CARDIOVASCULAR PHYSIOLOGY

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MATTHEW N. LEVY, M.D.

FOURTH EDITION

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PREFACE

This book is designed primarily for medical and graduate students. With this fundamental purpose in mind, an attempt has been made to emphasize general concepts and to ignore isolated facts, except where they are deemed to be essential. In accordance with this principle, little documentation is afforded for many of the assertions made, and only a few references have been included in the bibliographies at the end of each chapter. Review articles have been given preference over scientific papers, and articles have been selected primarily for their appropriateness for the beginning student, for the depth of the interpretation included in their discussion sections, and for the comprehensiveness of their bibliographies.

Because many of the broad principles of cardiovascular physiology are complex and confusing to the student, simplified models have been employed throughout the book. Unquestionably, there are advantages and disadvantages to this pedagogical device. In formulating a model, the instructor retains those elements and properties of the system under consideration that are deemed germane and discards those other components of the system that are deemed trivial. Furthermore, for those elements to be included in the model, the behavior of certain of these components is assumed to be less complex than is actually the case. One justification for such simplification is that this behavior is reasonably accurate over a certain limited range of values. However, once the underlying basis of the system is understood, the complicating details can then be added to approximate more closely the true system. Although models can serve an extremely useful function when employed properly, they can also lead to erroneous conclusions when misused. Therefore the reader must constantly be aware of the assumptions inherent in a given model and must decide whether a more detailed model is necessary at times to understand the specific problem under consideration.

In a sense normal physiology serves as a framework that students of medicine must comprehend before they can understand the derangements caused by disease or toxic agents. There is no intensive consideration of pathological physiology in this text. However, many examples of abnormal function are provided to illustrate more lucidly the behavior of the system under consideration and to indicate the direction in which students will be proceeding in their continuing efforts to understand the effect on the body of the multitude of disease processes that afflict humans.

In revising and updating this book, we have profited greatly from the many helpful criticisms and suggestions received from the readers, as well as from our own experience with the book in teaching cardiovascular physiology to medical and graduate students. We particularly want to thank Drs. B.R. Duling, R.A. Murphy, R. Rubio, and D.G. Ward. Approaches that have proved to be useful in development of some subjects have been re-

tained, whereas others that have not met our expectations or have proved to be too complex have been deleted. As a result some sections have undergone little change, but others have been considerably revised. Furthermore, the chapter on special circulations now contains sections on the pulmonary, renal, and splanchnic circulations in addition to those on skin, muscle, brain, and fetal circulation, which were present in previous editions of the book. Throughout the book attempts have been made to incorporate the most recent information, and where the subject is still controversial, this has been indicated. Emphasis has been placed on control mechanisms; thus, in order to present the clearest view of the various mechanisms involved in the regulation of the circulatory system, the component parts of the system are discussed individually. However, since the body functions as a whole, in the last chapter we have tried to show how the cardiovascular system operates in an integrated fashion in response to a physiological stimulus (exercise) and a pathophysiological stimulus (hemorrhage).

We wish to express our appreciation to our readers for their constructive comments and hope that they will continue to provide the input necessary for us to make further improvements in future editions. We also wish to thank the numerous investigators and publishers who have granted us permission to use illustrations from their publications. In most cases these illustrations have been altered somewhat to increase their didactic utility. In some cases unpublished data from our own studies have been presented. These investigations were supported by grants HL-10384 and HL-15758 from the U.S. Public Health Service, to which we are indebted.

Robert M. Berne
Matthew N. Levy

CHAPTER 1

THE CIRCUITRY

The circulatory, endocrine, and nervous systems constitute the principal coordinating and integrating systems of the body. Whereas the nervous system is primarily concerned with communications and the endocrine glands with regulation of certain body functions, the circulatory system serves to transport and distribute essential substances to the tissues and to remove by-products of metabolism. The circulatory system also shares in such homeostatic mechanisms as regulation of body temperature, humoral communication throughout the body, and adjustments of oxygen and nutrient supply in different physiological states.

The cardiovascular system that accomplishes these chores is made up of a pump, a series of distributing and collecting tubes, and an extensive system of thin vessels that permit rapid exchange between the tissues and the vascular channels. The primary purpose of this text is to discuss the function of the components of the vascular system and the control mechanisms (with their checks and balances) that are responsible for alteration of blood distribution necessary to meet the changing requirements of different tissues in response to a wide spectrum of physiological and pathological conditions.

Before considering the function of the parts of the circulatory system in detail, it is useful to consider it as a whole in a purely descriptive sense. The heart consists of two pumps in series: one to propel blood through the lungs for exchange of oxygen and carbon dioxide (the *pulmonary circulation*) and the other to propel blood to all other tissues of the body (the *systemic circulation*). Unidirectional flow through the heart is achieved by the appropriate arrangement of effective flap valves. Although the cardiac output is intermittent in character, continuous flow to the periphery occurs by virtue of distension of the aorta and its branches during ventricular contraction *(systole)* and elastic recoil of the walls of the large arteries with forward propulsion of the blood during ventricular relaxation *(diastole)*. Blood moves rapidly through the aorta and its arterial branches, which become narrower and whose walls become thinner and change histologically toward the periphery. From a predominantly elastic structure, the aorta, the peripheral arteries become more muscular in character until at the arterioles the muscular layers predominates (Fig. 1-1). As far out as the beginning of the arterioles, frictional resistance to blood flow is relatively small, and, despite a rapid flow in the arteries, the pressure drop from the root of the aorta to the point of origin of the arterioles is relatively small (Fig. 1-2). The arterioles, the stopcocks of the vascular tree, are the principal points of resistance to blood flow in the circulatory system. The large resistance offered by the arterioles is reflected by the considerable fall in pressure from arterioles to capillaries. Adjustment in the degree of contraction of the circular muscle of these small vessels permits regulation of tissue blood flow and aids in the control of arterial blood pressure.

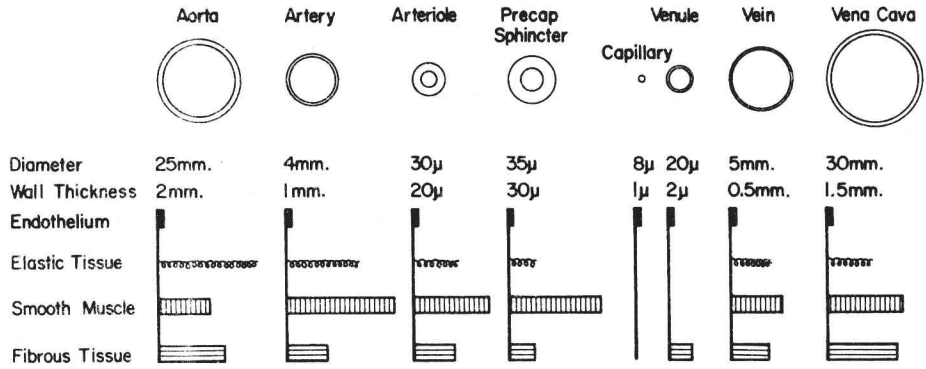

Fig. 1-1. Internal diameter, wall thickness, and relative amounts of the principal components of the vessel walls of the various blood vessels that compose the circulatory system. Cross sections of the vessels are not drawn to scale because of the huge range from aorta and venae cavae to capillary. (Redrawn from Burton, A. C.: Physiol. Rev. **34**:619, 1954.)

In addition to a sharp reduction in pressure across the arterioles, there is also a change from pulsatile to steady flow. The pulsatile character of arterial blood flow, caused by the intermittency of cardiac ejection, is damped at the capillary level by the combination of distensibility of the large arteries and frictional resistance in the arterioles. Many capillaries arise from each arteriole so that the total cross-sectional area of the capillary bed is very large, despite the fact that the cross-sectional area of each individual capillary is less than that of each arteriole. As a result, blood flow becomes quite slow in the capillaries, analogous to the decrease in flow rate seen at the wide regions of a river. Since the capillaries consist of short tubes whose walls are only one cell thick and since flow rate is slow, conditions in the capillaries are ideally suited for the exchange of diffusible substances between blood and tissue.

On its return to the heart from the capillaries, blood passes through venules and then through veins of increasing size. As the heart is approached, the number of veins decreases, the thickness and composition of the vein walls change (Fig. 1-1), the total cross-sectional area of the venous channels is progressively reduced, and velocity of blood flow increases (Fig. 1-2). Also note that the greatest proportion of the circulating blood is located in the venous vessels (Fig. 1-2). The cross-sectional area of the venae cavae is larger than that of the aorta (although not evident from Fig. 1-2 because cross-sectional areas of venae cavae and aorta are so close to zero with a scale that includes the capillaries), and hence the flow is slower than that in the aorta. Blood entering the right ventricle via the right atrium is then pumped through the pulmonary arterial system at mean pressures about one-seventh those developed in the systemic arteries. The blood then passes through the lung capillaries, where carbon dioxide is released and oxygen taken up. The oxygen-rich blood returns via the pulmonary veins to the left atrium and ventricle to complete the cycle. Thus in the normal intact circulation the total volume of blood is constant

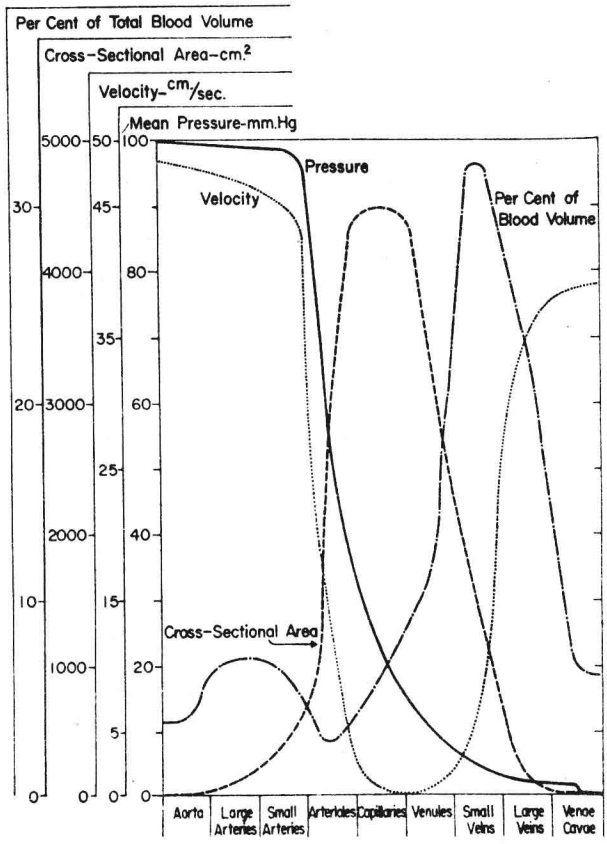

Fig. 1-2. Pressure, velocity of flow, cross-sectional area, and capacity of the blood vessels of the systemic circulation. The important features are the inverse relationship between velocity and cross-sectional area, the major pressure drop across the arterioles, the maximal cross-sectional area and minimal flow rate in the capillaries, and the large capacity of the venous system. The small but abrupt drop in pressure in the venae cavae indicates the point of entrance of these vessels into the thoracic cavity and reflects the effect of the negative intrathoracic pressure. To permit schematic representation of velocity and cross-sectional area on a single linear scale, only approximations are possible at the lower values.

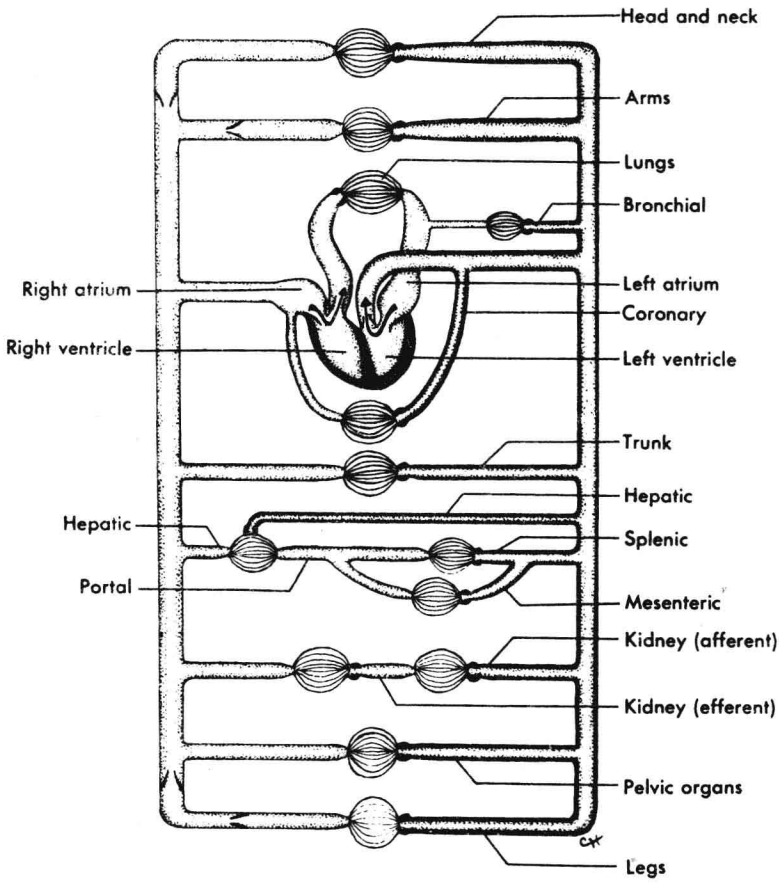

Fig. 1-3. Schematic diagram of the parallel and series arrangement of the vessels composing the circulatory system. The capillary beds are represented by thin lines connecting the arteries (on the right) with the veins (on the left). The crescent-shaped thickenings proximal to the capillary beds represent the arterioles (resistance vessels). (Redrawn from Green, H. D.: In Glasser, O., editor: Medical physics, vol. 1, Chicago, 1944, Year Book Medical Publishers, Inc.)

and an increase in the volume of blood in one area must be accompanied by a decrease in another. However, the velocity at which the blood circulates through the different regions of the body is determined by the output of the left ventricle and by the contractile state of the arterioles (resistance vessels) of these regions. The circulatory system is composed of conduits arranged in series and in parallel, as schematized in Fig. 1-3.

CHAPTER 2

ELECTRICAL ACTIVITY OF THE HEART

The experiments on "animal electricity" conducted by Galvani and Volta in the last half of the eighteenth and early nineteenth centuries prepared the stage for the discovery that electrical phenomena were involved in the spontaneous contractions of the heart. In 1855 Kölliker and Müller observed that when they placed the nerve of a nerve-muscle preparation in contact with the surface of a frog's heart, the muscle twitched with each cardiac contraction. This phenomenon may be observed in the laboratory by allowing the phrenic nerve of an anesthetized dog to lie across the exposed surface of the heart; the diaphragm will contract with each heartbeat. Precise measurement of this electrical activity was not feasible until the end of the past century, when the construction of sensitive, high-fidelity galvanometers permitted registration of the changes in electrical potential during the various phases of the cardiac cycle, which led to the science of electrocardiography. Furthermore, progress in electronics and the acquisition of knowledge concerning the cyclic changes in cardiac excitability have paved the way for the development of devices for converting various abnormal cardiac rhythms to normal rhythms and for maintaining normal heart rates in patients with severe conduction blocks (artificial pacemakers).

TRANSMEMBRANE POTENTIALS

The electrical behavior of single cardiac muscle cells has been investigated by inserting microelectrodes into the interior of cells from various regions of the heart. The potential changes recorded from a typical ventricular muscle fiber are illustrated schematically in Fig. 2-1. When two electrodes are situated in an electrolyte solution near a strip of quiescent cardiac muscle, there will be no potential difference measurable between the two electrodes (from point *A* to point *B*, Fig. 2-1). At point *B* one of the electrodes, a microelectrode with a tip diameter less than 1 μ, was inserted into the interior of a cardiac muscle fiber. Immediately the galvanometer recorded a potential difference across the cell membrane, indicating that the potential of the interior of the cell was

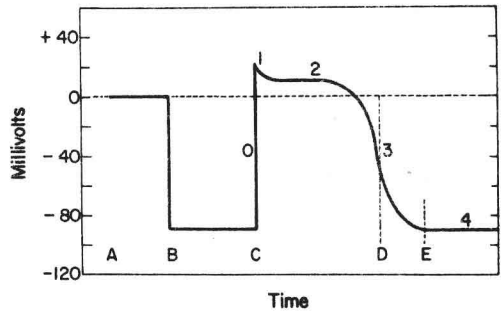

Fig. 2-1. Changes in potential recorded by an intracellular microelectrode. From time *A* to *B* the microelectrode was outside the fiber; at *B* the fiber was impaled by the electrode. At time *C* an action potential began in the impaled fiber. Time *C* to *D* represents the effective refractory period, and *D* to *E* represents the relative refractory period.

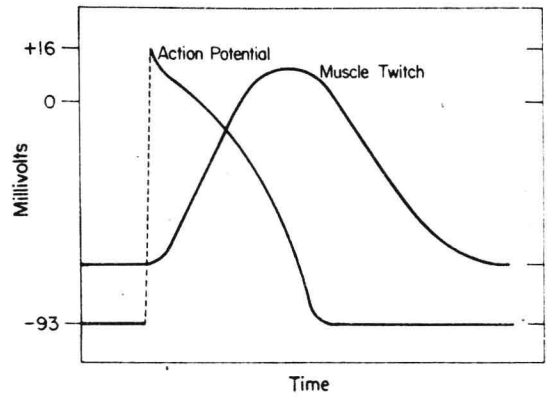

Fig. 2-2. Time relationships between the mechanical tension developed by a thin strip of ventricular muscle and the changes in transmembrane potential. (Redrawn from Kavaler, F., Fisher, V. J., and Stuckey, J. H.: Bull. N.Y. Acad. Med. **41**:592, 1965.)

about 90 mV. lower than that of the surrounding medium. Such electronegativity of the interior of the resting cell with respect to the exterior is also characteristic of skeletal and smooth muscle, of nerve, and indeed of most cells within the body. At point *C* a propagated action potential was transmitted to the cell impaled with the microelectrode. Very rapidly the cell membrane became depolarized; actually, the potential difference was reversed (positive over-shoot), so that the potential of the interior of the cell exceeded that of the exterior by about 20 mV. The rapid upstroke of the action potential is designated phase 0. Immediately after the upstroke, there was a brief period of partial repolarization (phase 1), followed by a *plateau* (phase 2) that persisted for about 0.1 to 0.2 second. The potential then became progressively more negative (phase 3), until the resting state of polarization was again attained (at point *E*). The process of rapid repolarization (phase 3) proceeds at a much slower rate of change than does the process of depolarization (phase 0). The interval from the completion of repolarization until the beginning of the next action potential is designated phase 4.

The time relationships between the electrical events and the actual mechanical contraction are shown in Fig. 2-2. It can be seen that rapid depolarization (phase 0) precedes tension development and that completion of repolarization coincides approximately with peak tension development. The duration of contraction tends to parallel the duration of the action potential. Also as the frequency of cardiac contraction is increased, there is a progressive reduction in the duration of both the action potential and the mechanical contraction.

Principal types of cardiac action potentials

Two main types of action potentials are observed in the heart, as shown in Fig. 2-3. One type, the so-called *fast response*, occurs in the normal myocardial fibers in the atria and ventricles and in the specialized conducting fibers (*Purkinje fibers*) in these chambers. The action potentials shown in Figs. 2-1 and 2-2 are also typical fast responses. The other type of action potential, the so-called *slow response*, is found

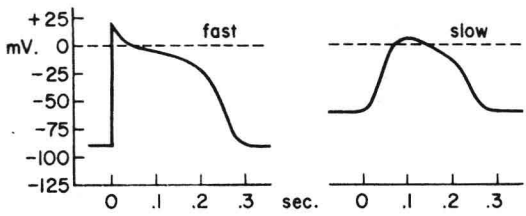

Fig. 2-3. A fast and a slow response action potential recorded from the same canine Purkinje fiber. In the left panel the Purkinje fiber bundle was perfused with a solution containing K^+ at a concentration of 4 mM. In the right panel epinephrine was added and the K^+ concentration was raised to 16 mM. (Redrawn from Wit, A. L., Rosen, M. R., and Hoffman, B. F.: Am. Heart J. **88**:515, 1974.)

in the *sinoatrial* (S-A) *node*, the natural pacemaker region of the heart, and in the *atrioventricular* (A-V) *node*, the specialized tissue involved in conducting the cardiac impulse from atria to ventricles. Furthermore, fast responses may be converted to slow responses either spontaneously or under certain experimental conditions. For example, in a myocardial fiber, a gradual shift of the resting membrane potential from its normal level of about -80 to -90 mV. to a value of about -60 mV. will cause a conversion of subsequent action potentials to the slow response. Such conversions may occur spontaneously in patients with severe coronary artery disease, in those regions of the heart in which the blood supply has been severely curtailed.

As shown in Fig. 2-3, not only is the resting membrane potential of the fast response considerably more negative than that of the slow response, but also the slope of the upstroke (phase 0), the amplitude of the action potential, and the extent of the overshoot of the fast response are greater than in the slow response. It will be explained later that the magnitude of the resting potential is largely responsible for these other distinctions between the fast and slow responses. Furthermore, the amplitude of the action potential and the rate of rise of the upstroke are important determinants of propagation velocity. Hence, in cardiac tissue characterized by the slow response, conduction velocity is very much slower and there is a much greater tendency for impulses to be blocked than in tissues displaying the fast response. Slow conduction and tendency toward block are conditions that increase the likelihood of certain rhythm disturbances in the heart.

Ionic basis of the resting potential

The various phases of the cardiac action potential are associated with changes in the permeability of the cell membrane, mainly to Na, K, and Ca ions. These changes in permeability produce alterations in the rate of passage of these ions across the membrane. Just as with all other cells in the body, the concentration of potassium ions inside a cardiac muscle cell, $[K^+]_i$, greatly exceeds the concentration outside the cell, $[K^+]_o$, as shown in Fig. 2-4. The reverse concentration gradient exists for Na ions and for unbound Ca ions. Furthermore, the resting cell membrane is relatively permeable to K^+, but much less so to Na^+ and Ca^{++}. Because of the high permeability to K^+, there tends to be a net diffusion of K^+ from the inside to the outside of the cell, in the direction of the concentration gradient, as shown on the right side of the cell in Fig. 2-4. Many of the anions (labeled A^-) inside the cell, such as the proteins, are not free to diffuse out with the K^+. Therefore, as the K^+ diffuses out of the cell and leaves the A^- behind, the deficiency of cations causes the interior of the cell to become electronegative, as shown on the left side of the cell in Fig. 2-4.

Therefore, two opposing forces are involved in the movement of K^+ across the cell membrane. A chemical force, based on the concentration gradient, results in the net outward diffusion of K^+. The counter force is an electrostatic one; the positively charged K ions

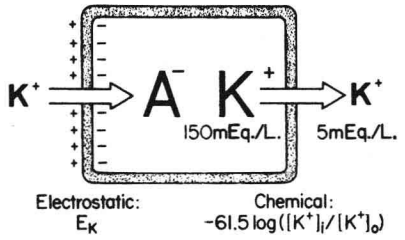

Fig. 2-4. The balance of chemical and electrostatic forces acting on a resting cardiac cell membrane, based on a 30:1 ratio of the intracellular to extracellular K^+ concentrations, and the existence of a nondiffusible anion (A^-) inside but not outside the cell.

are attracted to the interior of the cell by the negative potential that exists there. If the system came into equilibrium, the chemical and the electrostatic forces would be equal. This equilibrium is expressed by the Nernst equation for potassium:

$$E_K = -61.5 \log ([K^+]_i / [K^+]_o)$$

The right-hand term represents the chemical potential difference at the body temperature of 37° C. The left-hand term, E_K, represents the electrostatic potential difference that would exist across the cell membrane if K^+ were the only diffusible ion. E_K is called the *potassium equilibrium potential.* When the measured concentrations of $[K^+]_i$ and $[K^+]_o$ for mammalian myocardial cells are substituted into the Nernst equation, the calculated value of E_K equals about -90 to -100 mV. This value is close to, but slightly more negative than, the resting potential actually measured in myocardial cells. Therefore there is a small potential of about 10 to 15 mV. tending to drive K^+ out of the resting cell.

The balance of forces acting on the Na ions is entirely different in resting cardiac cells. The intracellular Na^+ concentration, $[Na^+]_i$, is much lower than the extracellular concentration, $[Na^+]_o$. At 37° C, the *sodium equilibrium potential,* E_{Na}, expressed by the Nernst equation is $-61.5 \log ([Na^+]_i / [Na^+]_o)$. For cardiac cells, E_{Na} is about $+40$ to $+60$ mV. At equilibrium, therefore, an electrostatic force of 40 to 60 mV., oriented with the inside of the cell more positive than the outside, would be necessary to counterbalance the chemical potential for Na^+. However, the actual polarization of the resting cell membrane is just the opposite. The resting membrane potential of myocardial fibers is about -80 to -90 mV. Hence both chemical and electrostatic forces act to pull extracellular Na^+ into the cell. The influx of Na^+ through the cell membrane is small, however, because the permeability of the resting membrane to Na^+ is very low. Nevertheless, it is mainly this small inward current of positively charged Na ions that causes the potential on the inside of the resting cell membrane to be slightly less negative than the value predicted by the Nernst equation for K^+.

The steady inward leak of Na^+ would cause a progressive depolarization of the resting cell membrane were it not for the metabolic pump that continuously extrudes Na^+ from the cell interior and pumps in K^+. The metabolic pump involves the enzyme, Na^+, K^+-activated ATPase, which is located in the cell membrane itself. Because the pump must move Na^+ against both a chemical and an electrostatic gradient, operation of the pump requires the expenditure of metabolic energy. Increases in $[Na^+]_i$ or in $[K^+]_o$ accelerate the activity of the pump. The quantity of Na^+ extruded by the pump slightly exceeds the quantity of K^+ transferred into the cell. Therefore, the pump itself tends to create a potential difference across the cell membrane, and thus it is termed an *electrogenic pump.* If the pump is partially inhibited, as by large doses of digitalis, the concentration gradients for Na^+ and K^+ are partially dissipated, and the resting membrane potential becomes less negative than normal.

The dependence of the transmembrane po-

tential, V_m, on the intracellular and extracellular concentrations of K^+ and Na^+ and on the permeabilities (P_K and P_{Na}) to these ions is described by the Goldman constant-field equation for Na^+ and K^+:

$$V_m = -61.5 \log \frac{[K^+]_i + (P_{Na}/P_K)[Na^+]_i}{[K^+]_o + (P_{Na}/P_K)[Na^+]_o}$$

For a given ion, the permeability, P, is defined as the net quantity of the ion that diffuses across each unit area of membrane per unit concentration gradient and per unit membrane thickness. It is apparent from the constant-field equation that it is the relative permeabilities to Na^+ and K^+, and not the absolute magnitude of each permeability, that determine the resting potential. In the resting cardiac cell, because P_{Na} is so much less than P_K (that is, $P_{Na}/P_K \cong 0.01$), the Goldman equation reduces essentially to the Nernst equation for K^+. When the ratio $[K^+]_i/[K^+]_o$ is decreased experimentally by raising $[K^+]_o$, the measured value of V_m (dashed line, Fig. 2-5) approximates that predicted by the Nernst equation for K^+ (continuous line). For extracellular K^+ concentrations of about 5 mM. and above, the measured values correspond closely with the predicted values. The measured levels are slightly less than those predicted by the Nernst equation because of the small but finite value of P_{Na}. For values of $[K^+]_o$ below about 5 mM., it has been found that the membrane properties become altered, such that there is a progressive reduction in P_K as $[K^+]_o$ is diminished. As P_K is decreased, the effect of the Na^+ gradient on the transmembrane potential becomes relatively more important, as predicted by the constant-field equation. This change in P_K accounts for the greater deviation of the measured V_m from that predicted by the Nernst equation for K^+ at low levels of $[K^+]_o$ (Fig. 2-5). Also, in accordance with the constant-field equation, changes in $[Na^+]_o$ have relatively little effect on resting V_m (Fig. 2-6), because of the low value of P_{Na}.

Ionic basis of the fast response

Any process that abruptly changes the resting membrane potential to a critical value (called the *threshold*) will result in a propagated action potential. The characteristics of fast response action potentials resemble those shown on the left side of Fig. 2-3. The rapid depolarization that takes place during phase 0 is related almost exclusively to the inrush of Na^+ by virtue of a sudden increase in the permeability of the cell membrane to Na^+. The amplitude of the action potential (the magnitude of the potential change during phase 0) varies linearly with the logarithm of $[Na^+]_o$, as shown in Fig. 2-6. When $[Na^+]_o$ is reduced from its normal value of about 140 mM. to about 10 to 30 mM., the cell is no longer excitable.

The physical and chemical forces responsible for these transmembrane movements of Na^+ are explained in Fig. 2-7. When the resting membrane potential, V_m, is suddenly changed to the threshold level of about -60 to -70 mV., there is a dramatic change in the properties of the cell membrane. It is believed that *fast channels* for Na^+ exist in the membrane, and that the flux of Na^+ through these channels is controlled by two polar components, referred to as "gates." The opening and closing of these gates are governed principally by the electrostatic charge, V_m, across the membrane. One of these gates, the *m* gate, tends to open the channel as V_m becomes less negative and is therefore called an *activation gate*. The other, the *h* gate, tends to close the channel as V_m becomes less negative and hence is called an *inactivation gate*. The *m* and *h* designations were originally employed by Hodgkin and Huxley in their mathematical model of conduction in nerve fibers.

With the cell at rest, V_m is about -80 to -90 mV. At this level, the *m* gates are closed and the *h* gates are wide open, as shown in Fig. 2-7, *A*. The concentration of Na^+ is much

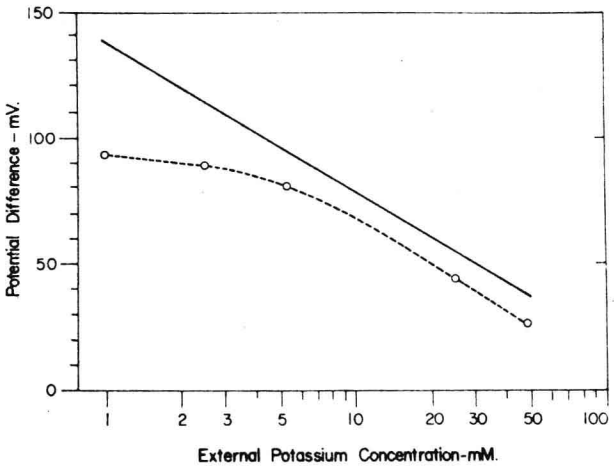

Fig. 2-5. Transmembrane potential of a cardiac muscle fiber varies inversely with the potassium concentration of the external medium (dashed curve). The continuous line represents the change in transmembrane potential predicted by the Nernst equation for E_K. (Redrawn from Page, E.: Circulation **26**:582, 1962.)

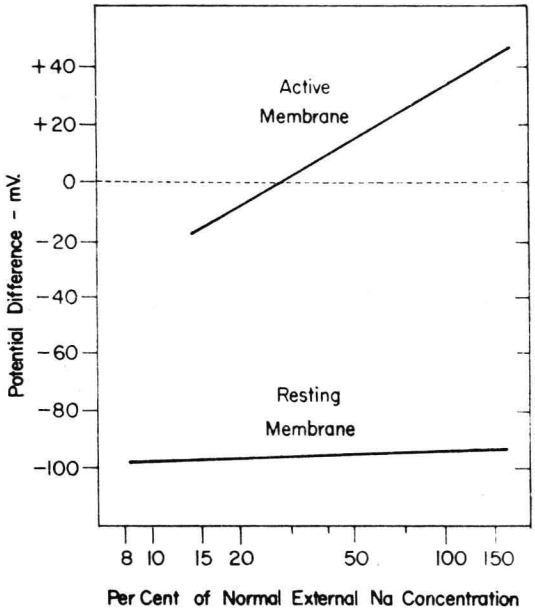

Fig. 2-6. Concentration of sodium in the external medium is a critical determinant of the amplitude of the action potential in cardiac muscle (upper curve) but has relatively little influence on the resting potential (lower curve). (Redrawn from Weidmann, S.: Elektrophysiologie der Herzmuskelfaser, Bern, 1956, Verlag Hans Huber.)

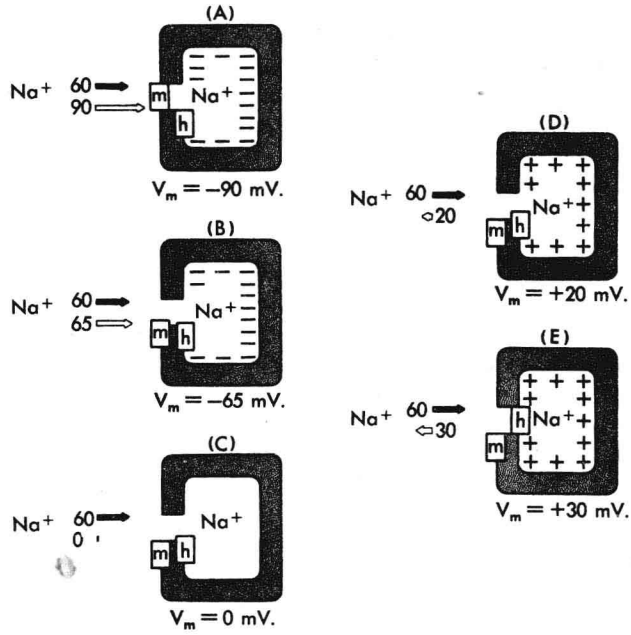

Fig. 2-7. The Na^+ permeability of a cardiac cell membrane during phase 4 (panel *A*) and during various stages of phase 0, when the transmembrane potential (V_m) had attained values of −65 mV. (panel *B*), 0 mV. (panel *C*), +20 mV. (panel *D*), and +30 mV. (panel *E*). The positions of the *m* and *h* electrostatic gates in the fast Na^+ channels are shown at the various levels of V_m. The electrostatic forces are represented by the white arrows, and the chemical (diffusional) forces by the black arrows.

greater outside than inside the cell, and the interior of the cell is electrically negative with respect to the exterior. Hence, both chemical and electrostatic forces are oriented to draw Na^+ into the cell. The electrostatic force in Fig. 2-7, *A*, is a potential difference of 90 mV., and it is represented by the white arrow. The chemical force, based on the difference in Na^+ concentration between the outside and inside of the cell, is represented by the black arrow. For a Na^+ concentration difference of about 130 mM., a potential difference of 60 mV. (inside more positive than the outside) would be necessary to counterbalance the chemical, or diffusional, force, according to the Nernst equation for Na^+. Therefore, we may represent the net chemical force favoring the inward movement of Na^+ in Fig. 2-7 (black arrows) as being equivalent to a potential of 60 mV. With the cell at rest, therefore, the total electrochemical force favoring the inward movement of Na^+ is 150 mV. (panel A). The *m* gates are closed, however, and therefore the permeability of the resting cell membrane to Na^+ is very low. Hence, virtually no Na^+ moves into the cell; that is, the *inward Na^+ current* is negligible.

Any process that tends to make V_m less negative tends to open the *m* gates, thereby "activating" the fast Na^+ channels. The activation of

the fast channels is therefore called a *voltage-dependent* phenomenon. The potential at which the *m* gates swing open varies somewhat from channel to channel in the cell membrane. As V_m becomes progressively less negative, therefore, more and more *m* gates will open. As the *m* gates open, Na^+ enters the cell (Fig. 2-7, *B*), by virtue of the chemical and electrostatic forces referred to before.

The entry of positively charged Na^+ into the interior of the cell tends to neutralize some of the negative charges inside the cell and thereby tends to diminish further the transmembrane potential, V_m. The resultant reduction in V_m, in turn, tends to open more *m* gates, thereby producing a still greater increase in the inward Na^+ current. Hence, this is called a *regenerative process*.

As V_m approaches the threshold value of about −65 mV., the remaining *m* gates rapidly swing open in the fast Na^+ channels, until virtually all of the *m* gates are open (Fig. 2-7, *B*). There is a rapid inrush of Na^+, which produces an abrupt reduction of V_m. This accounts for the rapid rate of change of V_m during phase 0 of the action potential (Fig. 2-1). The maximum rate of change of V_m (that is, the maximum dV_m/dt) has been found to be from 100 to 200 V./sec. in myocardial cells and from 500 to 1000 V./sec. in Purkinje fibers. Although the quantity of Na^+ that enters the cell during one action potential alters V_m by over 100 mV., it is too small to change the intracellular Na^+ concentration measurably. Therefore, the chemical force remains virtually constant, and only the electrostatic force changes throughout the action potential. Hence, the lengths of the black arrows in Fig. 2-7 remain constant at 60 mV., whereas the white arrows change in magnitude and direction.

As the Na^+ rushes into the cardiac cell during phase 0, the negative charges inside the cell are neutralized, and V_m becomes progressively less negative. When V_m becomes zero (Fig. 2-7, *C*), there is no longer an electrostatic force pulling Na^+ into the cell. As long as the fast Na^+ channels are open, however, Na^+ continues to enter the cell because of the large concentration gradient that still exists. This continuation of the inward Na^+ current causes the inside of the cell to become positively charged with respect to the exterior of the cell (Fig. 2-7, *D*). This reversal of the membrane polarity is the so-called overshoot of the cardiac action potential, which is evident in Fig. 2-1. Such a reversal of the electrostatic gradient would, of course, tend to repel the entry of Na^+ (Fig. 2-7, *D*). However, as long as the inwardly directed chemical forces exceed these outwardly directed electrostatic forces, the net flux of Na^+ will still be inward, although the rate of influx will be diminished. The inward Na^+ current finally ceases when the *h* (inactivation) gates close (Fig. 2-7, *E*).

The activity of the *h* gates is governed by the value of V_m just as is that of the *m* gates. However, whereas the *m* gates tend to open as V_m becomes less negative, the *h* gates tend to close under this same influence. Furthermore, the opening of the *m* gates occurs very rapidly (in about 0.1 to 0.2 msec.), whereas the closure of the *h* gates is a relatively slow process, requiring 1 msec. or more. Phase 0 is finally terminated when the *h* gates have closed and have thereby "inactivated" the fast Na^+ channels.

The *h* gates then remain closed until the cell has partially repolarized during phase 3 (at about point *D* in Fig. 2-1). Until these gates do reopen partially, the cell is refractory to further excitation. This mechanism therefore prevents a sustained, tetanic contraction of cardiac muscle, which would of course be inimical to the intermittent pumping action of the heart.

In cardiac cells that have a prominent plateau and especially in Purkinje fibers, phase 1 constitutes an early, brief period of limited repolarization between the end of the upstroke and the beginning of the plateau. This early phase of repolarization has been ascribed to a