Cardiac Hypertrophy: The Consequences for Diastole*

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Cardiac hypertrophy is an adaptive response that permits the heart to perform increased work while maintaining normal myocardial fiber stress and shortening. The pattern of hypertrophy that develops is specific to the inciting stress. When the stress is an increase in diastolic ventricular volume and wall stress, hypertrophy is associated with elongation and thickening of cardiac myocytes, which appear to be accomplished by both series and parallel addition of new sarcomeres. In contrast, chronic pressure overload results in a pattern of concentric hypertrophy in which there is a predominant increase in wall thickness relative to chamber radius, presumably due to the addition of new sarcomeres in parallel (1). Recent work (2) indicates that the mechanical factor that triggers an increase in protein synthesis is stretch of the ventricular wall as a consequence of increased systolic pressure.

Pressure Overload Hypertrophy

There is an extensive literature (3–15) concerning the interrelation between cardiac hypertrophy and myocardial contractility. In general, these studies support the hypothesis that in humans or animals with pressure overload hypertrophy, wall thickening usually keeps pace with the inciting stimulus to normalize systolic wall stress and preserve systolic shortening. It follows that if the extent of hypertrophy is inadequate, systolic wall stress will be excessively high, resulting in and accompanied by a secondary reduction in systolic fiber shortening. Thus, in many patients with aortic stenosis or hypertension, depression of the left ventricular ejection fraction is largely due to excessively high systolic wall stress rather than to irreversibly depressed contractility. However, other patients with chronic pressure overload hypertrophy appear to have intrinsic depression of myocardial contractility (14,15), the physiologic basis of which is uncertain.

Beneficial and detrimental aspects (Table 1). Thus, chronic pressure overload hypertrophy may be viewed as a beneficial adaptation that allows the ventricle to sustain increased work with the preservation of normal systolic wall stress and systolic shortening, and which may result in the performance of increased work with an improved metabolic and mechanical efficiency. However, in many instances the price that is paid for these benefits is the development of congestive heart failure due to diastolic dysfunction.

Diastolic Dysfunction

Impaired diastolic distensibility. Pressure overload hypertrophy results in progressive impairment of diastolic distensibility of the ventricle, manifested as a substantial increase in left ventricular filling pressure relative to diastolic volume (16–18). It is controversial whether this increase in left ventricular chamber stiffness is due primarily to increased wall thickness itself or whether it is also due in part to an increase in intrinsic muscle stiffness. In studies (17,19) of patients with aortic stenosis using simultaneous pressure and ultrasound measurements, left ventricular chamber stiffness appeared to be directly related to the extent of wall thickness. However, analyses (20) of the stress-strain characteristics of ventricles from patients with aortic stenosis indicate that intrinsic myocardial stiffness may also be increased in some patients.

The experimental studies that address this issue are conflicting. A marked increase in myocardial stiffness has been observed in most models of cardiac hypertrophy produced by abrupt constriction of the pulmonary artery (21,22). This increase in myocardial stiffness may be related to increased collagen and fibrosis from myocardial injury associated with the banding procedure (9). In contrast, in gradually developing pressure overload hypertrophy, there is no consistent increase in myocardial stiffness or fibrosis (10,23). These data suggest that if the development of hypertrophy is gradual, an obligatory and irreversible increase in myocardial stiffness may not occur. This concept is supported by ob-
sorvements (24) in patients relating diastolic function to myocardial structure and histology which have shown that potentially reversible increases in myocardial cell diameter and not fibrosis are the major determinant of end-diastolic properties in chronic aortic stenosis.

**Impaired ventricular relaxation and diastolic filling.** In addition to changes in passive diastolic properties, pressure overload hypertrophy is also characterized by impaired ventricular relaxation and early diastolic filling. Interpretation of indexes of isovolumic relaxation and diastolic filling requires caution because they are influenced by many factors including myocardial temperature, catecholamines, age, heart rate and the interplay between ventricular load and systolic shortening (25–27). In addition, it may be misleading to compare normal and hypertrophied hearts with marked differences in ventricular size by using the common approach of normalizing ventricular filling rates by dividing by instantaneous or end-diastolic volume (26). In the presence of cardiac dilation, filling indexes normalized in this fashion will be artifically depressed because of an increase in instantaneous or end-diastolic dimensions. With these caveats in mind, many recent studies support the concept that pressure overload hypertrophy is associated with impaired diastolic relaxation.

**Manifestations of abnormal diastolic function (Table 2).** In 1968, Stewart and coworkers (28) inferred that there was an impairment of left atrial emptying and left ventricular diastolic filling in patients with hypertrophic cardiomyopathy or valvular aortic stenosis. Subsequent studies have confirmed that many patients with either hypertrophic cardiomyopathy (29–32), or pressure overload hypertrophy due to hypertension (33,34) or aortic stenosis (26,35) have abnormal diastolic function evident as 1) slowing of isovolumic relaxation after aortic valve closure; 2) an impaired thinning rate of the left ventricular free wall; 3) a diminished extent and rate of left ventricular filling in early diastole; 4) prolongation of the time from end-systole to the time of peak diastolic filling; and 5) an increased dependence on the contribution of atrial contraction to diastolic filling. The impairment of the rate and extent of early diastolic filling is especially striking because these patients frequently have an elevated left atrial pressure, which would otherwise tend to constitute an increased driving force for flow across the mitral valve in early diastole and thus promote rapid early diastolic filling. These abnormalities of diastolic function clearly do not depend on the presence of coexisting systolic dysfunction (26). Recent studies of patients with mild hypertension (34) suggest that this impairment of the rate and extent of rapid ventricular filling may be a very early marker of the development of pressure overload hypertrophy.

In exceptional patients, the left ventricular diastolic waveform itself provides evidence of an extreme impairment of left ventricular relaxation and shows a continuous decay of left ventricular pressure that persists into late diastole after mitral valve opening when ventricular filling is occurring (31). Such patients underscore the methodologic and conceptual limitations of attempting to analyze left ventricular relaxation only during the very brief isovolumic interval by the use of indexes such as the time constant T. In such patients with advanced hypertrophy, left ventricular relaxation may not be complete by mitral valve opening and thus may influence mid- and late diastolic pressure.

**Mechanisms that may account for impaired relaxation in cardiac hypertrophy (Table 3).** First, increased ventricular wall thickness may account for the slowing of relaxation and diastolic filling. Several studies (26,34–36) have shown an inverse relation between diastolic relaxation and filling and left ventricular wall thickness in both children and adults with pressure overload hypertrophy. However, increased wall thickness or mass itself is unlikely to be the sole factor responsible for impaired relaxation in these patients because cardiac hypertrophy in young endurance athletes does not appear to be associated with impaired ventricular relaxation and filling (37,38).

Both the absolute load and the phase of the cardiac cycle when it is imposed modify left ventricular relaxation (27,39). In normal and hypertrophied papillary muscles, the imposition of increasing load during isotonic contraction results in reduction of both the extent of muscle shortening and the

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<th>Table 1. Pressure Overload Hypertrophy</th>
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<td><strong>Beneficial aspects</strong></td>
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<tr>
<td>Increases ventricular work</td>
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<td>Normalizes wall stress</td>
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<td>Normalizes systolic shortening</td>
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<td><strong>Detrimental aspects</strong></td>
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<tr>
<td>Decreases ventricular diastolic distensibility</td>
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<td>Impairs ventricular relaxation</td>
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<td>Impairs coronary vasodilator reserve, leading to subendocardial ischemia</td>
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<th>Table 2. Manifestations of Impaired Relaxation and Increased Resistance to Filling in Pressure Overload Hypertrophy</th>
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<td>4. Prolongation of the time from end-systole to the time of peak filling</td>
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<th>Table 3. Possible Mechanisms of Impaired Relaxation in Ventricular Hypertrophy</th>
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<tr>
<td>1. Increased wall thickness</td>
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<td>3. Fibrosis</td>
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<td>4. Impaired myocardial inactivation</td>
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rate of muscle lengthening (40,41). Raff and Glantz (42) studied left ventricular relaxation in the intact ejecting canine heart and concluded that relaxation slows after the elevation of the arterial systolic pressure and left ventricular end-diastolic pressure by volume loading. These observations raise the possibility that failure to normalize systolic wall stress, that is, afterload mismatch, could account for impaired relaxation in patients with pressure overload hypertrophy. However, recent studies indicate that abnormal left ventricular loading conditions are not usually the major cause of impaired relaxation and filling in cardiac hypertrophy. First, children with severe aortic stenosis almost invariably show vigorous systolic shortening associated with normal or low systolic wall stress. However, in both children and adults with aortic stenosis and preserved systolic function, early diastolic filling and wall thinning rates are impaired in comparison with findings in age-matched control subjects (26). In addition, substantial reduction of left ventricular systolic and diastolic pressures toward normal does not improve either left ventricular relaxation or early diastolic filling in adults with aortic stenosis and normal systolic function (43). Similar results have been reported from a study of baboons with pressure overload hypertrophy (44). These findings do not exclude the possibility that an acute increase in loading would be expected to impair systolic shortening and to exacerbate baseline abnormalities of diastolic relaxation and filling (44).

Ischemia and Pressure Overload Hypertrophy

Myocardial ischemia may play an important role in modulating ventricular relaxation in patients with cardiac hypertrophy, even in the absence of epicardial coronary artery stenoses. Myocardial relaxation and the termination of crossbridge cycling depends on the energy-dependent reuptake of calcium by sarcoplasmic reticulum. In both patients and animals without cardiac hypertrophy, transient ischemia or hypoxia profoundly impairs the rate and extent of left ventricular relaxation and decreases the distensibility of the ventricle (45–47). In animals with chronic pressure overload hypertrophy, relative subendocardial hypoperfusion with metabolic evidence of ischemia can be induced by interventions such as pacing tachycardia, which augment myocardial energy demand (48,49). Other studies (50,51) also support the view that cardiac hypertrophy is associated with a substantial decrease in coronary vasodilator reserve per unit mass of myocardium. The recent demonstration (52) of a shift from fatty acid to glucose metabolism in the subendocardium of rats with pressure overload hypertrophy supports the hypothesis that some animals with pressure overload hypertrophy may experience chronic or intermittent ischemia.

Coronary flow studies (53–55) indicate that impaired coronary vasodilator reserve occurs in patients with cardiac hypertrophy. Studies of patients with aortic stenosis also reveal hemodynamic and metabolic evidence of ischemia in response to the augmentation of energy demand (56,57), as well as histologic evidence of interstitial fibrosis compatible with ischemic injury (15,24). In addition, a reduced creatine phosphate content and high creatine kinase isozyme, MB fraction content suggesting an influence of myocardial ischemia was recently detected in left ventricular biopsy specimens from patients with aortic stenosis (58). Thus, repetitive episodes of subendocardial ischemia in patients with aortic stenosis could contribute to depressed rates of relaxation and diastolic filling.

The Calcium Hypothesis

Cardiac hypertrophy may also be associated with intrinsic biochemical alterations in cytosolic calcium transport that modify relaxation. Morgan and Morgan (59) reported a marked prolongation in the time course of the calcium transient studied with the bioluminescent protein aequorin in left ventricular muscle tissue from patients who underwent surgery for hypertrophic cardiomyopathy. These findings do not appear to be unique to the rare disorder of hypertrophic cardiomyopathy, and Gwathmey and Morgan (60) recently reported a similar prolongation of the intracellular calcium transient in association with prolonged tension decay in a ferret model of chronic pressure overload hypertrophy. These results do not appear to reflect changes in calcium availability for myofilament activation, myofilament sensitivity to calcium, or altered myosin isoform expression and are most consistent with the interpretation that hypertrophy in this model is associated with a decreased rate of reuptake, and perhaps release, of calcium by the sarcoplasmic reticulum.

Interplay between prolonged calcium reuptake and myocardial ischemia. Under aerobic conditions, this prolongation of calcium availability may reflect a beneficial adaptation of hypertrophied myocardium that permits the
sustained development of high systolic pressure. However, this adaptation may put the hypertrophied heart at jeopardy for an adverse interplay between an intrinsic prolongation of calcium reuptake and the superimposition of the intermittent ischemia due to reduced coronary vasodilator reserve. Depletion of high energy phosphates induced by intermittent ischemia would be expected to further impair the reuptake of calcium by the sarcoplasmic reticulum. Because high adenosine triphosphate levels also exert a regulatory effect that accelerates calcium transport by the sarcoplasmic reticulum, very slight reductions in high energy phosphate concentration could influence cytosolic calcium reuptake. In this regard, experiments performed with isolated sarcoplasmic reticulum preparations obtained during the development of mild hypertrophy show enhanced calcium transport, whereas advanced hypertrophy appears to result in depressed function of the sarcoplasmic reticulum (61–64). This seemingly paradoxical variation in sarcoplasmic reticulum function may be related in part to the degree of myocardial ischemia experienced by the experimental animal before study.

Thus, a potential interplay between ischemia and intrinsic changes in cytosolic calcium handling could explain the profound slowing of relaxation seen in some patients with hypertrophy (Fig. 1). It could also account for the fact that an overt impairment of relaxation is not an invariable accompaniment of hypertrophy such as that which occurs in young athletes. Finally, this interrelation may also account for the recent experimental finding that hearts with chronic pressure overload hypertrophy appear to show an enhanced susceptibility to develop impaired relaxation in response to tissue hypoxia in comparison with age-matched control hearts (65).

Conclusion

Impaired relaxation and ventricular filling are the harmful consequences of pressure overload hypertrophy, which develops as an otherwise successful adaptation to preserve normal systolic wall stress and systolic shortening. However, impaired relaxation is not an invariable consequence of an increase in ventricular mass, and it cannot be attributed solely either to an increase in wall thickness or to an afterload mismatch. Further work, including the development of new methods that permit assessment of intracellular calcium in normothermic working myocardium, is needed to better understand and ultimately treat diastolic dysfunction in patients with cardiac hypertrophy.

References

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