Cardiac electrophysiology: normal and ischemic ionic currents and the ECG

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Submitted 6 July 2016; accepted in final form 17 December 2016

Klabunde RE. Cardiac electrophysiology: normal and ischemic ionic currents and the ECG. Adv Physiol Educ 41: 29–37, 2017; doi:10.1152/advan.00105.2016.—Basic cardiac electrophysiology is foundational to understanding normal cardiac function in terms of rate and rhythm and initiation of cardiac muscle contraction. The primary clinical tool for assessing cardiac electrical events is the electrocardiogram (ECG), which provides global and regional information on rate, rhythm, and electrical conduction as well as changes in electrical activity associated with cardiac disease, particularly ischemic heart disease. This teaching review is written at a level appropriate for first- and second-year medical students. Specific concepts discussed include ion equilibrium potentials, electrochemical forces driving ion movements across membranes, the role of ion channels in determining membrane resting potentials and action potentials, and the conduction of action potentials within the heart. The electrophysiological basis for the ECG is then described, followed by discussion on how ischemia alters cellular electrophysiology and ECG recordings, with particular emphasis on changes in T waves and ST segments of the ECG.

THE CONTENT OF THIS TEACHING REVIEW is written at a level appropriate for first- and second-year medical students who are learning basic cardiac electrophysiology in normal and ischemic hearts. The first section examines the ionic basis for resting membrane potentials and cardiac action potentials, with a focus on nonpacemaker cells. Foundational concepts such as ion equilibrium potentials, electrochemical forces driving ion movements across membranes, and the role of ion channels in determining membrane potentials are discussed. Next, the electrophysiological basis for electrocardiogram (ECG) recordings is developed, emphasizing the use of 12-lead ECG recordings to view the heart from different anatomical perspectives. The final section discusses how myocardial ischemia alters cellular electrophysiology, the conduction of action potentials within the heart, and how these changes affect the ECG during ischemic events. This review helps to bridge important concepts that are often treated separately in basic physiology and clinical cardiology textbooks, with the goal of enhancing the reader’s understanding of the physiological basis for the effects of ischemia on cardiac electrical activity and the ECG.

Normal cardiac cellular electrophysiology. All living cells, because of the distribution of ions across the cell membrane, have a resting membrane potential that is negative inside the cell relative to the outside of the cell. The most important ions that contribute to the membrane potential are Na+, K+, Ca++, and Cl− (Table 1). In a typical cell, the concentration of K+ is higher inside the cell than outside. In contrast, Na+, Ca++, and Cl− have higher concentrations outside than inside the cell.

The high K+ concentration inside the cell relative to the outside (150 vs. 4 mM) sets up a concentration (chemical) gradient for the outward diffusion of K+. Because the membrane is permeable to K+, outward diffusion of the positively charged potassium creates a negative electrical potential inside the cell relative to the outside. The rate of outward K+ diffusion depends in part on the K+ concentration difference across membrane. If the K+ concentration outside of the cell is increased (e.g., from 4 to 20 mM), then the chemical gradient driving the outward diffusion of K+ will be reduced. This will lead to reduced movement (measured as electrical current) of K+ out of the cell and a less negative membrane potential (i.e., membrane becomes depolarized) compared with when the external K+ concentration is normal.

The effects of changes in ion concentration gradient on membrane potential can be described by the Nernst equation (2, 11, 19), which calculates the equilibrium potential for an ion. The equilibrium potential is the voltage required to maintain a given ion chemical gradient across the membrane. In the Nernst equation (Fig. 1), R = universal gas constant, T = temperature (K), z = no. of ion charges (e.g., z = 1 for K+ and Na+; z = 2 for Ca++), and F = Faraday constant. At normal body temperature and z = 1, RT/zF becomes −61 when the natural log (ln) is changed to log10. If the inside concentration for potassium [K+]i is 150 mM and the outside concentration [K+]o is 4 mM, then the calculated EK is −96 mV (EK = −61 log [K+]i/[K+]o). This means that when the membrane potential is −96 mV there is no net movement of K+ across the membrane, because the K+ is in electrochemical balance across the membrane. If [K+]o is increased to 20 mM, then the new EK is −53 mV. In other words, with a reduced chemical gradient, the EK is also reduced (less negative or depolarized) compared with 4 mM [K+]o. Therefore, increases in [K+]o can dramatically affect the EK and, as described later, the resting membrane potential. The equilibrium potentials calculated for Na+, Ca++, and Cl− are given in Table 1. Note that Na+ and Ca++ have very positive equilibrium potentials, whereas Cl− has an equilibrium potential (−90 mV) that is very near the resting membrane potential (resting Em).

Generally, the membrane potential is not the same as the equilibrium potential for K+. In nonpacemaker cardiomyocytes, the resting EK is about −90 mV, which is less negative than the equilibrium potential for K+ (−96 mV). Therefore, under resting conditions, K+ is not in electrochemical balance. Under this condition, the net electrochemical force (9, 11) acting on K+ is the resting Em − EK, or −90 mV minus −96
Therefore, when the cell membrane is depolarized, the net driving force acting on K⁺ to depolarization. In resting cardiac cells, the permeability to K⁺ is very high compared with when the membrane is depolarized, the net electrochemical force acting on K⁺ to drive it out of the cell is greatly increased compared with when the cell is at its resting E_m. However, it should be noted that even at resting E_m, when the net electrochemical force is small, it is still sufficient to drive K⁺ out of the cell.

This brings us to another concept that is important for understanding ion movement across membranes, and that is membrane permeability to the ion. For example, at a given net electrochemical force, the rate of outward movement of K⁺ will be reduced if the membrane permeability to K⁺ is reduced. K⁺, like each of the other primary ions, moves through the cell membrane via specific ion channels that can open and close in response to changes in membrane potential (voltage-operated channels) or ligands binding to receptors associated with the channel (receptor-operated channels) (9, 11). Reducing the number of open K⁺ channels in the membrane reduces the rate of outward movement of K⁺ at a given net electrochemical force (i.e., reduces K⁺ outward electrical current), which leads to depolarization. In resting cardiac cells, the permeability to K⁺ is very high compared with when the membrane is depolarized (11, 19). The relatively low net electrochemical force acting on K⁺ at resting E_m (about +6 mV) is offset by a very high membrane permeability to K⁺ (19), which produces a large outward movement of K⁺ (17) and maintains the resting E_m near the E_K. Because of this, K⁺ is the ion most responsible for the resting E_m.

Up to this point, the discussion has focused primarily on K⁺. But like K⁺, each of the other primary ions (Na⁺, Ca²⁺, and Cl⁻) has an associated equilibrium potential and a net electrochemical force that depends on the membrane potential (see Table 1). Therefore, changes in the concentration gradient for these ions and the membrane permeability for these ions can affect movement of these ions across the membrane.

Table 1. Primary ions involved in cardiac electrophysiology (11)

<table>
<thead>
<tr>
<th>Ion</th>
<th>Inside Concentration, mM</th>
<th>Outside Concentration, mM</th>
<th>Equilibrium Potential, mV</th>
<th>Net Electrochemical Force (mV) at resting E_m of ~90 mV</th>
</tr>
</thead>
<tbody>
<tr>
<td>K⁺</td>
<td>150</td>
<td>4</td>
<td>-96</td>
<td>+6</td>
</tr>
<tr>
<td>Na⁺</td>
<td>20</td>
<td>145</td>
<td>+52</td>
<td>-142</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>0.0001</td>
<td>2.5</td>
<td>+134</td>
<td>-224</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>4</td>
<td>120</td>
<td>-90</td>
<td>0</td>
</tr>
</tbody>
</table>

E_m, membrane potential.

mV, which equals +6 mV (Table 1). This is the force that is driving K⁺ out of the cell at resting E_m. If the cell depolarizes to 0 mV, then the net electrochemical force acting on K⁺ (E_m - E_K) is 0 mV minus -96 mV, which equals +96 mV. Therefore, when the membrane is depolarized, the net electrochemical force acting on K⁺ to drive it out of the cell is greatly increased compared with when the cell is at its resting E_m. Consequently, Na⁺ and Ca²⁺ contribute very little to the resting E_m compared with K⁺. Thereby contribute to the membrane potential. Although there are large electrochemical forces acting on Na⁺ and Ca²⁺ at resting E_m, the resting membrane permeability is very low for these ions, and therefore their movement into the cell is much less than the outward movement of K⁺ (11, 19). Consequently, Na⁺ and Ca²⁺ contribute very little to the resting E_m compared with K⁺.

The interaction between electrochemical forces and membrane permeability is described by the Goldman-Hodkin-Katz (GHK) equation (11, 19), where E_m is determined by the sum of the products of the relative conductance and the equilibrium potential for the major ions (Fig. 2). Ion conductance is an electrical term that reflects the membrane permeability to an ion (e.g., increasing membrane permeability to K⁺ by opening K⁺ channels increases K⁺ conductance). The ratio of g_Na over g_T represents the conductance of Na⁺ (g_0 Na) relative to the total membrane conductance for all the ions (g_T). In the second line of the equation (see Fig. 2), the relative conductance is denoted by g'. The equilibrium potential (E) value for each of the ions in the third line of the equation is taken from Table 1. In resting cells, g'_K is very high, whereas g'_Na, g'_Ca, and g'_Cl are relatively low. Therefore, the calculated and observed resting E_m (~90 mV) is close to E_K (~96 mV). If g' for each ion remains unchanged, then increasing [K⁺]o will depolarize the resting E_m because the calculated E_K becomes less negative. As described later, changes in g' for this ions account largely for the changes in E_m associated with action potentials.

Key Concepts:
- Resting E_m is determined largely by outward K⁺ currents because of the high permeability of the resting membrane to K⁺.
- If ion conductance is unchanged, then increasing the extracellular concentration of K⁺ causes membrane depolarization.

In a resting cardiac cell, K⁺ is moving out and Na⁺ and Ca²⁺ are moving into the cell, albeit at different rates. Nev-
ertheless, over time this leakage of ions would cause a loss in the chemical concentration gradients for these ions and abolish the membrane potential. Therefore, mechanisms are required to maintain the ion concentration gradients across the membrane.

This is accomplished by ion transport and exchange. Figure 3 describes three important mechanisms associated with the cardiac cell membrane (sarcolemma) that ensure the maintenance of ion concentration gradients. First, a Na⁺/K⁺-ATPase actively transports three Na⁺ ions out of the cell in exchange for two K⁺ ions that are transported into the cell (8, 11). This ensures that the Na⁺ entering the cell can be removed, and the K⁺ that is lost from the cell can be transported back into the cell. Because more Na⁺ is pumped out of the cell than K⁺ reentering the cell (3:2 ratio), this ATP-dependent pump generates a small net negative voltage inside the cell; therefore, this pump is said to be electrogenic. A second transport system removes Ca²⁺ that enters the cell in exchange for Na⁺ that enters the cell (4, 6, 11). This is a non-energy-dependent exchange pump. The entry of Na⁺ into the cell via this site is exchanged for Ca²⁺ that is translocated out of the cell. The ratio of Na⁺ to Ca²⁺ exchange is 3:1; therefore, this pump generates small net electrical currents. Although this exchange can operate in either direction depending on the ratio of Na⁺ to Ca²⁺ and membrane potential, in resting cells it generally results in net positive charges (Na⁺) entering the cell (4).

Finally, Ca²⁺ enters the cell that can also be removed by a Ca²⁺-ATPase pump (11, 15). This energy-dependent pump actively extrudes Ca²⁺ from the cell, and therefore it is also electrogenic, producing a small net negative voltage inside the cell.

**Fig. 4. Nonpacemaker cardiac action potential generation by ion currents (I).** Nos. 0—4 represent action potential phases. Gray horizontal bars represent the time period of current flow through specific Na⁺, Ca²⁺, and K⁺ channels. Inward Na⁺ and Ca²⁺ currents cause depolarization, whereas outward K⁺ currents cause repolarization. Used with permission from Klabunde RE (http://www.cvphysiology.com; 2016).

**Fig. 3. Ion pumps for maintenance of Na⁺, K⁺, and Ca²⁺ gradients across the cell membrane.** The Na⁺/K⁺-ATPase moves 3 Na⁺ out in exchange for 2 K⁺ ions (3:2 ratio of Na⁺ to K⁺). The Na⁺/Ca²⁺ exchanger generally operates to remove from the cell 1 Ca²⁺ in exchange for 3 Na⁺ that enter the cell. The Ca²⁺-ATPase transports 1 Ca²⁺ out of the cell with no exchange with other ions. Used with permission from Klabunde RE (http://www.cvphysiology.com, 2016).

**Action potentials and their conduction within the heart.**

The electrical properties of cardiac cells can be categorized into two basic cell types: pacemaker and nonpacemaker cells. Pacemaker cells are located primarily in the sinoatrial (SA) and atrioventricular (AV) nodes of the heart. The SA node, located in the upper posterior wall of the right atrium near the entrance of the superior vena cava, normally functions as the primary pacemaker site to drive the rate and rhythm of the heart. AV nodal pacemaker cells located in the inferior/posterior region of the interatrial septum are normally suppressed by the more rapid rate of the SA node.

Pacemaker cells undergo spontaneous depolarization (pacemaker potentials), and therefore, they have no true resting membrane potential (11). When the spontaneous depolarization reaches a threshold voltage (about −40 mV), it triggers a more rapid and complete depolarization followed by repolarization (i.e., an action potential is generated). The characteristic voltage changes of pacemaker action potentials differ in several ways from nonpacemaker action potentials, owing to unique characteristics of ion channels in pacemaker cells.

Nonpacemaker cardiac cells, which are the focus of this teaching review, comprise the atrial and ventricular cardiomyocytes and the Purkinje conduction system within the ventricles (11). They have true resting potentials (typically between −90 and −80 mV), undergo very rapid depolarization upon action potential initiation, and have a prolonged phase of depolarization (plateau phase) (Fig. 4). The duration of these action potentials can range from 200 to 400 ms, which is more than 10 times longer than action potentials found in nerve and skeletal muscle cells.

The resting E₉₀, as already discussed, is primarily generated by outward K⁺ currents (I₉₀) because the membrane permeability to Na⁺ and Ca²⁺ is very low in the resting cell, whereas K⁺ permeability is high. In resting cells, this outward movement of K⁺, which is sometimes referred to as “K⁺ leak currents,” involves K₁ channels that are open at resting membrane potentials (9, 17). This outward current drives the membrane potential to a value that is close to the equilibrium potential for K⁺. The resting potential is referred to as phase 4 of the action potential (see Fig. 4). When a cell is rapidly depolarized to a threshold voltage (about −70 mV) by an action potential generated by an adjacent cell, the membrane responds by opening fast Na⁺ channels and slow L-type Ca²⁺ channels and closing K⁺ channels (9, 14). According to the GHK equation (see Fig. 2), these conductance changes brought about by channel opening and closing depolarize the membrane potential toward the positive equilibrium potentials for Na⁺ and Ca²⁺, and away from the K⁺ equilibrium potential.

This rapid depolarization is referred to as phase 0 of the action potential. The cell then undergoes a small repolarization (phase 1) because fast Na⁺ channels close and a specific K⁺ channel (K₉₀ₐ) opens (9, 14, 17). However, the continued inward movement of Ca²⁺ through L-type Ca²⁺ channels maintains a depolarized state (phase 2 plateau) following phase 1. As these
Ca$^{++}$ channels begin to close, another type of K$^+$ channel opens (K$_o$) (9, 14, 17). The reduction of inward Ca$^{++}$ currents and the increase in outward K$^+$ currents causes repolarization (phase 3) and a return to the phase 4 resting potential that is maintained by open K$_o$ channels. It is important to note that ions move in and out of the cell during an action potential, but only a small number of ions relative to the internal and external pools of ions are involved in each action potential. Therefore, ion concentration gradients across the membrane do not change appreciably during action potentials. Furthermore, pumps and exchangers (see Fig. 3) ensure that the ion concentration gradients are maintained.

Key concepts:

- Action potentials are generated by changes in ion conductance via opening and closing of ion channels.
- Rapid inward movement of Na$^+$ is largely responsible for the rapid initial depolarization.
- Delayed inward movement of Ca$^{++}$ into the cell prolongs the depolarization phase of the action potential.
- Outward movement of K$^+$ is responsible for repolarizing the membrane back to the resting E$_{m}$.

As described already, the SA node is the normal pacemaker site of the heart. When SA nodal action potentials are generated, they rapidly spread through the muscular walls of the atrial chambers by cell-to-cell conduction via ion conducting gap junctions that are found where two cells are joined together (9, 16). The AV node is normally the only region between the atria and ventricles through which action potentials can pass from the atria into the ventricles (Fig. 5). It should be noted, however, that because the AV nodal cells are pacemaker type cells, they have a slow rate of depolarization (decreased phase 0 slope), which reduces the cell-to-cell conduction velocity (11). Therefore, there is a delay in the conduction of action potentials through the AV node, which permits more complete filling of the ventricles following atrial contraction. Just below the AV nodal cells is the short bundle of His that divides into the left and right bundle branches of the Purkinje system that travel down the left and right sides of the interventricular septum. The bundle branches give off smaller Purkinje fibers, which facilitate the rapid conduction of action potentials throughout the muscular walls of the ventricles. Conduction is very rapid in the specialized, noncontracting cardiomyocytes of the Purkinje system because they have a large number of fast Na$^+$ channels, particularly at gap junctions (16), and therefore, they undergo very fast phase 0 depolarization. Purkinje fibers within the ventricles terminate at cardiomyocytes that undergo contraction in response to depolarization.

**Normal cardiac electrocardiogram.** Electrical activation of the heart occurs as action potentials are propagated throughout the atria from the SA node, then directed into the ventricles by way of the AV node, and finally distributed throughout the ventricles by the Purkinje system. Depolarization and repolarization of the myocardium can be observed and quantified by placing electrodes on the surface of the body to measure the electrical activity within the heart. A recording of this activity is called an electrocardiogram (ECG). The ECG records changes in voltage, not absolute voltage. Therefore, when the heart is fully repolarized or depolarized, the ECG records zero voltage (isoelectric baseline).

Standards have been established for recording the ECG by placing electrodes at specific sites on the surface of the body (7, 11). These electrodes are configured electrically so that the electrical activity of the heart can be viewed at different angles, resulting in what is termed a 12-lead ECG. In practice, these 12 leads are recorded simultaneously so that the same electrical event in time can be viewed at 12 different angles. Six of these leads incorporate electrodes placed on the left and right arms and left and right legs. These leads view the heart at the following angles: 0° (lead I, left and right arms), +60° (lead II, right arm and left leg), +120° (lead III, left arm and left leg), −30° (lead aV$_L$, left arm positive), −150° (lead aV$_R$, right arm positive), and +90° (lead aV$_F$, left leg positive) (Fig. 6). By convention, 0° is the horizontal line between the left and right arms that passes through the heart. The arrowheads in Fig. 6 represent the positive electrode for a particular lead axis. The augmented leads (aV$_L$, aV$_R$, and aV$_F$) do not have a single positive electrode like leads I, II, and III. Instead, nonpositive leads are electrically coupled to serve as a composite negative electrode; this changes the viewing angle of the positive electrode placed on the limb. Therefore, the same electrical activity in the heart appears differently in each of the six limb leads, although the timing of the events representing the sequence of activation and repolarization is similar (see Fig. 6).

The remaining six leads of the ECG view the heart from the frontal plane that is perpendicular to the limb leads (Fig. 7). These leads are referred to as the precordial (or chest) leads and are abbreviated as V$_1$ – V$_6$. The V$_1$ recording electrode is placed on the chest to the right of the sternum over the fourth intercostal space, and the remaining leads are placed around the chest to the left of V$_1$, with V$_6$ placed laterally at the midaxillary line over the fifth intercostal space. Like the limb leads, the ECG waveforms appear different in each precordial lead because the electrical events of the heart are being viewed at a different angle.

There are rules of interpretation (11) for the limb and chest leads, which can be summarized as follows:
1. A wave of depolarization traveling toward a positive recording electrode displays a positive voltage on the ECG tracing.
2. A wave of repolarization moving away from a positive recording electrode displays a positive ECG voltage.
3. The voltage is negative if the depolarization wave is moving away from the positive recording electrode or a repolarization wave is moving toward the electrode.
4. Depolarization or repolarization waves traveling perpendicular to the lead axis of a positive recording electrode display no net voltage.
5. The magnitude of the recorded voltage is related to the mass of the muscle undergoing depolarization or repolarization.

There are specific components of the ECG tracing that are common to all of the leads (Fig. 8). Although these component waveforms may appear different in shape in different leads, their time attributes are similar. The first small deflection from the zero baseline voltage is the P wave, which represents atrial depolarization. This wave has a positive deflection in most leads but a smaller amplitude than other waves because the atrial muscle mass is small compared with the ventricles. The next wave, which is generally the largest in voltage amplitude, is the QRS complex, which represents ventricular depolarization. Finally, the last wave is the T wave, which is generated by ventricular repolarization. Atrial repolarization is not observed because it is masked by the much larger voltage changes in the QRS. Note that there is a significant time delay after the P wave before the appearance of the QRS. This largely represents the conduction delay that occurs within the AV node. The time period encompassing atrial depolarization and AV node delay is called the P-R interval. There is also a zero-voltage (isoelectric) segment between the QRS and T wave, which represents the time period during which the entire ventricle is in a depolarized state. The tracing is also isoelectric between
the T wave and appearance of the next P wave because the entire heart is repolarized during this period.

**Electrical vectors and ECG generation.** Ventricular depolarization begins as action potentials are propagated down the left and right bundle branches on either side of the ventricular septum. The left side of the septum is first to depolarize, and therefore, septal depolarization spreads from the left to right side of the septum (Fig. 9A). When this activity is being recording by lead II, the septal depolarization may show a small negative deflection (Q wave) or no discernable deflection because the depolarization is moving almost perpendicular to the lead axis (represented as an instantaneous mean electrical vector; Fig. 9, black arrow). A more lateral lead such as aVL would show a more prominent Q wave because the depolarization vector is moving away from the positive electrode of aVL. Following septal depolarization, the depolarization spreads into the apex of the heart (Fig. 9B). At this time, the instantaneous mean electrical vector is heading almost directly toward the positive recording electrode, which results in a large positive voltage (R wave) being recorded by lead II. If this were recorded by aVR, the QRS deflection would be negative at this time. Shortly thereafter, as depolarization engulfs the apex, depolarization waves move up into the walls of the right and left ventricles (Fig. 9C). In lead II, this would be recorded as a small positive voltage. Several milliseconds later, most of the left ventricle and all of the right are depolarized (Fig. 9D). At this time, the electrode may record a small negative voltage (S wave) because the wave of depolarization is moving away from the lead II positive electrode. This sequence of ventricular depolarization results in the QRS complex as recorded by lead II. Each of the other 11 leads will record the same sequence; however, the QRS will appear different because each of these leads views the heart from a different angle (see Figs. 6 and 7).

The entire sequence of ventricular depolarization represented by the QRS normally occurs in 0.06–0.10 s.

The sequence of ventricular repolarization differs markedly from depolarization, which accounts for why the T wave has a different appearance from the QRS. Based on the rules for ECG interpretation, one might think that the T wave should be negative because the first cells to depolarize should be first to repolarize, which would result in a wave of repolarization traveling toward the same electrode that recorded the QRS. The T wave, however, is normally upright in most leads and has a longer duration than the QRS. Why is this the case? The reason is that the last cells to depolarize are the first cells to repolarize (Fig. 10). The last cells to depolarize are located in the subepicardial region (below the outside surface) of the upper left ventricular free wall. The subepicardial cells repolarize first because they have shorter action potential durations than subendocardial cells (3, 14) (inner region of ventricle), and therefore, they undergo repolarization before the subendocardial cells despite those cells depolarizing before the subepicardial cells (see Fig. 10). Therefore, although an overlying recording electrode would record a positive QRS, the wave of repolarization normally travels away from the recording electrode, and by the rules of interpretation, this causes a positive deflection. The T wave is longer in duration than the QRS because it takes longer for the ventricles to repolarize than depolarize. The reason for this is that depolarization involves the high-speed Purkinje system to rapidly conduct action potentials throughout the ventricles, whereas the propagation of repolarization does not involve these pathways, and therefore, it is limited primarily to slower cell-to-cell conduction outside of the Purkinje system.

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**Fig. 9.** Generation of the ventricular QRS complex during ventricular depolarization. The recording electrode is configured as lead II. The small arrows represent individual instantaneous vectors; larger arrows represent the instantaneous mean electrical vectors, which determine the ECG voltage recorded a particular time point during depolarization. A: septal depolarization. B: apical depolarization. C: simultaneous left and right ventricular depolarization. D: completion of left ventricular depolarization. The lead axis for QRS tracing is 60° (lead II). Adapted and used with permission from Klabunde RE (http://www.cvphysiology.com, 2016).

**Fig. 10.** ECG recording of ventricular repolarization (T wave). Depolarization of the ventricular wall spreads from the subendocardial (inner wall) cells to the subepicardial (outer wall) cells, as shown by the solid arrow. In most leads, the T wave is upright (positive voltage) because the subepicardial (Epi) cells near the ventricular surface, which are the last cells to depolarize, are the first to repolarize. This occurs because subepicardial action potential durations are shorter than subendocardial (Endo) cells (compare solid and dashed action potentials). Therefore, the wave of repolarization travels away from the overlying recording electrode (dashed arrows represent repolarization vectors), which is opposite of the depolarization wave (solid arrow). Used with permission from Klabunde RE (http://www.cvphysiology.com, 2016).
Specific clinical criteria used for determining rate, rhythm, electrical axis, changes in specific time intervals, etc., can be found in clinical cardiology textbooks (7).

Key concepts:

- The ECG records electrical changes associated with depolarization (atrial P wave, ventricular QRS) and repolarization of the ventricles (T wave) and the timing of those events.
- By using a 12-lead configuration, the electrical activity of the heart can be viewed from different angles.
- The appearance of the QRS complex differs among the leads in terms of positive and negative deflections but not timing because each lead views the electrical activity of the heart from a different perspective, which can provide important clinical information as to regional electrical activity.
- The T wave is normally positive in most leads because the last cells to depolarize are the first to repolarize.

**Cellular electrophysiological basis for ECG changes during ischemia.** Ischemia is defined as inadequate blood flow, which reduces oxygen delivery to a tissue. This leads to a fall in tissue partial pressure of oxygen (hypoxia), which in turn causes intracellular ATP levels to decrease because oxygen is required by the mitochondria to make ATP (5). A decline in cellular ATP can affect a special type of K⁺ channel (K\textsubscript{ATP}) that is inactivated by normal cellular ATP levels (9, 18). When ATP falls, K\textsubscript{ATP} channels open and permit K⁺ to leave the cell. Although an increase in outward K⁺ movement would hyperpolarize the cell, the cell ends up in a more depolarized state because extracellular K⁺ concentration increases as intracellular K⁺ decreases. According to the Nernst and GHK equations, this decreases E\textsubscript{K}, leading to a less negative (depolarized) resting membrane potential (Fig. 11). Furthermore, the loss of ATP may reduce the activity of the Na\textsuperscript{+}/K\textsuperscript{+}-ATPase pump, leading to extracellular accumulation of K⁺ and a loss of the electrogenic contribution of the pump to the membrane potential (12). Therefore, pump inhibition may also contribute to depolarization.

Ischemia-induced depolarization also inactivates (closes) fast Na⁺ channels that are responsible for the rapid depolarization of phase 0 (5, 18). This is different from rapid depolarization to threshold, which opens the voltage-operated fast Na⁺ channels. Slow depolarization as it occurs in response to ischemia inactivates these channels, which reduces the number of fast Na⁺ channels available for rapid action potential generation. Because each Na⁺ channel has a slightly different response to graded depolarization, the number of channels inactivated increases with more severe ischemic depolarization. With fewer Na⁺ channels contributing to the initial depolarization, the slope of phase 0 (upstroke velocity) is reduced (5) (see Fig. 11). A resting membrane potential of about −55 mV causes all of the fast Na⁺ channels to become inactivated. An action potential may still occur under this condition; however, slow inward Ca\textsuperscript{2⁺} via L-type Ca\textsuperscript{2⁺} channels will be responsible for phase 0, and the rate of depolarization will be much slower. Finally, ischemic depolarization also shortens the action potential duration, which may be related to the opening of K\textsubscript{ATP} channels (1, 5, 18), leading to earlier phase 3 repolarization.

In atrial muscle, the Purkinje system and ventricular muscle ischemic depolarization can reduce conduction velocity or produce conduction blocks because action potential propagation in these tissues depends primarily on the opening of fast Na⁺ channels, which are inactivated by ischemia (5, 18). Ischemic depolarization of the AV node can depress conduction and cause AV blocks primarily by inactivation of L-type Ca\textsuperscript{2⁺} channels (5), which are responsible for phase 0 depolarization in nodal tissue.

Key concepts: cardiac ischemia causes

- increased extracellular K⁺ and a less negative E\textsubscript{K};
- myocyte depolarization;
- fast Na⁺ channel inactivation in nonpacemaker cells;
- depressed phase 0 slope of action potentials;
- reduced action potential conduction velocity.

Ischemia can alter the ECG in several different ways. Changes in rate and rhythm, along with conduction blocks, may occur, depending on the location of the ischemic region within the heart. For example, conduction blocks in the left or right bundle branches can produce a Q wave in the inferior leads (Fig. 11) and a QS wave in the standard leads. Conduction block may also occur in the left anterior descending coronary artery and cause a QS pattern in leads I, aVL, and V₅-V₆. This is particularly important in patients with left ventricular hypertrophy, as the Q wave may be diagnostic of myocardial infarction.

**Fig. 11. Effects of ischemia on ventricular action potentials.** Ischemic action potential (dashed tracing) has a less negative (depolarized) resting potential, slower phase 0 upstroke, and reduced duration.

**Fig. 12. Reversal of T wave by subendocardial ischemia.** Ischemic subendocardial cells (solid action potential) have a depolarized resting membrane potential and a shortened action potential duration (↓ APD), which can cause repolarization to occur before the subepicardial cells (dashed action potential) repolarize. This will lead to the repolarization wave (dashed arrows) traveling toward the overlying recording electrode, which is generally the same vector orientation as depolarization (solid arrow); this causes a negative deflection of the T wave. Used with permission from Klubunde RE (http://www.cvphysiology.com, 2016).
right bundle branches can occur (7), which alters the sequence of ventricular activation and prolongs ventricular activation times and increases QRS duration. Altered conduction may also lead to the development of reentry circuits and tachycardia, which increases the width of the QRS complex and alters T wave appearance (7).

Ventricular ischemia can alter repolarization and produce T wave inversion. As described previously, ischemia shortens the action potential duration of cells, which results in repolarization occurring earlier than normal. Because subendocardial cells are generally more susceptible to ischemia (10), when these cells become hypoxic they may repolarize before the subepicardial cells. When this occurs, the wave of repolarization travels from the subendocardial to subepicardial surface of the ventricular. Based on ECG rules of interpretation, this causes a negative deflection in the T wave recording by an electrode overlying that region of the ventricle (Fig. 12). The appearance of T wave inversion does not necessarily indicate myocardial ischemia, but it is often observed clinically during ischemic events.

Although myocardial ischemia frequently causes clinically significant changes in rate, rhythm, or conduction, these changes do not always occur with ischemia. The ECG, however, can provide additional evidence for ischemia by examining changes in the ST segment (7). This segment situated between the end of the QRS and the beginning of the T wave is normally isoelectric (0 mV on the ECG recording) because it represents the period in which all of the ventricular myocytes are depolarized. The ST segment, however, can become depressed or elevated under ischemic conditions. For example, a person with a history of exertional chest discomfort and suspected coronary disease may be evaluated by a stress ECG, which is commonly conducted by having the patient walk on treadmill at different workloads while a 12-lead ECG is recorded. If coronary blood flow is insufficient to support the increased oxygen demand of the heart during exercise, then the tissue will become hypoxic, and depression of the ST segment can occur (Fig. 13) (13).

This type of demand-induced ischemia affects the subendocardium more than the subepicardium (10). Subendocardial ischemia results in depolarization of that region of the ventricular wall (Fig. 14). Because other regions may still be adequately perfused during the exercise, there develops a voltage difference and diastolic injury currents between the normal and ischemic tissue. The injury currents are “diastolic” because they are most prominent when the rest of the ventricle is repolarized. Electrodes will record this injury current as a
positive voltage that occurs before the QRS and following the T wave when the ventricles are normally repolarized. When the ventricle becomes more uniformly depolarized after the QRS, the electrode will record a normal isoelectric ST segment. Therefore, ST segment depression or elevation.

ST segment elevation (Fig. 15) is generally a sign of more severe myocardial ischemia and occurs in the majority of acute myocardial infarctions that are caused by complete blockage of a coronary artery resulting from a ruptured atherosclerotic plaque with subsequent thrombus formation. If cardiac enzyme measurements (e.g., troponin) confirm the infarction (cellular death), then it is termed an ST elevated myocardial infarction (STEMI).

To understand why the ST segment becomes elevated, similar reasoning can be applied to what was described for ST depression. In the case of ST elevation, there is usually a transmural infarct involving the entire wall thickness of a ventricular region (7). This ischemic tissue becomes depolarized (Fig. 16) because of its inability to maintain normal ion gradients across the cell membranes. When the noninvolved myocardium is repolarized (between the end of the T wave and beginning of the QRS), there exists injury currents created by the separation of depolarized injured tissue and polarized normal tissue. A recording electrode overlying the ischemic tissue will record negative voltages because the electrical vector will be in a direction away from the electrode. Therefore, at a time when the entire ventricle should be repolarized and when the ECG baseline voltage should be zero, the electrode instead records a negative voltage. When the entire ventricle is depolarized with the appearance of the QRS, then the voltage difference between the ischemic and normal tissue disappears and the electrode records an isoelectric ST segment. However, this segment will appear elevated compared with the depressed baseline. Other ECG changes (e.g., formation of prominent Q waves) occur over the hours and weeks following a STEMI (7).

Key concepts: ventricular ischemia can produce
- rate and rhythm changes;
- conduction blocks;
- T wave reversal;
- ST segment depression or elevation.

Summary. This teaching review builds a foundation for understanding cellular electrophysiology in both the normal and ischemic myocardium. Resting membrane potentials and action potentials, which are determined by ion chemical gradients and changes in membrane ion conductance, are very sensitive to ischemia-induced tissue hypoxia. Ischemia leads to cellular depolarization by altering ion chemical gradients and membrane conductance to ions. These changes alter action potential depolarization and repolarization and depress their conducton within the heart, leading to altered ECG wave morphology, intervals, and segments. Therefore, characteristic changes in the ECG are useful in the diagnosis of myocardial ischemia and infarction.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS
R.E.K. prepared figures; R.E.K. drafted manuscript; R.E.K. edited and revised manuscript; R.E.K. approved final version of manuscript.

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