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Cardiac Hypertrophy and Arterial Compliance Following Drug Treatment in Hypertension

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Summary: The load of the heart in hypertension is related both to increased peripheral vascular resistance and decreased aortic compliance. From noninvasive studies involving determinations of pulse-wave velocity and systolic-diastolic variations of aortic arch diameter, it can be shown that increased aortic elastic modulus is strongly related to increased cardiac mass. The relationship is observed even after adjustment for the level of mean arterial pressure. It is suggested that decreased aortic compliance in hypertension causes a disproportionate increase in systolic pressure and end-systolic stress, thus contributing to promote cardiac hypertrophy. Such a possibility may have consequences for long-term antihypertensive therapy. Following converting enzyme inhibition and calcium blockade, important dissociations may be observed between the antihypertensive effect and the cardiac and arterial changes. **Key Words:** Essential hypertension—Aortic compliance—Cardiac hypertrophy—Converting enzyme inhibition—Calcium blockade.

The dominant factor contributing to the development of cardiac hypertrophy in hypertension is increased end-systolic stress (1,2). According to the Laplace law, end-systolic stress is influenced by the geometrical properties of the ventricle as well as by the level of systolic blood pressure. Increased systolic blood pressure depends on peak ejection velocity and on aortic wave velocity, and therefore involves changes in both cardiac performance and physical properties of the arterial system (1,2).

Classically, the degree of cardiac hypertrophy is predominantly related to the level of mean arterial pressure and vascular resistance and hence to the degree of constriction of small arteries (3). However, the capacitive properties of the arterial system (i.e., aortic compliance) may also be responsible for the development of cardiac mass (4). In the literature related to hypertensive cardiac hypertrophy, several lines of evidence indirectly suggest this possibility. First, in cross-sectional studies the correlation coefficient relating cardiac mass to blood pressure is relatively low, indicating that factors other than vascular resistance might play a role in the development of cardiac structure (3). Second, cardiac hypertrophy is better correlated with systolic than with diastolic pressure (3), and the level of systolic pressure is largely influenced by modifications in aortic compliance, particularly in the elderly (5,6). Finally, the heart during systole "sees" a load that is mainly composed of the aortic chamber contents (7). This observation suggests that the reduction in aortic compliance might cause a predominant increase in systolic pressure and end-systolic stress, contributing to promote cardiac hypertrophy.

This article extensively evaluates the relationships between aortic compliance and cardiac hypertrophy in subjects with sustained essential hypertension without and following antihypertensive therapy.

CARDIAC HYPERTROPHY AND AORTIC COMPLIANCE IN UNTREATED PATIENTS WITH HYPERTENSION

The relationships between cardiac hypertrophy and large artery compliance are difficult to analyze in hypertension. Indeed, the simple mechanical effect of the elevated distending pressure may mechanically reduce this parameter (1,2). Therefore, the principal difficulty is to demonstrate that the reduction in arterial compliance may influence "per se" the degree of cardiac hypertrophy independent of the blood pressure level. Invasive studies of vascular impedance have shown both in hypertensive humans and rats (8,9) that the degree of cardiac hypertrophy is closely related to the physical properties of the large arterial system inde-

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pendent of mean arterial pressure: the more altered the physical properties of the arterial tree, the higher the degree of cardiac hypertrophy. In these studies, the physical properties of the arterial system were evaluated from characteristic impedance measured at the site of the aortic arch. This parameter evaluates the characteristics of the pulsatile component of the pressure-volume relationship within the arterial tree and is directly related to the velocity of pulse wave and inversely related to the cross-sectional area of the aorta (1,2). Recently both of these hemodynamic parameters were evaluated in humans using noninvasive techniques. Cardiac mass was determined by echocardiography and aortic parameters were evaluated by noninvasive measurements of pulse-wave velocity and aortic diameter.

The determination of aortic arch diameter was performed in 16 patients with sustained essential hypertension by comparison with 15 normal subjects with age, sex, and body surface area in the same range (10). In all subjects, brachial mean arterial pressure, pulse pressure (PP), cardiac mass (judged on echocardiography), and carotid femoral pulse-wave velocity (PWV) were measured together with ultrasonic determinations of aortic-arch diastolic (DD) and systolic (SD) diameters (echography with suprasternal window). For each subject, pulsatile change in aortic diameter (dD = SD − DD), strain (dD/DD), as well as aortic arch elastic modulus Ep (PP × DD/dD) were calculated. Compared with normal subjects, the hypertensive subjects characteristically showed an increase in aortic arch diameter (DD: 29.6 ± 1.0 vs. 25.4 ± 1.0 mm; $p < 0.01$), in Ep (1.072 ± 0.127 vs. 0.526 ± 0.045 10^5 $N \cdot m^{-2}$; $p < 0.001$), and PWV (11.8 ± 0.5 vs. 8.9 ± 0.3 m/s; $p < 0.001$). In the study population, a positive correlation was observed between Ep and cardiac mass ($r = 0.60$; $p < 0.01$) even after adjustment for mean blood pressure, suggesting that the increase in aortic elastic modulus might influence the degree of cardiac hypertrophy independent of the blood pressure level.

In another study (11) pulse-wave velocity, used as an index of arterial stiffness, was studied in normotensive and hypertensive subjects in conjunction with cardiac mass evaluated from echocardiography. In the overall population, cardiac mass was significantly correlated with carotid-femoral pulse-wave velocity. The correlation disappeared after adjustment for systolic pressure (and not for diastolic pressure), suggesting that decreased aortic distensibility influenced the degree of cardiac hypertrophy through a resulting disproportionate increase in systolic pressure and end-systolic stress. This interpretation was further confirmed by two observations: (a) the positive correlation observed between cardiac mass and diastolic pressure disappeared after adjustment for systolic pressure, whereas (b) the positive correlation observed between cardiac mass and systolic pressure did not change after adjustment for diastolic blood pressure.

These findings strongly suggest that the degree of reduction in aortic compliance and distensibility in hypertensive patients contribute to the development of cardiac hypertrophy independent of the increases in blood pressure and vascular resistance. This interpretation agrees with the clinical and experimental evidence that reduced aortic compliance in hypertension is not the simple mechanical consequence of the elevated blood pressure but rather reflects intrinsic modifications of the hypertensive arterial wall with substantial changes in the structure of large vessels (5).

CARDIAC HYPERTROPHY AND ARTERIAL COMPLIANCE IN PATIENTS TREATED FOR HYPERTENSION

Following antihypertensive therapy, several observations have indicated that the reversion of cardiac hypertrophy could be dissociated from the blood pressure reduction (3). In hypertensive animals it has been observed that, for an equivalent blood pressure reduction, converting enzyme inhibition and blockade of the autonomic nervous system by propranolol or methyldopa was associated with regression of cardiac hypertrophy whereas no comparable finding was observed with dihydralazine and minoxidil. The generally accepted interpretation for such findings was that nonhemodynamic mechanisms such as those produced by the renin-angiotensin system or the sympathetic nervous system participated directly to the regression of cardiac hypertrophy independent of blood pressure changes. However, from the basic relationships between the heart and large vessels, another interpretation could be proposed: through the maintenance of reduced arterial compliance, large vessels could contribute to maintain a certain degree of cardiac hypertrophy with some antihypertensive treatments despite an adequate blood pressure reduction.

To test this hypothesis, the changes in the heart and large vessels following long-term converting enzyme inhibition was studied in hypertensive humans (12,13). As reported with other converting enzyme inhibitors (3), a 12-week treatment with perindopril caused a significant decrease in left ventricular mass in hypertensives subjects, principally due to a decrease in septal thickness and posterior wall thickness. Arterial compliance increased in parallel. However, 4 weeks after treatment was stopped, cardiac mass remained low, whereas blood pressure and arterial compliance had returned toward baseline values. After restarting treatment for 1 year, cardiac mass further decreased, whereas arterial compliance increased, but no more than at the beginning of treatment. Such findings strongly suggested that the time constant for reversal of cardiac and arterial changes was different in treated hypertensives. As reversal of structural changes has been observed characteristically for the increased cardiac mass, one possibility is that reversal of structural changes may be different in large vessels, in which it is particularly difficult to modify the collagen content of the arterial wall.

Another observation is provided by the study of calcium-entry blockade produced by verapamil (14). The study was performed in 13 subjects with sustained essential hypertension. Echo-Doppler methods were used to evaluate cardiac structure and function, maximum aortic acceleration (used as an indirect index of cardiac performance), and carotid-femoral pulse-wave velocity. Measurements were performed in baseline conditions, following 12 weeks of active treatment, and then after 4 weeks of placebo. Blood pressure significantly decreased with a slight reduction in cardiac output and a more substantial decrease in heart rate. No significant changes occurred in maximum acceleration or in the curve relating percent fractional shortening to end-systolic stress, suggesting minimal changes in cardiac performance. Cardiac mass decreased by 6.3% whereas pulse-wave velocity did not change, suggesting that the small decrease in cardiac mass could be related to the lack of improvement in the capacitive component of vascular impedance. Thus, calcium blockade due to verapamil resulted in a dissociation between the antihypertensive effect and the smaller changes in cardiac and arterial parameters.

In conclusion, in untreated hypertensive subjects strong relationship are observed between cardiac mass and arterial compliance, whereas dissociation between the antihypertensive effect and cardiac and arterial changes may be observed following antihypertensive therapy by converting enzyme inhibition and calcium blockade.

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