The Human Cardiovascular System

Facts and Concepts

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Dedication

To Dr. L. Vandendriessche, formerly Rector of the Universitaire Instelling Antwerpen, and the Board of Trustees of the Francqui Foundation, Brussels: the former for sponsoring Dr. Shepherd for an International Francqui Chair at the University of Antwerp and the latter for providing the award. These events permitted two long-time colleagues to continue their collaboration in research and to develop the groundwork for this overview of the cardiovascular system.

Prologomenon

The prologue to any textbook demands of the authors the reasons why it merits publication. In this endeavor, we were reminiscing, in congenial circumstances, about our combined total of over fifty years of research on the cardiovascular system, and over ten in collaborative studies. These ranged from the analysis of the behavior of the circulation in human limbs, the hemodynamic events in the human heart studied by heart catheterization, the role of the veins in circulatory control, the regulation of arterial blood pressure by the cardiovascular reflexes, and the responses of isolated blood vessels to local, humoral, and nervous stimuli. All of this reminded us of the complexity of the cardiovascular system and the difficulties faced by scholars of any age, confronted with the outpouring of years of information in original and review articles, symposia and textbooks, from which they must identify key facts. We decided to challenge ourselves to write a clear and concise description of the current knowledge of cardiovascular function which would relate the physiology and pharmacology of the circulatory system to its common diseases and which would endeavor to separate facts from concepts, and hopefully, from personal bias.

The text is designed for use by medical students, graduate students, residents, and other medical professionals desiring a modern review of the circulation. Based on our own experience in research and teaching, we have tried to summarize the most important aspects of cardiovascular function and have stressed the continuous interaction between the components of the system. We have tried to make each statement understandable to both of us, on the supposition that if this were achieved, anyone who reads the text would comprehend it.

The text is extensively illustrated with original diagrams that serve to summarize important components and events within the system. Particular attention has been paid to the index and to cross-references in the text so that the reader can rapidly gain access to the pertinent facts. All discussion of methodology has been placed in the final chapters so that the reader's thought processes are not as easily interrupted by complex mathematical derivations as are those of the authors. Selected references are cited at the end of each chapter; the majority are reviews by outstanding investigators of specific aspects of the circulation in health and disease and provide the advanced student with a key to further reading.

As for the reasons why this book merits publication, others must make the judgment. We offer no apologia. Suffice it to say we have enjoyed the challenge of this transatlantic overview of the cardiovascular system and if those who read it become as fascinated as we are by its intricacy and are stimulated to become active in its affairs, this will be our reward.

Acknowledgments

Our special thanks are due to Robert R. Lorenz and Tony J. Verbeuren, long-time friends and collaborators in research, who combined their knowledge of the circulation with artistic skills to transform our ideas for the illustrations of the text into graphic realities. In addition, many friends and colleagues kindly gave permission to reproduce classic illustrations selected from their work. We are indebted to Nancy J. Rusch and R. Clinton Webb for constructive criticism of the text. We also thank Liliane Van den Eynde and Joan Y. Krage for their patience in typing version after version of the manuscript. We acknowledge the pleasure we have had in the scientific collaboration and social interchange with the many Research Fellows with whom we have worked both at the Mayo Graduate School of Medicine and at the University of Antwerp. We are grateful to Raven Press and especially to Dr. Diana Schneider and Ms. Rita Scheman for the efficient way in which they collaborated with us, and for proceeding rapidly and smoothly from the typescript to the final product.

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1

From Historical Hallmarks to Modern Concepts of Cardiovascular Control

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"Coepi egomet mecum cogitare, an motionem quandam quasi in circulo haberet"
William Harvey[1]

William Harvey, who discovered the basic principles of the circulation of the blood, was so impressed by its complexity that he stated in the first chapter of his classic book *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (1628) that he almost felt that the motion of the heart and blood was to be comprehended only by God. Indeed, when studying the cardiovascular system it is easy to become so engrossed with its complexity that one overlooks its primary role, namely to ensure at every moment the survival of all cells of the body.

For unicellular organisms the problem is a simple one. Surrounded by water, these cells can take up nutrients directly from and eliminate waste directly into their environment; in this way they ensure the constancy of the intracellular conditions necessary for their proper function. As evolution proceeded, multicellular complexes developed whereby groups of cells emerged to fulfill the various functions which initially were performed within the single cell. This organization of cells has reached its most advanced development in the higher vertebrates. Regardless of the function they subserve, all cells of the organism, just as their single cell predecessors, must receive nutrients and eliminate their waste prod-

[1] Translation: I began to think within myself whether it [the blood] might have a sort of motion, as it were, in a circle."

ucts. Each living cell of the organism is surrounded by a small amount of extracellular fluid. For each cell to function properly the composition of this fluid, the *milieu intérieur,* may vary only within narrow limits (Claude Bernard, 1866). To achieve this there must be a continuous stream of nutrients from the outside world to the extracellular fluid, and a continuous stream of waste products from the cells to the outside world. Therefore the organism needs specialized tissues for exchange (lung, gut, and kidney) and a transport system (blood and cardiovascular system) to link these tissues with the individual cells.

CIRCULATION OF THE BLOOD

Harvey's classic experiments dispelled the concept that the blood ebbed and flowed in the vascular system, an idea which had dominated medical thinking from the time of Galen 15 centuries earlier. Harvey recognized that the blood returning from the peripheral tissues and organs through the great veins enters a thin-walled collecting chamber (atrium) of the right heart, and that when this chamber is filled it contracts and forces the blood into a thicker-walled chamber (right ventricle). The subsequent contraction of this ventricle expels the blood through the pulmonary artery into the lungs, from which it returns to the left heart. A similar succession of events brings the blood from the left atrium to the thick-walled left ventricle (Fig. 1–1). The latter propels the blood into a large channel (aorta), which conveys it to the peripheral organs of the body (Fig. 1–2). The forward motion of the blood through the various cavities of the heart is made possible by the presence of valves between the atria and the ventricles, and between the ventricles and the great vessels which leave them. The alternating sequence of contraction (emptying) and relaxation (filling) of the heart chambers, known as systole and diastole, respectively, permits the heart to function as a pump. Harvey also recognized the important role of the valves in the venous system of the extremities in assisting the forward movement of the blood from periphery back to the heart.

A century later Hales (1733) measured the postmortem capacity of the left ventricle. By assuming that the whole ventricular content was expelled with each systole, and by knowing the frequency of contraction from measuring the pulse rate, he estimated that each ventricle expels about 4.5 liters of blood per minute (cardiac output), a value surprisingly close to that measured directly with modern technology in living subjects (p. 289). Since both sides of the heart are in series in the same circuit (Fig. 1–1), both ventricles must pump the same average amount of blood per unit of time. The cardiac output is determined by the number of times the heart beats per minute (heart rate) multiplied by the amount of blood pumped out per beat (stroke volume). The remarkable performance of the cardiovascular system is illustrated by the fact that in the human at rest the heart beats about 100,000 times a day, and the ventricles move approximately 16,000 liters of blood around the vascular tree. During strenuous exercise, this amount may increase temporarily by as much as four or five times.

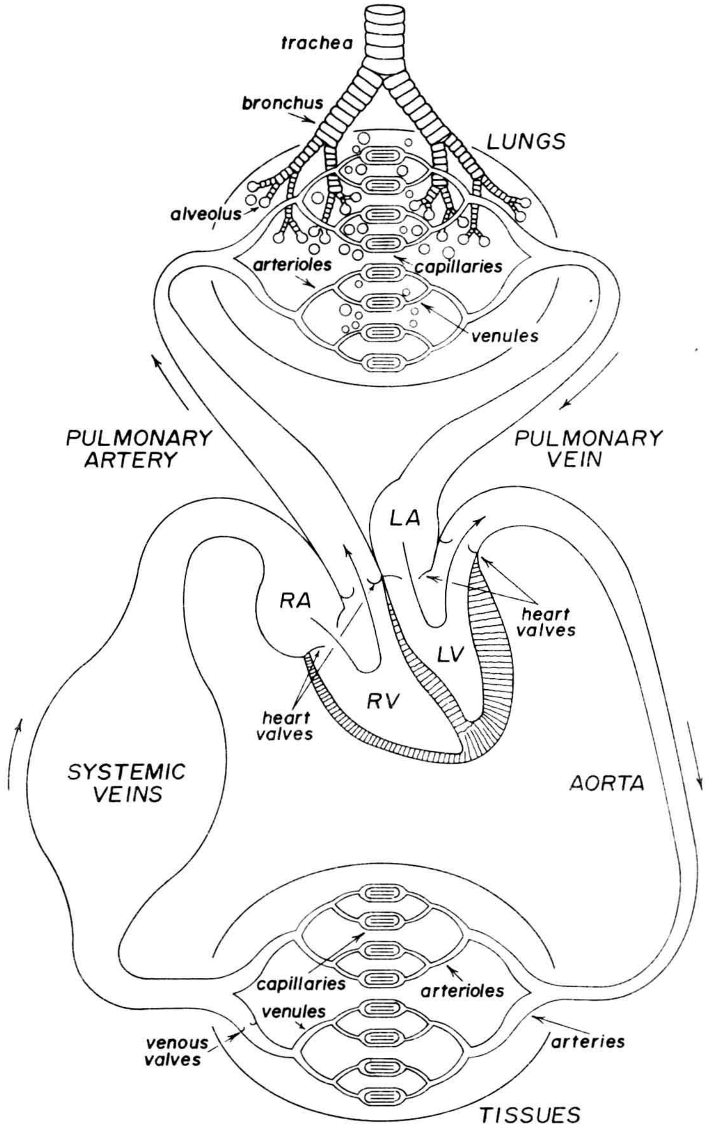


FIG. 1–1. The cardiovascular system. The heart, blood vessels, and lungs provide for exchange of gases between the atmosphere and the tissues. The right and left side of the heart are two pumps arranged in series on the same circuit. The oxygenated blood (arterial blood) returning from the lungs by the pulmonary veins enters the left atrium (LA) and the left ventricle (LV). Contraction of the latter expels the blood into the aorta, which ramifies into numerous arteries for distribution of the blood to the tissues. The end branches of the arteries (arterioles) give rise to the exchange vessels (capillaries) where oxygen and foodstuffs pass to the tissues and carbon dioxide and waste products are taken up by the blood (venous blood). The capillaries reunite to form the venules and veins, which return the venous blood to the right atrium (RA) and right ventricle (RV). The contraction of the right ventricle propels the blood into the pulmonary artery and its branches. In the pulmonary capillaries the carbon dioxide diffuses to the small air sacs (alveoli), and oxygen is taken up from the latter by the blood. The alveoli are connected to the atmosphere by the bronchial tree and the trachea. The presence of valves in the heart and the limb veins ensures forward movement of the blood.

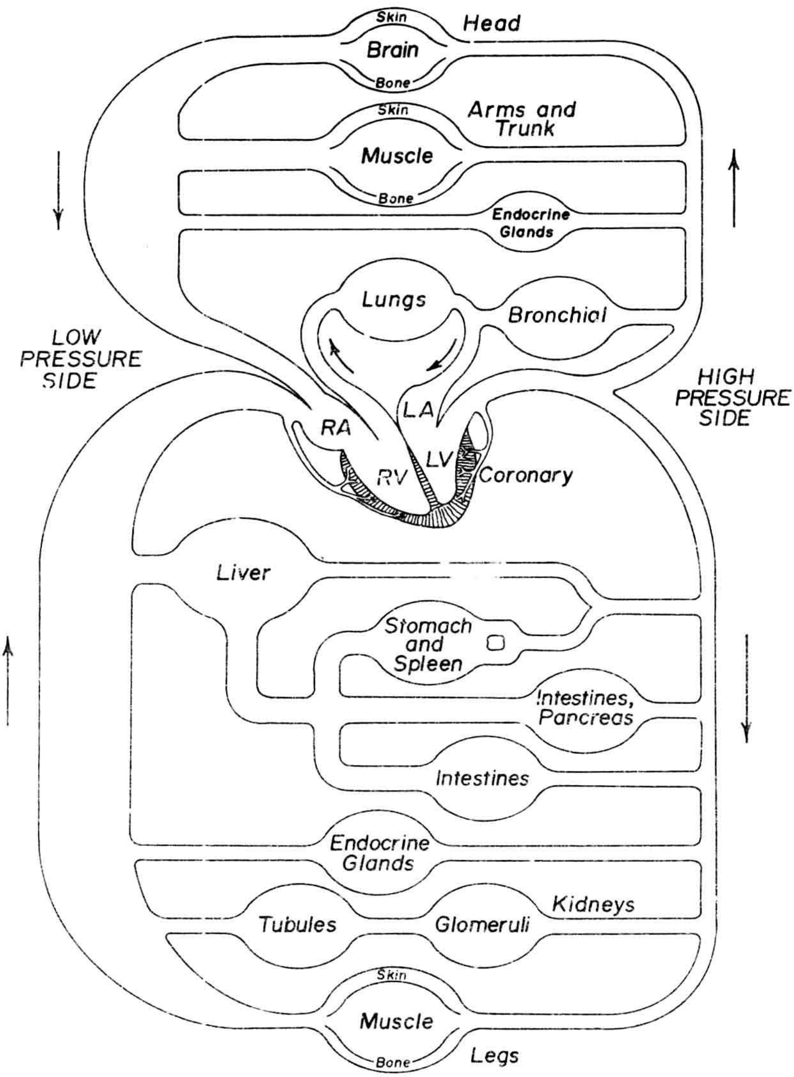


FIG. 1–2. Distribution of blood to the systemic vascular beds. The various vascular beds are arranged in parallel. Within each bed the consecutive sections (arteries, arterioles, capillaries, venules, and veins) are arranged in series. In the kidney the blood passes through two consecutive capillary beds. Venous blood from the spleen and gastrointestinal organs passes through a second capillary network, the portal circulation, in the liver. The greater proportion of the blood volume resides within the venous side of the circulation.

The completion of the description of the cardiovascular circuit came when the communication channels between arteries and veins, assumed to exist by Harvey, were described by Malppighi in 1661 and called capillaries. The capillaries, in the lungs and other organs, soon were recognized as the sites of exchange between the body cells and the transport system (the blood) and between the latter and the outside world. Lower (1669) showed that the function of the pulmonary capillaries is to replenish the blood with oxygen. Starling (1896) demonstrated that the direction and the quantity of the fluid which moves across the capillary wall are determined mainly by the balance between the pressure of the blood which tends to push fluid into the tissues (capillary hydrostatic pressure) and the attraction of fluid exerted by the plasma proteins (colloid osmotic pressure).

PRESSURES AND FLOWS WITHIN THE VASCULAR SYSTEM

Prior to Harvey, Vesalius (1543) had recognized that the contraction of the heart creates the arterial pulsation. Although Harvey understood that the high arterial pressure provides the driving force for the circulation, it remained for Hales to make the first direct measurement of arterial blood pressure, which he did by determining the height that blood rose in a vertical tube inserted

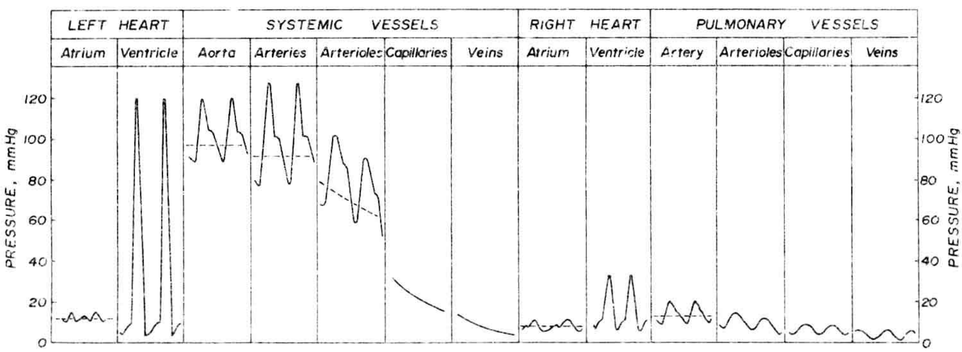


FIG. 1–3. Pressure changes in the human cardiovascular system. In the left atrium the pressure is low but pulsatile because of the rhythmic contractions of the atrial muscle. The main generator of pressure is the muscle of the left ventricle; in the latter cavity the pressure alternates with each cardiac cycle from near zero (diastole) to about 120 mm Hg (systole). When the pressure in the ventricle exceeds that in the aorta, the aortic semilunar valves open, the ventricle and aorta become a common chamber, and the pressure in both rises in unison. The rise in aortic pressure causes an expansion of the aorta and the large arteries because of their elasticity and because blood enters the arterial tree faster than it leaves it through the small-bore arterioles. When the ventricle starts to relax, the aortic valve closes. As the ventricle continues to relax, the pressure within it drops quickly to near zero, but the pressure in the aorta falls slowly throughout ventricular diastole as the distended arterial tree recoils and blood continues to flow to the capillaries through the arterioles. The major loss of pressure occurs at the arterioles because of the high resistance to flow they offer. The pressure in the capillaries and veins decreases further to approximate zero in the great veins entering the right atrium; the flow in the systemic capillaries and veins is relatively nonpulsatile. The right side of the heart generates a pressure pattern similar to that in the systemic circulation, but the systolic pressure in the pulmonary artery is about six times less than that of the aorta, and the flow in the pulmonary capillaries is pulsatile. Mean pressures are indicated by dotted lines. In the large arteries the mean pressure is lower than in the aorta although the systolic pressure is higher owing to reflection of the pulse waves.

into one of the main arteries of a mare. Years later the use of the mercury manometer and modern manometers allowing exact measurement of dynamic changes in pressure (p. 288), as well as the ability to pass catheters into all parts of the cardiovascular system (p. 287), has permitted precise determination of the pressure changes throughout the circulatory system (Fig. 1–3) (Table 1—Appendix). Although the same amount of blood is pumped by the two ventricles, the pressure generated by the left is about six times greater than that generated by the right. The high pressure in the aorta ensures adequate delivery of blood to all organs; the low pressure in the pulmonary artery ensures that no fluid leaves the lung capillaries, which would cause flooding of the air sacs of the lung and prevent adequate uptake of oxygen from the outside air.

By contrasting the intermittent flow from the ventricles with the steady flow in the veins, Hales deduced that the large arteries, because of their distensibility

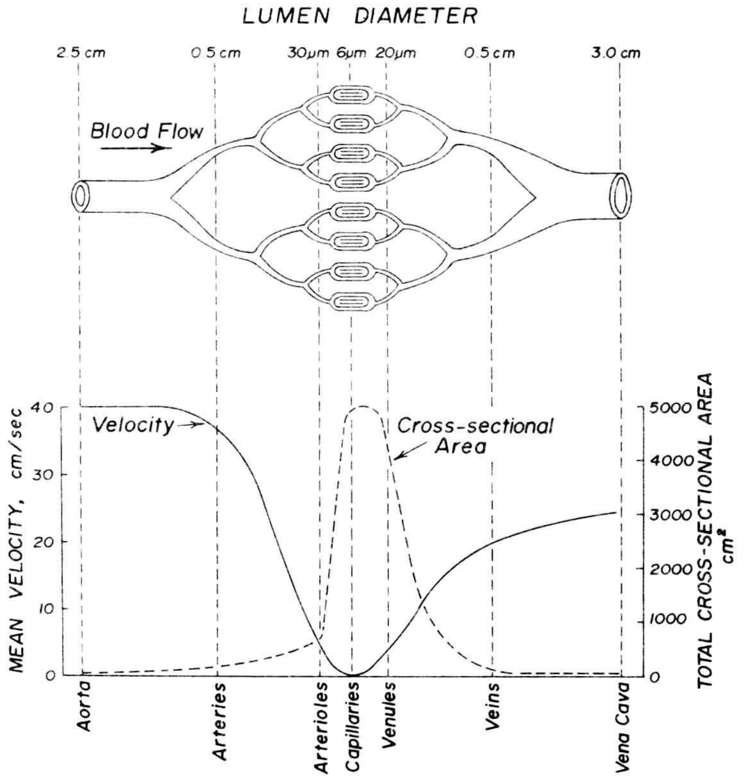


FIG. 1–4. Changes in estimated total cross-sectional area *(dotted line)* and mean velocity of flow *(solid line)* in consecutive segments of the systemic blood vessels. Since the flow through each segment is the same, the velocity is highest in the aorta and the caval veins, which have the smallest cross-sectional area, and lowest in the capillaries where the cross-sectional area is very large. This favors the exchange between blood and tissues.

(elastic properties), act as a depulsator to dampen the pulsatile output of the heart into a continuous flow of blood to the tissues and organs of the body. As the main arteries pass to the latter, they branch and become progressively smaller; the smallest branches are called arterioles, from which the capillaries originate. Although the individual vessels become smaller in diameter as the branching occurs, their number multiplies to such an extent that the total cross-sectional area of each consecutive section of the vascular tree increases, to reach a maximum at the capillary level. When the capillaries reunite to form venules, and the latter to form veins, there is a progressive decrease in total cross-sectional area. Since the amount of blood passing per unit of time through each cross-section is the same, the velocity of flow decreases progressively toward the

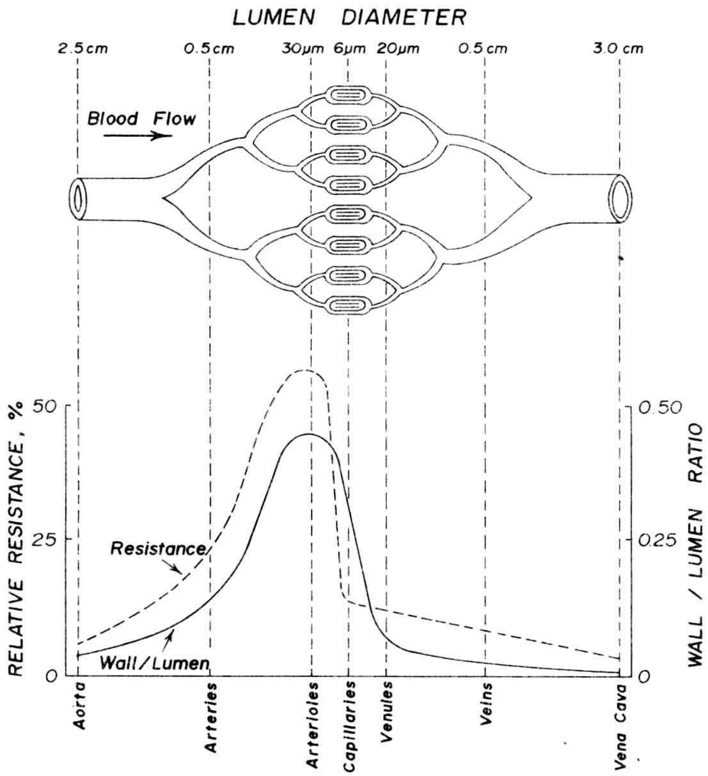
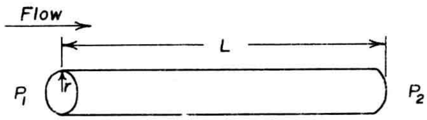


FIG. 1–5. Changes in the wall-to-lumen ratio *(solid line)* and in relative resistance to blood flow *(dotted line)* of the systemic blood vessels. The arterioles have the greatest wall-to-lumen ratio because of the large amount of smooth muscle in their wall relative to their size. Variations in the degree of contraction of this muscle permit control of the blood supply to the individual vascular beds and of the total resistance to flow through the systemic vascular bed. The low wall-to-lumen ratio of the capillaries is due to the absence of muscle in their walls, and that of the veins to their large diameter relative to the amount of muscle they contain.



$$F = (P_1 - P_2)\frac{\pi r^4}{8L \times \eta}$$

$$R = \frac{8}{\pi} \times \frac{L \times \eta}{r^4}$$

$$R = \frac{(P_1 - P_2)}{F}$$

FIG. 1–6. Relations between pressure, flow, and resistance derived from Poiseuille's (1842) work on cylindrical tubes. R = resistance (dyne-sec/cm^5). L = length (mm). η = viscosity (poise). r = radius (mm). P = pressure (mm Hg). F = flow (ml/min). Strictly speaking, these equations apply only for Newtonian fluids flowing in a nonpulsatile manner through rigid tubes, whereas in the vascular system a pulsatile non-Newtonian fluid flows through distensible tubes. However, they illustrate the importance of alterations in diameter as the key determinant of the resistance to flow in blood vessels because the resistance is inversely proportional to the fourth power of the radius.

periphery and is lowest at the capillary level; when returning toward the right heart the velocity of flow augments progressively. This creates optimal conditions for exchange in the capillaries (Fig. 1–4).

Hales, in another important discovery, established that the major resistance to flow is offered by the minute vessels of the tissues, the arterioles (resistance vessels), and hence that they are the site of the greatest pressure drop between the arteries and the veins (Fig. 1–3). He showed that water and brandy at different temperatures can affect the resistance of the arterioles and thus demonstrated that the blood vessels can undergo active changes in diameter (vasomotion), as was confirmed 150 years later by Claude Bernard. Indeed the arterioles combine a small diameter with an abundance of muscle in their wall (Fig. 1–5). When this muscle contracts or relaxes, the diameter of the arteriole decreases or increases, respectively. The work of Poiseuille (1842) predicts that such changes in diameter profoundly affect the resistance to flow since in cylindrical tubes this is inversely proportional to the fourth power of the radius (Fig. 1–6). Changes in arteriolar diameter affect the quantity of blood flowing to the capillaries subserved by the arterioles and the pressure within the capillaries. On the other hand, the resultant of all arteriolar resistances (systemic vascular resistance), together with the cardiac output, dictates the level of arterial blood pressure because the latter is determined by the product of the former two (Figs. 1–7 and 1–8).

BLOOD VOLUME, VENOUS RETURN, AND CARDIAC FILLING

Early experiments, including those in which blood was drained from decapitated criminals, indicated that the blood volume approximates 1/14th the body

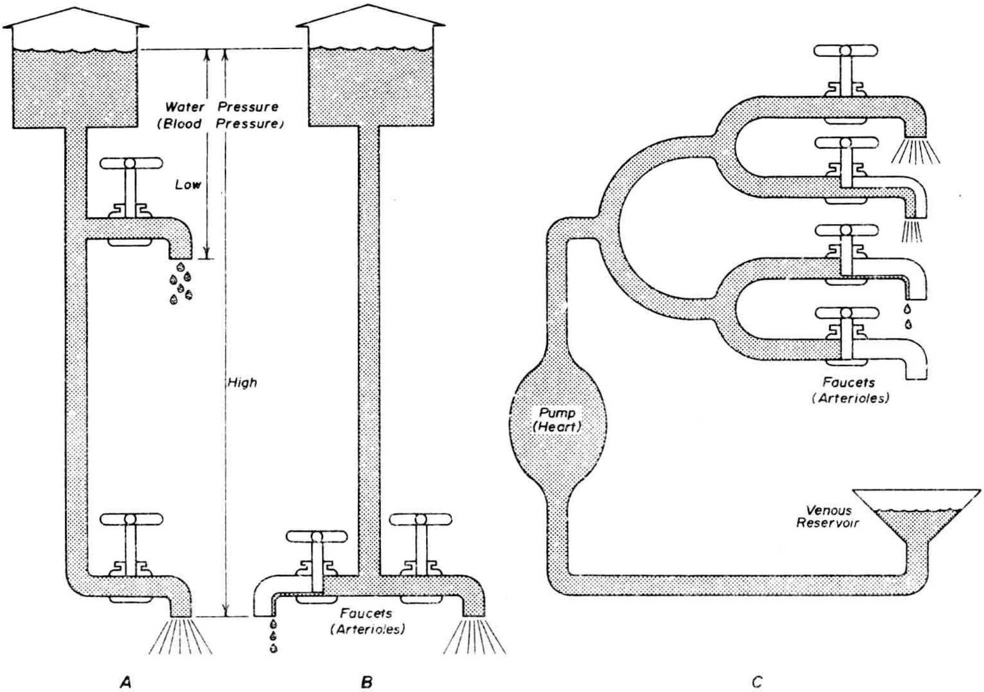


FIG. 1–7. A: If a different pressure head is applied to identical resistances (faucets of the same diameter, fully open), the circuit with the highest pressure (lower faucet) will allow the greatest flow. This means that for an identical degree of opening of a given arteriole, the flow through it is directly proportional to the pressure head (mean blood pressure). **B:** For a constant-pressure head the amount of fluid flowing through a circuit depends directly on the encountered resistance (e.g., identical faucets with different degrees of opening). The circuit with the lowest resistance *(right)* allows the most flow. This means that, provided the mean blood pressure is kept constant, the degree of opening of the arteriole determines the amount of flow through it. **C:** For a given output of the pump, the pressure is determined by the resultant of the individual resistances. If more faucets close, the pressure increases and vice versa. If the total resistance changes, the only way to maintain a constant pressure in the system is to alter the pumping rate.

weight, a value close to the 5 to 6 liters obtained for an average adult by modern methods. Thus in the human, as in most mammals, the heart at rest pumps the equivalent of the total blood volume per minute. The greater part of the blood volume is contained in the low-pressure side of the circulation, which includes the postcapillary systemic veins, the right heart, the pulmonary vessels, and the left atrium (Figs. 1–2 and 1–3). The work of Frank (1895) and Starling (1914) showed that the degree of filling of the heart is an essential factor in determining its stroke volume. The systemic veins (capacitance vessels) play the dynamic role of ensuring the filling of the heart. Like the arterioles, the veins contain muscle in their walls, and this muscle permits active alterations of vascular capacity (Fig. 1–9).

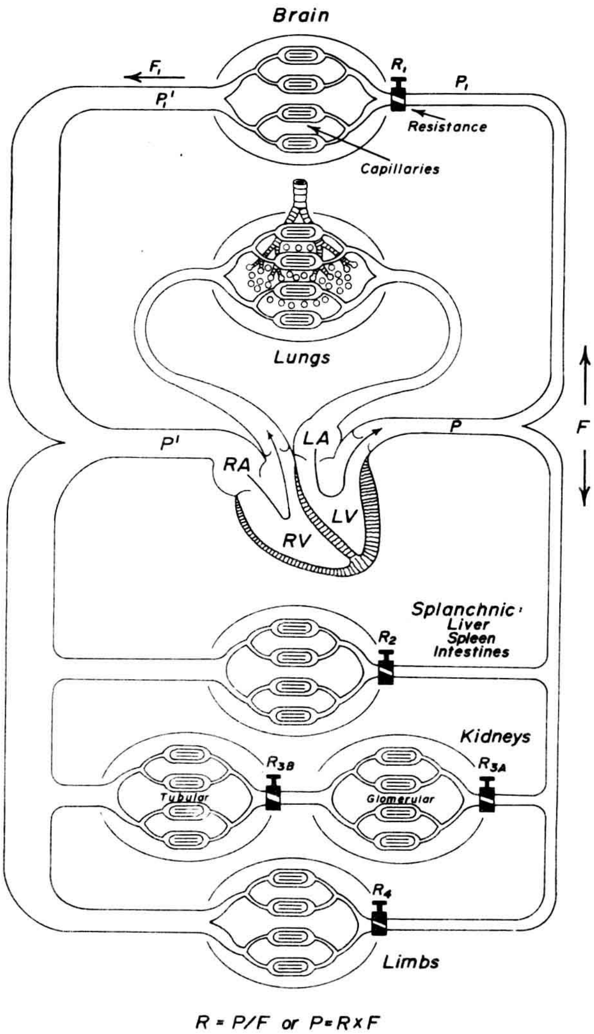


FIG. 1–8. Interdependence of pressure, flow, and resistance to flow. For the systemic circulation as a whole, the arterial pressure (P) is determined by the product of the cardiac output (F) and the resistance to flow (R) offered by the various vascular beds arranged in parallel ($1/R = 1/R_1 + 1/R_2 + 1/R_3 + 1/R_4 + \ldots . 1/R_x$). When two resistances are arranged in series (e.g., in the kidney) their total resistance equals the sum of the individual resistances ($R_3 = R_{3a} + R_{3b}$). Since the systemic arterial blood pressure remains relatively constant, the flow through the individual beds is inversely proportional to the resistance they offer, which is determined mainly by their arterioles.

CONTROL OF THE CIRCULATION

Claude Bernard (1851) recognized that integration of the function of the cardiovascular system depends mainly on the nervous system. Loewi (1921) demonstrated that the signals from the nerve cells to the muscle cells is transmit-