Introduction to Cardiac Electrophysiology, the Electrocardiogram, and Cardiac Arrhythmias

Alfred E. Buxton, M.D., Kristin E. Ellison, M.D., Malcolm M. Kirk, M.D., Gregory F. Michaud, M.D.

INTRODUCTION

Overall cardiac output (the amount of blood the heart pumps around the body every minute) is a function of how much blood the heart ejects with every beat, and the heart rate. Many factors work in concert to regulate heart rate. A thorough understanding of normal mechanisms of cardiac electrical activation and modifying factors is a necessary precursor to understanding disease states, and their appropriate treatment.

General Outline

I. Basic Electrophysiology
   A. Membranes, ions, currents
   B. Resting membrane potential
   C. Action potentials, excitability, refractoriness
   D. Intercellular conduction
   E. Normal impulse formation

II. Conduction System Anatomy
   A. Sinus node and atrium
   B. Atrioventricular (AV) node
   C. His-Purkinje system and ventricles
   4) Abnormal connections

III. The Electrocardiogram
   4) Correlation with anatomy and activation
   5) Lead system, placement

IV. Bradycardias (slow heartbeats)
   A. Abnormal impulse formation
   B. Abnormal impulse transmission
   C. Treatment strategies

V. Tachycardias (fast heartbeats)
   A. Mechanisms
   B. Distinguishing between mechanisms
   C. Treatment strategies
   D. Specific tachyarrhythmias
I. BASIC ELECTROPHYSIOLOGY

A. Membranes, Ions, Currents

Cardiac electrical activity is determined by transmembrane potential - the potential, or voltage, difference between the intracellular and extracellular environments. This potential difference can only exist because of the selectively-permeable cardiac cell membrane. This membrane is composed of a lipid bilayer in which are situated specialized proteins that form channels that allow passage of certain ions at specific times between the intra- and extracellular spaces (Figs. I-1,2). Normally, in the resting state the intracellular compartment has more negative than positive ions, and is thus polarized to a negative potential relative to the extracellular space (about -85 to -90 mV for most cardiac cells).

Fig. I-11 Section of a cardiac cell membrane, with standard lipid bilayer inside and through which proteins are inserted. The sodium channel (upper diagram - SCN5A) and the potassium channels (lower diagram) bridge the membrane to permit charged ion passage through the non-polar lipid layers. From Roden DM, Spooner PM. Inherited Long QT Syndromes: A paradigm for understanding arrhythmogenesis: proceedings of an NHLBI, NIH, ORDR Workshop. J Cardiovasc Electrophys 2000; 10:1664-1683.
Changes in cell membrane potential are due to flow of positively-charged ions which may occur directly to and from the extracellular space through specialized "pores" in the membrane called ionic channels, or between adjoining cardiac cells through gap junctions. These latter connections are critical for the normal rapid spread of electrical activity throughout the heart.

![Fig. I-2. Biophysicist’s concept of an ion channel. An intrinsic membrane protein that forms a low-energy path (or pore) for ions to cross the membrane lipid barrier(1). In the pore is a narrow region called a selectivity filter (2). The channel has gates that open and shut (3) to control the flow of ions. The gates are regulated by membrane potential or by ligand binding. In this model of a voltage-sensitive channel, a voltage sensor is depicted as a charged structure within the protein.]


Each membrane channel is rather selective for its particular ion (Na\(^+\), K\(^+\), Ca\(^{++}\)). How much of each ion passes through its own channel at any time (its current) depends on how much driving force there is for the ion's travel (roughly equivalent to the potential difference for that ion), and how readily the channel will allow its passage (its conductance – the inverse of resistance).

It so happens that the extracellular sodium and calcium concentrations are far in excess of their intracellular concentrations, and thus when the channels are conducting, these ions move into the cell carrying positive current. This has the effect of depolarizing the cell membrane (i.e., neutralizing the resting negative potential); potassium, on the other hand, has a higher intra- than extracellular concentration and thus tends to carry current outwards, i.e., repolarize or even hyperpolarize the cell membrane. The net current shifts determine the actual membrane potential.

### B. Resting Membrane Potential

Ionic channels are open, and thus conduct ionic current, for only a very short period during each cardiac cycle. Physiologic "gates" govern the duration of Na\(^+\) and Ca\(^{++}\) channel opening for Na\(^+\), these gates come in 2 flavors, "activation" and inactivation" (Fig. I-3). Both gates must be open in order for current to flow. At rest, nearly all of the activation ("m") gates are closed; and
although inactivation (‘h”) gates are open – sodium conductance (gNa) is very small and sodium current flow (iNa) thus minimal. (Ca ++ channels have similar gating functions but with slower kinetics.) Most of a cardiac cell’s time is spent in an equilibrium state in which net transmembrane current is zero, the resting membrane potential; it happens that the resting potential is close to the equilibrium potential for potassium (Ek) such that the driving force for potassium (and thus ik) is small, and just balances the small iNa. Determinants of gate opening and closing states, and thus depolarization, are discussed below.

![Diagram of gates regulating ion flow](image)

**Fig. I-3.** Schema depicting concept of gates regulating ion flow through rapid (ie Na channel) and slow (i.e. Ca channel) inward currents through cardiac cell membranes. Three states are depicted. For the Na channel, during the resting state (top row) the activation (m) gates are closed, and the inactivation (h) gates are open. The activated state (middle row) occurs when both m and h gates open in response to a stimulus. This allows Na ions to rush into the cell, down their electrochemical gradient, depolarizing the cell, producing the upstroke of the action potential (lower figure). Depolarization results in closing of the h (inactivation) gates, shutting off the inward flow of Na ions. When the upstroke of the action potential depolarizes the cell to the threshold level for the slow channel, the d gates open, and the slow inward current flows contributing to the plateau phase of the action potential. The f gates of the slow channel close more slowly than the h gates of the fast channel. (modified from Wit, AL, Bigger, JT. Possible electrophysiological mechanisms for lethal arrhythmias accompanying myocardial ischemia and infarction. Circulation 1975;52 (Suppl.3):96.)

**C. Action Potentials, Excitability, Refractoriness**

When sodium and calcium ions start flooding into the cell, the intracellular potential increases (becomes less negative), even exceeding zero, the process of depolarization (Fig. 3,4). If there were no mechanism to return these ions to their resting, pre-depolarized concentrations, the concentration gradients of each ion would quickly vanish and none of us would have very many heartbeats. Fortunately, we came equipped with a means of restoring these gradients, and
thus the resting potential. This process is mediated by the Na\(^+\)-K\(^+\) exchange pump, an energy-dependent/ATP-consuming device. (This pump expels 3 Na\(^+\) ions for every 2 K\(^+\) ions admitted.) The calcium gradient is restored by a specific Na\(^+\)-Ca\(^{++}\) exchange, deriving its energy from the Na\(^+\) gradient.

Fig. I-4. A generic cardiac action potential. The Upstroke is termed "Phase 0", Rapid Repolarization is "Phase 1", Plateau is "Phase 2", Final Repolarization is "Phase 3", and Diastole is "Phase 4". Not all cells normally depolarize in diastole. From Fozzard, HA and Arnsdorf, MF, "Cardiac Electrophysiology", in Fozzard, HA, Haber, E, Jennings, RB, Katz, AM, and Morgan, HE, (eds) The Heart and Cardiovascular System. Scientific Foundations. New York Raven Press, 1986

The action potential (AP) is the curve of voltage change over time during the depolarization/repolarization of the cardiac cell (Figs. I-4,5). The sodium current is turned on, and then off very quickly, early in the course of the action potential; Na\(^+\) thus mediates the rapid upstroke (phase 0) of the AP. Calcium influx occurs slightly later and lasts longer, accounting for the plateau (phase 2) of the AP, and mediates muscle contraction. These are followed by K\(^+\) efflux from the cell, leading to repolarization (phase 3) back to the resting membrane potential (phase 4). Cells with this type of "fast-response" AP comprise most of the heart (atrium, ventricles, His-Purkinje system); other cells (in the sinoatrial and atrioventricular nodes) have "slow-response" APs (Fig. 5), in which Na\(^+\) is less important, and Ca\(^{++}\) more important, in mediating phase 0.
The capability of a cell to respond to an external stimulus by depolarizing and forming an AP is known as excitability. The states of the m and h gates discussed above are voltage-dependent; that is, at certain membrane potentials, the h gate will be open, the m closed, etc. As noted, at resting membrane potential, the m gates are closed/h gates open, and negligible Na+ current flows; when an external stimulus arrives (either from an electrode or from an adjacent cell), membrane potential shifts toward 0 mV. When it reaches about -60 mV, though, the m gates open quickly allowing Na+ ions to rush into the cell and relieve their gradient, which shifts the membrane potential further toward 0. At the same time, the h (inactivation) gates begin to close, preventing further Na+ influx. Both gates are open, then, for only a few milliseconds. Once the h gates close (Fig. 3), Na+ influx stops and no matter how large a stimulus is applied, the cell cannot reopen the channel to generate another AP, the cell is at that time inexcitable or refractory. During phases 2 and 3 of the AP, the m and h gates gradually recover their ability to respond. A stimulus applied near the end of phase 3 can open only those channels whose h gates have returned to the open state. If not enough have opened to allow enough Na+ influx to result in a self-sustaining AP, the cell is said to be in the absolute refractory period. (Fig. I-6). If
a stimulus arrives few milliseconds later, when more h gates have recovered, enough channels will have opened to conduct some Na+ current but not a normal amount; this gives rise to a slower upstroke in phase 0, and is termed the *relative refractory period*. Stimuli occurring still later encounter essentially all gates at the ready, and a normal AP results (fully-excitable).

Fig. I-6.

**Action Potential Refractory Periods**

Fig. I-6  Effect of resting membrane potential (RMP) on action potential (AP) upstroke. A stimulus applied as shown results in very different appearing APs depending on the RMP, which determines how many m gates will be open. At a normal RMP (-90 mV), a normal AP upstroke results; at less negative RMPs, a progressively delayed and slower AP upstroke is seen, until at RMP of -60 mV or less negative, no AP results.

Calcium channels, like sodium, also have voltage-dependent activation and inactivation gates and behave in a manner roughly similar in response to excitable current. However, there are a number of important differences, as shown below:

A corollary of the voltage dependence of the h gate is that cells whose resting membrane potential is not as negative as normal (say, -75 mV) will have fewer h gates open, less Na+ influx, and will be less excitable. A slower upstroke of phase 0 will result. At membrane potentials more positive than about -60 mV, a stimulus will not result in an AP. Such a situation might occur with elevated extracellular [K+], which shifts the resting membrane potential to a less negative level. This has a clinical correlate: high serum [K+] can quickly result in death due to cardiac inexcitability, heralded on the ECG by gradual widening and slurring of the ventricular depolarization wave.
D. Intercellular Conduction

In order for the heart to accomplish anything of hemodynamic significance, it must be able to put forth a coordinated contraction of cells nearly simultaneously. This requires that its overall electrical activation occurs very rapidly. Determinants of the speed of cell-cell transmission (conduction velocity) include the rapidity with which the potential difference develops between cells, the magnitude of the excitatory current, and the resistance to intercellular current flow (mediated largely by gap junctions). Factors which may adversely affect conduction velocity (cell-cell transmission) include a decrease in the efficacy (strength) of the excitatory stimulus (partially depolarized resting membrane potential), decreased membrane receptiveness (partially depolarized membrane [hyperkalemia, ischemia]; stimulus occurring during relative refractory period; drugs which block the sodium channel), and increased resistance to axial current flow (decrease in number of gap junctions).

E. Normal Impulse Formation

The initiation of a heartbeat is governed by automaticity; this is defined as the occurrence of spontaneous cellular depolarization resulting in an action potential. That is, left alone, cells which possess automaticity will fire repeatedly on their own due to spontaneous depolarization during phase 4 of the AP toward the threshold potential. The rate of their firing depends on the type of cell, as well as the extracellular environment as illustrated below.

Normally, automaticity of sinus nodal cells determines the heart rate; cells in the His-Purkinje system serve as back-up subsidiary pacemakers in case the sinus node or atrioventricular conduction fails. The sinus node controls the heart rate most of the time because its rate of discharge is faster than the His cells. Cardiac cells in other areas do not normally display automaticity.