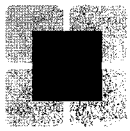

Cardiac function and dysfunction in hypertension

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- **BACKGROUND** Hypertension is the most common condition of increased left ventricular afterload that affects the cardiovascular system.
- **OBJECTIVE** To review the effects of increased blood pressure on cardiac function.
- **SUMMARY** In early or borderline hypertension, cardiac output increases but intravascular volume remains normal. In uncomplicated established hypertension, left ventricular systolic function is generally normal at rest; however, the left ventricular filling rate is reduced in approximately 30% of hypertensive patients without associated alterations in systolic function. In the presence of left ventricular hypertrophy, overall left ventricular systolic performance remains within normal limits; however, left hypertrophy in hypertension is associated with a high morbidity rate, possibly due to increased collagen concentration leading to reduced left ventricular compliance, fewer adrenergic receptors, reduced responsiveness of the adenylate cyclase system, and reduced coronary flow reserve. Acute increases in blood pressure in a hypertensive patient may worsen cardiac function, particularly in the presence of medications that interfere with the adrenergic support of the heart. New, accurate, noninvasive techniques can assess cardiac structural and functional aspects of hypertension under precise circumstances.
- **CONCLUSIONS** Assessing both systolic and diastolic function is important in the follow-up of hypertensive patients and in the choice of therapy.

■ INDEX TERMS: HYPERTENSION; VENTRICULAR FUNCTION; CARDIAC OUTPUT; HEART HYPERTROPHY; ADRENERGIC BETA RECEPTOR BLOCKADERS
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MUCH OF OUR understanding of the pathologic consequences of pressure overload in patients has been derived from studies in valvular heart disease. However, hypertension is the most common condition of increased left ventricular afterload that affects the cardiovascular system.[1] The net cardiac function at any particular time depends upon preexisting cardiac structural and functional alterations, the prevalent blood pressure, the rate of increase of blood pressure, and neurohumoral factors. One must consider all these factors to understand the effects of hypertension on cardiac function.

CARDIAC FUNCTION IN EARLY OR BORDERLINE HYPERTENSION

In early or borderline hypertension, cardiac output increases but intravascular volume remains normal.[2–4] This hemodynamic pattern has been attributed to venoconstriction with resultant redistribution of blood volume from the peripheral circulation to the heart and lungs. A more clearly hyperkinetic circulation has also been described in patients with borderline hypertension, who have faster heart rates, greater left ventricular

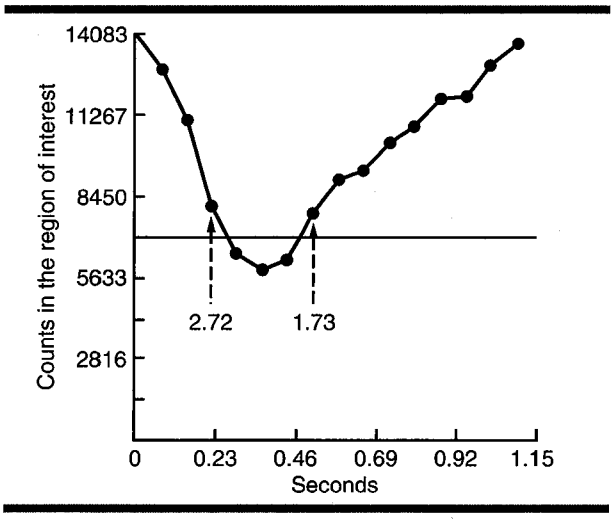

FIGURE 1. Left ventricular volume curve in a hypertensive patient. The blood pressure was 142/99 mm Hg and the heart rate was 52 beats per minute. The curve is obtained by gated blood pool scanning with technetium-99m-tagged red blood cells and represents events in the cardiac cycle. The downsloping segment represents systole and the upsloping segment represents diastole. The horizontal line represents the 50% cutoff levels of counts in the left ventricular region of interest (Y axis). The left ventricular ejection fraction was 52%. Arrows denote the sites of the maximum rates of left ventricular ejection (left) and filling (right); these rates are shown below the arrows and are expressed in Herz. Note that the maximum rate of filling is lower than the maximum rate of ejection. Both the maximum rate of ejection and the ejection fraction were within the normal range. From Fouad-Tarazi, reference 9.

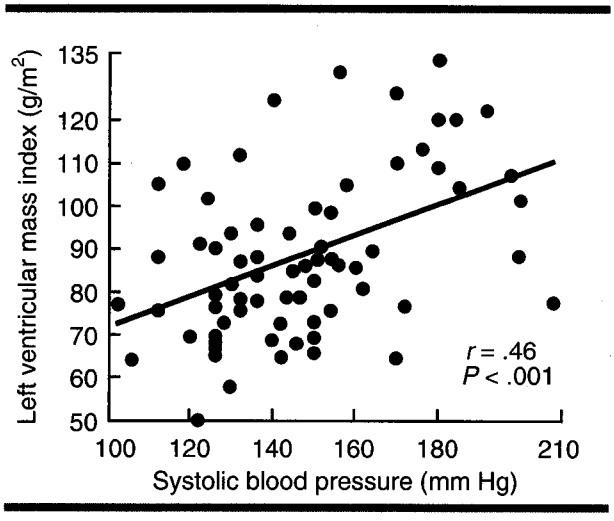

FIGURE 2. Correlation between systolic blood pressure and left ventricular mass in hypertensive patients. Although the correlation was significant, the r value was only .46, and there was a marked dispersion of data points. From Abi-Samra et al, reference 14.

ejection rates, greater ventricular contractility, and greater cardiac output than normal counterparts.[5-7]

In experiments in animals, pressure overload rapidly develops after bilateral renal artery occlusion or banding or coarctation of the aorta. In these models, the function of the heart may remain normal or may even become accentuated. In our experience, bilateral renal artery occlusion in dogs resulted in the rapid development of hypertension and left ventricular hypertrophy; left ventricular systolic function remained normal in the initial 3 weeks, but the peak rate of left ventricular filling increased rather than decreased during this period. Therefore, under these circumstances, factors other than increased afterload could play a role in the determination of cardiac function, including the adrenergic nervous system or perhaps the renin-angiotensin system. However, one cannot rule out the effect of changes in coronary perfusion or local cardiac factors.

CARDIAC FUNCTION IN ESTABLISHED HYPERTENSION

In chronic hypertension, the left ventricle adapts to the increased afterload. Left ventricular systolic function has been reported to be normal at rest in most patients with uncomplicated established essential hypertension. However, electrocardiographic changes in the P wave were described as early as in 1965; these denote left atrial enlargement, even in the absence of signs of left ventricular hypertrophy.[8]

More recently, noninvasive techniques such as radionuclide angiography and echocardiography have allowed us to assess left ventricular diastolic function directly. The left ventricular filling rate is depressed in approximately 30% of hypertensive patients before any alterations in systolic function are apparent (*Figure 1*).[9] The mechanisms underlying this abnormality are not known, although several factors could be involved, including abnormalities in adrenergic drive, coronary blood flow, calcium reuptake, and left ventricular structure.

The functional and clinical implications of this abnormality of left ventricular filling are not yet well defined. However, we have demonstrated an association between abnormalities of left ventricular diastolic filling rate in hypertension and the peripheral vascular regulatory mechanisms in response

TABLE
POSSIBLE CAUSES OF DISSOCIATION BETWEEN BLOOD PRESSURE AND LEFT VENTRICULAR MASS*

Hemodynamic causes
Inaccurate or approximate estimate of afterload
Casual vs continuous blood pressure recording
Concomitant increases in volume load
Neurohumoral causes
Sympathetic stimulation
Activation of the renin-angiotensin system
Influence of other hormones (eg, thyroxin, growth hormone)
Associated cardiac disease
Aging and genetic factors

*From Fouad, reference 31

to neural vasoconstrictive stimuli.[10] Also, "flash pulmonary edema" could be the result of fluid overload in a noncompliant heart with abnormal left ventricular diastolic filling capacity.[11]

ASSESSMENT OF THE FUNCTION OF THE HYPERTROPHIED HEART

A striking observation in most studies of cardiac structure and function in hypertension has been the dissociation between blood pressure and left ventricular mass. Hartford and coworkers[12] found a correlation of only .26 between mean arterial pressure and echocardiographically determined left ventricular mass. In our laboratory,[13] the correlation between left ventricular mass and systolic blood pressure was .46 (*Figure 2*). Possible causes of this dissociation are listed in the *Table*.

Part of the problem is that arterial pressure per se is not an accurate expression of afterload, which is better determined by left ventricular wall stress. The calculated left ventricular wall stress takes into consideration not only the arterial pressure but also left ventricular wall thickness and left ventricular cavity dimensions. The relationship between calculated left ventricular wall stress and left ventricular mass, however, proved to be complex. On the one hand, one would expect that the greater the afterload, the more marked the hypertrophy. On the other hand, greater thickening of the myocardium could help reduce wall stress. In fact, an inverse correlation was reported between left ventricular peak systolic stress and left ventricular mass in hypertensive patients.

Overall ventricular performance in hypertensive patients with left ventricular hypertrophy has been reported repeatedly to be normal. In our experience, left ventricular fractional shortening was within

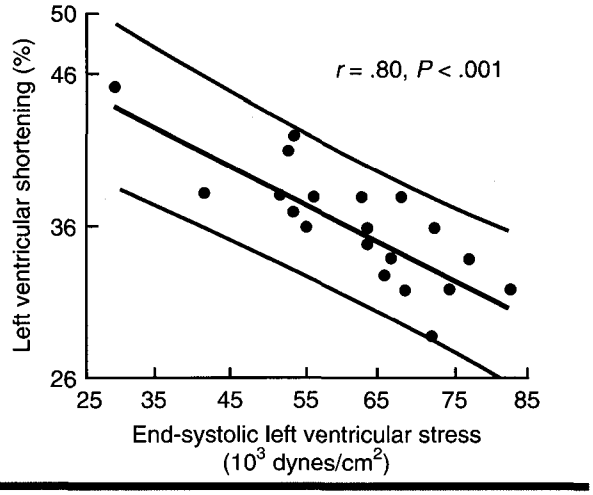

FIGURE 3. Inverse correlation between end-systolic stress and left ventricular fractional shortening in 20 normal subjects. From Fouad, reference 13.

normal limits when assessed in relation to: (1) an index of preload derived from the left ventricular end-diastolic cavity dimension, (2) an index of afterload (the left ventricular end-systolic stress), and (3) an index of contractility (the ratio of systolic blood pressure to end-systolic volume).[14] The relationship between left ventricular end-systolic stress and left ventricular fractional shortening is illustrated in *Figure 3*. Left ventricular end-systolic stress correlated inversely with left ventricular fractional shortening both in hypertensive patients and in a parallel group of normal volunteers. Other centers also reported a similar correlation in hypertensive patients.

A multivariate regression analysis confirmed that afterload was the major determinant of left ventricular systolic function in hypertensive patients, especially patients with left ventricular dilatation. In contrast, left ventricular contractility was the major factor governing left ventricular function in normal individuals and in patients with isolated septal hypertrophy. The mechanisms underlying the shift in factors controlling left ventricular function are not completely clarified, but may include adrenergic support, the Frank-Starling mechanism, and others.

Although the structural alterations in the hypertrophied left ventricle could be considered "adaptive," at least initially, they are linked to important functional changes. Indeed, left ventricular hypertrophy in hypertension is associated with a high

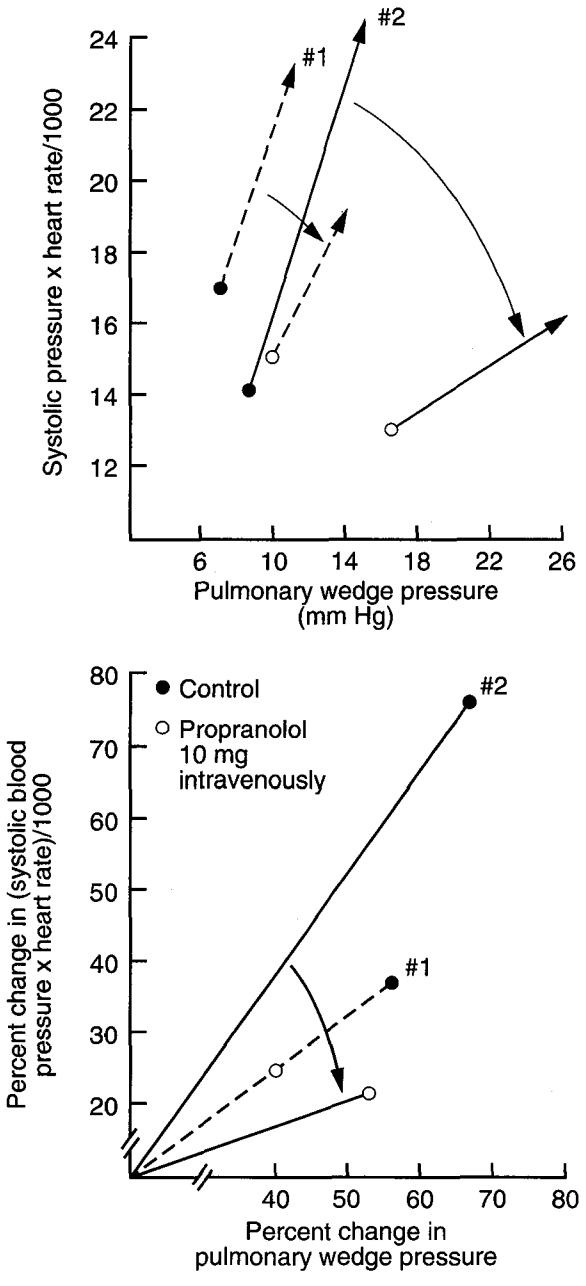

FIGURE 4. Effect of beta-adrenergic blockade on cardiac response to the stress of static exercise in two patients. The effect in these patients was quite different, although both appeared to have an equivalent degree of cardiac performance before beta blockade. The changes with static exercise before and after propranolol are expressed in the top panel as absolute numbers and in the bottom panel as percent change. From Alicandri et al, reference 19.

morbidity rate. For example, increased collagen concentration in the myocardium has been linked to reduction in left ventricular compliance, the recognition of which is of paramount importance for the understanding of left ventricular function in hypertension. At the cellular level, left ventricular hypertrophy is associated with a reduction in adrenergic receptors and reduced responsiveness to stimuli of the adenylate cyclase system.[15]

Coronary flow reserve is also reduced in the hypertensive hypertrophied heart.[16,17] Such alterations may form the seed for the evolution from cardiac compensation to decompensation, particularly when other factors such as sodium retention or blood volume expansion or both become superimposed.

Thus, prevention or regression of left ventricular hypertrophy has become an important goal in the treatment of hypertension. Reports from many centers over the past few years have unequivocally demonstrated that regression of left ventricular hypertrophy can be produced in hypertensive hearts, both in experimental models and in man. Several studies have shown preservation of systolic function and possible improvement of diastolic and neurogenic function during regression of left ventricular hypertrophy, at least with some drugs.

EFFECT OF ACUTE PRESSURE OVERLOAD ON CARDIAC FUNCTION IN HYPERTENSION

Evidence for a subtle impairment of cardiac response to stress in hypertension has been reported both in experimental animals and in patients with essential hypertension. A rapid increase in blood pressure in hypertensive humans may be induced by dynamic exercise, static exercise, or intravenous infusion of pharmacologic vasoconstrictors such as phenylephrine or angiotensin II. Lund-Johansen[18] reported a lower stroke index during dynamic exercise in patients with hypertension (even in young patients) than in age-matched controls.

Figure 4 illustrates our experience in hypertensive patients compared with normal volunteers subjected to static exercise (hand-grip test) before and after beta-blockade.[19] All our patients and subjects had normal resting pulmonary wedge pressure. The relationship of cardiac work to left ventricular filling pressure under the stress of increased cardiac load was normal in two thirds of the hypertensive patients (16 of 24); in contrast, the other eight patients had an abnormal response.

These data indicate a wide spectrum of cardiac function among hypertensive patients, which can be detected only when cardiac stress is increased. This subtle reduction in the level of cardiac performance, at least in some hypertensive patients, might reflect an early reduction in left ventricular compliance in hypertension. However, other factors such as biochemical, neural, and vascular effects cannot be ruled out.

Although the circulatory responses to static exercise[20] involve sympathetic stimulation of the heart and peripheral vessels, the reflex increase in systemic pressure is not abolished by acute beta-adrenergic blockade. Therefore, beta-blockade with propranolol (10 mg intravenously) resulted in a greater reduction in cardiac performance in our hypertensive patients with impaired baseline function than in those with normal baseline cardiac function. These findings suggest that adrenergic support of cardiac performance might be important in at least some hypertensive patients who have no evidence of heart failure. Adrenergic blockers, particularly beta blockers, should be used with caution in such patients, and cardiac functional indices should be observed closely.

CONCLUSIONS

In hypertension, the heart can show a wide variety of structural and functional changes. The alterations in function can affect systolic as well as diastolic performance. Indeed, diastolic changes might occur much earlier than the reduction in systolic function. Both aspects can be influenced by treatment via reduction in arterial pressure, interference with neurohumoral factors, and regression of hypertrophy.

Generalizations cannot be made concerning the changes affecting cardiac function and dysfunction in hypertension because of the interplay of multiple factors leading to conflicting responses. Assessment of the heart in hypertension necessitates evaluation of cardiac structure and function in individual patients.

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