Biochemical "Defect" in the Hypertrophied and Failing Heart

Deleterious or Compensatory?

By ARNOLD M. KATZ, M.D.

"It is generally established that the normal heart may become incapable of maintaining an adequate cardiac output or preventing venous engorgement whenever it is presented acutely with an overwhelming load beyond its pumping capacity. This state is not failure of a diseased heart, but it has been designated 'failure' by many. It is more difficult to define the situation where such an overload sets up a vicious cycle which progressively potentiates the load upon the heart for hours or days. After a lapse of time, this load strains the mechanisms available for compensation to the point where venous congestion or reduced cardiac output becomes evident. Does this turning point mean that the heart has become abnormal, in a functional sense, and, therefore, is it now to be a case of heart failure in the accepted sense? . . . How much of the circulatory change is due to the load and how much to mechanisms called upon to meet the load? When does myocardial deterioration begin, and when does myocardial failure start? . . . How can one determine whether it is cardiac loading or myocardial failure which is responsible for invoking the compensatory mechanisms?"

THE EXTENT to which alterations in the myocardium contribute to the clinical deterioration of patients with long-standing hemodynamic overloading represented a major unanswered question at the Second National Conference on Cardiovascular Diseases, held in Washington, D.C. in November 1964 under the joint auspices of the U.S. Public Health Service and the American Heart Association. At that time, it had not been clearly established that myocardial function was reduced in the heart subjected to long-standing mechanical stress such as occurs in aortic stenosis or mitral insufficiency. Prior to 1964, studies of cardiac function in various pathologic states were complicated by the unsolved problem of dissociating circulatory abnormalities from those arising in the myocardium itself. The major advances in our understanding of cardiac contraction over the last decade have provided at least partial answers to many of these questions and it is now well established that prolonged hemodynamic stress leads to reduced myocardial contractility. Studies of cardiac muscle mechanics, in spite of many unresolved controversies, clearly show that contractility is reduced in the heart that hypertrophies or fails after prolonged hemodynamic overloading. This effect has been demonstrated in the hearts of experimental animals and, subject to some reservations about the precision of this approach in the intact ventricle, a depression of myocardial function appears to accompany long-standing hemodynamic stress in man.
DEFECT IN FAILING HEART

At this time it is appropriate to ask whether impaired contractility in the chronically overloaded heart is wholly deleterious, in that it hastens the death of these patients, or whether, instead, the reduced contractility represents a compensatory mechanism that actually prolongs life. Similarly, must we consider the evidence for attenuation of certain biochemical reactions in the hypertrophied or failing heart to indicate the existence of “defects” that contribute to the death of these patients, or is it possible that, instead, these molecular alterations represent compensatory mechanisms that sustain life, though at a reduced pace of activity?

In 1964, at the time of the Second National Conference on Cardiovascular Diseases, most available studies of the biochemistry of the hypertrophied and failing heart had been directed to the hypothesis that the production of high-energy phosphate compounds (adenosine triphosphate, the immediate fuel for contraction, and phosphocreatine, the “ready reserve” of phosphate-bond energy) was abnormal under conditions of hemodynamic stress. A number of these early studies pointed toward the existence of significant abnormalities in energy production, but refinements in both preparative methods and analytic technics do not support the view that oxidative energy production is seriously deranged in these hearts.\(^4\) There is evidence, however, that alterations in mitochondrial energy production may occur in hearts of animals after prolonged, severe congestive failure.\(^5\)\(^6\) The lack of a major defect in energy production is also supported by the finding that ATP levels are not depressed in the hypertrophied or failing myocardium,\(^7\) although a slight fall in phosphocreatine may indicate some impairment in the ability of energy production to remain abreast of the increased energy demands, particularly in the more severe states of congestive heart failure. Thus, it now appears that alterations in the pathways of energy production and the reserves of high-energy phosphate compounds cannot themselves account for the reduced contractility of the hypertrophied heart, although they may be of pathogenetic significance in the more severely failing heart. For this reason, attention has shifted to an examination of the energy-consuming reactions that are responsible for cardiac function, most significantly those responsible for the initiation and execution of the contractile process itself.

As knowledge in any specific area of investigation is linked inevitably to the advance of the field as a whole, so the study of the contractile process in the hypertrophied and failing heart has gained from the tremendous growth of our understanding of the chemistry of muscular contraction. Questions that could not even be asked 10 years ago are now being answered, and the work of the pioneers in this area, once considered to be the province of the basic scientist, is now coming to be increasingly important in the understanding of human disease. Thus, we are now in a position to search for the causes of reduced contractility in the hemodynamically stressed human heart and to define such alterations in terms of specific changes in the interactions of the heart’s contractile proteins and in the processes of excitation-contraction coupling responsible for both the initiation and gradation of the heart’s contractile response.

The role of changes in the physicochemical properties of the myosin molecule in heart failure, a major controversy of the late 1950’s and early 1960’s, has now been resolved. There is general agreement that the physicochemical and structural characteristics of this contractile protein, which makes up the thick filament of muscle and is instrumental in both energy utilization and motion, are normal in the failing heart.\(^8\) On the other hand, there a growing body of evidence that more subtle alterations in this molecule appear in the hemodynamically stressed heart. These alterations can account for both a depression of myosin ATPase (i.e. the rate of liberation of chemical energy, measured as hydrolysis of ATP in vitro)\(^8\)\(^-\)\(^12\) (Conway CR, Heazlitt RA, Montag J: Personal communication) and a reduction in myocardial contractility in the living heart. This change, which could occur if an altered low molecular weight subunit of the myosin molecule was produced in the overloaded heart, would decrease contractility by reducing maximum shortening velocity in the myocardium.\(^8\)

Changes that may relate to excitation-contraction coupling have also been described in the hypertrophied and failing heart. These abnormalities, which have been identified in a number of in vitro systems believed to represent the heart’s sarcoplasmic reticulum, all point toward an impairment in the properties of those systems responsible for the delivery of calcium ion to activate the heart’s contractile proteins.\(^13\)\(^-\)\(^16\) While these findings cannot yet be interpreted fully, they indicate that the number of tension-generating sites activated in the chronically overloaded heart is depressed. Unlike the reduction in myosin ATPase, which can be predicted to influence maximal shortening velocity at zero load, a reduction in the amount of calcium...
delivered to the heart’s contractile proteins at the onset of systole would, at least on theoretic grounds, be expected to reduce the maximum force generated during systole. Marked depletion of norepinephrine in the failing heart like the changes mentioned above, may lead to a reduction in myocardial contractility.

At the present time, these alterations in the biochemical properties of the hypertrophied and failing heart are usually considered to be “defects” that contribute to the clinical deterioration of the patient with heart failure. Yet it is possible that, instead, the reduction in contractility is compensatory in that it prolongs life by easing the burden on the chronically overloaded heart. Since the heart is required to contract without pause for the lifetime of the organism, it follows that the energy-consuming processes of muscular contraction cannot proceed more rapidly than can the energy-producing reactions that resupply chemical energy (ATP). In the face of a sustained hemodynamic load, which inevitably increases energy utilization by the heart, an attenuation of the intrinsic energy demands by the myocardium might be important for survival. Thus, the production of a myosin which contains altered light subunits that cause a decrease in the energy utilization rate could enable the myocardium to function more efficiently in the face of the increased wall tension when the heart dilates, or when intraventricular pressure is increased. Such an increase in the efficiency of contraction by individual cells would, however, probably not be readily detectable by analyses of cardiac oxygen consumption and external work because of the many difficulties in relating organ efficiency to cellular efficiency. Although such an enhancement of cellular efficiency would be achieved at the cost of a reduction in overall contractile performance, this price may well be warranted in terms of a prolongation of survival, albeit at a lower level of function. Similarly, a reduction in the delivery of Ca to the cardiac contractile proteins and an attenuation of the inotropic and chronotropic responses to stress might also prolong life in the face of severe cardiovascular abnormalities, although an increase in mechanical efficiency is less apparent in these cases. These considerations should raise important questions as to the potential beneficial consequences of altered biochemical function in the chronically overloaded heart, and may lead to a reevaluation of the commonly held belief that these alterations represent “defects” that serve only to hasten the clinical deterioration of these patients.

Positive inotropic agents such as digitalis clearly improve myocardial performance in heart failure while acute administration of a negative inotropic agent like propranolol causes obvious clinical deterioration in this condition. It is not inconceivable, however, that chronic administration of these drugs could have the opposite effect on long-term survival. Thus, in the ischemic heart where an imbalance between energy production and energy consumption is due to attenuation of the former, rather than augmentation of the latter as occurs in the overloaded heart, it has recently been shown that positive inotropy can increase the amount of ischemic damage while negative inotropy reduces the extent of necrosis. Application of these concepts to clinical therapy in the chronically overloaded heart, however, is obviously speculative, although this approach may warrant evaluation in experimental animals.

References

Circulation, Volume XLVII, May 1973
19. Awan MZ, Goldspink G: Energetics of the development and maintenance of isometric tension by mammalian fast and slow muscles. J Mechanochem Cell Motility 1: 97, 1972
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ARNOLD M. KATZ

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