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Electrophysiological Foundations of Cardiac Arrhythmias

A Bridge Between Basic Mechanisms and Clinical Electrophysiology

Second Edition

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PREFACE

Why Is Basic Cardiac Electrophysiology Important?

Approximately 55 years ago, the introduction of programmed electrical stimulation of the heart together with the recording of intracardiac electrograms, including that of the bundle of His, opened the door for better understanding of the underlying mechanisms of different types of cardiac arrhythmias. This initial diagnostic phase led to new therapeutic possibilities, such as arrhythmia surgery, better selection of antiarrhythmic drugs, antitachycardia pacing, and catheter ablation. In those 55 years, the number of cardiologists involved in cardiac arrhythmia management and the complexity of diagnosis and treatment options increased remarkably.

Of great importance has been a parallel increase in knowledge of the basic electrophysiology of the heart that has been essential for understanding the mechanisms of arrhythmogenesis and their clinical expression. A major factor was the introduction of the microelectrode technique for recording transmembrane action potentials from heart cells. This has led the authors of this book to the firm belief that practitioners of clinical cardiac electrophysiology should have a solid foundation in the basic electrophysiology responsible for the rhythm abnormalities that they are treating. This reasoning is two-fold.

First, understanding the electrophysiologic mechanism of an arrhythmia can help in selecting the appropriate treatment. Initially, the mechanism may not always be evident, but requires some probing to discover it. Appropriate reasoning and interpretations of test results to successfully identify the mechanism is based on knowledge of the electrophysiological properties of the different mechanisms.

Second, the development of modern clinical cardiac electrophysiology has been built on a foundation of the basic science of cardiac electrophysiology, without which the discipline would have stagnated. Discoveries that have moved the field forward and enabled it to accomplish previously unimaginable goals have been based on the interactions of laboratory and clinical research on basic mechanisms. For expert clinical practice and to make new discoveries in the field, current practitioners of clinical cardiac electrophysiology must have a solid basic knowledge foundation of basic electrophysiology.

This book is designed to lead the reader through the pathway from basic cardiac electrophysiology over the bridge to clinical cardiac electrophysiology. Basic cellular electrophysiology of the three main categories of arrhythmogenesis (automaticity, triggered activity, and reentry—see the Introduction and Table i-1) is described in sufficient detail to understand how alterations in cellular electrophysiology cause an arrhythmia. Then, these cellular electrophysiological mechanisms are related to the ECG appearance of that arrhythmia and how the arrhythmia responds to interventions such as programmed electrical stimulation and selected pharmacological agents that are mechanism-specific. Therapy for arrhythmias is not part of this curriculum.

In writing this book, it has not been our intent to provide a complete review or description of either the basic or the clinical electrophysiology of the heart. These fields are now so extensive that a complete review of both would be impossible undertakings for the authors and would require a number of contributors who are expert in all aspects of both basic and clinical cardiac electrophysiology. Rather, it is our purpose to provide the basic foundations of both cellular electrophysiology and the electrophysiology of selected arrhythmias, so that readers will be able to advance their education with additional texts written by experts. These texts typically assume the fundamental knowledge of basic and clinical electrophysiology found in this book.

This is the second edition of the book originally published in 2017. We have tried to make it more user-friendly by eliminating details that may not have been necessary for the understanding of basic concepts, shortening the book by about a third.

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INTRODUCTION

How This Book Is Organized

Although there are many kinds of clinical arrhythmias with many different pathological causes, in the final analysis, they all are the result of critical alterations in cardiac cellular electrophysiology. Since cellular electrophysiology is so important, it is the foundation for the description of mechanisms causing arrhythmias in this book. It is presented in the context of an arrhythmia mechanism and examples of the clinical arrhythmias that this mechanism causes.

The different cellular mechanisms that form the organization of the book are presented in **Table i-1**.

Table i-1 Electrophysiological Mechanisms of Cardiac Arrhythmias

I. Abnormal Impulse Initiation
A. Automaticity • normal automaticity • abnormal automaticity
B. Triggered Activity • delayed afterdepolarizations • early afterdepolarizations
II. Altered (Abnormal) Impulse Conduction
A. Conduction block leading to ectopic pacemaker "escape"
B. Unidirectional block and reentry • anatomical reentry • functional reentry

(Modified from Hoffman, BF, Rosen MR. Cellular mechanisms of cardiac arrhythmias. *Circ Res.* 1981;49:1–15.)

ABNORMAL IMPULSE INITIATION

This topic constitutes Chapters 1–8 of this book. The term "impulse initiation" is used to describe an electrical signal (impulse) that arises in a single cell or group of closely coupled cells through depolarization (decrease in negativity) of the cell membrane potential to a threshold that initiates an action potential. Once initiated, the action potential(s) form an electrical impulse that spreads to other regions of the heart.

Table i-1 subdivides the causes for impulse initiation into two categories: (A) automaticity and (B) triggered activity. Each has its own unique cellular mechanism resulting in the membrane depolarization that initiates impulses.

Automaticity

Automaticity is the result of spontaneous (diastolic) depolarization (SDD). **Chapters 1–4** describe the cellular mechanisms of automaticity and provide examples of the clinical arrhythmias that it causes. Automaticity is divided into two kinds, normal (**Chapters 1–3**) and abnormal (**Chapter 4**). Normal automaticity is found in the primary pacemaker of the heart—the sinus node (**Chapter 2**)—as well as in subsidiary or latent pacemakers found in certain regions of the atria, A-V junction, and ventricular specialized conducting system (**Chapter 3**). Impulse initiation is a normal property of these latent pacemakers.

On the other hand, abnormal automaticity (**Chapter 4**) occurs in cardiac cells when major (abnormal) changes occur in their transmembrane potentials due to pathology. Working atrial and ventricular myocardial cells do not normally have spontaneous diastolic depolarization and do not normally initiate spontaneous impulses. However, when their resting potentials are reduced sufficiently by disease, spontaneous diastolic depolarization may occur and cause repetitive impulse initiation, a phenomenon called depolarization-induced abnormal automaticity. Atrial and ventricular tachycardias occurring in a number of different diseases can be caused by abnormal automaticity.

Triggered Activity

Triggered activity (Table i-1 B), is a form of impulse initiation caused by afterdepolarizations. Afterdepolarizations are abnormal oscillations in membrane potential that occur after the rapid depolarization (Phase 0) of an action potential. Chapters 5–8 describe the electrophysiological mechanisms for afterdepolarizations and provides

examples of the clinical arrhythmias that they cause. There are two types of afterdepolarizations that cause triggered activity. One type is delayed until repolarization is complete or nearly complete (delayed afterdepolarizations [DADs]) (**Chapters 5** and **6**). The other type is early, occurring before repolarization is complete (early after depolarizations [EADs]) (**Chapters 7** and **8**).

ALTERED (ABNORMAL) IMPULSE CONDUCTION

Altered (abnormal) impulse conduction (heading II in Table i-1) includes both arrhythmias due to conduction block leading to ectopic pacemaker escape and arrhythmias due to unidirectional block and reentry.

Conduction Block Leading to Ectopic Pacemaker "Escape"

Conduction block leading to ectopic pacemaker "escape" (subheading II, A) is described in **Chapters 1–4** as a mechanism for occurrence of some arrhythmias caused by normal and abnormal automaticity.

Unidirectional Block and Reentry

Unidirectional block and reentry are the subjects of **Chapters 9–12**. **Chapter 9** describes the basic cellular electrophysiology of impulse conduction in the heart and how this process is altered by disease to slow it or to cause it to fail (conduction block). These basic cellular concepts are then applied to the different mechanisms that cause reentrant excitation, a process whereby the propagating impulse can circulate and return to re-excite regions that it has already excited without the requirement for new impulse initiation. Reentrant circuits are described that are dependent on anatomical structures as well as functional properties of cardiac muscle and the characteristic responses to electrical stimulation and some pharmacological agents.

Chapters 10–12 describe the process of reentry in different regions of the heart (atria, A-V junction, ventricles). Each chapter also provides example arrhythmias that are caused by this mechanism.

THE BRIDGE BETWEEN BASIC MECHANISMS AND CLINICAL ELECTROPHYSIOLOGY

The purpose of this book is to explain how basic cardiac electrophysiology can elucidate mechanisms causing cardiac arrhythmias, that is, to provide a bridge between basic mechanisms and clinical electrophysiology. Concepts from basic electrophysiology are interwoven with the arrhythmia mechanisms and examples of clinical arrhythmias in order to show the close interrelationships between basic and clinical electrophysiology. With the appropriate background from medical school physiology, we hope these basic concepts are understandable as encountered while progressing through the book.

This same bridge is also a pathway from clinical arrhythmias to basic mechanisms. It is our belief that as the student becomes more familiar with the mechanisms of arrhythmogenesis, the information obtained from clinical electrophysiology will become easier to assimilate and to utilize for improved diagnosis and treatment of real-world arrhythmias.

SOURCES

Josephson ME. *Josephson's Clinical Cardiac Electrophysiology: Techniques and Interpretations* (5th ed.). Philadelphia, PA: Wolters Kluwer; 2016.

Wellens HJJ, Conover M. *The ECG in Emergency Decision Making.* St. Louis, MO: Saunders Elsevier; 2006.

CHAPTER 1

Basic Principles of Normal Automaticity

Automaticity is the term used to indicate the mechanism for the initiation of an electrical signal in a single cell or group of closely interacting (coupled) cells. This signal, in the form of an action potential, arises from spontaneous depolarization of the membrane potential. The action potential is the electrical signal or impulse that excites the heart, and the cell(s) that generate this signal are called "pacemakers."

"Normal automaticity" is found in the primary pacemaker of the heart, the sinus node, as well as in certain subsidiary or latent pacemakers that can become the pacemaker under special conditions (hence the term, latent). Impulse initiation is an intrinsic property of these latent pacemakers, as it is in the sinus node. ("Abnormal automaticity," described in Chapter 4, is related to pathological changes in a region of the heart, often where the cells do not have intrinsic pacemaker properties, although there are exceptions.) The recording of the transmembrane resting potential (often referred to here as simply the membrane potential) and action potentials as well as the membrane currents of individual myocardial cells has provided much of the information necessary for understanding the mechanism by which certain myocardial cells can generate impulses spontaneously by normal automaticity.

The cause of normal automaticity in the sinus node and latent pacemakers is a spontaneous decline (becoming less negative) in the membrane potential during diastole or phase 4. This decline in membrane potential is referred to as either the "pacemaker potential," "phase 4 depolarization," or "spontaneous diastolic depolarization" (SDD). **Figure 1-1** illustrates an action potential with a pacemaker potential in a myocardial cell with the property of normal automaticity and compares the automatic cell with a cell without normal automaticity (nonautomatic cell).

Panel A shows a nonautomatic cell with a steady level of resting (diastolic) potential during phase 4 (the resting potential [RP]) between action potentials (purple arrow). This type of cell must be excited from an external source (green arrow), either another connected cell or an applied electrical stimulus, to initiate an action potential. The action potential is comprised of phase 0 (rapid depolarization phase or "upstroke") and phases 1, 2, and 3 (repolarization phases).

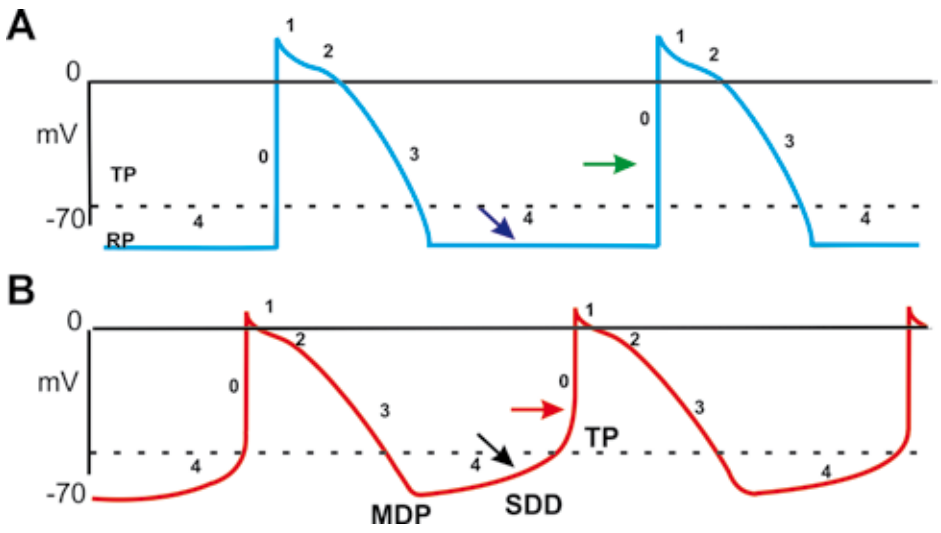

Figure 1-1 Diagrams of transmembrane action potentials characteristic of a nonautomatic cell (**Panel A**) and a normal automatic cell (**Panel B**). In each panel, the horizontal black line indicates "0" potential and the horizontal dashed line is the threshold potential (TP).

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Panel B shows a cell with normal automaticity. Spontaneous diastolic depolarization (the pacemaker potential) is that part of the membrane potential labeled "SDD" (black arrow) coinciding with phase 4 of the membrane potential. In Panel B, the membrane potential moves spontaneously in a positive direction from the maximum potential during diastole (maximum diastolic potential [MDP]) with a negative value of –70 mV until it reaches the threshold potential (TP), which is less negative at –60 mV. At this point, the inward depolarizing current (phase 0, red arrow) is activated, and this in turn causes the cell to generate an action potential. Phase 0 is responsible for conduction of the action potential from the pacemaker cell to surrounding cells. Depolarization of membrane potential during SDD represents the summation of a number of inward and outward transmembrane currents with depolarization resulting because inward current dominates.

In later chapters, we describe the specific ion channels and membrane currents that are involved in the genesis of the pacemaker depolarization, but these details are not necessary at this point for understanding the role of automaticity in causing arrhythmias.

General Principles of Normal Automaticity

1. Control of rate of automatic impulse initiation
2. Relationship between sinus node and latent pacemakers
3. Electrophysiological causes of ectopic automatic arrhythmias
4. General ECG characteristics of automatic arrhythmias
5. Effects of electrical stimulation and pharmacological agents on normal automaticity

CONTROL OF RATE OF AUTOMATIC IMPULSE INITIATION

The rate of automatic impulse initiation is determined by two major factors: the characteristics of the transmembrane potential and electrical coupling between pacemaker and nonpacemaker cells.

Transmembrane Potential

The intrinsic rate at which pacemaker cells initiate impulses is determined by the amount of time it takes for the membrane potential to move from its maximal negativity (maximum diastolic potential, MDP) after repolarization to the threshold potential to generate an action potential or impulse. Time to threshold potential is in turn dependent on the interplay of several factors (**Figure 1-2**), including:

- The level of the "maximum diastolic potential" (MDP), which is the maximum negativity attained after repolarization of the action potential. This term is used instead of resting potential (RP) since the membrane potential in a pacemaker cell does not have a period of rest as it does in a nonpacemaker cell (Figure 1-1, Panel B).
- The level of the "threshold potential" (TP) for initiation of phase 0 of the action potential. The threshold potential is the membrane potential at which the inward current causing phase 0 becomes regenerative to cause a conducted action potential.
- The slope of "spontaneous diastolic depolarization" (SDD), which is the rate of change of phase 4, also referred to as the pacemaker potential. This slope is dependent on the speed of activation and the magnitude of net inward current. Sometimes there may be two different slopes if the rate of change is not constant.
- The "action potential duration" (APD) is the time from depolarization phase 0 to complete repolarization at the end of phase 3.

These features of the transmembrane potential are under the control of the ion channels, pumps, and exchangers involved in the genesis of the pacemaker potential and action potential, which will be described in detail later in this chapter and in Chapters 2 and 3. A change in any one of the above parameters caused by changes in the membrane currents will alter the time required for SDD to move the membrane potential from its MDP to the TP, and thereby alter the rate of impulse initiation. Understanding the interplay of these factors is necessary for understanding how automatic arrhythmias occur.

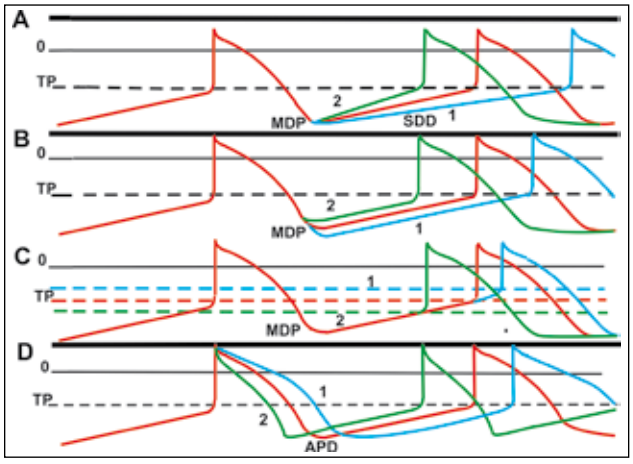

Figure 1-2 Factors that control intrinsic rate. **Panel A** shows effects of changes in slope of spontaneous diastolic depolarization (SDD). **Panel B** shows effects of changes in maximum diastolic potential (MDP). **Panel C** shows effects of changes in threshold potential (TP). **Panel D** shows effects of changes in action potential duration (APD).

Figure 1-2 illustrates how these parameters control the spontaneous rate. Panel A shows how changes in the slope of SDD can change the rate of automatic impulse initiation. The red trace shows action potentials with the initial intrinsic or automatic rate of the pacemaker cell, that is determined by the time required for SDD caused by the pacemaker current(s), to move the membrane potential from the MDP to TP. The blue trace (labeled 1) shows the effect of a decrease in the slope of SDD. This would be caused by a decrease in net inward pacemaker current, resulting in a longer interval between action potentials and a decrease in heart rate because of the longer time required for membrane potential to reach the threshold potential. Modest parasympathetic (vagal) activation is one condition that results in a decreased slope of SDD of sinus node pacemaker cells to slow the heart rate. Some antiarrhythmic drugs also have this effect on latent pacemakers. The green trace (labeled 2) shows the effect of an increase in the slope of SDD that increases heart rate. This would be caused by an increase in the net inward pacemaker current, which reduces the time to reach threshold potential and decreases the time between action potentials. Sympathetic activation, which accelerates the heart rate, is an example of this condition.

Figure 1-2, Panel B illustrates how a change in the MDP can change the rate of automatic impulse initiation. If the MDP increases (becomes more negative), going from the nadir of the solid red trace (initial intrinsic value) to the blue trace (labeled 1), then the SDD (or pacemaker potential) takes longer to reach threshold potential and the rate of impulse initiation slows. This occurs even if the slope of the SDD is not altered as shown in the figure. An increase in MDP results from a net increase in outward current during diastole which usually is also accompanied by a decrease in slope of SDD. Strong vagal activation causes an increase in MDP of sinus pacemaker cells in addition to the decreased slope of SDD, both of which slow sinus rate. Conversely, a decrease in the MDP (going from red to green trace, labeled 2), decreases the time it takes to go from MDP to TP and increases the rate of impulse initiation even if the slope of SDD is not altered as shown in the figure. However, a decrease in outward current during diastole that decreases MDP, often increases the slope of SDD. A simultaneous increase in sympathetic activity and decrease in vagal activity can produce this change and increase the sinus rate.

Figure 1-2, Panel C illustrates the effect of changes in TP on the rate of impulse initiation. The TP (dashed lines) is the membrane potential required for initiation of the upstroke (phase 0) of the action potential. When the TP is decreased from the initial level indicated by the red dashed line (associated with the solid red line action potential) to the less negative TP (blue dashed line, labeled 1), then the SDD must proceed for a longer time before an impulse is finally initiated (rapid upstroke, solid blue trace). Thus the heart rate is slower. Conversely, an increase in TP (from red to more negative green dashed line, labeled 2) accelerates the heart rate because SDD must proceed for a shorter time before an impulse is initiated, shown by the earlier green action potential.

Don't be confused by this terminology corresponding to negative values in which an *increase* in "potential"—the difference between the measured value and 0—is actually more negative, while a *decrease* in potential is less negative. On the other hand, when the term "threshold" is used by itself, an increase in threshold means "more difficult to excite" while a decrease in threshold means "more excitable."

Figure 1-2, Panel D, shows how changes in the APD can alter the rate of impulse initiation. The APD is controlled in part by the membrane currents that determine the time course for repolarization (phases 1, 2, and 3). SDD begins after completion of action potential repolarization. If APD lengthens (increases), as illustrated by the change from the red action potential at the left to the blue action potential (labeled 1) at the left, and the diastolic time remains constant, the rate of impulse initiation decreases (compare onset of the second red action potential with the later second blue action potential). A decrease in action potential duration shown by the green action potential (labeled 2) at the left compared with the red action potential, accelerates the rate (compare the earlier onset of the second green action potential with the later onset of the second red action potential) when diastolic time remains constant. Changes in APD do not normally apply to the physiological control of rate, but may be instrumental in the rate effect of drugs that alter repolarization.

Electrical Coupling Between Pacemaker and Nonpacemaker Cells

In addition to the changes discussed in Figure 1-2, electrical coupling between pacemaker and nonpacemaker cells provided by gap junctions, reduces the slope of SDD and slows or inhibits pacemaker cell impulse initiation by electrotonic current flow. The way this effect is exerted is diagrammed in **Figure 1-3**.

The lower part of the figure diagrams two adjacent cells, P and NP (yellow cylinder). Cell P is a pacemaker cell (action potential is above it) with SDD (black trace) and cell NP is a nonpacemaker cell (action potential is above it) with a more negative membrane potential during phase 4 (black trace). The broken double black lines between the two cells represents the adjacent cell membranes

(sarcolemmae) of each cell, which abut to form the intercalated disk. In the disks are structures called "gap junctions," specialized regions of close interaction between the sarcolemmae of neighboring myocytes in which clusters of channels, formed by proteins called connexins, bridge the paired plasma membranes to connect the intracellular spaces of cell P and cell NP. Because gap-junctional membrane is several orders of magnitude more permeable than nonjunctional plasma membrane, it provides low resistance pathways for "electrotonic current flow" between myocardial cells (represented by the curved black arrows), which is important for impulse propagation. (The mechanism for impulse propagation is described in detail in, Chapter 9, Figure 9-4). Electrotonic current flow in the absence of propagation also influences impulse initiation by automaticity.

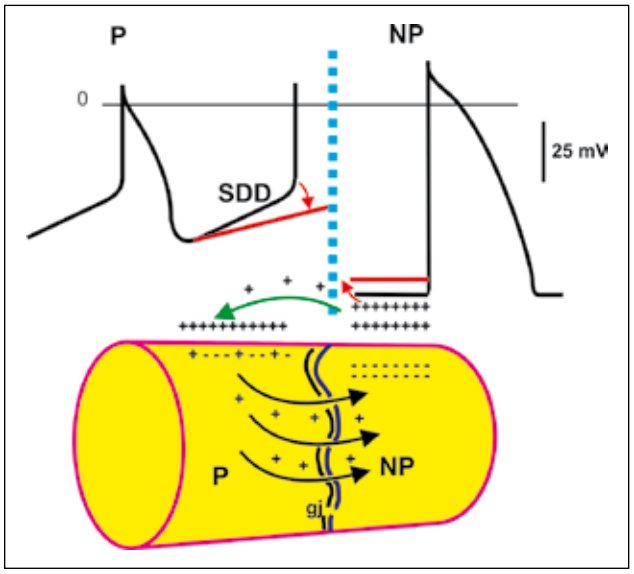

Figure 1-3 Influence of electrical coupling of pacemaker cell (P) to nonpacemaker cell (NP) on spontaneous diastolic depolarization (SDD).

During SDD, the membrane potential in the pacemaker cell (black trace in P) becomes much less negative than the membrane potential in the adjacent well coupled nonpacemaker cell (black trace in NP). As a result of this potential difference, current (positive charges) flows intracellularly from the pacemaker cell (P) towards the nonpacemaker cell (NP) through the gap junction channels (curved black arrows and + signs). It also flows in extracellular space from the nonpacemaker cell (NP) to the pacemaker cell (P), also down the potential gradient (curved green arrow and + signs). The addition of positive charges outside the membrane of P and removal of + charges from the inside of the membrane caused by the current flow push the membrane potential of the pacemaker cell in a negative direction and retards SDD (red arrow shows shift in slope of SDD from black to red trace) in the pacemaker cell. It also decreases the membrane potential of the nonpacemaker cell (red arrow in NP, from black to red trace).

The efficacy of this inhibitory effect of electrotonic current flow on SDD is dependent on the magnitude of the electrotonic current, which in turn is influenced by the conductance (ability to pass current) of the gap junctions. One determinant of conductance is the isoform of the connexin protein that forms the gap junction. There are five connexin isoforms that form gap junctions in the human heart. The conventional nomenclature for a connexin (Cx) includes a suffix referring to its molecular weight. Some connexin proteins (Cx40 and Cx43) have high conductance, and others (Cx45) have low conductance. Different types of connexins are located in different regions of the heart. In the sinus node region, where pacemaker cells are coupled to nonpacemaker atrial cells with a more negative membrane potential, it is important that the gap junctions between the two cell types have low conductance, or sinus node pacemaker activity might be silenced. However, the conductance must still be sufficient to allow impulse propagation. More details on gap junction function are described in Chapters 2–4, since a decrease in coupling between cells caused by changes in gap junctions can enhance automaticity and cause arrhythmias.

RELATIONSHIP BETWEEN SINUS NODE AND LATENT PACEMAKERS

Cells with normal pacemaker properties occur throughout the heart. There is a hierarchy of pacemaker impulse initiation such that the sinus node is normally the primary pacemaker. With the sinus node functioning normally, other pacemaker sites are effectively "silent." Why does impulse initiation in the normal heart reside in the sinus node and not at one of the ectopic sites, since they also have the property of normal automaticity? Two factors are involved: the hierarchy of pacemakers and overdrive suppression.

Sinus Node as the Primary Pacemaker in the Hierarchy of Pacemakers

The sinus node is the prototype of normal automaticity and the dominant pacemaker in the normal heart. In addition, there are other special regions throughout the heart where myocardial cells have the normal, intrinsic ability to initiate impulses by automaticity. Myocardial cells at these ectopic sites are called latent or subsidiary pacemakers (**Figure 1-4**).

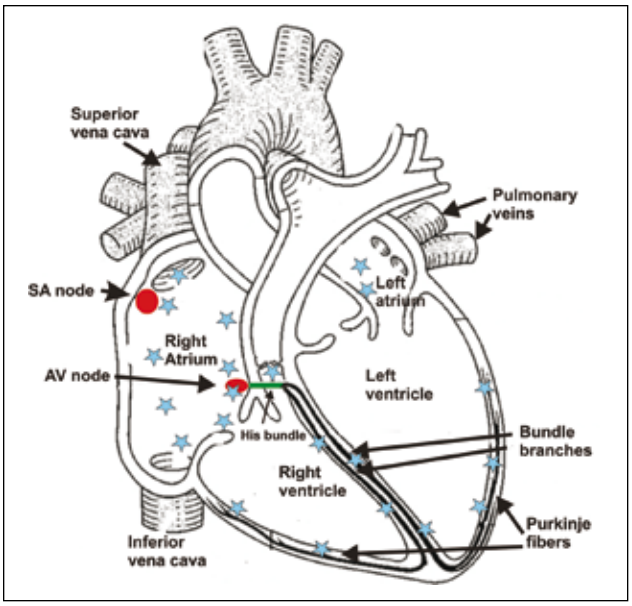

Figure 1-4 Location of pacemakers with normal automaticity (**blue stars**).

They include multiple sites in the right and left atria, the atrioventricular (AV) junction (AV node and His bundle), and the specialized conducting system of the ventricles (Purkinje system). Pacemaker cells at some of these sites such as the AV junction and Purkinje system can be identified by a specific histological structure while most pacemaker cells in the atria usually appear the same as the working myocardial cells with typical contractile structure and function.

The latent pacemakers have membrane currents causing SDD similar in many aspects to the mechanism described for the sinus node in Chapter 2 (Figure 2-6). In general, latent pacemaker sites with normal automaticity, like the sinus node, have cells with an isoform of a specific gene called the *HCN* gene (HCN stands for Hyperpolarization-activated Cyclic Nucleotide-gated). This gene controls the expression of a membrane channel that is involved in the genesis of the pacemaker current. Myocardial cells in atria and ventricles classified as "working," i.e., performing the contractile function, do not normally express pacemaker ability, although under pathological conditions, they may express abnormal automaticity (see Chapter 4).

Hierarchy of Pacemakers

Under normal conditions there is a difference in intrinsic rates among different pacemaker cells in various regions of the heart, which is called the hierarchy of pacemakers. The intrinsic rate is the rate at which a cell initiates automatic impulses in the absence of external inhibitory or stimulatory factors such as the autonomic nervous system. The sinus node pacemakers have the fastest intrinsic rates, followed by atrial pacemakers, AV nodal pacemakers, His bundle pacemakers, and then the Purkinje pacemakers in the distal ventricular conducting system. Because the sinus node has the fastest intrinsic rate, the latent pacemakers are excited by propagated impulses from the sinus node and discharge an action potential before sufficient time passes to allow them to depolarize spontaneously to threshold potential and initiate an impulse.

Overdrive Suppression of Latent Pacemakers by the Sinus Node

Not only are latent pacemakers prevented from initiating an impulse because they are depolarized by propagating electrical activity originating in the sinus node, but also, the SDD of latent pacemaker cells is actually inhibited when the cells are repeatedly depolarized by the impulses from the sinus node—a phenomenon called "overdrive suppression." The effect of overdrive suppression can be seen when there is sudden failure of the sinus node pacemaker to initiate impulses or failure of the impulses to conduct into the location of the latent pacemaker. Latent pacemaker impulse initiation does not arise immediately but is generally preceded by a period of quiescence. Overdrive suppression is exemplified by this period of quiescence after sudden inhibition of the sinus node pacemaker by vagal activity.

Figure 1-5 shows the ECG during vagal activation by carotid sinus massage beginning at the "R" in the top tracing, in a normal human subject. The quiescent period prior to the appearance of a junctional beat (first impulse in the second tracing) reflects the suppressive influence of overdrive suppression exerted on the latent pacemakers, including this junctional pacemaker, by the dominant sinus node pacemaker. Several more junctional beats occur prior to reappearance of sinus rhythm after carotid message is terminated at the x in the third tracing. The junctional pacemaker is not suppressed by the vagal activation (as are atrial pacemakers and mid AV nodal pacemakers), perhaps because it is in the lower AV node or His bundle where the vagus exerts little effect (see Chapter 3). In humans, ventricular pacemaker escape is rare after vagal activation, the usual site of escape being in the AV junction.

CHAPTER 5

Basic Principles of Delayed Afterdepolarizations (DADs) and Triggered Action Potentials

Triggered activity is the second form of impulse initiation listed in the Introduction's Table i-1. "Triggered activity" is the term used to describe impulse initiation that is dependent on afterdepolarizations. It is distinct from automaticity as described in Chapters 1–4, which results from spontaneous diastolic depolarization. Afterdepolarizations are oscillations in membrane potential that follow the primary depolarization phase (0) of an action potential. **Figure 5-1** shows the two types of afterdepolarizations that can cause triggered arrhythmias.

Figure 5-1, Panel A illustrates a delayed afterdepolarization (DAD) (red arrow following action potential 1). It is not initiated until repolarization is complete or nearly complete and therefore is delayed with respect to repolarization. DADs and DAD triggered arrhythmias are the subjects of this chapter and Chapter 6. By way of comparison, in Panel B, the second type of afterdepolarization, referred to as an early afterdepolarization (EAD), is shown by the red arrow following action potential 1. It is manifested as an interruption in repolarization of the action potential and is therefore early with respect to repolarization. (The blue arrow shows normal repolarization.) Early afterdepolarizations and the arrhythmias that they cause are described in Chapters 7 and 8.

An afterdepolarization does not initiate an arrhythmia until its amplitude is large enough to reach the threshold potential for activation of a regenerative inward current that causes an action potential. In Figure 5-1, Panels A and B, this occurs following action potential 2 (second set of red arrows). These action potentials are referred to as triggered action potentials (action potential 3, in green) and the arrhythmias they cause are called triggered arrhythmias. Therefore, for triggered activity to occur, at least one action potential must precede it (in Panels A and B, the trigger is action potential 2) in contrast to automaticity, which can arise de novo in the absence of prior electrical activity. (For example, Figure 1-5 shows an escape rhythm caused by automaticity after sinus node inhibition, the first impulse arises without an immediately preceding "trigger.")

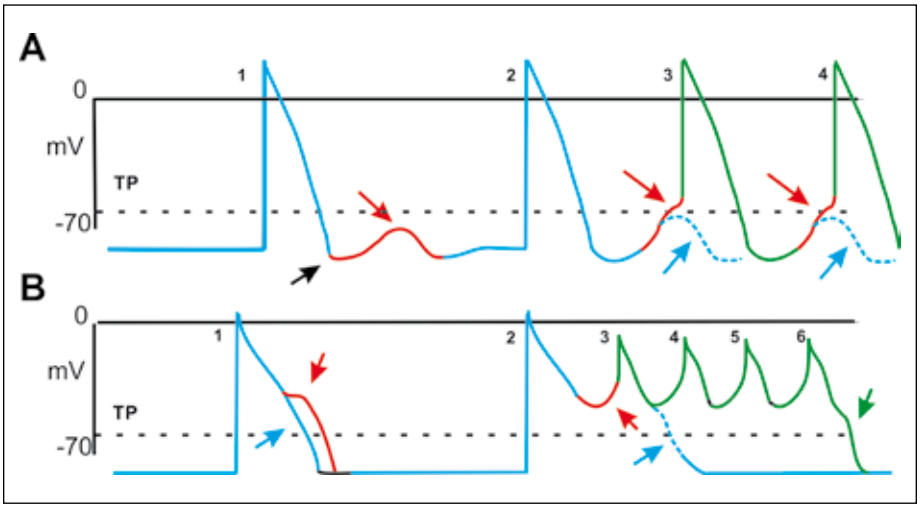

Figure 5-1 There are two types of afterdepolarizations. **Panel A:** Delayed afterdepolarizations (DADs) and DAD-induced triggered action potentials. **Panel B:** Early afterdepolarizations (EADs) and EAD-induced triggered action potentials. Voltage calibration is at the **left** with 0 potential indicated; TP, threshold potential (**dashed line**).

Electrophysiological Foundations of Cardiac Arrhythmias: A Bridge Between Basic Mechanisms and Clinical Electrophysiology, Second Edition.

CHARACTERISTIC APPEARANCE OF DADS AND DAD-TRIGGERED ACTION POTENTIALS

Figure 5-1, Panel A shows the general features of DADs. An action potential of a myocardial cell at the left (in light blue, labeled 1) is followed after complete repolarization by a low-amplitude and short-duration depolarization of the membrane potential (in red with red arrow) that is caused by a transient net inward current during diastole. The afterdepolarization is coupled to and caused by the previous action potential (see below for a description of the mechanism). The DAD may be preceded by an after-hyperpolarization (black arrow following action potential 1), during which the membrane potential becomes transiently more negative than the membrane potential just prior to its initiation. The transient nature of the afterdepolarization clearly distinguishes it from normal spontaneous diastolic (automatic, phase 4) depolarization (SDD), during which the membrane potential declines until an action potential is initiated (Figure 1-1, Panel B).

DAD-Triggered Action Potentials

In Figure 5-1, Panel A, the DAD following action potential 2 is larger, and its depolarization (in red, red arrows) reaches the threshold potential (TP, dashed horizontal line) resulting in a regenerative inward current (Na^+ or Ca^{2+}, depending on the level of the membrane potential) to cause an action potential (action potential 3 in green) called a triggered impulse. The dashed curve in blue and the blue arrow show the time course of the DAD if no triggered action potential had been initiated. This emphasizes that the triggered action potential arises from a DAD. DADs do not always reach threshold (following action potential 1), so that triggerable cells may sometimes be activated regularly (during sinus rhythm) without becoming rhythmically active. The conditions under which they reach threshold are described below. A triggered action potential is also followed by a DAD (red trace and arrow following action potential 3) that may or may not reach threshold. When it does, the first triggered action potential is followed by a second triggered action potential (action potential 4 in green), arising from the DAD caused by the previous action potential. The blue dashed curve associated with action potential 4 shows the membrane potential had the DAD not reached threshold potential. This process can continue, resulting in a series of triggered action potentials that eventually stop when a DAD does not reach threshold potential.

CELLULAR MECHANISMS OF DADS AND DAD-TRIGGERED ACTIVITY: THE ROLE OF CALCIUM

DADs and the triggered activity that they cause result from an oscillatory membrane current originally referred to as the transient inward current (TI or I_{TI}). This current is distinct from the pacemaker current that causes normal automaticity. A distinguishing feature of I_{TI} is that it is associated with abnormalities in intracellular calcium cycling between the sarcoplasmic reticulum (SR) and myoplasm. This intracellular Ca^{2+} cycling normally plays an important role in coupling the action potential to myocardial contraction, a process called excitation-contraction coupling in the forward mode.

Excitation-Contraction (EC) Coupling; Forward Mode

Owing to the importance of Ca^{2+} and SR function in the genesis of DAD-triggered arrhythmias, the normal physiology of EC coupling is first briefly described. Normal EC coupling is sometimes referred to as "forward-mode EC coupling," since excitation (in the form of the action potential) precedes and causes contraction. Ca^{2+} enters the cell during the action potential plateau phase (2) to initiate contraction. Abnormalities that cause DADs and triggered arrhythmias result from "reverse-mode EC coupling," since the Ca^{2+} trigger for contraction from the SR precedes excitation that occurs in the form of a DAD.

Figure 5-2, Panels A and B illustrate the normal movement of Ca^{2+} back and forth between myoplasm (MYO) and sarcoplasmic reticulum (SR) during systole (Panel A) and diastole (Panel B).

The SR is a network of tubular membranes depicted as the red rectangular area in the center of each panel in Figure 5-2. It is the main store of intracellular Ca^{2+} (blue dots). Some of this Ca^{2+} in the SR is free, and some is bound to SR proteins, the most important of which is calsequestrin 2 (Casq2), the cardiac isoform of the protein. Casq2 has a high capacity for binding Ca^{2+} (50%–70% of SR Ca^{2+} is bound to it), but a low affinity for Ca^{2+}; thus, it can readily release free Ca^{2+} when required. Therefore, Casq2 is a major determinant of the ability of the SR to store and release Ca^{2+}, and abnormalities in its function can sometimes cause DAD-triggered arrhythmias.

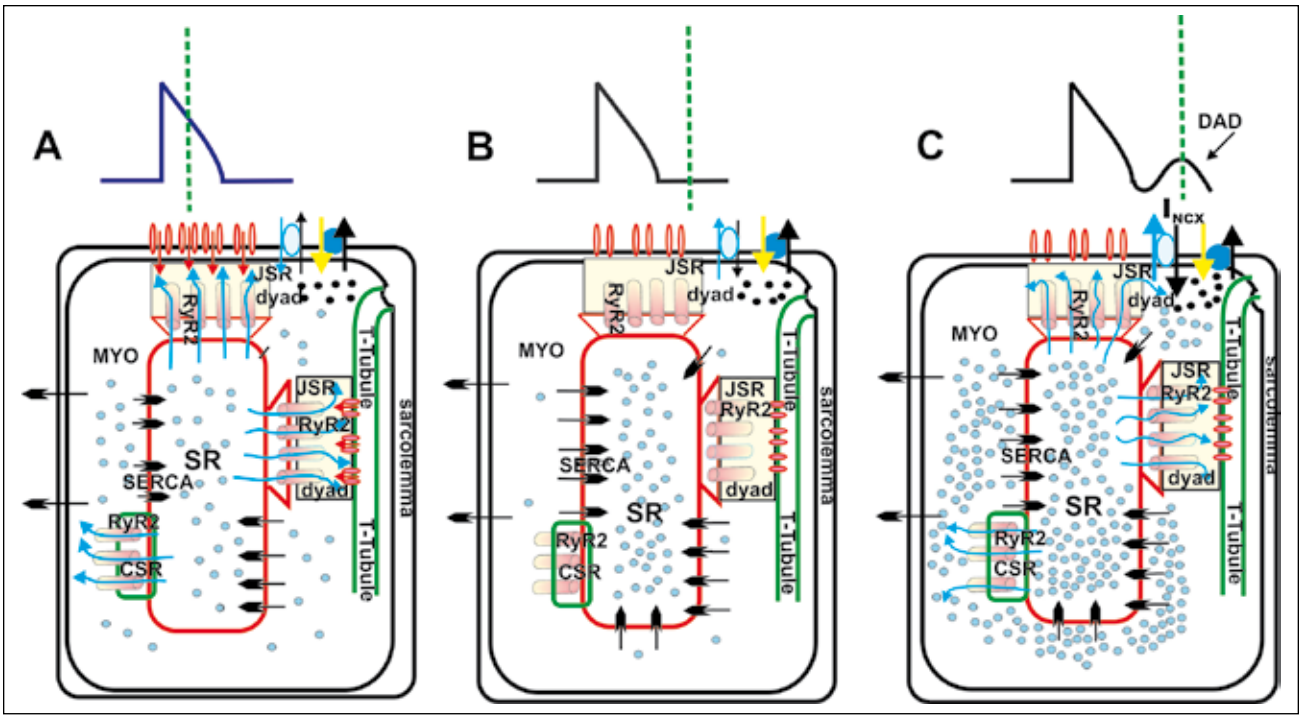

Figure 5-2 Ca^{2+} cycling between myoplasm (MYO) and sarcoplasmic reticulum (SR) in a ventricular muscle. SR outlined in **red**, t-tubules outlined in **green**. CSR; corbular sarcoplasmic reticulum, SR release channels (RyR2) in junctional sarcoplasmic reticulum (JSR). Sarcoplasmic reticulum Ca^{2+} ATPase-dependent pumps (SERCA: **Large black arrowheads**). L-type Ca^{2+} channels: **Small red ovals**. Na^+–Ca^{2+} exchanger: **Light blue oval** in sarcolemma. Na^+–K^+ pump: **Dark blue circle**. Ca^{2+} ions: **Small blue circles**. **Panel A:** Systole (**vertical dashed line** above). **Panel B:** Diastole (**vertical dashed line** above). **Panel C:** DAD formation (in diastole). **Arrows** explained in text.

Free Ca^{2+} is released from the SR into the myoplasm through calcium release channels in the SR membrane (blue arrows, Panel A) called ryanodine receptors (RyR2). The latter are named as such because they were first discovered to respond to the plant alkaloid ryanodine that opens the channels. The number "2" indicates the predominant isoform of the receptor in cardiac myocytes. Ca^{2+} is normally released from the SR during the plateau phase of the transmembrane action potential (Panel A, vertical dashed line on the action potential). The release is triggered mostly by the entrance of Ca^{2+} into the cell via I_{CaL}, through the L-type calcium channel (short red arrows, and small red ovals). This Ca^{2+} binds to the external surface of the RyR2 receptors, opening the Ca^{2+} release channels, a process called Ca^{2+}-induced Ca^{2+} release. The L-type calcium channels are located in invaginations of the sarcolemma forming T tubules that closely abut the junctional sarcoplasmic reticulum (JSR) in terminal cisternae to form dyads. Dyads are also formed where SR abuts non-t-tubular, sarcolemmal membranes (top border). There also may be some net inward Ca^{2+} movement via the Na^+–Ca^{2+} exchanger operating in the forward mode (moves Ca^{2+} into the cell and Na^+ out of the cell) (light blue oval; blue arrow indicates Ca^{2+}, black arrow is Na^+) during the action potential plateau. Notably, the majority of Ca^{2+} that interacts with the contractile proteins in working ventricular and atrial cells, comes from the SR and not directly from Ca^{2+} flux through the L-type channels. The excitation triggers contraction, hence the term "forward" EC coupling.

Ca^{2+} release through the RyR2 operated channels (blue arrows) terminates when SR free Ca^{2+} falls below a threshold level. Ca^{2+}-induced Ca^{2+} release results in about 40%–60% depletion of Ca^{2+} from the SR. RyR2 channel closure may be brought about by an interaction of Casq2 with the channel proteins. Casq2 is the putative SR luminal Ca^{2+} sensor and inhibits RyR2 channel opening when Ca^{2+} is low, causing a temporary state of refractoriness of the channels after each Ca^{2+} release, thus preventing Ca^{2+} release during diastole.

Following the Ca^{2+} release that triggers contraction (Panel A), the myoplasmic Ca^{2+} is reduced by two mechanisms: (1) resequestration into the SR by calcium pumps in the SR membrane (Figure 5-2, Panel B, SERCA, black arrowheads) through active transport with energy supplied by ATPase, and (2) extrusion from the cell mostly by the Na^+–Ca^{2+} exchanger in the sarcolemma operating in the reverse mode at the negative diastolic potential (note reverse direction of the light blue arrow at the blue oval, which represents the Na^+–Ca^{2+} exchanger in Figure 5-2,

Panel B). The function of the exchanger in this reverse mode is described in Chapter 2 in relation to its role in generating an inward current that contributes to the pacemaker potential.

When the Na^+–Ca^{2+} exchanger operates in the reverse mode, it moves more positive charges (3 Na^+, indicated by black arrow in Figure 5-2, Panel B) into the cell than out (1 Ca^{2+}, blue arrow) at diastolic membrane potentials. The movement of Na^+ is down its concentration gradient and generates the energy for moving Ca^{2+} out of the cell against its concentration and electrical gradients (inside 10^{-4} mM free Ca^{2+}, outside 1.8 mM; inside the cell is negative relative to outside the cell, which is positive). The concentration gradient for Na^+ is maintained by the Na^+–K^+ pump that maintains myoplasmic Na^+ at low levels (~ 2–4 mM) (Figure 5-2, Panel B, blue circle, black arrow is Na^+ out of cell in exchange for K^+ into cell, yellow arrow). A small amount of Ca^{2+} is also extruded from the cell by ATPase-dependent sarcolemmal calcium pumps (black arrows at left of the diagram). Under normal circumstances, myoplasmic free Ca^{2+} is reduced to a very low levels during diastole (blue circles) (Figure 5-2, Panel B) resulting in relaxation. Note the steady level of membrane potential during diastole (vertical dashed line) in Panel B.

Spontaneous Diastolic SR Calcium Release and DADs

DADs occur under conditions in which SR Ca^{2+} levels are abnormally elevated called Ca^{2+} overload. They also occur if there are abnormalities in RyR2 function caused by mutations or in acquired pathology (ischemic heart failure) that affects RyR2 receptor function.

Figure 5-2, Panel C shows the mechanism for DADs during Ca^{2+} overload as indicated by the increase in blue circles in Panel C compared to Panels A and B. One cause of Ca^{2+} overload is an increase in Ca^{2+} entering the cell through the L-type Ca^{2+} channels during action potentials, for example, during sympathetic stimulation. Another cause is a decrease in Ca^{2+} extrusion from the cell by the Na^+–Ca^{2+} exchanger as occurs with digitalis toxicity (described in Figure 5-8). Under these conditions, there is increased activity of the SR calcium pumps (Figure 5-2 Panel C, SERCA, black arrows). SERCA senses the increased Ca^{2+} entering the cell (in the myoplasm (MYO) and increases its activity to remove Ca^{2+} from the MYO into the SR in an attempt to maintain the low diastolic level of Ca^{2+} necessary for relaxation. This results in Ca^{2+} "overload" of the SR (blue dots in **Figure 5-2**, Panel C). The SR cannot accommodate this overload and spontaneously releases some of the Ca^{2+} back into the myoplasm through the RYR2 Ca^{2+} release channels after repolarization and during diastole (curved blue arrows); these releases are called calcium sparks since they can be detected by fluorescent microscopy. There is a threshold level of diastolic SR Ca^{2+} that causes RyR2 channels to open, releasing Ca^{2+} into the myoplasm in the absence of membrane depolarization. This process is called store overload-induced Ca^{2+} release. RyR2 receptors may also be sensitive to elevated myoplasmic Ca^{2+}, which causes release channels to open. Furthermore, this diastolic Ca^{2+} release is delayed from the previous major Ca^{2+} release during the action potential plateau that causes contraction because of refractoriness of the release channels that results in the occurrence of DADs to be delayed after complete repolarization. The amount of diastolic Ca^{2+} release from the SR, as well as the rapidity of the release, is related to the amount of Ca^{2+} in the SR. The elevated diastolic Ca^{2+} in the myoplasm is the source of the transient inward (I_{TI}) current that causes DADs (vertical dashed line on action potential above) (described in more detail below). The diastolic release of Ca^{2+} may also be associated with an after-contraction with minimal force following systole, since the contractile mechanism is also activated. Ca^{2+} overload may also be associated with an increase in tonic (diastolic) tension.

The description of Figure 5-2 is an oversimplification of the Ca^{2+} release process. Rather than the SR being one functional unit as shown in Panels A–C, it is many functional units that are formed because the RyR2 channels are clustered and aligned in a specific anatomical pattern to allow for uniform Ca^{2+} release from the SR during the action potential (forward-mode EC coupling). The orderly pattern of RyR2 channels on the SR sets up a series of potential release sites of Ca^{2+} in the cell. When overload of SR occurs to cause DADs, a wave of Ca^{2+} propagates from one ryanodine cluster to another (Ca^{2+} sparks) through the myocyte. The summated Ca^{2+} released causes the DAD that is shown in Figure 5-2, Panel C.

Figure 5-3 shows a ventricular myocyte where a Ca^{2+} wave (indicated by bright fluorescence) has started from spontaneous Ca^{2+} release from the SR (a). This Ca^{2+} wave then propagates the length of the cell (b-p). The increased intracellular Ca^{2+} during the wave is sensed by the Na^+–Ca^{2+} exchanger, which extrudes the Ca^{2+} to produce membrane depolarization as a DAD (see below). This is an example of reverse-mode EC coupling where the increase in myoplasmic Ca^{2+} in the form of a wave, activates Ca^{2+}-dependent membrane ionic current changes.

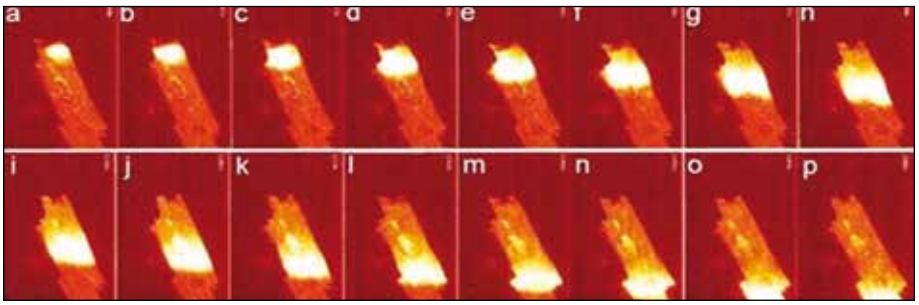

Figure 5-3 Cell-wide Ca^{2+} wave in ventricular myocyte. Images are of a myocyte loaded with a dye that fluoresces with an increase in myoplasmic Ca^{2+}.

In other situations, such as heart failure, ischemic disease, or genetic mutations, SR Ca^{2+} concentration may not be elevated and may even be reduced, but alterations in Ca^{2+} release channel function may still cause transient abnormally high myoplasmic Ca^{2+} levels during diastole that causes DADs. These pathophysiological conditions are described in more detail in the next chapter on DAD arrhythmias.

DADs in Purkinje Cells

Purkinje cells of the ventricular conducting system are more prone to the development of DADs than ventricular muscle, resulting in the Purkinje system being an important source of triggered arrhythmias. Purkinje cells have a microanatomy that is different than ventricular muscle cells depicted in Figure 5-2. In Purkinje cells, t-tubules are absent, and Ca^{2+} entering through the L-type channels propagates as a wave from the influx points to the core of the cell to access the RyR2 receptors that are not in direct contact with the sarcolemma, called the corbular sarcoplasmic reticulum (CSR) (Figure 5-2, Panel A). The special microanatomy of the SR in Purkinje cells with different forms of Ca^{2+} release channels leads to larger Ca^{2+} release from the SR and Ca^{2+} wave propagation. Increased Na^+ entry during the action potential (both during phase 0 and the plateau phase (2) of repolarization) leads to an increase in intracellular Ca^{2+} through the actions of the Na^+–Ca^{2+} exchanger. Increased Ca^{2+} entry during the long plateau phase compared to atrial and ventricular muscle also enhances occurrence of DADs. Purkinje cells also have a weaker I_{K1} than in ventricular muscle. As such, there is less outward current at the resting potential to oppose DADs. DADs are also facilitated by weak gap junctional coupling of Purkinje cells to surrounding myocardium, because Purkinje strands are often separated in bundles from underlying muscle. Normally, muscle cells are tightly coupled in three dimensions to surrounding myocardium. As explained in Figure 1-3, such coupling can prevent membrane depolarization because of the flow of electrotonic current during diastole, in this case inhibiting the formation of DADs in muscle cells.

Relationship Between Diastolic Ca^{2+} and Ionic Currents Causing DADs

In the presence of SR Ca^{2+} overload and excessive Ca^{2+} release from the SR into the myoplasm during diastole, the Na^+–Ca^{2+} exchanger extrudes the elevated Ca^{2+} from the cell in exchange for Na^+ (1 Ca^{2+} for 3 Na^+) generating the net inward current (I_{NCX}) causing the DAD (reverse-mode EC coupling) (Figure 5-2 Panel C, light blue oval, blue arrow is Ca^{2+} moving out of cell, black arrow labeled I_{NCX} is the inward Na^+ current). To reiterate, Ca^{2+} is actively extruded by the Na^+–Ca^{2+} exchanger against a concentration gradient requiring energy expenditure (blue arrow), since free diastolic levels are lower than extracellular concentrations of Ca^{2+} even when intracellular Ca^{2+} is increased in situations where DADs are generated. On the other hand, Na^+ moves down an electrochemical gradient (black arrow) from a higher extracellular to lower intracellular concentration. The energy for Ca^{2+} extrusion comes from the movement of Na^+ ions down this gradient and not the splitting of ATP molecules. The current carried by Na^+ movement causing the DAD is transient and decreases as Ca^{2+} at the internal surface of the sarcolemmal membrane is reduced by the exchanger, hence the nomenclature transient inward current (TI or I_{TI}). I_{NCX} is used synonymously with I_{TI}. The magnitude of I_{NCX} is directly related to the Ca^{2+} that is extruded, and this in turn is directly related to the diastolic Ca^{2+} concentration in the myoplasm.

In addition to I_{NCX}, other inward currents have been proposed to contribute to DADs. One current is a non-specific membrane current, which was originally designated to be the primary TI current. The membrane channel of this current was proposed to be Ca^{2+} sensitive, opening with elevated diastolic Ca^{2+}, with non-specific permeability to cations. Since Na^+ is the predominant cation in extracellular space, it is the primary charge carrier of this current. Another possible contributor to the TI current under certain conditions is a calcium-activated chloride current.

ELECTROPHYSIOLOGIC PROPERTIES OF DADS AND TRIGGERED ACTIVITY

In general, the magnitude of DADs as well as coupling interval to the preceding action potential are related to the diastolic Ca^{2+} levels and the rapidity of Ca^{2+} release from the SR. Therefore, events that change the diastolic Ca^{2+} levels and speed of release affect the occurrence and characteristics of triggered arrhythmias.

Dependence on Action Potential Characteristics

One of the factors that controls the size of DADs and the propensity for occurrence of triggered activity is the characteristics of the action potentials that precede them.

Effects of Action Potential Duration

The duration of the action potential (APD)—time from depolarization to complete repolarization—influences the intracellular and diastolic Ca^{2+} levels that cause DADs. Ca^{2+} enters the cell during the plateau phase of the action potential via I_{CaL}, which inactivates as repolarization proceeds to levels more negative than around –60 mV. Therefore, shortening the action potential duration decreases I_{CaL}, which suppresses DADs while lengthening it increases I_{CaL} and enhances DADs. Changes in action potential duration can be brought about by changes in the repolarizing I_K current (see Figure 7-2 for description of repolarizing membrane currents), a decrease of which prolongs APD, and an increase of which shortens APD. A number of drugs can alter I_K, thereby influencing DADs. For example, Class IA drugs (Vaughan Williams classification) that decrease I_K can increase DAD amplitude by lengthening APD and cause triggered activity in the experimental laboratory and possibly in patients.

Effect of Initial Membrane Potential

The amplitude of DADs is dependent on the level of membrane potential at which they arise. Although they may occur in cells with normal resting potentials of ~ –80 to –90 mV, amplitude can increase as membrane potential becomes less negative. Part of this effect may result from a decrease in outward (I_{K1}) current, which occurs during membrane depolarization, and part may result from an increase in I_{TI} current (I_{NCX}). DADs can occur at low diastolic membrane potentials where normal automaticity does not occur because I_f is inactivated (see Figure 4-3). Therefore, DADs may occur in disease-induced depolarized cells as well as cells with normal levels of membrane potential.

Dependence on Cycle Length (Rate and Prematurity)

The effects of cycle length at which action potentials occur, on DADs and DAD-dependent triggered activity differ from their effects on automaticity. These differences provide a basis for distinguishing triggered arrhythmias from automatic arrhythmias and for using electrical stimulation protocols for identifying triggered activity as a cause of arrhythmias. Some of the key differences are as follows:

- Automaticity of ectopic pacemakers is not initiated by an increase in rate (decrease in cycle length) of the dominant (sinus node) pacemaker or by electrical stimulation and is transiently suppressed by overdrive (overdrive suppression).
- DADs are enhanced by an increase in rate (decrease in cycle length) at which triggerable cells are stimulated. Therefore, triggered arrhythmias can be initiated by decreasing the cycle length and triggered activity can be accelerated by overdrive (overdrive acceleration).

Effect Rate on DAD Amplitude, Coupling Interval, and Triggered Activity

This effect of rate (or triggering cycle length) is illustrated in **Figure 5-4**, which is a diagram of action potentials recorded from a cell with DADs. At the left in each panel, the first three action potentials (in black) occur at a cycle length of 1000 ms. The small black arrows point out the DADs. Such subthreshold DADs might occur during sinus rhythm and not be noticed on the ECG.

In Panel A, the cycle length decreases to 800 ms (blue action potentials) and DAD amplitude increases (blue arrow), but does not reach the threshold for initiating a triggered action potential. In the diagram the cycle length is decreased for 10 sec (double black vertical bars indicate break in time scale; only last 3 sec are shown to the right of the bar) as might occur with an increase in sinus rate or during pacing.

In Panel B, the cycle length is decreased from 1000 ms (black action potentials at left) to 600 ms (blue action potentials). There is an increase in the amplitude of the DADs (blue arrow) that causes one to reach threshold (red arrow), initiating a triggered action potential (red arrow and action potential). The DAD following the triggered action potential does not reach threshold (red arrow at the far right) and triggered activity stops after one impulse. This is analogous to an increase in heart rate or pacing rate triggering a premature impulse.

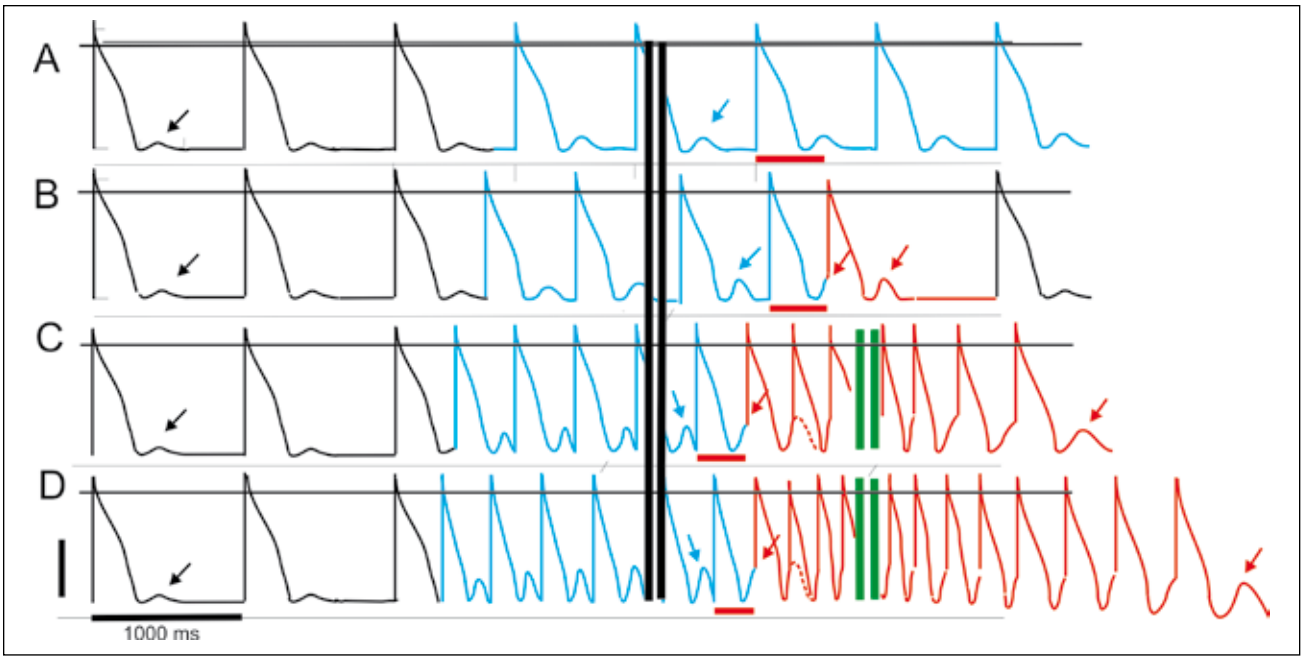

Figure 5-4 Effects of rate expressed as cycle length on DADs and triggered activity.

In Panel C, the cycle length decreases from 1000 ms (black action potentials at left) to 400 ms (blue action potentials). The DAD amplitudes increase even more (blue arrow). A DAD reaches threshold (red arrow) to trigger an action potential (in red) that is followed by a series of triggered action potentials since the DAD after each action potential also reaches threshold potential (dashed red trace indicates DAD of the triggered action potential; green vertical bars indicate a break in the time scale of 10 sec). Triggered activity stops when a DAD fails to reach threshold potential (red arrow at the far right). This is analogous to an increase in spontaneous or stimulated heart rate triggering a tachycardia.

In Panel D, cycle length decreases from 1000 ms (black action potentials at the left) to 300 ms (blue action potentials). The DAD amplitude is even larger (blue arrow). A DAD reaches threshold (red arrow), initiating a triggered action potential (red) that is followed by a DAD (dashed trace) that also initiates a triggered action potential. Each triggered action potential triggers the next one through the same mechanism. After a period of 10 sec—the break in time scale indicated by the green vertical bars—triggered activity terminates, with the last triggered impulse followed by a DAD that does not reach threshold (red arrow at the far right). Panel D also illustrates that the rate of triggered activity is faster and duration is longer when initiated at a shorter cycle length.

The relationship between stimulus cycle length (labeled as activation or triggering cycle length, Act/Trig CL) and DAD amplitude and coupling interval is shown in **Figure 5-5**. The DAD amplitude is shown to increase as cycle length decreases (red circles and line).

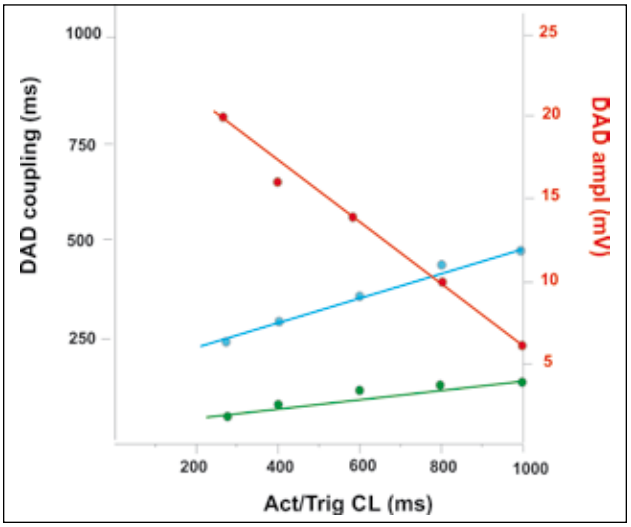

Figure 5-5 Effects of stimulus cycle length expressed as activation or triggering cycle length (Act/Trig CL, abscissa) on DAD amplitude in mV (right ordinate, **red line**) and DAD coupling interval (**green** and **blue lines**).

The direct relationship between stimulus cycle length (Act/Trig CL) and coupling interval of the DAD or first triggered impulse to the action potential upstroke (phase 0) is also shown in Figure 5-5 (blue line). This was also shown in Figure 5-4 where the coupling intervals between the DAD and the preceding action potential decrease as the cycle length decreases. As a result, the coupling interval between the first triggered action potential and the preceding triggering action potential decreases (horizontal red bars in Figure 5-4, Panels B–D) as the stimulus cycle length decreases. The direct relationship is caused by two factors. One is that the peak of the DAD occurs sooner after complete action potential repolarization because of increased speed of Ca^{2+} release from the SR as indicated by the green circles and line. The second is that the APD decreases as the cycle length decreases, which is the usual effect of cycle length on APD owing to an increase in I_p and I_K, outward currents that accelerate repolarization (described in Figure 7-7). (The blue line represents the combination of the two factors).

Single Premature Impulses as Triggers

A decrease of even a single cycle length in the form of a premature impulse also increases the amplitude of DADs and decreases the coupling interval and can trigger impulse initiation as illustrated in **Figure 5-6**.

In Figure 5-6, Panels A–D, action potentials at the left (shown in black) are occurring at a cycle length of 1000 ms and are associated with DADs that are subthreshold (black arrows). In Panel A, a premature action potential at a coupling interval of 800 ms (in blue) is followed by a DAD with a larger amplitude (blue arrow) that is still subthreshold. Likewise, in Panel B, the premature action potential at a coupling interval of 600 ms (in blue) is followed by a DAD with a larger amplitude than in A (blue arrow) but which is also subthreshold. In Panel C, the premature action potential (in blue) at a coupling interval of 500 ms is followed by a DAD that does reach threshold (blue arrow) for triggering an action potential (in red), which is then followed by a short series of triggered action potentials (in red) that terminates with a subthreshold DAD (red arrow at the far right). In Panel D, at a still shorter premature coupling interval of 300 ms, the DAD following the premature action potential (in blue) also reaches threshold (blue arrow) to trigger a longer period of triggered action potentials (in red), (vertical green bars in Panel D indicate a break of 10 sec in the time scale) which terminates with a subthreshold DAD (red arrow at the far right). (Whereas the figure shows a longer period of triggered activity initiated at a shorter coupling interval, this does not always occur.)

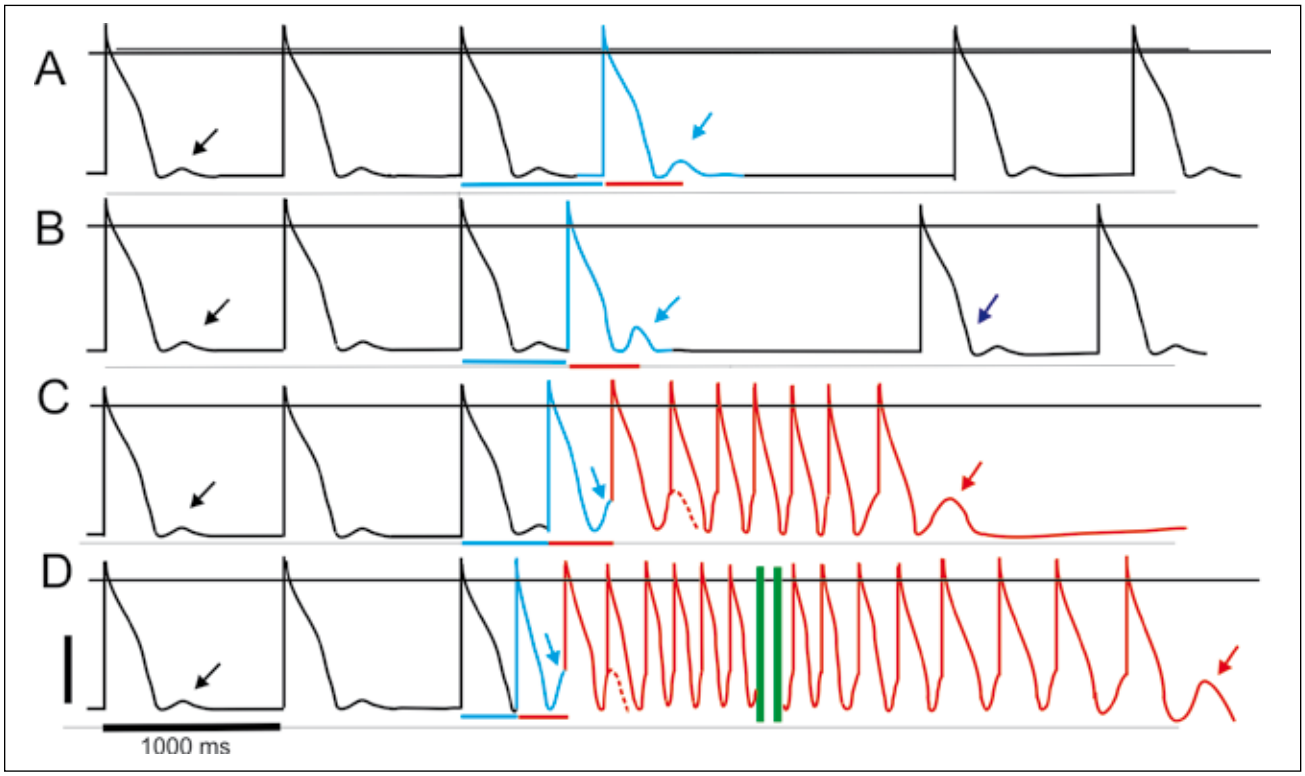

Figure 5-6 Effects of a decrease in a single cycle length (a premature impulse) on DADs and triggered activity.

Similar to the direct relationship between stimulation rate (cycle length) and coupling interval of the DAD described in Figure 5-5, the coupling interval of the DAD and/or the first triggered impulse to the single premature impulse decreases as the premature cycle length decreases. This relationship is shown in Figure 5-6. The blue horizontal bar below the action potentials is the coupling interval of the premature impulse which decreases from Panels A–D. The red horizontal bar is the coupling interval of the peak of the DAD of the premature impulse (A, B) or first triggered impulse (C, D), which also decreases. As with the effects of rate, shortening of the coupling interval of the DAD and first triggered impulse results from shortening of APD and shortening of the interval between peak DAD amplitude and complete repolarization of the preceding action potential.

The effects of rate (cycle length) and premature impulses on the amplitude and coupling interval of DADs is related to their effects on the amount of Ca^{2+} in the myoplasm during diastole. As described above (see Figure 5-2), Ca^{2+} enters the myocardial cell during the plateau phase of the action potential and is taken up into the SR, as well as causing SR Ca^{2+} release. Thus, a greater number of action potentials as occurs with an increase in rate/decreased cycle length results in more Ca^{2+} entering into the cell and the SR, as well as more Ca^{2+} being released from the SR during diastole. The elevated diastolic Ca^{2+} that generates the I_{NCX} or I_{TI} current and the DAD is increased. The rate of release of Ca^{2+} from the SR also increases as SR Ca^{2+} increases, causing DADs to occur earlier relative to repolarization.

Related clinical observations. Although the relationship between the initiation of triggered activity and preceding cycle length described above can often be observed in clinical studies (see Chapter 6), the direct relationship between activation cycle length and coupling interval of the first triggered impulse is not always observed. The increase in rapidity of SR Ca^{2+} release with decreased cycle length that underlies this relationship may reach a maximum beyond which no further increase occurs. The cycle length at which this occurs varies under different conditions and in different tissues. It might sometimes occur at relatively long cycle lengths, and as a result, shortening the cycle length at which tachycardia is initiated in clinical stimulation protocols will not produce the expected decreased coupling interval.

An increase in rate initiating triggered activity causes more Ca^{2+} release than a single premature activation, accounting for the more likely initiation of triggered arrhythmias by overdrive than by premature activation. This contrasts with the characteristics of reentry (the other arrhythmogenic mechanism initiated by stimulation), where premature stimulation is usually more effective in initiating arrhythmias than overdrive (see Chapter 9 for an explanation). The higher level of diastolic Ca^{2+} during more rapid rates of pacing accounts for the observation that it is easier to initiate triggered arrhythmias by premature activation during more rapid pacing rates, since DAD amplitude is closer to threshold. Slow rates often potentiate the initiation of reentry, but in some situations, rapid rates also favor induction of reentry by premature impulses.

Triggered Activity Rate and Duration

The rate of triggered activity is governed by the time it takes for a DAD to depolarize the membrane potential from the maximum diastolic potential (MDP) to the threshold potential for initiating an action potential. Therefore, rate is dependent on the relationship between MDP, rate of DAD depolarization, and threshold potential (similar to rate of automaticity; see Figure 1-2). APD also influences triggered activity rates, with faster rates associated with shorter action potential durations.

Warm Up

The rate of DAD depolarization increases and APD shortens progressively during the initial impulses of triggered activity. Because of the decreased cycle length of the first triggered impulse related to the decreased DAD coupling interval, the second triggered impulse will also have a decreased cycle length because of the decreased coupling interval of the preceding DAD, resulting in more Ca^{2+} entering the cell, increasing the DAD amplitude and decreasing the coupling interval of the next triggered impulse. The increased Ca^{2+} causes a gradual decrease in triggered cycle length (called "warm up") until a steady state is reached (Figures 5-4 and 5-6, Panels C and D).

Another factor that may contribute to the decrease in cycle length during triggered activity is a slow and gradual depolarization of the MDP (membrane potential becomes less negative) moving MDP closer to the threshold potential. This depolarization can result from accumulation of K^+ just outside the cell membrane (coming from the movement of K^+ from intra- to extracellular space carried by the repolarizing I_K), if circulation is not sufficient to rapidly wash it away.

Duration and Termination

As described above, the rate of triggered activity may increase and the duration of the period of triggered activity become longer as the triggering cycle length decreases. These features are also related to the amount of Ca^{2+} entering the cell during the triggering cycle length, with

more Ca^{2+} entering at shorter cycle lengths. This relationship can sometimes be seen in clinical studies and provide evidence for DAD-triggered arrhythmias as described in Chapter 6.

Triggered activity can be sustained or paroxysmal. Before terminating spontaneously, it may gradually slow (Panel D in Figure 5-4 and Figure 5-6). The slowing and termination results from an increased activity of the Na^+–K^+ pump and outward I_p. In cells with high (more negative –70 to –90 mV) levels of membrane potential, Na^+ enters during phase 0 of each triggered action potential and is pumped out of the cell by the Na^+–K^+ pump generating I_p as described in Figure 1-6. As the triggered rate speeds up, the amount of Na^+ entering the cell increases. The increase in outward I_p current opposes the inward current causing the DADs, eventually decreasing the rate and amplitude of the DADs, thereby slowing the rate of the triggered action potentials. In addition, I_p moves membrane potential in a negative direction, gradually moving maximum diastolic potential of the DAD further from the threshold for activation of a triggered action potential until triggered activity stops when the peak DAD amplitude does not reach this threshold potential (Figure 5-4, Panel D, and Figure 5-6, Panel D, red arrows at the right). In situations in which the Na^+–K^+ pump is not able to generate sufficient I_p such as in digitalis toxicity where the pump is partially inhibited, other mechanisms related to Ca^{2+} overload effects on ion channels contribute to termination of triggered activity.

After the termination of triggered activity, membrane potential may be more negative (hyperpolarized) than before because of persistent increased I_p. This effect gradually diminishes as I_p returns intracellular Na^+ towards normal. As a result, another episode of triggered activity cannot quickly occur, since the hyperpolarized membrane potential and increased outward I_p prevent DADs from reaching the threshold potential. With time, as I_p diminishes, triggered activity can again be induced. This property is sometimes observed in clinical studies on triggered arrhythmias in which another arrhythmic episode cannot be immediately initiated after initiation and termination of a triggered arrhythmia by electrical stimulation.

Effects of Overdrive Stimulation During Triggered Activity

The factors that govern rate and spontaneous termination of triggered activity are also involved in the response of ongoing triggered activity to overdrive stimulation. These effects are important when considering the effects of overdrive on clinical triggered arrhythmias (**Figure 5-7**).

Figure 5-7 shows a diagram of triggered action potentials after a long period of triggered activity at the left in black. During each action potential, Na^+ (blue arrow) and Ca^{2+} (green arrow) enter the cell, and K^+ (red arrow) leaves the cell. The Na^+–Ca^{2+} exchanger (green oval) generates the TI current by extruding 1 Ca^{2+} for 3 Na^+ ($I_{NCX,}$ downward blue arrow) causing the DADs perpetuating triggered activity. Na^+–K^+ pump activity (blue circle) extrudes 3 Na^+ (upward blue arrow) in exchange for 2 K^+ (downward red arrow).

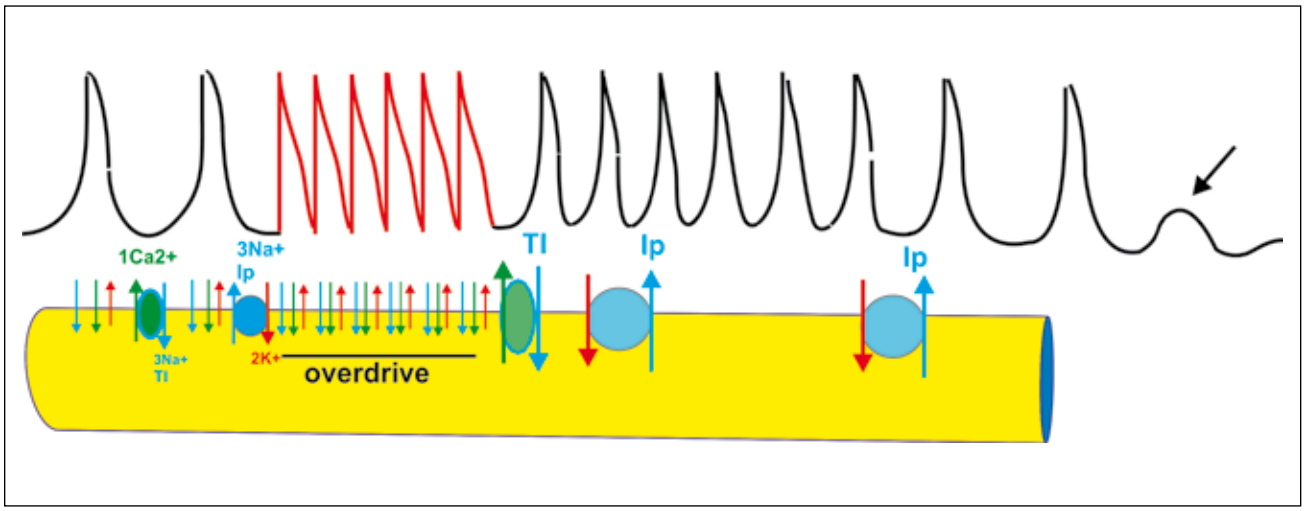

Figure 5-7 Triggered arrhythmia response to overdrive.

The red action potentials show a period of overdrive, during which there is increased Na^+ and Ca^{2+} entering and K^+ leaving the cell during the action potentials. At the end of the period of overdrive (action potentials are black again), there is increased activity of the Na^+–Ca^{2+} exchanger (larger green oval) because of the increased Ca^{2+} that entered during overdrive, enhancing I_{NCX} and TI, causing overdrive acceleration. The Na^+–K^+ pump activity also is increased (larger blue circle), generating more outward I_p that eventually overcomes the increased inward I_{NCX}, causing the DADs to become smaller, and hyperpolarizing the membrane potential until triggered activity stops when a DAD fails to reach threshold potential (arrow at the far right).

Thus, at an appropriate overdrive rate, the overdrive is followed by overdrive acceleration, then slowing, and finally termination. Slower overdrive rates may only cause acceleration followed by a return to the pre overdrive cycle length. Faster overdrive rates may cause immediate termination. As for spontaneous termination, when the Na^+–K^+ pump is partially inhibited by digitalis toxicity (see Figure 5-8), I_p is less important in overdrive termination and increased intracellular Ca^{2+} effects on ion channels may be more important.

Effects of the Autonomic Nervous System

Sympathetic Stimulation

The sympathetic nervous system is an important factor controlling the initiation and rate of DAD-dependent triggered activity. Sympathetic activation or β_1-adrenergic agonist drugs can result in the appearance of DADs in atrial, specialized ventricular (Purkinje) and ventricular muscle cells and likely A-V nodal cells (Figure 6-1). When DADs are already present, sympathetic activation increases the amplitude and rate of depolarization of DADs, decreases their coupling interval and increases the rate and duration of triggered activity.

The sympathetic nervous system exerts its effect on DADs through the effects of norepinephrine to increase Ca^{2+} entry into cells through the L-type Ca^{2+} channels. β_1-receptor activation by catecholamines results in phosphorylation of the L-type Ca^{2+} channels, which increases opening of the channels and L-type Ca^{2+} current, I_{CaL}. RyR2 receptors in SR Ca^{2+} release channels are also phosphorylated, increasing their release activity. Norepinephrine also increases activity of the calcium pump (SERCA) to move more Ca^{2+} into the SR, because phosphorylation of the protein phospholamban removes its inhibitory effects on the pump.

Parasympathetic Suppression

The parasympathetics (vagus nerve) can suppress DADs and triggered activity in atrial, A-V nodal and ventricular tissues (Purkinje fibers and ventricular muscle). In atrial and A-V nodal cells, acetylcholine released from parasympathetic nerve endings acts on the M_2 subtype of muscarinic receptors to slow and terminate triggered activity. This effect is brought about through a G protein-mediated increase in outward K^+ current through K_{ACh} channels. The increase in outward current opposes the inward current during DADs (decreases net inward current) that decreases their amplitudes and makes the membrane potential more negative, preventing DADs from reaching threshold potential. Acetylcholine also decreases inward L-type Ca^{2+} current (I_{CaL}) by suppressing adenylate cyclase to reduce intracellular Ca^{2+} loading. Although ACh does not increase a K_{ACh} channel current in ventricular tissues, it can prevent the increase in cyclic AMP (cAMP) that underlies the formation of DADs under sympathetic stimulation by the process of accentuated antagonism described in Chapter 1.

DADS Caused by Digitalis Toxicity

Digitalis is used as adjunct therapy in heart failure and for rate control in atrial fibrillation. In addition to enhancing automaticity (Chapter 1), the drug can cause arrhythmias due to triggered activity (described in detail in Chapter 6). The mechanism for the arrhythmogenic effect of digitalis to cause DADs and triggered activity is linked to the mechanism for its positive inotropic effects in the atria and ventricles. Digitalis binds to high-affinity isoforms of the Na^+–K^+ pump to block pump activity. In therapeutic amounts, only a small fraction of pumps in the sarcolemma are blocked, with a consequent increase in intracellular Na^+ concentration. The increase in Na^+ concentration throughout the cytoplasm (referred to as the bulk phase) is very small, but the increase in Na^+ concentration in restricted intracellular spaces (an intracellular region that is not in equilibrium with the bulk phase) can be substantial. Such a restricted space important for digitalis effects on contractility and arrhythmogenesis is diagrammed in **Figure 5-8**.

Figure 5-8 illustrates that the restricted space (separated from the bulk phase of the myoplasm) where there can be a substantial increase in Na^+ concentration, is located in the regions where the terminal cisternae of the junctional SR (JSR) abut the sarcolemma membrane. Here, there may be co-localization of L-type Ca^{2+} channels and I_{CaL} (red ovals and arrow), high affinity Na^+–K^+ pumps (large dark blue circle), Na^+–Ca^{2+} exchangers (large light blue oval) and RyR2 receptors, all of which have a role in DAD formation.

CHAPTER 9

Basic Principles of Reentry: Altered Conduction and Reentrant Excitation

Overview and General Principles

Altered impulse conduction represents the second major category of arrhythmia mechanisms (Introduction, Table i-1). One means whereby altered impulse conduction results in the occurrence of arrhythmias is the manifestation of latent pacemakers that occurs when sinoatrial (S-A) or atrioventricular (A-V) block is present (described in Chapters 1-4. Altered impulse conduction also causes reentrant excitation (reentry), a mechanism for arrhythmias that does not depend on the generation of *de novo* impulses, as occurs with the mechanisms of automaticity and triggered activity.

REQUIREMENTS FOR REENTRY

While the underlying detailed mechanisms of clinical reentrant arrhythmias are more complicated, a simple ring model of reentry describing impulse movement in a circular pathway (circus movement) provides the foundation for these more complicated concepts.

The Ring Model

The basic principles underlying reentrant excitation are shown in a schematic diagram of a ring of excitable cardiac muscle with a central inexcitable region (in black) in **Figure 9-1**. The ring is a model of an anatomical reentrant circuit—an anatomically fixed pathway around an anatomical obstacle. Conducting impulses are indicated by the blue arrows, with the arrowhead showing the leading edge or head of the propagating impulse (the wave front), and the blue segment of the tail of the arrow indicating inexcitable myocardium (the effective refractory period) that the impulse has just excited. In Figure 9-1, the red segment of the tail indicates partially recovered myocardium during the relative refractory period. (Note that in other figures, e.g., Figure 9-14, the length of the arrow tail does not indicate the inexcitable or partially recovered myocardium as it does in Figure 9-1. Where not otherwise indicated, the entire arrow simply represents the direction of impulse propagation.)

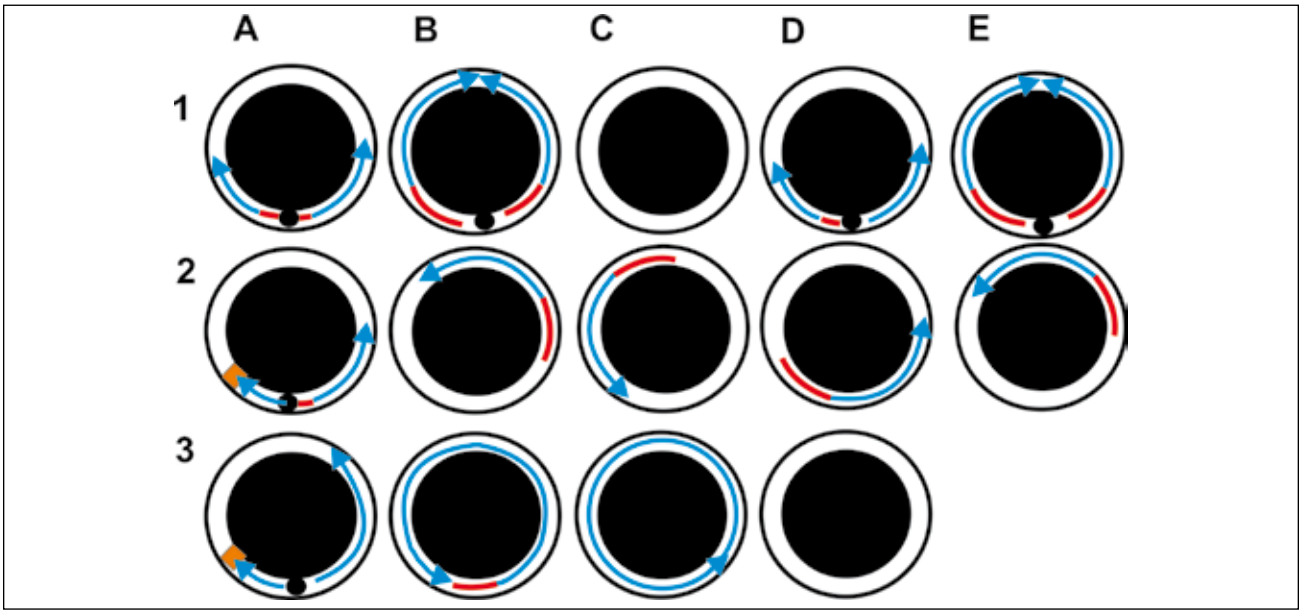

Figure 9-1 Model of reentry in an anatomical circular pathway. The diagrams show snapshots of the sequence of impulse propagation (**arrows**) over a period of time (across the row from **A–E**) after initiation at the **black dot in Column A1–A3**.

Electrophysiological Foundations of Cardiac Arrhythmias: A Bridge Between Basic Mechanisms and Clinical Electrophysiology, Second Edition.

Figure 9-1, row 1 diagrams bidirectional impulse conduction. Snapshot A1 illustrates impulses initiated at a point (black dot), propagating away from the site of origin in opposite directions in the ring. During the time period between A1 and B1, the two impulses reach the distal side of the ring where they collide (blue arrows in snapshot B1). The impulses die out because they are surrounded by tissue that has just been excited and that remains refractory for a period of time that outlasts the time for propagation. This pattern is somewhat analogous to an impulse originating in the sinus node (black dot) that dies out after exciting atria and ventricles because it is surrounded by effectively refractory myocardium and runs into the inexcitable fibrous annulus after depolarization of the ventricles. After a period of quiescence, (C1), a new impulse must be initiated for subsequent activation (at the black dot) (D1 and E1), analogous to the next sinus impulse.

Unidirectional Conduction Block Under Special Conditions

Diagrams in row 2, A2–E2, show how the propagating impulse can persist to reexcite, i.e., reenter, regions it has already excited.

In snapshot A2, excitation again is initiated at the black dot. By temporarily causing conduction block in the right-to-left (clockwise) direction near the site of stimulation (at the brown rectangle), excitation is induced to progress in only one direction, to the right (counterclockwise), around the ring (blue arrow). Mechanisms for transient block in the *in situ* heart that cause clinical arrhythmias are described in Figures 9-14, 9-15, and 9-16. After an impulse is conducting in one direction around the ring (B2–E2 show snap shots of the impulse at progressive time periods), if conduction is restored in the region of the block, the impulse can then return to its site of origin and reexcite (reenter) tissue it previously has excited (D2 and E2). Thus, the block is unidirectional (only clockwise) and the impulse can conduct counterclockwise. The ring forms a reentrant pathway or circuit. The impulse can also continue to circulate, repeating the pattern of snapshots B2–E2. This simple model demonstrates that for reentry to occur, a region of block must be present, even if only transiently (the brown rectangle in Panel A2). The block is necessary to launch propagation of the impulse in one direction and to prevent early excitation of the pathway (at the left side of the ring) that eventually becomes the return pathway that the impulse then uses to reenter the region it reexcites. In the ring model shown in Figure 9-1, identical circular movement would occur if, instead of transient block, permanent conduction block occurred in the clockwise direction (brown-shaded area of Panel A2), also known as unidirectional block. Electrophysiological mechanisms for permanent unidirectional conduction block are described later in Figures 9-15 and 9-16.

Importance of the Wavelength of the Conducting Impulse in Reentry

In addition to unidirectional conduction block, for reentry to occur, the impulse that is conducting around the circuit must always find excitable tissue in the direction in which it is propagating, i.e., the tissue that was excited in the previous transit around the ring must have recovered excitability. In order for this requirement to be fulfilled, the conduction time around the ring must be longer than the effective refractory period of the myocardium that comprises the ring. For purposes of describing the mechanism for reentry, the concept of wavelength of the conducting impulse can be used.

A definition of "wavelength" (λ is the distance traveled by the depolarization wave during the time the tissue restores its excitability sufficiently to propagate another impulse. Thus, wavelength (λ) = conduction velocity (θ) × effective refractory period (ERP). In Figure 9-1, A2–E2, the length of the blue arrow (from arrowhead to the end of blue tail) is the wavelength of the conducting impulse, the time between the head of the wavefront and recovery of excitability, even though recovery is not complete. The end of the blue tail signifies the functional refractory period, which is the earliest time that an impulse can propagate following a prior excitation. The myocardium in front of the arrowhead in Panels C2 to E2 has recovered as indicated by the unshaded region. This requirement that conduction around the circuit must take long enough to allow recovery from the effective refractory period can be expressed in terms of the relationship between the wavelength (λ) of the conducting impulse (the length from blue arrowhead to end of blue tail) and the length of the reentrant pathway (path length, l). In other words, the wavelength (λ) of the reentrant impulse must be shorter than the length of the pathway ($\lambda < l$). In Figure 9-1, A2–E2, the wavelength is significantly less than the path length, leaving a large part of the circuit excitable, enabling it to be reexcited by a propagating wavefront.

Spatial and temporal excitable gaps. The excitable region of the circuit forms the spatial excitable gap which is the distance occupied by the excitable region at any moment in time. The spatial excitable gap is comprised of a partially excitable gap where myocardium is still relatively refractory (curved red line), and a fully excitable gap where myocardium has completely recovered excitability (unshaded region).

In clinical studies to evaluate the excitable gap during a reentrant tachycardia, only a temporal excitable gap or excitable period can be identified, which is the time interval of excitability between the head of activation of one impulse and the tail of refractoriness of the prior impulse. This will be described in detail in Chapters 10, 11, and 12 on clinical reentrant arrhythmias. The temporal excitable gap is measured by stimulating premature impulses, usually outside the circuit, and observing the resetting response that results from the premature impulse entering and conducting around the circuit (described in detail in Figure 9-27, and Figure 9-28). The spatial excitable gap cannot usually be evaluated, since it would require stimulating at multiple sites within the circuit to evaluate how much of the circuit is excitable, which cannot usually be done in clinical studies.

Figure 9-1, row 3 A3–D3, diagrams a situation where the wavelength is longer than the path length ($\theta > l$), precluding reentry, since there is no excitable gap. Snapshot A3 shows initiation of conduction in one direction (counterclockwise) because of the region of transient block in the clockwise direction (brown-shaded region). Conduction velocity is much more rapid so that by Snapshot B3, the impulse has almost completed its transit around the circuit without providing enough time for recovery of excitability, indicated by the long length of the blue arrow. In C3, the wavefront (arrowhead) collides with its refractory tail and blocks. The reentering impulse dies out (D3).

In general, for reentrant circuits of the same length, the excitable gap decreases as the wavelength increases, either because of an increased conduction velocity or an increased effective refractory period. This is one reason that reentrant circuits causing fast tachycardias usually have small excitable gaps when the increase in the wavelength is caused by a faster conduction velocity.

Relation of wavelength to the propagating action potential. **Figure 9-2** pictures the wavelength of the conducting impulse as it relates to a propagating normal ventricular muscle action potential with typical voltage-dependent recovery of excitability. Panel A shows the time course of a ventricular muscle action potential. The voltage scale is on the ordinate. Time is indicated by the red arrow below it on the abscissa, beginning at 0 and ending at 400 ms. The depolarization phase 0 occurs first at time 0, followed by repolarization phases 1, 2, and 3, which end at time 400 ms. The effective refractory period ends at the vertical dashed green line (300 ms) followed by the relative refractory period. The conduction velocity of the action potential is not displayed in this kind of representation, and changes in velocity do not influence the appearance of the action potential as long as phase 0 and repolarization time are not altered.

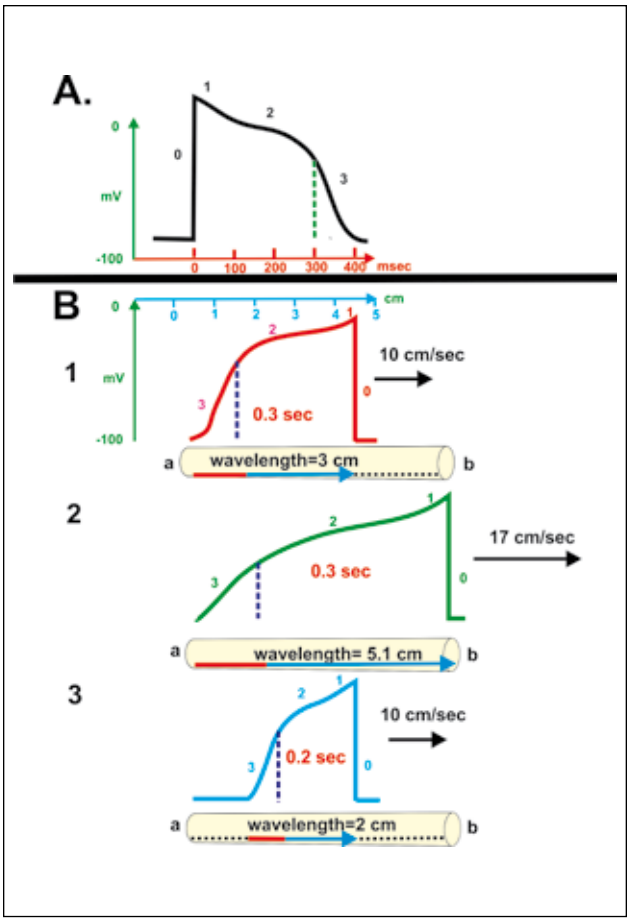

Figure 9-2 **Panel A** shows an action potential as it is traditionally displayed. **Panel B** (**1, 2, 3**) shows how much space the action potential waveform occupies (the wavelength).

Figure 9-2, Panel B shows a different way of depicting the action potential; it shows the action potential in space as it propagates along a 7-cm long muscle bundle from left to right. The muscle bundle depicted here represents a circular reentrant pathway that has been cut through and laid out in a straight line—the two ends, a and b, were attached before cutting. In this representation, the voltage scale is still on the ordinate, but the abscissa represents distance or space in cm (in blue at the top of the panel). The initial phase 0 of the action potential is now at the right, leading the movement of the depolarizing wavefront (blue arrowhead) as it conducts over the bundle.

At the time shown in Panel B1, action potential 1 has propagated for about 4.5 cm along the bundle. Action potential repolarization phases 1–3 trail the leading phase 0. The effective refractory period is between phase 0 and the vertical dashed purple line, showing the spatial extent of the tissue that is refractory in the muscle bundle. Repolarization to the end of the effective refractory period takes 0.3 sec. The wavelength of the action potential is the space occupied by the action potential between

phase 0 and the end of the effective refractory period. It is dependent on both the conduction velocity (10 cm/sec in B1) and time for repolarization to the end of the effective refractory period (0.3 sec in B1) and is the product of these two values (wavelength = 3 cm). The extent of the wavelength is also shown by the blue arrowhead to end of blue arrow tail that corresponds with phase 0 of the action potential to the end of the effective refractory period. In muscle cells in diseased regions, the effective refractory period may extend further, beyond complete repolarization, called "postrepolarization refractoriness" (see Figure 9-7). Nevertheless, the concept of wavelength is still the same.

The impulse as represented by the wavelength does not occupy the entire muscle bundle, there is a region in front of it (dashed line in front of arrowhead) which has not yet been excited and is still completely excitable. This represents the fully excitable gap of the reentrant circuit. There is also a relatively refractory region between the end of the effective refractory period and complete repolarization at the left of the bundle, which represents a partially excitable gap (red segment of arrow tail).

In Panel B2, action potential 2 shows what happens to the wavelength when conduction velocity of the impulse increases to 17 cm/sec but the time for repolarization remains at 0.3 sec (factors that control conduction velocity are described later in this chapter). Phase 0 depolarization moves more rapidly from left to right down the length of the muscle bundle, propagating about 7 cm at the time shown. The impulse propagates a longer distance during the 0.3 sec required for repolarization to the end of the effective refractory period. As a result, the wavelength of the impulse expands to approximately 5 cm; conduction velocity of 17 cm/sec × 0.3 sec = 5.1 cm. There is no fully excitable gap (no dashed line ahead of the impulse). (Remember that the fiber bundle in the figure represents a circular reentrant pathway: the end of the bundle "b" connects to the beginning of the bundle "a".) The extent of the wavelength is also shown by the blue arrowhead to blue arrow tail which coincides with the action potential from phase 0 to the end of the effective refractory period. Part of the bundle indicated by the red line, is relatively refractory forming a partially excitable gap. The impulse can still conduct around the circuit in this partially excitable gap.

Panel B3, action potential 3 shows the effects of reducing the duration of the action potential by accelerating repolarization to 0.2 sec. The conduction velocity is 10 cm/sec, the same as in B1. Now, as the impulse moves over the same distance as in B1, the more rapid repolarization shortens the wavelength of the impulse to 2 cm so that it occupies less of the bundle (blue arrowhead to end of blue tail), leaving an extensive region of the bundle that is fully excitable. There is a large fully excitable gap (dashed line) as well as a partially excitable gap (red line).

Effect of variable conduction velocity and repolarization. At the beginning of the chapter, Figure 9-1 represents a simple model of a reentrant circuit where the wavelength remains constant during transit of the impulse around the circuit because conduction velocity and repolarization remain constant. If conduction velocity and refractory period vary from site to site in a circuit, the wavelength will change during propagation of the reentrant impulse, as diagrammed in **Figure 9-3**. Specific examples of clinical arrhythmias that show these features are described in subsequent chapters.

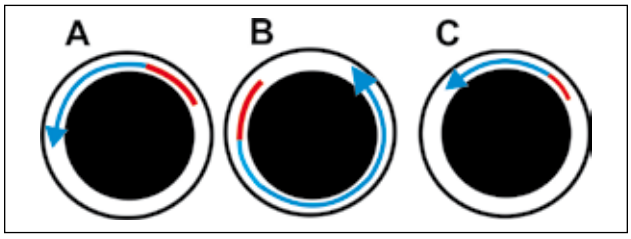

Figure 9-3 Reentry in a circuit in which wavelength changes in different regions of the reentrant pathway.

Figure 9-3 diagrams the propagating wavefront (blue arrowheads) and the effectively refractory (blue) and partially refractory (red) tail, at three different positions (A, B, and C) in a reentrant circuit. Conduction velocity is slower in the segments of the circuit in Snapshots A and C, resulting in a shorter wavelength (blue arrowhead to blue tail) than in Snapshot B, where conduction velocity is rapid causing a long wavelength (blue arrowhead to blue tail). Therefore, the spatial duration of the fully excitable gap when the propagating impulse is at the position in B, is much smaller than when the impulse is at the positions in A and C. However, the average wavelength must still be less than the path length.

Location and Form of Reentrant Circuits

Reentrant circuits can be located almost anywhere in the heart and can assume a variety of sizes and shapes. The size and location of an anatomically defined reentrant circuit remains fixed and results in what may be called "ordered reentry." Anatomical circuits have a central anatomical obstacle (Figures 9-1) that prevents the impulse from taking a "short cut" that would preexcite a segment of the pathway and stop reentry. The circuit may also be functional and its existence, size and shape determined by electrophysiological properties of the cardiac cells rather than an anatomically defined pathway. The size and location of reentrant circuits dependent on functional properties can be ordered but also may change with time

leading to random reentry. Nevertheless, the relationship between path length and wavelength still apply. Reentrant circuits can also be a combination of anatomical and functional components. The different kinds of reentry are described in Figures 9-17 to 9-21.

The model of the reentrant circuit diagrammed in Figure 9-1 is modified for the description of clinical arrhythmias, the modification being dependent on the location of the reentrant circuit.

NECESSARY ELECTROPHYSIOLOGICAL PROPERTIES FOR REENTRY

The basic electrophysiological properties that facilitate reentry are slow conduction, unidirectional conduction block, and time for recovery of excitability.

Slow Conduction of the Propagating Wavefront

For reentry to occur, the conducting impulse must be delayed sufficiently in its transit through the reentrant pathway to allow regions in front of it to recover excitability (delayed until the effective refractory period ends). In other words, the wavelength must be shorter than the path length. If, for example, the impulse conducted at a normal velocity of 50 cm/sec in a reentrant pathway in the atrium, with an effective refractory period of 150 ms, it would have to conduct for at least 150 ms before it could return and reexcite a region it had previously excited. This means the conduction pathway must be at least 7.5 cm long (the value of the wavelength, $\lambda = \theta$ (50 cm/sec) × ERP (0.15 sec) for reentry to occur. Such long reentrant pathways, functionally isolated from the rest of the heart, are not likely to occur.

According to the concepts described in Figures 9-1 and 9-2, the length of the pathway necessary for reentry can be shortened if the conduction velocity is slowed. For example, if conduction velocity is slowed to 0.05 cm/sec, as can occur in diseased cardiac muscle, the reentrant circuit need be no more than 7.5 mm in length, which can readily exist. A slow conduction velocity can be a consequence of changes in active membrane properties determining the characteristics of inward currents depolarizing the membrane (phase 0) during the action potential or it can be a consequence of changes in passive properties governing the flow of current between cardiac cells through gap junctional channels; the axial current. Both often participate simultaneously. The factors that affect conduction velocity are described in the next section.

Effects of the Depolarization Phase (0) of the Action Potential on Conduction

Important features of transmembrane action potentials that govern the speed of propagation are (1) the amplitude of the action potential (positivity of phase 0) which reflects the magnitude of the inward depolarizing current, and (2) the rate at which phase 0 depolarizes the cell (dv/dt_{max} of phase 0 in volts/s, also expressed as $\dot{V}_{max}$), which indicates the speed at which the inward current reaches maximum intensity. Reduction of these parameters slows conduction. Figure 9-4, Panels A–C show the mechanism for normal rapid conduction and the effects of reducing the amplitude and dv/dt_{max} ($\dot{V}_{max}$) of phase 0, in a simple model of linear conduction through a strand of three myocardial cells (labeled 1, 2, and 3) with phase 0 of the action potentials dependent on I_{Na}. The cells are physically connected by the intercalated disks and electrically connected internally by channels in gap junctions that reside in the disks (in yellow). The model does not take into account microscopic discontinuities formed by the gap junctions that have an additional influence on conduction properties.

Panel A shows the three cells in the strand at rest with a resting potential of inside –90 mV negative with respect to the outside (red line above cells), within the normal range for atrial and ventricular cells. In Panel B, cell A is excited and inward I_{Na} (red arrows) generates an action potential (above the cell in red), with the inside of the cell becoming +30 mV with respect to the outside (also within the normal range). The juxtaposition of the excited cell (1) and the adjacent unexcited cells (2 and 3) results in flow of positive charges intracellularly (referred to as the axial current) between excited (cell 1) and unexcited cells (2 and 3) (from positive to negative) through the gap junction connections, indicated by the curved blue arrows (Panel B). The current, when large enough, can flow for several cells (from cell 1 to cells 2 and 3) as shown in the diagram. Some of the axial current (capacitive current) supplies positive charges to the inside of the membranes of the downstream cells (2 and 3), depolarizing their membrane potential to the threshold potential (~ –70 mV) so that they generate action potentials (red action potentials above cells 2 and 3 in Panel C).

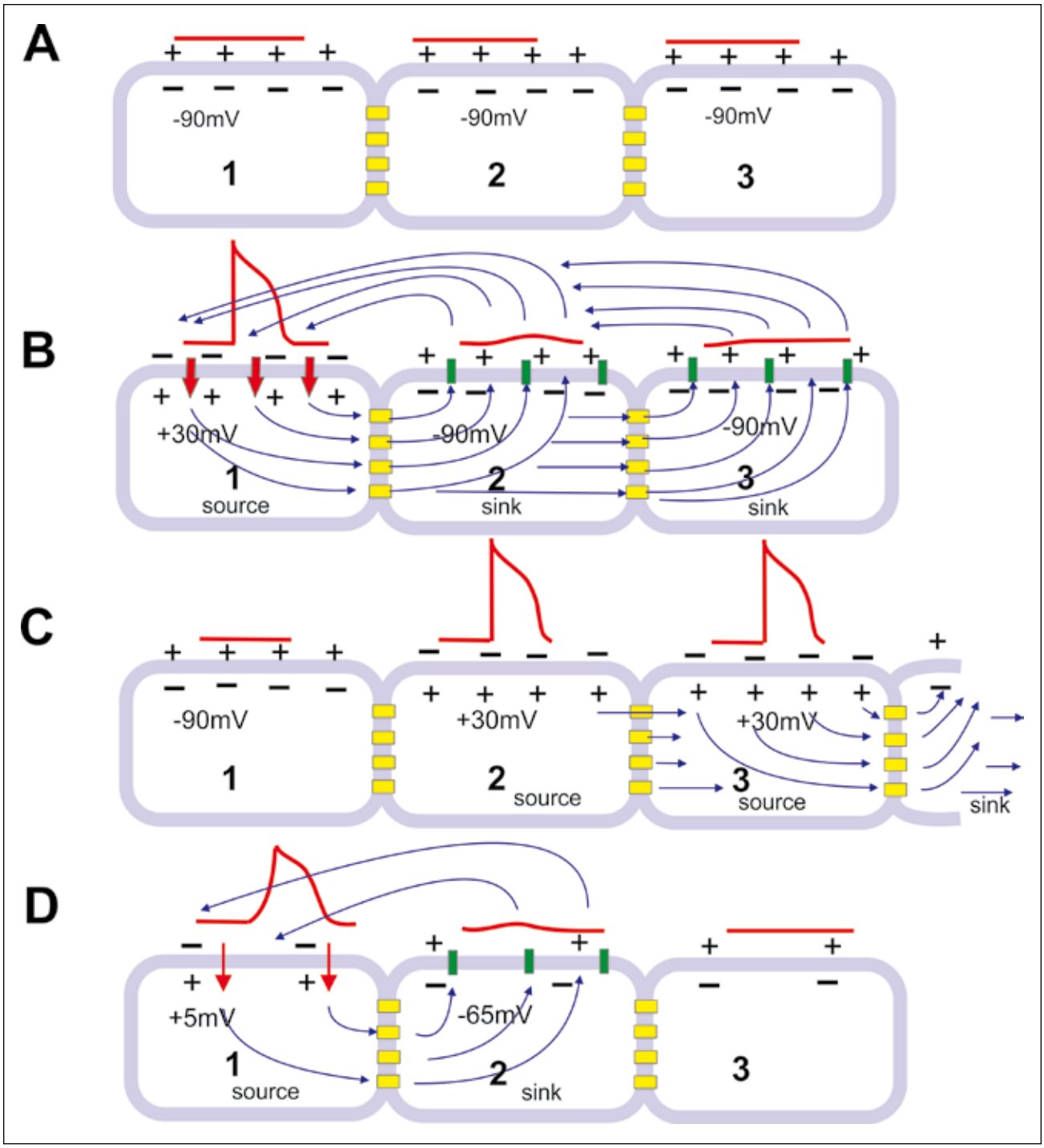

Figure 9-4 Diagram of conduction in a linear strand of three cells (**rectangles 1–3**) connected by gap junctional channels (**yellow**).

In Panel B, ionic current also flows out of cells 2 and 3 through the I_{K1} channel (green rectangles). In extracellular space, current generated by the transmembrane current flow in cells 2 and 3, flows from these cells back to the excited cell, from positive to negative (blue arrows right to left), completing the circuit. This is the current detected in electrogram and ECG recordings. The excited cell (1) generating the current in Panel B is the "source," the unexcited cell(s) (2 and 3) are the "sink." The action potential has conducted from cell 1 to cells 2 and 3 in Panel C (cell 1 has repolarized to reestablish its resting membrane potential of –90 mV, red line above cell). Once threshold is reached and an action potential is generated in cells 2 and 3, the newly excited cells switch from being a sink to being a source, generating axial current to depolarize downstream cells, perpetuating the process of action potential (impulse) propagation (Panel C).

Safety factor. For normal conduction to occur, the number of positive charges delivered by the source to the sink (Figure 9-4, Panel B cell 1) should be greater than the number of positive charges leaving the cells at the sink (cells 2 and 3). This property is responsible for depolarization of the membrane potential to threshold for generation of the action potential in cells of the sink. There is an "impedance match" between the source and the sink, meaning that the resistance to axial current flow (impedance) allows sufficient axial current that "matches" the requirements for depolarization of the sink to threshold potential. The ability to conduct from one cell to the next can be expressed in terms of the "safety factor" for conduction. This is a measurement of reliability (robustness) of conduction expressed as the ratio of the amount of net current generated by the source (cell 1) to the minimal amount of current required to excite the neighboring sink cells (2 and 3). A safety factor greater than 1 indicates more than sufficient current generated by the source for propagation, while a safety factor less than 1 causes propagation to fail because the sink is not depolarized to threshold potential. In myocardial cells with phase 0 caused by I_{Na} the safety factor is about 1.5 whereas it is smaller in the SA and A-V nodes (but still sufficient for propagation) that have depolarization phases dependent on the relatively weak I_{CaL}.

Determinants of Conduction Velocity

The conduction velocity depends on (1) the properties of the ionic current generated by the source (magnitude and speed to reach maximum intensity (dv/dt_{max}), (2) the resistance to intracellular and intercellular current flow between source and sink, which is the axial resistance or impedance, provided by myoplasm and gap junctions, and (3) the membrane properties of the sink. These properties influence how much axial current flows to unexcited sites ahead of the propagating wavefront, the distance at which the current can depolarize the membrane potential to threshold, and the amount of current needed to depolarize the sink to threshold.

An additional factor that must be kept in mind, but that is usually not emphasized, is the resistance to current flow in the extracellular space, which is part of the local electrical circuit. The extracellular space is actually compartmentalized into the microvascular tree and interstitial space. Only the resistance (impedance) of the interstitial space affects current flow. The microvascular tree is insulated from the interstitial space. Therefore, changes in extracellular resistance will also affect conduction velocity. However, the influence of changes in extracellular space with disease on conduction is uncertain. One example might be that an increase in interstitial fluid could decrease extracellular resistance to enhance velocity but this effect might be offset by changes in the other factors that affect conduction.

Na^+ channel properties. Figure 9-4, Panel D shows the effects of a reduction in the inward current at the source, in a cell with a reduced resting potential of –65 mV (0 potential not shown for measurement of resting potential) that inactivates a fraction of Na^+ channels, decreasing the net inward I_{Na} (see Chapter 4, Figure 4-5 for a description of the effects of resting membrane depolarization on the Na^+ channel). In cell 1, the decreased rate (dv/dt_{max}) and amount of current during phase 0 depolarizes the membrane potential only to +5 mV (red action potential), reducing the amount of source and axial current (blue arrows). This in turn decreases the rapidity at which cells in the pathway of propagation are depolarized to threshold potential and the distance in front of the propagating action potential that is depolarized (axial current flows only to cell 2 in the diagram), slowing conduction. A further reduction in axial current caused by inactivation of more Na^+ channels would lead to conduction block when source current is insufficient to depolarize the sink to threshold.

The relationship of I_{Na} to conduction velocity, determined in a computer model, is shown in **Figure 9-5**. I_{Na} is expressed on the abscissa as membrane excitability or the percent of maximum Na^+ conductance (%$\bar{g}$Na), a measurement of the ease at which ions flow through the channel. Conduction velocity on the left (ordinate) slows by about two-thirds to 17 cm/sec as %$\bar{g}$Na decreases before block occurs (horizontal bar at end of solid curved line), although in studies on tissue, velocity may be slower. The safety factor for conduction (dashed line, right ordinate) also decreases in parallel until conduction blocks when the safety factor falls below 1.