EDITORIAL

On the Difference Between the Heart's Output and Its Contractile State

The heart's prime function is to deliver sufficient oxygenated blood to meet the metabolic requirements of the tissues, and heart failure is said to exist when the heart is unable to pump blood at a rate commensurate with these requirements. Accordingly, an accurate measure of the heart's ability to perform this task, i.e., the determination of the cardiac output, has properly been considered a key test of cardiac function. The development of cardiac catheterization techniques in the early 1940's provided the clinical physiologist, for the first time, with the ability to sample mixed venous blood and, thereby, to apply the Fick principle to the measurement of the cardiac output. This approach, and the theoretically closely related indicator-dilution method, have remained cornerstones on which much of the structure of modern cardiology is built. It is, therefore, understandable that the clinician tends to view the cardiac output, at rest and during various levels of activity, as a prime index of the heart's ability to carry out its major function, and that therapeutic interventions in patients with heart disease are frequently evaluated in terms of their effects on cardiac output.

As valuable as measurements of cardiac output may be, their limitations are frequently not recognized. Two major problems exist. The first is technical, and relates to the inaccuracies in the measurement, which continue to plague investigators and clinicians alike. It is fair to say that these technical problems are most serious in the critically ill patient in whom rapid fluctuations in cardiac output occur. In this editorial, I should like to deal primarily with the second problem, which is that the cardiac output and the heart's contractile state cannot be related to one another in a simple manner. Characterization of contractile state is of prime importance in assessment of cardiac function. However, the contractile state is only one of several determinants of the heart's ability to eject blood. Thus, measurement of the cardiac output alone is of limited value in characterization of this important variable. What then controls the volume of blood ejected by the heart besides myocardial contractility? Since, at any given ventricular end-diastolic volume and heart rate, the cardiac output is a function of the extent of myocardial fiber shortening, it may be appropriate to rephrase the question and inquire what factors, besides myocardial contractility, determine the extent of myocardial fiber shortening.

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Rather than limiting their attention to the intact ventricle, cardiovascular physiologists have appreciated for a number of years that a fruitful approach to the solution of this problem may be the examination of isolated heart muscle. The geometric arrangement of cardiac muscle in situ is complex, with spiraling intertwining fiber bundles complicating analysis of the behavior of the individual myocardial cell. For this reason, papillary muscles or trabeculae carneae, whose fibers run in a parallel fashion, have provided a suitable model for study. Also, study of the tissue in a myograph allows precise control of the muscle's physical and chemical environments, loading conditions, and contraction frequency, and the elucidation of the effect on fiber shortening by individually varying these influences.

The extent of shortening during each contraction appears to be dependent on three separate factors: (1) the preload, which determines the heart muscle fiber's end-diastolic length; (2) the afterload, which is closely related to the intramyocardial systolic tension; and (3) the contractile or inotropic state of the myocardium. At any level of the contractile state, the extent of shortening varies directly with the preload and inversely with the afterload. When the latter is progressively raised, an increasing proportion of the muscle's contractile activity is expended in the generation of tension, and a smaller fraction is expended in myocardial fiber shortening. Only when afterload and preload are constant will the extent of myocardial fiber shortening depend directly on the heart's contractile state. Obviously, the total extent of muscular shortening per minute also depends on the contraction frequency, and heart rate is the fourth major determinant of cardiac output.

Although the aforementioned, complex geometric arrangement of myocardial fibers makes it more difficult to express the fundamental determinants of the extent of contraction in vivo in precise terms, it is evident that the same principles that affect the extent of shortening of isolated cardiac muscle influence the stroke volume of the intact heart. For example, when aortic outflow impedance is gradually raised while ventricular end-diastolic volume is held constant, stroke volume declines until a level of impedance is reached at which the maximum force-generating capacity of the myocardium is exceeded, and the contraction becomes isovolumetric, i.e., ventricular ejection ceases. Conversely, when afterload is reduced, the impedance to ventricular ejection falls, and stroke volume rises. This may occur as a result of arteriolar dilatation, a reduction in blood viscosity, as occurs in anemia, or the opening of an arteriovenous fistula.

From these considerations, it should be clear that when changes in afterload occur, there will be reciprocal changes in cardiac output which need not reflect changes in the myocardial contractile state. For example, if cardiac output rises following surgical correction of severe aortic stenosis or the successful treatment of hypertension, it may simply be due to the reduction in afterload. Similarly, the elevated cardiac output associated with severe anemia (low blood viscosity), fever (arteriolar dilatation), or patent ductus arteriosus (arteriovenous fistula), may be explained in simple mechanical terms alone; an augmented contractile state, such as occurs with cardiac sympathetic stimulation, need not necessarily be invoked.

The effects of simple alterations of preload on cardiac output are even more widely appreciated. Thus, the depression of cardiac output which occurs with hypovolemia (hemorrhagic shock), displacement of blood from the thorax (positive pressure ventilation), or cardiac compression (pericardial tamponade), may be explained solely on the basis of a reduction of preload; and the elevated cardiac output in some patients with polycythemia vera or acute glomerulonephritis need not reflect an augmented contractile state, but instead a higher preload resulting from hypervolemia.

There is considerable evidence that when the contractile state of the myocardium is normal, cardiac output is dependent more
upon peripheral factors and the influence these factors exert on the ventricular preload and afterload, than on central factors, i.e., on the contractile state of the myocardium. For example, it has been shown that both digitalis glycosides and the application of paired electrical stimulation, while exerting powerful inotropic influences, do not elevate cardiac output in normal human subjects or experimental animals. However, in the presence of heart failure these influences elevate cardiac output.\(^1\) It was the practice to ascribe these differences in the response to cardiac glycosides of the cardiac output of normal and failing hearts to a fundamental difference in the response of normal and failing heart muscle. Rather, it now appears that a strong positive inotropic influence is exerted by digitalis compounds and by post Extrasystolic potentiation, not only in failing but in nonfailing hearts as well.

In the nonfailing heart, the cardiac output is not limited by the level of the contractile state of the normal myocardium, and augmentation of the latter does not elevate cardiac output. In contrast, in heart failure, the myocardial contractile state is depressed, and this depression limits cardiac output; hence, augmentation of the contractile state raises the output.

The relation between a chain and one of its links may be a useful, though oversimplified, analogy for explaining the relation between cardiac output and myocardial contractile state. The total weight that a chain can support will be increased only if its weakest link is strengthened. Thus, in a patient with heart failure and depressed contractile state, an improvement of the contractile state, which may be thought of as strengthening the weakest link, will, of course, result in an elevation of the cardiac output. On the other hand, when one of the other three major links of the chain, i.e., preload, afterload, or heart rate, is limiting, then it is not surprising that strengthening the non-limiting link, i.e., improving the myocardial contractile state, does not improve cardiac output.

In the intact individual, all four of the principal determinants of cardiac output are interdependent, and a simple change in one will affect the others. For example, an elevation of afterload produced by peripheral vasoconstriction will in turn evoke a small increase in preload, and the latter will oppose the depression of stroke volume anticipated from the augmented afterload. The activity of the autonomic nervous system will minimize the increase in afterload by inducing reflex changes in vascular resistance, venous tone, heart rate, and cardiac contractile state.

The mammalian organism has evolved an extremely effective set of control systems which normally serve to adjust the heart's output to the metabolic demands of the tissues under a wide variety of conditions. When these demands are elevated, as during physical exertion, the myocardial contractile state is stimulated by the sympathetic nervous system, and the cardiac output rises. However, this stimulation of the contractile state may not play an important role in the elevation of the cardiac output. Witness, for instance, the almost normal increment in cardiac output that occurs during exercise in the presence of pharmacologic\(^2\) or surgical denervation of the heart,\(^3\) despite the absence of the normal increment in the myocardial contractile state. How can this increase in cardiac output which occurs during exercise in the subject lacking cardiac sympathetic support be explained? It can be explained primarily by a decrease in afterload, as a consequence of the metabolic vasodilation that occurs in skeletal muscle during exercise, and, to a lesser extent, on a small increase of preload, i.e., an elevation of ventricular end-diastolic volume. This explanation is supported by the studies of Warner et al., which demonstrated that the exercise-induced elevation of cardiac output can be blocked by prevention of the normal reduction of peripheral resistance,\(^4\) as well as by studies from our laboratories, which showed that the normal slight decrease of ventricular end-diastolic volume which is observed in supine subjects during light exercise does not occur, and may even be reversed, when exercise is
carried out in the presence of beta-adrenergic blockade.\(^5\)

Understanding of the regulation of cardiac output is an enormously complex problem, and the identification of the four principal determinants of cardiac output represents a starting point for the solution. The precise manner in which these four determinants interact in normal and abnormal circulatory states is now undergoing intensive study. Undoubtedly, important details will be filled in with a "systems analysis" approach. However, our state of knowledge at this time does make it clear that equating a change in cardiac output with a similar directional change in myocardial contractile state is an unwarranted oversimplification.

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References

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