SYMPOSIUM ON CONGESTIVE HEART FAILURE

Hemodynamic Aspects of Congestive Heart Failure

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The 3 articles in this issue on congestive heart failure comprise the first of 10 contributions on this subject. The remaining 7 articles will be published in the February and March issues.—Editor.

In this discussion of the hemodynamic aspects of congestive heart failure, we propose to review clinical observations and the results of animal experiments. On this basis, our concepts concerning the sequence of changes in the heart that lead to congestive heart failure are summarized.

It is well known that congestive heart failure, while starting as a deficit of myocardial performance, ends as a syndrome in which many organs, particularly the kidney, lungs, and liver, are altered, as are many homeostatic functions. Certain aspects of this subject have been considered in previous reviews,1-9 or are dealt with in other sections of this symposium. In the present review, we will confine ourselves primarily to the heart, and especially to those of its alterations, physical or chemical, that are recognized as having some possible bearing on the disturbed hemodynamics of congestive heart failure.

Congestive Heart Failure Defined

The function of the heart is to eject the blood that is returned to it. It is obvious, then, that the heart is as much the servant of the circulation as its master. It is often difficult or impossible, in man, to separate clearly the primary hemodynamic manifestations of a diseased heart muscle from those of a primarily compromised circulation, or from secondary circulatory adjustments.

An inadequate circulation (circulatory insufficiency or failure) is manifest by a low cardiac output in relation to the current needs of the body, or by the accumulation of undue quantities of blood in the systemic or pulmonary venous system, or both (congestive circulatory failure). On the other hand, the term heart failure in this report is considered to be synonymous with myocardial failure, which implies as its starting point an inadequate myocardial contraction with reference to the circulatory load. It should be clearly recognized that there are many extracardiac causes of circulatory failure and that myocardial failure is only one of the cardiac abnormalities, structural or functional, which may result in circulatory failure.

Just as myocardial failure is not a necessary condition of circulatory failure, so the absence of circulatory failure is no guarantee of an uncompromised myocardium. A normal circulation may be maintained by an augmented cardiac effort, with a resulting decrease in cardiac reserve.

Myocardial effort is directed toward meeting 2 types of load. The heart must accelerate

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The studies of the department in this area have been supported recently by the American Heart Association, National Heart Institute, and the Michael Reese Research Foundation, among others.

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Circulation, Volume XXI, January 1960
or put the overcame time, Tachyeardia of variety cardium inereased load. Dilatationi the muscle heart musele, while applying increased load. More subtile are the processes within the heart muscle itself, for the most part neurogenically or hormonally conditioned, which determine the behavior of the myocardium from beat to beat (see below).

"Myocardial reserve" relates cardiac effort, however measured, to the maximum effort of which the heart is capable with respect to the particular aspect considered. Increased work loads obviously narrow the gap between existing and maximal efforts, while myocardial disease narrows the gap by reducing the possible effort maximum. The concept of cardiac reserve has limited usefulness clinically, however, since it encompasses so many factors and there is no standard way of applying it. For example, hypertrophy of a ventricle increases cardiac reserve in one sense, but reduces it in another, since as hypertrophy develops, there is less potential for further hypertrophy.

The following incomplete tabulation serves to illustrate by means of clinical examples the relationship of circulatory to myocardial failure. Circulatory failure results from

1. Interference with systemic venous return due to factors remote from the heart (such as hemorrhage, peripheral vascular collapse, shock), or in the heart region (such as pericardial tamponade, constrictive pericarditis, tricuspid stenosis). Congestion is generally a feature of the latter group but not of the former. Myocardial failure is not a necessary concomitant of these states.

2. Interference with the pumping or filling mechanics of the ventricles due to some architectural abnormality. This need not be associated initially with myocardial failure (viz., acute pulmonary edema due to mitral stenosis), but ultimately leads to circulatory failure on the basis of failure of one or both ventricles (e.g., semilunar valvar stenosis or insufficiency, mitral stenosis or insufficiency, tricuspid insufficiency, arterial hypertension of either circuit, pulmonary emboli or thrombosis). In all these conditions, forward flow through the arteries, though initially normal, is small in relation to the amount of effort that the heart must exert.

3. Primary diseases of the myocardium that lead to muscle failure. These may be due to localized loss of substance (as in myocardial infarct), or to diffuse involvement (as in myocarditis, amyloidosis).

4. Any stimulus to high output of one or both ventricles, be it hypervolemia (as in excessive intravenous infusion of blood or other fluid, and possibly acute glomerulonephritis), drastic reduction in peripheral vascular resistance (as in systemic A-V fistula, beriberi, hyperthyroidism, Paget's disease), hypoxia (as in anemia, chronic cor pulmonale), or possibly a direct metabolic effect on the myocardium (as might occur in hyperthyroidism). Also included in this group are uncomplicated congenital cardiovascular malformations with large left-to-right shunts. In these conditions, systemic flow may be reduced while pulmonary flow is increased, and the diastolic load to one or the other ventricle is markedly increased (the right ventricle in interatrial septal defect, the left ventricle in patent ductus arteriosus). With the exception of the last-mentioned conditions, the obvious hemodynamic manifestations of "high output" circulatory failure are by definition congestive only, at least initially. However, the presence of a high cardiac output must not be taken to imply that flow to all organs, e.g., the kidneys, is necessarily high, or even normal. The controversy continues as to whether myocardial failure per se in man may occur
simply on the basis of an "overwhelming" diastolic load. Certainly some of the conditions leading to high output circulatory failure have an additional primary deleterious effect on the myocardium itself (as in the hypoxic group, beriberi, and possibly in acute glomerulonephritis and hyperthyroidism), and then myocardial failure may be precipitated much as it may be under the stimulus to high output of physical exercise. In other instances (as in "iatrogenic" hypervolemia, arteriovenous fistula, "malignant" ductus arteriosus), the only effect of the underlying process on the myocardium is hemodynamic, and it would seem unlikely in such instances that there must invariably be a separate myocardial disease. Thus, it is by no means ruled out that these "high output states" can lead to congestive heart failure, as defined, insofar as they may give rise to a diastolic load with which even a normal ventricle cannot cope. Here congestion may be in part the cause and in part the result of myocardial failure.

It is obvious that in a given clinical condition, the causes of circulatory failure may be multiple. Further, compensatory mechanisms within the heart itself (such as inapparent dilatation) or at the periphery (such as slightly increased oxygen extraction) may prevent myocardial failure from being manifest in its earliest stages.

A given entity may not fit into a single group. For example, the behavior of endocardial fibroelastosis in a given case may classify it in any of the first 3 groups. Functional derangements of the heart or circulation (vaso-vagal syncope, rapid heart action, cardiac arrest) also may result in circulatory failure in the absence of myocardial failure.

These groups constitute a crude therapeutic classification. There is no doubt that the best treatment of any hemodynamic abnormality is a direct attack on the primary cause. This is the only effective approach to the conditions in group 1, while measures (such as digitalis) aimed at supporting the compromised myocardium may be very effective in groups 2 and 3. The clinical response to such measures is characteristically erratic in the heterogeneous group 4.

**Congestive Heart Failure in Man**

Considerable knowledge concerning the heart and circulation in health and disease has been obtained through the use of newer techniques such as cardiac catheterization. It is, of course, not possible to explore the human heart with the same precision, under stable conditions, or with the opportunity to alter these conditions, as is the case in animal experiments. Sometimes the imperfections and limitations of the methods employed in man have been ignored or minimized in attempts to evaluate the basic importance of the findings. While there is little reason to doubt the validity of most observations, their implications are limited with regard to basic understanding of myocardial function in health and disease because of the inadequate methodology. On the other hand, such studies have to some extent indicated the necessary direction of more basic work.

Cardiac catheterization of the right side of the heart, and, to a lesser extent, of the left, has contributed to knowledge in this field insofar as it has made possible the adequate measurement of pressures and mean flows in the cardiovascular system of normal individuals and patients in heart failure. Such measurements have been made with the subject at rest, on exercise, under the influence of certain drugs (e.g., epinephrine), and during certain other procedures such as rapid intravenous infusion or venesection. Many of these studies have been attempts to investigate the validity of Starling's law in the intact human being.

Hemodynamic studies of normal individuals at rest and exercise have indicated the normal range of minute and average stroke outputs and the expected low levels of right and left ventricular diastolic pressures (the latter measured via the pulmonary arterial wedge). There has been, in general, no consistent relationship between ventricular diastolic pressure changes and alterations in stroke volume, heart rate, minute output, or
external work (per minute or per beat).* One study, in which intrathoracic pressure was measured, thus allowing determination of true right ventricular diastolic pressure, demonstrated a direct relationship between this pressure, as a measure of right ventricular filling pressure, and cardiac output as an index of myocardial effort.14 The effects of rapid intravenous infusion or venesection on the relationship of ventricular diastolic or atrial pressure to cardiac output or external work have not been consistent from study to study.10, 15-18 Epinephrine, however, was shown, many years ago, to alter cardiac output independently of right atrial pressure.10, 15

The more gross hemodynamic aspects of congestive heart failure, as in groups 2 and 3 above, have also been revealed by catheterization. The measurable hemodynamic expressions of poor myocardial contractility are essentially those of circulatory insufficiency, i.e., high ventricular diastolic pressure (congestion with the cause localized to one or both ventricles) and diminished cardiac output. On exercise, diastolic pressure rises further while minute output (as measured) may rise slightly, remain stationary, or even fall.19, 20 Of course, circulatory insufficiency, not demonstrable at rest, may become apparent on exercise. When cardiac output is determined by the Fick principle, inadequacy in congestive heart failure is characterized by a large A-V oxygen difference relative to the level of oxygen consumption, indicating that the tissues compensate for the reduced rate of flow by greater oxygen extraction per unit of available blood. Low cardiac output may also be a feature of myxedema, but here oxygen consumption is often low and the A-V oxygen difference at rest and exercise is not relatively widened,21, 22 indicating that flow remains proportional to the oxygen demands of the body.

*The classical parameters of external work are minute cardiac output and blood pressure in the great vessel leaving the ventricle under study. Stroke work (average) is external work per minute divided by heart rate. The work done in imparting kinetic energy to the ejected blood is usually neglected.20

Such studies have also revealed that ventricular end-diastolic pressures well above the normal range may be associated with marked ventricular hypertrophy (as in aortic or pulmonic stenosis) in the absence of other evidence of heart failure.23, 24 It is postulated that this is due to marked thickening of the ventricular wall which has altered the distensibility of the relaxed chamber.

Circulatory alterations caused by rapidly acting digitalis preparations have been studied in cases of congestive heart failure. In general, right (and indirectly determined left) ventricular diastolic pressure falls (reducing congestion) while cardiac output rises and the heart rate (inconstantly) slows. There is, however, no unanimity among the various observers about the order in which these changes occur. Sometimes, there has been a fall in venous pressure followed by a rise in cardiac output25 suggesting an effect of digitalis on the venous system similar to venesection, leading to a fall in pressure and venous return so as to "decompress" an incompetent ventricle.26 In other instances, cardiac output rises without change in venous pressure, or with a subsequent fall in this pressure,27, 28 indicating the more accepted myocardial effect of digitalis. Venous pressure may also fall without a rise in cardiac output.29 The heart rate may be slowed as a primary effect of digitalis (particularly in atrial fibrillation), or slowing may reflect improvement in the myocardium.

Increased cardiac output with or without increased ventricular diastolic pressures (directly or indirectly measured) has been demonstrated in many of the "high output" states.30-37 In contrast to groups 2 and 3, high venous or atrial pressures, when present, are not characteristically altered by digitalization.38 In one study, digitalis was found to have an effect in patients with large (apparently dilated) hearts who were clinically not in failure, similar to its action on the normal heart.39

In brief, then, while low cardiac output, dilated ventricular chambers, and high ventricular diastolic pressures, collectively
characterize myocardial failure, each can exist alone under conditions in which myocardial failure is apparently absent.

Such observations are valuable but present a very incomplete picture. There is the difficulty of assessing the alterations in cardiovascular pressures against the background of respiratory variations in intrathoracic pressure. Further, the observations are only spot samples in a long drawn-out process, as obtained in the closed circulation of an intact human being. Again, the possible beat-to-beat changes in stroke volume and the possible changes in stroke volume of one ventricle independently of the other cannot be detected in man. Consequently, it has, for example, so far been impossible to record directly the momentary disparity in output between the 2 ventricles that is presumed to play a part in the development of pulmonary congestion in left ventricular failure, or to lead to its relief on treatment.

Basic to a full understanding of the behavior of the normal or failing heart as a pump, is knowledge of (1) the indices of myocardial performance or effort, (2) the factors influencing myocardial effort, and (3) the energy cost of such effort. As mentioned, clinical work directed to these matters has been dominated by the concept that relates cardiac effort to ventricular end-diastolic volume, as enunciated by Starling and his followers. Thus, external work, per minute or average per stroke, has so far been the only index of myocardial performance measurable in man. As detailed below, there are strong theoretical objections to its use as such. So far as factors influencing myocardial effort are concerned, ventricular end-diastolic pressure is a highly questionable index of end-diastolic volume. Attempts have been made to determine end-diastolic volume in man through the determination of residual volume by radiographic or dye-dilution techniques (end-diastolic volume = residual volume + stroke volume), but these are difficult to apply and again would yield average values. The clinical observation that the normal human heart decreases in size radiologically upon change from supine to erect position, and at the commencement of physical exercise, casts doubt on end-diastolic volume as the only, or even the most important, influence on myocardial effort.

With reference to the third point, measurements of cardiac oxygen consumption in man have been based on measurements of flow in the coronary sinus and its oxygen content. However, the coronary sinus flow is not a certain measure of total coronary flow, nor does it necessarily indicate the mural flow in the left ventricle or any fixed portion of it in comparisons of a group of individuals. In fact, recently the septal branch of the left descending coronary artery in the dog has been shown to drain principally via thebesian channels. Even in the same person, the drainage area of the coronary sinus may shift when the state of the individual is altered by drug or other procedure. There is sufficient uncertainty, therefore, in this method to lead one to demand qualified evaluation of the data obtained when it is at variance with animal studies in which coronary flow measurements are more precise. This is further necessitated by the well-known fact that the coronary sinus blood does not represent an exact constant index of total coronary venous blood oxygen (or substrate) content.

The data based on the coronary sinus method are, however, the best so far available in man. These indicate a correlation between external work of the heart and myocardial oxygen consumption. It is also reported that the myocardial oxygen consumption of the area drained by the coronary sinus is normal in the presence of congestive heart failure. Also, it rises on exercise as in the normal, and is unaffected by digitalis. The increase in myocardial oxygen consumption in the normal individual on exercise has been attributed to adjustments according to Starling's law. This is open to question because, among other reasons, no measurements of end-diastolic volume were made. But more significant reasons for doubt are the newer con-
cepts of the performance of the heart that have recently arisen as a result of animal studies. They have been summarized elsewhere and are discussed below as they relate to the development of a basic understanding of heart failure.

Mechanisms Involved in Experimental Cardiac Failure

Steps Involved in Muscle Contraction

Obviously congestive heart failure as defined must ultimately be referred to incompetence of the cardiac muscle, either as a primary event or secondary to an excessive load. We are concerned with the fundamental nature of the myocardial incompetence. Since energy is necessary for this performance of work, cardiac muscle energetics (metabolic sources of energy for myocardial contraction and its conversion to mechanical energy) is a good starting point for a systematic discussion of this matter. The terminology of Wollenberger is useful in this connection. Energy liberation is defined as the process concerned with the supply of energy and includes both the enzymatic oxidation of substrates, such as glucose, lactate, and the coupled transfer of energy derived from oxidative processes to the so-called high-energy compounds such as adenosinetriphosphate, adenosinediphosphate, creatine phosphate—the process of oxidative phosphorylation. Energy utilization, on the other hand, is defined as the process concerned with the expenditure of the liberated and stored energy in the development of contractile tension and heat. In the strict sense, therefore, energy utilization is chemical-mechanical coupling—the link between energy liberation and its utilization as contractile tension. This subject has been recently reviewed by Hajdu and Leonard.

Contractile tension in turn, once produced, is manifest only as muscle tension and heat, no external work being accomplished. Even in expresses it into the arteries. The amount of this conversion of tension to work depends on existing conditions, particularly on the amount and nature of the load on the heart. When the load is too great, or if other conditions prevent muscle shortening, energy utilization is manifest only as muscle tension and heat, no external work being accomplished. Even in this (isometric or, more accurately, isovolumic) type of contraction, however, shortening of the contractile elements of the heart muscle fiber still takes place, but, since the volume of the heart is not reduced the only result of this shortening is the rearrangement of the shape of the ventricle and a stretching of the elastic elements within the heart wall, which are in series with the contractile elements.

Possible Defects in Energy Transformation Which Lead to Heart Failure

On the basis of the foregoing considerations, heart muscle failure could, at least theoretically, result from (1) partial failure in energy liberation, either at the oxidative level or the chemical energy transfer level, or both; (2) inefficiency of energy utilization in the development of tension; or (3) inefficient conversion of contractile tension into external work. In the last 2 circumstances, an inordinate expenditure of energy would be necessary in order to maintain the normal capacity to do "external" work.

Impairment of Oxygen Use as a Cause of Heart Failure

Studies of oxygen usage, and of most of the common carbohydrate, lipid and amino acid substrates have been made in the normal and failing heart. For the most part, these studies relied on coronary arteriovenous differences and simultaneous determinations of coronary flow correlated with parameters of cardiac effort. Since the substrates studied may be transmuted, stored, or oxidized and since their complete oxidation may require amounts of oxygen different from that consumed in terms of actual measurement, such data would not appear to give a true picture of the rate of substrate utilization within the heart muscle. Oxygen usage, on the other hand, serves as a much better index of the over-all rate of oxidative metabolism. Since oxygen cannot be stored in significant amounts in the heart muscle, its disappearance rate
would seem a reliable index of its utilization. Because anaerobic energy-yielding reactions are relatively less important in comparison with the high yield of cardiac aerobic reactions, it is generally held that cardiac oxygen usage is a good index of the total amount of energy furnished for contraction and maintenance. This is borne out by the good correlation between indices relating cardiac effort to oxygen usage.

Comparison of the normal and failing heart reveals little difference in the rate of cardiac oxygen usage. Thus, one is tempted to conclude that energy liberation, including transfer of oxidative energy in a form useful to the contraction process, is normal in heart failure. This appears to be substantiated by the lack of difference in the levels of the various high-energy phosphorus compounds or energy-storage substances between the normal and failing heart.

Attempts to gain insight into the mechanism of chemical-mechanical coupling have been beset by major difficulties. Chief among these is the disparity between the findings in muscle models and in intact muscle. Studies of muscle models have shown a utilization of adenosinetriphosphate during contraction and revealed the relationship of myosin as an adenosinetriphosphatase. Intact muscle, on the other hand, shows no discernible decrease in adenosinetriphosphate in a single twitch and there is no apparent difference in turnover rate of adenosinetriphosphate between contracting and resting muscle. Also, wide divergencies can be demonstrated when the rate of hydrolysis of adenosinetriphosphate is related to contraction in muscle preparations. Therefore, it is hazardous in our present state of knowledge to speculate concerning the role of chemical-mechanical coupling in heart failure. However, emerging considerations regarding these mechanisms provide attractive pathways for future exploration of cause and effect relationships in cardiac failure.

Apart from the possibility of a defect in energy liberation, the integrity of the contractile protein (actinomyosin) comes into question in failure of the heart muscle. It is conceivable that acute or chronic failure might alter the character of such proteins and affect muscle response even in the presence of an adequate energy supply and its utilization up to this point. Indeed, two lines of investigation suggest that this is more than a possibility. Olson and Piatnek found molecular weight changes in cardiac myosin after experimentally induced failure, and Benson et al. noted a decrease in the tension response of glycerol-extracted myocardial fibers from failing hearts. However, the possibility that changes in elasticity could explain these results was not excluded in Benson's experiments.

While evidence to the contrary seems virtually complete, the possibility still exists that heart failure, at least under some circumstances, may be caused primarily by a defect in energy liberation that is not revealed by measurements of oxygen consumption and concentration of high-energy compounds. In myocardial infarction, in which viable muscle is destroyed, there can be no doubt that heart muscle failure is due to loss of liberated energy, and a similar state may be more subtly induced in other disease states of the muscle (as in group 3 above). In cases such as these, the evidence of a deficit in energy liberation will be mirrored in a diminished cardiac effort. As recovery occurs, or compensatory

*One other concept should be mentioned in this connection. The heart in situ, as distinct from the isolated heart or that of the heart-lung preparation, may take up substrate from the blood as an energy source and pass incompletely degraded products back into the blood for oxidation in other organs. While this process of catabolism of substrate and degraded material must be small normally, the possibility exists that it may be significantly augmented in myocardial failure, thereby making the oxygen consumption of the heart a less perfect index of its energy liberation. For example, the cycle of blood glucose going to the heart and myocardial lactic acid passing back to the blood may be augmented in heart failure. This is an action which spares the heart, while yielding energy for it. The above must be considered only as a theoretical possibility.
mechanisms, e.g., hypertrophy of surrounding muscle, come into play. Energy liberation, as well as heart function, will tend to return to normal.

Experimental studies by and large however, have led most reviewers to conclude that it is the process of energy utilization that is abnormal in heart failure. Until clean experimental evidence to the contrary is forthcoming, we cannot favor impairment of energy liberation as the ordinary mode of heart muscle failure. This conclusion appears to be supported by the fact that the external mechanical efficiency of the heart, the ratio of external work done to oxygen used, is decreased in heart failure. Furthermore, it has been shown that measures taken to reverse failure also serve to restore toward normal this index of efficiency, both in the animal and clinically. Unfortunately, this argument based on changes in external mechanical efficiency may be spurious, since the reduction in cardiac output and increase in heart rate that accompany heart failure would lead to a decrease in external mechanical efficiency even in the nonfailing heart. Thus, it may turn out that the reduction of efficiency is a secondary phenomenon accompanying changes in cardiac output and heart rate rather than a primary feature of heart failure. This matter cannot be regarded as settled.

**Impairment of Chemical Energy Utilization for External Work as a Cause of Heart Failure**

External work—used in the calculation of external mechanical efficiency—really does not exemplify the conversion of chemical to mechanical energy appearing as muscle tension. In our view, the ideal index to myocardial effort would be the accurate determination of muscle tension of the ventricles, actual external work being incidental.

Some insight into the mechanism defect in heart failure may be revealed by a consideration of the development of tension in contracting heart muscle. The earliest studies of cardiac muscle were concerned with finding analogies between skeletal and cardiac muscle activity. O. Frank constructed idealized curves based on pressure-volume changes in the cardiac cycle and explained them on the basis of length-tension changes seen in skeletal muscle. Characteristic curves relating pressure to volume were constructed for the heart in diastole and in systole, in both isometric and isotonic contraction. The actual pressure-volume changes occurring during a cardiac cycle were then superimposed upon this, to represent the actual expenditure of energy appearing as heart work. Later, Starling and his associates elaborated the general principles governing control of energy expenditure using the mammalian heart-lung preparation. They extended Frank's observations by relating ventricular end-diastolic volume (i.e., the length of the muscle fiber) to the energy set free in the following systole.

In our own previous studies, the pressure-volume relationships that Frank had demonstrated and Starling had applied to the mammalian heart were used to define the viscous-elastic properties of the fully relaxed and fully contracted heart. The curves so derived indicate respectively the diastolic and systolic tone of the heart. Diastolic tone can affect the end-diastolic volume and systolic tone helps to determine the systolic residue of the heart.

Further studies by Starling and others were based primarily on measurable hemodynamic variables. Exhaustive investigations were made of the effects of altering vascular resistance, venous return, and heart rate upon end-diastolic volume, end-diastolic pressure, and the extent of contraction. The preoccupation of these investigations with hemodynamic studies of this type led to neglect of the concept of tension. On the other hand, Wiggers and Katz, in 1928, analyzed the intraventricular pressure curve and suggested that the area beneath the isometric portions of the curve and that part during ejection above arterial diastolic pressure should be taken to represent the "static effort," while that beneath the arterial diastolic pressure during the ejection portion of the curve should be considered as an index of "dynamic effort."
This distinction served to emphasize the large differences in tension expenditure associated with different aspects of muscle contraction during the cardiac cycle. These concepts of the character of the heart’s effort were interpreted in terms of time-tension relationships found in skeletal muscle, in which a correlation between oxygen consumption and the duration of tension development had been demonstrated.74

Understanding of functional relationships has been materially advanced by morphologic considerations. Anatomic studies reveal that the majority of the myocardial fibers have both their origin and insertion on the valve rings, while a few are attached to the chordae tendineae or follow a circumferential path around the ventricles.72 These facts added to the known physical relationships governing pressure and tension in a hollow viscus led to the realization that, other things being equal, a ventricle that is initially filled with a larger blood volume will require augmented contractile tension in elaborating the pressure necessary to open the semilunar valves and to maintain it above the arterial diastolic level. The extent of shortening thereafter and the relation of ejected volume to end-diastolic volume will determine the direction and rate of tension change associated with ejection.

Burch et al.,78 in 1952, presented an extended theoretical analysis of these factors, with special reference to the consequence of cardiac dilatation such as is seen in heart failure. It was shown that contractile tension usually decreases in the normal heart during ejection because of the rapid decrease in internal surface area as the heart volume declines, and despite the continuing increase in pressure from the diastolic level to the systolic peak. However, when the heart is dilated, as in failure, ejection of the usual stroke volume is associated with relatively little shortening. Since the decrease in internal surface area is proportionately less, an increase in contractile tension may be required under these circumstances in order to raise blood pressure to the same systolic peak.

Another aspect of this same question has come under investigation in our laboratory74 and that of Sarnoff et al.75 In these studies, indices of tension were sought in relation to the oxygen cost in the intact heart. Evaluation of blood pressure, heart rate, and cardiac output showed that the first 2 were more closely related to oxygen requirements than the last. Thus, for any given heart size, blood pressure may be taken as a direct function of contractile tension per beat, and heart rate as a measure of the number of times tension is created. Together they serve admirably as an index to total tension developed over any period of time. The studies demonstrated directly that minute cardiac output, which receives so much attention in the calculation of external work and efficiency, is of minor importance as a measure of cardiac effort, whereas heart rate, which is usually ignored in these calculations, is of great importance.

Recently, we approached the problem of tension conversion to external work and the energy cost of tension development directly by measuring the oxygen cost of left ventricular tension in the absence of external work.76 A fluid-filled balloon placed in the otherwise empty ventricle permitted the calculation of tension per beat exerted on the balloon along with the concomitant oxygen cost. The results indicated that oxygen cost is directly related to energy expenditure as tension per beat. The further conversion of the developed tension as external work is a secondary, far less significant factor that is related to the mechanical advantages or disadvantages dictated by the range of size and shape of the heart during its cycle.

It would seem logical to conclude from the above considerations that heart failure does not appear to be related to defects in energy utilization for tension development. Rather, it would seem that muscle tension in heart failure is not as productive of external work as in the normal heart. This relative ineffectiveness of muscle tension appears to depend on changes in heart size and shape with heart failure. Rushmer77 in his elegant studies of
size changes in the intact unanesthetized animal has emphasized the range of dimensional changes in various diameters of the nonfailing heart. Further studies are needed along these lines, in which attention should be paid to the role of dilatation in the failing heart, and to its detrimental effect on the utilization of tension as external work. Perhaps it will turn out that this relationship fixes the limit of dilatation as a compensatory mechanism.

While it appears that the dilated failing heart requires considerably more contractile tension to meet the needs of a given load, no indication has been given as to how this dilatation comes about. It was evident in the "heart-lung period" that important differences could be discerned in the response to load between a fresh and a "tired" heart-lung preparation, as well as before and after treatment with insulin and glucose. Primarily, these differences consisted in alterations in responsiveness of the heart—a greater output or an increased pressure being noted in the fresh heart or the one treated with insulin and glucose. This is consistent in any consistent increase in end-diastolic volume. These facts indicate that other mechanisms of cardiac control exist in the heart-lung preparation which the natural neural and humoral influences on the heart muscle are absent. On the other hand, as depletion gradually progresses, the heart in the heart-lung preparation still responded with augmented effort to an increase in load, this adjustment now being dependent primarily on the increase in end-diastolic volume. This last mechanism can therefore be considered to be the basic primitive adjustment upon which other mechanisms of finer adjustment are superimposed.

The failing heart during this early period of investigation was considered as merely an enlarged version of the normal heart. Enlargement in turn was considered as due in part to an increased filling pressure gradient and in part to a decrease in diastolic tone. The ability of such a heart to meet the demands for flow in the body was viewed as depending on whether or not it had reached the maximum size beyond which output would decline.

Newer information, based on a more intact nondeteriorating preparation subject to the usual neural and humoral stimuli, makes possible a better comparison between normal and failing hearts in terms of their responsiveness to various hemodynamic situations.

The distinctive characteristics of such a preparation may be briefly summarized:

1. The normal heart does not usually empty with each stroke, in fact as much as 50 percent of the end-diastolic volume remains as end-systolic residue.79

2. The normal heart, at rest, has a characteristic size in relation to body size and weight for each species.80

3. The normal heart generally has a greater volume in the supine than in the erect position, and has a characteristic relation of number of beats per minute to stroke volume (such that the rate is greater for smaller outputs).81

4. In the face of a growing load, the normal heart may first decrease in size—meeting the increased output demands with greater stroke volume through mobilization of end-systolic residue. Further load may then lead to an increase in heart rate. Only when the load is increased still further does the heart increase in size and bring end-diastolic volume into play.

5. Wild animals of a given species have larger hearts in relation to their body size and weight than tame ones. This relation has also been found in trained athletes as contrasted with untrained individuals. In athletes, there appear to be a greater end-systolic residue and a characteristically slower heart rate in relation to a given work-load. Further, in athletes, an increase in load tends to cause a greater stroke volume with minimal increases in heart rate as contrasted with the untrained person in whom heart rate acceleration is marked and early.

The failing heart appears to resemble the trained heart in the sense that both are
enlarged and both appear to have augmented end-systolic residues. Superficially the failing heart would seem to have the same potential advantages as does the trained heart, i.e., a lower heart rate for a given output and a greater reserve of mobilization. However, the epitome of heart failure seems to be the loss of these 2 advantages. Systolic residue does not appear to be available for the augmentation of stroke volume in meeting the challenge of an increased work load. Nor does end-diastolic volume appear to be so effective. Instead, tachycardia is the mechanism by which an attempt is made to increase minute-output. Because these advantages are lacking, the failing heart has been likened to the heart in the deteriorated heart-lung preparation, which also lacks these capacities. Like the latter, the failing heart needs a greater end-diastolic volume in order to increase output and overcome augmented systolic loads, rather than being able to draw upon end-systolic residue in the first instance and to react independently of end-diastolic volume in the second instance. Apparently this dependence of myocardial effort on end-diastolic volume represents a primitive regulation, or the last resort of a failing heart.

**Contractility and Distensibility of the Heart in Failure**

The capacity to mobilize end-systolic volume and in general to react independently of end-diastolic volume is attributed to that characteristic of muscle known as contractility. Contractility has so far lacked a sufficiently precise definition. In the cardiovascular literature one finds it referred to several phenomena relating to the responsiveness of the entire heart or heart muscle strips. A positive inotropic response usually indicates augmented force of contraction after drug or hormonal exhibition or neural stimulation. Treppe (the staircase effect) encompasses augmented contraction following (1) a period of rest, (2) post-extrasystolic potentiation, and (3) increased frequency of stimulation. Catacholamine exhibition and changes in the ionic milieu, notably a decrease in potassium ion and an increase in calcium ion, also augment contractility.

It appears at present that contractility is, in its broad sense, a manifestation of responsiveness to many different stimuli, some mediated via the autonomic nervous system and others via humoral pathways. Rushmer’s efforts to elucidate this responsiveness in the normal, unanesthetized animal must be singled out as noteworthy and revolutionary.

The most important characteristic of contractility for the purpose of this discussion appears to be an ability to vary the extent of shortening for a given end-diastolic volume. More marked shortening in these circumstances has the effect of mobilizing the systolic residue of the heart. Thus, it would seem that the failing heart—dependent on a minimal mode of responsiveness—dilated and unable to mobilize the large systolic residue, lacks or is relatively deficient in that property of muscle considered as contractility.

Clear experimental evidence relating to differences in contractility, or similar properties (otherwise designated), between the failing and normal heart is not yet available. Perhaps restating these concepts will stimulate much-needed research in this direction.

Several recent studies that have provided further insight into the intrinsic nature of contractility are reviewed here on the basis of their potential significance in the understanding of changes in failing cardiac muscle. Abbott and Mommaerts, in a study of the inotropic mechanism of isolated papillary muscle, considered the change in muscle response to be an alteration of the force-velocity relationship of the contracting mechanism. Hill had demonstrated that the velocity of contraction is empirically related to the load that could be defined by a specific characteristic curve. Thus, knowing the work-load and the conditions of contraction, one can calculate the velocity. Force-velocity curves were found not to be superimposable after inotropic augmentation, implying that the beat of papillary muscle became both faster.
and stronger on stimulation. Thus, a greater beat frequency shifted the optimal efficiency of the muscle so as to cause a greater velocity of shortening. To quote: "The heart adjusts its internal characteristics so that at greater speeds of action it is optimally efficient at greater speeds of shortening."787

Alternatively, a change in contractility may depend on an alteration of the "active state." This alludes to a muscle change that precedes and coexists with the actual contraction, and without which a contractile response is impossible. The "active state" is presumed to be a state of readiness to contract that must occur after stimulation and before the manifest response. The duration of the active state is appreciably shorter than the mechanical response. It has been shown that an increased duration of the active state leads to a higher and more sustained twitch tension. Abbott and Mommaerts found that the duration of the active state was unchanged or even decreased when the intensity of contraction was increased.87 Trendelenburg and Lüllman89 also failed to find any apparent change in the duration of the active state associated with increased stimulation frequency or with alteration of the length-tension relationship. Niedergerke,86 however, found that a milieu rich in calcium ion did increase the duration of the active state of cardiac muscle.

The special significance of the active state for the intensity of the ensuing contraction provides an attractive speculation on one possible advantage of cardiac dilatation. Before stimulated muscle begins to shorten, the contracting elements take up the slack of the elastic components in series with them. Prior stretch, which would passively remove this slack or even stretch the elastic elements, would permit the fuller use of the active state for the actual act of shortening. Thus, there is an advantage to a certain degree of dilatation in that the full potential of the active state for shortening can be utilized. However, such an advantage may only be temporary. Chronically stretched fibers may lose their resting tension and thereby the mechanical advantage of the stretch, as a result of plastic elongation and "creep." These are essentially hysteresis phenomena and occur after prolonged extension under load, so that the initial length is not attained upon release. Such changes in physical properties may become irreversible in the dilatation of the failing heart.60

Contractility is only one inherent property of the heart. Distensibility is another. While contractility is associated with the extent, velocity, and force of shortening, distensibility is associated with the extent, and rate of relaxation of a ventricle. The extent of relaxation has been appreciated for some time and labeled as the diastolic tone of the heart.67 The course of relaxation is important in setting the mode of contraction of the heart. The velocity and duration of relaxation appear to have special significance in terms of the rate of filling of the heart when filling time is limited as in tachycardia. The phase of active relaxation appears to be more closely related to the restitutive chemical processes that are required for sustained activity. Brewster et al.,91 have shown that the enzymatic reactions that occur during relaxation have a large Q10, and a large energy transfer, as would be expected in relation to chemical-mechanical coupling. Contraction, on the other hand, is associated with processes having a small Q10, usually associated with ionic forces and insufficient to account for contraction energy expenditures. Further, it has been found that the metabolic rate in diastole is related to its duration.

Hill and Howarth92 have presented evidence that the act of stretching a skeletal muscle fiber is associated with the addition of energy to the fiber. Active relaxation (in terms of energy exchange) and passive extension of the fibers by the inflowing blood thus would appear to be related. Part of the chemical energy potential may be lost when forces in the muscle resist extension through incomplete relaxation. Buckley and her associates93, 94 have made an extensive study of the relaxation process in the mammalian ventricle, par-
particularly with reference to impedance and compliance during filling. These terms are antonyms and relate to the resistance to filling and the extent to which the ventricle walls expand upon being filled. The amount of filling is related not only to the time available for filling but also to these concurrent changes in the physical properties of the muscle that resist or facilitate filling. These impedance changes were related by Buckley et al., to changes in its viscous-elastic properties—a relationship already noted previously by others in the consideration of the systolic and diastolic tone of the heart. Most recently, Buckley et al.\textsuperscript{94} found that a decrease in compliance and an increase in impedance occur during acute heart failure in the dog, changes which were irreversible. This represents another dimension in physical properties, similar to those considered relative to the systolic phase of the cardiac cycle. They are likewise subject to change and may be involved in the process leading to or resulting from cardiac muscle failure in man.

Conclusions

From all of this it would seem that the phenomena of heart failure reside in the heart muscle and are involved in its size, shape, and the physical properties during relaxation and contraction that determine its distensibility and contractility. These last are set by the metabolism and chemical milieu of the cardiac muscle, and are primarily physical, chemical, and biophysical in character. They may be determined by anatomic and geometric alterations as well. At present, it would seem that the energetics of the heart in terms of energy release and of utilization of chemical energy for the development of muscle tension are less often involved in heart muscle failure, than is the conversion of tension to external work. This background has made the development of heart muscle failure easier to understand. It would be hazardous to say that the subject is settled, but it is safe to assume that the directions for further study have been established.

Our purpose has been to review the subject of hemodynamics in congestive heart failure as it stands today. The picture of course is still crude, but the outlines depicting the true nature of congestive heart failure are dimly discernible. Future work will doubtlessly bring it into sharper focus.

Conclusions in Interlingua

Le objectivo del presente articulo es revisar le hemodynamica de congestive disfallimento cardiaco secundo le stato currente del recerca. Le autores insiste que le ver natura de congestive disfallimento cardiaco ben que illo es certo non ancora clar, comencia al minus devenir recognoscibile in su contornos general. Investigationes futur va sin dubita succeder a focalisar lo plus netemente.

Super le base del datos jam establite il pare que le phenomenos de disfallimento cardiaco ha lor sito in le myocardio e es interessate in le dimensiones e le conformation de illo si ben que como in su proprietates physie de relaxacion e de contraction le quales determina su distensibilitate e su contractilitate. Iste ultimes depende del metabolismo e del chimismo del myocardio e es principalmente de character physie, chimic, e biophyse. Illos etiam pote esser determinate per alterations anatomic e geometric. Al tempore presente il pare que le energetica del corde—i.e. le provision de energia e le utilisation de energia chimic in le disfallimento de tension muscular—es interessate minus frequentemente in disfallimento myocardial que le conversion de tension in labor externe.

Iste constatazioni fornii un plus firme base pro le comprension del disfallimento myocardial. Le autores assezse que il essera risose mantener que le question es resolvite sed que il es permisible insister que al minus le direction in que investigationes futur debe avantiar es clarmente establit.

References


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