CARDIOVASCULAR DYNAMICS

Fourth Edition

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Preface to the Fourth Edition

The basic objectives and approaches of *Cardiovascular Dynamics* are unchanged from the previous edition. Reliance on schematic representation remains a central theme, and the work attempts to convey concepts regarding the mechanisms by which organs function and are controlled rather than focusing on the quantitative aspects of physiological data derived from controlled experiments on experimental animals. During the past decade, the technologies of measurement have advanced so rapidly that it is now possible to elicit from normal human subjects without discomfort or hazard information that could previously be measured only in the physiology laboratory. In recognition of progress in clinical instrumentation, a new chapter was added to direct attention to the methods of measurement of hemodynamic phenomena (Chapter 2). If there appears to be excessive emphasis on the applications of ultrasound as a source of cardiovascular information, this can be explained, if not excused, on the basis of the great interest in this type of energy probe for many years in my own laboratory. The functional anatomy of the heart and its control were combined into a single chapter (Chapter 3), which includes some diverse views regarding the basic nature of cardiac responses to stresses and loads.

The origins and functional significance of atherosclerosis receive somewhat more attention in this edition than in previous ones because of its recognized importance. In response to suggestions from friends and colleagues, some material on hypertrophy and myopathies was included in the last chapter (Chapter 14).

I acknowledge with thanks the contributions of Dr. Warren Guntheroth for his help in revising Chapters 8 and 12 and Dr. John Blackmon for his contributions to Chapters 13 and 14. Dr. Gene Strandness provided the material on diagnosis of peripheral vascular disease in the third edition and much of this material is presented with the discussion of atherosclerosis in Chapter 9. Dr. Dennis Reichenbach was kind enough to provide electron micrographs of heart muscle and blood capillaries. Dr. Steve Johnson provided echocardiograms of the heart from his extensive files.

ROBERT F. RUSHMER, M.D.

Acknowledgments

A book of this sort represents a small sample of facts and concepts selectively extracted from a vast store of material on the subject. The final content of this manuscript has been greatly influenced by a series of investigations accomplished in association with a closely knit research team representing several fields of interest. The ingenuity, persistence and technical competence of this group were indispensable to the successful completion of the studies summarized in this text. The various research projects were supported in part by grants from the National Heart Institute of the National Institutes of Health, United States Public Health Service; the Washington State Heart Association and the American Heart Association.

I gratefully acknowledge the wholehearted cooperation of the W. B. Saunders Company in the production of the book.

Most of the illustrations from the first edition were designed and executed by the author, although many were refined and labeled by Miss Jessie Phillips, Miss Virginia Brooks, Mrs. Mary Jane Owens and Ms. Hedi Nurk.

The contributions of Dr. Warren Guntheroth, Dr. John Blackmon, and Dr. D. E. Strandness to the third edition and their aid in the current revision are gratefully acknowledged. They have added an important clinical flavor to the discussions of various forms of cardiovascular disease presented in the later chapters of the book.

Several of the original illustrations in this book first appeared in articles by the author and his associates in the following journals: *American Journal of Physiology* (Fig. 7–6); *Circulation* (Fig. 5–2); *Circulation Research* (Figs. 3–14, 5–10); *Handbook of Physiology, Section II, Vol. I* (Figs. 3–31, 6–13, 6–14); *Physiological Reviews* (Fig. 7–4). I wish to express my appreciation to the publishers of these journals for permission to reproduce the illustrations.

ROBERT F. RUSHMER, M.D.

Preface to the Third Edition

Cardiovascular Dynamics is an extensive revision, enlargement and reorganization of a book originally published under the title *Cardiac Diagnosis: A Physiologic Approach.* The components of the cardiovascular system are presented in terms of their structure, function and control under normal conditions, followed by consideration of the changes induced by common disease states. This text was designed for students of the cardiovascular system in the broadest sense—from first year medical students to experienced cardiologists. It is specifically intended for use in vertical teaching, i.e., as a supplemental text for courses in Physiology, Physical Diagnosis and Clinical Cardiology.

The most important forms of cardiovascular disease are included among the examples employed to elucidate the nature of abnormal cardiovascular function. However, the text is not intended as a handbook for the practice of cardiology since it was not considered appropriate to detail all forms of cardiovascular disease.

With the passage of years, the most significant deficiency of the second edition of *Cardiovascular Dynamics* appeared to reside in the treatment of the examples of cardiovascular diseases from the clinical point of view. Circumstances have caused me to become progressively divorced from the continuous contact with patients required to maintain clinical competence. Responsibility for preparing the chapters dealing with cardiovascular diagnosis and management has been delegated to some colleagues whose knowledge of these subjects is vastly greater than my own. We all trust that this step will render the third edition more authoritative and useful for the cardiologists than the previous ones.

Many of the same illustrations are utilized since the basic concepts of cardiovascular function, control and disease have not changed too much in the past few years. New illustrations have been prepared according to the same objectives and approaches as in previous editions wherever possible.

Important ideas in each chapter have been illustrated in order to facilitate discussion and visualization of concepts. The figures are intended to explain ideas rather than offer evidence for arguments. Realism in the schematic drawings has been retained as much as possible to provide visual images of physiologic and pathologic mechanisms in situ rather than abstractions. The legend for

each figure is self-explanatory and the illustrations are thus rendered independent of the text. Cross references are made to figures rather than text pages in the belief that it is more efficient to refresh the memory by studying pictures than by re-reading the text.

Graphs and tables have been avoided for two reasons: (*a*) their interpretation is often difficult and tedious and (*b*) it seems more important to understand why certain phenomena occur rather than how much specific variables are altered under experimental conditions. Graphs tend to suggest cause-and-effect relations which may not exist. When experimental records are reproduced, a schematic representation of the experimental method is included in most instances.

At the risk of appearing excessively biased, I have tried to avoid exhaustive presentations of conflicting viewpoints. If a single hypothesis appeared adequate to explain a particular phenomenon, alternative explanations have not necessarily been included. Attention has been directed to many deficiencies in current knowledge which can be corrected only by further investigations.

ROBERT F. RUSHMER, M.D.

Contents

CHAPTER ONE

Properties of the Vascular System

The human organism begins as a single cell and through progressive stages of growth tends to retrace the full evolutionary pathway over uncounted eons. In the process of embryological development, the fertilized egg cell divides until the average fetus weighs something over 7 pounds and contains some 2,000,000,000,000 cells, averaging only about 20 micrometers or 0.02 mm. in diameter. The newborn baby does not survive unless gas exchanges with the external environment are promptly established by rapid accommodations of both the pulmonary and cardiovascular systems. In humans, the advanced degree of cellular specialization and consequent dependence on uninterrupted supply of life-giving materials is indicated by the effects of arresting the circulation to vital organs. For example, cessation of blood flow to the brain for only a few seconds produces unconsciousness and for a few minutes more leads to irreparable brain damage. In contrast, a tourniquet on a limb for half an hour produces temporary paralysis, with complete recovery of function a few minutes after release of the constriction.

The differences in the degrees of specialization and the rates of metabolism of specialized cells dictate the required rates of delivery of the essential ingredients for their function. Obviously, uninterrupted exchanges are essential for the function of the brain or of contracting muscle (like the heart), while less specialized cells functioning at lower levels of activity can survive and function under less ideal circumstances. For cells involved in energy transformations, the most crucial requirement is an adequate delivery of oxygen—the substance with maximal rates of utilization and relatively limited storage capacity.

Maintenance of vital processes within living cells is dependent upon continuity of exchanges with their external environment. Simple, unicellular microorganisms are completely immersed and enveloped by relatively enormous volumes of surrounding water from which they can derive their essential requirements. The delivery of required metabolic fuels, oxygen and other components to the cell surface is based on a combination of diffusion and convection.

The Nature of Diffusion

Diffusion is the process by which substances are dispersed from regions

of higher concentration to regions of lower concentration. It is common experience that a drop of dye placed in a container of fluid will promptly begin to spread in all directions even if the liquid is motionless and not stirred (Fig. 1–1*A*). Over a period of several hours, the dye molecules will penetrate to all portions of the liquid and become equally distributed throughout the entire volume. The dispersion of the dye molecules results from "thermal agitation" characterized by rapid movement and frequent collisions of molecules, commonly known as Brownian motion. The probability that a molecule will move in directions away from the region of high concentration is much greater than the likelihood that it would backtrack toward the region of higher concentration. As a result, more molecules are moving away from the source of dye than are moving toward it. The

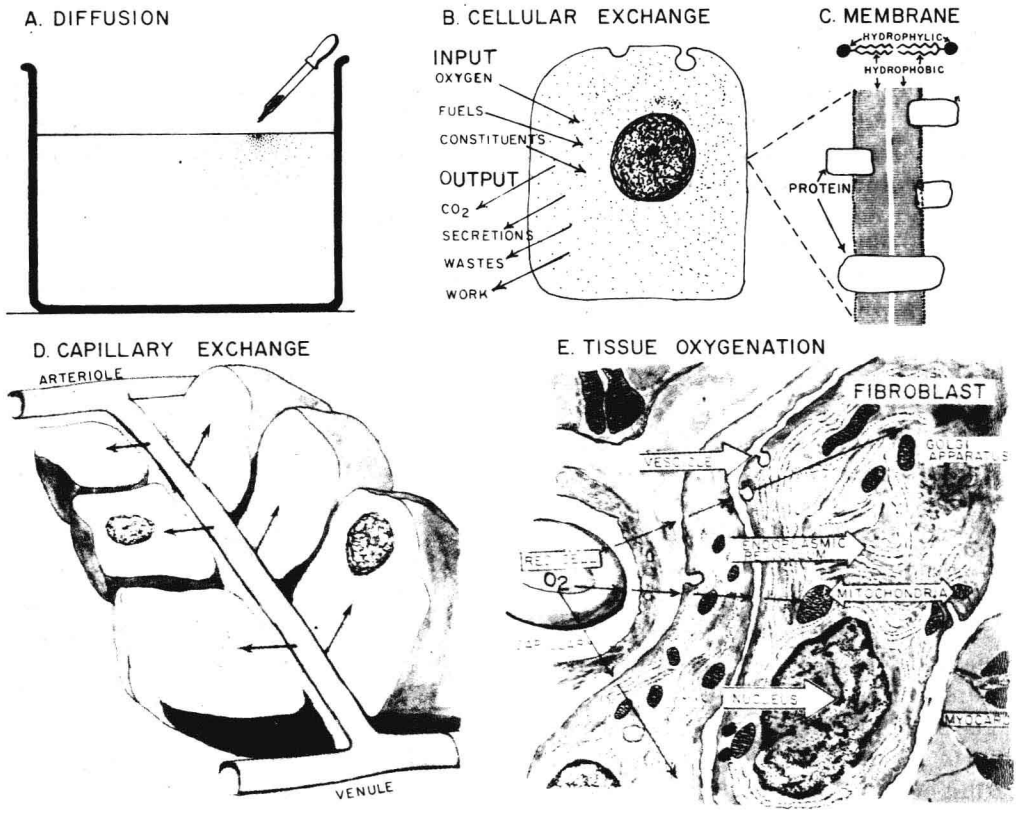

FIGURE 1–1

A, Diffusion is the process by which substances become equally distributed throughout contiguous liquids by movement of molecules from regions of high concentration to adjacent regions of lower concentration.

B, Essential materials diffuse into living cells by diffusion along concentration gradients, while metabolic products and wastes diffuse outward through cell membranes to extracellular spaces.

C, The cell membranes are believed to be composed of double layers of molecules oriented with water soluble complexes facing outward and lipid soluble ends of molecules oriented toward the center of the membrane.

D, The anatomical relation between blood capillaries and living cells is illustrated schematically to indicate how materials can be transported by circulation in the blood and by diffusion from blood to tissue cells.

E, The body cells are comparable to miniature chemical factories, and the complexity of their structure imposes obstacles to the free diffusion of materials from blood to the sites of metabolic processes inside the cells.

process of diffusion affects each ion or molecule individually. For example, if a drop of dye, a lump of sugar and a small quantity of urea were introduced into three different regions of the container, each will move independently away from its site of higher concentration and independently achieve uniform distribution throughout the entire volume of water.

The process of diffusion occurs slowly over long distances but extremely rapidly over very short distances. For instance, a molecule of water could theoretically move from a man's head to his foot without any circulation or convection of his body fluids, but the process would require over 100 years on the average. If a cylinder of tissue 1 cm. in diameter were suddenly immersed in an atmosphere of oxygen, it would become 90 per cent saturated in about 3 hours. In contrast, a cylinder of tissue 0.7 mm. in diameter would reach 90 per cent saturation with oxygen in only about 54 sec. and a nerve cell only 7 micrometers (μm.) in diameter would require only 0.0054 sec. for 90 per cent saturation. The rate of diffusion is dependent upon the concentration gradient, that is, the relationship between the distance of diffusion and the difference in concentration across that distance. As the distance of diffusion from the surface to the center of tissues is reduced, the concentration gradient becomes steeper and the rate of diffusion is accelerated.

A single cell of small dimensions can survive by diffusion alone if it is bathed in a large expanse of liquid with which it can effect the essential exchanges (Fig. 1–1*B*). As the cell utilizes its oxygen, the concentration of this substance diminishes within the cell, establishing a concentration gradient which impels oxygen molecules from the surrounding fluid through the cell membrane and into the cell protoplasm. The more rapid the rate of utilization, the steeper the concentration gradients and the more rapidly the molecules move in through the cell membrane. The substances which are produced within the cell, either by combinations or dissociation of molecules, attain higher concentrations within the cell, producing diffusion gradients that propel them outward into the extracellular fluid. Increased amounts of CO_2 and other waste products establish outward concentration gradients toward the external environment. Heat produced by cellular metabolism is dissipated by thermal gradients. The diffusion of substances into cells or through tissues is complicated by the barriers imposed by tissue stroma, cell membranes and cell protoplasm (Fig. 1–1E).

Cell Membranes

Membranes are involved in virtually all cell processes. Cytoplasmic membranes form the outer envelopes, enclose the structure of cells and play a role in regulating the internal environment. The permeability of the cell membrane for various types of ions and molecules helps to establish and maintain a marked difference in composition between the intracellular and extracellular fluids. In addition, this external membrane is involved in active transport of materials against concentration gradients and in the maintenance of a substantial electrical potential. Other membranes within the cell are seen to enclose important internal structures, such as the nucleus, mitochondria and lysosomes, and to form the endoplasmic reticulum. The mitochondrial membrane is believed to be the site of manufacture

of adenosine triphosphate (ATP), which is the basic energy source for metabolic activity. There is widespread agreement that the external and internal membranes have many features in common.

Cell membranes are envisioned as double layers of molecules composed of pairs of lipid molecules joined by a glycerol group at the "head" end. The paired fatty acid chains are insoluble in water (hydrophobic) and extend inward toward the center of the membrane. The phospholipid end of the molecule is hydrophylic and is oriented toward the external surface of the membrane (Fig. 1–1*C*). The two layers are arranged back-to-back to present the hydrophylic surfaces to the inside of the cell and to the outside environment, with the lipid chains forming a highly structured lipid barrier sandwiched between them. The bilayer is about 45 nanometers (nm.) thick and serves as an anchorage for the other major component of the membrane—namely, protein. Protein molecules are associated with the membrane either by being loosely attached to the surface or by forming integral parts of the membrane (Fig. 1–1*C*). Thus, the affiliated proteins and glycoproteins can be viewed as contributing to the structural integrity of the membrane, serving as enzymes or as pumping mechanisms for transport of materials into or out of the cells. The many different functions of membranes are attributable to the diversity of proteins involved. Their various functions are under intensive study. For example, important functions are subserved by active sites on the mitochondria and the endoplasmic reticulum in energy transformations and protein synthesis, respectively. The role of cell membranes in the excitability of cells (myocardium) will be considered in greater detail in subsequent sections (see Chapter 8).

Oxygen Delivery by Tissue Capillaries

In a large, complex mass of cells, like the mammalian body, rapid diffusion along steep concentration gradients is achieved by providing a continuous flow of blood in the vicinity of all the cells. The streams of blood must necessarily be distributed through channels which impose minimal retardation to diffusion through their walls. These requirements are satisfied by hundreds of millions of thin-walled capillaries distributed profusely throughout every portion of the body. The number of capillaries per volume of tissue (capillary density) reflects the types and levels of activity of the individual tissues. A simplified version of the relation of these thin-walled capillaries to metabolically active tissue cells is presented in Figure 1–1*D*.

Blood with high concentrations of oxygen and low concentrations of carbon dioxide is brought into the immediate vicinity of each cell. Thus, the diffusion distances are minimized and steep concentration gradients are maintained so long as blood flows without interruption. The concentration gradients are steepest at the arteriolar end of the capillary and tend to flatten toward the venous end of the capillary as exchanges occur along its length. Even a temporary cessation of blood flow in capillaries is promptly followed by flattening of the concentration gradients as the various constituents of the fluids approach uniform dispersion through the region.

The rates at which these exchanges occur can stress the imagination, as described below.

The diffusion of substances through water (Fig. 1–1*A*) is far easier to visualize and study than the movement of molecules through complex heterogeneous structures like living cells. The internal organization of cells, as revealed by electron microscopy, is intricate and complicated; this is suggested by the schematic diagram in Figure 1–1*E*. At the left margin is a capillary containing a red blood cell (erythrocyte). The very thin capillary wall is seen to contain numerous opacities and clear circular areas (vesicles). Just outside the capillary is a sparse extravascular space containing intracellular materials. A slender cell process, containing many oval bodies, some with intricate internal structures like a many-folded membrane (mitochondria) and others appearing more homogeneous (lysosomes), may be seen. A large ovoid nucleus in the lower center is surrounded by an intricate pattern of channels (endoplasmic reticulum). In the external membrane of this cell are invaginations that appear to be stages in the development of vesicles by elaboration of cell membranes to form pouches which close off to engulf a sample of the material in the extracellular space or to release materials from within the cell to the outside (see *Phagocytosis and Pinocytosis* below).

Since the internal composition of cells is known to be different from the extracellular environment, it is clear that the movement of material across the cell membranes and cytoplasm may occur either by diffusion or by active transport. The process of diffusion may well be retarded for certain substances by some of these structures. Other substances may be actively transported, even unidirectionally, by chemical binding or pumping mechanisms. One intriguing conceptual mechanism for active transport is the process commonly called pinocytosis.

Phagocytosis and Pinocytosis

It is not too difficult to imagine how oxygen can penetrate a cell membrane with ease. It is a relatively small molecule and is somewhat soluble in fat. However, many constituents of cells, up to and including proteins, are rather large molecules. For example, some cells exude collagen or excrete protein, catalytic enzymes or hormonal secretions, and these must somehow penetrate the complex cell membranes. The process of engulfing particles (phagocytosis) has long been well established for unicellular organisms and certain blood cells. The electron microscope displays large numbers of vesicles in cells and deep invaginations in the external cell membranes that appear to be developing into vesicles. The process of vesicle formation in the external cell membranes is called pinocytosis (cell drinking) and is frequently envisioned as a means by which large molecules and even particles might pass into the internal cellular protoplasm or completely through cells, to be released on the opposite side. The exact role of pinocytosis in transport across cell membranes remains a subject for debate (see *The Structure of Capillary Walls*, page 19).

Ultrastructure of Tissues

The natural tendency toward generalization and simplification in at-