
Perspectives and Future Trends in Cellular Electrophysiology: Implications for the Clinician

LEONARD S. GETTES, MD, FACC

Chapel Hill, North Carolina

As a result of single fiber electrophysiologic studies, the clinical approach to the electrical behavior of the heart has improved. Three areas are examined: 1) the electrocardiographic waveform, 2) normal and abnormal cardiac rhythms, and 3) the mechanism of action of antiarrhythmic drugs. In each area, the results of single fiber studies have provided a conceptual framework for

diagnostic and therapeutic decisions. These studies have also enabled investigators to test hypotheses formulated from clinical observations. It may be only a slight exaggeration to attribute many of our recent advances in each of the three areas to the development and use of the microelectrode.

In 1951, the characteristics of the Purkinje fiber action potential recorded by microelectrodes were described by Draper and Weidmann (1). These pivotal experiments gave birth to the discipline of cardiac cellular electrophysiology. Since then, work by membrane physiologists, pharmacologists and clinicians has resulted in a body of knowledge that has permitted the application of fundamental information to clinical events, the formulation of hypotheses regarding electrical phenomena in the intact heart based on findings in single fibers, and the testing of hypotheses regarding single cell activity based on clinical and electrocardiographic observations. These studies have enhanced our understanding of the electrocardiographic waveform, normal and abnormal cardiac rhythms and the mechanism of action of cardioactive drugs. In this review, I will attempt to show how advances in cellular electrophysiology over the last 30 years have influenced patient care in these areas and will attempt to predict some future advances in cellular electrophysiology that may increase our appreciation of normally occurring events and of the pathophysiology and treatment of electrical abnormalities of the heart.

From the Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina. This research was supported by Grant HL-23624 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Address for reprints: Leonard S. Gettes MD, Division of Cardiology, 353 Burnett-Womack Building 229H, University of North Carolina, Chapel Hill, North Carolina 27514.

Electrocardiographic Waveform

It is generally understood and accepted that the electrocardiogram relates directly to the action potential of the single cardiac fiber, with the QRS complex reflecting the rapid upstroke (phase 0), the ST segment reflecting the plateau (phase 2) and the T wave reflecting the phase of rapid repolarization (phase 3). The TP segment relates to the resting membrane potential (phase 4) (Fig. 1). In a variety of situations, the waveform of these electrocardiographic components can be explained by changes in single fiber transmembrane action potential. Conversely, changes in the action potential can accurately predict changes in the electrocardiographic waveform.

The electrocardiogram may be thought of as representing the resultant electrical forces generated by the voltage gradients created by the sequential depolarization and repolarization of the myocardial cells. It is, in a sense, an analog voltmeter with the output recorded on paper running at 25 to 50 mm/s. The electrocardiogram reflects the electrical characteristics of the individual cells and the sequence of their depolarization and repolarization. Factors that alter either of these may cause changes in the waveform of the electrogram recorded at the body surface, that is, the clinical electrocardiogram.

Changes in action potential caused by increased extracellular potassium. Changes in serum electrolytes and cardioactive drugs are examples of factors that alter the electrical characteristics of the individual cells and the electrocardiogram. One of the best examples of this relation is the change caused by increasing extracellular potassium

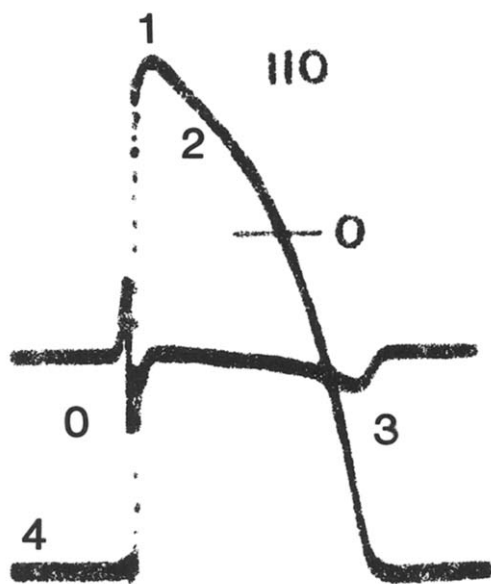
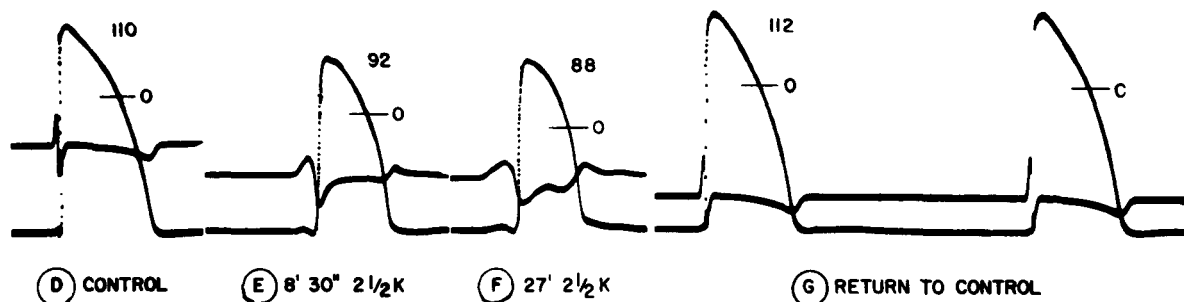


Figure 1. Simultaneously recorded ventricular transmembrane potential and epicardial electrogram from a Langedorf perfused spontaneously beating rabbit heart. The figure illustrates the relation between the various phases (0 to 4) of the action potential and the waveform of the electrogram.

concentration (Fig. 2) (2,3). Increasing extracellular potassium alters the ratio between extracellular and intracellular potassium. This ratio is the major determinant of the resting membrane potential, and an increase in extracellular potassium causes the resting membrane potential to become less negative. Changes in the resting potential influence the magnitude of the rapid inward current that is responsible for the upstroke of the action potential. As the membrane potential becomes less negative, the maximal inward current declines and the maximal rate of rise of the action potential upstroke

Figure 2. Simultaneously recorded ventricular transmembrane action potentials and epicardial electrograms from isolated Langendorff perfused rabbit heart as potassium concentration in the perfusate is increased from control (4.8 mM) (D) to 2.5 times control (12.0 mM) (E and F). Note that widening of the QRS complex is associated with slowing of the upstroke of the action potential as reflected by the narrowed spacing between the dots, and that the changes in T wave and QT interval are associated with changes in the repolarization phase of the action potential. (Reprinted from Gettes LS, et al. [2], with permission.)



(Vmax) decreases (4-6). The relation between the changes in membrane potential induced by increasing extracellular potassium and the magnitude of Vmax is shown in Figure 3. In addition, the action potential amplitude and the voltage level of the action potential plateau decrease in response to increased extracellular potassium. An increase in extracellular potassium also renders the membrane more permeable to the efflux of potassium ions from the cell (7). Thus, despite a diminished ionic gradient across the cell membrane, potassium efflux is enhanced. Because the action potential plateau is caused by relative balance between a diminishing inward current and an increasing outward current due mostly to potassium, an increase in potassium efflux shortens plateau duration. The enhanced potassium efflux also accelerates the phase of rapid repolarization and probably contributes to the decrease in the rate of spontaneous depolarization in pacemaker fibers induced by increases in extracellular potassium (8).

Electrocardiographic effects of increased extracellular potassium. The electrocardiographic manifestations of an increase in extracellular potassium are well known and consist of peaking of the T wave, shortening of the QT interval, loss of P wave amplitude and prolongation of P wave and QRS durations (Fig. 2) (3). The T wave peaking and the QT interval shortening are caused by the effects of high potassium levels on plateau duration and the rate of rapid repolarization. The change in P wave and QRS durations reflects the slowing of impulse propagation in atrial and ventricular muscle that results primarily from the decreased rate of depolarization of the individual cells. Changes in repolarization (that is, T wave and QT interval) occur at lower potassium levels than do changes in depolarization (P wave and QRS durations). This can be attributed to the fact that the membrane must be depolarized by about 15 mV before a significant change in Vmax occurs (Fig. 3). This change in voltage occurs when potassium is increased from 5.4 to approximately 8 mEq/liter. Moreover, the change in conduction varies as the square root of the change in Vmax provided that no other factors important in determining conduction are altered (9). Thus, a 25% slowing of conduction requires a change in Vmax that approaches 50%.

Effects of other electrolyte changes and cardioactive drugs. In a similar manner, the effects of hypokalemia

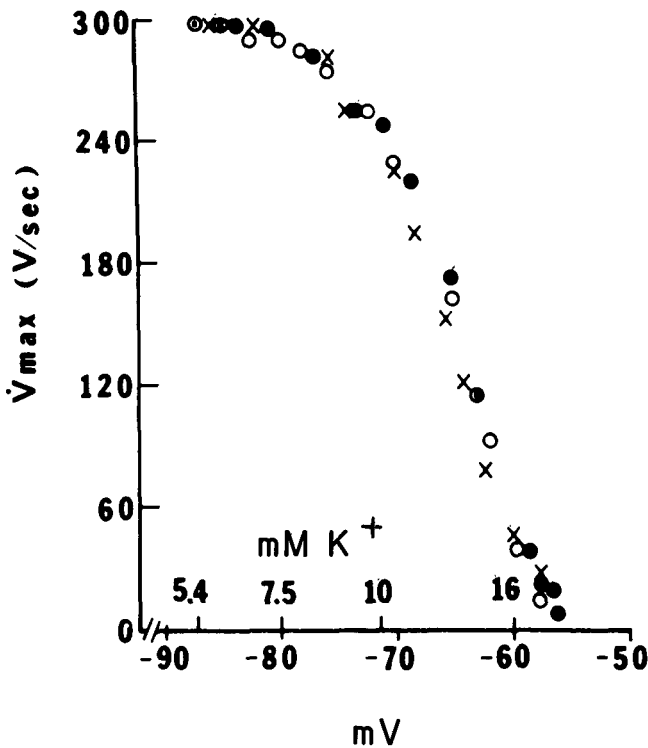


Figure 3. Relation between the changes in resting potential expressed in mV (horizontal axis, **below**) and maximal rate of rise of the action potential upstroke (V_{max} = vertical axis) as potassium concentration is raised from 5.4 to 20 mM (horizontal axis, **above**). The **closed circles** represent control observations; the **open circles** represent the effects of 1 $\mu\text{g/ml}$ of verapamil; and the **crosses** represent the effects of 3 $\mu\text{g/ml}$ of verapamil. (Reprinted from Chen CA, Gettes LS [32], with permission.)

and hyper- and hypocalcemia on the electrocardiographic waveform can readily be explained by the effects of these ionic changes on the cardiac action potential (3,10). The effect of cardioactive drugs on the electrocardiographic waveform can also be understood in terms of their effects on the action potential of the individual cells (8,11). For

instance, the effects of digitalis on the ST segment and T wave correlate with the effects of the drug on the plateau and rapid repolarization phases of the action potential. The effects of quinidine, procainamide and disopyramide phosphate on the QRS complex correlate with the slowing of the action potential upstroke induced by these drugs.

Acute ischemia and infarction. The electrocardiographic manifestations of acute ischemia and infarction are also explained by the changes in the action potential of the single fiber. The acute interpretation of coronary flow results in a series of rapidly occurring metabolic and ionic changes, including an increase in extracellular potassium (12-15), a decrease in extracellular pH (15,16), an increase in partial pressure of carbon dioxide (PCO_2) (17) and a decrease of partial pressure of oxygen (PO_2) within the ischemic zone. The simultaneously occurring changes in the ventricular myocardial action potential consist of a depolarization of the resting membrane, a decrease in upstroke velocity, overshoot and plateau voltage and an initial decrease in action potential duration (18-20). Later, action potential duration lengthens. These changes are primarily due to the effects of a high potassium concentration, although the concomitant change in other metabolic factors such as pH and PO_2 modify these changes (20,21). As a result, the resting potential of the ischemic cells becomes more positive (or less negative) than the resting potential in the nonischemic cells. This difference would cause changes in the TP segment of the electrocardiogram. The repolarization phases in the ischemic cells are less positive (or more negative) than in the normal cells. This difference will cause changes in the ST segment of the electrocardiogram. However, the vector of the ST segment change will be opposite to the vector of change in the TQ segment (Fig. 4) (22,23).

The clinical electrocardiogram cannot distinguish between primary TP or ST segment changes. Rather, it reflects the voltage difference between these two components and

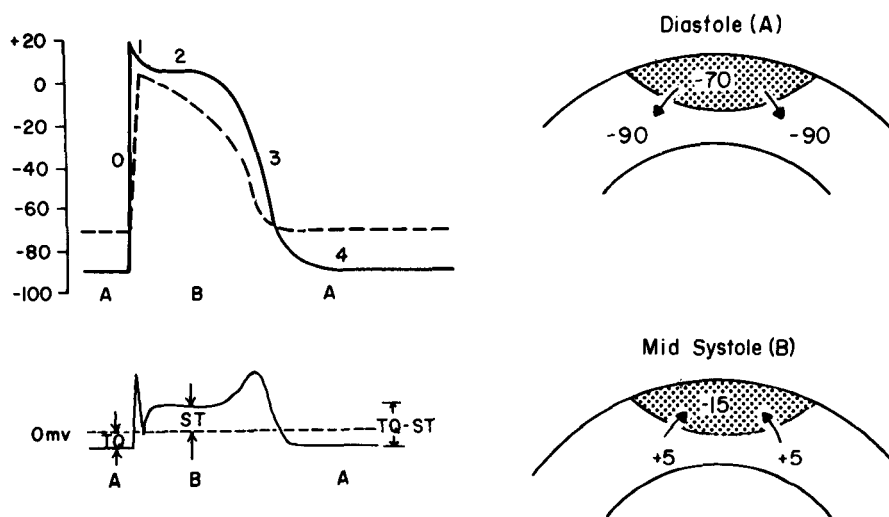


Figure 4. Schematic representation of the action potential and electrocardiographic changes associated with acute subepicardial ischemia. Action potentials at top left represent ischemic (**broken curve**) and normal (**solid curve**) tissue. The numbers indicate the various phases of the action potential. The electrocardiogram (**bottom left**) represents that recorded by an electrode overlying the ischemic area. The TQ segment is located below the isoelectric line and the ST segment above. A = diastole; B = systole. The panels on the right show the potential differences existing at the boundary between the normal and ischemic tissues. The **top right panel** shows the transmembrane potentials occurring during electrical diastole (A), the **bottom right panel** shows the transmembrane potentials existing at mid-systole (B). The **arrows** indicate the direction of the current flow at the boundary. (Reprinted from Holland RP, Brooks H [23], with permission.)

appears as either an elevation or a depression of the ST segment relative to the TP segment (Fig. 4). Whether ST elevation or depression occurs depends on 1) the location of the ischemic zone, that is, on the anterior, posterior or inferior wall in the epicardial or endocardial regions; and 2) the position of the recording electrode on the body surface (24). Inversion of the T wave may be explained by changes in the sequence of repolarization. The sequence of repolarization is altered in part by slowed conduction that can be attributed to the decrease in the maximal rate of rise of the action potential and to cell to cell uncoupling (25,26). Consequently, activation is delayed, causing a secondary delay in repolarization, and thus the sequence of repolarization is altered. The subsequent prolongation of the terminal repolarization phase will also alter the sequence of repolarization.

The development of transient Q waves, which may occur during acute ischemia (27,28), can be explained by the inexcitability of the cells within the ischemic zone. This occurs when the ionic and metabolic changes depolarize the resting membrane to levels that prevent a propagated depolarization from occurring. If the ischemic process is reversed before the development of irreversible cell change, the Q waves may be transient. However, if the cells become irreversibly damaged and necrotic, the abnormalities in propagation and the Q wave persist.

Conduction disturbances. The electrocardiographic manifestations of the various intraventricular conduction disturbances that characterize fascicular blocks, bundle branch blocks and ventricular preexcitation are explained by changes in the sequence of depolarization and repolarization induced by anatomic lesions.

Understanding of Normal and Abnormal Cardiac Rhythms

Cellular Electrophysiology

Our current understanding of arrhythmias can largely be attributed to studies in single fibers. Although it is difficult in the clinical setting to determine the electrophysiologic mechanism responsible for an arrhythmia, single fiber studies have provided an increasing body of knowledge to explain the abnormalities of impulse formation and propagation that express themselves clinically as disturbances in cardiac rhythm. Four examples illustrate the advances in cellular electrophysiology that apply directly to our thinking about cardiac rhythms. These are 1) discovery of the slow calcium-sensitive inward current, 2) recognition of afterdepolarizations and triggered activity, 3) delineation of the electrophysiology of premature beats, and 4) appreciation of electrotonus as a factor in impulse formation and propagation.

Slow calcium inward current. Katz (29) has presented

a detailed history of the discovery of the slow calcium-sensitive inward current. Its importance is reviewed in monographs (30,31). The slow current is responsible for sinus node electrical activity and for slow conduction in the upper portion of the atrioventricular (AV) node. The slow calcium-sensitive current also provides a mechanism for very slow conduction in other fibers (see references in 30 and 31). The maximal upstroke velocity of cells dependent on the slow current for depolarization is in the range of 5 to 20 V/s. In contrast, the maximal upstroke velocity of "normal" ventricular fibers having a resting potential of approximately -80 to -90 mV ranges between 100 and 300 V/s, and fully repolarized Purkinje fibers depolarize at maximal rates of 500 to 1,000 V/s. Because, as already discussed, the maximal upstroke velocity of the action potential is a major determinant of conduction velocity, it is reasonable to predict that calcium-dependent cells should conduct at 1/20th to 1/200th the speed of normally conducting ventricular or Purkinje fibers provided that no other determinants of conduction are significantly altered. Although slowing of the upstroke of similar magnitude may result from a depressed but still active sodium-dependent rapid channel (32), the availability of the calcium channel provides a mechanism for slow impulse propagation in cells in which the sodium system is totally unavailable or inactive. The slower the conduction, the smaller the pathway required for a reentrant circuit (33). Likewise, the smaller the reentrant pathway, the greater the difficulty in differentiating it from a focus of enhanced automaticity.

The slow calcium-sensitive current has also been implicated in the genesis of repetitive activity that can occur in both ventricular and Purkinje fibers when they are depolarized to a level at which the sodium system is totally inactivated (Fig. 5) (34, see references in 30 and 31). Spontaneous repetitive activity of a similar type has also been observed in stretched fibers (35).

Afterdepolarizations. The identification of afterdepolarizations, either in the terminal portion of the repolarization of the action potential or after the return to the resting potential, has provided another mechanism for arrhythmias (Fig. 6). Afterdepolarizations may be induced by alterations in ionic composition and by drugs, particularly catecholamines and digitalis (36,37). The afterpotentials involve the slow channel (see references in 30 and 31) and result in a form of automaticity that is triggered and terminated by a single properly timed extrastimulus. Thus, this form of abnormal impulse formation is difficult to distinguish from reentry, although its occurrence has been suspected in certain clinical arrhythmias (38,39) and guidelines for identifying its presence have been defined (40).

Premature beats. Single fiber studies have shown that early premature responses are characterized by a slowed action potential upstroke and shortened action potential duration (4,6,41-43). These findings have been based on the

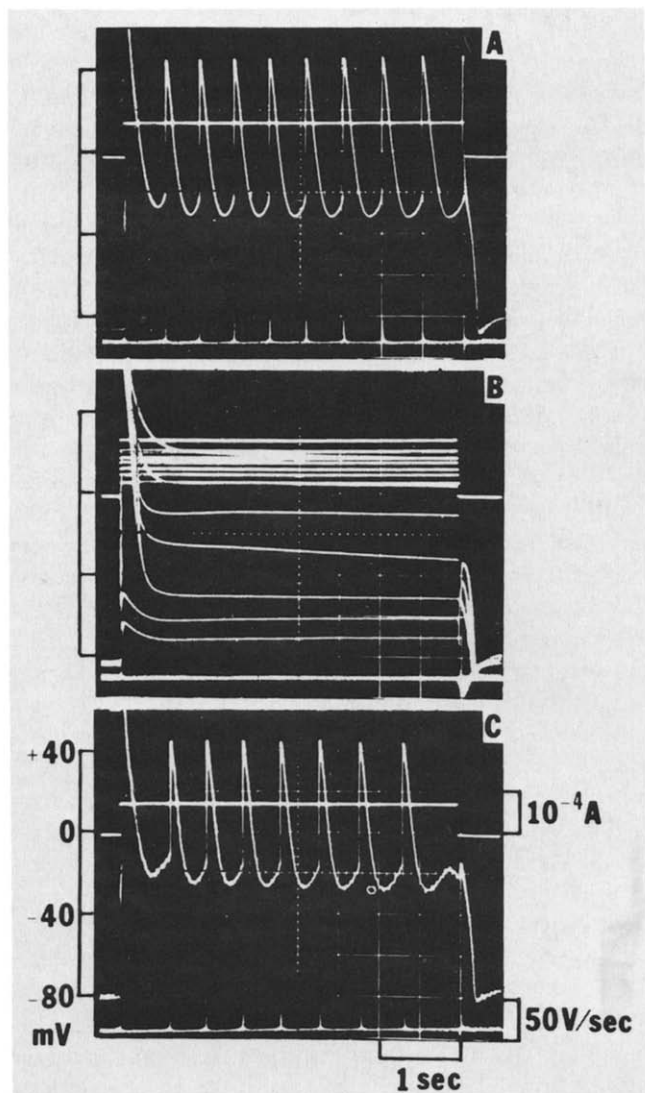


Figure 5. Repetitive activity induced in guinea pig papillary muscle by depolarizing pulses. **Panel A**, control observation after depolarization to -32mV . **Panel B**, after 6mM manganese chloride which prevents the automatic activity. **Panel C**, 30 minutes after return to the control solution. (Reprinted from Imanishi S, Surawicz B [34], by permission of the American Heart Association, Inc.)

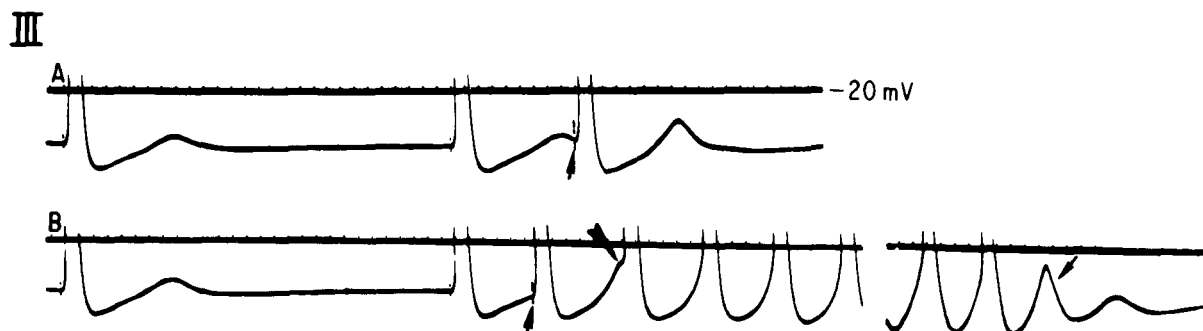
inactivation and reactivation characteristics of the various current systems responsible for the action potential. They help explain the slowed conduction and shortened refractory periods that characterize early premature responses in the intact heart (44,45), particularly when these responses arise from the downslope of the T wave (the vulnerable period) and thus from incompletely repolarized fibers. These studies have shown that steady state and premature responses with the same interstimulus interval have different electrophysiologic characteristics, thereby establishing the importance of the diastolic interval rather than the coupling interval as the determining factor for the characteristics of premature beats. These observations, in turn, explain the ability of premature responses to induce reentry. Moreover, the studies indicate that the effects of interventions, such as ischemia and cardioactive drugs, on the premature response cannot be predicted from their effect on the nonpremature (steady state) response.

Electrotonic influences. The fourth advance in cellular electrophysiology that has influenced our thinking about clinical arrhythmias is the demonstration that electrotonic influences can alter action potential duration (46), lead to reflection (47) and modulate the rate of spontaneously depolarizing fibers (48) so that a parasystolic focus can generate responses that are indistinguishable from those caused by entry.

Initiation of Clinical Arrhythmias

The proliferation of information obtained largely from single fiber studies, and recently reviewed by Hoffman and Rosen (49), has rendered past attempts to attribute arrhythmias to a single mechanism overly simplistic. It has become in-

Figure 6. The lower portions of action potentials recorded from the anterior leaflet of the mitral valve in the monkey in the presence of epinephrine, $1.0\ \mu\text{g/ml}$. Note the afterdepolarization that occurs after the completion of repolarization. **Panel A**, a premature response (arrow) is induced in the repolarization phase of the previous afterdepolarization. Note that the amplitude of the afterdepolarization of the premature response has increased. **Panel B**, the premature response is induced before the afterdepolarization of the preceding response would have occurred. A spontaneous action potential arises from the afterdepolarization of the premature response and sustained automatic activity occurs. (Reprinted from Wit AL, Cranefield PF. *Circ Res* 1976;38:85-98, by permission of the American Heart Association, Inc.)



creasingly apparent that many clinical arrhythmias owe their genesis to more than one mechanism, and that a single clinical observation may be explained equally well by several different mechanisms. For instance, an understanding of repetitive paroxysmal supraventricular tachycardias, a hallmark of reentry within the atrioventricular junction, requires knowledge of the cause of the initiating beat which is usually premature and of the cause of the changes in conduction and refractoriness that permit unidirectional block and formation of functionally discrete conduction pathways. The initiating beat, whether supraventricular or ventricular, may be due to enhanced automaticity, reentry or reflection. As indicated previously, several mechanisms for enhanced automaticity which are capable of providing a spontaneous impulse have been defined. Moreover, because reentry and reflection can occur in a very small group of cells, it may be virtually impossible to determine the cause of the initiating beat.

Conduction slowing can be due to depression of the rapid inward current or to the presence of cells that are dependent on the slow calcium-sensitive inward current for depolarization. In some situations, cell to cell uncoupling may cause slow conduction. The ability of the initiating beat to enter only one limb of a reentrant circuit within the atrioventricular junction implies that the cells within the junction must have dissimilar properties. Such dissimilarities have been shown to exist within the cells of the atrioventricular node (50). A difference of a few milliseconds in the duration of the action potential and, therefore, the duration of the refractory period in adjacent cells, can cause an early premature beat to be blocked in some cells and to conduct slowly in other cells. This slow conduction allows the refractory group of cells to recover their excitability and thereby permits the creation of the reentry circuit.

Mechanism of ischemia-related arrhythmias. The mechanism of ischemia-related arrhythmias is now largely understood as a result of cellular electrophysiologic studies. The ionic and metabolic changes referred to earlier are inhomogeneous and result in a juxtaposition of cells with significant differences in their electrophysiologic properties (Fig. 7) (19). This creates differences in conduction and refractoriness that are most marked at the lateral borders of the ischemic zone but extend throughout the zone. Areas of unidirectional conduction result, and reentry is facilitated. The slowed conduction required for reentry occurs because of the decrease in the resting membrane potential, which causes a decrease in the maximal rate of rise of the action potential upstroke and probably because of cell to cell uncoupling. If the extracellular potassium increases to sufficiently high levels (approximately 12 to 15 mEq/liter), the membrane is depolarized to a potential that totally suppresses the sodium current. However, the calcium current then is capable of depolarizing the membrane. Both mechanisms—the depressed rapid channel and the slow channel—are probably important in the genesis of the conduction slowing.

These changes in conduction and refractoriness may provide an environment that permits reentry to occur and induces a premature beat that promotes a self-sustaining arrhythmia (51). Myocardial fiber stretch may stimulate spontaneous diastolic depolarization and provide a second mechanism for the premature beats that initiate self-sustaining arrhythmias. Another mechanism may be related to the effect of catecholamines both on cells of the Purkinje fiber type and on ventricular cells depolarized to levels at which automaticity occurs by way of the slow channel. A fourth mechanism for explaining the initiating event is the voltage difference between adjacent cells. This may act as a battery capable of producing a threshold current (52). Each of these various mechanisms has been demonstrated in intact hearts and modeled in single fibers.

Many other supraventricular and ventricular arrhythmias, such as those that occur in patients with Wolff-Parkinson-White syndrome or ventricular aneurysm and those related to hypopotassemia, digitalis and other cardioactive drugs, can be explained largely from the information derived from single cell preparations.

Figure 7. Transmembrane action potentials recorded from the epicardial surface of the pig after 9 minutes of ischemia. The action potentials are recorded from the center of the ischemic zone by microelectrodes 2.5 cm apart. The **upper panel** shows a 2:1 response to an applied stimulus, while the **lower panel** shows a 1:1 response, illustrating the inhomogeneity of the electrical activity within the center of the ischemic zone. (Reprinted from Downar E, Janse MJ, Durrer D [19], by permission of the American Heart Association, Inc.)

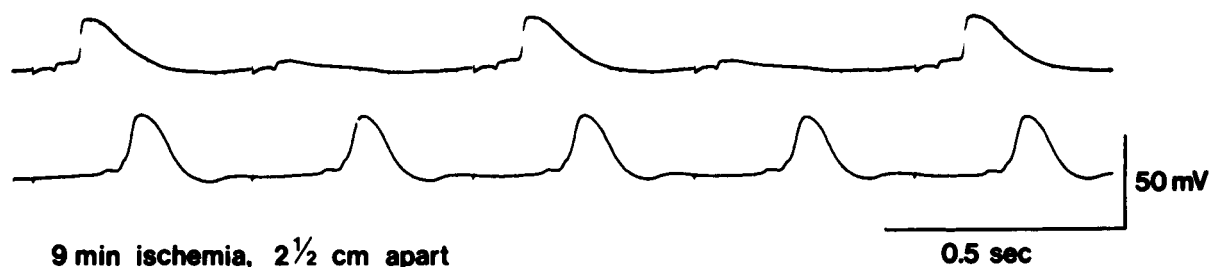
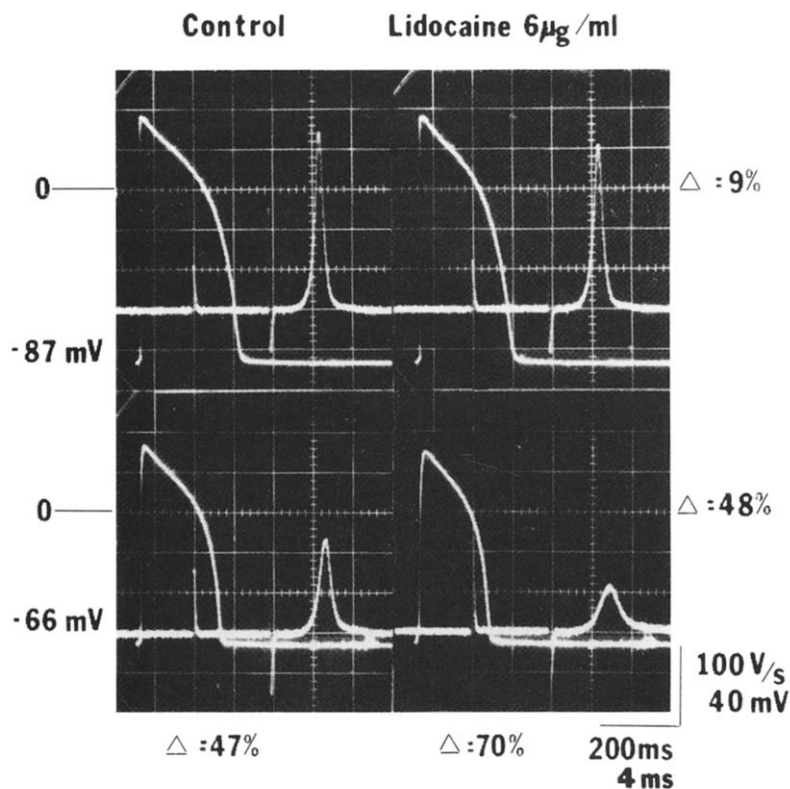


Figure 8. Effect of lidocaine on transmembrane action potentials and differentiated upstrokes in guinea pig papillary muscles, recorded at a faster speed and displayed to the right of the action potential. The peak of the differentiated upstroke signal represents the maximal rate of rise of the action potential upstroke. The resting membrane potential is decreased from -87 to -66 mV (**lower panel**) by increasing potassium concentration in the perfusate from 5.4 to 10 mM. Note that the decrease in the maximal rate of rise induced by lidocaine is greater when the resting potential is -66 mV than when it is -87 mV, illustrating the voltage dependence. (Reprinted from Chen CM, Gettes LS, Katzung BG [57], by permission of the American Heart Association, Inc.)



Mechanism of Action of Cardioactive Drugs

A desire to understand the mechanism of action of currently available antiarrhythmic drugs and to develop drugs with specific modes of action has occupied cellular cardiac electrophysiologists and electropharmacologists since the application of the microelectrode to the study of cardiac cells. These studies have shown that the cardioactive drugs are capable of altering the various ionic currents responsible for spontaneous diastolic depolarization, the rapid upstroke of the action potential, the plateau phase and the phase of rapid repolarization and that most currently used cardioactive drugs can alter several of these components.

Differences in antiarrhythmic drugs. Because antiarrhythmic drugs exhibit significant differences in their predominant effects, they have been classified in several ways (53-56). For instance, lidocaine and the lidocaine analogs, such as mexiletine and tocainide, have a greater influence on the upstroke of depolarized fibers than on the upstroke of normal fibers (57-59); that is, they exhibit voltage dependency (Fig. 8). However, quinidine and procainamide have nearly the same influence on normal and depolarized fibers (57). Verapamil influences the upstroke only of those cells in which the slow calcium-dependent current is the responsible depolarizing current system (see references in 30 and 31). The drug has little, if any, effect on the action

potential upstroke of cells dependent on the sodium system (Fig. 3).

These differences are reflected in the intact heart of experimental animals and human beings. For instance, lidocaine slows conduction in depressed fibers but not in normal fibers as reflected by slowing of conduction in infarcted tissues and a lack of effect on the QRS complex (60,61). Quinidine slows conduction in all cells, as reflected by the widening of the QRS complex that frequently characterizes its use. In contrast, verapamil has no effect on the QRS complex, but slows conduction across the atrioventricular node, as reflected by PR prolongation (62-64). The drugs also exert different influences on repolarization (56), as illustrated by the effect or the lack thereof of the various antiarrhythmic drugs on the QT interval, ST segment and T wave. The lidocaine-like and quinidine-like drugs share the ability to prolong refractoriness to a greater degree than can be explained by their effect on the repolarization limb of the action potential. This characteristic prolongs the coupling interval of the earliest premature beat. Finally the binding characteristics of the drugs with the various ionic channels result in rate or use dependency (Fig. 9) (65-68). This factor can be used to predict whether the effect of the drug on conduction will be more pronounced at more rapid rates.

Clinical applications. The various single fiber studies have provided valuable new insights into the mechanism of

action of the antiarrhythmic drugs and have established a rational framework for many therapeutic combinations. Although the treatment of arrhythmias remains largely empirical, it has become increasingly apparent that the understanding of drug action gained from single fiber studies permits a more complete understanding of the mechanism of the arrhythmia itself. For instance, if an arrhythmia responded to an agent with lidocaine-like effects on the action potential upstroke after being unresponsive to quinidine, one could speculate that depolarized fibers were more important than normal fibers in the genesis of the arrhythmias, and that the slowing or interruption of conduction in the partially depolarized fibers was a more important factor than was a change in the conduction or refractoriness of the normal fibers. The ability of a drug with verapamil-like effects to terminate a supraventricular or ventricular arrhythmia would suggest that the slow channel was involved in the genesis of the arrhythmia. Furthermore, the knowledge that verapamil is of specific utility in slowing conduction across the atrioventricular junction has helped predict its now documented ability to slow the ventricular response in atrial fibrillation or flutter and to convert atrioventricular junctional reentry tachycardia to sinus rhythm (69,70).

Single fiber studies have also contributed to our understanding of the electrophysiologic effects of neurotransmitters. For instance, the information that acetylcholine inhibits the slow channel and accentuates potassium efflux, and that the beta-adrenergic agonists are slow channel stimuli (see references in 71), helps explain the effects of carotid sinus stimulation, exercise and a variety of stimuli to the sympathetic and parasympathetic nervous systems on the electrical activity of the heart.

Future Trends

Technologic advances. Our increased understanding of cardiac electrical activity that has occurred in the last 30 years can be traced to several major conceptual and technological advances. Clearly, the application of the microelectrode to the study of cardiac fibers formed the keystone for subsequent advances. The use of the voltage clamp to measure the net ionic currents flowing across the cell membrane (72) and its combined use with specific ionic channel blocking agents permitted the more precise definition of the various currents and an understanding of specific membrane channels. The demonstration of the slow inward current dependent on calcium ions provided an explanation for excitation-contraction coupling, the unique features of sinus and atrioventricular nodal fibers and a mechanism for very slow conduction. The use of ion-specific electrodes (73) capable of measuring extracellular and intracellular ionic activities allowed, among other things, greater insight into the characteristics of the various ionic pumps and the causes of the electrical manifestations of ischemia. The use of the computer to simulate empirically derived observations (68,74) has permitted the mathematical characterizations of the ionic channels and a broader understanding of the interaction of cardioactive drugs with the membrane ionic channels. The use of computers has also promoted a greater understanding of the factors that determine conduction (75) and of the conditions that permit and sustain reentry (76).

Future progress. It is reasonable to assume that progress in these areas will continue and that new techniques will have an equal impact on our understanding of clinical phenomena. Studies in individual myocytes (77) may help

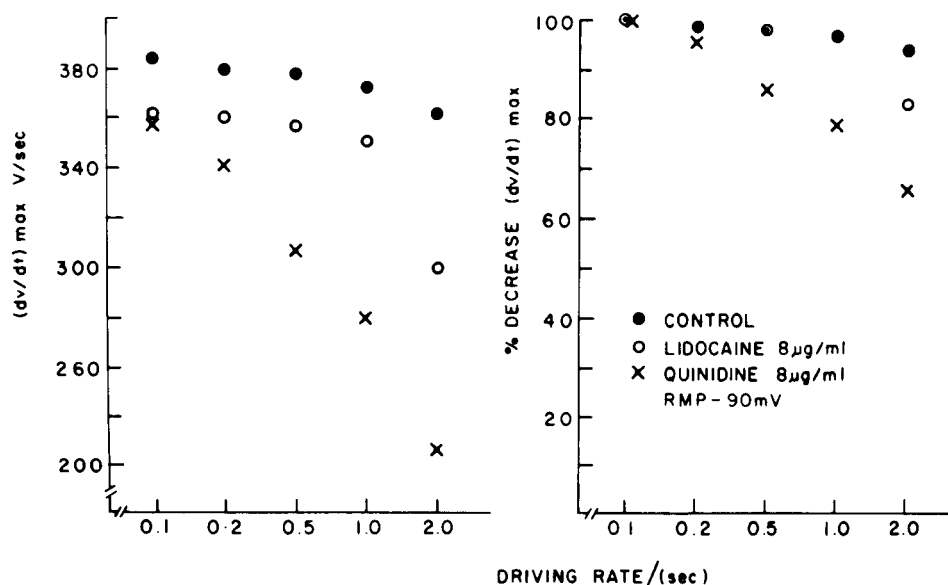


Figure 9. Effect of increasing stimulation frequency from 0.1 to 2.0 on maximal rate of rise in the action potential upstroke (dv/dt) max during control perfusion (●) and after the introduction of lidocaine (○) and quinidine (×) in guinea pig papillary muscle. Note that the rate-dependent effects of quinidine are more marked than those of lidocaine. RMP = resting membrane potential. (Reprinted from Chen CM, Gettes LS, Katzung BG [57], by permission of the American Heart Association, Inc.)

us determine how cells interact with one another and how they couple. Such information will broaden our understanding of conduction and refractoriness. The ability to voltage clamp a small patch of membrane (78) holds the promise of a greater understanding of the biophysics of ionic channels, particularly the rapid sodium channel (79), which should broaden our understanding of normal and abnormal electrical behavior and the mechanism of action of antiarrhythmic drugs. It is clear that continued research will try to identify the mechanisms underlying clinical arrhythmias, to define more precisely the role of the various current systems, particularly the slow calcium-sensitive current, in the genesis of clinical arrhythmias and to understand the modification of electrophysiologic properties induced by cardiac diseases and drugs.

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