Modern Cardiovascular Physiology

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Preface

During the past 20 years, research has revitalized cardiovascular physiology. Discoveries of lasting value have been made in cell physiology, rheology, microcirculation, regulation, and, most important, transport. Much of this information has not yet been incorporated into the thinking of scientists and physicians. The title of this book reflects emphasis on these subjects, and their relevance to medicine and research.

The book is intended for both medical and graduate students. The latter may choose to ignore some of the more clinically oriented material. For convenience, such passages are identified in the margin by the heading Clinical Application. The book should also be useful to cardiology fellows and clinicians interested in updating their knowledge. It is assumed that the reader has been exposed to basic biochemistry and histology; cell physiology and anatomy are helpful but not essential.

Two themes pervade the book. The first is the concept of a factor of safety or reserve of function. The second is the systems concept. The text is divided into five parts. The first two deal with the biophysical essentials. The third is concerned with microcirculation and transport, especially O_2 transport. The fourth describes the special features of selected regional circulations. This idiosyncratic material has been simplified by use of a common approach. The final part develops the regulation of pressure, flow, and volume and the integration of cardiovascular controls with voluntary behavior.

It is essential to know the facts, but this is merely the first step in understanding. One must then organize facts around principles or generalizations. Care has been taken to state unifying ideas explicitly. Finally, one must learn to apply information to practical problems; *if you cannot use it, you do not really know it.* The problem sets at the end of each part are to be regarded as integral to the text. Normal values and other aids are provided in the Appendixes to encourage quantitative thinking.

Experience indicates that long reference lists discourage supplementary reading. References are therefore highly selected.

Those titles marked with an asterisk are particularly recommended. The level of presentation can be raised appreciably by use of this material. Access to the literature is provided by citing recent reviews or monographs.

No text is free of error, and others might prefer a different emphasis or point of view. I would be most grateful for critical comments from students and colleagues.

C. R. H.

Acknowledgments

I deeply appreciate the support of The University of Rochester and of my colleagues in the Department of Physiology during the years the book was written. The University of Hawaii provided a haven, essential for continuity of thought. Every chapter was reviewed by at least one nationally recognized expert. To each reviewer I again offer my heartfelt thanks. I also thank the many authors and publishers who granted permission to use their material. In many instances modification was required for didactic reasons. Responsibility for errors and change of emphasis introduced by such modifications is entirely mine. Ms. Eileen Williams typed the entire manuscript, Mrs. Joyce Latone prepared all the original illustrations, and the friendly staff at Little, Brown and Company provided expert assistance throughout.

The book could not have been written without my wife's constant encouragement and support. Her contribution in library research and manuscript preparation was invaluable. Indeed, working together on *our* book has been one of the most rewarding aspects of authorship.

C. R. H.

Overview, Concepts, and Themes

First things first: The circulation is a *transport system,* which delivers O_2, substrate, and essential nutrients to individual cells and removes CO_2, urea, and heat to the environment. In addition to these external exchanges, the circulation moves metabolites into and out of storage depots and brings clotting factors, antibody, and leukocytes to sites of injury. Finally, by transporting hormones to receptor sites, the circulation serves as a major channel of intercellular communication. Most of this text is concerned with properties of cardiovascular muscles and the intricacies of hemodynamics and regulation—in other words, with how the circulation works. In considering these *means* it helps to constantly ask oneself how they contribute to transport *ends.*

Properties of the Heart

The first requirement for a transport system based on bulk flow is a suitable pump. The power and reliability of the human heart are astonishing. It performs about 10^9 strokes every day, without ever resting more than a few hundred milliseconds. Daily, it lifts about 1000 kg (1 metric ton) 10 meters and in the course of a lifetime performs about 1000 kilowatt-hours of external, useful work. This performance cannot be matched by any inanimate device. The reason, of course, is that the heart is constantly being renewed and remodeled by metabolic turnover of its chemical components. The heart beating in your chest today is not the same one that served you a year ago.

The heart's reliability is due not only to metabolic repair but also to its intrinsic physiological properties. It does not need the central nervous system to tell it what to do. It can beat rhythmically and even adjust its output over a modest range outside the body, if given proper support. Cardiac rhythmicity depends on electrical properties of the surface membrane that allow certain cells to act as pacemakers. Other membrane properties insure that the stimulus is distributed so rapidly that all ventricular muscle cells contract in unison. This intercellular communication is essential for life; only if contraction is coordinated can the heart develop tension in its walls and pressure on its contents. Many diseases alter cardiac rhythm, cell-to-cell conduction, or

both. Rational diagnosis and therapy of these disorders demand thorough understanding of the underlying ionic mechanisms.

The salient mechanical property of the heart is its response to stretch. If distended by an increase in venous return, it automatically contracts more strongly and empties itself of the larger volume. In this way an isolated heart can regulate its own contractility. Nevertheless, cardiac nerves play an essential role. Nerves create no new mechanism; they merely amplify, suppress, or change the rate of ongoing processes. This is true not only for the heart, but throughout physiology. For example, nerves control tension by modifying the heart's intrinsic response to stretch and change heart rate by modifying the normal pacemaker. The main effect is to extend greatly the *range* of cardiac output under conditions of stress.

According to the National Center for Health Statistics, diseases of the heart account for roughly half the deaths from all causes in the United States and other "developed" countries. If the heart is so powerful and reliable, why this rampant epidemic? The answer is that sclerotic disease of the coronary vessels can limit transport of O_2 and metabolites to the myocardium.

Adequacy of Transport

What constitutes "adequate" transport? On first thought, one might judge the circulation a success if each and every cell were as free of transport constraints as a unicellular organism in seawater. This ideal might have been attempted early in evolution, but, as animals became larger, literally billions of minute vessels were required. Perfect order in such populations was impossible, and large (though highly local) differences in microvascular geometry appeared.

The simplest way nature could have dealt with this heterogeneity would have been to set *mean* blood flow and the number of available capillaries high enough to insure delivery to each and every site at all times. This would correspond to our initial notion of "adequacy." To do this, however, the vast majority of tissue loci would have to be overperfused, and the size and energy cost of circulation would be enormous. Nature selected economy; transport was set to the minimum required by the bulk of the cell population, and carte blanche for all cells was abandoned.*

*Lung, kidney, skin, and portions of the gastrointestinal tract are exceptions to the rule that mean flow is the minimum necessary to nourish tissue. These organs are concerned with direct exchanges with the environment. Flow through them is controlled to support the exchanges and under most circumstances greatly exceeds the metabolic needs of the organs.

Local transport is modified by *active vasomotion.* The arterioles, which are the principal sites of resistance to flow, constrict and dilate, often rhythmically. Thus, local blood flow varies with time. Diffusion distances also vary, because only a fraction of the capillaries present in a tissue is perfused with erythrocytes under normal circumstances. Capillary control depends largely on vasomotion of sphincterlike structures at or near the capillary origin. By rotating the location of sites at which transport is insufficient, active vasomotion permits *mean* flow and capillarity to be much lower than would be possible otherwise. Other functions of active vasomotion will be developed in Chapters 18 and 19. In view of the heterogeneity of the microcirculation, judgments about the "adequacy" of transport must be based on very large cell populations. The simplest and most practical criterion is the ability to perform a physiological function. For example, circulatory adequacy for a contracting muscle can be judged by ability to develop tension.

Conflicting Functions and Circulatory Priorities

The mammalian circulation permits an incredible range of activity; in world-class athletes the rate of O_2 consumption ($\dot{V}O_2$) may briefly increase 25-fold! Maximal function of all organs cannot be supported simultaneously, however, so a system of priorities is required. These priorities are based on the metabolic needs of the individual organs, as determined locally, and the requirements of the whole animal, as determined by the brain.

The various organs are connected in parallel, so resistance to flow through each of them can be altered separately. The brain controls resistances by means of nerve mediators that cause minute vessels to constrict or dilate. Local controls depend largely on vasodilator substances whose release is coupled to tissue metabolism. Neural and metabolic controls operate as a system of checks and balances. If the brain "throttles" flow to an organ, metabolic controls can override it and prevent tissue injury. Conversely, local controls can be restrained in the interests of the animal. Some examples should clarify these ideas.

A built-in mechanism independent of the brain dilates vessels in skeletal muscle when work begins. This increases flow. However, the extent of the increase depends not only on the vessels but also on the output of the heart and the fraction of that output available to muscle. Initially, the central nervous system stimulates the heart and limits flow to skin, kidney, and GI tract. Thus extrinsic and intrinsic controls act together to increase muscle flow.

As work goes on, body temperature rises, because heat production is high and heat loss is decreased by low skin flow. The rise in temperature is detected by the brain, which now must choose between support of muscle contraction and defense of body temperature. Temperature has the higher priority; cutaneous vessels dilate, flow is diverted from muscle to skin, and maximum muscle work can no longer be sustained. The reverse situation (neural controls overriden in the interest of local metabolism) is also important, not only in the normal animal, but also in the development of shock.

The two most flow-dependent organs are the heart and the brain. They are continuously active, have a high metabolic rate, and are essential for life. Coronary and cerebral vessels have exceptionally powerful metabolic controls, whereas their extrinsic neural controls are weak. This imbalance implements their high priority for flow; in adversity, the heart and the brain have the first crack at the cardiac output.

Reserves and Safety Factors

Priorities are necessitated by limits or maxima. However, physiological systems seldom operate "flat out," and then only briefly; recall our discussion of maximal exercise. The difference between the usual value of some parameter or function and its maximum should be regarded as a *reserve,* which can be called upon to compensate for stress or disease. For example, an athlete's cardiac output may be 5 liters per minute at rest and 25 liters per minute during brief maximal effort. The difference of 20 liters per minute is the athlete's reserve of cardiac output. Often it is preferable to express the reserve in relative terms, i.e., the cardiac output can be expanded fivefold. A list of reserves and expansion factors for cardiovascular variables is provided in Appendix 3.

A related concept is that of a factor of safety. This refers to the ability of a system to function well over a wide range of some parameter. A good example is O_2 transport in blood. About 99 percent of the O_2 is bound to hemoglobin. The extent to which hemoglobin is saturated with O_2 depends on the partial pressure of O_2 (PO_2): Hemoglobin is about 95 percent saturated at 100 mm Hg PO_2 and 90 percent saturated at 60 mm Hg. Thus PO_2 can fall 40 mm Hg with little effect on O_2 transport. The range 60 to 100 mm Hg is a *factor of safety* for PO_2. The concept implies that disaster may follow if the margin of safety is exceeded, and this is often the case.

The effect of any stimulus is conditioned by the reserve of the function(s) under consideration. For example, the larger the cardiac output reserve, the longer an increase in cardiac output can be maintained, as explained in Chapter 16. One of the principal

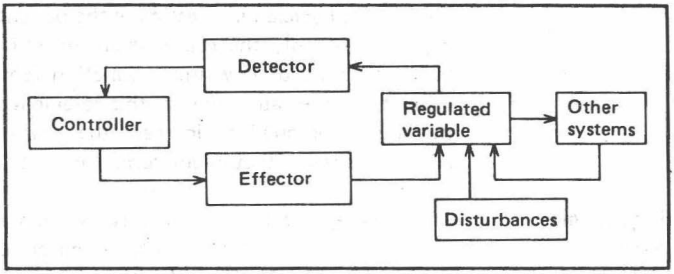
tasks of a physician is to estimate the patient's reserves. Diagnosis includes not only the cause of an illness but also a semiquantitative estimate of how much function remains. Prognosis is an estimate of the rate at which this reserve may disappear. Finally, therapy is designed to increase the reserve and to prevent or eliminate stresses that might compromise it.

Physiological Systems

Concepts related to systems pervade modern science and medicine. A system is a set of interacting components with special properties that arise from the interactions. For example, a watch is a set of interacting gears and springs that has the property of telling time. The same components are not a system if interaction is prevented; a pile of watch parts will not tell time. To use a system we need not identify its components or know how it works; we can consider it a "black box" that does something. For example, we can use a watch without knowing whether it contains a spring or battery.

Physiologists are mainly concerned with temporal and causal relations: A stimulus (cause, input to a system) produces a certain response (effect, output). The output of many physiological systems is an appropriate, though not necessarily constant, value of some variable, such as blood pressure, despite the tendency of extraneous factors to cause inappropriate change. Variables appropriately adjusted by a system are said to be *regulated.* Regulatory systems consist of a *controller,* an *effector,* and a *detector.* The cardiovascular effectors are muscle cells. The controller is usually the brain and autonomic nerves, and the detector is generally a bioelectric transducer that converts the value of the regulated quantity into action potentials in a sensory nerve. Not all systems depend on nerves, however. The important *autoregulatory* systems discussed in Chapter 1 depend instead on built-in properties of the effectors. These intrinsic properties serve as transducer and controller.

It is convenient to summarize the organization of systems with diagrams as in the accompanying figure. The arrows mean "leads to," or "has an effect on." The way in which a system component transforms its input into an output is called its *transfer function.* Notice that the regulated variable is influenced by the output of other systems, and by disturbances. Consequently, the controller must know the value of the variable in order to keep it constant. This is why the detector (more often called receptor) is so important. It measures the regulated variable and feeds this information back to the controller. Notice in the figure that this results in a closed loop. *Feedback* is considered negative if it acts to minimize disturbances. All physiological



Conceptual diagram of a regulatory system based on negative feedback.

regulations are based on closed-loop, negative feedback systems. It follows that if a variable is regulated, a receptor for it exists. We shall see that the performance of neural systems that regulate circulation is often limited by the properties of the receptor and the feedback signal.

Certain drugs and diseases produce their effects by opening negative feedback loops; examples are considered in Part V. Alternatively, disease (or an experimental maneuver) may create a system where none normally exists. In most such instances, feedback is positive—it tends to promote disturbance. This in turn causes an even larger disturbance, and so on. Such conditions progress rapidly and are often fatal unless the positive feedback can be eliminated. Examples are cited in Chapter 9.

Reserves, safety factors, and concepts related to systems are themes that recur throughout this book. They should become part of your thinking, not only about circulation, but also about medicine and research generally.

Reference

Vital Statistics Rates in the United States, USPHS Publication #1677. Washington, D.C.: National Center for Health Statistics, 1977.

Contents

I : Properties of Cardiovascular Muscles

1 : Cardiac Mechanics: Starling's Law Updated

. . . the mechanical energy set free on passage from the resting to the contracting state depends on the area of chemically active surfaces, i.e., on the length of the muscle fiber. This simple formula serves to "explain" the whole behavior of the isolated mammalian heart . . .
—S. W. Patterson, H. Piper, and E. H. Starling, *J. Physiol.* 48:465, 1914.

And so we believe today. The formula is by no means simple, however, if we wish to substitute ultrastructural and chemical understanding for the word *explain.* (Note that Starling et al. qualified that word with quotation marks.) We begin at the molecular level, where some of the most basic properties of the heart are encoded in the structure and arrangement of the contractile proteins.[1]

The Sarcomere

Each cardiac muscle fiber is a single cell, about 100 μ long. Bundles of thick and thin filaments are interspersed between long rows of mitochondria. The latter account for more than one-third of cell volume, reflecting the high and constant aerobic metabolism that supports cardiac function. The filaments are arranged in linearly repetitive arrays called *sarcomeres,* delineated by a Z disc at either end; see Figure 1-1. The length of every sarcomere in a fiber is almost exactly the same, so the macroscopic fiber length (and muscle length) corresponds to a unique microscopic sarcomere length. These lengths vary with cardiac filling and other factors.

The Z disc consists of a fine mesh of filaments, rather like a hemp rope. The thin filament traverses and is anchored to the Z disc. The thick filaments interdigitate with the thin ones. The thick filaments are fixed in a hexagonal three-dimensional array by spacers (M-line filaments) located at the center of the sarcomere. The thin filaments lie at the trigonal points of the array.

[1]The following "refresher" should be familiar to those who have studied histology. Others would be wise to consult Reference 6 at the end of this chapter.