Cardiac Hypertrophy as Early Adjustments to a Chronically Sustained Mechanical Overload

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There is a distinct inverse relationship between the force and the extent or velocity of muscle shortening in isolated muscle at a constant resting muscle length or in the intact heart with the preload and inotropic state held constant. In the normal ventricle, however, preload is usually allowed to increase as the aortic pressure is augmented, and the stroke volume tends to be maintained constant. Such complex interaction between increases in preload and afterload can be analyzed by a two dimensional framework in terms of the appropriateness of the matching between afterload and the level of inotropic state as modulated by preload.

The initial response to chronic volume overload consists of near maximum use of the Frank-Starling mechanism. An increase in afterload due to the wall thinning and increased chamber size does not produce a fall of wall shortening. As an eccentric hypertrophy develops with series addition of sarcomeres, a delivery of much larger stroke volume is attained without any further use of the Frank-Starling mechanism, with a optimal extent of wall shortening per unit of circumference.

Acute severe pressure overloading causes an acute afterload mismatch despite the maximum use of preload reserve. Subsequently, chronic adaptation takes place with development of concentric hypertrophy which returns the ventricle to the control force-velocity curve. As wall thickening accomplishes a decrease in wall stress, wall shortening also becomes normal.

Thus, chronic mechanical overload is initially adjusted by an adequate hypertrophy to correct afterload mismatch. Inadequate hypertrophy results in an elevation of wall stress and produces a decrease in stroke volume with the expenditure of the preload. The long standing hypertrophy may cause substantial depression of inotropic state with overt heart failure. Further study will be needed how and when the pathological process overcomes the physiological adaptations.

THE definition of afterload includes all factors that oppose active shortening of the ventricular fibers,¹ including the aortic input impedance which reflects those forces external to the heart and place a load on the left ventricle.² The impedance is related to the ratio of

pressure to flow and is determined by the viscous and internal forces of the blood and stiffness of the wall of the blood vessel.³ Though it might well provide a detailed description of afterload, the calculations are complex and are not feasible to perform on the intact heart by routine hemodynamic measures.

Defined in more simplified terms, afterload represents the stress in the wall of the ventricle during ejection.¹ According to the Laplace concept, the stress can be related directly to the product of systolic pressure and the size of the

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Fig.1. Effects of acute alterations in loading on cardiac performance. A simplified version of force-velocity length relation for analyzing the acute responses to altered preload and afterload is shown. A set of curves showing inverse relationship between ventricular wall shortening and afterload at a given level of preload is illustrated encompassing the full range of preload variations.

Normal left ventricle (point A) operates at a relatively narrow range of Vcf and afterload as indicated by dashed lines. If the afterload is acutely increased while preload and inotropic state are held constant, stroke volume falls to point B. When both preload and afterload are increased simultaneously, again without a change in inotropic state, stroke volume may remain constant (point C). When the limit of preload reserve is reduced (as at high left ventricular pressure with full extension of sarcomeres), any further increase in afterload results in a fall in fiber shortening (point D).

The positive inotropic stimulation enhances the preload reserve by upward shift of the force-velocity curve and Vcf may not drop with even greater increase in afterload (point E). (Reproduced from Ross (4) by permission)

ventricular chamber and inversely proportional to the thickness of the ventricular wall. Thus, both the heart with elevated systolic pressure, and that with increased left ventricular volume which produces thinning of the ventricular wall are associated with a higher wall stress despite the presence of the normal systolic pressure.

Recently, a two-dimensional model has been developed to understand the complex interaction of preload, afterload and contractility. In this model, the shortening of the left ventricular wall during ejection is considered to reflect the appropriateness of the matching between the existing afterload and the level of inotropic state as modulated by the preload reserve (Fig. 1)^{4,5} When preload is not allowed to increase in association with the increase in afterload, the ventricle moves down a force-velocity (or shortening) curve. This inability to maintain

forward ejection characteristics when afterload is increased, is defined as an afterload mismatch. The framework can also be applied to analysis of the ventricular response to chronically altered loading conditions. It will be the purpose of this brief review to describe the mechanism of adaptations of the left ventricle to sustained mechanical overload in terms of this matching between the level of afterload and the level of contractility. For comparison of the heart with different size and shape, ejection measures were corrected for end-diastolic dimension and the afterload as the force per unit area of muscle (wall stress).

Chronic Volume Overload

We studied the responses of the left ventricle to sustained volume overload in a chronic conscious animal model utilizing a micromanometer and pairs of ultrasonic crystals for

Fig.2. Representative tracings obtained in a single dog during the adaptation to chronic volume overload produced by chordal sectioning.

From top to bottom: left ventricular pressure (LVP), its first derivative (dP/dt), internal diameter, and wall thickness.

measurement of left ventricular (LV) internal diameter, the thickness of LV free wall and the longitudinal segment length in the anterior wall⁶. Following the control study in the unanesthetized state, the chest was reopened and mitral regurgitation was created by sectioning the chordae tendineae. Subsequent studies performed serially in the conscious state clearly documented progressive LV dilatation and moderate LV hypertrophy, end-diastolic diameter increasing by 9% above control at one week and by 11% at 4 weeks. The end-diastolic wall thickness was decreased initially but returned to the control value later. Thus, the development of hypertrophy was shown by an increase in cross sectional area by 8% at 4 weeks. These changes were accompanied by a consistent reduction in both peak and end-diastolic wall stress.

The ejection measures normalized for end-diastolic circumference (percent shortening, mean circumferential shortening ratio (Vcf) was significantly augmented after mitral regurgitation but showed no detectable changes between early and late studies.

Despite progressive increase in diameter, the longitudinal segment length remained the same throughout the study period, suggesting that the ventricle assumes a more globular appearance as

Fig.3. Diagrammatic responses of the force-velocity relation to acute and chronic volume overloading.

A stippled circles represent a cross-sectional view of the left ventricular chamber and wall. The normal basal state is shown at point A, acute response at point B, and the chronic adaptations with eccentric hypertrophy have occurred at point C at several weeks later.

EDV = end-diastolic volume; SV = stroke volume; EjF% = ejection fraction.

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Fig.4. Representative tracings showing serial changes of the left ventricle during the chronic adaptation to sustained increase in afterload. Recordings were made during control study and 30 min 13 days and 21 days after aortic constriction. LV = left ventricular

an additional compensatory mechanism (Fig. 2). These results confirmed the previous findings in anesthetized dogs.⁷

Using cinecardiographic techniques, Ross and McCullagh also studied the responses to chronic volume overloading in conscious dogs induced by means of a large arterio-venous fistula.^{8,9} The average changes in percent shortening and mean Vcf were not different between measurements early post shunt at one week and late at about 10 weeks after creation of the shunt. However, in that experiment they observed one animal that developed severe cardiac failure with apparent reduction in ejection characteristics.

These authors also studied the mechanism of the ascending limb of normal ventricular function on the ultrastructural basis. When hearts were rapidly fixed at various end-diastolic pressures over the range between 2 and 20 mmHg, an uneven distribution of sarcomere lengths was noted across the wall at lower filling pressures, the mean sarcomere length being longest just inside the midwall layer and becoming progressively shorter toward the epicardium. At an end-diastolic pressure of 20 mmHg, the difference in sarcomere lengths between layers was small, which indicated the exhaustion of the Frank-Starling reserve.¹⁰

Subsequently, physiological significance of the limits of the Frank-Starling reserve mechanism for ventricular performance was demonstrated in an open-chest dog in which mitral valve was replaced with a ball valve prosthesis to mitral regurgitation.¹¹ Acute alteration of cardiac filling by rapid volume infusion in this preparation at a relatively high level of aortic pressure, resulted in an appearance of descending limb of cardiac performance at the LV end-diastolic pressures in excess of 30 mmHg. This elevated filling pressure was always accompanied by an increase in LV systolic pressure, and calculated wall stress rose somewhat on the descending limb. Under these conditions the application of further slight increase in peak LV pressure resulted in a striking reduction in ventricular ejection; when the limit of preload reserve is approached at any given level of inotropic state, any further increase in afterload induces an afterload mismatch.¹²

For successive adaptations to chronic volume overload, an initial acute increase in fiber and sarcomere length is followed by progressive left ventricular dilatation and moderate left ventricular hypertrophy, hereby midwall sarcomere length is not increased further beyond that observed with acute volume overloading, but sarcomeres increase in number and are added

Fig. 5. Relations between mean Vcf and left ventricular pressure (LVP) (left panel) or mean wall stress (WSt) (right panel). The data obtained in control state are shown by solid lines and those after hypertrophy by dashed lines. (Reproduced from Sasayama et al. (20) by permission)

in series. Thus, the overall cardiac performance is enhanced during chronic volume overload mediated through normal performance of each unit of circumference of the enlarged chamber without any further use of the Frank-Starling mechanism^{8,9}

These responses are summarized diagrammatically by Ross as shown in Fig. 3. The early response consists of near-maximum use of the Frank-Starling mechanism and some increase in afterload due to increased heart size and decreased wall thickness. As a result of an interplay between these two factors, Vcf remained substantially the same and the afterload mismatch does not occur (A-B). When the adaptation for the sustained volume overload has been fully attained, further progressive dilatation is associated with a shape change and slight increase in wall thickness. Thus, although the enlarged ventricle allows larger stroke volume, force and velocity corrected to per unit muscle remained the same as in the acute stage (B-C). The rightwardly displaced force-velocity curves under acute and chronic condition overlap, indicating that the maximum use of the Frank-Starling mechanism is similarly maintained in the chronic stage^{4,5}

In addition, an augmented adrenergic activity along with the maximum use of the Frank-Starling mechanism has been suggested to act as a funda-

mental compensation of the acute volume overload.^{13,14} However, we observed that an initially elevated plasma norepinephrine was reduced significantly in the later stage. Thus, it has been postulated that an increase in wall tension might stimulate the sympathetic nervous system to release norepinephrine in the myocardium and the hypertrophy process is limited along with the decrease in norepinephrine level⁶

Chronic Pressure Overload

It is well known that the ventricle has the particular capacity to respond to functional demands by increasing muscle mass. In the early studies, performance of the hypertrophied ventricle was examined in terms of muscle function rather than pump function.¹⁵⁻¹⁸ These studies, however, provide somewhat contradictory results. More recently, we conducted an experiment to study the response of the intact left ventricle to a sustained afterload increase in the conscious unsedated dog.^{19,20} As described in the previous section, dogs were instrumented with pairs of ultrasonic crystals to measure dynamic and serial changes in internal chamber diameter and in wall thickness. Left ventricular pressure was measured with a high-fidelity micromanometer. Heart rate was controlled if necessary by atrial pacing during the study.

Subsequent to the control recording, supra-

ventricular aortic constriction was produced by inflating a rubber cuff placed around the ascending aorta to elevate the systolic pressure from 140 to 220 mmHg. The pressure level was maintained sufficiently stable throughout the study. Immediately after acute pressure loading, there was significant dilatation of the left ventricular chamber together with wall thinning. Thus, calculated wall stress increased by 55% above control, while measures of shortening characteristics significantly decreased (percent shortening by 24% and mean Vcf by 39% from control).

Within nine days after aortic constriction, end-diastolic pressure and diameter continued to increase (end-diastolic diameter by 4% above control). There was small but significant increase in wall thickness and the cross sectional area of the left ventricular wall increased by 10%. Thus, despite a constant peak systolic left ventricular pressure, peak wall stress fell to 37% above control, while percent shortening and mean Vcf remained reduced at -12% and -20% of control, respectively. During the late compensated phase of concentric hypertrophy (mean 2.5 weeks), the left ventricular wall cross sectional area increased further to 15% above control, and wall stress fell to 22% above control. The end-diastolic diameter returned to control and mean Vcf increased to -7% of control (non significant). At 24 hours after release of the cuff, the peak wall stress, percent shortening, mean Vcf and peak dP/dt were not significantly different from control (Fig. 4).¹⁹

As an additional measure of the level of inotropic state in the hypertrophied ventricle, mean force-velocity and wall stress-diameter loops in single contraction were analyzed over a range of matched systolic pressures during acute aortic constrictions both before and after induction of chronic hypertrophy. The pressure-velocity relation obtained by relating mean Vcf to corresponding pressure shifted to the left in the hypertrophied ventricle indicating significant hyperfunction at each matched pressure level. Also, hyperfunction of the hypertrophied ventricle was evident under basal conditions, mean Vcf being augmented over control because of a concomitant decrease in mean wall stress. However, when mean Vcf was related to mean wall stress at various stress levels, the force-velocity relations of the hypertrophied ventricle fell on the same line as during control (Fig. 5).²⁰ Thus, there was no evidence of altered inotropic

Fig. 6. Diagrammatic responses of the force-velocity relation to acute and chronic pressure overloading.

Normal state is shown at point A, acute response at point B, and chronic response with concentric hypertrophy at point C.

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state in the concentrically hypertrophied ventricle subjected to a sustained pressure overload. The lack of change of the stress-diameter relation at end-ejection further support the above conclusion.

These responses to sustained chronic pressure loading are diagrammatically illustrated in Fig. 6. The left ventricle in the basal normal state operates at point A on the force-velocity relation.^{4,5} Acute severe pressure overloading produces an initial afterload mismatch between the degree of afterloading and the level of left ventricular contractility because of inadequate compensation by the Frank-Starling mechanism despite the maximum use of the preload reserve (point B). Subsequently, as successful adaptation occurs with the sustained systolic pressure overload, the chamber returns to normal size with normal ejection phase measures. The force-velocity curve returns to the normal position although the left ventricle now has a much thicker wall (point C). Thus the early afterload mismatch can be corrected by the wall thickening alone without a change in inotropic state allowing normal ejection characteristics without encroachment upon the preload reserve.

In clinical settings, systolic pump failure of the left ventricle with decreased cardiac output at an increased filling pressure is frequently

observed in patients with advanced left ventricular pressure overload.

Using cineangiography together with intraventricular pressure measurement. Gunther and Grossman²¹ recently analyzed the relationship between wall stress and fiber shortening in 14 patients with pressure overload hypertrophy from aortic stenosis, and varying degrees of ejection fraction ranging from 0.19 to 0.85. They demonstrated a constant inverse correlation between wall stress and Vcf ($r = 0.91$) or ejection fraction ($r = 0.96$). Stress shortening values for normal subjects fell on the same line as those for patients with aortic stenosis, whereas the values for patients with cardiomyopathies were considerably below this line. These data offered additional support for the concept that intrinsic contractility of hypertrophied myocardium was not necessarily depressed. In addition their results indicated that poor cardiac performance in some patients with aortic stenosis occurred only when hypertrophy was inadequate and unable to maintain systolic wall stress within normal limits, merely manifesting afterload mismatch.

It should be emphasized, however, that experimental and clinical data do not imply that myocardium of the hypertrophied ventricle caused by pressure overload is unaccompanied by intrinsic depression of inotropic state under all circumstances. Pfeffer et al²¹ demonstrated in spontaneous hypertensive rat studies a sequential transition from an earlier stable stage of hypertrophy with the well maintained pumping ability to a later stage of progressive deterioration of myocardial function. We also assessed contractility of the hypertrophied ventricle in patients with systemic hypertension by wall stress diameter relation with the use of M-mode echocardiography together with brachial arterial pressure measurement.^{23,24} Dynamic responses of the hypertrophied ventricle to acute pressure reduction by nitroprusside infusion was compared with the same relation obtained in normal subjects (end-diastolic wall thickness ranged from 0.6 to 0.9 cm) over a range of matched systolic pressure induced by methoxamine administration. In those patients with moderate hypertrophy (end-diastolic wall thickness 1.0 to 1.2 cm), the linear wall stress-diameter relation at end-systole did not differ from the control group. In those with a larger wall thickness (1.3 cm or more), this relation clearly shifted to the right associated with a reduced slope. These

observations are quite consistent with Meerson's classical description of the sequence of events in development of hypertrophy; the initial myocardial damage, the stable hyperfunction and a gradual deterioration of myocardial function leading to overt heart failure.²⁵ Further studies are needed to elucidate factors responsible for this later wear and tear process.²⁶

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