EDITORIAL COMMENT

Pressure Overload Hypertrophy and Congestive Heart Failure*

Where Is the “Achilles’ Heel”?

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Chronic left ventricular (LV) pressure overload states, as seen in long-standing systemic arterial hypertension or LV outflow tract obstruction, are well tolerated for many years. In such pathophysiologic circumstances, an increase in the ratio of LV wall thickness to chamber radius mitigates, but does not necessarily fully normalize, the afterload or forces against which the myocardium shortens during systole (1,2).

Although beneficial, this adaptive response, also known as concentric hypertrophy, may also cause a reduction in LV chamber distensibility and, in some instances, an increase in the elastic stiffness of the myocardium (3–5). With extended passage of time the increased afterload imposed by hypertension or LV outflow obstruction outstrips all salutary adaptive mechanisms, preload reserve becomes exhausted despite LV chamber dilation and basal contractility becomes mismatched to the level of afterload, provoking a lower extent and speed of shortening of the LV chamber (6).

Concomitant elevation of both the LV end-diastolic pressure and left atrial mean pressure gives rise to pulmonary capillary and alveolar congestion, whereas reduced systolic fractional shortening is associated with an inadequate cardiac output either at rest or with exercise. The patient with a pressure overload condition is then exhibiting the clinical syndrome of congestive heart failure (CHF).

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VENTRICULAR REMODELING IN PRESSURE OVERLOAD STATES

Though this traditional biomechanical construct of the pathophysiology of pressure overload hypertrophy has validity, it fails today to capture fully the much broader adaptations (genetic, molecular, neurohormonal) that are known to accompany the development of ventricular dilation, and other clinical manifestations of heart failure, in diseases associated with pressure overload hypertrophy.

These latter changes have come to be known as “cardiac remodeling,” a term that, at first reception, connotes gross pathoanatomic change but which, by extended definition, encompasses a host of alterations in homeostatic machineries (endocrine, autocrine and paracrine) that, under normal conditions, control vascular tone, blood volume, basal contractile state, programmed cell death (apoptosis), as well as the architectural integrity and organization of myocardial sarcomeres (7–10).

These homeostatic mechanisms, like concentric hypertrophy, can be considered protective and reparative but also detrimental (11). With sustained pressure overload, experimental and clinical evidence shows that tissue heterogeneity develops with an imbalance struck between the muscular and nonmuscular components of the myocardium. Scarring replaces necrotic myocytes, and a reactive fibrosis is observed in the interstitium and perivascular areas. Hypertrophy and hyperplasia of vascular smooth cells lead to medial thickening and loss of coronary arteriolar vasodilator reserve. Associated with these changes, the left ventricle dilates, myocardial contractility may be either normal or diminished (2,12–15), diastolic chamber stiffness is variably normal or decreased (3–5) and myocardial stiffness may be variably normal or increased (3–5). What seems indisputable is that in humans we witness an augmented incidence of CHF, arrhythmias and coronary events (16).

RELATIVE PATHOGENIC ROLES OF MYOCARDIAL CONTRACTILITY AND CARDIAC REMODELING

It is within this broader construct of the natural history of pressure overload hypertrophy that the question has been posed: “How important is reduced contractility itself, as opposed to other effects of cardiac remodeling, in the manifestations of CHF?” In this issue of the JACC, Norton et al. (17) report on their pursuit of this question in a rat model of pressure overload hypertrophy created by suprarenal artery banding. Approximately one-half of the pressure overload hypertrophy animals studied developed manifestations of CHF (POH-F group), with lung edema, significant LV chamber dilation and a nonsignificant increase in wall thickness compared to control rats. The other one-half showed concentric myocardial hypertrophy in response to the pressure overload, but no evidence of LV chamber dilation or an increase in their lung weight to body weight ratio (POH-NF group). Compared to controls, both POH groups showed reduction in myocardial contractility when assessed by ex vivo end-systolic stress-strain relations; by contrast, the in vivo systolic myocardial end-systolic myocardial stiffness analysis failed to detect a depression of myocardial contractility. The in vivo stress-shortening relations suggested a small and equivalent decrement in the two POH groups, compared to controls. Despite this essential equivalency of myocardial contractility, whether normal or depressed, only the POH-F group manifested ventricular dilation, wall thinning and lung edema, leading the investigators to conclude that CHF was dependent “primarily” upon the processes of remodeling.

It is important to recognize that CHF could not be
attributed solely and categorically to one pathogenetic mechanism as opposed to the other. Although there is inconsistency between the in vivo and ex vivo systolic stiffness analyses, some reduction in contractility appeared to be operative in both groups, a conclusion shared by the investigators (17). This depression may be time-dependent and witnessed only if the offending disease process has been operative for a sufficient period of time. For example, in the Mursky et al. study (3) of the evolution of LV dysfunction in the spontaneously hypertensive rat (SHR), the ejection fraction-afterload relations of 6- and 12-month-old rats were similar to those of normotensive rats of all ages; however, a depression in contractile state of the SHR group occurred at 18 months and was further depressed at 24 months (3). Importantly, this depression of contractile state was evident before the left ventricle dilated and before any deterioration of cardiac performance was witnessed.

The adequacy of the Norton et al. (17) approach to detection of depressed myocardial contractility should also be examined. An acute upward or downward shift in the position and slope of the end-systolic pressure-dimension relation is relatively well accepted as reliable measures of acute enhancement or declination of contractility, respectively. Nevertheless, because of the important influence of intrinsic ventricular size (or chamber remodeling based upon increased sarcomeres laid down in series) on the pressure-diameter or pressure-volume relation, most investigators in the field now analyze myocardial contractility by an end-systolic force-normalized dimension relation.

Myocardial stiffness, calculated from the stiffness constant of the mid-wall stress-strain relation, is particularly appealing for overcoming the confounding effects of chamber size (18). Use of this construct would seem particularly important in an experimental or clinical investigation where chamber remodeling is occurring. Thus, the finding that end-systolic myocardial stiffness was equivalent in both POH groups, despite significant dilation only in those showing CHF, appears supportable. It leaves open the question, however, of why the in vivo and ex vivo end-systolic analyses were not consistent.

Contractility was also assessed in the Norton et al. study (17) by examining the mid-wall fractional shortening-stress relation and comparing groups at an end-systolic iso-stress of 75 g cm$^{-2}$. The slopes of the regression lines of these relations in both POH groups showed an equivalent tendency to depression compared to the control group. By statistical analysis, however, no significant differences existed among all three groups. Some sensitivity for detection of depressed contractility may have been lost by analysis of only end-systolic stress as the measure of afterload. Although end-systolic stress can be rationally construed as the force that ultimately ends ventricular shortening, it does not quantitate the average forces that resist shortening throughout systole. Determination of mean ejection stress would more properly provide this measure (19).

It is important to recognize that there was no third POH group that manifested CHF while exhibiting manifestations of cardiac remodeling and unequivocally normal contractility. Thus, I believe one would have to conclude that it is the combination of both pathogenetic processes that ultimately leads to the syndrome of CHF in sustained pressure overload hypertrophy.

**Role of diastolic dysfunction in CHF.** It does not appear that alterations in the diastolic properties of the left ventricle contributed to the development of pulmonary congestion in the POH-F group. Nevertheless, we do not have available in these experiments measurements of LV end-diastolic pressure, pulmonary capillary wedge pressures or in vivo LV diastolic stiffness parameters. The investigators (17) did analyze ex vivo diastolic stiffness of the POH-NF versus the POH-F groups and found that there was a trend toward a more compliant pressure-volume curve (reduced exponential chamber stiffness constant) in the POH-F group. The ex vivo myocardial stiffness constant did not differ significantly among the control, POH-NF and POH-F groups.

**Acuteness and duration of pressure overload: effects on myocardial contractility and remodeling**

The experiment by Norton et al. (17) represents the analysis of an acutely imposed pressure overload, extending out to 20 weeks, at which time the animals were sacrificed. This is not equivalent to the slowly developing pressure overload of human hypertension or aortic valve obstruction imposed over many years. There was no serial evaluation of LV function between the time of imposition of the suprarenal band and the evaluation presacrifice at 20 weeks. Thus, we do not know whether the POH-F group manifested heart failure because of the adverse consequences of remodeling or the failure to develop adequate hypertrophy.

Conversely, we do not know whether a longer period of observation might have uncovered more definitive signs of reduced contractility and CHF in a higher proportion of rats. Other experimental studies where an acute pressure overload has been applied have shown an initial phase where the heart dilates with invocation of preload reserve, the ventricular wall thins, wall stress acutely augments and myocardial shortening significantly declines (both an acute afterload excess and reduction of myocardial contractility)—point A to point B in Figure 1 (2,20,21). As concentric hypertrophy develops, cavity dilation diminishes, wall stress is lessened, myocardial shortening improves and the ventricle is once again operating on its original force-velocity curve—point B to point C in Figure 1. Then, as adverse remodeling develops, the ventricle again begins to dilate, invoking the residual preload reserve, LV shortening again diminishes and wall stress (no longer fully compensated) augments—points C to D in Figure 1. However, it is conceivable that the transition between points B and C did not occur at all in the POH-F rats and an inadequate amount of hypertrophy developed—points B to D in Figure 1.
Such a phenomenon was noted by Tagawa et al. (20) in a dog model of aortic stenosis studied over a period of eight weeks. Dogs with hypertrophy alone had a very substantial increase in LV mass and preservation of a normal ejection and mean systolic wall stress. Dogs with hypertrophy and associated failure had a substantial but lesser increase in LV mass and a reduction in ejection fraction, as well as a marked increase in mean systolic wall stress (20).

More recently, published serial observations in a pig pressure overload model suggested that the early period of LV dilation and reduced myocardial contractility lasts approximately 12 h, with a relatively broad standard deviation at that point as to the recovery of ventricular shortening (21). It appears, nevertheless, that most pressure overload experimental models pass through a period of compensated concentric hypertrophy before showing signs of CHF. As noted above, the duration of a pressure overload state, as shown in the Mirsky et al. (3) experiment, undoubtedly influences the development of depressed myocardial contractility.

**MOLECULAR MECHANISMS THAT UNDERLIE ADVERSE REMODELING**

If adverse remodeling is ultimately the “Achilles’ heel” of pressure overload hypertrophy, what are the molecular mechanisms that underlie both the development of concentric hypertrophy and the transition from the compensated to the decompensated state? Evidence that bears on this question continues to accumulate rapidly. In the late 1980s and early 1990s it was shown that the pathologic hypertrophy of mechanically overloaded hearts was associated with changes in gene and protein expression that reprised that of the fetal heart (22,23). Further evidence developed that pressure overload hypertrophy is induced by a number of candidate signaling pathways involving humoral growth factors (angiotensin II, endothelin-1, insulin-like growth factor-I), inhibition of pathways of apoptosis of myocytes (gp130 ligands), catecholamines, associated G proteins and downstream kinase effectors (8,24). The latter signaling molecules include protein kinase C, tyrosine kinases, the mitogen-activated protein kinase family, Ras, and the Janus kinase/signal transducer and activator of transcription family.

Also, Ca$^{2+}$ has been shown to be an important second messenger in cell growth and survival. In response to growth stimuli, cytosolic Ca$^{2+}$ increases, and calcineurin, a ubiquitous phosphatase, is activated, resulting in dephosphorylation of a class of transcription factors (nuclear factors of activated T cells), which then regulate expression of specific genes. Although controversial, calcineurin appears to be a requisite mediator of myocardial hypertrophy (25–27). If calcineurin inhibitory proteins are transgenically expressed in the mouse heart, concentric hypertrophy secondary to abdominal aorta-bandling or long-term infusion of the $\beta$-adrenergic agonist isoproterenol is significantly inhibited. Moreover, adenoviral $\Delta$Cain (a calcineurin inhibitor) has been used to transfect the myocardium before aortic banding. Seven days later, pressure overload hypertrophy was found to be diminished by 40%. These experiments suggest that calcineurin plays a critical role in the hypertrophic response to pressure overload. Nevertheless, essentially complete inhibition of calcineurin served to attenuate but not completely prevent concentric hypertrophy, suggesting that redundant signaling pathways exist.
Although the molecular mechanisms behind the development of concentric hypertrophy are progressively forthcoming, the correlates of the transition from a compensated to a decompensated pressure overload state are less well defined. One promising finding, now reported in both animal models and man, is increased microtubule component of the extramyofilament cytoskeleton. Upregulation of α-tubulin and β-tubulin, the major microtubule proteins, persists during prolonged, compensated right ventricular pressure overload hypertrophy and also after the development of right ventricular failure (20). It has been shown that this increased density of microtubule network imposes an increased viscous load on the shortening sarcomeres during contraction, a finding that can be reversed by depolymerization of the microtubules. Recently, in this Journal, Zile et al. (19) reported that patients undergoing aortic valve replacement for aortic stenosis exhibited a markedly augmented microtubule protein in biopsy specimens in those individuals with borderline or overtly abnormal LV shortening.

FUTURE DIRECTIONS OF RESEARCH
The observations by Norton et al. (17) provide further impetus to research efforts aimed at unraveling the complex mechanisms behind “cardiac remodeling” and, in particular, the transition to CHF in pressure overload hypertrophy states. Once molecular biological correlates of the transition to heart failure are better understood, investigation of their inhibition and reversibility will be required. Only then will clinical cardiologists move beyond the laudable improvements in treatment of CHF of pressure overload hypertrophy that were formulated in the twentieth century. It is hoped we will have a rationale for more than manipulating loading conditions, enhancing contractility, and correcting mechanical defects of cardiac function.

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