Second Edition

CIRCULATORY PHYSIOLOGY:

Cardiac Output and its Regulation

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ARTHUR C. GUYTON, M.D.
Professor and Chairman of the Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Mississippi

CARL E. JONES, Ph.D.
Assistant Professor of the Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Mississippi

THOMAS G. COLEMAN, Ph.D.
Associate Professor of the Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Mississippi

1973
W. B. SAUNDERS COMPANY • Philadelphia • London • Toronto

W B Saunders Company West Washington Square
Philadelphia, Pa 19105

12 Dyott Street
London, WC1A 1DB

833 Oxford Street
Toronto 18, Ontario

Circulatory Physiology Cardiac Output and Its Regulation ISBN 0-7216-4360-4

Print No. 9 8 7 6 5 4 3 2 1

PREFACE

The first edition of this monograph, which was published approximately ten years ago, had essentially a twofold purpose. The primary goal was to present an analysis of cardiac output regulation which had been developed largely in our department of physiology, and which has proved very useful in directing our thoughts regarding the principles of cardiac output regulation. A second goal was to offer an overall philosophy of the regulation of cardiac output, a philosophy which would explain principally the intimate relationship between the metabolic rate of the tissues of the body and cardiac output but which would also take into account the effects of cardiovascular reflexes, blood volume, blood viscosity, cardiac integrity, and other factors on cardiac output.

In the Second Edition of this monograph, the goals underlying the writing of the First Edition have been maintained. However, certain major changes have been made in the text itself. First, the results of a host of studies, both by ourselves and by others, which have been performed since the writing of the First Edition have been included, and an attempt has been made to show how these data fit into the scheme of cardiac output regulation. This portion of the revision was written mainly by Dr. Carl E. Jones. In this connection, we would like to emphasize that, although the physiological mechanisms involved in the regulation of cardiac output have been studied intensely during the past ten years, the basic concepts of cardiac output regulation have not been significantly altered. Rather, the new research has served more to substantiate the scheme of cardiac output regulation originally presented in this book.

The second major change appearing in this edition is the addition of three new chapters relating to topics which were not included in the first edition. The first two of these new chapters deal with the use of computers to simulate circulatory dynamics. Chapter 16 presents a computer analysis of ventricular function, showing particularly how one can determine the overall pumping ability of the left ventricle from such basic factors as anatomy of the heart, myocardial integrity, the physical laws governing fluid dynamics, degree of autonomic stimulation, input pressure to the ventricle, and output pressure. Chapter 17 shows how computers may be used to analyze function of the entire circulatory system. Presented in

this chapter is a complex analysis which allows one to predict the effect of almost any circulatory change on cardiac output.

The third new chapter briefly reviews the problems which have been encountered in the search for a usable artificial heart and discusses the overall philosophy of cardiac output regulation when using an artificial heart. The major emphasis of this chapter is that the mechanisms regulating cardiac output from an artificial heart are essentially the same as those regulating cardiac output from the human heart.

It was stated in the Preface to the First Edition of this monograph that the attempt to formulate an overall picture of cardiac output regulation could have been considered by the reader to be premature. Indeed, ten years later and with a great quantity of additional data, such a statement is, perhaps, still appropriate. However, we believe that the research of the past decade has gone far toward validating the concepts presented in that text and in the present one. Therefore, we sincerely hope that the information, concepts, and philosophies offered in this monograph will be of value to the reader interested in cardiovascular physiology.

Since the revision of this book was the work of three authors, it is important to explain the division of labor. Most of the revision was accomplished by Dr. Carl E. Jones, including the literature search, updating most of the chapters, and rewriting major portions of many of the chapters. Chapter 16, which presents the computer analysis of ventricular function, was written by Dr. Thomas G. Coleman. And Chapter 17, which presents a computer analysis of the entire circulation, was written by Dr. Arthur C. Guyton.

The authors wish to express their deepest appreciation to the many persons who helped in the preparation of this book. Acknowledgment is given to the members of the Department of Physiology and Biophysics, whose experiments afforded much of the scientific basis of this monograph and whose thoughts and ideas were immensely useful. In this regard, special thanks is given to Drs. Jack W. Crowell, Elvin E. Smith, Aubrey E. Taylor, Harris J. Granger, Allen W. Cowley, Jr., and Luis G. Navar. We also extend wholehearted gratitude to Mrs. Billie Howard, Mrs. Linda Rice, and Mrs. Maryann Davila for their excellent secretarial help, to Miss Tomiko Mita and Mrs. Carolyn Hull for preparing the figures, and to the staff of the W. B. Saunders Company for their invaluable assistance in preparing the entire manuscript.

ARTHUR C. GUYTON
CARL E. JONES
THOMAS G. COLEMAN

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I

NORMAL VALUES AND METHODS FOR MEASURING CARDIAC OUTPUT

Chapter 1

NORMAL CARDIAC OUTPUT AND ITS VARIATIONS

Cardiac Output and the Mixing of Body Fluids

Each of the one hundred trillion cells of the body is a living automaton capable of existing, of continuing life functions, and in most instances even of regenerating as long as it remains in an appropriate and constant internal fluid environment. The heart supplies a motive power for mixing most of the body fluids, keeping a stream of fluid flowing continually through all parts of the body. Molecular diffusion allows fluid and dissolved substances to move back and forth between the flowing blood and the interstitial and intracellular fluids. Thus, a constant "internal environment" of the body is maintained.

To provide this mixing of the body fluids, the cardiac output normally moves all the blood completely around the circulation about once a minute. Then, to keep the blood mixed with the fluids in the interstitial spaces, diffusion occurs through the capillary membranes at a rate equal approximately to 45 times the total blood volume every minute (Pappenheimer, 1953). That is, 45 blood volumes of fluid diffuse both outward and inward through the capillary membranes per minute, which obviously allows almost instant interchange between the fluid of the blood and the fluid lying immediately outside the capillaries. Mixing is almost 100 per cent complete, even in the areas most remote from the capillaries, in less than 30 minutes (Elkinton, 1955).

Transport of Nutrients and Wastes

A corollary to the mixing function of cardiac output is the transport of nutrients and wastes from one part of the body to another. First, we might mention substances transmitted from organ to organ, such as acetoacetic acid from the liver to the cells elsewhere in the body, hormones from the endocrine glands to all regions of the body, fats from storage depots to the liver or directly to other functional cells of the body, and so forth. However, we usually consider the major function of cardiac output to be transport of nutrients from the input organs of the body, the gut and lungs, to the cells, and then transport of wastes from the cells to the output

organs of the body, the lungs and the kidneys. The principal nutrients that must be carried to the cells include oxygen, glucose, fatty acids, and amino acids, while the principal wastes are carbon dioxide and nitrogenous metabolic end products.

A sufficiently diminished cardiac output can kill the cells because of failure to transport adequate quantities of any single one of the nutrients or wastes, but transport of some of these is more important than transport of others. Normally there is a "safety factor" for the transport of each of them. For instance, even at normal cardiac output, oxygen can be transported to the cells at rates as great as three times the usual amount simply by removal of a larger proportion of the oxygen from the hemoglobin as it passes through the capillaries. In other words, the *utilization coefficient* for oxygen can rise to approximately three times normal even without an increase in cardiac output. Thus, the safety factor for delivery of oxygen to the tissues is approximately three fold.

If we calculate the safety factors for the other principal nutrients and wastes, they are approximately the following: glucose, thirty fold; fatty acid, twenty-eight fold; amino acids, thirty-six fold; carbon dioxide, twenty-five fold; and nitrogenous wastes, 480 fold. One sees immediately a major difference between the safety factor for transport of oxygen and the safety factors for the other substances, for oxygen is the one substance of them all that is most nearly "flow limited." If the cardiac output falls below one-third normal, the function of almost all of the tissues of the body will become seriously impaired because of oxygen lack, and yet transport of the other substances will not be significantly affected. For this reason, cardiac output must always be regulated at a level high enough to supply oxygen to the tissues, and, if this is achieved, then the transport of the other necessary substances will be insured.

RELATIONSHIP OF CARDIAC OUTPUT TO METABOLISM

Ever since the problem of cardiac output regulation began to be studied, research workers have recognized that output increases approximately in proportion to increase in body metabolism. The one physiological condition under which the body's metabolism increases the greatest is exercise; in extreme exercise in the well-trained athlete, this increase can be to as great as 15 to 20 times the basal level. Since the circulatory system has a safety factor for oxygen transport of only 3 to 1, more than a three fold increase in body metabolism would immediately cause a serious oxygen deficit in the functional tissues were it not for a simultaneous increase in cardiac output. However, the cardiac output does increase approximately in proportion to the degree of exercise, as shown by the solid curve of Figure 1–1. Assuming a normal cardiac output of slightly over 5 liters per minute, and noting that the cardiac output at the highest measured work output level is slightly over 30 liters per minute (Christensen, 1931), it is evident that the cardiac output can increase up to six times normal. Then, if we will recall that the utilization coefficient for oxygen can increase approximately three fold, we can calculate that delivery of oxygen to the tissues during the most severe exercise performed by the subject depicted

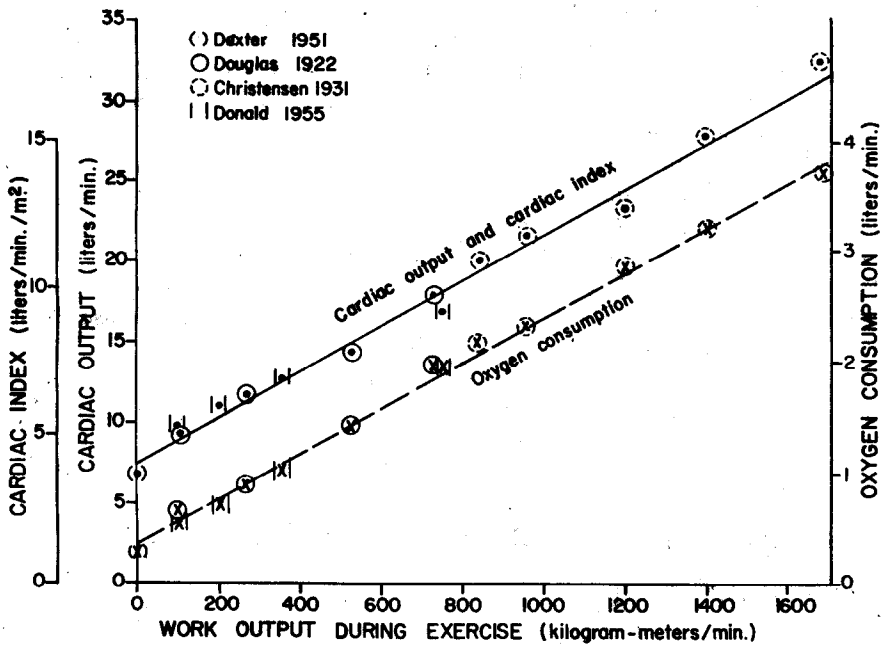

Figure 1–1. Relationship between cardiac output and work output (solid curve) and between oxygen consumption and work output (dashed curve) during exercise. [Data derived from studies by Douglas and Haldane (1922); Christensen and Mitteilung (1931); Dexter, Whittenberger, Haynes, Goodale, Gorlin, and Sawyer (1951); and Donald, Bishop, Cumming, and Wade (1955).]

in Figure 1–1 could have increased approximately eighteen fold. This fact is confirmed by the dashed curve of the figure, which shows the actual increase in oxygen usage. Furthermore, the body work output also increased approximately proportionately, as depicted by the abscissa.

DEPENDENCE OF CARDIAC OUTPUT REGULATION ON OXYGEN SUPPLY TO THE TISSUES

One can understand from the foregoing discussion that it would be highly desirable for the cardiac output to be regulated by the availability of oxygen to the tissues. This teleological reasoning leads us to suspect that oxygen availability to the tissues might well be one of the major factors controlling the overall total cardiac output. This subject will be discussed in detail later in this monograph, but to anticipate later discussions, particularly in Chapter 19, we can point out the following factors which indicate that cardiac output is regulated at least to a major extent by the availability of oxygen to the tissues. First, decreased oxygen concentration in the atmosphere (Grollman, 1930b; Cross, 1958; Gorlin, 1954), decreased ability of the blood to transport oxygen, such as results from anemia (Richardson, 1959), and decreased ability of the tissues to utilize oxygen in cyanide poisoning (Huckabee, 1960; Öberg, 1961) all cause the cardiac

output to increase in proportion to the decrease in oxygen availability to the tissues up to the point at which the heart fails, thus illustrating that lack of oxygen *per se* will increase the cardiac output. Second, decrease in the arterial oxygen saturation (Yonce, 1959; Crawford, 1959; Ross, 1962) causes vascular dilatation, decreasing the peripheral resistance as much as four fold and causing a concomitant increase in cardiac output. Third, simple correlation studies have shown a very high correlation between oxygen consumption and cardiac output during increased body metabolism (Douglas, 1922; Christensen, 1931; Dexter, 1951; and Donald, 1955). For instance, Figure 1–1 illustrates that oxygen consumption and cardiac output both increase proportionately when the work output increases from zero up to maximum values during exercise.

After this brief introduction, we will leave for more complete discussion at later points in the book the mechanism by which cardiac output keeps in step with the metabolism of the body.

NORMAL VALUES FOR CARDIAC OUTPUT

CARDIAC OUTPUT IN MAN

Even though Harvey discovered the circulation of the blood over 300 years ago, accurate measurements of cardiac output in man have been made only during the last 30 years. Furthermore, only two methods have proved to be consistently accurate in measuring the output (Hamilton, 1944, 1945a, 1953). One of these has been the direct Fick procedure, the theory of which was propounded by Fick in the latter part of the eighteenth century (Fick, 1870) but was not applied to man until 1930 (Grollman, 1932). The second method has been the indicator-dilution method (Stewart, 1897), which is actually a special application of the Fick principle. Because of their importance, these two methods will be discussed in detail in Chapters 2 and 3. However, it is worth mentioning here that several other indirect methods utilizing the transfer of gases between the pulmonary alveoli and the pulmonary blood were utilized extensively between 1910 and 1940 for the measurement of cardiac output (Grollman, 1932). The most famous of these, the acetylene method, was used very actively from 1928 to 1940. Critical studies, however, in the last 25 years have proved that the acetylene method gives a cardiac output value in normal man approximately two-thirds that measured by either the Fick or the dilution method (Handbook of Circulation, 1959). Unfortunately, the percentage error of the gas methods may not remain the same under all conditions, so that their quantitative correctness, even when using a correction factor, is still doubtful. It is unfortunate that cardiac output measurements in man are much more difficult using either the Fick or the indicator-dilution method than when using some of the gas methods. For this reason, many of our concepts regarding the different factors that regulate cardiac output are still based on earlier measurements made by gas methods that were utilized in literally thousands of cardiac output measurements in man (Grollman, 1932) in contrast to much less common usage of the Fick and dilution methods in recent years.

The Cardiac Index Method for Expressing Cardiac Output in Man

Before giving normal values for cardiac output, it is necessary to point out that cardiac output is frequently expressed in terms of the *cardiac index.* In using this, a correction is made for the size of the individual based on the surface area of the body. The cardiac index mathematically is expressed by the following formula:

$$\text{Cardiac index (l./min./meters}^2) = \frac{\text{Cardiac output (l./min.)}}{\text{Surface area (meters}^2)}$$

The average normal man is usually considered to have a surface area of 1.73 square meters (Stead, 1950), and the surface area is calculated from the following formula developed by Dubois (1936) for use in metabolism studies:

$$\underset{\text{(square meters)}}{\text{Body surface area}} = \underset{\text{(kilograms)}}{\text{Weight}^{0.425}} \times \underset{\text{(centimeters)}}{\text{Height}^{0.725}} \times 0.007184$$

Figure 1-2 is a chart based on this formula from which the surface area can be determined within an accuracy of less than 2 per cent from a person's height and weight.

Inserting the average body surface area of 1.73 sq. meters into the above relationship between cardiac output and cardiac index, we find for the average normal man

$$\text{Cardiac output} = 1.73 \times \text{Cardiac index}$$

The validity of the cardiac index as a means for comparing cardiac outputs from individual to individual will be discussed later in the chapter.

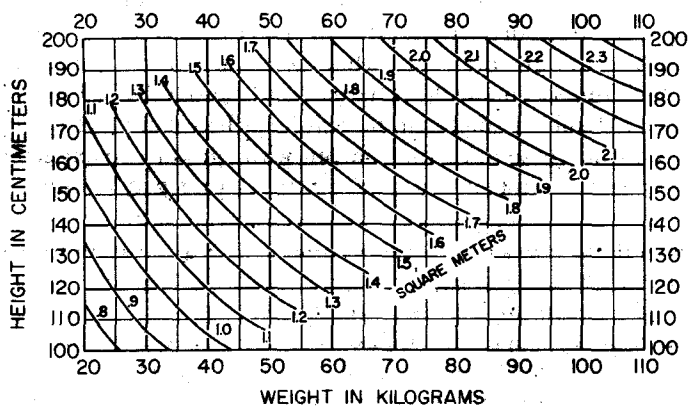

Figure 1-2. Chart for determining body surface area from height and weight (Dubois, 1936).

Cardiac Outputs Measured by the Fick and Indicator-Dilution Methods

Approximately 400 measurements of cardiac output made by the Fick and indicator-dilution methods in normal adult man have been collected in the Handbook of Circulation (1959). In these, the cardiac index averaged 3.52 liters per square meter per minute, which, for the average sized man, would be 6.08 liters per minute. These values have also been borne out almost exactly in still newer studies by Barratt-Boyes (1958), who have found a cardiac index of 3.5 in 26 subjects, and by Reeves (1961a), who found a cardiac index of 3.63 in 50 subjects. Furthermore, the average measurements by the Fick and dilution methods have been almost identical. In three different studies, the indicator-dilution and Fick methods have been compared in the same individuals. Hamilton and co-workers (1948) found in five individuals that the dilution method gave an 11 per cent greater cardiac output than the Fick method; Werko and coworkers (1949) found in six individuals that the dilution method gave a 6 per cent greater output; and Doyle and colleagues (1953) found in 53 individuals that the Fick method gave a 9 per cent greater output. If one considers the greater number of persons studied by Doyle, the two methods average out to give almost identical cardiac outputs.

Of historical importance is that the acetylene method in 151 different measurements (Handbook of Circulation, 1959) gave an average cardiac index of 2.24. If this is compared with the results using the Fick and indicator-dilution methods, the latter two give cardiac outputs averaging 55 per cent greater than those measured by the acetylene method.

Effect of Age on Cardiac Output

It is well known that body metabolism is affected greatly by age so that we would expect the cardiac output, which correlates very highly with body metabolism, also to be affected by age. Brandfonbrener and coworkers (1955) analyzed results from 77 different individuals in age groups from the teens through the eighties, with approximately equal representation in each of the decades. Figure 1–3 is constructed principally from Brandfonbrener's data with additional data for youths taken from Brotmacher (1957) and for newborn infants from Prec (1953, 1955).

Brandfonbrener's data show that the cardiac index decreases an average of 24.4 ml./sq. meter/min./year. Cournand (1945) found a similar figure of 26.2 ml./sq. meter/min./year in a less complete series of individuals. This decrease in cardiac output with age is to be expected because of the general decline in metabolic rate as one grows older (Boothby, 1929).

One might wonder why the cardiac index for the newborn baby as shown in Figure 1–3 is considerably less than that for older persons, particularly since we usually consider the metabolic rate per unit mass of tissue to be much greater in early childhood than at any other time of life. However, when one realizes the artificiality of the cardiac index as a means of expressing cardiac output, he can understand the low cardiac index for the newborn infant. The reason for this is that weight for weight, the newborn

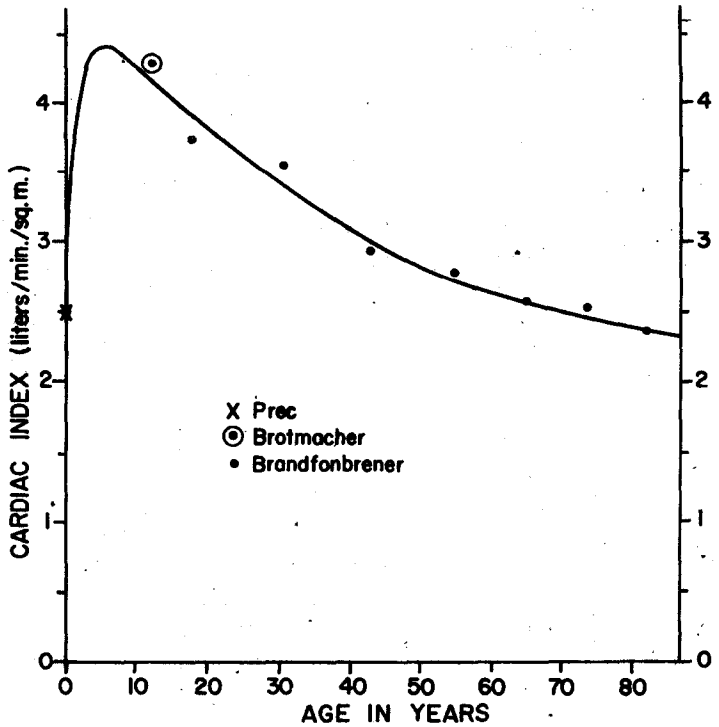

Figure 1-3. Cardiac index at different ages. Data mainly from Brandfonbrener, Landowne, and Shock (1955) but also from Brotmacher and Fleming (1957b) for youths and from Prec and Cassels (1953) for newborn infants.

infant has a far greater surface area than an adult. If the cardiac output is expressed on the basis of weight instead of surface area, we find the expected greater cardiac output per unit weight in the newborn infant (about two times as great) than in the adult. This phenomenon is also true in relation to metabolism; that is, the metabolic rate *per square meter* is less in a newborn infant than in the adult, but on a weight basis is much greater (Dubois, 1936).

Effect of Sex on Cardiac Ouput

Though one would expect the cardiac output of females to be less than that of males, there are not enough accurate data available to determine whether this is true. Furthermore, there would be real difficulty in deciding whether it is true because most females are considerably smaller than males, and comparison of cardiac outputs of persons of different weights and different sizes is still very artificial, as will be discussed later in the chapter in relation to the validity of the cardiac index.

However, if we assume that the cardiac index is proportional to the basal metabolic rate, we would expect the cardiac index of the female, except in early childhood, to be 7 to 10 per cent less than that of the male (Boothby, 1929).