Cardiac Arrhythmias

Electrophysiologic Basis for Clinical Interpretation

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Preface

The past several decades have witnessed major advances in the understanding and management of cardiac arrhythmias. With the advent of the coronary care units and our ability to treat patients with potentially serious cardiac arrhythmias more efficiently, interest in the entire field of electrophysiology has matured rapidly. Precise interpretation of cardiac dysrhythmias in the management of medical and surgical patients has become extremely important. It is now mandatory that all physicians and paramedical personnel treating cardiac patients have a fundamental understanding of cardiac dysrhythmias.

While numerous textbooks have adequately illustrated interesting typical and unusual examples of various cardiac dysrhythmias, few have tried to correlate the fundamental electrophysiologic mechanisms with their clinical counterparts. It is now more than two decades since the publication of *Clinical Electrocardiography, Part I: The Arrhythmias** by Drs. L.N. Katz and A. Pick, which was one of the initial such attempts. The present text develops a particular subject from its basic physiologic principles with subsequent clinical application in a rather structured fashion, so that the student can systematically interpret simple as well as complex cardiac arrhythmias. In many instances, precise fundamental experimental knowledge is available, but in other areas much is still unknown. The majority of the text is based on the experimental and clinical observations of the authors. It is acknowledged that some of the views expressed in this monograph are not entirely in agreement with those of other serious investigators. However, the differences are clearly expressed and the arguments are left for the reader to decide in the future as more precise information becomes available.

The book includes discussions of newer electrophysiologic mechanisms such as the slow response and early or delayed afterdepolarizations, as well as the more commonly known physiologic concepts that have been brought into sharp focus by ultramicroelectrode techniques. Mechanisms of the atrial arrhythmias are explored in full with frequent reference to both hemodynamic and electrophysiologic correlations. The AV junctional rhythms have been updated both in the sense of terminology and by incorporating the recent experimental and clinical observations.

An interesting departure from the classical concepts of Wenckebach and Mobitz is presented in the chapter on AV block, as importance is placed on the level of the conduction disorder rather than on the behavior of the PR interval or specific classification according to the older criteria. The electrophysiologic basis for these concepts is clearly described. Ultramicroelectrode techniques have

*Philadelphia, Lea & Febiger, 1956.

elucidated certain mechanisms of the AV conduction disturbances which could not have been possible to suspect with His bundle recordings. The text includes the revolutionary concepts of the fascicular block and fascicular rhythms.

The ventricular arrhythmias are discussed in terms of their electrophysiologic mechanisms, and attempts are made to identify the site of impulse formation of the ectopic beats. Several newer concepts of parasystole may surprise the reader. Fundamental mechanisms engendering ventricular fibrillation are also revealed by the ultramicroelectrode.

No specific chapter was reserved for a discussion of pacemaker rhythms, although some complex problems related to cardiac pacing are touched upon in several chapters. While the treatment of cardiac arrhythmias is not a primary goal of this monograph, some of the more recent electrophysiologic and electropharmacologic concepts are reviewed in the final chapter. Since this area of the discussion must necessarily change rapidly with clinical pharmacology, no particular emphasis has been assigned to any single or group of antiarrhythmic agents.

The descriptive illustrations of the clinical electrocardiograms were based on the experience gained through the years in conducting the core curriculum on "Mechanisms and Therapy of Cardiac Arrhythmias." The student is urged to use deductive reasoning in conjunction with pocket calipers. More complex arrhythmias should be left for later study while the student gains confidence with the relatively simple records. This monograph was in no way intended to serve as a repository or an atlas of cardiac arrhythmias. The records have been deliberately selected for their teaching, illustrative, and electrophysiologic interest.

The authors gratefully acknowledge the infinite work of many scientists who have contributed so much to the understanding of electrophysiology of the cardiac arrhythmias. The numerous references attest to our recognition of their contributions. The authors also wish to thank Drs. Langendorf, Pick, and Katz, whose encouragement and influence kindled the burning and lasting interest to begin the electrophysiologic studies to establish a basis for our understanding of these dysrhythmias.

Yoshio Watanabe, M.D.

Leonard S. Dreifus, M.D.

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1.
Introduction

DEFINITION OF CARDIAC ARRHYTHMIA

Literally, the term arrhythmia implies absence of rhythm, and hence, it readily suggests irregularities of the heartbeat. In a broader sense, however, cardiac arrhythmia can probably be defined as any deviation from normal cardiac rhythmicity, the requirements being as follows[1]: (1) The rhythm originates in the sinus (sinoatrial) node. In other words, the sinus node assumes the role of pacemaker of the heart. (2) The frequency of sinoatrial impulse formation is within an optimal range. This range usually is between 60 and 100 per minute in adults. (3) Within this range, the rate must be reasonably regular. Although different criteria for regularity are being used by different schools, variations of the sinus cycle exceeding 0.12 seconds within short periods of time (e.g., 5 to 10 seconds) would perhaps qualify for sinus arrhythmia. (4) Every sinus impulse is transmitted to the ventricles through the normal atrioventricular (AV) conducting system, and with a normal, constant conduction time. Normal AV conduction time, as expressed by the PR interval on the electrocardiogram, ranges from 0.12 to 0.21 seconds in adults. (5) Intraventricular conduction is also normal, with the impulse traveling through the His bundle, bundle branches or fascicles, and the peripheral Purkinje network. Normal intraventricular conduction is accompanied by a QRS duration of not more than 0.10 seconds in the limb leads.

From the above discussion, it becomes readily apparent that cardiac arrhythmias include alterations in the site, frequency, or regularity of impulse formation, as well as abnormal conduction of excitation.[1-3] Thus, disorders such as first-degree AV block and bundle branch block are also discussed in this text, even though the rhythm is of sinus origin and quite regular.

BASIC KNOWLEDGE IN CARDIAC ELECTROPHYSIOLOGY

Classically, mechanisms of cardiac arrhythmia were divided into two major categories, (1) abnormalities of impulse formation and (2) disturbances of conduction of excitation. Their combinations are also often invoked to explain the genesis

of certain rhythm disorders. Since it is now well established that these mechanisms are closely related to altered electrical properties of the myocardial cell membrane, basic knowledge in cellular electrophysiology is a prerequisite for an in-depth discussion of cardiac arrhythmias.[4-12] The widespread use of His bundle electrocardiography in clinical cardiology has further increased the enthusiasm in the electrophysiological approach to the understanding of rhythm disorders. Several electrophysiological mechanisms of arrhythmia are listed in Table 1-1.

Membrane Potential, Excitability, and Refractoriness of Cardiac Cells[13-16]

Similar to the cells of other excitable tissues such as nerve and skeletal muscle, the myocardial cells have a polarized membrane, with a negative charge inside and a positive charge outside during the so-called electrical diastole, or phase 4. This voltage drop across the membrane (transmembrane potential), as determined by the use of intracellular microelectrode techniques, amounts to approximately −90 mV in most fibers of mammalian atria and ventricles (Fig. 1-1). This is called the membrane resting potential. When a stimulus (most commonly electrical, but possibly mechanical or chemical) is given to these cells, a current flows across the membrane causing a reduction in the membrane potential (reduction implies a decrease in its absolute value), or depolarization. If depolarization brings the membrane potential to a critical level (the threshold potential), a rapid reversal of the membrane potential to +30 to +40 mV usually ensues. The latter is

Table 1-1
Electrophysiological Mechanisms of Cardiac Arrhythmias

I. Abnormalities of impulse formation
  A. Alterations of physiological automaticity in the specialized conducting fibers
    1. Enhanced automaticity
    2. Depressed automaticity
  B. Development of abnormal automaticity in the atrial and ventricular muscle fibers
  C. Other mechanisms of impulse formation
    1. Oscillations of membrane potential
    2. Delayed afterdepolarization (transient depolarization)
    3. Early afterdepolarization
    4. Local potential differences causing reexcitation of certain fibers, due to either asynchronous repolarization or partial depolarization
II. Disturbances of conduction of excitation
  A. Decremental conduction
  B. Inhomogeneous conduction
  C. Conduction delay and block
  D. Unidirectional block
  E. Reentry
III. Combined disturbances of impulse formation and conduction
  A. Parasystole
  B. Ectopic rhythms with exit block
  C. Fibrillation

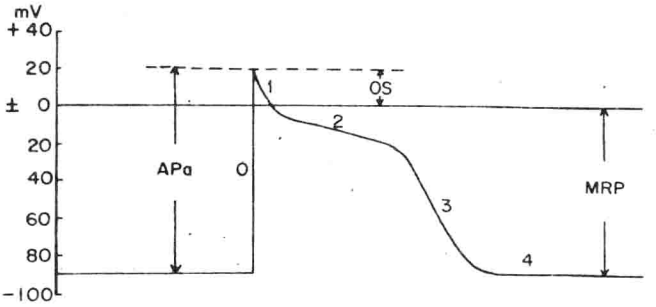

Figure 1-1. Various phases of transmembrane potential. APa, action potential amplitude; OS, overshoot; MRP, membrane resting potential. (Reproduced from ref. 1.)

called the overshoot. This rapid depolarization is designated as phase 0, and in normal atrial, Purkinje, and ventricular fibers, this phase is 1 msec or shorter. The amount of current or the stimulus strength required to reduce the membrane potential to the threshold potential determines the excitability of a given cell. Thus, the smaller this requirement, the higher the excitability, and vice versa. If a stimulus fails to shift the membrane potential to the critical level, termination of the stimulus results in restoration of the original resting potential, and transition to the rapid phase 0 does not occur. This is termed a subthreshold stimulus. In contrast, once the membrane potential is decreased to the threshold potential (suprathreshold stimulation), rapid upstroke of phase 0 continues, even with cessation of stimulation, to bring about full depolarization. This process has been called regenerative depolarization.

Phase 0 is immediately followed by repolarization, which brings the membrane potential back to the resting level. Three phases are often identified in this process of repolarization. The initial, rapid repolarization phase is called phase 1, which is most prominent in Purkinje fibers and may be absent in other fiber types.[15] The intermediate phase of slow repolarization (often not apparent in atrial muscle fibers) is designated as phase 2, or plateau; and the final, more rapid repolarization phase is called phase 3. The entire sequence of potential change from the beginning of depolarization to the end of repolarization forms an action potential, and the action potential amplitude is determined between the resting potential and the peak of phase 0 (see Fig. 1-1). The duration of action potential in myocardial cells is much longer than that of nerve or skeletal muscle fibers, attaining a value of several hundred milliseconds. Until repolarization restores the membrane potential to a certain level, the cells cannot be reexcited (or depolarized) by a stimulus of any strength. This period corresponds to the absolute (or effective) refractory period.[13-15] The relative refractory period then follows, during which the cells are reexcited only with the application of stronger stimuli than during the electrical diastole or phase 4 (Fig. 1-2). Under physiological conditions, the membrane resting potential, as well as the excitability, remains practically unchanged during phase 4 in the "working myocardial fibers" of the atria and the ventricles. In certain cells (mainly Purkinje fibers), a brief period may be observed toward the end of phase 3 repolarization during which the cells could be reexcited with weaker stimuli than during phase 4. This is the supernormal period of excitability.[13,15,17] One possible explanation is that when repolarization has

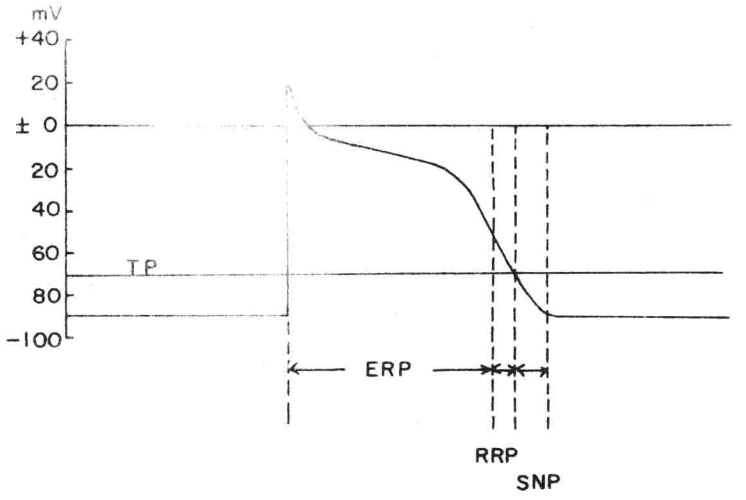

Figure 1-2. Transmembrane action potential and the refractory period. TP, threshold potential; ERP, effective refractory period; RRP, relative refractory period; SNP, supernormal period. (Reproduced from ref. 1.)

progressed beyond the threshold potential but has not attained the resting potential, the membrane potential is closer to the threshold potential, and hence, less current is required to produce sufficient depolarization to the threshold level compared with the electrical diastole (see Fig. 6-35).

The duration of action potential varies depending on fiber types and, in general, it is progressively prolonged from the atrial fiber through the AV node and His bundle to the peripheral Purkinje fiber (Fig. 1-3).[6,15] Even in the same single fiber, this duration is altered by various physiological and pharmacological factors. The most important physiological determinant of the action potential duration is the cycle length or frequency of excitation, with a longer cycle length (or slower heart rate) associated with a longer action potential duration and vice versa. Such effects of cycle length, however, are not identical in different cell types, usually being more marked in Purkinje than in ventricular muscle fibers, for instance. Although the length of the refractory period tends to parallel the action potential duration, the end of repolarization by no means denotes the restoration of diastolic excitability. Nevertheless, changes in the excitability and refractoriness play an important role in the genesis of cardiac arrhythmias,[4-12] and knowledge of these relationships is also mandatory in fully understanding the pharmacology of various antiarrhythmic agents.

Automaticity and Other Mechanisms of Impulse Formation

In ordinary or working myocardial fibers of the atria and the ventricles, the membrane resting potential usually remains constant, and its reduction to the threshold potential is produced by the propagation of an impulse (wave of excitation). On the other hand, there is a group of cardiac cells that could undergo spontaneous membrane depolarization and form impulses of their own. The most

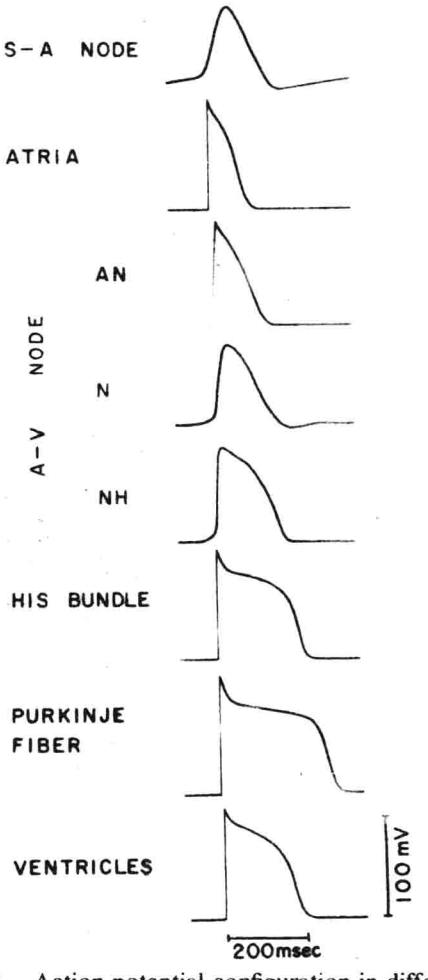

Figure 1-3. Action potential configuration in different fiber types. Note progressive prolongation of action potential duration from the atria to the peripheral Purkinje fibers. (Reproduced from ref. 6.)

typical of these specialized fibers is the cells of the sinoatrial node.[15,18] The characteristic behavior of their membrane potential is schematically illustrated in the top half of Figure 1-4. These cells show a progressive decrease in their membrane potential during phase 4, which is called the diastolic (phase 4) depolarization. When this slow diastolic depolarization brings the membrane potential to the threshold level, a smooth transition to the more rapid depolarization of phase 0 produces an action potential. The ability to form de novo impulses is termed automaticity, and diastolic depolarization is the prerequisite for automatic impulse formation. Under physiological conditions, automaticity is found only in the fibers of the specialized conducting system including the sinus node, intraatrial conducting system, certain regions of the AV node, His bundle, bundle branches or fascicles, and peripheral Purkinje network (Fig. 1-4, *bottom*).[5,15]

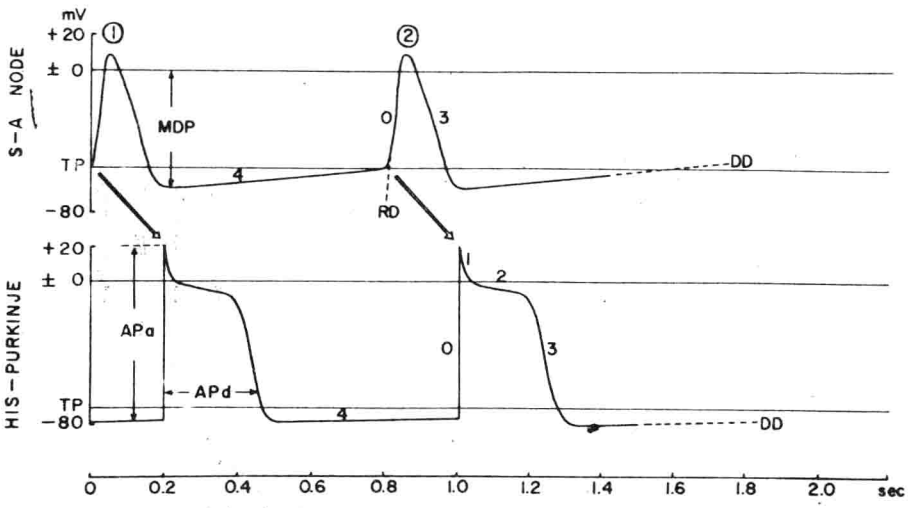

Figure 1-4. Automaticity in the SA node and His-Purkinje system. TP, threshold potential; MDP, maximal diastolic potential; RD, rate of depolarization; DD, diastolic depolarization; APa, action potential amplitude; and APd, action potential duration at 80% of repolarization. Note smooth transition from phase 4 to phase 0 in the pacemaker cell. (Reproduced from ref. 6.)

As stated above, many fibers of the AV conducting system possess automaticity. However, the slope of diastolic depolarization varies widely from one fiber type to another, usually being steepest in the SA node. Hence, the progressive decrease in the membrane potential which starts in numerous fibers immediately after one heartbeat attains the threshold potential first in the SA node. Thus, other specialized fibers are preempted into the rapid upstroke of phase 0 by the propagated sinus impulse before their phase 4 depolarization reaches the threshold potential. This is the major reason why the SA node normally acts as the pacemaker of the entire heart. Various electrophysiological observations indicate that when an automatic fiber is discharged by extrinsic stimuli (more commonly in a rapid, repetitive manner, but often even singly), its automaticity tends to be depressed.[18-22] This phenomenon of so-called overdrive suppression may play a partial role in maintaining the dominance of the sinus pacemaker over the remaining specialized fibers and potential subsidiary pacemakers.

However, the above statement also readily indicates that the question of which area of the specialized tissue becomes the pacemaker under a given condition is determined by the relative rapidity with which the threshold potential is attained through diastolic depolarization in individual automatic cells. Thus, if automaticity is markedly enhanced in certain specialized fibers outside the sinus node, impulses formed in this area will gain the control of the entire heart at a rate faster than that of the sinus rhythm. Most cases of nonparoxysmal ectopic tachycardia probably result from this mechanism.[1,6] The role of automatic activity in producing single premature beats has not been established except in parasystole. On the other hand, when automaticity is severely depressed in a majority of specialized fibers including the SA node, it leads to an extreme slowing of the cardiac rhythm or even to the abolition of all the pacemakers and ventricular

standstill. It is, therefore, apparent that both enhancement and depression of automaticity can engender serious disturbances of impulse formation. The effects of automaticity on conduction of excitation will be discussed in the next section.

It has often been pointed out that the working myocardial fibers of the atria and the ventricles could develop diastolic depolarization and automatic impulse formation under certain pathophysiological conditions.[23,24] Admittedly, those conditions reported earlier, such as perfusion with a potassium- and calcium-free medium,[24] were highly abnormal and almost incompatible with life, and hence, the possibility of this mechanism playing a role in the genesis of clinical arrhythmias was considered quite remote.[6] More recent observations, however, suggest that automaticity in the atrial and ventricular muscle fibers could be produced by partial depolarization of the cell membrane, or the loss of resting potential.[25] If this holds true in the in situ heart in the presence of ischemic or other heart disease, it is possible that ectopic impulse formation may arise in the ordinary myocardial tissues and readily contribute to various rhythm disturbances. We shall designate this mechanism as abnormal automaticity in the working myocardium, in contradistinction to physiological automaticity in specialized conducting fibers as discussed above. It should further be pointed out that this type of automatic activity is apparently dependent on the so-called slow ionic channels.[25-29] Electrophysiologic characteristics as well as implications of slow channels will be further discussed with reference to various conduction phenomena.

Aside from the physiological and abnormal automaticity, several other modes of impulse formation have been recognized, as listed in Table 1-1. These include oscillations of membrane potential, so-called afterdepolarizations[25] or transient depolarizations,[30] and localized potential differences.[5,6,13] In contrast to automaticity, most of these mechanisms require an initial heartbeat in order to become operative and generate new impulses. In the SA nodal or Purkinje fibers, for instance, a series of subthreshold oscillations of the membrane potential may follow a full-sized action potential under certain experimental conditions including sodium-free media containing isoproterenol,[19] lowering of extracellular potassium concentration in the presence of sodium,[31] and many others.[25] Such oscillations gradually increase their amplitude, finally reach the threshold potential, and go into the rapid depolarization of phase 0. However, the frequency of such oscillatory membrane potentials is often not too different from that of impulse formation through the intrinsic automaticity of these fibers. Hence, this mechanism may be related to more physiological impulse formation, although certain investigators appear to believe it represents an entirely different entity.[25] Other types of oscillatory potentials, as seen in aconitine-treated ventricular fibers, which were reported earlier by Matsuda et al.,[32] indeed produced abnormal impulse formation of increasing frequency, depicting their role in the flutterlike arrhythmia.

Recently, increasing attention is being paid to the phenomena of afterdepolarizations, which apparently have two different types. The first one is a transient decrease in membrane potential after the end of an action potential, seen mainly in ouabain-treated Purkinje fibers.[30] The degree of this depolarization is relatively small when the frequency of basic driving is low, and it returns to the original membrane potential; but with increasingly higher rates of drive, the loss of membrane potential reaches the threshold potential and generates a new action potential (Fig. 1-5). This is called a delayed afterdepolarization,[25] and it appears to

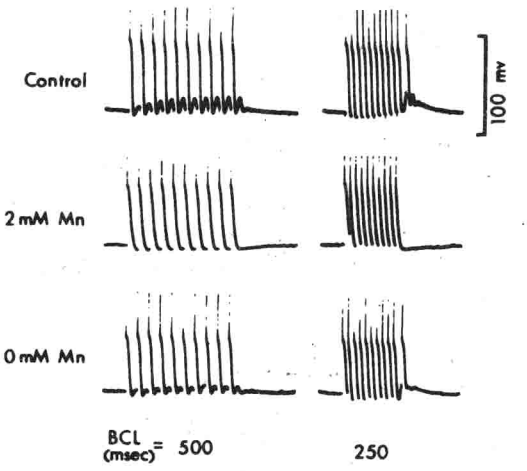

Figure 1-5. Delayed afterdepolarization in acetylstrophanthidin-treated canine Purkinje fibers. When the fiber is electrically driven at a basic cycle length (BCL) of 500 msec, each action potential is followed by a transient subthreshold depolarization. Shortening of the cycle length to 250 msec causes the afterdepolarization following the last driven response to become suprathreshold and generate a new action potential. This is followed by another subthreshold afterdepolarization. Manganese at a concentration of 2 mM abolishes the afterdepolarization at both cycle lengths, whereas its effect is reversible after elimination of Mn^{++} from the perfusate as shown at the bottom. (Reproduced with permission from ref. 30.)

depend on the slow inward currents, since it is enhanced by high calcium concentration and abolished by manganese (See Table 1-3). Ferrier and Moe claim that this mechanism most probably is responsible for the so-called ventricular bigeminy observed in digitalis excess.[30]

A second variety, termed early afterdepolarization, represents the following: In aconitine-treated ventricular muscle fibers, repolarization is temporarily brought to a halt at around −70 mV, from which a depolarization starts causing bursts of several brief action potentials.[32,33] Only after these discharges does the membrane fully repolarize to the resting level. A similar phenomenon was observed also after treatment with veratrine.[13,34] Furthermore, when ouabain-treated Purkinje fibers were depolarized by the passage of a current to a level of −40 to −60 mV, repetitive impulse formation, at a rate faster than the original automatic rhythm in this tissue, developed.[25,35] Action potentials produced by this mechanism showed a much slower rate of phase 0 depolarization typical of slow responses, and are thought to depend on slow inward currents. Although it is still questionable that partial depolarization of ischemic or injured cells could become of sufficient magnitude to cause these events in the clinical setting, the possibility of this mechanism playing a role in certain tachyarrhythmias, especially in the presence of excessive cardiac glycosides, cannot be ruled out.

Another possible mechanism of abnormal impulse formation involves local potential differences between fibers.[5,6,13] If there is a marked difference between the rate of repolarization of two adjacent fiber groups, the resultant abnormal potential difference may bring the membrane potential of the more rapidly repolarized fibers to their threshold potential and generate an extra action potential.[36] When a decrease in the resting membrane potential (partial depolarization) in injured myocardium produces a persistent potential difference at the boundary between the abnormal and more normal cardiac tissues, so-called injury currents may well cause abnormal impulse formation through one of the above-mentioned mechanisms. Although in most instances such potential gradients are not expected to become sufficiently steep because of the gradual pathophysiological changes at the boundary of injured and more normal myocardial tissues, electrotonic interactions of neighboring fiber groups causing abnormal impulse formation have been reported under certain experimental conditions.[37] It is also apparent that this mechanism cannot be readily distinguished from the so-called microreentry movement.

Factors Controlling Conduction of Excitation

In addition to abnormal impulse formation, disturbances of conduction constitute the other major mechanism in the genesis of cardiac arrhythmias.[1-3] Factors controlling impulse transmission in general (Table 1-2) and certain specific considerations on atrioventricular conduction have been extensively reviewed by us earlier.[38,39] Several of these points will be discussed in this section.

The first important physiological determinant of conductivity is the effectiveness of stimuli produced by depolarization of upstream fibers. In principle, the greater the amplitude and upstroke velocity of an action potential, the more effective it is as a stimulus and the greater the conduction velocity between fibers, and vice versa. In the working muscle fibers of the atria and ventricles, as well as in the Purkinje fibers, where phase 0 depolarization depends predominantly on rapid transmembrane inflow of sodium ions (the fast Na channel), deeper (or more negative) membrane potentials at the onset of phase 0 are associated with increased amplitude and upstroke velocity.[14,15,40,41] This is explained by an increased availability of the Na carrier system as a function of membrane potential,[40] and this relationship is expressed by the so-called membrane responsiveness curve (Fig. 1-6).

The membrane responsiveness curve in a given cardiac cell remains unchanged when the physiological environment is stable, although its characteristics can be altered under certain conditions. Quinidine, for example, is known to shift this curve lower and to the right.[41] Then the maximal rate of depolarization is decreased without any change in the level of membrane potential (Fig. 1-6).[42] If the curve is shifted higher and to the left, the upstroke velocity of phase 0, as well as the conduction velocity, is increased without an increase in the membrane potential.[43] On the other hand, a reduction in the membrane potential, for whatever reasons, brings about a slowing of phase 0 depolarization. Factors known to decrease the membrane potential include partial depolarization of the cell membrane due to high extracellular potassium concentrations,[15,25] ischemia or hypoxia, and excessive administration of certain antiarrhythmic agents.[44,45] Con-