ZIAD F. ISSA
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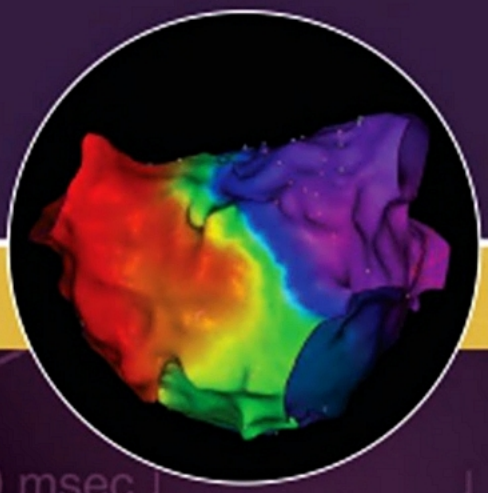
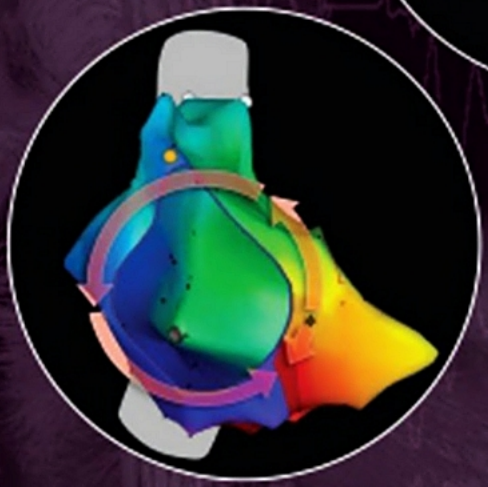
DOUGLAS P. ZIPES

CLINICAL ARRHYTHMOLOGY AND ELECTROPHYSIOLOGY

A COMPANION TO BRAUNWALD'S HEART DISEASE

THIRD EDITION





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CLINICAL ARRHYTHMOLOGY AND ELECTROPHYSIOLOGY

A COMPANION TO **BRAUNWALD'S HEART DISEASE**

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THIRD EDITION

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CLINICAL ARRHYTHMOLOGY AND ELECTROPHYSIOLOGY:
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Douglas P. Zipes:

My wife, Joan, and my children, Debbie, Jeff, and David

We also thank the Elsevier support team that helped bring this edition to fruition.

FOREWORD

Disturbances in cardiac rhythm occur in a large proportion of the population. Arrhythmias can have sequelae that range from life-shortening to inconsequential. Sudden cardiac deaths and chronic disability are among the most frequent serious complications resulting from arrhythmias.

The eleventh edition of *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine* includes an excellent section on rhythm disturbances carefully edited and largely written by Douglas Zipes and Gordon Tomaselli, the most accomplished and respected investigators and clinicians in this field. However, there are many subjects that simply cannot be discussed in sufficient detail, even in a 2000-page, densely packed book. For this reason, the current editors and I decided to commission a series of companions to the parent title. We were extremely fortunate to enlist Dr. Zipes' help in editing and writing *Clinical Arrhythmology and Electrophysiology*. Dr. Zipes, in turn, enlisted two talented collaborators, Drs. Ziad F. Issa and John M. Miller, to work with him to produce this excellent volume.

This third edition is superbly illustrated, with the number of figures and tables increasing substantially from its predecessor. What has not changed, however, is the very high quality of the content, which is accurate, authoritative, and clear; second, it is as up-to-date as last month's journals; and third, the writing style and illustrations are consistent throughout with little, if any, duplication. As this important branch of cardiology has grown, so has this book.

The first seven chapters ("Molecular Mechanisms of Cardiac Electrical Activity," "Cardiac Ion Channels," "Electrophysiological Mechanisms of Cardiac Arrhythmias," "Electrophysiological Testing: Tools and Techniques," "Conventional Intracardiac Mapping Techniques," "Advanced Mapping and Navigation Modalities," and "Ablation Energy Sources") provide a superb introduction to the field. This is followed by 24 chapters on individual arrhythmias, each following a similar outline. Here, the authors lead us from a basic understanding of the arrhythmia to its clinical recognition, natural history, and management. The latter is moving rapidly from being largely drug-based to device-based, although many patients receive combination device-drug therapy. These options, as well as ablation therapy, are clearly spelled out as they apply to each arrhythmia. The final chapter discusses the complications of catheter ablation of cardiac arrhythmias.

We are proud to include *Clinical Arrhythmology and Electrophysiology* as a companion to *Braunwald's Heart Disease*, and we are fully confident that it will prove to be valuable to cardiologists, internists, investigators, and trainees.

Eugene Braunwald, MD
Peter Libby, MD
Robert Bonow, MD
Douglas Mann, MD
Gordon Tomaselli, MD

PREFACE

The third edition of *Clinical Arrhythmology and Electrophysiology* maintains its unique style, written by just the three of us. Once again, we can "explain, integrate, coordinate, and educate in a comprehensive, cohesive fashion while avoiding redundancies and contradictions." We liken it to a comprehensive travel guide written by an expert who has actually stayed in that unique hotel or eaten in that special restaurant. We have experienced the progress first-hand, from basic science to clinical application, and are able to pass on our experiences to you. In addition, as before, readers have the opportunity to delve deeper into basic mechanisms or invasive procedures…or not…depending on the level of interest.

We have thoroughly revised and updated all chapters. In addition, we have greatly expanded the book by increasing the total number of pages from 700 to over 1100 and increased the number of figures to almost 1000 in print and over 200 online. A unique feature of our book are 74 new videos that take the reader into our electrophysiology labs to become a "fly on the wall" observing electrophysiology procedures. We believe the adage that "one picture is worth a thousand words," and we invite you to learn with us during actual procedures.

Our textbook, written as a companion to the *Braunwald's Heart Disease* series, is for learners of all stages. We hope you enjoy, learn, and expand your care of arrhythmia patients.

Ziad F. Issa
John M. Miller
Douglas P. Zipes

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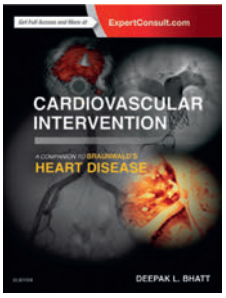

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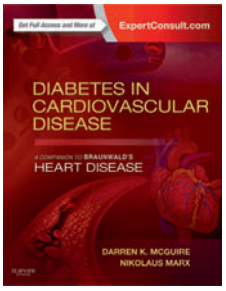

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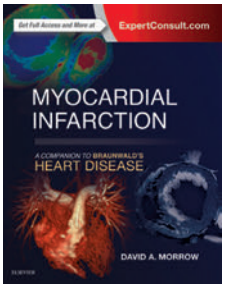

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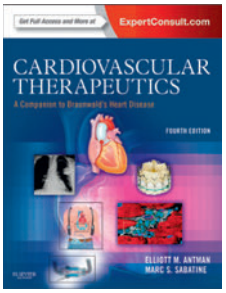

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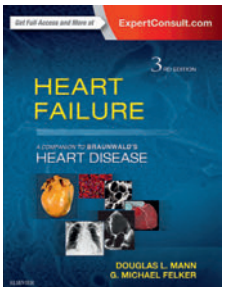

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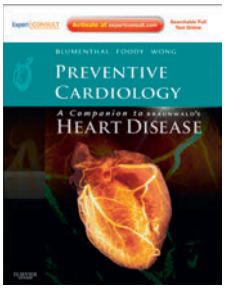

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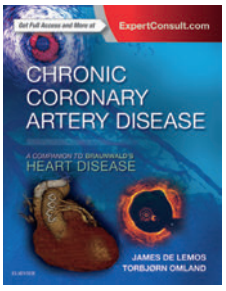

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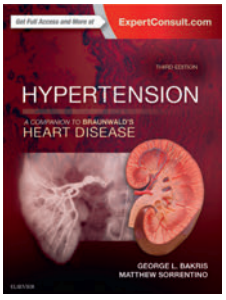

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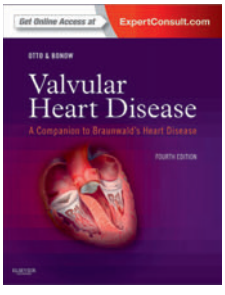

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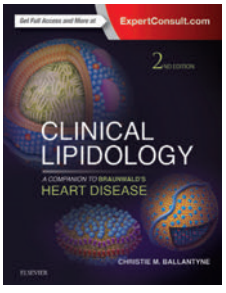

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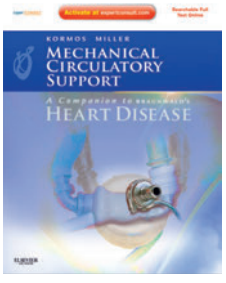

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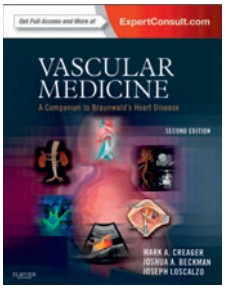

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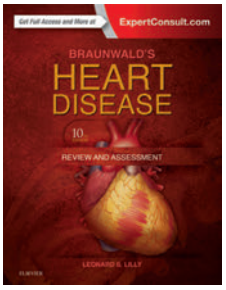

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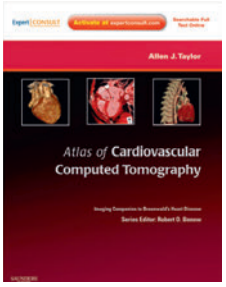

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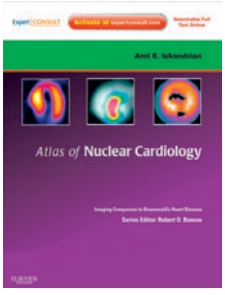

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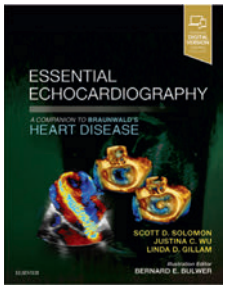

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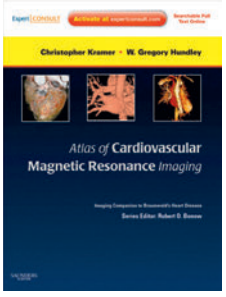

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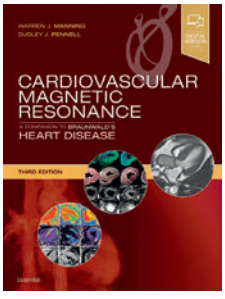

MANNING AND PENNELL
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1

Molecular Mechanisms of Cardiac Electrical Activity

OUTLINE

IONIC EQUILIBRIUM

The lipid bilayer of the cell membrane is hydrophobic and impermeable to water-soluble substances such as ions. Hence, for the hydrophilic ions to be able to cross the membrane, they need hydrophilic paths that span the membrane (i.e., pores), which are provided by transmembrane proteins called ion channels. Once a hydrophilic pore is available, ions move passively across the membrane, driven by two forces: the electrical gradient (voltage difference) and chemical gradient (concentration difference). The chemical gradient forces the ions to move from a compartment of a higher concentration to one of lower concentration. The electrical gradient forces ions to move in the direction of their inverse sign (i.e., cations [positively charged ions] move toward a negatively charged compartment, whereas anions [negatively charged ions] move toward a positively charged compartment). Because the chemical and electrical gradients can oppose each other, the direction of net ion movement will depend on the relative contributions of chemical gradient and electrical potential (i.e., the net electrochemical gradient), so that ions tend to move spontaneously from a higher to a lower electrochemical potential.[1]

The movement of an ion down its chemical gradient in one direction across the cell membrane results in build-up of excess charge carried by the ion on one side of the membrane, which generates an electrical gradient that impedes (repels) continuing ionic movement in the same direction. When the driving force of the electrical gradient across the membrane becomes equal and opposite to the force generated by the chemical gradient, the ion is said to be in electrochemical equilibrium, and the net transmembrane flux (or current) of that particular ion is zero. In this setting, the membrane electrical potential is called the equilibrium potential (E_{ion}) ("reversal potential" or "Nernst potential") of that individual ion. Any further current flow would reverse the balance of forces and therefore reverse the current direction until equilibrium is restored, hence the name "reversal potential."[2] The E_{ion} for a given ion measures the voltage that the ion concentration gradient generates when it acts as a battery, and it depends on its concentration on either side of the membrane and the temperature. At membrane voltages more positive to the reversal potential of the ion, passive ion movement is outward, whereas it is inward at a membrane potential (E_m) more negative to the Nernst potential of that channel.[1]

When multiple ions across a membrane are removed from their electrochemical equilibrium, each ion will tend to force the E_m toward its own E_{ion}. The contribution of each ion type to the overall E_m at any given moment is determined by the instantaneous permeability of the plasma membrane to that ion. The larger the membrane conductance to a particular ion, the greater is the ability of that ion to bring the E_m toward its own E_{ion}. Hence the E_m is the average of the E_{ion} of all the ions to which the membrane is permeable, weighed according to the membrane conductance of each individual ion relative to the total ionic conductance of the membrane.[1]

TRANSMEMBRANE POTENTIALS

All living cells, including cardiomyocytes, maintain a difference in the concentration of ions across their membranes. There is a slight excess of positive ions on the outside of the membrane and a slight excess of negative ions on the inside of the membrane, resulting in a difference in the electrical charge (i.e., voltage, potential difference, or electrical gradient) across the cell membrane, called the E_m (also known as membrane voltage or transmembrane potential). A membrane that exhibits an electrical gradient is said to be polarized.

In nonexcitable cells, and in excitable cells in their baseline states (i.e., not conducting electrical signals), the E_m is held at a relatively stable value, called the resting E_m. All cells have a negative resting E_m (i.e., the cytoplasm is electrically negative relative to the extracellular fluid), which arises from the interaction of ion channels and ion pumps embedded in the membrane that maintain different ion concentrations on the intracellular and extracellular sides of the membrane.

When an ion channel opens, it allows ion flux across the membrane that generates an electrical current (I). This current affects the E_m, depending on the membrane resistance (R), which refers to the ratio between the E_m and electrical current, as shown in Ohm's law: $E = I \times R$, or $R = E/I$. Resistance arises from the fact that the membrane impedes the movement of charges across it; hence the cell membrane functions as a *resistor* (i.e., when current is passed through the membrane, there is a voltage drop that is predictable from Ohm's law). Conductance describes the ability of a membrane to allow the flux of charged ions in one direction across the membrane. The more permeable the membrane is to a particular ion, the greater is the conductance of the membrane to that ion (Table 1.1). Membrane conductance (g) is the reciprocal of resistance: $g = 1/R$.

Because the lipid bilayer of the cell membrane is very thin, accumulation of charged ions on one side gives rise to an electrical force

TABLE 1.1 Definitions Related to Electrical Properties of Cell Membranes

Term	Unit	Definition
Charge (electric charge, Q)	Coulombs	• The physical property of matter that causes it to experience a force (electrostatic attraction or repulsion) in the presence of other matter. • There are two types of electric charges: positive and negative. Like charges repel and unlike attract.
Voltage (potential difference, V)	Volt (V)	• A separation of unlike charge in space; the greater the amount of charge separated, the larger the voltage, and the greater the tendency for the charges to flow toward each other. • Voltage is always measured at one point with respect to another point. There cannot be a voltage at one point in space. • Voltage is the ability to drive an electric current across a resistance.
Current (I)	Amperes (A)	• A flow of electrical charges.
Resistance (R)	Ohm (Ω)	• A measure of the difficulty with which current flows in a circuit; the greater the difficulty, the greater the resistance.
Conductance (g)	Siemen (S)	• A measure of the ease with which current flows in a circuit. • Conductance is the reciprocal of the resistance.
Capacitance (C)	Farad	• The ability of a body to store an electrical charge. • A material with a large capacitance holds more electric charge at a given voltage, than one with low capacitance.
Membrane potential (transmembrane potential, membrane voltage, E_m)	Volt (V)	• The difference in electrical potential between the interior and the exterior of a biological cell.
Equilibrium potential of an ion (E_{ion}) (reversal potential, Nernst potential)	Volt (V)	• The value of the E_m at which diffusive and electrical gradients for a particular ion counterbalance, so that there is no net ion flow across the membrane (i.e., electrochemical equilibrium). • In other words, equilibrium potential is the membrane potential necessary to maintain a given concentration difference or the membrane potential that will result from maintenance of a given concentration difference. • An ion will be in electrochemical equilibrium if $E_m = E_{ion}$.
Ionic current (I_{ion})	Amperes (A)	• Electrical current generated by the flux of charged ions across the cell membrane.
Capacitive current (nonfaradaic current, double-layer current)		• The electric current generated by the movement of electrons toward and away from the surfaces of the cell membrane. • This current does not involve movement of charged ions across the cell membrane, it only causes accumulation (or removal) of electrical charges on membrane surface.

(potential) that pulls oppositely charged particles toward the other side. Hence the cell membrane functions as a *capacitor* (i.e., capable of separating and storing charge). Although the absolute potential differences across the cell membrane are small, they give rise to enormous electrical potential gradients because they occur across a very thin surface. As a consequence, apparently small changes in E_m can produce large changes in potential gradient and powerful forces that are able to induce molecular rearrangement in membrane proteins, such as those required for opening and closing ion channels embedded in the cell membrane. The capacitance of the membrane is generally fixed and unaffected by the molecules that are embedded in it. In contrast, membrane resistance is highly variable and depends on the conductance of ion channels embedded in the membrane.[3]

The sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-) ions are the major charge carriers, and their movement across the cell membrane creates a flow of current that generates excitation and signals in cardiac myocytes. The electrical current generated by the flux of an ion across the membrane is determined by the membrane conductance to that ion (g_{ion}) and the potential (voltage) difference across the membrane. The potential difference represents the potential at which there is no net ion flux (i.e., the E_{ion}) and the actual E_m: current $= g_{ion} \times (E_m - E_{ion})$.

By convention, an inward current increases the electropositivity within the cell (i.e., causes depolarization of the E_m [to become less negative]) and can result from either the movement of positively charged ions (most commonly Na^+ or Ca^{2+}) into the cell or the efflux of negatively charged ions (e.g., Cl^-) out of the cell. An outward current increases the electronegativity within the cell (i.e., causes hyperpolarization of the E_m [to become more negative]) and can result from either the movement of anions into the cell or the efflux of cations (most commonly K^+) out of the cell.

Opening and closing of ion channels can induce a departure from the relatively static resting E_m, which is called *depolarization* if the interior voltage rises (becomes less negative) or *hyperpolarization* if the interior voltage becomes more negative. The most important ion fluxes that depolarize or repolarize the membrane are passive (i.e., the ions move down their electrochemical gradient without requiring the expenditure of energy), occurring through transmembrane ion channels. In excitable cells a sufficiently large depolarization can evoke a short-lasting all-or-none event called an *action potential,* in which the E_m very rapidly undergoes specific and large dynamic voltage changes.

Both resting E_m and dynamic voltage changes such as the action potential are caused by specific changes in membrane permeabilities for Na^+, K^+, Ca^{2+}, and Cl^-, which, in turn, result from concerted changes in functional activity of various ion channels, ion transporters, and ion exchangers.

CARDIAC ACTION POTENTIAL

During physiological electrical activity, the E_m is a continuous function of time. The current flowing through the cell membrane, at each instant, is provided by multiple channels and transporters carrying charge in

opposite directions because of their different ion selectivity. The algebraic summation of these contributions is referred to as net transmembrane current.

The cardiac action potential reflects a balance between inward and outward currents. When a depolarizing stimulus (typically generated by an electric current from an adjacent cell) abruptly changes the E_m of a resting cardiomyocyte to a critical value (the threshold level), the properties of the cell membrane and ion conductances change dramatically, precipitating a sequence of events involving the influx and efflux of multiple ions that together produce the action potential of the cell. In this fashion an electrical stimulus is conducted from one cell to the cells adjacent to it.[4]

Unlike skeletal muscle, cardiac muscle is electrically coupled so that the wave of depolarization propagates from one cell to the next, independent of neuronal input. The heart is activated by *capacitive currents* generated when a wave of depolarization approaches a region of the heart that is at its resting potential. Unlike ionic currents, which are generated by the flux of charged ions across the cell membrane, capacitive currents are generated by the movement of electrons toward and away from the surfaces of the membrane. These electrotonic potential changes are passive and independent of membrane conductance. The resulting decrease in positive charge at the outer side of the cell membrane reduces the negative charge on the intracellular surface of the membrane. These charge movements, which are carried by electrons, generate a capacitive current. When an excitatory stimulus causes the E_m to become less negative and beyond a threshold level (approximately −65 mV for working atrial and ventricular cardiomyocytes), Na^+ channels activate (open) and permit an inward Na^+ current (I_{Na}), resulting in a rapid shift of the E_m to a positive voltage range. This event triggers a series of successive opening and closure of selectively permeable ion channels. The direction and magnitude of passive movement (and the resulting current) of an ion at any given transmembrane voltage are determined by the ratio of the intracellular and extracellular concentrations and the reversal potential of that ion, with the net flux being larger when ions move from the more concentrated side.

The "threshold potential" is the lowest E_m at which opening of enough Na^+ channels (or Ca^{2+} channels in the setting of nodal cells) is able to initiate the sequence of channel openings needed to generate a propagated action potential. Small (subthreshold) stimuli depolarize the membrane in proportion to the strength of the stimulus and cause only local responses because they do not open enough Na^+ channels to generate depolarizing currents large enough to activate nearby resting cells (i.e., insufficient to initiate a regenerative action potential). On the other hand, when the stimulus is sufficiently intense to reduce the E_m to a threshold value, regenerative action potential results, whereby intracellular movement of Na^+ depolarizes the membrane more, a process that increases conductance to Na^+ more, which allows more Na^+ to enter, and so on. In this fashion the extent of subsequent depolarization becomes independent of the initial depolarizing stimulus, and more intense stimuli do not produce larger action potential responses; rather, an all-or-none response results.[4]

Electrical changes in the action potential follow a relatively fixed time and voltage relationship that differs according to specific cell types. Although the entire action potential takes only a few milliseconds in nerve cells, the cardiac action potential lasts several hundred milliseconds. The course of the action potential can be divided into five phases (numbered 0 to 4). Phase 4 is the resting E_m, and it describes the E_m when the cell is not being stimulated.

During the cardiac action potential, membrane voltages fluctuate in the range of −94 to +30 mV (Fig. 1.1). With physiological external K^+ concentration, the reversal potential of K^+ (E_K) is approximately −94 mV, and passive K^+ movement during an action potential is out of the cell. On the other hand, because the calculated reversal potential of a cardiac Ca^{2+} channel (E_{Ca}) is +64 mV, passive Ca^{2+} flux is into the cell.

In normal atrial and ventricular myocytes and in His-Purkinje fibers, action potentials have very rapid upstrokes, mediated by the fast inward I_{Na}. These potentials are called *fast response* potentials. In contrast, action potentials in the normal sinus and atrioventricular (AV) nodal cells and many types of diseased tissues have very slow upstrokes, mediated by a slow inward, predominantly L-type voltage-gated Ca^{2+} current (I_{CaL}), rather than by the fast inward I_{Na} (Fig. 1.2). These potentials have been termed *slow response* potentials.

Fast Response Action Potential

Phase 4: The Resting Membrane Potential

The E_m of resting atrial and ventricular cardiomyocytes remains steady throughout diastole. The resting E_m is caused by the differences in ionic concentrations across the membrane and the selective membrane permeability (conductance) to various ions. Large concentration gradients of Na^+, K^+, Ca^{2+}, and Cl^- across the cell membrane are maintained by the ion pumps and exchangers (Table 1.2).[4]

Under normal conditions, the resting membrane is most permeable to K^+ and relatively impermeable to other ions. K^+ has the largest resting membrane conductance (g_K is 100 times greater than g_{Na}) because of the abundance of open K^+ channels at rest, whereas Na^+ and Ca^{2+} channels are generally closed. Thus K^+ exerts the largest influence on the resting E_m. As a consequence, the resulting E_m is almost always close to the K^+ reversal potential (E_m approximates E_K). The actual resting E_m is slightly less negative than E_K because the cell membrane is slightly permeable to other ions.

The inwardly rectifying K^+ (Kir) channels underlie an outward K^+ current (I_{K1}) responsible for maintaining the resting potential near the E_K in atrial, His-Purkinje, and ventricular cells, under normal conditions. Kir channels preferentially allow currents of K^+ ions to flow into the cell with a strongly voltage-dependent decline of K^+ efflux (i.e., reduction of outward current) on membrane depolarization. As such, I_{K1} is a strong rectifier that passes K^+ currents over a limited range of E_m. At a negative E_m, I_{K1} conductance is much larger than that of any other current; thus it clamps the resting E_m close to the reversal potential for K^+ (E_K) **(see Chapter 2 for detailed discussion on the concept of rectification).** I_{K1} density is much higher in ventricular than in atrial myocytes, a feature that largely prevents the ventricular cell from having diastolic membrane depolarization and pacemaker activity. By contrast, I_{K1} is almost absent in sinus and AV nodal cells, thus allowing for relatively more depolarized resting diastolic potentials compared with atrial and ventricular myocytes (Table 1.3). The effect of outward K^+ current to resist membrane depolarization (keeping voltage fixed) is sometimes referred to as a voltage clamping effect.[2]

A unique property of Kir currents is the unusual dependence of rectification on extracellular K^+ concentration. Specifically, with an

TABLE 1.2 Intracellular and Extracellular Ion Concentrations and Equilibrium Potentials in Cardiomyocytes

Ion	Extracellular Concentration (mM)	Intracellular Concentration (mM)	Equilibrium Potential (mV)
Na^+	135–145	10	+70
K^+	3.5–5.0	155	−94
Ca^{2+}	2	0.0001	+132
Cl^-	87	30	−28

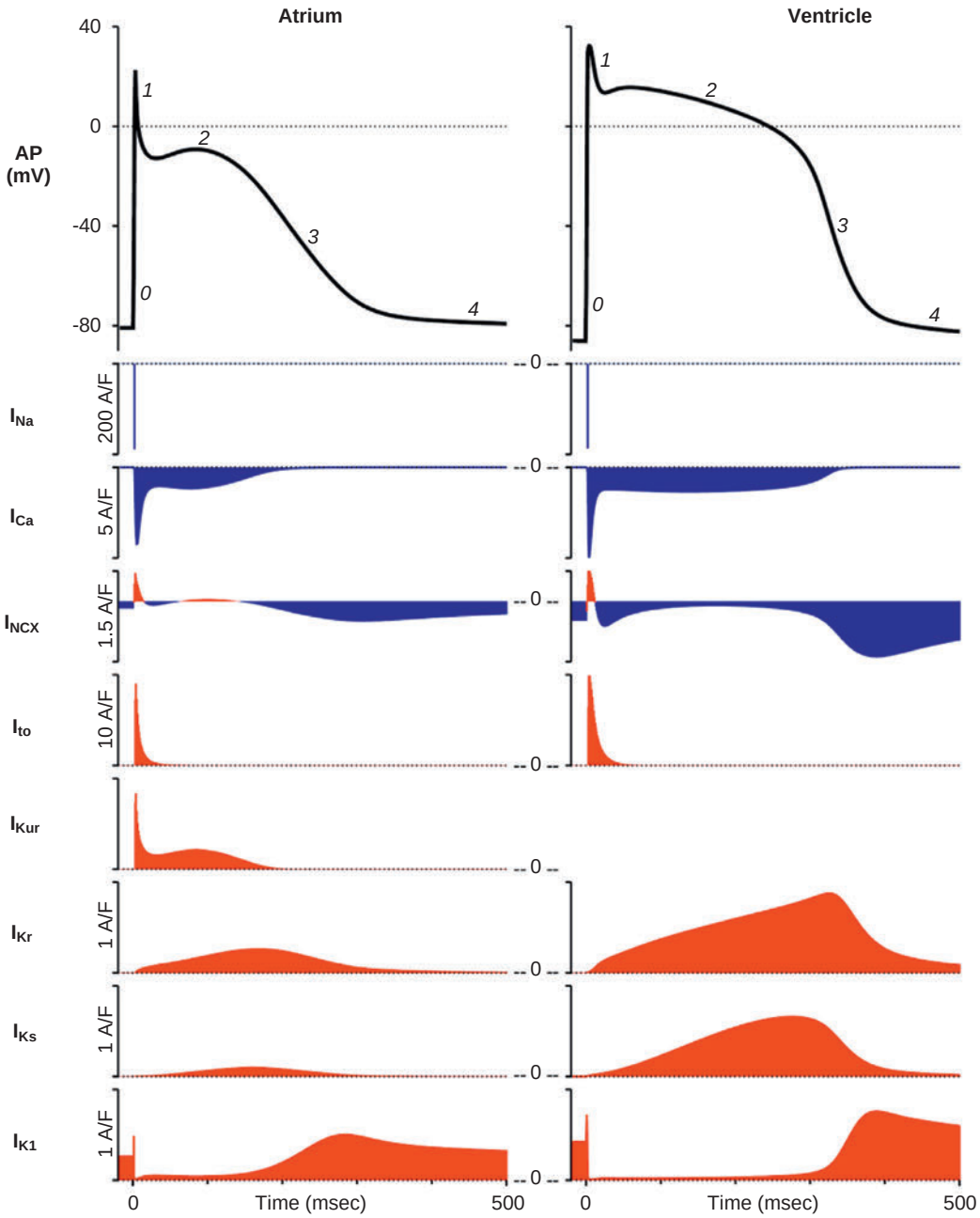


Fig. 1.1 Contribution of Depolarizing Inward and Repolarizing Outward Currents to the Atrial and Ventricular Action Potential *(AP).* The top panel from the atrial *(left)* and ventricular *(right)* myocytes. The five phases of the AP are labeled: *0* = upstroke of the AP represents depolarization of the membrane; *1* = initial repolarization; *2* = plateau phase; *3* = late repolarization; *4* = the resting (diastolic) phase. The rate of change of the AP is directly proportional to the sum of the underlying transmembrane ion currents *(lower panels)*. Inward currents *(blue)* depolarize the membrane, whereas outward currents *(red)* contribute to repolarization. Compared with an atrial AP, the ventricular AP typically has longer duration, higher plateau potential (phase 2), and more negative resting membrane potential (phase 4). I_{Ca}, L-type Ca^{2+} current; I_{Na}, Na^+ current; I_{NCX}, Na^+-Ca^{2+} exchanger; I_{Kr}, rapidly activating delayed rectifier K^+ current; I_{Ks}, slowly activating delayed rectifier K^+ current; I_{Kur}, ultrarapidly activating delayed rectifier K^+ current; I_{K1}, inward rectifier K^+ current; I_{to}, transient outward K^+ current. (With permission from Oudit GY, Backx PH. Voltage-gated potassium channels. In: Zipes DP, Jalife J, eds. *Cardiac Electrophysiology: From Cell to Bedside*. 7th ed. Philadelphia: Elsevier; 2018.)

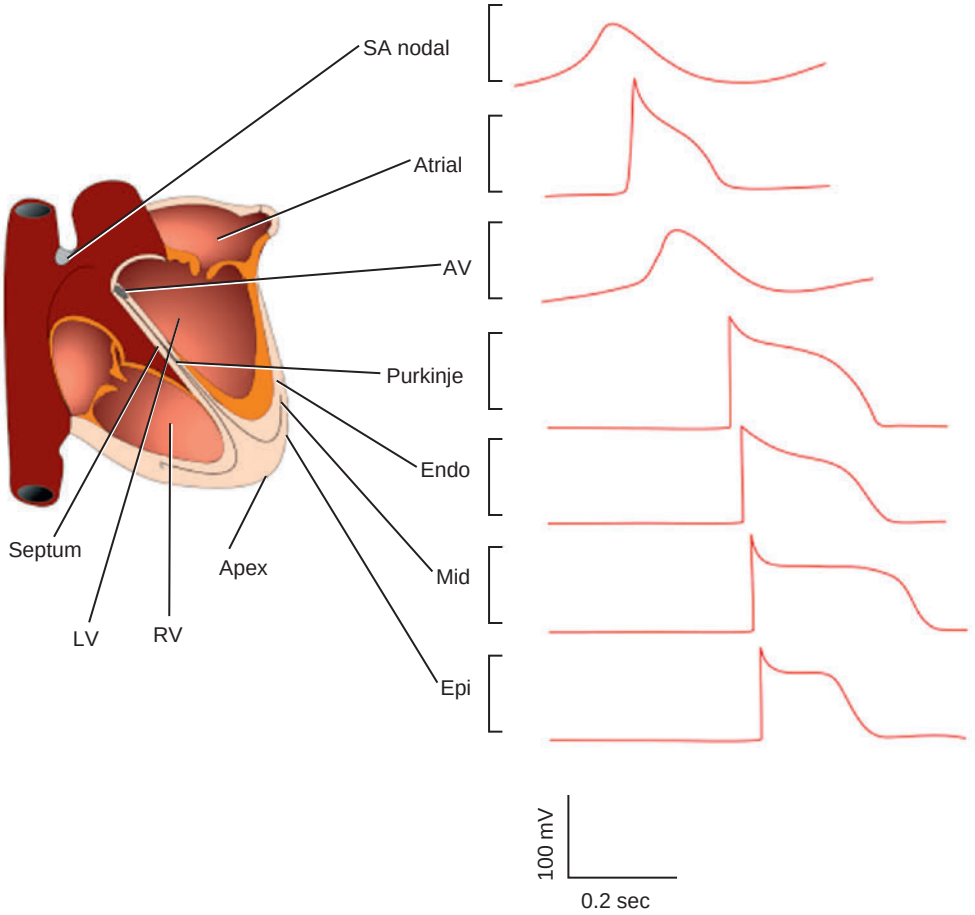


Fig. 1.2 Action Potential Waveforms, Displaced in Time to Reflect the Temporal Sequence of Propagation, Vary in Different Regions of the Heart. *AV*, Atrioventricular (node); *Endo*, endocardial; *Epi*, epicardial; *LV*, left ventricle; *Mid*, midmyocardial; *RV*, right ventricle; *SA*, sinoatrial. (Modified with permission from Nerbonne JM. Heterogeneous expression of repolarizing potassium currents in the mammalian myocardium. In Zipes DP, Jalife J, eds. *Cardiac Electrophysiology: From Cell to Bedside*. 5th ed. Philadelphia: Saunders; 2009:293–305.)

TABLE 1.3 Regional Differences in Cardiac Action Potential

Property	Sinus Nodal Cell	Atrial Muscle Cell	AV Nodal Cell	Purkinje Fiber	Ventricular Muscle Cell
Resting potential (mV)	–50 to –60	–80 to –90	–60 to –70	–90 to –95	–80 to –90
Action potential amplitude (mV)	+60 to +70	+110 to +120	+70 to +80	+120	+110 to +120
Action potential duration (msec)	100 to 300	100 to 300	100 to 300	300 to 500	200 to 300

AV, Atrioventricular.

increase in extracellular K^+, the I_{K1} current-voltage relationship shifts nearly in parallel with the E_K and leads to a crossover phenomenon. One important consequence of such behavior is that at potentials positive to the crossover, K^+ conductance increases rather than decreases, against an expectation based on a reduced driving force for K^+ ions as a result of elevated extracellular K^+ concentration.[5]

The resting E_m is also powered by the Na^+-K^+ adenosine triphosphatase (ATPase) (the Na^+-K^+ pump), which helps to establish concentration gradients of Na^+ and K^+ across the cell membrane. Under physiological conditions, the Na^+-K^+ pump transports two K^+ ions into the cell against its chemical gradient and three Na^+ ions outside against its electrochemical gradient at the expense of one ATP molecule. Because the stoichiometry of ion movement is not 1:1, the Na^+-K^+ pump is electrogenic and generates a net outward movement of positive charges (i.e., an outward current). At faster heart rates, the rate of Na^+-K^+ pumping increases to maintain the same ionic gradients, thus counteracting the intracellular gain of Na^+ and loss of K^+ with each depolarization.

Ca^{2+} does not contribute directly to the resting E_m because the voltage-activated Ca^{2+} channels are closed at the hyperpolarized resting E_m. However, changes in intracellular free Ca^{2+} concentration can affect other membrane conductance values. Increases in intracellular Ca^{2+}

levels can stimulate the Na^+-Ca^{2+} exchanger ($I_{Na\text{-}Ca}$), which exchanges three Na^+ ions for one Ca^{2+} ion; the direction depends on the Na^+ and Ca^{2+} concentrations on the two sides of the membrane and the E_m difference. At resting E_m and during a spontaneous sarcoplasmic reticulum Ca^{2+} release event, this exchanger would generate a net Na^+ influx, possibly causing transient membrane depolarizations.

Phase 0: The Upstroke—Rapid Depolarization

On excitation of an atrial, ventricular, or Purkinje cardiomyocyte by electrical stimuli from adjacent cells, its resting E_m (approximately −85 mV) depolarizes, leading to opening (activation) of Na^+ channels from its resting (closed) state and enabling a large and rapid influx of Na^+ ions (inward I_{Na}) into the cell down their electrochemical gradient. As a consequence of increased Na^+ conductance, the excited membrane no longer behaves like a K^+ electrode (i.e., exclusively permeable to K^+) but more closely approximates an Na^+ electrode, and the E_m moves toward the E_{Na} (see Table 1.2). Once an excitatory stimulus depolarizes the E_m beyond the threshold for activation of Na^+ channels (approximately −65 mV), the activated I_{Na} is regenerative and no longer depends on the initial depolarizing stimulus. As a consequence, the influx of Na^+ ions further depolarizes the membrane and thereby increases conductance to Na^+ more, which allows more Na^+ to enter the cell (thus "regenerative").[6]

Normally, activation of Na^+ channels is transient; fast inactivation (closing of the channel pore) starts simultaneously with activation, but because inactivation is slightly delayed relative to activation, the channels remain transiently (less than 1 millisecond) open to conduct I_{Na} during phase 0 of the action potential before it closes. In addition, the influx of Na^+ into the cell increases the positive intracellular charges and reduces the driving force for Na^+. When the E_{Na} is reached, no further Na^+ ions enter the cell.

The rate at which depolarization occurs during phase 0 (i.e., the maximum rate of change of voltage over time [dV/dt_{max}]) is a reasonable approximation of the rate and magnitude of Na^+ entry into the cell and a determinant of conduction velocity for the propagated action potential (see later).

The threshold for activation of I_{CaL} is approximately −30 to −40 mV. Although I_{CaL} is normally activated during phase 0 by the regenerative depolarization caused by the fast I_{Na}, I_{CaL} is much smaller than the peak I_{Na}. Furthermore, the amplitude of I_{CaL} is not maximal near the action potential peak because of the time-dependent nature of I_{CaL} activation, as well as the low driving force ($E_m - E_{Ca}$) for I_{CaL}. Therefore I_{CaL} contributes little to the action potential until the fast I_{Na} is inactivated, after completion of phase 0. As a result, I_{CaL} affects mainly the plateau of action potentials recorded in atrial and ventricular muscle and His-Purkinje fibers. On the other hand, I_{CaL} plays a prominent role in the upstroke of slow response action potentials in partially depolarized cells in which the fast Na^+ channels have been inactivated.

Phase 1: Early Repolarization

Phase 0 is followed by phase 1 (early repolarization), during which the membrane repolarizes rapidly and transiently to almost 0 mV (early notch), partly because of the inactivation of I_{Na} and concomitant activation of several outward currents. The transient outward K^+ current (I_{to}) is mainly responsible for phase 1 of the action potential. I_{to} rapidly activates (with time constants less than 10 milliseconds) by depolarization and then rapidly inactivates (25 to 80 milliseconds for the fast component of I_{to} [$I_{to,f}$], and 80 to 200 milliseconds for the slow component of I_{to} [$I_{to,s}$]). The influx of K^+ ions via I_{to} channels partially repolarizes the membrane, thus shaping the rapid repolarization (phase 1) of the action potential and setting the height of the initial plateau (phase 2) (see Fig. 1.1). In addition, an Na^+ outward current through the Na^+-Ca^{2+} exchanger operating in reverse mode likely contributes to this early phase of repolarization.[4]

Phase 2: The Plateau

Phase 2 (plateau) represents a delicate balance between the depolarizing inward currents (I_{CaL} and a small residual component of inward I_{Na}) and the repolarizing outward currents (ultrarapidly [I_{Kur}], rapidly [I_{Kr}], and slowly [I_{Ks}] activating delayed outward rectifying currents) (see Fig. 1.1). Phase 2 is the longest phase of the action potential, lasting tens (atrium) to hundreds of milliseconds (His-Purkinje system and ventricle). The plateau phase is unique among excitable cells and marks the phase of Ca^{2+} entry into the cell. It is the phase that most clearly distinguishes the cardiac action potential from the brief action potentials of skeletal muscle and nerve.[4,7,8]

I_{CaL} is activated by membrane depolarization, is largely responsible for the action potential plateau, and is a major determinant of the duration of the plateau phase. I_{CaL} also links membrane depolarization to myocardial contraction. L-type Ca^{2+} channels activate on membrane depolarization to potentials positive to −40 mV. I_{CaL} peaks at an E_m of 0 to +10 mV and tends to reverse at +60 to +70 mV, following a bell-shaped current-voltage relationship.

Na^+ channels also make a contribution, although minor, to the plateau phase. After phase 0 of the action potential, some Na^+ channels occasionally fail to inactivate or exhibit prolonged opening or reopening repetitively for hundreds of milliseconds after variable and prolonged latencies, resulting in a small inward I_{Na} (with a magnitude of less than 1% of the peak I_{Na}). This persistent or "late" I_{Na} (I_{NaL}), along with I_{CaL}, helps to maintain the action potential plateau.[9]

I_{Kr} and I_{Ks} are activated at depolarized membrane potentials. I_{Kr} activates relatively fast (in the order of tens of milliseconds) on membrane depolarization, thus allowing outward diffusion of K^+ ions in accordance with its electrochemical gradient, but voltage-dependent inactivation thereafter is very fast. Hence only limited numbers of channels remain in the open state, whereas a considerable fraction resides in the nonconducting inactivated state. The fast voltage-dependent inactivation limits outward current through the channel at positive voltages and thus helps to maintain the action potential plateau phase that controls contraction and prevents premature excitation. However, as the voltage becomes less positive at the end of the plateau phase of repolarization, the channels recover rapidly from inactivation; this process leads to a progressive increase in I_{Kr} amplitudes during action potential phases 2 and 3, with maximal outward current occurring before the final rapid declining phase of the action potential.[10]

I_{Ks}, which is approximately 10 times larger than I_{Kr}, also contributes to the plateau phase. I_{Ks} activates in response to membrane depolarization to potentials positive to −30 mV and gradually increases during the plateau phase because its time course of activation is extremely slow, slower than any other known K^+ current. In fact, steady-state amplitude of I_{Ks} is achieved only with extremely long membrane depolarization. Hence the contribution of I_{Ks} to the net repolarizing current is greatest late in the plateau phase, particularly during action potentials of long duration. Importantly, although I_{Ks} activates slowly compared with action potential duration, it is also slowly inactivated. As heart rate increases, I_{Ks} increases because channel deactivation is slow and incomplete during the shortened diastole. This allows I_{Ks} channels to accumulate in the open state during rapid successive action potentials and mediate the faster rate of repolarization. Hence I_{Ks} plays an important role in determining the rate-dependent shortening of the cardiac action potential.[5]

I_{Kur} is detected only in human atria but not in the ventricles, such that it is the predominant delayed rectifier current responsible for atrial repolarization and is a basis for the much shorter duration of the action

potential in the atrium. I_{Kur} activates rapidly on depolarization in the plateau range and displays outward rectification, but it inactivates slowly during the time course of the action potential.

The Na^+-Ca^{2+} exchanger operating in forward mode (three Na^+ ions in for one Ca^{2+} ion out) and the Na^+-K^+ pump provide minor current components during phase 2.

Importantly, during the plateau phase, membrane conductance to all ions falls to rather low values. Thus less change in current is required near plateau levels than near resting potential levels to produce the same changes in E_m. In particular, K^+ conductance falls during the plateau phase as a result of inward rectification of I_{K1} (i.e., voltage-dependent decline of K^+ efflux and hence reduction of outward current) on membrane depolarization, in spite of the large electrochemical driving force on K^+ ions during the positive phase of the action potential (phases 0, 1, and 2). This property allows membrane depolarization following Na^+ channel activation, slows membrane repolarization, and helps to maintain a more prolonged cardiac action potential. This also confers energetic efficiency in the generation of the action potential.[11,12]

Phase 3: Final Rapid Repolarization

Phase 3 is the phase of rapid repolarization that restores the E_m to its resting value. Phase 3 is mediated by the increasing conductance of the delayed outward rectifying currents (I_{Kr} and I_{Ks}), the inwardly rectifying K^+ currents (I_{K1} and acetylcholine-activated K^+ current [I_{KACh}]), and time-dependent inactivation of I_{CaL} (see Fig. 1.1). Final repolarization during phase 3 results from K^+ efflux through the I_{K1} channels, which open at potentials negative to −20 mV.[4]

Phase 4: Restoration of Resting Membrane Potential

During the action potential, Na^+ and Ca^{2+} ions enter the cell and depolarize the E_m. Although the E_m is quickly repolarized by the efflux of K^+ ions, restoration of transmembrane ionic concentration gradients to the baseline resting state is necessary. This is achieved by the Na^+-K^+ ATPase (Na^+-K^+ pump, which exchanges two K^+ ions inside and three Na^+ ions outside) and by the Na^+-Ca^{2+} exchanger ($I_{Na\text{-}Ca}$, which exchanges three Na^+ ions for one Ca^{2+} ion).[4]

Reduction of cytosolic Ca^{2+} concentration during diastole is achieved by the reuptake Ca^{2+} by the sarcoplasmic reticulum via activation of the sarco/endoplasmic reticulum calcium-ATPase calcium pump (SERCA), in addition to extrusion across the sarcolemma via the Na^+-Ca^{2+} exchanger. In the human heart under resting conditions, the time required for cardiac myocyte depolarization, contraction, relaxation, and recovery is approximately 600 milliseconds.

Regional Heterogeneity of the Action Potential

Substantial differences in expression levels of ion channels underlie the considerable heterogeneity in action potential duration and configuration between cardiomyocytes located in different regions of the heart. The characteristics of the action potential differ in atrial versus ventricular myocardium, as well as across the ventricular myocardial wall from endocardium, midmyocardium, to epicardium (see Fig. 1.2).

Atrioventricular Heterogeneity of the Action Potential

Compared with the atrium, ventricular myocytes maintain a slightly more hyperpolarized resting E_m (approximately −85 mV vs. −80 mV). In addition, the action potential duration is longer, the plateau phase reaches a more depolarized E_m (approximately +20 mV), and phase 3 repolarization curve is steeper in ventricular myocytes as compared with the atrial action potential (see Table 1.3).

The differences in action potential configuration between atria and ventricles are mainly related to differences in ionic current densities and ion channel expression (especially K^+ channels) between ventricular and atrial myocytes. Although I_{Kr} and I_{Ks} densities are similar in atrial and ventricular myocytes, I_{Kur} is detected only in human atria and not in the ventricles. In fact, I_{Kur} is the predominant delayed rectifier current responsible for human atrial repolarization, with only small contribution of I_{Kr} and I_{Ks}.

Furthermore, the density of I_{to} is twofold higher in the atria compared with ventricular myocytes. In addition, I_{to} subtypes ($I_{to,f}$ and $I_{to,s}$) are differentially expressed in the heart. $I_{to,f}$ is the principal subtype expressed in human atrium. Conversely, $I_{to,s}$ is larger and $I_{to,f}$ is smaller in the ventricles compared with atrial tissue.[8]

The markedly higher densities of $I_{to,f}$, together with the expression of I_{Kur}, accelerate the early phase of repolarization and lead to lower plateau potentials and shorter action potential durations in atrial as compared with ventricular cells.[13]

I_{K1} density is much higher in ventricular than in atrial myocytes, and this explains the steep repolarization phase in the ventricles (where the more abundant I_{K1} plays a larger role in accelerating the terminal portion of repolarization) and the shallower phase in the atria. Furthermore, the higher I_{K1} channel expression underlies the hyperpolarized resting E_m in ventricular myocytes, and prevents the ventricular cell from exhibiting pacemaker activity.[14]

Several other K^+ channels are atrial selective and potentially contribute significantly to the atrial, but not ventricular, action potential. These include I_{KACh}, two-pore K^+ channels (K_{2P}), and small-conductance Ca^{2+}-activated K^+ (SK) channels.

Ventricular Regional Heterogeneity of the Action Potential

Action potential differences exist among the different layers across the ventricular wall, between the left and right ventricles, and from the apical region to the base.

Three distinct action potential waveforms have been distinguished from three predominant cell types contributing to the transmural heterogeneity of ventricular repolarization: the epicardial, midmyocardial, and endocardial cardiomyocytes. The most notable differences among these three layers are the prominent phase 1 notch and the spike and dome morphology of epicardial and midmyocardial action potentials compared with endocardium. The action potential duration of epicardial myocytes is shorter than that of endocardial myocytes. The duration of the action potential is longest in midmyocardial myocytes.[8,14]

The distinct notch phase in the action potential waveform of epicardial myocytes has mainly been attributed to the regional differences in I_{to} density across the myocardial wall. In human ventricles, I_{to} densities are much higher in the epicardium and midmyocardium than in the endocardium. Furthermore, although both $I_{to,f}$ and $I_{to,s}$ are expressed in the ventricle, $I_{to,f}$ is more prominent in the epicardium and midmyocardium than in the endocardium, whereas $I_{to,s}$ is mainly present in the endocardium and Purkinje cells. A prominent I_{to}-mediated action potential notch in ventricular epicardium but not endocardium produces a transmural voltage gradient during early ventricular repolarization that registers as a J wave or J point elevation on the electrocardiogram (ECG).[8,14]

Some experimental studies in wedge preparations strongly suggest the presence of a subpopulation of cells in the midmyocardium (referred to as the M cells) that exhibits distinct electrophysiological (EP) properties, although the presence of M cells has not been consistently confirmed by intact heart experiments. The putative M cells appear to have the longest action potential duration across the myocardial wall, largely attributed to their weaker I_{Ks} current but stronger late I_{Na} and Na^+-Ca^{2+} exchanger currents. Hence the M cells have been proposed to underlie the EP basis for transmural ventricular dispersion of repolarization and the T wave on the surface ECG, with the peak of the T wave (in wedge preparations) coinciding with the end of epicardial repolarization and

the end of the T wave coinciding with the end of repolarization of the M cells. Although the role of M cells under physiological conditions remains controversial, these cells appear to have a significant role in arrhythmogenesis under a variety of pathological conditions, such as the long QT and Brugada syndromes, secondary to exaggeration of transmural repolarization gradients.

In addition to the transmural action potential gradient that exists across the three layers of myocardium in the left and right ventricles, the right ventricular (RV) action potential duration overall is shorter and the spike and dome morphology is more pronounced compared with that of the left ventricle (LV). These differences have been attributed to higher I_{to} densities in the right than in the left ventricular myocytes.[14]

Evidence also suggests an apicobasal ventricular action potential heterogeneity. Action potential duration appears to be shorter in LV base compared with the apex. Larger I_{to} and I_{Ks} in apical compared with basal myocytes likely underlie those observations.[14]

Slow Response Action Potential

In normal atrial and ventricular myocytes and in the His-Purkinje fibers, action potentials have very rapid upstrokes mediated by the fast inward I_{Na}. These potentials are called fast response potentials. In contrast, action potentials in the normal sinus and AV nodal cells and many types of diseased tissue have very slow upstrokes, mediated predominantly by the slow inward I_{CaL}, rather than by the fast inward I_{Na} (see Fig. 1.2). These potentials have been termed *slow response potentials*.[4]

As noted, action potentials of pacemaker cells in the sinus and AV nodes are significantly different from those in working atrial and ventricular myocardium. Slow response action potentials are characterized by a more depolarized E_m at the onset of phase 4 (−50 to −65 mV), slow diastolic depolarization during phase 4, and reduced action potential amplitude. Furthermore, the rate of depolarization in phase 0 is much slower than that in the working myocardial cells, resulting in reduced conduction velocity of the cardiac impulse in the nodal regions (see Table 1.3). Cells in the His-Purkinje system can also exhibit phase 4 depolarization under special circumstances (when Na^+ channels are inactivated by pathological processes).

Phase 4: Diastolic Depolarization

The sinus and AV nodal cells lack the inward rectifier K^+ current (I_{K1}), which acts to stabilize the resting E_m in the normal working atrial and ventricular myocardium and Purkinje fibers. Sinus and AV nodal excitable cells exhibit a spontaneous, slow, and progressive decline in the E_m during diastole (spontaneous diastolic depolarization or phase 4 depolarization) that underlies normal automaticity and pacemaking function. Once this spontaneous depolarization reaches threshold (approximately −40 mV), a new action potential is generated.[15]

The ionic mechanisms responsible for diastolic depolarization and normal pacemaker activity in the sinus node are still controversial. Originally, a major role was attributed to the decay of the delayed K^+ conductance (an outward current) activated during the preceding action potential (the I_K-decay theory). This model of pacemaker depolarization lost favor upon the discovery of the "funny" current (I_f), sometimes referred to as the pacemaker current. I_f is a hyperpolarization-activated inward current that is carried largely by Na^+ and, to a lesser extent, K^+ ions. Once activated, I_f depolarizes the membrane to a level where the Ca^{2+} current activates to initiate an action potential.[15,16]

Other ionic currents gated by membrane depolarization (i.e., I_{CaL} and T-type Ca^{2+} current [I_{CaT}]), nongated and nonspecific background leak currents, and a current generated by the Na^+-Ca^{2+} exchanger have also been proposed to be involved in pacemaking. The "membrane clock" (also referred to as the "voltage clock" or "ion channel clock") refers to the time- and voltage-dependent membrane ion channels underlying pacemaking activity, including the decay of the outward rectifier K^+ current and the activation of several inward currents (I_f, I_{CaL}, I_{CaT}, and I_{Na}).

Newer evidence suggests that the sarcoplasmic reticulum, a major Ca^{2+} store in sinus nodal cells, can function as a physiological clock (the so-called calcium clock) within the cardiac pacemaker cells and has a substantial impact on late diastolic depolarization.[15,17]

There remains some degree of uncertainty about the relative role of I_f versus that of intracellular Ca^{2+} cycling in controlling the normal pacemaker cell automaticity. Furthermore, the interactions between the membrane clock and the intracellular calcium clock and cellular mechanisms underlying this internal Ca^{2+} clock are not completely elucidated. A further debate has arisen around their individual (or mutual) relevance in mediating the positive and negative chronotropic effects of neurotransmitters. Nevertheless, these interactions are of fundamental importance for understanding the integration of pacemaker mechanisms at the cellular level **(see Chapter 3 for detailed discussion on the mechanisms of automaticity and pacemaker activity).**[14]

Phase 0: The Upstroke—Slow Depolarization

I_{K1} is almost absent in sinus and AV nodal cells, thus allowing for relatively more depolarized resting diastolic potentials (−50 to −65 mV) compared with atrial and ventricular myocytes and facilitating diastolic depolarization mediated by the inward currents (e.g., I_f). At the depolarized level of the maximum diastolic potential of pacemaker cells, most Na^+ channels are inactivated and unavailable for phase 0 depolarization. Consequently, action potential upstroke is mainly achieved by I_{CaL}.[15]

L-type Ca^{2+} channels activate on depolarization to potentials positive to −40 mV, and I_{CaL} peaks at 0 to +10 mV. The peak amplitude I_{CaL} is less than 10% that of I_{Na}, and the time required for activation and inactivation of I_{CaL} is approximately an order of magnitude slower than that for I_{Na}. As a consequence, the rate of depolarization in phase 0 (dV/dt) is much slower and the peak amplitude of the action potential is less than that in the working myocardial cells.

EXCITABILITY

Excitability of a cardiac cell describes the ease with which the cell responds to a stimulus with a regenerative action potential. A certain minimum charge must be applied to the cell membrane to elicit a regenerative action potential (i.e., the stimulus should be sufficiently intense to reduce the E_m to the threshold value). Excitability is inversely related to the charge required for excitation.

Excitability of a cardiac cell depends on the passive and active properties of the cell membrane. The passive properties include the membrane resistance and capacitance and the intercellular resistance. The most important determinant of reduced excitability is the reduced availability of Na^+ channels. The more negative the E_m is, the more Na^+ channels are available for activation, the greater the influx of Na^+ into the cell during phase 0, and the greater the conduction velocity. In contrast, membrane depolarization to levels of −60 to −70 mV can inactivate half the Na^+ channels, and depolarization to −50 mV or less can inactivate all the Na^+ channels, thereby rendering Na^+ channels unavailable for mediating an action potential upstroke and thus reducing tissue excitability (Fig. 1.3).

Reduced excitability is physiologically observed during the relative refractory period (occurring during phase 3 of the action potential, before full recovery of E_m). At less negative potentials of the cell membrane, a portion of Na^+ channels will still be inactivated and unavailable

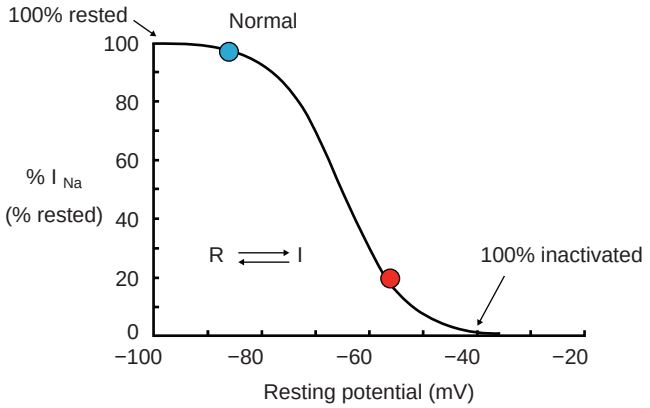


Fig. 1.3 Cellular Excitability. Relationship between transmembrane action potential from single ventricular muscle fiber and excitability of fiber to cathodal stimulation. Amplitudes of peak sodium current (I_{Na}) and proportion of Na^+ channels in the resting state are depicted as a function of resting membrane potential. *I*, Inactivation of Na^+ channels; *R*, recovery of Na^+ channels. (Redrawn from Rosen MS, Wit AL, Hoffman BF. Electrophysiology and pharmacology of cardiac arrhythmias. I. Cellular electrophysiology of the mammalian heart. *Am Heart J.* 1974;88:380.)

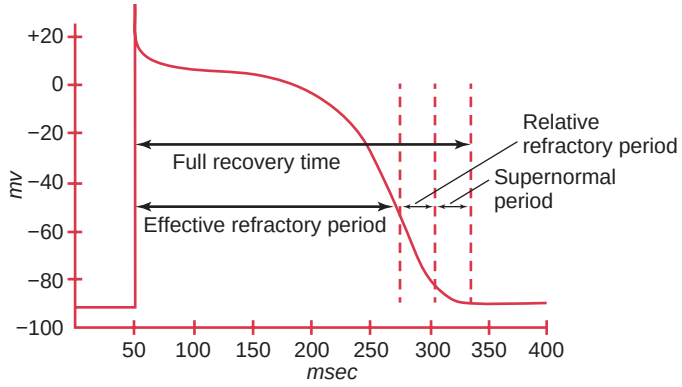


Fig. 1.4 Cellular Refractory Periods. See text for details. (Redrawn from Rosen MS, Wit AL, Hoffman BF. Electrophysiology and pharmacology of cardiac arrhythmias. I. Cellular electrophysiology of the mammalian heart. *Am Heart J.* 1974;88:380.)

for activation. As a result, initiation of a propagating action potential will require a larger-than-normal stimulus. Even then, I_{Na} and phase 0 of the resulting action potential are reduced, and conduction of a premature stimulus occurring during that period is slowed.

On the other hand, supernormal excitability can be observed during a brief period at the end of phase 3 of the action potential. During the supernormal period, excitation is possible in response to an otherwise subthreshold stimulus; that same stimulus fails to elicit a response earlier and later than the supernormal period. Two factors are responsible for supernormality: the availability of fast Na^+ channels and the proximity of the E_m to threshold potential. During the supernormal phase of excitability, the cell has recovered enough to respond to a stimulus (i.e., an adequate number of Na^+ channels is available for activation). At the same time, because the E_m is still reduced, it requires only a little additional depolarization to bring the fiber to threshold; thus a stimulus that is smaller than is normally required is now able to elicit an action potential. However, because Na^+ channels are still not fully activated, the resulting action potential is still somewhat reduced from normal in amplitude and propagation velocity.[18] In general, the later the second stimulus comes, the more the Na^+ channels are reactivated, and the more rapid the upstroke of the second action potential.

Reduced membrane excitability can occur in certain pathophysiological conditions, including genetic mutations that result in loss of Na^+ channel function, Na^+ channel blockade with class I antiarrhythmic drugs, and acute myocardial ischemia.[19]

Action potentials with reduced upstroke velocity resulting from partial inactivation of Na^+ channels are called "depressed fast responses." Importantly, refractoriness in cells with reduced E_m can outlast voltage recovery of the action potential (i.e., the cell can still be refractory or partially refractory after the resting E_m returns to its most negative value).

REFRACTORINESS

During a cardiac cycle, once an action potential is initiated, the cardiomyocyte becomes inexcitable to stimulation (i.e., unable to initiate another action potential in response to a stimulus of threshold intensity) for some duration of time (which is generally slightly shorter than the duration of the "true" action potential duration) until its membrane has repolarized to a certain level. With repolarization, Na^+ channels normally recover rapidly from inactivation (within 10 milliseconds) and are ready to open again. Refractoriness is determined, in part, by the action potential duration and the E_m, and the degree of refractoriness primarily reflects the number of Na^+ channels that have recovered from their inactive state. The period of refractoriness to stimulation is physiologically necessary for the mechanical function of the heart; it allows only gradual recovery of excitability, thus permitting relaxation of cardiac muscle before subsequent activation. In addition, the refractory period acts as a protective mechanism by preventing multiple, compounded action potentials from occurring (i.e., it limits the frequency of depolarization and heart rate). Therefore refractoriness is a determinant of susceptibility to arrhythmias. In general, shorter refractoriness facilitates reentry and arrhythmias.[9]

There are different levels of refractoriness during the action potential (Fig. 1.4). During the *absolute refractory period* (which extends over phases 0, 1, 2, and part of phase 3 of the action potential), no stimulus, regardless of its strength, can reexcite the cell. After the absolute refractory period, a stimulus can cause some cellular depolarization, but it does not lead to a propagated action potential. The sum of this period (which includes a short interval of phase 3 of the action potential) and the absolute refractory period is termed the *effective refractory period* (ERP, ending during phase 3 at an E_m of approximately −60 mV). The ERP is followed by the *relative refractory period*, which extends over the middle and late parts of phase 3 (at an E_m of approximately −60 mV during phase 3) to the end of phase 3 of the action potential. During the relative refractory period, initiation of a second action potential is more difficult but not impossible; a larger-than-normal stimulus can result in activation of the cell and lead to a propagating action potential (Fig. 1.5). However, the upstroke of the new action potential is less steep and of lower amplitude and its conduction velocity is reduced compared with normal. As noted, there is a brief period in phase 3, the supernormal period, during which excitation is possible in response to an otherwise subthreshold stimulus (supernormal excitability).[18]

In pacemaking tissues, I_{Na} is predominantly absent and excitability is mediated by the activation of I_{CaL}. After inactivation, the transition of Ca^{2+} channels from the inactivated to the closed resting state (i.e., recovery from inactivation) is relatively slow. The time constant for recovery from inactivation depends on both the E_m and the intracellular Ca^{2+} concentration (typically 100 to 200 milliseconds at −80 mV and low intracellular Ca^{2+} concentration). This means that I_{CaL} must recover from inactivation between action potentials. As a result, excitability in

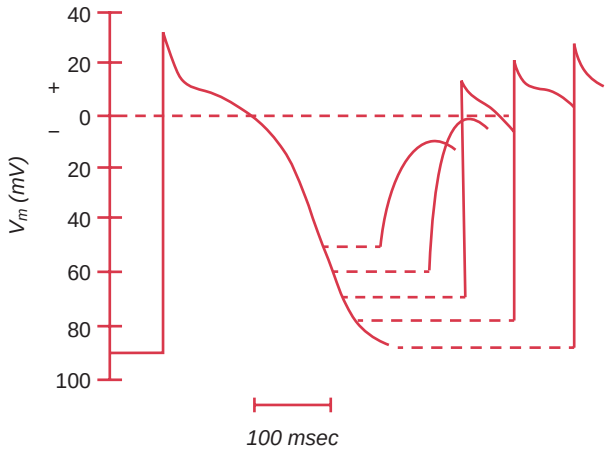


Fig. 1.5 Excitability as a Function of Latency. The changes in action potential amplitude and shape of the upstroke as action potentials are initiated at different stages of the relative refractory period of the preceding excitation. (Redrawn from Rosen MS, Wit AL, Hoffman BF. Electrophysiology and pharmacology of cardiac arrhythmias. I. Cellular electrophysiology of the mammalian heart. *Am Heart J.* 1974;88:380.)

pacemaking cells may not be recovered by the end of phase 3 of the action potential and full restoration of maximum diastolic potential because L-type Ca^{2+} channels require longer time to recovery from inactivation to be able to mediate the upstroke of a new action potential. In other words, sinus and AV nodal cells remain refractory for a time interval that is longer than the time it takes for full membrane repolarization to occur, a phenomenon termed *postrepolarization refractoriness*. This can also occur in working myocardium during some disease states such as myocardial infarction.

PROPAGATION

Cardiac excitation involves generation of the action potential by individual cells, followed by propagation of the electrical impulse along the cardiac muscle fiber and rapidly from cell to cell throughout the cardiac tissue. Conduction velocity refers to the speed of propagation of the action potential through cardiac tissue. The conduction velocity varies in cardiac tissues, ranging from 0.05 m/s in the atrioventricular node (AVN), to 0.5 m/s in atrial and ventricular working myocardium, 2 m/s in the bundle branches, and up to 4 m/s in Purkinje fibers.[20] In most regions of the heart, conduction does not occur as a continuous process; rather, the propagating electrical wavefronts interact with structural boundaries that exist at the cellular level (cell membranes, intercellular gap junctions, the three-dimensional [3-D] arrangement of cardiomyocytes), as well as at the more macroscopic level (microvasculature, connective tissue barriers, trabeculation).[21,22]

Intracellular Propagation

Once initiated, the action potential propagates along the cell membrane until the entire cardiomyocyte is depolarized. The velocity of propagation increases with increasing cell diameter, action potential amplitude, and the initial rate of the rise of the action potential.

An action potential traveling along a cardiac muscle fiber is propagated by local circuit currents, much as it does in nerve and skeletal muscle. Conduction velocity along the cardiac fiber is directly related to the action potential amplitude (i.e., the voltage difference between the fully depolarized and the fully polarized regions) and the rate of change of potential (i.e., the rate of rise of phase 0 of the action potential [dV/dt]). These factors depend on the amplitude of I_{Na}, which, in turn, is directly related to the E_m at the time of stimulation, the availability of Na^+ channels for stimulation, and the size of the Na^+ electrochemical potential gradient across the cell membrane.

Normally, the charge flow across depolarizing ion channels (I_{Na}) is significantly larger than the charge needed to excite the same cell, providing sufficient extra stimulatory current to drive propagation forward. This property (referred to as "propagation reserve" or "safety of propagation") helps to maintain action potential propagation under different physiological and pathophysiological conditions.[23] Working atrial and ventricular myocardium and, in particular, Purkinje fibers have high concentrations of Na^+ channels (Purkinje fibers contain up to 1 million Na^+ channels per cell), which help to generate a large depolarizing current flow (I_{Na}) during the action potential. The large I_{Na} spreads quickly within and between cells to support rapid conduction.

Reduction of membrane excitability leads to a reduction in the rate or amplitude of depolarization (I_{Na}) during phase 0 of the action potential. Conduction velocity decreases monotonically with progressive reduction of membrane excitability. When the safety factor for conduction falls to less than 1 (i.e., the source current becomes less than the current necessary for excitation of downstream tissue), conduction can no longer be sustained, and failure (conduction block) occurs.

In tissues with slow response action potentials (sinus and AV nodes), the upstroke of the action potential is formed by I_{CaL} instead of I_{Na}. Because I_{CaL} has lower amplitude and slower activation kinetics than I_{Na}, slow response action potentials exhibit reduced amplitudes and upstroke velocities. Hence slow conduction (approximately 0.1 to 0.2 m/s) and prolonged refractoriness are characteristic features of nodal tissues. These cells also have a reduced safety factor for conduction, which means that the stimulating efficacy of the propagating impulse is low, and conduction block occurs easily.

Intercellular Propagation

Propagation of action potentials from one cell to adjacent cells is achieved by direct ionic current spread (without electrochemical synapses) via specialized, low resistance intercellular connections (gap junctional channels) located mainly in arrays within the intercalated disks. Gap junctions facilitate impulse propagation throughout the heart, so that the heart behaves electrically as a functional syncytium, resulting in a coordinated mechanical function.[22]

Gap junctional channels connect neighboring cells and allow biochemical and low-resistance electrical coupling. Although the resistivity of the gap junctional membrane for the passage of ions and small molecules and for electrical propagation is several orders of magnitude lower compared with uncoupled cell membranes, gap junction coupling provides a resistance pathway that is several orders of magnitude higher than the cytoplasmic intracellular resistivity (conduction delay is approximately 0.21 to 0.27 milliseconds at gap junctions, and 0.05 to 0.1 milliseconds at the cell membrane).[24] As a consequence, impulse propagation along single cell chains of cardiomyocytes is saltatory, in which the high-resistance intercellular junctions alternate with the low cytoplasmic resistance. However, this feature is lost in intact multicellular tissue due to lateral gap junctional coupling which serves to average local small differences in activation times of individual cardiomyocytes at the excitation wavefront.[19]

The number, size, and molecular composition of the gap junction channels contribute to the specific propagation properties of a given tissue. Tissue-specific connexin expression and gap junction spatial distribution, as well as the variation in the structural composition of gap junction channels, allow for a greater versatility of gap junction physiological features and enable disparate conduction properties in cardiac tissue.[25]

Three different connexins are prominently expressed in the atrial and ventricular myocardium: connexin 40 (Cx40), connexin 43 (Cx43), and connexin 45 (Cx45), named for their molecular masses. A fourth connexin has been described in the AVN (Cx31.9). Cx40 gap junction channels exhibit the largest conductance and Cx45 the smallest. The myocytes of the sinus node and AVN are equipped with small, sparse, and dispersed gap junctions containing Cx45, a connexin that forms low conductance channels, thus underlying the relatively poor intercellular coupling in nodal tissues, a property that is linked to slowing of conduction. In contrast, atrial myocardium gap junctions consist mainly of Cx43 and Cx40, ventricular myocardium of Cx43, and the and Purkinje fibers of Cx40.[24,25]

Importantly, there is a high redundancy in connexin expression in the heart with regard to conduction of electrical impulse, and a large reduction of intercellular coupling is required to cause major slowing of conduction velocity. It has been shown that a 50% reduction in Cx43 does not alter ventricular impulse conduction. Cx43 expression must decrease by 90% to affect conduction, but even then conduction velocity is reduced only by 20%.[25,26]

Similar to its behavior during reduced membrane excitability, conduction velocity decreases monotonically with reduction in intercellular coupling. Of note, partial gap junctional uncoupling was shown to result in conduction velocities that are over an order of magnitude slower than those obtained during a maximal reduction of excitability before conduction failure develops.[19,23]

An alternative to the generally accepted understanding of gap junction–mediated intercellular impulse propagation is the electric field mechanism (also referred to as "ephaptic transmission"). Electrical field coupling (ephaptic coupling) refers to the initiation of an action potential in a nonactivated downstream cell by the electrical field caused by an activated upstream cell. This model postulates that activation spreads along tracts of cardiac cells in a saltatory fashion driven by the negative potential that develops in the restricted cleft space between cells when an action potential develops in the prejunctional membrane. The large I_{Na} in the proximal side of an intercellular cleft at the intercalated disks (where Na^+ channels are concentrated) generates a negative extracellular potential within the cleft, which depolarizes the distal membrane and activates its Na^+ channels. Thus propagation can continue downstream in the absence of gap junctions, provided there is a large I_{Na} at the intercalated disk and a narrow (2 to 5 nm) intercellular cleft that separates the two opposing cells. Computer simulation studies suggest that, under certain conditions, ephaptic coupling may play a role in cardiac impulse propagation, and that ephaptic transmission can explain the insensitivity of conduction velocity to reduced intercellular gap junction coupling. However, the importance and contribution of ephaptic transmission to action potential propagation in normal cardiac tissue are currently unclear and remain difficult to define.[22,24,25]

Anisotropic Conduction

Anisotropy refers to directionally dependent conduction velocity. Isotropic conduction is uniform in all directions; anisotropic conduction is not. Anisotropy is a normal feature of heart muscle and is related to the differences in longitudinal and transverse conduction velocities, which are attributable to the lower resistivity of myocardium in the longitudinal (parallel to the long axis of the myocardial fiber bundles) versus the transverse direction (eFig. 1.1).[25]

In normal adult working myocardium, a given cardiomyocyte is electrically coupled to an average of approximately 11 adjacent cells, with gap junctions being predominantly localized at the intercalated discs at the ends of the rod-shaped cells. Lateral (side-to-side) gap junctions in nondisc lateral membranes of cardiomyocytes are much less abundant and occur more often in atrial than ventricular tissues. This particular subcellular distribution of gap junctions is a main determinant of anisotropic conduction in the heart; a wavefront must traverse more cells in the transverse direction than over an equivalent distance in the longitudinal direction because cell diameter is much smaller than cell length. In addition, less intercellular gap junctional coupling occurs and hence greater resistance and slower conduction transversely than longitudinally.[19,24]

A further level of anisotropy exists in the normal working myocardium secondary to discontinuities of 3-D myocyte architecture at the tissue scale. The myocardium is not a continuum. Distinct layers or bundles of myocytes are evident in the atria and ventricles, at dimensions ranging from approximately 100 μm to several millimeters.[22] The myocardial tissue is not uniformly connected transverse to the myofiber direction. Ventricular myocytes are arranged in layers four to six cells thick (referred to as sheets, myolaminae, or sheetlets) that are separated by clefts of connective tissue, across which there is little direct cell-to-cell coupling. These layers form a branching network. In addition to the laminar myocyte architecture, transmural myofiber rotation adds further complexity to cellular organization. In a normal heart, myocardial fiber direction changes (gradually) from the endocardium to the epicardium by nearly 90 degrees. A lower axial resistivity in the longitudinal myofiber and myolaminar orientation than in the transverse direction further exacerbates electrical anisotropy.[22]

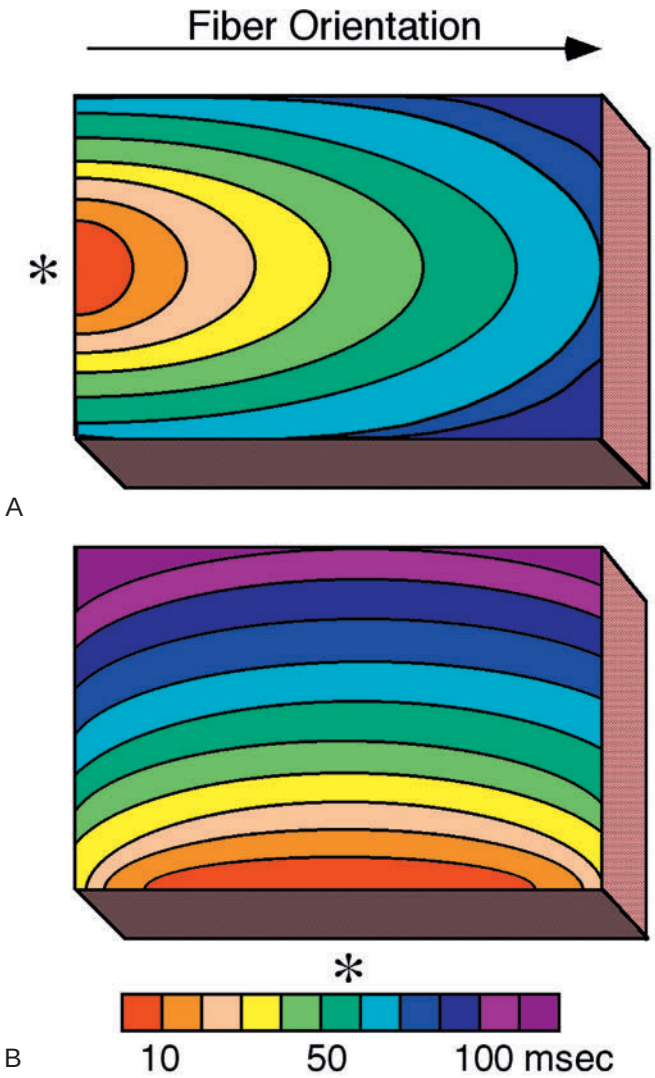
Source-Sink Relationship

Source-sink relationships reflect the interplay between the main factors influencing source current (the rate of rise of the upstroke and amplitude of the action potential) and those that influence the current requirements of the sink (the membrane resistance, the difference between the resting and threshold potentials, cell-to-cell coupling, and tissue geometry).

During action potential propagation, an excited cell serves as a source of electrical charge for depolarizing neighboring unexcited cells. The requirements of adjacent resting cells to reach the threshold E_m constitute an electrical sink (load) for the excited cell. For propagation to succeed, the excited cell must provide sufficient charge to bring the E_m at a site in the sink from its diastolic value to the threshold. Once threshold is reached and an action potential is generated, the load on the excited cell is removed, and the newly excited cell switches from being a sink to being a source for the downstream tissue, thus perpetuating the process of action potential propagation. Action potentials are "regenerative" because they can be conducted over large distances without attenuation. Propagation will continue to be successful as long as the active sources can generate enough current to satisfy local sinks. Alternatively, if the sink overwhelms the source, propagation will fail.[27]

The current provided by the source must reach the sink. The pathway between the source and the sink includes intracellular resistance (provided by the cytoplasm) and intercellular resistance (provided by the gap junctions). Extracellular resistance plays a role, but it can often be neglected. The coupling resistance is mainly determined by resistance of the gap junctions. Therefore the number and distribution of gap junctions, as well as the conductance of the gap junction proteins (connexins) and the geometry of the source-sink relationship, are important factors for propagation of the action potential.[21,28]

A major cause for source-sink mismatch is an abrupt change in the structure of the cellular network, such as that which occurs at the Purkinje fiber–ventricular muscle junction. Each Purkinje fiber (source) transfers the impulse to hundreds or thousands of ventricular cardiomyocytes (sink). This mismatch can potentially result in dispersion of the source current to many neighboring cells (sink), and in each of these the accumulated charge may be too low to trigger an action potential, leading to conduction failure.[12,29] Nonetheless, in a



eFig. 1.1 Anisotropic Conduction. Progression of activation wavefronts in blocks of ventricular myocardium with longitudinal fiber orientation are shown. A wavefront stimulated *(asterisk)* at the left edge progresses more rapidly (wider isochrone spacing, [A]) than one starting perpendicularly (B) because of more favorable conduction parameters in the former direction.