HEART DISEASE

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PREFACE

KNOWLEDGE in the basic and clinical sciences related to the practice of cardiology has increased to an extent almost beyond belief during the past 30 years. New investigative techniques utilizing electronic apparatus, computers, radioisotopes, and other instrumentation have made possible extraordinary progress in classic circulatory physiology. These developments have led to different ways of looking at physiology and to new and broad concepts. Thus, it is not overstating the case to insist that every modern physician and surgeon interested in cardiovascular disease must now have a firm grounding in circulatory physiology.

Aside from the newer trends in circulatory physiology, two new avenues of exploration—molecular biology and regulatory biology—have revolutionized and will continue to change our concepts of the circulatory system and its diseases. The revolution in physiology initiated by molecular biology is one in which ultrastructure, as revealed by the electron microscope, is being linked more and more closely with the chemistry, enzymology, energetics, and physiology of the cells that constitute the muscles of the heart and those of the blood vessels. Studies of the ultrastructure of the capillary lining in various organs are yielding better insight into the transfer of substances between the vascular system and the extracellular spaces and the intracellular contents. Molecular biology of nerve and skeletal muscle has provided new insight into the nature of the pacemaker of the heart, conduction within the heart, cardiac cell-membrane function, and the excitatory process occurring on the heart cell surface. Similarly, the intimate anatomy of the mitochondria and the sarcoplasmic reticulum has begun to reveal not only the details of the chemical changes within the cell but also of excitation-contraction coupling and the role that the several cations play in this regard. Knowledge of the architecture of the actual contractile elements has grown apace, as has information about the chemistry and physiology of the several proteins that make up these elements. Although knowledge applicable to smooth muscle cells of vessels is not as advanced as that for heart muscle cells, the pathway for acquiring such knowledge is at hand.

However, it is not sufficient merely to define the functions of the parts of the cell, of the entire cell, or even of the groups of cells that constitute the various elements of the circulatory apparatus. Such knowledge is, in a sense, static. It is also necessary to understand how the circulatory system responds to changing circumstances, especially during exercise and emotional stress. This involves a physiology different from that disclosed by molecular biology. It is an integrative physiology that derives from regulatory biology. Thus, integrative physiology requires an understanding of the role of the nervous system and humoral factors in regulating the circulatory system in concert with the respiratory system under conditions of stress. This regulation involves the sensory apparatus; the afferent, connecting, and efferent neurons; the catecholamines and other stores at the nerve endings and, in addition, the various types of autoregulation existing in the circulatory apparatus; the feedback mechanisms; and the integrative properties of the central nervous system. Regulatory biology, therefore, is truly a multifaceted activity requiring that the expert in circulatory physiology become equally knowledgeable in respiratory, nervous, and hormonal physiology.

To present the essence of this new kind of physiology as part of the fabric of clinical cardiology is a formidable task for any teacher, if only because of the tremendous volume of knowledge and the rapidity with which it has been accumulated. The efforts by the

authors to achieve this goal were guided by two major considerations: (1) to employ the most effective method in presenting this material to the practicing physician and (2) to make appropriate choices as to what must be included and what might be safely omitted.

To achieve the first objective, the text has been divided into a number of sections that deal successively with modern physiology of circulation, pathophysiology of heart disease, applied clinical physiology of diagnosis and manifestations of heart disease, specific diseases of the heart, and, finally, treatment of heart disease. This approach frequently requires the reader to consult several chapters in order to encompass the entire spectrum of a particular disorder of the circulation or a particular disease of the heart. Each of these chapters is written as a self-standing entity but is, at the same time, interdigitated with other relevant chapters in such a way as to provide integration without unnecessary repetition. For example, a basic understanding of congestive heart failure will be gained by reading the chapters on functional anatomy and metabolism of the heart, regulation of cardiac performance, clinical manifestations of heart failure, and treatment of heart failure. A fuller understanding will be achieved by studying, in addition, the chapters on coronary circulation, physiology of the pulmonary circulation, and pathogenesis of pulmonary hypertension. Similarly, in a disease such as systemic hypertension, a total view will dictate reading, as a minimum, the chapters on physiology of the systemic circulation, pathogenesis of systemic hypertension, hypertensive cardiovascular diseases, and treatment of hypertensive diseases.

This manner of presentation permits the physician, depending upon his background and personal preference, to approach a particular subject in a step-by-step fashion, starting with basic physiologic and pathophysiologic mechanisms and ending with the purely clinical aspects; or, alternatively, to direct his attention to a particular aspect of a subject without the necessity of working his way through a myriad of related topics. Thus, to learn about the hemodynamics of heart failure or the treatment of heart failure the reader need not immediately concern himself with the properties of contractile proteins, the mechanism of contraction, or excitation-contraction coupling. Any of these related topics may be perused in any independent order in accordance with the reader's personal method of study or the dictates of a specific educational need. Doubtless, some will find that this separation of interrelated subject matter imposes to some extent on a sense of continuity. However, experience with this didactic method over the past 25 years and testing many of these interrelated chapters on a number of "trial-horse" physicians have led the authors to believe in its general usefulness.

The second objective, concerned with what to include and what to omit, was approached by having the clinical author (E. N. S.) write the first draft of each chapter. This decision was prompted by the rather arbitrary premise that his physiologic background and largely clinical activities were a suitable basis for a preliminary decision as to what tools the practicing physician requires in the area of cardiovascular diseases. These first drafts were then amended, expanded, or tempered by the physiologist author (L. N. K.). Finally, by the processes of discussion, debate, bullying, coaxing, and compromise, a final draft of each chapter was jointly produced. The authors are aware that the chapters dealing with physiology and pathophysiology may not satisfy investigators in these fields. However, the subject matter represents what the authors believe the practicing physician requires as a background and can reasonably be expected to carry around as his working fund of knowledge in clinical cardiology.

It is, of course, evident to readers and writers alike that no such work can be brought to fruition without the indispensable efforts of many individuals who have assisted the authors. Well-earned tribute is due a number of individuals cited below and by others too numerous to mention by name.

The authors are particularly indebted to Dr. Aaron B. Shaffer, who, in addition to writing the chapter on congenital heart disease and collaborating on the chapter on

rheumatic heart disease, read each of the early and final drafts, proofread galleys, and contributed significantly in both helpful criticism and clarity of expression. Special thanks are also due Dr. Stanley K. Brockman, for contributing the chapter on surgery of the cardiac patient; Dr. Arnold M. Katz, for his contributions to the chapters on ischemic heart disease and metabolic diseases of the heart; Dr. Richard Langendorf, for his invaluable guidance and criticism in the preparation of the chapter on the treatment of arrhythmias; and Dr. Alfred Pick, for his advice on the chapter on cellular electrophysiology as well as for his provision of many of the electrocardiograms and his guidance in the selection of others. Grateful acknowledgment is also made to Drs. Eric Reiss and Gerald Glick, for their encouragement and for the latitude they extended to one of us (E. N. S.) in the performance of his departmental duties so that this book could become a reality. All original line-cut illustrations are the work of Mrs. June Pedigo, who met unreasonable deadlines with good-natured equanimity. Our warm thanks are expressed to Alice Brauer, who patiently spent countless hours of her "leisure" time to assure the accuracy of each of the bibliographic citations. We are also grateful to the late Jean Anne Stavrokopoulos and to Barbara Shapiro and Margaret Sendzimer, who, as secretaries, rendered such able assistance in the early days of this project. A special debt of gratitude is owed to two persons: our secretary, Joyce Jones, whose matchless organizational ability and speed of execution were indispensable to the completion of this work and whom we view virtually as a junior partner; and Marian Segal, who, in the final days of manuscript preparation, labored tirelessly and with good humor to help us meet our commitments.

Our indebtedness is lovingly expressed to Aline Katz and Marlyn Silber for their unstinting dedication to this project, and to the latter for her reading and correcting of galleys and page proof. Finally, deep appreciation is gratefully acknowledged to Miss Joan C. Zulch, Medical Editor, Macmillan Publishing Co., Inc., whose forbearance, patience, gentle humor, and expertise were indispensable to the creation of this volume.

E. N. S. and L. N. K.

At the time of this writing, it is known throughout the world of science that Dr. Katz died on April 2, 1973, a few months before the completion of this work. The many tributes recounting the remarkable qualities of this great and dedicated man do not soften my feelings of personal loss, and the deep sense of disappointment that Dr. Katz did not live to see this book in print. Consolation is to be found only in the store of exhilarating experiences that are mine as the result of working together on a daily basis for so many years with "The Boss." It is hoped the reader will find this volume a fitting monument to him.

E. N. S.

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PART

I

THE PHYSIOLOGIC BASIS OF HEART DISEASE

SECTION

A

THE HEART AS A BIOLOGIC MACHINE

> The heart is a principal muscle, in respect of force, and it is much more powerful than the other muscles.
> —LEONARDO DA VINCI

TRADITIONAL physiologists view the heart as a muscular pump inserted into the circulation to provide a continuous flow of blood to the tissues of the body. From this point of view, the action of the mammalian heart has been likened to that of a reciprocating pump. In both, the action is pulsatile, valves are required to give direction to the stream, and the output of the pump is adjustable in terms of either its frequency or its volume displacement, or of both frequency and volume displacement simultaneously.

This kind of analysis of cardiac pumping in terms of classic hydraulic physics has produced much of the knowledge that forms the basis of modern cardiac physiology. But the heart is no mere pump. It differs fundamentally from mechanical pump systems, regardless of their intricacies, in that it is self-energizing: mechanical pumps require an outside force for activation; the heart develops its own force within the walls of its chambers. Thus, conceptually, it is more meaningful to view the heart as a biologic engine, an engine that converts the chemical energy of metabolism into mechanical energy (Mommaerts, 1963). The heart is, moreover, inherently automatic in maintaining its beating.

The salient mechanical features of this machine, ignoring for the moment the intricate mechanisms involved, are (Brecher and Galletti, 1963):

1. The ability to deliver volumes ranging from 3 to 30 liters per minute against pressures up to 300 mm Hg.

2. Flow velocities, even at maximal cardiac output, that do not exceed the limit of tolerance for mechanical trauma to blood corpuscles.

3. Viscoelastic properties of its walls that confer cavity distensibility in the relaxed stage over a wide range of volume increments with little increase in intraventricular or intraatrial pressures; thus, without the necessity of a change in its frequency, the heart can readily accommodate and deliver varying blood volumes.

4. Valves that open and close rapidly, offering minimal impedance to flow, and seal completely against high pressures.

5. Pumping action automatically regulated through sensing feedback mechanisms (assumed, but not precisely identified) that integrate hemodynamic and metabolic "data" and adapt the output to tissue demands.

These features enable the human heart to maintain adequate perfusion of the body under all possible conditions. To understand how the heart is capable of such versatile performance, it is necessary to examine (1) the structural organization of the heart on a gross, microscopic, and ultramicroscopic level (*functional anatomy*); (2) the logistics of oxygen

and substrate supply (*coronary circulation*); (3) the machinery for energy production and transformation (*metabolism and energetics*); (4) the phenomena that initiate contraction, affect the duration of contraction and relaxation, and achieve almost synchronous contraction of all the muscle cells (*electrophysiology*); and (5) the mechanisms that confer upon the heart its ability to participate in the adaptation of the organism to various states of activity (*regulation of cardiac performance*).

The chapters in this section, then, are concerned with a presentation of how structure and function are integrated into a unique biologic system, the mammalian heart.

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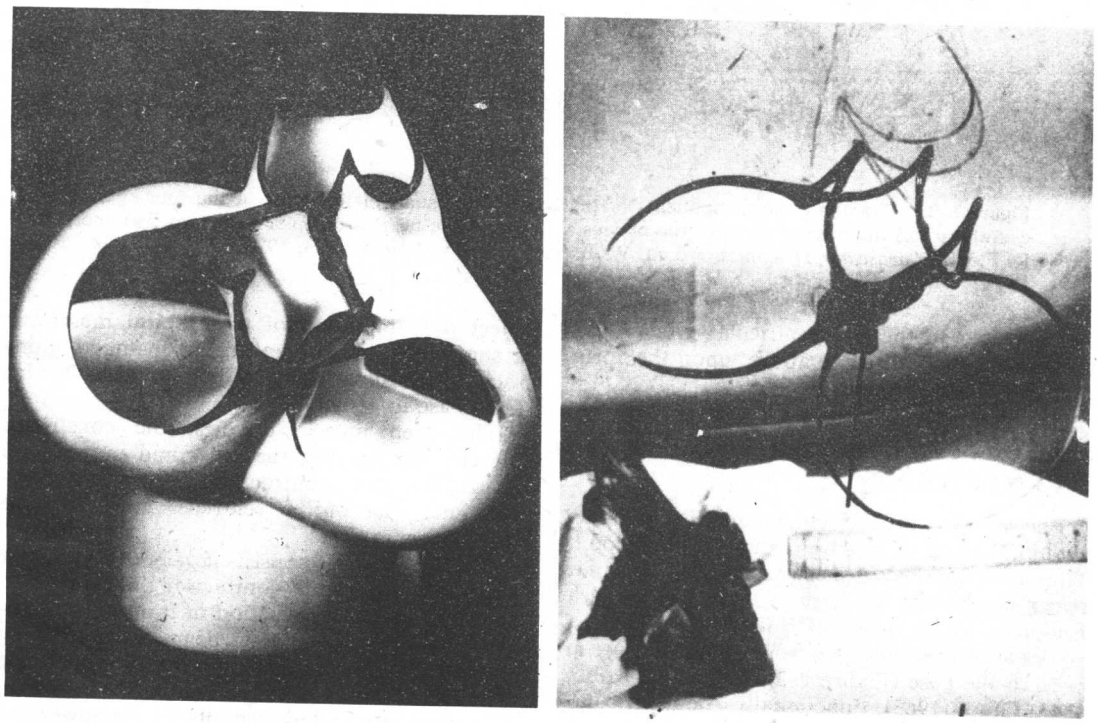
Mommaerts, W. F. H. M.: The muscle cell and its functional architecture. *Am. J. Med.*, **35**:606, 1963.

CHAPTER

1

The Functional Anatomy of the Heart

THE ANATOMIC components of the heart consist of a connective tissue framework to which are attached the atria, the ventricles, the valves, and the roots of the pulmonary artery and the aorta, all of which are enveloped by a serofibrinous sac, the pericardium. The framework, or "skeleton," is formed by four fibrous valve rings which have been thought to be continuous with one another (Rushmer, 1970). However, this appears to be an oversimplification of the actual anatomy, since it has been shown (Zimmerman and Bailey, 1962) that the skeletal structures of the semilunar valves are triple-scalloped collagenous lines and that the mitral valve "ring" is actually U-shaped with the major portion of the septal leaflet suspended from fibrous cords that are extensions of the central fibrous body of the heart (Figure 1–1). The atria and arterial trunks are attached to the superior surface of this platelike connective tissue skeleton; the ventricles and atrioventricular valves, to the inferior surface (Figure 1–2). The pericardium is



A B

Figure 1–1. A recently revised concept of the fibrous skeleton of the heart. **A** is a three-dimensional model of the ventricular part of the heart; the dark portions represent the fibrous skeletal structures. **B** is a three-dimensional model of the true fibrous skeleton; the two horizontal prongs on the left are the fila coronaria (fibrous cords) of the mitral orifice. (From Zimmerman, J.: The functional and surgical anatomy of the heart. *Ann. R. Coll. Surg. Engl.*, **39**:348, 1966.)

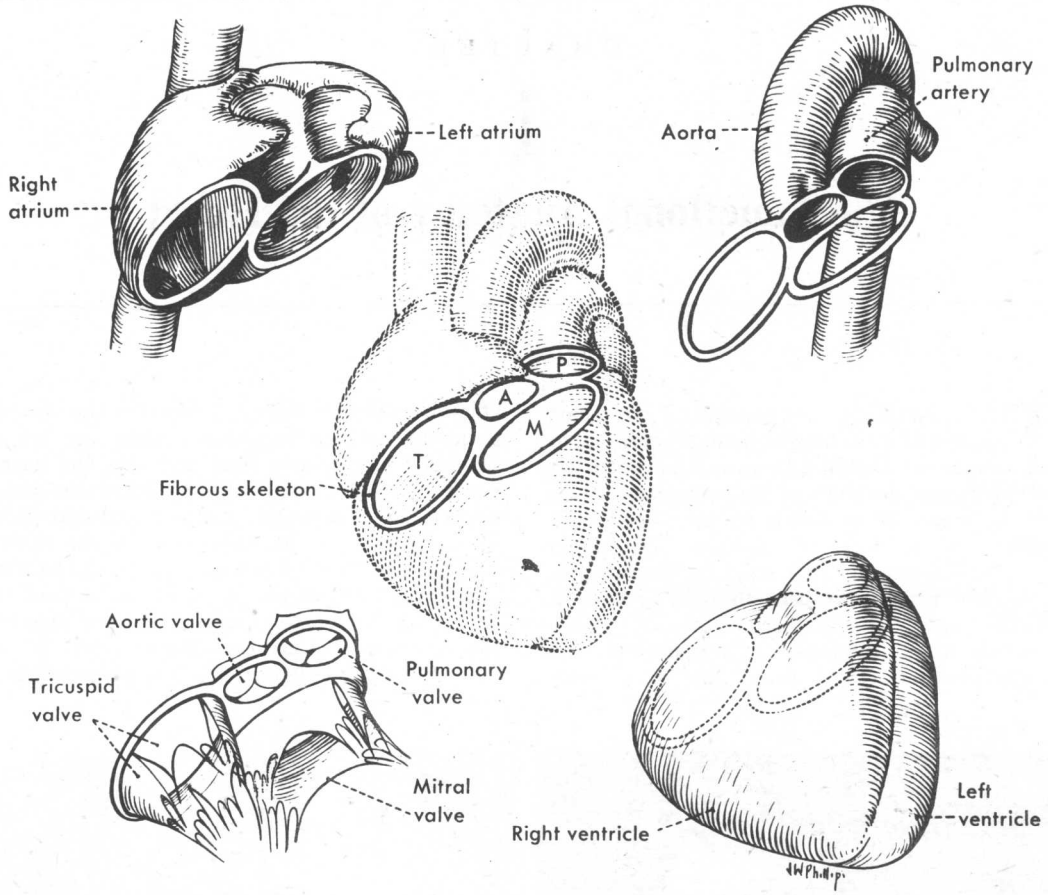


Figure 1–2. The anatomic components of the heart. The usual relationships of the four cardiac chambers and the arterial roots to the fibrous skeleton of the heart are depicted. (From Rushmer, R. F.: *Cardiovascular Dynamics*, 3rd ed. W. B. Saunders Co., Philadelphia, 1970.)

not attached to the atrioventricular groove, but rather at a short distance above, upon the aorta and main pulmonary artery.

ARCHITECTURE OF THE VENTRICLES

The ventricles are the actual pumps that provide most of the energy for the circulation of the blood. They are composed of sheets of muscle fibers that sweep down from the base of the ventricles in a complex helical array of spirals that form a vortex at or near the apex, from which they sweep back to the base (Figure 1–3) (Robb and Robb, 1942; Grant, 1965). Functionally, the ventricular musculature may be regarded as consisting of two groups of muscle bundles: (1) the inner and outer spiral muscles and (2) the deep constrictor muscles (Rushmer *et al.*, 1953). In each ventricle the myocardial fibers tend to be spatially arranged in three directions. The inner and outer layers are spiral muscles that follow oblique courses perpendicular to one another. The combined effect of contraction of these spiral muscles is a shortening of the ventricular chambers along their longitudinal axis, leading to a shortening from base to apex.

The deep muscle bundles, the constrictor muscles, lie between the inner and outer spiral layers, and their contraction reduces the transverse diameter of the ventricles much like the clenching of a fist.

The left ventricle consists largely of constrictor fibers; accordingly, its contraction during ejection primarily effects a reduction in transverse chamber diameter with a lesser degree of shortening along the longitudinal axis. Since the volume of a cylinder decreases with the square of its radius, this constrictor action accounts for the power and volume of normal left ventricular ejection. By contrast, spiral muscles predominate in the right ventricle, and its contraction produces a large degree of base-to-apex chamber shortening with relatively little approximation of the free wall toward the interventricular septum. However, the slight movement of the free wall of the right

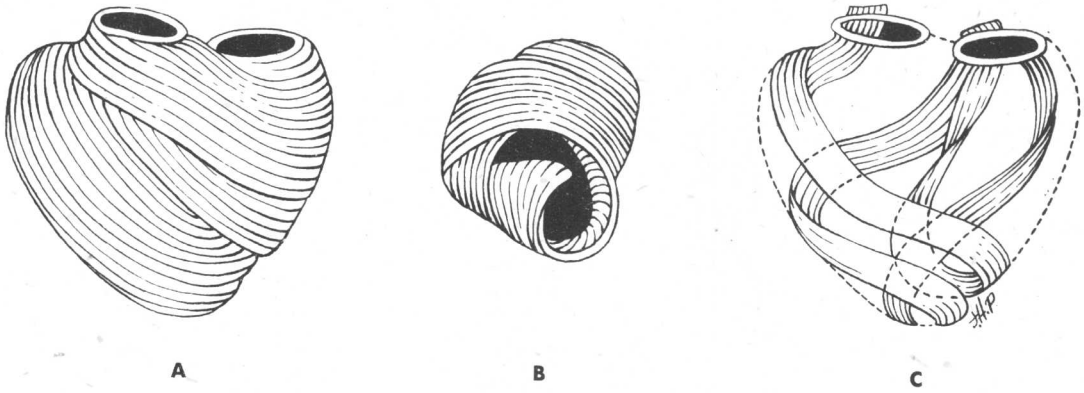


Figure 1–3. The superficial fibers of the ventricles, showing their origin from the valve rings, spiraling toward the apex, and returning to the valve rings. (Modified from Grant and Basmajian, 1965.)

ventricle toward the septum, occurring at the same time as longitudinal shortening, is very effective in ejecting blood.

These anatomic and architectural characteristics reflect the type of work that each ventricular chamber performs. The chamber of the right ventricle is a relatively narrow space between two broad surfaces, actually being little more than a cleft between the interventricular septum and the thin free wall. Thus, the right ventricle, like an old-fashioned bellows, has a large surface area per unit of volume. As a consequence, it is effectively adapted to pumping large volumes against a low resistance with relatively slight degrees of muscle shortening (Rushmer and Thal, 1951, 1952). By contrast, the surface area of the thick-walled left ventricle in relation to its volume is small by reason of its more nearly spherical geometry. Thus, the left ventricle is ideally suited to function as a high-pressure pumping system.

Understanding the basis for the different architecture of the two ventricles can be facilitated by considering, from a purely mechanical point of view, the amount of tension that myocardial fibers must develop in order to elevate intraventricular pressure. According to the Laplace formula ($P = T/r$) for a thin-walled sphere, the pressure (P) is determined by the relationship between the level of wall tension (T) and the radius (r) of the chamber. By analogy to such a sphere, the myocardial fibers during ventricular contraction must develop higher tensions to produce a given intraventricular pressure as these fibers form circles with larger radii (Figure 1–4).

Since the free wall of the right ventricle approximates a segment of a sphere with a relatively large radius, the right ventricle can accommodate greatly increased stroke volume with very slight distention of the chamber or lengthening of its individual muscle fibers. However, as one would anticipate from the law of Laplace, elevation of chamber pressure to high levels is beyond the tension-developing capacity of the *normal* right ventricle. In short, the right ventricle is an effective volume pump normally but suffers a serious mechanical disadvantage when subjected to high outflow pressures, that is, acute pulmonary hypertension. However, if pulmonary hypertension develops gradually, the right ventricular wall becomes thick and its cavity becomes shaped like that of the normal left ventricle. Hence, the right ventricle is converted from a low-pressure pump to a high-pressure pump (Figure 1–5*C*).

Furthermore, it is evident, in accordance with the law of Laplace, that dilatation per se is not an advantageous response of the left ventricle to increased pressure loads inasmuch as the myocardial fibers in a distended chamber must then exert even more tension than would be necessary in a small chamber. Instead, its walls become thicker in response to increased pressure loads as a consequence of hypertrophy of the individual myocardial fibers, a mechanism that, it may be presumed, enables the walls to exert increased contractile tension (Grossman *et al.*, 1974). However, there are circumstances when the left ventricle is subjected to sustained volume loads, such as occurs with insufficiency of the aortic valve. In these instances, the walls of the left ventricle remain relatively thin in relation to chamber size, and the surface area is considerably increased out of proportion to the concomitant myocardial hypertrophy. The markedly dilated left ventricle (Figure 1–5*B*) then comes to resemble the normal right ventricle.

The major portion of the septum is highly muscular (Armour and Randall, 1970), but data on the function of this musculature are sketchy. However, recent studies in the canine heart demonstrate active participation of the septum in contractile events, with development of marked

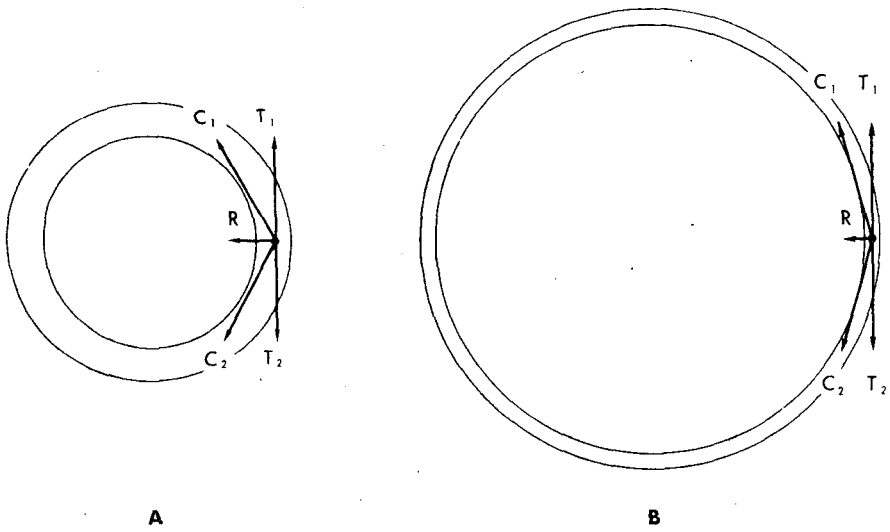


Figure 1–4. A diagram representing a transection of the left (**A**) and right (**B**) ventricles to show the tension forces operating upon any point in the wall, represented by the dot, in the center of the wall equidistant from endocardium and epicardium. These forces consist of the two circumferentially oriented tension forces, C_1 and C_2, of such a magnitude that the two tangential tension forces, T_1 and T_2, into which they can be vectorally resolved are opposite in direction but equal in magnitude to each other. The other vector is a centripetally directed tension force, R, which is equal and opposite to the centrifugally directed force exerted by the pressure in the heart's cavity at this point.

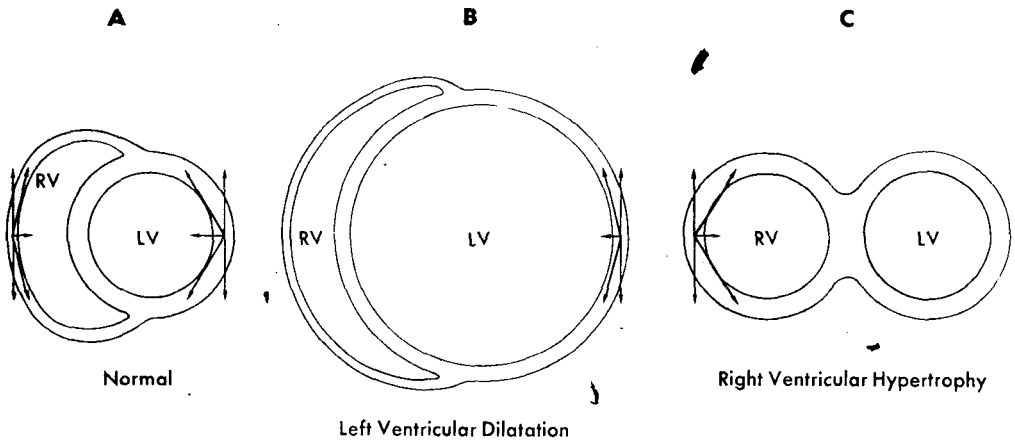


Figure 1–5. Diagram showing the effect of left ventricular dilatation (**B**) and right ventricular hypertrophy (**C**) on the shape, size, and thickness of the wall of the two ventricles, as compared to the normal (**A**). The circumferentially oriented tension forces will depend upon the radius and intracavitary pressure. Consequently, in **B** the large radius in the left ventricle requires an inordinate wall tension to maintain the chamber pressure. On the other hand, in **C** the hypertrophy of the right heart ("left ventricularization") reduces cavity size, enabling the chamber wall to attain the tension required by the increased ventricular pressure. The latter is aided by the development of a more circular cavity shape. The arrows in the walls of the right and left ventricle are drawn as in Figure 1–4 (the conventions are the same as in that figure). The vector size shows the resolution of forces, not their magnitude.

augmentation in contractile force and elevation in intramyocardial pressures; contractile patterns of either side of the septum, or of the cranial and caudal portions of either side of the septum, appear to contribute significantly to cardiac power and to regulation of cardiac output (Armour *et al.*, 1973).

ARCHITECTURE OF THE ATRIA

Each atrium lies, not above, but *behind* and to the right of its corresponding ventricle. Since the plane of the interatrial septum is angled at approximately 45° to the median plane, the right atrium lies as much in front of the left atrium as beside it (Figure 1–6) (Walmsley and Watson, 1966). The anterior half of the medial wall of the right atrium is intimately related to the first portion of the aorta, including the aortic valve, and to the left ventricular outflow tract in the region of the membranous part of the interventricular septum. These relations have practical implications today since inadvertent puncture of the root of the aorta may occur during attempts to enter the left atrium by transseptal catheterization (Brockenbrough *et al.*, 1962; Libanoff and Silver, 1965).

The atria are the booster pumps in the circulation and augment the movement of blood from the "feed lines" (pulmonary and systemic veins) into the power-generating elements (the ventricles) of the system (Sarnoff and Mitchell, 1961). Since the atria supply most of the blood to the ventricles passively, and only a small fraction (5 to 25 per cent) is actively propelled by the atrial musculature against negligible resistance, the normal atria do not need to be thick-walled. Consequently, the arrangement of muscle fibers is much simpler than in the ventricles.

Two groups of fibers are discernible. The first group invests each atrium and surrounds the orifices of its veins. These myocardial venous sleeves are more developed around the superior than around the inferior pulmonary veins, but the significance of these structural differences is entirely unknown (Eliakim *et al.*, 1961). It is thought that they may act as sphincters that impede the regurgitation of blood into the veins during atrial systole (Burch and Romney, 1954). In addition to these annular fibers, looped fibers directly beneath the endocardium run from the anterior to the posterior segments of the atrioventricular junction.

The second group of fibers is common to both

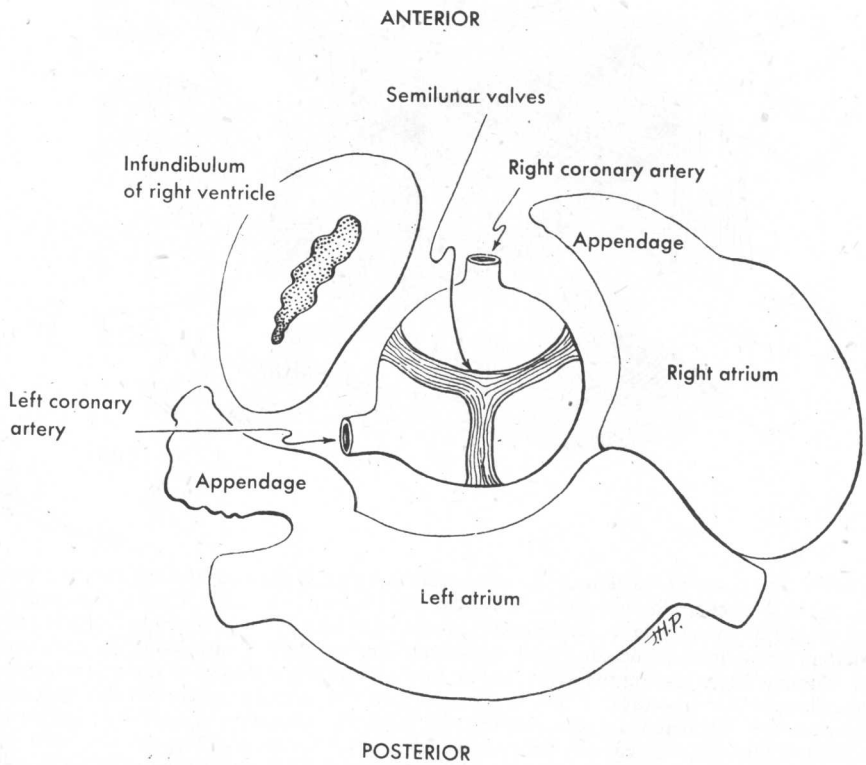


Figure 1–6. Transverse section of the heart showing the atria, the aortic root, and the infundibulum of the right ventricle. Note that only the posterior half of the medial wall of the right atrium is constituted by the interatrial septum; anteriorly it is intimately related to the aorta. (Modified from Walmsley and Watson, 1966.)