Cardiac Physiology for the Clinician

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Preface

Formal medical education is of necessity dated. This is particularly true today because of the rapid advances being made in the many medical sciences disciplines. The development of new techniques has led to more complex research approaches and more sophisticated results.

This treatise is meant to be an aid in updating one's knowledge. The contributions have been written by experts in the cardiovascular field who have endeavored to present difficult concepts and data from technical papers in simplified and understandable form. The major new breakthroughs in the understanding of cardiac function are discussed and areas of disagreement pointed out. The interested reader will find in the literature quoted at the end of each chapter additional material to satisfy the most enquiring mind.

The general plan of this treatise is to present recent advances in normal and abnormal cardiac physiology. The topics treated include the general electrophysiology of cardiac cells: properties of automatic discharge, conduction, and contraction. Since the needs of the body vary from time to time, mechanisms must be available which *control* these functions. This control is analyzed at the nervous, peripheral (heart), and cellular levels. Advances in the understanding of abnormal situations and their treatment are also reviewed in the chapters on arrhythmias, cardiac failure, and digitalis.

Mario Vassalle, M.D.

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CHAPTER 1

Electrophysiology of the Heart Cells

MARIO VASSALLE

INTRODUCTION

Recent research has brought an awareness that different cardiac cells have many similarities and dissimilarities. An integrated cardiac action

can be produced only by specialization within the component parts of the heart, and therefore differences among cells are to be expected. Many normal and abnormal findings, analyzed in other chapters of this text, require an understanding of the basic events responsible for the electrical manifestations of the cardiac cells. For example, one might mention the modality by which digitalis affects the electrical and mechanical properties of different cardiac tissues (see Chapter 8). With this realization in mind, we shall now consider pertinent information on recent developments in cardiac electrophysiology. In this first chapter, we will consider the basis for electrical manifestations of cellular activity; specific aspects of the function of different tissues are illustrated in later chapters.

THE RESTING POTENTIAL

Each cardiac cell is surrounded by a plasma membrane, and the intracellular ionic composition sharply differs from that of the interstitial fluid surrounding the cells. These ionic gradients are the basis for the potential difference across the plasma membrane, both at rest and during activity.

At rest, all cardiac cells are polarized. That is, the inside of the cell is negatively charged with respect to the outside. A precise measurement of the absolute value of the resting potential was obtained when micro-

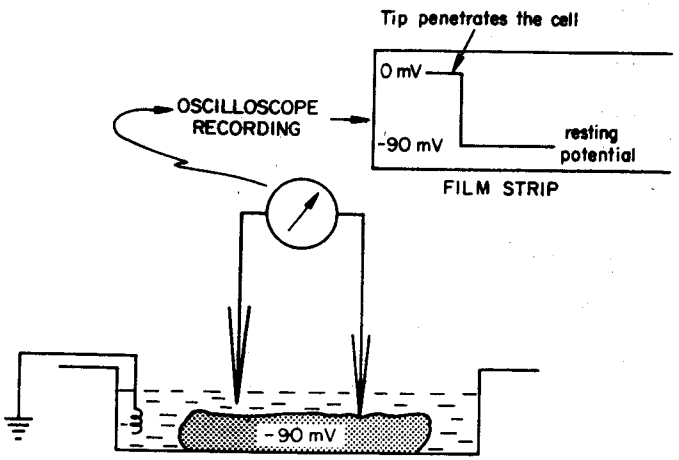

Fig. 1-1. Microelectric recording. As soon as the tip of one microelectrode penetrates a fiber, the oscilloscope trace shifts from the reference 0 potential to a potential that is negative inside. This is the resting potential (—90 mV in the figure).

electrodes with a tip diameter of less than 0.5 μm were developed, as the tip of an electrode could be introduced through the plasma membrane without producing any significant or persistent damage. This procedure has been widely employed and many substantial advances in cardiac electrophysiology are due to its use. In a typical experiment, two glass microelectrodes, filled with a conducting (3 M) potassium solution are connected by cathode followers to an oscilloscope (Fig. 1-1). The tissue under study is perfused in a physiological solution of appropriate ionic composition, oxygenated and warmed to a selected temperature. When the tips of the electrodes are in the solution outside the cell in the grounded tissue bath, the zero reference potential is recorded (Fig. 1-1). As the tip of one electrode is inserted by means of a micromanipulator into the fiber, the trace of the oscilloscope suddenly jumps to a negative value of the order of 0.1 V (Fig. 1-1). This potential is 50 to 100 times larger than that recorded with a standard ECG lead. If the impaled cell is not a pacemaker, the resting potential will not vary with time until the cell is excited from an outside source.

The Nature of the Resting Potential

As mentioned above, the ionic composition of the cell interior markedly differs from that of the interstitial space. Let us assume that initially the cell is neutral inside. As far as potassium ions are concerned, the internal concentration of potassium ($[K]_i$) is about 150 mmoles/liter of tissue water and the external concentration is about 2.7 mM (Fig. 1-2A). Such a concentration gradient favors the efflux of potassium from the inside to the outside of the cell. This force (chemical gradient) is represented in Fig. 1-2A by the arrow pointing outward. Under the chemical gradient, relatively few potassium ions leave the cell and indiffusible anions (presumably of a protein nature) are left behind. This means that progressively unmatched negative charges will render the inside more and more negative until an electrical gradient (arrow pointing inward in Fig. 1-2B) is established that is equal and opposite to the concentration gradient. Thus, the internal potassium concentration does not run down its gradient because a force develops (the electrical gradient) that acts in an opposite direction. This is an equilibrium situation where potassium diffuses in and out the cell but there is no net transfer of charges, since there is no net force acting in either direction. Such an equilibrium situation is defined by the Nernst equation

$$E_K = \frac{RT}{F} \ln \frac{[K]_i}{[K]_o}$$

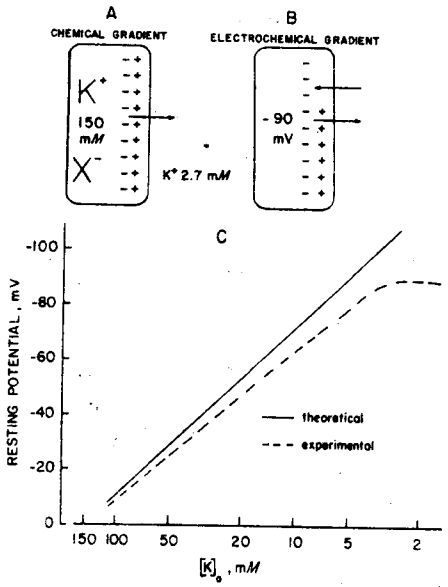

Fig. 1-2. The establishment of the resting potential. (A) The cell is assumed to have no potential because positive K^+ ions are matched by negative protein (X) charges. A chemical gradient directed outward favors the efflux of K^+. (B) As a consequence of some K^+ loss, the inside of the cell has become sufficiently negative to oppose any further net K efflux. (C) Changes in resting potential in the different extracellular K concentration are compared with expected theoretical changes.

where E_K is the potassium equilibrium potential, R is the gas constant, T is the absolute temperature, F is the Faraday constant, and $[K]_o$ and $[K]_i$ are the outside and inside potassium concentrations, respectively. The Nernst equation states that for a given ratio of concentrations of an ion across the cell membrane, a potential exists that will maintain the concentration ratio unaltered.

The Resting Potential Is a Potassium Diffusion Potential

From the Nernst equation it follows that increasing the outside potassium concentration should reduce the resting potential, if indeed the resting potential is due to a potassium diffusion potential. This would be expected, since the concentration gradient would be immediately reduced while the electrical gradient would not: the initially unbalanced electrical gradient will thus cause a net inward movement of potassium ions. This influx of positive charges reduces the potential until the electrical gradient is again equal and opposite to the new concentration gradient. This

has been verified experimentally in several tissues (Fig. 1-2C), although the agreement between the experimental and theoretical curves is not perfect, especially at low $[K]_o$ (see below). This behavior of the cell membrane potential is the basis for changes found in some of the cardiac functions when potassium levels are increased either in the plasma (e.g., kidney insufficiency) or locally (e.g., myocardial infarct or anoxia). As we shall see, lowering the resting potential also affects the action potential. This change, in turn, may underlie disturbances in conduction and rhythm (see Chapter 6).

Ions other than potassium may modify the resting potential but do not determine it. Thus, the resting potential does not permanently vary when the external concentration of Na^+, Ca^{2+}, Mg^{2+}, or Cl^- is changed.

Steady-State Potential versus Equilibrium Potential

Given the ratio of inside to outside concentrations, one would expect the resting potential to be identical to the potassium equilibrium potential only if the membrane were permeable to potassium exclusively. It is now recognized that the membrane at rest is permeable to other ions as well, although to a lesser degree than to potassium. Sodium in particular is important in this respect because it is positively charged and is far more concentrated outside than inside the cell (Fig. 1-3A). This means that even though the membrane is less permeable to Na than K, an inward leak of sodium will occur at rest because of sodium's electrochemical gradient. Several types of experiments (e.g., radioactive sodium, potassium depletion, and low temperature) have demonstrated that sodium can and does enter the resting cell. One might expect this leak of positive charges to make the resting potential less negative than the potassium equilibrium potential. In fact, the resting potential consistently has been found in several tissues to be smaller (less negative) than the equilibrium potential predicted by the Nernst equation. In other words, the resting potential is less negative than would be expected on the basis of the ratio of K concentrations across the cell membrane. This discrepancy is favored by another factor: not only does sodium leak into the fiber at rest, but potassium conductance falls at high (more negative) potential—thus making the small sodium conductance relatively more important in determining the value of the resting potential.

Quite clearly, the cell is not in an equilibrium state. If the Na ions entering the cells are not extruded, the resting potential would slowly decline and eventually disappear. The extrusion of sodium from the cell is against the electrochemical gradient for this ion and therefore requires energy. The metabolism-dependent mechanism, which extrudes the

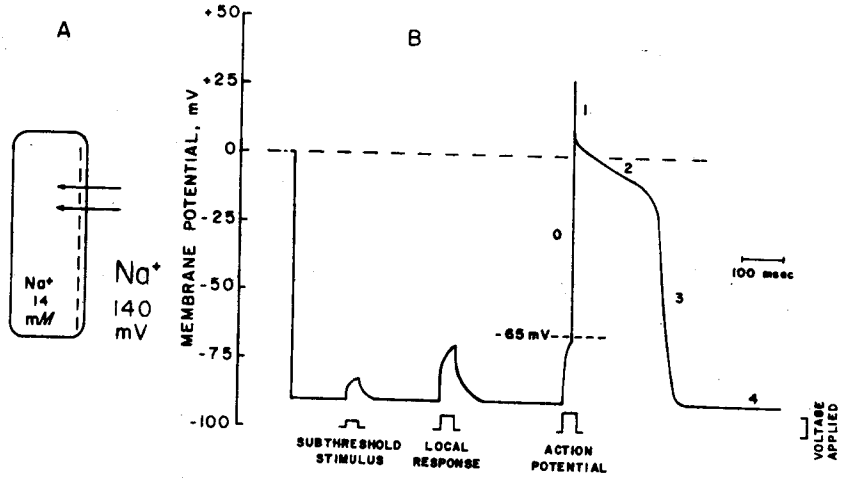

Fig. 1-3. Sodium and the action potential. (A) At rest both the chemical and electrical gradients for sodium ions are directed inward. (B) The trace begins at 0 mV potential. As the microelectrode enters the fiber, there is a sudden shift of the trace to about −90 mV (resting potential). As an electrical stimulus is given, there is a small depolarization that subsides at the end of the electrical pulse (subthreshold stimulus). As stimulus strength is increased, the increment in response is larger than that of the stimulus (local response). With a larger depolarization, threshold is attained and full response is obtained (action potential).

sodium that leaks in, has been called the sodium pump or the sodium–potassium pump (see below). If the activity of the pump is inhibited, the resting potential does indeed decline to less negative values. This shows that, because of the small sodium leak at rest, the resting potential is not an equilibrium potential but rather a steady-state potential. This potential will remain steady as long as the passive inward leak of sodium is equal to its active outward extrusion.

In summary, the resting potential is *determined* by the outward diffusion of potassium under its concentration gradient drive, but is *maintained* by a metabolic energy-requiring process that extrudes the Na leaked in.

THE ACTION POTENTIAL

Electrical Events

The resting potential is said to *decrease* (or the membrane to depolarize) when the inside potential becomes less negative and thus closer to zero potential. If the resting potential is made to decrease by a few millivolts by means of a short pulse, at the end of the pulse the resting potential resumes its original value (Fig. 1-3B). However, as the strength of

the depolarizing pulse is increased, the potential displacement becomes larger than expected (local response). With a still stronger depolarization, the fiber attains a potential (threshold potential) at which a series of potential changes (action potential) are initiated, as illustrated in Fig. 1-3B for a ventricular muscle fiber. Once the threshold is attained, the membrane abruptly depolarizes to zero and in fact reverses its polarity (phase 0), the inside now being positive by some 30 mV. This reversal is not maintained and is followed by an initial rapid repolarization (phase 1). The repolarization continues at a far slower rate during the plateau (phase 2), until it accelerates again during phase 3 to once more reach the resting potential. During diastole (phase 4), the membrane potential exhibits a steady value in nonpacemaker cells. In pacemaker cells there is instead a slow decline in potential during phase 4 (see Chapter 2; and Hoffman and Cranfield, 1960).

The electrical events occurring on excitation constitute the action potential. The major features of cardiac action potentials are (1) a rapid transient reversal of membrane polarity and (2) their long duration with respect to action potentials of other tissues (e.g., nerve and skeletal muscle). These two features are important in cardiac muscle with respect to conduction (Chapter 6) and contraction (Chapter 3), respectively.

The magnitude of the spike and of the reversal varies in different heart tissues (Fig. 1-4). The spike is smallest (and slowest) in the sinus and

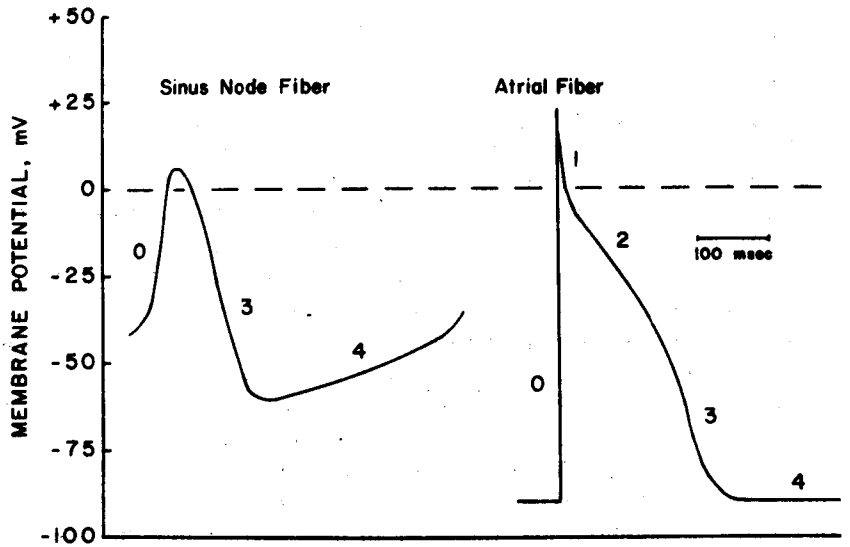

Fig. 1-4. Action potentials of fibers from the sinus node and the atrial musculature. It is apparent that the two action potentials differ sharply in amplitude and configuration.

AV nodes. In the sinus, the maximum diastolic potential is also rather small (—60 mV), and diastolic depolarization attains the threshold at an even lower value (—45 mV). Since there is little or no overshoot, the total amplitude of the spike is small. A similar situation prevails in the AV node, where diastolic depolarization is far less pronounced than in the sinus node and the upstroke is often characterized by a slow wave or notch. The fastest spike is present in Purkinje fibers (see Chapter 2, Fig. 2-4), and these fibers, together with the atrial (Fig. 1-4) and ventricular muscle (Fig. 1-3) fibers, also exhibit a distinct overshoot. The overshoot is usually largest in the Purkinje fibers. All cardiac action potentials are rather long (300–500 msec), the longest action potential being exhibited by Purkinje fibers. The duration of the action potential is affected by many variables (e.g., temperature, neurohormones, and frequency). When the frequency of discharge increases, the duration of the action potential decreases.

Ionic Events Underlying the Action Potential

The change in potential during activity signifies that charges have moved in relation to the plasma membrane. For example, rapid depolarization could readily be accounted for by a movement of positive charges into the cell. Repolarization, in turn, has to be brought about by a net loss of positive charges. Understanding the ionic events and the laws governing the movements of ions during the action potential offers an appreciation of abnormalities of cardiac action, such as in the different situations illustrated in subsequent chapters.

The remarkable progress in the analysis of the action potential of cardiac tissues in recent years has been fostered by a new technique to control membrane potential and measure ionic currents ("voltage clamp" method). With the microelectrode method illustrated above, the time course of potential changes during the action potential can be easily detected. However, the method is limited, in that the information gained about the ions carrying the currents during the action potential is somewhat indirect. Instead, with the voltage clamp technique it is possible to impose a voltage and study the currents associated with such a voltage step. In cardiac muscle, this technique has been applied in two forms. In one method (Fig. 1-5), two microelectrodes are inserted intracellularly into a short (< 2 mm) piece of Purkinje fiber. One electrode is used to record the potential and the other to pass current into the fiber. An amplifier is used to pass both the current pulse needed to displace the potential to the selected value and the additional current required to keep the voltage "clamped" at that value. Thus, it is possible to impose and

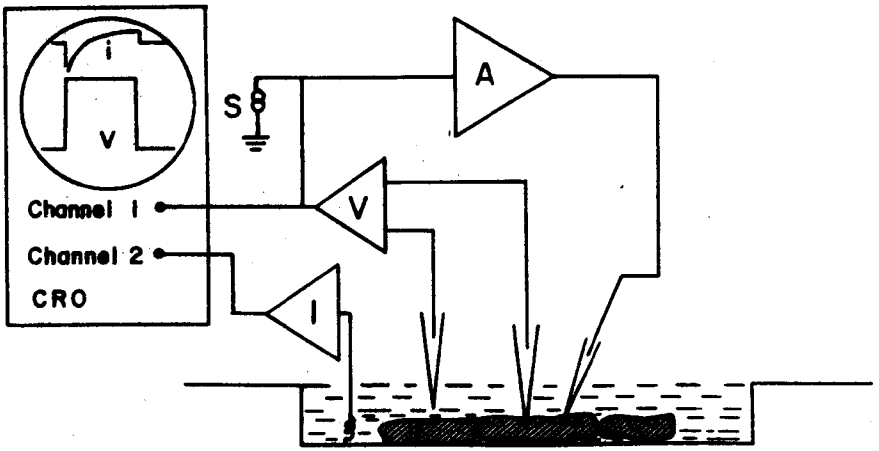

Fig. 1-5. Voltage clamp technique. Schematic presentation of the set-up. Two microelectrodes are inserted intracellularly; one is used to pass current and the other to measure the membrane potential. The voltage (v) and current (i) traces are displayed on the oscilloscope screen. A, feedback amplifier; V, potential amplifier; I, current amplifier; S, stimulator; CRO, cathode ray oscilloscope.

maintain a given voltage on a known patch of cell membrane. The currents crossing the cell membrane as a function of the voltage imposed and as a function of time can then be measured. By manipulating the ionic composition of the extracellular fluid, it is then possible to identify the ions that carry a given current in a certain range of potentials.

The other method of voltage clamping is the sucrose gap, used for ventricular and atrial muscle fiber. Simply stated, the principle is to control the potential of a small segment of muscle by excluding any extracellular flow of current in short adjacent segments exposed to the nonconducting sucrose.

In a somewhat different form, the voltage clamp technique was first applied to the analysis of the action potential of nerves. The results obtained in cardiac tissues are less conclusive because of several technical limitations. Furthermore, the results obtained in one type of cardiac tissue do not necessarily apply to another. Yet a picture is emerging that, although incomplete, clearly shows many events in cardiac tissues and the fact that these events are far more complex than in nerve.

The Upstroke

The Fast Sodium Channel

Sodium is more concentrated outside than inside the cell (Fig. 1-3A). Furthermore, the inside of the cell is negatively charged and Na