *delay* the subsequent discharge, while similar depolarizations induced in the second half of the cardiac cycle *accelerate* it (Fig. 7 to 10). Fixed coupling may be produced, and its presence does not exclude a parasystolic mechanism. From these studies, it may be inferred that premature ventricular complexes due to parasystolic discharge are probably more common than previously thought.

Modulating Influences

All of these electrical events are modulated by a variety of other factors, such as the autonomic nervous system, hemodynamics and blood flow, chamber geometry and wall motion changes (65–68) and effects of ischemia. The latter may alter regional myocardial pH, partial pressure of oxygen (Po_2) and potassium concentrations, and cause the development of lysophosphatides, oxygen free radicals and other metabolites that influence electrophysiologic properties. In this presentation, I will consider interactions between ischemia and the autonomic nervous system.

Ischemia and the autonomic nervous system. Although it is clear that the autonomic nervous system influences the development of cardiac arrhythmias in the ischemic and nonischemic heart, knowledge of the mechanisms by which this occurs is still evolving. Myocardial ischemia initiates both efferent and afferent autonomic activity that may become excessive early after myocardial infarction (69,70). Afferent activation may result from excitation of sensory mechanoreceptors or chemoreceptors, or both, located in the ventricular wall. Inferior myocardial ischemia/infarction is more prone to activate vagal afferents compared with anterior myocardial ischemia, which more commonly produces an enhanced adrenergic state (71,72). Sinus tachycardia and hypertension after anterior myocardial infarction and



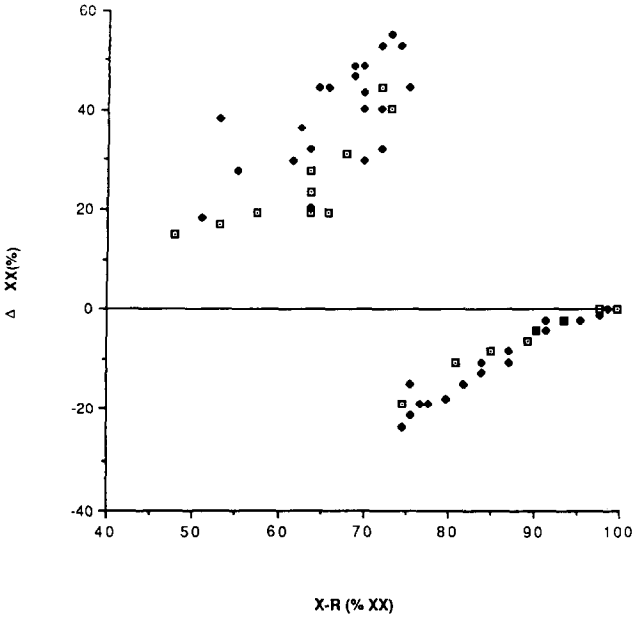


Figure 10. Graph of the electrocardiogram in Figure 9 shows modulated cycle length changes (Δ XX) expressed as a percent of the pure parasystolic cycle (XX), as a function of the interval between the last X discharge and the intervening beat of sinus origin (X-R) and in terms of percent XX. **Open symbols** show data measured during sequences X-R-R-X. **Closed symbols** show data measured when two X discharges were separated by three or more R responses (that is, X-R-R-R... X). XX represents the mean of all pure parasystolic cycles.

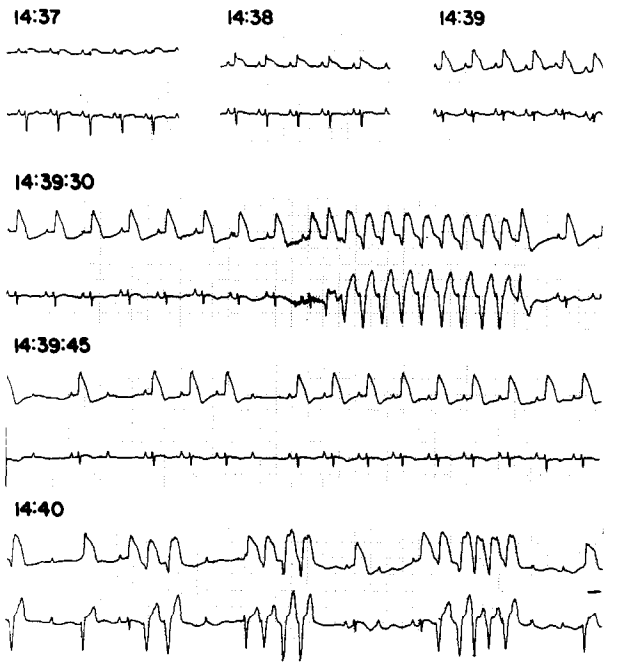


Figure 11. Long-term electrocardiographic recording in a patient with atypical angina. The top channel reflects an inferior lead; the bottom channel records an anterior lead. Note progressive ST segment elevation in the inferior lead, eventually resembling a monophasic action potential (**top tracing**). Bursts of nonsustained ventricular tachycardia result (**second tracing**). Then, sinus slowing and Wenckebach atrioventricular block occur, probably from a vasodepressor reflex response elicited by ischemia of the inferior myocardial wall (**third tracing**). In the **bottom tracing**, both atrioventricular block and ventricular arrhythmias are apparent. Numbers indicate time (for example, 2:37 pm). Reproduced with permission from Zipes (176).

sinus bradycardia or AV node block and hypotension after an inferior myocardial infarction are well recognized clinical states (Fig. 11).

Sympathetic stimulation. A large body of experimental evidence (73,74) suggests that stimulation of cardiac sympathetic nerves during myocardial ischemia enhances the development of ventricular arrhythmias, while surgical interruption or pharmacologic blockade of efferent sympathetic response is antiarrhythmic in most models. Although the antiarrhythmic effectiveness of beta-adrenoceptor blockade has been established in animals and patients (75), experimental data (29,76,77) suggest that alpha-1 adrenoceptor blockade also produces important antiarrhythmic effects during both coronary occlusion and reperfusion.

Vagal stimulation. In general, vagal tone is antiarrhythmic for both supraventricular and ventricular arrhythmias (73) due to direct electrophysiologic actions on the heart and indirect effects that antagonize sympathetic actions and slow the heart rate. Rarely does excessive vagal stimulation provoke arrhythmias. Atropine may be arrhythmogenic during acute myocardial ischemia, at least in part as a result of an excessive increase in heart rate.

Autonomic modulation of arrhythmia development can be mediated by multiple processes, including direct electrophysiologic actions on impulse formation or conduction, or both, effects on infarct size and ischemic metabolism, coronary blood flow, platelet clumping, free radial formation and other actions (74). Very likely, antiarrhythmic and arrhythmogenic autonomic effects compete. For example, sympathetic stimulation might be antiarrhythmic by improving contractility and coronary flow in a failing heart, but the increases in myocardial oxygen demand may cause some cardiac arrhythmias (78).

Some relevant ischemic animal models. Several interesting models establishing the importance of autonomic-ischemic interactions have been investigated. Skinner et al. (79) showed that awake pigs psychologically stressed by being unacclimatized to the research laboratory developed ventricular fibrillation more often and with less latency after coronary occlusion than did pigs adapted to the laboratory before undergoing coronary occlusion. Cooling the frontothalamic brain tracts in the unacclimatized pigs prevented ventricular fibrillation. This finding, extrapolated to the clinical setting, naturally raises interesting speculations

about the arrhythmogenic actions of anxiety during acute myocardial ischemia/infarction, such as experienced by patient J.D.

In other studies, Schwartz et al. (80) demonstrated that reflex vagal responses predicted by tests of baroreflex sensitivity may protect exercising dogs against the development of ventricular fibrillation during acute myocardial ischemia superimposed on a subacute myocardial infarction. Dogs with less vagal responsiveness were more prone to fibrillation. Deconditioning could transfer dogs from the protected group to the unprotected group with fibrillation. Appropriate changes in the baroflex sensitivity slope also resulted. Conditioning exercises reversed the process. Preliminary studies (81) are underway to investigate the applicability of baroflex sensitivity tests in patients.

Recently, Verrier et al. (82) made the important observation that anger in dogs results in a sympathetically mediated obstruction of partially constricted coronary vessels, but also vasodilation of normal coronary arteries. The vasoconstriction can be so intense as to obstruct blood flow completely in the affected vessel. Importantly, the ischemic response occurred late, *after* the anger had subsided. Some ventricular arrhythmias occurred during the late ischemic response. Conceivably, platelet thrombi play a role in the development of coronary obstruction in this model (83). Such delayed changes may help explain the onset of late ventricular fibrillation in patients during the cool-down period *after* completion of a stress test. Vagal stimulation reduced vasoconstriction in dogs, perhaps as a result of a reduction in heart rate. Verrier and Lown (84) also reported that fear increases plasma epinephrine concentration and can result in ventricular arrhythmias that also can be annulled by increases in vagal tone.

Effect of ischemia/infarction on autonomic innervation of the myocardium. Despite the importance of these and other examples, however, significant gaps exit in understanding exactly how changes in autonomic action influence ischemic-related arrhythmias in the intact heart. This gap, at least in part, is explained by the generally overlooked concept that ischemia/infarction might *directly* alter autonomic innervation (that is, in addition to the afferent reflexes triggered by the ischemia and the induced efferent neural discharge, the area of ischemia/infarction may directly alter neural function). A parallel can be found in the ischemia-induced changes of cellular myocardial electrophysiologic properties. Loss of membrane potential, reduced conduction velocity and excitability and increased electrical resistance in myocardium subjected to ischemia are some of these well characterized alterations (85). However, much less is known about the effects of ischemia/infarction on autonomic nerves located in the ischemic region of the myocardium and, if changes in the nerves occur, what functional consequences they exert (86).

As an example, cats with healed myocardial infarction exhibit some myocardial areas with enhanced refractory period shortening during bilateral sympathetic stimulation, a form of supersensitivity (87). Alpha-1 (76) and beta-adrenoceptor (88) density may increase. One study (89) shows no change in beta-adrenoceptor density. Cardiac tissue subjected to ischemia may respond differently to autonomic impulses; for example, Purkinje fibers from infarcted hearts may develop delayed afterdepolarizations and triggered activity during alpha-adrenoceptor stimulation not seen in normal Purkinje fibers (44).

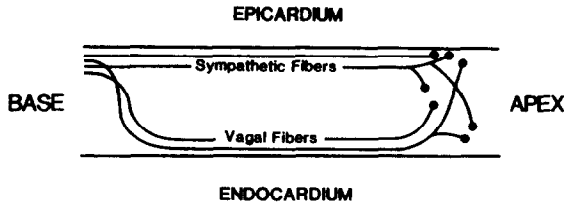


Figure 12. Schematic representation of the functional pathways of afferent and efferent sympathetic and vagal innervation to the ventricle. Impulses in afferent pathways travel apex-to-base, whereas impulses in efferent pathways travel base to apex. Filled circles indicate nerve endings. Reproduced with permission from Grune & Stratton, Inc. (177).

We have found (90–93) *that transmural myocardial infarction produces efferent sympathetic and vagal denervation in the area of the infarction and at noninfarcted sites apical (distal) to the infarction.* A subendocardial infarction that spares the epicardium does not interrupt sympathetic transmission, but does interrupt the vagal response because sympathetic fibers are located in the subepicardium and vagal fibers in the subendocardium (Fig. 12). Neural responsiveness becomes attenuated or lost within minutes after the onset of ischemia (93). The mechanism responsible for such early changes may relate to the cumulative effects of hyperkalemia, hypoxia, acidosis and other substances generated by the ischemic myocardium within which the nerves lie (94). After denervation, the myocardium may develop denervation supersensitivity (91) and subsequent reinnervation (Fig. 13) (95), and these changes may be responsible for some cardiac arrhythmias (92). Preliminary findings (96) obtained with imaging techniques suggest that similar denervation occurs in the ventricles of patients after myocardial infarction.

Although it is quite clear that ischemia may generate afferent cardiac reflexes, ischemia and infarction may also interrupt afferent reflexes within minutes of its onset (97,98). Transient ischemia may reversibly interrupt afferent reflexes (98), an observation that may have important clinical implications. Because afferent sympathetic fibers appear to mediate cardiac pain (99,100), interruption of afferent neurotransmission by ischemia could eliminate pain perception. Thus, painless ischemia or infarction might be explained by a type of transient (or permanent) "autodenervation" in-

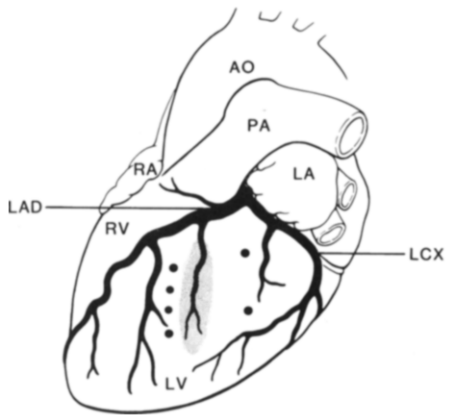


Figure 13. Schematic representation of a canine model of ischemic/infarction-induced autonomic denervation. Myocardial infarction is indicated by **finely stippled area**. Bipolar electrodes (**solid circles**) are positioned to measure changes in ventricular effective refractory period during neural stimulation in normally innervated regions above (basal to) and in denervated regions below (apical to) the infarction. AO = aorta; LCX = left circumflex coronary artery; LA = left atrium; LAD = left anterior descending coronary artery; LV = left ventricle; PA = pulmonary artery; RA = right atrium; RV = right ventricle. During testing of afferent reflexes, pieces of gauze soaked in bradykinin or nicotine are applied at the electrode sites shown.

duced by ischemia/infarction. After restoration of flow, normal neural function could return (98).

Therapy of Cardiac Arrhythmias

Therapy of cardiac arrhythmias can be divided into three major categories: pharmacologic, electrical and surgical.

Pharmacologic Therapy

Choice of drugs. Although many new antiarrhythmic drugs are now available and more are forthcoming (Table 2), with few exceptions the actions of most of the new agents resemble those of existing drugs such as quinidine and procainamide. This is because, in large part, we still do not understand how drugs suppress cardiac arrhythmias and, for this reason, there is a lack of innovative approaches to develop new drugs. At present, we determine the properties of antiarrhythmic drugs rather than their antiarrhythmic properties. Then, on the basis of of our understanding of the mechanisms responsible for cardiac arrhythmias, we predict cardiac responses and drug actions that we believe should be antiarrhythmic. Because drugs may be effective through a myriad of direct and indirect actions, it is difficult in the intact arrhythmic heart to determine antiarrhythmic mechanisms.

Despite the lengthy list of new antiarrhythmic agents (Table 2), the choice of drug, particularly for treating patients with ventricular arrhythmias, remains empiric and is often made on the basis of the drug's side effect profile rather than any degree of difference in efficacy. Selection of drugs to treat supraventricular tachycardias can be predicated on our knowledge of the mechanism of the arrhythmia to a much greater degree than can the choice of drugs to treat ventricular tachyarrhythmias. Further, the drug classification currently used (101,102) has many problems (103) and may provide little help in drug selection.

Table 2. Classification of Antiarrhythmic Drugs

Class I.	Drugs that block the fast sodium current
	A. Drugs that reduce V̇max and prolong repolarization and refractoriness
	1. Quinidine
	2. Procainamide
	3. Disopyramide
	B. Drugs that usually produce less reduction of V̇max and shorten repolarization and refractoriness
	1. Tocainide
	2. Mexiletine
	3. Phenytoin
	4. Lidocaine
	5. Ethmozine
	C. Drugs that reduce V̇max, primarily slow conduction and may prolong repolarization and refractoriness minimally
	1. Flecainide
	2. Encainide
	3. Lorcainide
	4. Propafenone
Class II.	Drugs that block beta adrenoreceptors
	A. Propranolol
	B. Timolol
	C. Atenolol
	D. Metoprolol
	E. Others
Class III.	Drugs that block potassium channels and prolong repolarization and refractoriness
	A. Sotalol
	B. Amiodarone
	C. Bretylium
Class IV.	Drugs that block the slow calcium channel
	A. Verapamil
	B. Nifedipine
	C. Diltiazem

Modulated receptor hypothesis. Nevertheless, significant progress has been made in understanding how drugs affect cardiac tissue. The discussion that follows deals with several aspects, beginning with the modulated receptor hypothesis (104).

Most antiarrhythmic drugs interfere with the passage of ions such as calcium, sodium or potassium across the cell membrane. Drugs affect passive membrane properties as well, but much less is known about this area. Let us consider the sodium channel, which is responsible for the depolarization phase of normal atrial and ventricular muscle and of the His-Purkinje system. Drugs gain entry to sarcolemmal channels where they bind in or near the channels only during

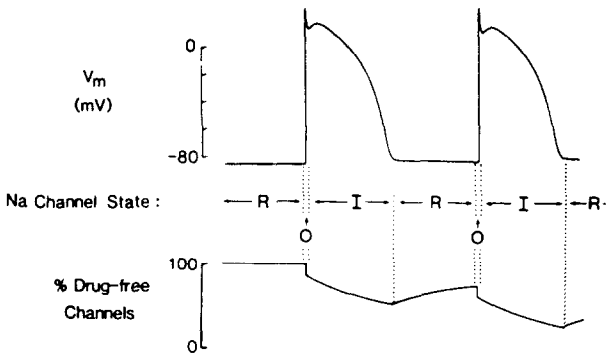


Figure 14. Schematic illustration of the time-dependent changes in sodium (Na) channel states, rested (R), open (O) and inactivated (I), associated with cardiac action potentials (**top**) and the resulting changing level of sodium channel block (**bottom**) by a local anesthetic-type antiarrhythmic drug. Note that this drug causes some block during the open channel state (upstroke of the action potential) and additional block during the inactivated state (plateau). During diastole, partial recovery from block occurs because the affinity of the drug for the channel is low. Reproduced with permission from *Anesthesiology* (178).

certain phases of the action potential, such as when the channel gates are cycled or used (use dependence) and when they are in an inactivated state (voltage dependence). Therefore, the drug would exert greater inhibitory effects on the sodium channel and on the upstroke of the action potential at more rapid rates of stimulation and after longer periods of stimulation. As a result, depression of the upstroke would be greater after an action potential depolarization rather than after a rest period. This effect might be due to preferential interaction of the antiarrhythmic drug with either the open or the inactive channel and little interaction with the resting channels of the quiescent cell. With increased time spent in diastole (slower rate), a greater proportion of receptors become drug-free and the drug exerts less effect. Agents in class IB (Table 2) exhibit rapid kinetics of onset and offset or use-dependent block of the fast channel (that is, they bind and dissociate quickly from the receptors). Class IC drugs have slow kinetics, and class IA drugs have intermediate kinetics (104).

Figure 14 illustrates this concept of drug kinetics. During depolarization, the sodium channels are open, depicted by the O. During repolarization (plateau of the action potential), the sodium channels are in an inactive state (I), and in late diastole, they are in a rest state (R). In this example, the drug binds to, and thus blocks, some of the sodium channels during the open state, and more during the inactive state. Drug dissociates from the channels during the rest state. In the bottom portion of the tracing, the percent of drug-free sodium channels is shown. From this example, one would predict that as the heart rate increased and diastole shortened much more than did the action potential duration, the drug would have less opportunity to dissociate from the sodium channel. Thus, at a more rapid rate, more sodium channels would be blocked by the drug. Because sodium conductance is a major determinant of conduction velocity, the drug may be expected to produce greater slowing of conduction at faster heart rates. This type of rate or use dependency has now been established for a variety of antiarrhythmic agents, and may explain why some drugs may be more effective at suppressing rapid than at suppressing slower tachyarrhythmias (104).

Quinidine and procainamide have the highest affinities for the activated state and, therefore, primarily block the sodium channels when they are open. Lidocaine, mexiletine and tocainide have the highest affinities during the inactivated state and, therefore, preferentially block sodium channels when they are closed. The short action potential duration of atrial muscle cells has a relatively short inactivated state, and this fact explains, in part, why the class IB agents normally exert little effect on atrial arrhythmias. Quinidine, acting primarily on the activated state, affects both atrial and ventricular action potentials. Lidocaine and related drugs also shorten action potential duration by increasing potassium conductance or by decreasing the sodium residual or window current. Shortening action potential duration shortens the duration of the inactivated state and the opportunity for the drug to produce inactivation state-dependent block of the sodium current.

Drug interactions. Many other important aspects of antiarrhythmic therapy have been studied in the past several years, such as the interactions among drugs. Simultaneous administration of two antiarrhythmic drugs may result in additive or inhibitory interactions, depending on the drugs. Interactions are often predictable from the modulated receptor hypothesis. As an example, the effect of a drug with a high affinity for the inactivated state can be potentiated by another drug that increases the duration of the inactivated state (that is, lengthens the plateau of the action potential) (104). It was recently shown (105) that a metabolite of lidocaine, glycylxylidide, can displace the parent drug from the receptor. We also know that one drug can alter the rate of metabolism and elimination of another drug to increase or decrease dose requirements (Table 3) (106).

Drug metabolites. Some drugs such as encainide and procainamide have active metabolites. The drugs undergo extensive hepatic metabolism that produces altered compounds with electrophysiologic actions that may be the same or different from those of the parent compound (107–109). We also know that many drugs are metabolized according to genetically determined metabolic pathways. For example, 5% to 10% of the North American and European white population have difficulty hydroxylating debrisoquine, an antihypertensive drug (110). The defect is inherited as an autosomal-recessive trait in which patients lack a specific cytochrome-P450 enzyme because of incorrectly spliced messenger ribonucleic acids (RNAs) (111). Lack of this

Table 3. Pharmacokinetic Interactions of Antiarrhythmic Drugs

Agents	Effects
Phenytoin	Increases clearance of
Phenobarbital	Quinidine
Rifampin	Disopyramide
	Mexiletine
	Digitoxin
Cimetidine	Reduces clearance of
	Quinidine
	Lidocaine
	Procainamide
	Flecainide
	Ethmozin
Amiodarone	Reduces clearance of
	Warfarin
	Phenytoin
	Quinidine
	Procainamide
	Digoxin
Digoxin	Clearance reduced by
	Quinidine
	Verapamil
	Amiodarone
	Volume of distribution reduced by
	Quinidine
Lidocaine	Clearance reduced by
	Propranolol
	Cimetidine

Reproduced with permission from Roden (106).

enzyme affects the metabolism of several antiarrhythmic drugs, such as encainide and propafenone, some beta-blockers and other commonly prescribed drugs (110). Patients may be at high risk for developing adverse drug effects because they do not metabolize the drug as rapidly as the rest of the population and, therefore, may require less drug than the remaining 90% of the population to achieve the same pharmacodynamic end point. In contrast, if a major drug action is due to the effects of an active metabolite, with ordinary drug doses these patients may not develop sufficient concentrations of the metabolite to achieve a therapeutic response (106).

Surgical Therapy

Drugs remain the mainstay of antiarrhythmic therapy. However, drug therapy is frequently not well tolerated or is ineffective, particularly in patients with life-threatening ventricular tachyarrhythmias and reduced ventricular function. For many of these patients, selection of nonpharmacologic approaches alone or in combination with drugs may be preferable.

Patients with supraventricular arrhythmias and accessory pathways. The use of surgery to treat cardiac arrhythmias has become increasingly popular in the last decade (112–114). The goal of surgery is to isolate, excise or otherwise interrupt tissue critical for the initiation or maintanence of the tachycardia, while at the same time preserving or improving myocardial function. Successful surgery provides a cure for the patient with a cardiac arrhythmia, in contrast to drug therapy, which just keeps the arrhythmia suppressed. Candidates are patients who have symptomatic recurrent tachyarrhythmias despite adequate drug treatment or patients who are not candidates for long-term drug therapy. Patients with the Wolff-Parkinson-White syndrome serve as the prototypical example of an arrhythmia treated admirably with surgery. Interruption of the accessory pathway with use of an endocardial (112,114) or epicardial (113,115) approach (Fig. 15) achieves a cure rate exceeding 95%, with a mortality approaching zero. Surgery for patients who have AV node reentrant tachycardia is relatively new, but initial cure rates are similar to that for surgery for the Wolff-Parkinson-White syndrome (116,117).

Patients with ventricular tachyarrhythmias. Surgery for patients with ventricular tachyarrhythmias has similarly improved (113,114,118,119). Candidates include patients with recurrent sustained symptomatic ventricular tachyarrhythmias despite adequate drug treatment or those who are not candidates for long-term drug therapy. For patients with coronary artery disease, electrophysiologically guided surgery appears preferable to blind resection and involves resection, isolation or ablation of ventricular tissue (generally endocardium) involved in the tachycardia (Fig. 16). Success rates judged by prevention of a symptomatic recurrence of the arrhythmia with or without drug treatment generally range between 70% and 80% (119). However, the perioperative mortality rate is still relatively high, about 15%. Surgery for patients with ventricular tachyarrhythmias unassociated with coronary artery disease depends on the type of heart disease. Mapping the location of the ventricular arrhythmia is mandatory for these patients.

Electrical Therapy

Devices. The automatic implantable cardioverter/defibrillator (AICD) is the only implantable device commercially available in the United States that electrically cardioverts or defibrillates ventricular tachyarrhythmias, or both, in patients. The AICD is capable of delivering 25 to 35 J shocks and recycling three additional times after the first initial shock. Its projected life span is about 2 years (or 100 shocks) (120–122). Lower energy shocks in the range of 2 J have been used for transvenous cardioversion of ventricular tachycardia, but are inadequate without backup defibrillation capabilities (123,124).

Indications. Patients considered for device implantation are those resuscitated from ventricular fibrillation in the absence of acute myocardial infarction or other disorders with a remedial cause. These patients have ventricular

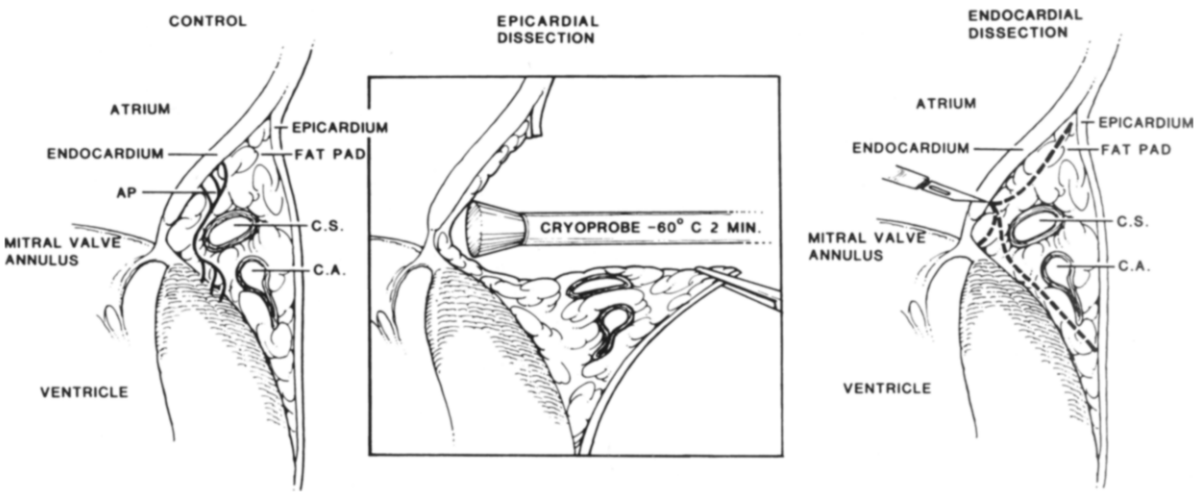


Figure 15. Schematic diagram illustrating the surgical technique for dissection at the atrioventricular groove (**left panel**), using an epicardial approach with cryoablation (**middle panel**) and an endocardial dissection (**right**). AP = accessory pathway; C.A. = coronary artery; C.S. = coronary sinus.

tachyarrhythmias inducible electrically or that occur spontaneously despite drugs or surgery, or both. Some may still be candidates who do not have inducible ventricular tachyarrhythmias. Patients who have hypotensive episodes of sustained ventricular tachycardia in the absence of acute myocardial infarction or a remedial cause and whose ventricular tachycardia remains inducible despite drug treatment or surgery, or both, are also candidates (121,122).

Patients for whom the device may be indicated include those with unexplained syncope who have inducible ventricular tachyarrhythmias causing syncope despite drug treatment, those with a family history of sudden cardiac death associated with entities such as hypertrophic cardiomyopathy and those who have unexplained syncope with the long QT syndrome.

Contraindications to AICD implantation. These include patients who, despite drug treatment, have very frequent episodes of sustained or nonsustained supraventricular or ventricular tachycardia causing frequent device discharge, patients with a short projected life span because of heart failure, cancer, or other diseases, psychological reluctance to accept the device or a slow ventricular tachycardia (usually <140 beats/min) (121).

Selection of patients and follow-up. Prospective patients should undergo cardiac catheterization to determine whether concomitant surgery is necessary, an electrophysiologic study to establish device applicability, safety and efficacy and extensive in-hospital monitoring. Implantation is generally by sternotomy, left thorocatomy, subxiphoid or subcos-

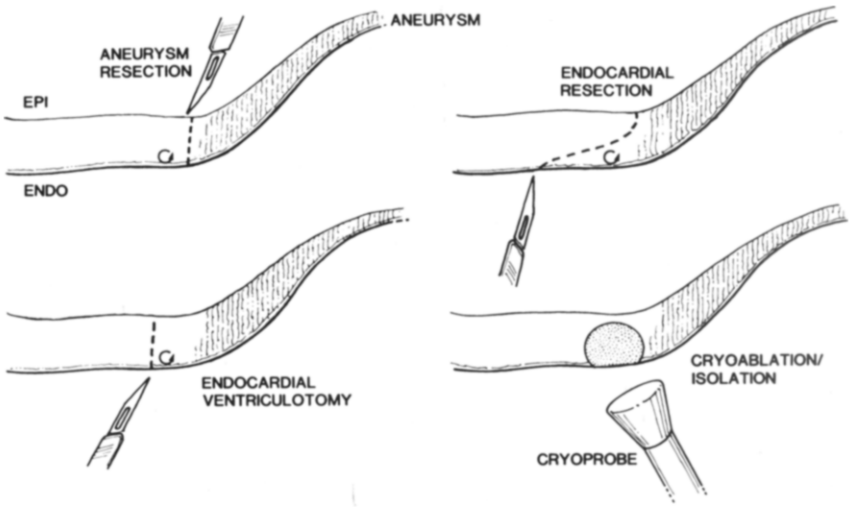


Figure 16. Surgery for ventricular tachycardia in patients with coronary artery disease. **Top left**, Aneurysm resection alone, which leaves the arrhythmogenic tissue untouched (**small circle with arrow**). **Bottom left,** Endocardial (ENDO) ventriculotomy, which isolates the arrhythmogenic tissue from the rest of the ventricle. **Top right,** Endocardial resection, which eliminates aneurysm and arrthythmogenic myocardium. **Bottom right,** Cryoablation, which ablates or isolates arrhythmogenic tissue. EPI = epicardium.

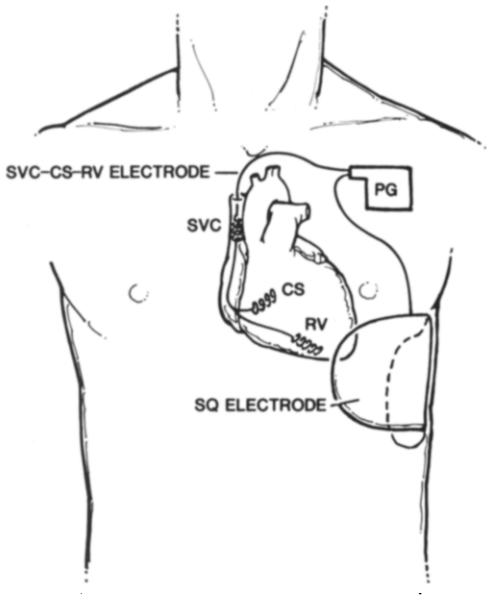


Figure 17. Schematic diagram illustrating electrode sites for nonthoracotomy implantation of a cardioversion-defibrillation device. Electrodes can be placed in the superior vena cava (SVC), coronary sinus (CS) and right ventricular apex (RV). An additional cardiac electrode can be placed subcutaneously over the region of the cardiac apex. Leads are connected to the pulse generator (PG). At the present time, the size of the pulse generator precludes its subclavicular placement and requires implantation in the abdominal wall. SQ = subcutaneous electrode.

tal approach. Transvenous approaches are evolving (Fig. 17). Concomitant coronary artery bypass grafting, endocardial resection for ventricular tachycardia or other surgical procedures may be performed.

In a long-term follow-up study (121) of 270 patients with the AICD, actuarial mortality of sudden cardiac death was approximately 0.9% at 1 year and 4.4% at 5 years. Complications included inappropriate shocks (20%), lead problems (1% to 2%), infection (<2%), operative death (<3%) and elevated defibrillation thresholds (<2%).

Future devices. Devices are being developed that will be able to deliver sequential shocks (125,126), shocks with a biphasic wave form, shocks at multiple programmable energy levels, pacing for bradyarrhythmias or tachyarrhythmias and extensive monitoring capabilities. One such device is a multiprogrammable pacemaker-cardioverter-defibrillator with telemetry that can be used for bradycardia (VVI) pacing, competitive antitachycardia pacing, low energy synchronous cardioversion and high energy asynchronous defibrillation. The purpose of this device is to deliver staged electrical therapy that escalates in intensity according to programmable steps in response to the underlying cardiac rhythm. With the device's external programmer, one can perform noninvasive electrophysiologic studies. Importantly, it has extensive recording capabilities and can store the number of episodes of ventricular tachycardia and fibrillation, types of therapy delivered and response to therapy, as well as 20 cycle lengths preceding and 10 cycle lengths following delivery of therapy.

Ablation. *Supraventricular tachyarrhythmias.* Another form of electrical therapy for arrhythmias is the use of ablation techniques employing a catheter electrode connected to an energy-delivering source, such as a defibrillator (127,128). Capacitor discharge creates a high energy shock delivered over the catheter electrode, which can destroy areas of the heart involved in the genesis or maintenance of a tachyarrhythmia or interrupt conduction in the AV node-His bundle in patients with recurrent rapid supraventricular tachycardia. Figure 18 illustrates the creation of heart block in a 22 year old patient with a 6 year history of recurrent exercise-related atrial tachycardia, flutter and fibrillation. Ventricular rates of 200 to 250 beats/min (in the absence of an accessory pathway) could not be slowed despite extensive pharmacologic trials, including amiodarone. After creation of heart block and implantation of an activity-sensing pacemaker, the patient became asymptomatic. Although he has a new disease (heart block and pacemaker dependency), it is clearly preferable to his pre-existing problem.

Ventricular tachyarrhythmias. The rate of successful creation of partial or complete heart block in patients with supraventricular tachycardia approaches 90%, whereas <50% of patients with ventricular tachycardia are treated successfully by catheter ablation (129,130). Success has been higher in some series (131). Recently, ablation of the right bundle branch has been shown to eliminate ventricular tachycardia in patients with bundle branch reentry (49). A 2% late sudden death rate occurs in patients after creation of heart block and pacemaker implantation (129). The sudden death may be due to the patients' intrinsic disease or possibly to the ablation procedure.

Electrical ablation for patients with Wolff-Parkinson-White syndrome (132) and atrial tachyarrhythmias is still evolving. Radiofrequency (133) and laser (134) ablation techniques are undergoing investigation and may become practical in the future (135).

Prognosis

There has been much progress in improving the ability to establish the prognosis of patients with ventricular arrhythmias using noninvasive and invasive techniques.

Noninvasive Techniques

Electrocardiographic signal averaging. Noninvasive assessments demonstrate that suppression of spontaneous ventricular arrhythmias occurring at rest or during exercise by an antiarrhythmic drug indicates a better prognosis compared with lack of suppression (136). Signal averaging ap-

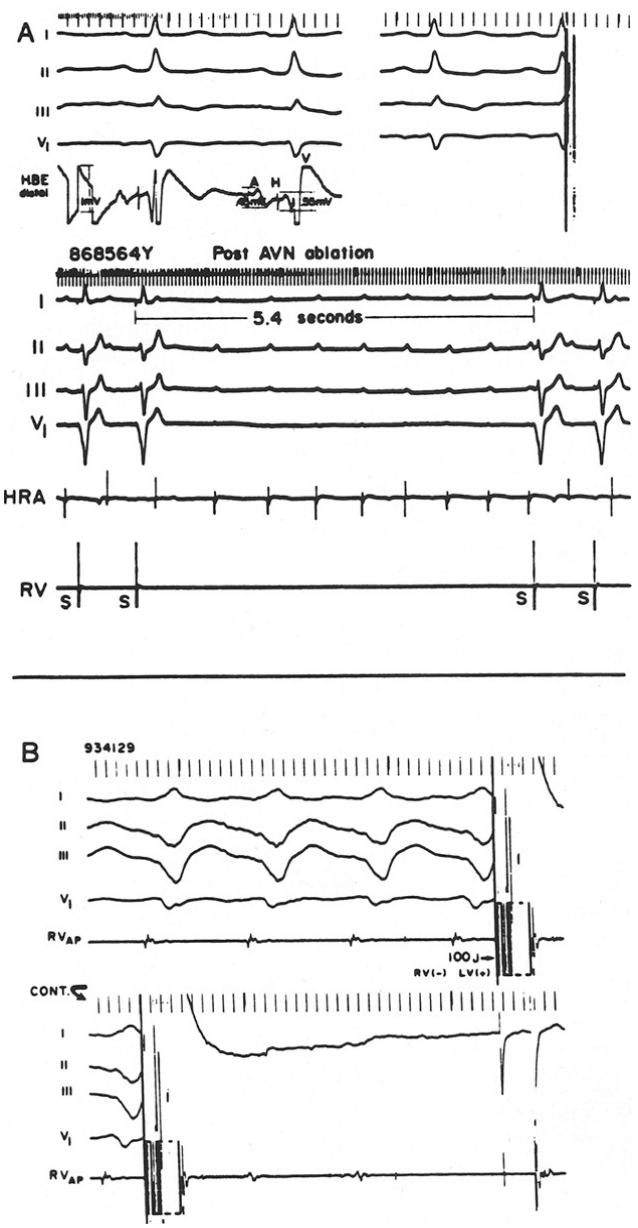


Figure 18. Electrode catheter ablation of atrioventricular (AV) conduction and ventricular tachycardia. **Panel A, top,** Leads I, II, III and V_1 and a His bundle electrogram (HBE) during sinus rhythm before the delivery of the shock. Amplitude of the atrial and His bundle electrogram is given. At the **dark vertical line** in the **top right panel**, 200 joules are delivered between the cathodal electrode situated at the His bundle and an anodal patch on the patient's back. In the **bottom of panel A**, the rhythm immediately after the shock is displayed. The patient is now pacemaker-dependent; turning off the pacemaker for 5.4 s illustrates underlying complete AV heart block. AVN = atrioventricular node; HRA = high right atrial electrogram recording; RV = right ventricular electrogram recording; S = stimulus. **Panel B** illustrates an attempt at ablation of ventricular tachycardia with the site of origin located near the apical portion of the interventricular septum. The first of several 100 joule shocks was delivered between the anodal electrode placed in the left ventricular apex and the cathodal electrode placed in the right ventricular apex. The delivery of the shock in the **top right** is reproduced in the **bottom left of the panel**. The ventricular tachycardia is terminated, and the patients' dual chamber pacemaker paces the atrium and then the ventricle after a slight pause. The electrogram recording at the left ventricular apex occurred 40 ms in advance of the onset of the QRS complex (not shown). CONT. = control; LV = left ventricle; RV = right ventricle; RV_{AP} = right ventricular electrogram recorded at the apex. Reproduced with permission from Zipes (179).

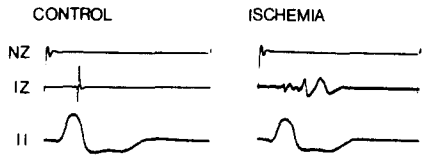


Figure 19. Ischemic-induced conduction delay. Electrode recordings are obtained in this open chest anesthetized dog from a normal zone (NZ) and ischemic zone (IZ) in the left ventricular myocardium. During ischemia, the ischemic zone electrogram recording demonstrates significant conduction delay, which continues past the QRS complex and into the ST segment and T wave.

pears to improve the predictive accuracy of noninvasive testing (137,138). It is a technique used to amplify electrical signals from the heart that have a voltage that is too small to be recorded in the standard scalar ECG (139,140). Ischemia and infarction can cause marked slowing of conduction that results in delayed electrical activity that can be recognized in the terminal portion of the QRS complex or early portion of the ST segment (Fig. 19) (141). This fragmented low amplitude cardiac electrical activity may be the electrical event recorded in the signal-averaged ECG and may identify patients at risk for developing ventricular tachycardia (137–140).

In Figure 20 (137), the QRS complex has been amplified by signal averaging. In the top panel, the QRS duration is not prolonged and the voltage in the last 40 ms of the QRS complex is still very large (that is, 95 μV). In the middle panel, note the fragmented and low amplitude potentials recorded in the terminal portion of the QRS complex (shaded area), prolonging its duration. The voltage of these late potentials recorded during the last 40 ms of the QRS complex is only 4 μV. In the bottom panel, the QRS duration is also prolonged, and the voltage in the terminal portion is in the range of 14 μV. In this study (137), the presence of spontaneous ventricular ectopic activity, abnormal late potentials and reduced ejection fraction each contributed independently to the prognosis of patients after their recovery from acute myocardial infarction. Patients who had all three risk factors had an event rate of 50% for experiencing sustained ventricular tachycardia or sudden death within 1 year. Patients who had a normal ejection fraction with abnormal late potentials or patients who had no late potentials and a reduced ejection fraction had a better prognosis.

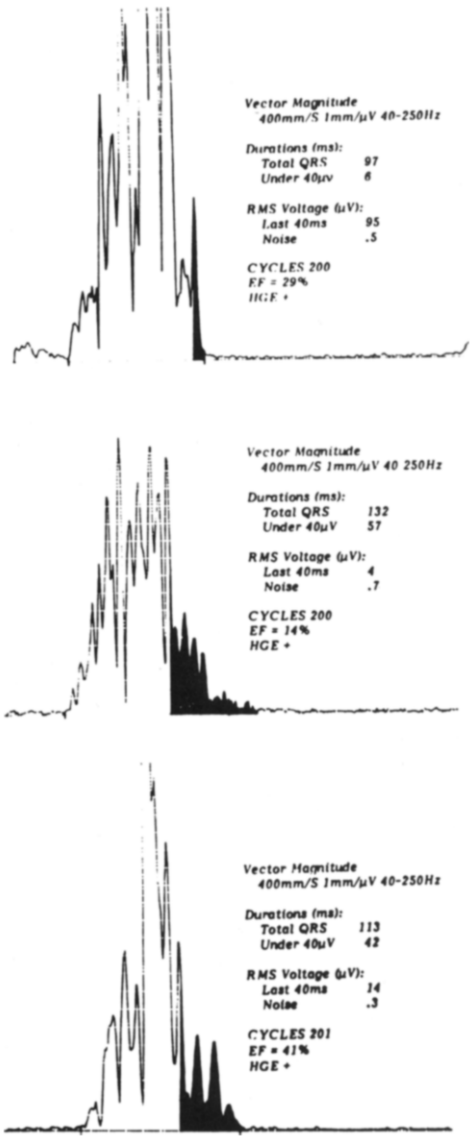


Figure 20. Signal-averaged electrocardiograms. **Top panel,** Signal-averaged electrocardiogram of a patient with a history of a myocardial infarction, but no subsequent arrhythmic event. The duration of the signal-averaged QRS complex is normal (97 ms), with normal duration of terminal signals <40 μV (6 ms) and a normal root mean square (RMS) voltage of the terminal 40 ms (95 μV). The patient had an abnormal ejection fraction (EF) of 29% and high grade ventricular ectopic activity (HGE^+). **Middle panel,** Signal-averaged electrocardiogram of a patient with anterior wall myocardial infarction and documented sustained ventricular tachycardia during follow-up study. The QRS duration is prolonged (132 ms), as is the duration of low amplitude signals that were <40 μV (57 ms) (**shaded area**). The root mean square voltage of the terminal 40 ms (4 μV) was abnormal. Ejection fraction was reduced (14%) and high grade ventricular ectopic activity was present. **Bottom panel,** The patient had inferior myocardial infarction and ventricular fibrillation during follow-up study. The QRS duration was normal (113 ms), but there was abnormal duration of the low amplitude signal that was <40 μV (42 ms) (**shaded area**). The root mean square voltage of the terminal 40 ms (14 μV) was abnormal. Ejection fraction was 41% and high grade ventricular ectopic activity was present. Reproduced with permission from Gomes et al. (137).

Invasive Techniques

Electrophysiologic study. Therapy can be selected and prognosis predicted according to the results of an electrophysiologic study (142–144). In general, when a drug prevents electrical induction of a tachycardia initiated in a control state, the drug will be highly successful in preventing spontaneous occurrences of the tachycardia. Reinitiation of the tachycardia during drug therapy does not mean that the patient will necessarily experience a recurrence, but makes such a recurrence much more likely. Importantly, recent data (145) suggest that the hemodynamic consequences of the spontaneous recurrence will resemble the patient's hemodynamic response to the laboratory-induced event. Thus, if the tachycardia remains electrically inducible but the drug slows the rate so that the patient tolerates the arrhythmia, the patient may similarly survive spontaneous recurrent arrhythmias equally well.

Invasive versus noninvasive assessment. A comparison of an invasive and noninvasive assessment is underway (Mason J, personal communication). In one study (143) of patients who had recurrent ventricular tachycardia, prognosis was predicted more accurately by the results of an electrophysiologic study than by the results of a noninvasive approach. In example shown in Figure 21, patients who were predicted to be arrhythmia-free by an electrophysiologic study had a much better prognosis for recurrence of ventricular tachyarrhythmia than did patients who were predicted to be arrhythmia-free by a noninvasive approach (143). However, existing data suggest that both approaches have merit and, in the final analysis, they test different phenomena. Theoretically, noninvasive assessments test for the presence of a trigger to start the arrhythmia and the myocardial substrate to maintain it. In an electrophysiologic study, the trigger (premature electrical stimulation) is supplied and the presence of a substrate is tested. An effective drug that only eliminated the trigger might fail to prevent electrical induction of the tachycardia. Responses from both types of testing are important, and together may be more useful than either alone in identifying the patient with an acceptable therapeutic response.

Future Directions

Therapy and Prognosis

New antiarrhythmic agents and drugs for ablation. What does the future offer? New antiarrhythmic agents are being developed and tested that will increase our capabilities of suppressing arrhythmias. However, novel and imaginary approaches are needed. One could envision new antiarrhythmic agents that were site specific, preferentially traveling to arrhythmogenic areas, perhaps on the basis of new antibody-binding techniques (146,147). Drugs might concentrate in regions of myocardial damage that have been made unique

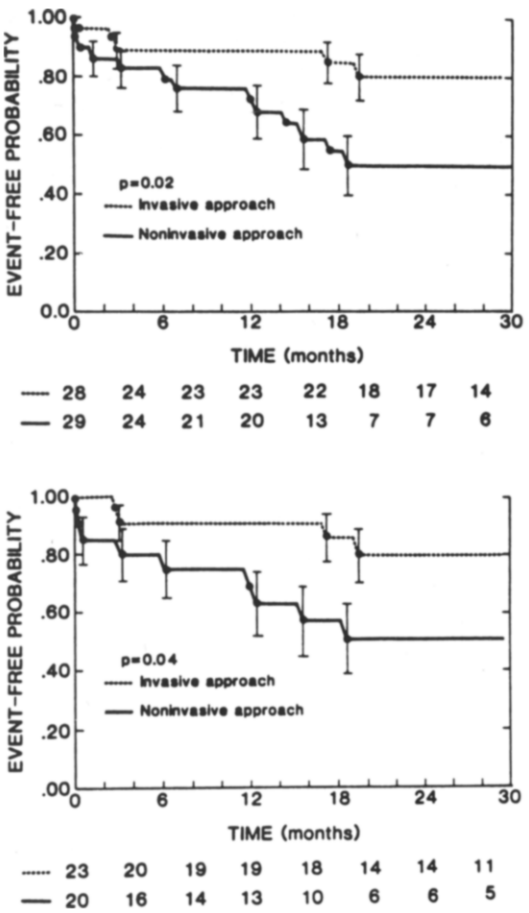


Figure 21. Actuarial probabilities of freedom from recurrence of symptomatic sustained ventricular tachyarrhythmia among all randomized patients (**upper panel**) and randomized patients with inducible sustained ventricular tachycardia at baseline (**lower panel**). Patients randomly assigned to the invasive approach are represented by the **dashed lines**. Those assigned to the noninvasive approach are represented by the **solid lines**. **Vertical bars** represent standard errors of the estimate. The numbers below each panel indicate the numbers of patients at risk at various points during the follow-up period. Reproduced with permission from Mitchell et al. (143).

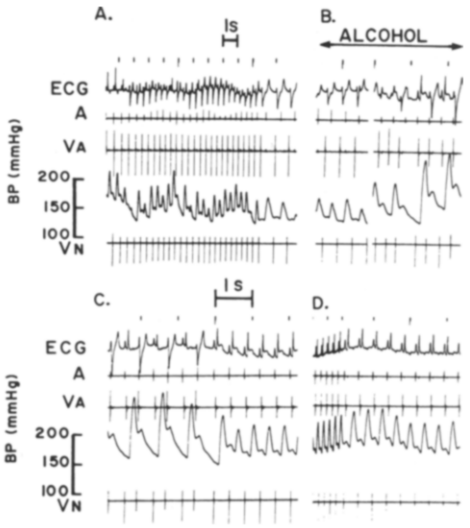


Figure 22. Termination of ventricular tachycardia with 100% alcohol injected through cannulation of an occluded coronary artery. In **each panel**, surface electrocardiographic (ECG) lead II, atrial electrogram (A), ventricular electrogram recorded from the region injected with alcohol (V_A), arterial blood pressure (BP) and ventricular electrogram recorded from the normal area (V_N) are arranged from **top to bottom**. **Panel A,** Ventricular tachycardia begins with a fusion beat after two sinus-initiated beats. **Panel B,** During ventricular tachycardia, 1 ml of 100% alcohol at room temperature was injected. Ventricular tachycardia was replaced by premature ventricular complexes and then sinus rhythm. **Panel C,** ST segment elevation and dimunition of V_A electrogram are apparent. **Panel D,** This ECG recorded 20 min after alcohol injection demonstrates resolution of ST segment elevation, T wave inversion and sinus rhythm. This dog was unusual in that it was quite hypertensive before initiation of ventricular tachycardia (**panel A**), with return to the same blood pressure before ventricular tachycardia after alcohol injection. Study performed as reported in reference 150.

because of increased intracellular calcium concentrations, reduced membrane potential or other attributes. Drugs might uncouple arrhythmogenic areas (148) by acting specifically on gap junctions.

Drugs could be developed that actually ablate areas of the myocardium, analogous to thyroid ablation by iodine-131. Several years ago we showed (149) that a chemical caustic applied to the left ventricular endocardium could ablate ventricular tachycardia. More recently, we demonstrated (150) that alcohol or phenol injected into the coronary artery perfusing the area of origin of a ventricular tachycardia could ablate the arrhythmia (Fig. 22). Injection of iced saline solution (151) or antiarrhythmic drugs (151a) into the relevant coronary artery may be used to verify appropriate catheter location (Fig. 23) before administration of phenol or alcohol. Thus, therapy to eliminate ventricular tachycardia could be accomplished during selective coronary arteriography. Conceivably a similar approach could be used in patients with AV node reentrant tachycardia. A dilute alcohol injection into the AV node artery might be sufficient to alter the timing necessary for maintenance of the tachycardia without necessarily producing AV block requiring pacemaker treatment.

Electrical therapeutic advances. These advances will provide transvenous cardioverters-defibrillators that will have the multiple functions and programmable flexibility mentioned earlier. They will more accurately differentiate ventricular from supraventricular tachycardias using electrogram characteristics (152), QRS duration, atrial activity and biosensory end points. Nonthoracotomy implantation will become the rule (Fig. 17) (153). Use of external automatic defibrillators in the home and public places will increase (154).

Safer, more focused catheter ablation techniques employing alternative energy sources will become available. An area ripe for further exploration, relatively uninvestiga-

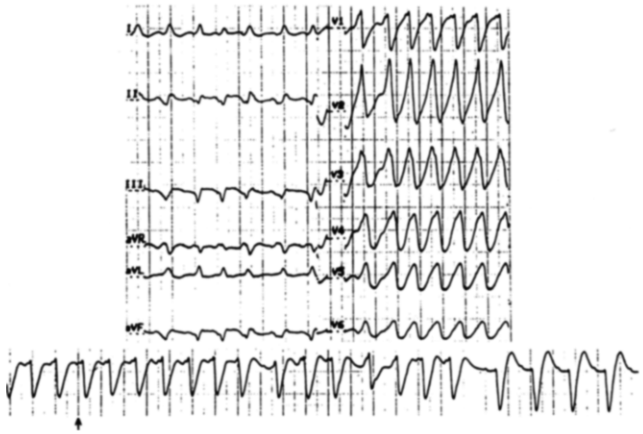


Figure 23. Iced saline injection. Twelve lead electrocardiogram of ventricular tachycardia is shown in the **top panel**. Ten milliliters of iced saline (**arrow, lower panel**) injected into a distal septal perforator coronary artery terminates the ventricular tachycardia (V_1, **lower panel**). Study performed with James C. Dillon, MD and William M. Miles, MD.

ted at present, is the electrical prevention of tachyarrhythmias through a variety of approaches (155,156).

Surgical advances. Surgical therapies will continue to advance with improved mapping capabilities, particularly for ventricular tachycardias, and the development of new surgical approaches for treating patients who have recurrent or chronic atrial fibrillation (157) and atrial flutter (158). Recurrent atrial fibrillation is often a difficult management problem, producing symptoms because of loss of atrial systole, ventricular rate control and palpitation. Drug therapy frequently is ineffective for these patients.

Improved risk stratification. Risk stratification to classify patients after myocardial infarction or after an episode of ventricular tachycardia or cardiac arrest due to ventricular fibrillation will improve to the point where screening procedures will accurately identify patients at increased risk of developing life-threatening arrhythmias before a serious event. As implantable devices improve, it is quite conceivable that a transvenous cardioverter-defibrillator will be inserted prophylactically in high risk patients, such as those with congestive heart failure, spontaneous ventricular arrhythmias and an abnormal signal-averaged ECG.

Mechanisms and Pathogenesis of Arrhythmias

The future offers an extraordinarily rich potential for a better understanding of the pathogenesis of cardiac arrhythmias. The last 20 years have witnessed an unprecedented burst of new knowledge about mechanisms of tachycardias in humans, derived primarily from catheter electrode techniques (159). Further new knowledge will come with the development of new tools that will allow us to gain additional

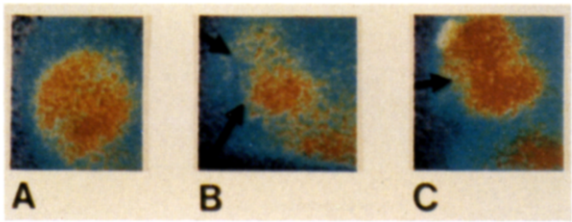


Figure 24. Preoperative left lateral metaiodobenzylguanidine (MIBG) images showing homogeneous uptake (**A**). MIBG image obtained 9 weeks after latex injection, with a documented transmural myocardial infarction showing an anteroapical defect (**arrows**) (**B**). Simultaneous postoperative thallium image showing a small anterior wall defect (**C**) (**arrow**). **White dot** in **left upper part of C** is an artifact. Reproduced with permission from the American Heart Association, Inc. (95).

information about the heart and arrhythmias in vivo (160). Monophasic action potential recordings may become useful, particularly for recording afterdepolarizations (10,11,32–34,36). New imaging techniques that will increase understanding of biochemical changes in the myocardium involved in arrhythmias (161), discriminate scar from ischemia tissue (162) or clarify electrolyte and pH shifts (163) may be helpful.

New imaging of myocardial innervation after infarction. Cardiac images of sympathetic innervaton may provide useful information. Metaiodobenzylguanidine (MIBG), an analogue of guanethidine, is taken up by sympathetic nerve terminals in a fashion similar to norepinephrine. Labeled with iodine-123, a gamma-emitter, MIBG can be used to provide a scintigraphic image of sympathetic nerve terminals in the heart (164). As demonstrated in the canine studies elaborated earlier (90–4) myocardial infarction creates sympathetic denervation of the myocardium apical to the site of myocardial infarction, which appears as a defect in the MIBG image (Fig. 24). Ten to 14 weeks later, reinnervation occurs in dogs. If an MIBG image of sympathetic innervation is performed simultaneously with a thallium image (the latter to indicate areas of myocardial blood flow and cell viability), myocardium generating a normal thallium image but no MIBG uptake should represent viable but denervated areas of the ventricle (95). Such images representing apparent denervation have been found in patients after myocardial infarction. How important they are to the genesis of ventricular arrhythmias is still being explored (96).

Microbiologic approaches. Subcellular approaches to understanding physiology, often using the powerful tools of molecular biology, have captivated research interest in the last several years and promise to provide greater understanding of many basic electrophysiologic concepts. To focus briefly on one small area, consider several events involved in the control of calcium in excitation-contraction coupling (Fig. 25). Calcium channels in the sarcolemma (outer cell membrane) reach a certain voltage that permits

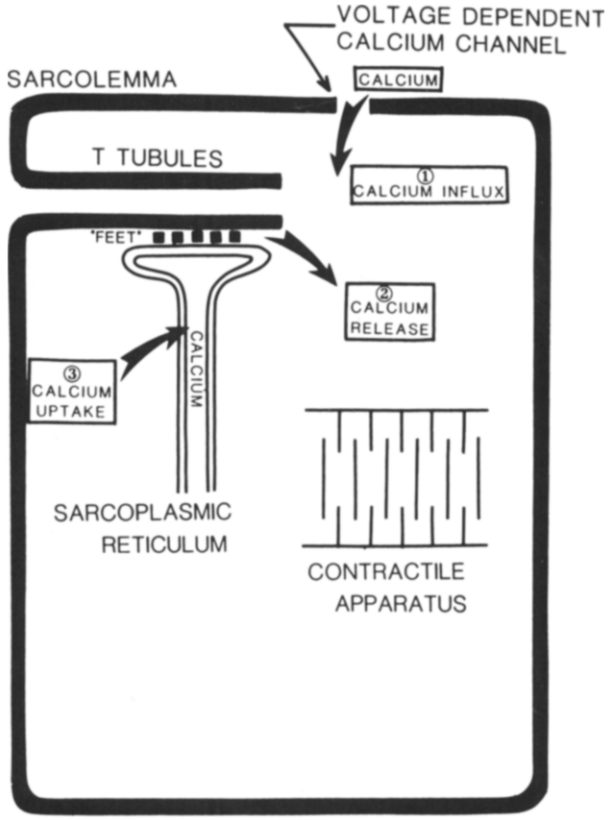


Figure 25. Schematic diagram of calcium control. Calcium enters the cell one through a voltage-dependent calcium channel in the cell membrane (sarcolemma). The increase in cytosolic calcium concentration triggers calcium release two from the sarcoplasmic reticulum to interact with the contractile proteins. Calcium is then taken up by the sarcoplasmic reticulum three. See text for details.

small amounts of calcium to enter the interior of the cell (cytosol) (165). This increase in cytosolic calcium then triggers a release of more calcium into the cytosol from the sarcoplasmic reticulum to interact with the contractile proteins. During diastole, calcium is pumped back into the sarcoplasmic reticulum with each cardiac cycle. Feet proteins connecting the T tubular system with the sarcoplasmic reticulum have been purified, and are the putative channels releasing calcium from the sarcoplasmic reticulum to the cytosol (166,167). The channel has a tetrameric appearance (Fig. 26) (166). The sarcoplasmic reticulum uptake pump is regulated by phosphorylation of the protein phospholamban (168). Because the sarcoplasmic reticulum membrane is inaccessible to standard electrophysiologic techniques, novel approaches to study calcium uptake and release across this membrane have been required.

One way to do this is to create an artificial membrane that allows the proteins to behave as channels (169).

Purified phospholipids are painted onto a plastic membrane separating two chambers containing electrolyte solu-

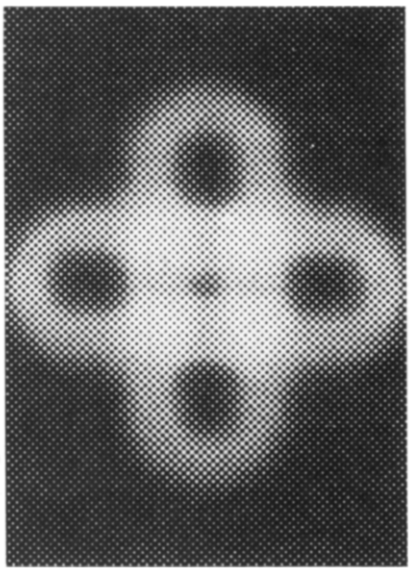


Figure 26. Schematic drawing of authors' interpretation of electron micrographs of the calcium channel complex. Reproduced with permission from Lai et al. (166).

tions. The membrane has a small hole in it. A channel protein (for example, the tetrameric feet protein or phospholamban) is added to the bath, and incorporates into the lipid bilayer. Activity of these channel proteins can now be recorded as discrete changes in the conductance of ions from one side of the membrane to the other because the feet proteins and phospholamban function as selective channels (Fig. 27).

Conclusions

New understanding of complex phenomena such as ionic currents and excitation-contraction coupling at the molecular level using the approaches just outlined, studies of isolated "patches" of membrane removed from the cell to investigate single channel activity (170), advances in understanding receptor physiology (171–173) and development of techniques to clone receptors and channels (174) have provided new insights into subcellular and cellular function. However, these advances must be used to formulate hypotheses that can be tested in intact cells, organs and organisms. The excitement of molecular studies must not preempt the effort to understand the mechanisms in intact animals and humans. The behavior of isolated cells or pieces of cells, and now isolated proteins, indicates only what these substances are *capable* of doing, not necessarily what they are *actually* doing in vivo (4). Only by integrating the knowledge generated from subcellular techniques with our knowledge of functionally intact systems complete with blood flow, autonomic responses and, yes, even a brain, can we begin to

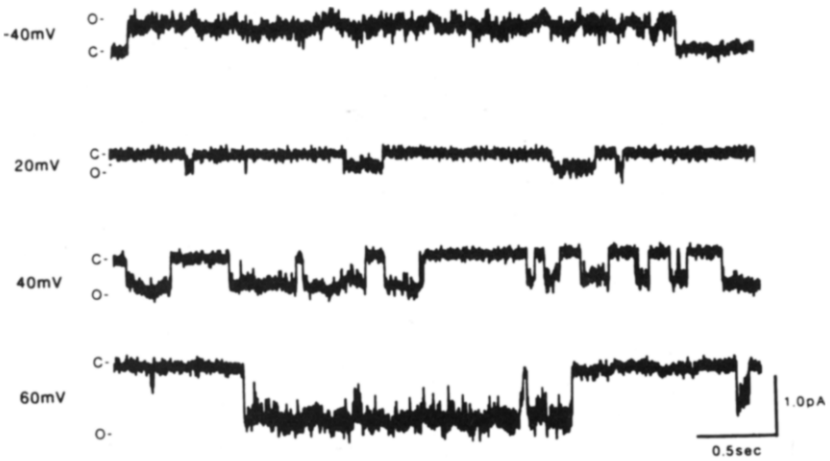


Figure 27. The purified sarcoplasmic reticulum protein phospholamban was incorporated into a lipid bilayer. Phospholamban was purified from canine heart. This figure shows representative examples of single channel activity at a variety of membrane potentials. C denotes the closed state of the channel, O denotes the open state. Single channel openings are recorded as discrete current deflections (square-shaped contours) from the baseline O to C. The magnitude of the deflection is related to the amount of calcium passing through the channel. The channel activity was recorded with 10 mM $CaCl_2$ bathing both sides of the bilayer. pA = picoamps. Reproduced with permission from Kovacs et al. (168).

understand why J.D. developed ventricular fibrillation after he learned that his mother had just died.*

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*J.D. underwent defibrillation and was treated with beta-adrenoceptor blocking drugs and aspirin. He has done well for 2 years since the infarction.

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