Cardiac Responses to Increased Afterload

State-of-the-Art Review

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BEFORE the advent of effective antihypertensive therapy, heart failure was the most common cause of death from hypertension.1 Today, hypertension remains the most common cause of left ventricular (LV) hypertrophy in adults2-4 and the most common precursor of congestive heart failure.4-5 It has usually been assumed that the link between increased arterial pressure and cardiac dysfunction was straightforward, a mechanical proposition between an increased load and an overworked pump. As happens so often, the relationship proved much more complex.

It has been proven that the heart does not respond similarly to all types of overload,6 that cardiac hypertrophy is not a homogenous entity,6-7 and that arterial pressure is not linearly related to cardiac dysfunction in all types or at all stages of hypertension.8-10 Pressure overload evokes cardiac responses that are different from volume overload or intense exercise.8-11 Whether all types of pressure overload evoke the same type of cardiac responses is one of the questions we address, as is the closely related question of whether all types of hypertension are associated with the same pattern of cardiac hypertrophy. The proposition that hypertension is not a single or homogeneous disease is universally accepted in discussions of the genesis and mechanisms of the rise in arterial pressure; it has not usually been advanced in the analysis of its cardiac consequences.

This discussion is not only of theoretical value; its clinical implications may lead to a fundamental reevaluation of our therapeutic aims and guidelines. The recent observations of significant cardiac hypertrophy in borderline hypertension11-13 showed that structural myocardial changes are not limited to advanced stages of the disease, and that cardiac problems may be present from the earliest stages. The demonstration that cardiac hypertrophy can be reversed by medical antihypertensive therapy14-17 is lending urgency to the question of whether cardiac hypertrophy is advantageous or the first step to failure. Basic to these questions is the nature of the increased cardiac load in hypertension. Stepped-care therapy is based on diastolic blood pressure levels; it is questionable whether this variable describes adequately the load that the heart must bear when arterial pressure is elevated.

Definition of Afterload

The "afterload" for any contracting muscle is the total force that opposes shortening, minus the stretching force that existed prior to contraction. For cardiac muscle, the afterload is the force against which the myocardial fibers must contact during the ejection phase of systole. Force equals pressure times area, by definition. The total force opposing LV contraction (i.e., the afterload) is the product of the LV pressure and the internal surface area of the LV cavity.

In hypertensive subjects, of course, the arterial and LV pressures are abnormally high during systole, and, therefore, the LV afterload tends to be high. The internal surface area of the LV varies directly with the volume of blood in the ventricle. If the hypertensive subject also has a dilated LV, the internal area of the LV will be greater than that for a normal subject. Hence, for any given pressure, the afterload tends to increase as the ventricular volume becomes greater. The internal surface area of the ventricular cavity is extremely difficult to measure precisely. Furthermore, both pressure and area change continually throughout ejection. Therefore, it is difficult to assess afterload accurately.

Alternative Criteria of Afterload

Because of the difficulties of assessing LV afterload precisely, various alternative criteria have been used. Most commonly, the peak (or systolic) aortic pressure is taken as an index of afterload mainly because it
can be measured so readily. However, other indices have also been used. Each index has certain advantages for specific applications.

Milnor has strongly advocated the arterial impedance as the critical measure of ventricular afterload. The advantages of this criterion is that the impedance depends exclusively on the characteristics (i.e., resistance, compliance, and geometry) of the external system into which the ventricle must eject blood. The arterial impedance does not depend on the characteristics of the heart itself, whereas all of the other criteria of afterload do depend in part on the performance of the heart. For example, the peak systolic aortic pressure depends as much on ventricular performance as it does on peripheral resistance or arterial compliance.

However, the arterial impedance is difficult to measure and even to express. High-fidelity pressure and flow curves must be obtained, and must be subjected to a complicated harmonic (Fourier) analysis and other mathematical manipulations. The results are then represented by two complicated curves: one, the amplitude of the impedance as a function of frequency, the other the phase of the impedance as a function of frequency. In addition to these obvious problems related to complexity, the arterial impedance may not be the best criterion to apply to the question of the effect of increased afterload on the heart in hypertensive subjects. The physician treating a hypertensive patient wishes to know what effects the afterload has on cardiac output, on the energy requirements of the myocardium, and on the tendency to induce myocardial hypertrophy. These effects depend at least as much on cardiac as on vascular factors. Pronounced and equivalent increases in arterial impedance can occur, for example, in hypovolemic shock, as in severe hypertension. The same high arterial impedance will be associated with markedly different cardiac outputs, myocardial oxygen consumptions, and tendencies toward hypertrophy in these two different cardiovascular states.

Other criteria of afterload that have been found useful for specific purposes are the LV pressure at the end of ejection and the area of the LV pressure curve throughout ejection. The end-systolic pressure is a critical determinant of stroke volume, as explained below (see p II-12). The area under the systolic portion of the LV pressure curve has been termed the "tension-time index" and has been found to correlate well with the myocardial oxygen consumption.

An estimate of the force opposing LV contraction could be obtained from the calculation of myocardial wall stress. The latter (σ) is a function of pressure (P), internal radius (R), and wall thickness (h) of the LV, as expressed in the simplified formula: σ = PR/2h . . . (Eq. 1). Left ventricular wall stress obviously changes continuously throughout the cardiac cycle, describing a curve that might be quite different from intraventricular pressure curves. Some values (peak systolic stress, end-systolic stress, and average systolic stress) have been used as estimates of afterload; of particular significance for clinical investigations is the possibility of obtaining them noninvasively from cuff systolic pressure and echocardiographic tracings. Calculation of stress has added a new dimension to clinical evaluation of the cardiac effects of hypertension. The demonstration that antihypertensive drugs could have divergent effects on blood pressure and ventricular hypertrophy implies that LV stress could increase, decrease, or remain unchanged, depending on the relative variations of P, R, and h during treatment and that these changes in stress might not be predicted from determinations of pressure alone. In more practical terms, physicians have to be content only with determinations of arterial pressure. The essential accuracy of auscultatory readings has been confirmed if meticulous attention is given to details of this deceptively simple method. Indeed, it has been shown that calculations of LV systolic wall stress using cuff systolic pressure closely matched those derived from intraventricular pressure records by Millar catheters. Cardiac work is related to systolic rather than diastolic arterial pressure load. Against this background, it is obvious that the traditional reliance on diastolic or mean arterial pressure to evaluate the cardiac effects of hypertension does not take into account the other important determinants of afterload. If for clinical purposes one has to depend on determination of arterial pressure alone, then the systolic not diastolic level is the value closest to a correct evaluation of the load imposed on the heart by hypertension. This indeed was shown to be the case in all studies correlating cardiac hypertrophy with arterial pressure levels.

In summary, cardiac afterload can be calculated in a variety of ways; the choice of a particular index will depend in part on the function examined and on the degree of precision required. Practical considerations may impose clinical constraints, but under these conditions, it is time to recognize in practice the particular significance of systolic as opposed to diastolic pressure levels.

Mechanical Effects of Increased Afterload

Isolated Myocardial Strips

The immediate effects of a change in afterload on the contraction of cardiac muscle can be appreciated by observing the contractile responses of isolated myocardial strips. Figure 1 displays the results of experiments conducted by Sonnenblick on cat papillary muscle; velocity of shortening, extent of shortening, work, and power vary with the total load against which the cardiac muscle strip contracts. In each of the four panels, a given curve represents the changes obtained for a given preload, which is the stretching force applied prior to contraction. The total load, plotted along the abscissa, is the sum of this given preload plus the variable afterload. Panel B in figure 1 shows that for a given preload, the extent of shortening diminishes as the afterload
FIGURE 1. Changes in velocity of shortening, extent of shortening, work, and power in a cat papillary muscle that was induced to contract from preloads of 0.2, 0.4, and 0.6 g. At each preload, the muscle was made to contract against a range of afterloads from zero to that against which it was no longer able to shorten. Total load, plotted along the abscissa, is the sum of the pre- and afterloads. (Reprinted with permission from Am J Physiol 202: 931, 1962.)

FIGURE 2. Changes in aortic flow, electrocardiogram, aortic pressure, left ventricular (LV) pressure, LV end-diastolic pressure, and LV dp/dt in a dog in which the aortic pressure was suddenly changed during diastole. In each panel, the first beat occurred under control conditions, the second beat against altered afterload. In the panels from left to right, the afterloads during the second beat were progressively greater. (Reprinted with permission from Circulation Research 18: 149, 1966.)

(and hence, the total load) is increased; this is illustrated by each of the three curves in the panel. However, as the diastolic length of the muscle is increased by augmenting the preload, the extent of shortening during an induced contraction is increased for any given total load. Myocardial work and power increase progressively with total load up to some optimum level; with greater loads, these functions then diminish progressively. Work equals force times distance (extent of shortening). Hence, zero work is done either when the load is zero or when the load is so great that the muscle cannot shorten (isometric contraction). Power equals the time rate of change of work; when work is zero, power also is zero. The muscle strip is capable of shortening against greater total loads as the preload is increased (fig. 1, Panels C and D). Also, the optimum total load increases as the preload is raised.

Whole Heart Preparations

Several groups of investigators have succeeded in determining the influence of variations in afterload on cardiac performance prior to the onset of adaptive changes. Monroe and French\(^{10}\) and Imperial et al.\(^{11}\) changed arterial impedance abruptly during ventricular diastole and observed the influence on ventricular performance during the next ventricular systole; the greater the impedance, the greater the peak ventricular systolic pressure and the lesser the stroke volume. Responses to increased afterload resembled those obtained in isolated myocardial strips (e.g., fig. 1, Panel B) in that the peak ventricular systolic pressure is analogous to the total loss and the stroke volume is analogous to the extent of shortening. Ross et al.\(^{12}\) changed LV afterload by rapidly injecting blood into or withdrawing blood from the aorta between beats. As the afterload was increased (fig. 2), peak LV systolic pressure increased and stroke volume...
decreased. The peak aortic flow is analogous to the peak velocity of shortening of a myocardial strip; the progressive reduction in peak aortic flow with increasing afterload is equivalent to the inverse force-velocity relationship in cardiac muscle strip.

More recent studies have helped to define precisely the influence of afterload changes on the volume of the ventricles during ejection. Studies from several laboratories have shown that the volume reached by the ventricles at the end of ejection (the end-systolic volume) depends on the afterload and contractility, but is independent of the end-diastolic volume and the stroke volume. For a given state of contractility, the end-systolic volume is delimited by the isovolumic pressure-volume relationship. In isovolumetric contractions (i.e., with no change in volume), the peak pressure generated by the ventricle varies with the end-diastolic volume; this is a manifestation of the well-known Frank-Starling mechanism. The normal ventricle, it has been found, that, under these conditions, the pressure-volume relationship is virtually linear over the physiological range of end-diastolic pressures.

When the ventricle contracts and ejects blood, the concomitant changes in pressure and volume may be displayed as a pressure-volume loop. The end-systolic pressure-volume coordinates of these ejecting beats falls on or slightly below the isovolumic pressure-volume curve. The prevailing pressure and volume at the end of ejection closely approximate the values obtained at the peak of an isovolumetric contraction originating from a comparable volume. In a study by Weber and Janicki, the heart was caused to contract from a constant end-diastolic fiber length (fig. 3, Point a) against three different afterloads; Curves 1, 2, and 3 in figure 3 represent the response to high, intermediate, and low afterloads respectively. The wall forces and circumferential fiber lengths at the end of systolic (Points c₁, c₂, and c₃) varied directly with the afterload, but the stroke volumes (as reflected by the differences between end-diastolic and end-systolic fiber lengths) varied inversely with the afterload. The dashed line indicated the peak force-length relationship that was obtained for the same heart when it was caused to contract isovolumetrically over a range of volumes. Note how closely Points c₁, c₂, and c₃ fall to this dashed line.

The ventricular myocardium develops a force during ejection that depends on the prevailing level of pressure and on the ventricular dimensions. A myocardial fiber can no longer shorten when it attains a force that is maximal for its prevailing length; this marks the end of ejection. The maximum force for a given fiber length is attained by an isometric contraction. Hence, the pressure-volume coordinates at the end of ejection are virtually identical to the values attained during an isovolumetric contraction that occurs at the corresponding end-systolic volume for the ejecting beat.

**Cardiac Hypertrophy in Response to Increased Afterload**

Cardiac hypertrophy is the usual response to prolonged or repeated increases in afterload; it is one of the pathological hallmarks of hypertension. However, rather than being a late and irreversible complication of the disease, it has recently been shown to be an early response that can play an important role in the evolution of the disease. Folkow has demonstrated how closely intertwined in the progress of hypertension are the structural cardiovascular alterations and functional neurohumoral influences, each exerting important interactions on the other. The rate at which the heart can adapt its design when exposed to changes in pressure was found to be rapid enough.

![Figure 3](http://hyper.ahajournals.org/)

**Figure 3.** Force length loops for an isolated, supported dog heart contracting against three different loading conditions, but from a constant end-diastolic length (Point a). Curves 1, 2, and 3 represent responses to high, intermediate, and low afterloads, respectively. As the ventricle shortened against progressively small afterloads, there was a progressively greater stroke volume (as reflected by the differences between end-systolic and end-diastolic fiber lengths). Note that the end-systolic forces and lengths (Points c₁, c₂, and c₃) fall along the force-length curve (dashed line) derived from a series of isovolumetric contractions. (Reprinted, with modification, from Am J Physiol 232: H-241, 1977.)
to suggest that structural alterations must be taken in account as dynamic participants in the response to hypertension and its treatment.

The exact stimulus initiating cardiac hypertrophy is not known, although it is likely to be related to an increase in myocardial tension as the ventricle contracts against a greater resistance. Biochemical changes in the myocardium can follow very rapidly (within hours) the imposition of an extra load on the heart. Their nature and rate of progress differ widely depending on the initiating stimulus and type of consequent hypertrophy.

Ventricular Hypertrophy in Clinical Hypertension

The development of LVH is an important landmark in the clinical evolution of hypertension. The presence of LVH, as detected by the EKG, was found to be an extremely lethal risk attribute in the Framingham study, within 5 years of its appearance, 35% of the men and 20% of the women with this finding were dead. Even higher figures for 5 years mortality were reported by Sokolow and Perloff from a study of hypertension antedating the advent of effective anti-hypertensive therapy. In the Framingham study, the risk of cardiac failure in patients with EKG criteria for LVH was three times higher than that associated with hypertension in general.

Although hypertension is the most common cause of pressure overload hypertrophy, our concepts of cardiac performance in that situation have been mostly derived from studies of aortic stenosis or of experimental banding of the large vessels. Studies of cardiac involvement by hypertension have all too often been restricted, largely because of ethical reasons, to determinations of cardiac output which could not by themselves allow a full understanding of myocardial responses to the increased load. However, it is not certain whether one can, with any degree of assurance, extrapolate directly to hypertension the results obtained from studies of other types of hypertrophy (even those due to pressure overload). There are too many differences between aortic narrowing and increased systemic pressure, and these disparities could modify cardiac responses. Some of these differences are:

1. Duration of load
2. Role of large vessels
3. Driving pressure of coronary circulation
4. Peripheral vascular disease
   a) Influence on impedance
   b) Coronary vascular disease
5. Associated neurohumoral disturbance.

Noninvasive ultrasound or radioisotopic techniques are rapidly modifying our understanding of cardiac responses to hypertension. Before their advent, most of our knowledge was based on EKG studies. Although, electrocardiographic patterns do to some extent reveal changes in LV mass, they are not very sensitive signs of LVH. On the other hand, echocardiography has introduced a new dimension in this domain by allowing a more precise look at ventricular geometry and some quantitation of LV wall thickness and mass. It has revealed a more complex picture of LVH than simple concentric hypertrophy. LVH was found to occur quite early in some adolescents with borderline blood pressure elevation, a finding similar to that described by our group and others in spontaneously hypertensive rats. Unexpectedly rapid changes in wall thickness and mass were reported to occur with antihypertensive therapy; asynergic-septal hypertrophy was reported to occur, particularly in early hypertension, not necessarily due to a genetically transmitted cardiomyopathy but secondary to LV pressure overload. Obviously, much remains to be established, particularly as regards to the factors modulating the development of hypertrophy and the clinical significance of changes in ventricular mass.

Arterial Pressure Levels and Left Ventricular Hypertrophy

Both the incidence and degree of LVH were found to correlate poorly with arterial pressure levels. This is not surprising, since arterial pressure is not per se an accurate measure of afterload. The significance of that fact, however, was often overlooked in part because of the assumption that cardiac hypertrophy was simply a graded response to the increasing pressure levels. Exceptions to that rule were attributed to coexisting coronary arterial disease or cardiomyopathy. These explanations have been challenged for both animal and human hypertension. In animals, where cardiac weight and other variables could be defined more precisely than in man, the relationship between arterial pressure and LV weight was found to vary widely among different types of hypertension. A close relationship was found in renovascular hypertension but not with DOCA hypertension, while cardiac hypertrophy was noted even before significant hypertension in SHR. The conclusions derived from the development of hypertensive hypertrophy were substantiated by observations made during its reversal by antihypertensive measures. Drugs that were equipotent with respect to blood pressure control had divergent effects on left ventricular mass. Thus, neither the development nor reversal of hypertrophy appeared to be simple expressions of quantitative alterations in blood pressure levels.

Functional Consequences of Left Ventricular Hypertrophy

Whether LVH is a useful compensatory process or the first step toward depressed contractility and eventual decompensation is still debated. The implications of any answer to that problem are of enormous importance in hypertension, where reversal of myocardial hypertrophy can be obtained by some antihypertensive drugs.

The functional consequences of LVH can be viewed from two aspects, the effect of hypertrophy on intrin-
sic myocardial contractility and its mechanical consequences on myocardial wall stress. Studies of the first aspect showed a wide array of findings depending on the type of pressure load and its duration. Earlier studies with papillary muscles from animals with aortic or pulmonary artery constriction indicated a reduced inotropic state, evidenced by depressed force-velocity curves. However, later studies suggested that this depression might be only transient and that myocardial contractility returned to normal about 2 to 2.5 months following pulmonary artery banding in cats or aortic constriction in dogs. A somewhat different pattern emerged from similar studies of hypertensive models; not only did they differ from the above but they also appeared to differ according to the experimental model of hypertension.

The main findings in the early state (8 weeks) of Goldblatt hypertension in rats showed a decrease in shortening velocity at zero load but no change in maximum instantaneous power. Papillary muscles from hearts of the same model with significant ventricular hypertrophy (+50% in weight) showed significant prolongation of isotropic time to peak tension and of time to half-relaxation but were still able to maintain normal levels of peak isotropic tension. However, as hypertensive rats were followed for 6 months, the maximum instantaneous power was gradually reduced below the control norm over the same period. In contrast, the LV papillary muscles of younger SHR showed normal contractility and relaxation parameters. Only at about 40 weeks of age was the first sign of depressed contractility seen (depressed isotonic shortening velocity). At age 60 to 80 weeks, maximum isotropic tension was significantly reduced.

The inscription of cardiac function curves by rapid volume expansion has likewise revealed a time dependent reduction in cardiac performance during the evolution of hypertension. A conflict persists as regard to the results obtained in younger SHR's. Spech et al. reported a reduced maximal pumping capacity in SHR age 17 to 29 weeks, whereas Pfeffer et al. and others found that cardiac function was well maintained during the developmental phase of cardiac hypertrophy and well through the first 12 to 18 months of life. It is not easy to reconcile these differences, many of which may be due to technical reasons. In favor of the latter's conclusion, however, is its general agreement with the results obtained by Bürger and Strauer in papillary muscle studies. The important point remains that cardiac performance, which might be normal in the early stages of hypertrophy, eventually falls at some later point in its evolution.

The ability of the heart to increase its output obviously depends on both preload conditions and the level of resistance to ejection, as well as on myocardial muscle mass. In a sequence of impressive studies, Hallbäck and her collaborators have shown that the performance of the hypertrophied ventricle of the SHR varies in comparison with that of normal controls, depending on both filling pressure and afterload conditions. The hypertrophied ventricles performed better than control when working against a high pressure load. Conversely, at low preload levels, the stroke volume was lower in SHR than in normotensive rats at their respective in vivo pressure levels. Under those conditions, the higher pressure against which the SHR was working reduced its stroke volume. At high cardiac filling pressures, however, when the full resources of the hypertrophied ventricle are mobilized, cardiac performance was superior in SHR compared to controls.

These results indicate that it is not really possible to describe the full spectrum of the cardiac consequences of hypertrophy from a description of cardiac function curves alone. There are many mechanisms by which the hypertrophied LV could compensate for the higher load it has to carry. These include dependence on higher preload, mobilization of adrenergic support, and alterations in ventricular geometry. With regard to the first, the studies of the Göteborg group as well as those of Saragoca and Tarazi showed that both in SHR and renovascular hypertension the hypertrophied heart responded to a volume or pressure overload by higher LV filling pressure. This increased end-diastolic pressure was not due to a reduction in LV distensibility but signified a greater end-diastolic volume. Simultaneously, with this greater dependence on heterometric autoregulation, myocardial inotropic responses to isoproterenol were blunted in direct correlation with the increase in ventricular weight (fig. 4). That reduction in responsiveness, which was documented by many, seemed to imply a reduced ability to depend on adrenergic support. Consonant with this are reports of reduced density of cardiac beta-adrenergic receptors in various types of hypertensive hypertrophy.

The central relocation of intravascular volume seen in human and experimental hypertension would seem to agree with the concept.

**Figure 4.** Inotropic response to isoproterenol infusion (as determined from $\Delta P/dt/P_{\text{ao}}$ at developed LV pressure of 40 mm Hg) was inversely correlated with ventricular weight in rats with renovascular hypertension (RHR) and sham-operated controls. (Reprinted with permission from Hypertension 3 (suppl I): I-171, 1981.)
Cardiac Hypertrophy and Myocardial Wall Stress

The stress imposed on the myocardial wall is one of the main determinants of myocardial oxygen requirements and could well be one of the important factors in the evolution of hypertrophy. The level of stress obviously depends on the way by which hypertrophy alters the geometry of the LV. Grossman et al. and Gaasch have clearly demonstrated the dependence of LV function on the ratio of wall thickness to radius of the ventricle; Strauer came to the same conclusions utilizing the ratio of LV volume to its mass. Whatever the index of function used, the velocity of circumferential fiber shortening (Vcf) or the ejection fraction, the results from many centers have been remarkably consistent; the greater the dilation of the heart's cavity in relation to thickening of its wall, the more marked the depression of its function.

These observations are readily explained by the effect of myocardial hypertrophy on wall stress; Equation 1 implies that the greater the LV dilation, the higher the stress on its wall, unless this is counterbalanced by greater thickness of the wall. Although unavoidable simplifications and assumptions are involved in the extrapolation to the complicated geometry of the LV of calculations based on simple ellipsoid or spherical models, the remarkable uniformity of results from many centers underlines the basic validity of this approach. Hypertrophy could, therefore, be viewed as a compensatory process to reduce the higher tension imposed by higher pressure levels.

The clinical implications are obvious; whereas concentric hypertrophy could be viewed as a potentially useful compensatory process, eccentric ventricular hypertrophy was associated with greater stress and depressed performance. Few would doubt the second half of this statement; dilation in excess of hypertrophy (inadequate ventricular hypertrophy) is associated with reduced ventricular function. The net effect of concentric hypertrophy, however, has proven more difficult to define; reduction of wall stress by the increased thickness of the myocardium is a direct consequence of the interaction of forces described in Equation 1. However, hypertrophy has other consequences such as reduced compliance of the increased ventricular mass, alterations in myocardial composition, and secondary changes in coronary perfusion — all of which may interfere with different aspects of cardiac function in systole or diastole. The progression from concentric hypertrophy to ventricular dilation in heart failure has been more predicated on the basis of group comparisons than on direct evidence of progression in man. The frequency of that progression or the factors influencing it still remains to be determined.

Since the measurements needed for the calculation of stress and cardiac performance depended to a great extent on invasive techniques, the initial concepts were derived from studies of aortic stenosis and cardiomyopathy. Their application to hypertension lagged because of the legitimate ethical concerns regarding LV catheterization in asymptomatic subjects. Moreover, questions arose regarding the applicability to hypertension of conclusions derived from aortic stenosis or experimental coarctation. The differences between these types of pressure load are many, as listed above (see p II-12). Possibly adding to these differences is also the possible impact of altered sympathetic tone or of activation of the renin-angiotensin system in hypertension. Even within hypertension, cardiac catecholamine concentration differed markedly from one model of the disease to another.

However, as echocardiographic techniques were developed and studies of the heart in hypertension increased rapidly, the early conclusions seemed to confirm the basic concepts developed from other models. The spectrum of cardiac involvement in hypertension, however, appeared wider than originally postulated. Guazzi et al. described a clear differentiation in indices of performance among hypertensive patients based on: (1) presence of echocardiographic signs of LVH; (2) thickness of posterior LV wall and; (3) magnitude of the LV short axis diameter. Fouad et al. found that among hypertensive patients, the variable most closely related to cardiac performance was end-systolic stress, which showed a highly significant inverse correlation with both the degree (% shortening) and velocity (Vcf) of LV contraction ($r = -0.80$ and $-0.74$ respectively, $p < 0.001$ for both) (figs. 5 and 6). This correlation was found consistently in the whole group of patients investigated, whether treated

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**Figure 5.** The degree of shortening of the left ventricular minor axis (\% shortening) was inversely related to end-systolic stress in this group of 65 hypertensive patients; end-systolic stress was calculated from auscultatory systolic pressure and from simultaneous echocardiographic recording, as described by Wilson et al. (see ref. 22). The data were derived from Fouad et al. (see ref. 92).
or not, and seemed to describe the relationship expected between afterload and ventricular performance. 87

In contrast, the correlations between the same indices of cardiac performance and other levels of LV stress (peak or average systolic stress) were much weaker or did not even attain statistical significance. These results emphasize the diagnostic value of the end-systolic pressure/volume relationship for assessment of myocardial contractility. 84-87 Another aspect of these results worth emphasizing is the relatively high value of the correlation between end-systolic stress and LV contraction (% shortening) (r² = 64%). This correlation was obtained irrespective of concomitant sympatholytic or other forms of therapy and suggests the biologic importance of the mechanical conditions under which the heart operates.

Factors Other Than Wall Stress

Important as these biophysical considerations are, however, they are not the only determinants of cardiac function in hypertensive patients. Alterations in myocardial contractility, in cardioadrenergic drive, and coincident coronary atherosclerosis may all have significant influences, and it is not always easy to define the relative roles they play. The heart's ability to sustain an increased pressure load is remarkably dependent on the level of sympathetic activity. 81 That level varies considerably among hypertensive patients 84, 86 and so does the dependence of the heart on adrenergic drive to meet any added stress. 85, 86 Little is known about factors that govern this dependence in hypertensive patients. The presence of heart failure or obvious cardiomegaly is a serious risk for sympatholytic therapy; apart from these classical signs, however, we did not find it possible to separate by simple clinical hemodynamic or ECG examination those patients who tolerated well guanethidine or propranolol from those whose cardiac performance was depressed by sympathetic blockade. 86

Given the importance of adrenergic blockade in the treatment of hypertension, the importance of determining its effect on cardiac performance in patients with cardiac hypertrophy hardly needs stressing. Recent studies have suggested that reversal of hypertensive cardiac hypertrophy is favored by those anti-hypertensive drugs that interfere with, or at least do not stimulate, sympathetic activity. 8, 84, 87 The interaction of blood pressure fluctuations, cardiac performance, and level of cardioadrenergic drive obviously needs better definition in hypertension.

Coronary Blood Flow and Left Ventricular Hypertrophy in Hypertension

Clinicians have long suspected that myocardial perfusion might be impaired in hypertension. Initial studies, however, showed rather consistently that coronary blood flow per unit mass of myocardium was within normal limits. 87, 88 Only recently has the problem been examined in more detail, particularly the response of coronary vessels to vasodilator stimuli and the distribution of flow between the endocardium and epicardium. 89, 90

Most studies have indeed confirmed that coronary flow in pressure LVH was usually normal at rest (in proportion to myocardial mass). However, in response to vasodilator stimuli, there was often, albeit not always, a reduced capacity for coronary vasodilation. 89, 108 Apparently, a greater portion of that capacity must have been used to maintain an adequate myocardial perfusion at rest, leaving a reduced coronary vascular reserve. The extent of that reduction differed widely amongst various studies, but this is not surprising given the large number of factors that can influence coronary vasodilation. These include the relation of coronary perfusion pressure to degree of LVH and the extent of structural changes in the coronary vessels. 89 In cases with reduced coronary reserve, the coronary flow might not be able to meet the additional demands imposed by increased cardiac work. Under these conditions, the subendocardial region would be at particular risk of ischemic injury. 108

Antihypertensive therapy can influence coronary blood flow in many ways; fears that therapeutic lowering of a raised blood pressure would lead to coronary insufficiency or to myocardial infarction have not, in our experience, been substantiated. On the contrary, reduction of the pressure load and therefore of the excessive myocardial oxygen requirements will help relieve coronary insufficiency and reduce anginal episodes. It is important, however, to avoid in patients with cardiac disease or in older patients the reflex
tachycardia and hyperkinetic circulation that occur with some vasodilators, such as hydralazine, diazoxide or minoxidil. One must also consider, in addition to these early pharmacologic effects, the long-term consequences of antihypertensive therapy on cardiac hypertrophy and on the coronary vessels. Wicker and Tarazi found that, in rats with renovascular hypertension, reversal of LVH led to restoration of coronary vascular reserve if the latter had been reduced by the hypertrophy. Of particular importance was the relation between arterial pressure and myocardial mass. Parallel changes in both did not greatly alter coronary blood flow per gram ventricular weight, but reduction of blood pressure without reversal of hypertrophy was associated with a significant reduction in the coronary flow response to maximal vasodilation. It is obvious that much remains to be elucidated regarding the coronary effects of prolonged antihypertensive therapy. The situation becomes even more complex if coronary atherosclerosis is added to the effects of hypertension and cardiac hypertrophy. Interference with the vasodilating capacity of coronary vessels may then aggravate the effects of a coronary stenosis or obstruction.

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