Arterial distensibility and left ventricular hypertrophy in patients with sustained essential hypertension

Reduced aortic distensibility and compliance may participate in the genesis of cardiac hypertrophy in patients with hypertension. In these patients the increase in end-systolic stress, a determinant factor contributing to the development of cardiac hypertrophy, is influenced not only by the geometric properties of the ventricle but also by the level of systolic pressure. In patients with sustained essential hypertension, the degree of cardiac hypertrophy correlates significantly with the increase in aortic rigidity, which is assessed by the calculation of the characteristic impedance, by the measurement of carotid-femoral pulse-wave velocity, or by the calculation of the Peterson elastic modulus at the level of the aortic arch. Dihydralazine-like substances are unable to modify arterial stiffness, whereas calcium-entry blockers and converting-enzyme inhibitors improve arterial stiffness when achieving the same degree of blood pressure reduction. Modifications in the stiffness of the aorta and other large arteries must be considered to understand reversion of cardiac hypertrophy as a result of antihypertensive treatment. (Am Heart J 1991;122:1210-4.)

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In patients with essential hypertension, cardiac hypertrophy is usually considered a simple consequence of the long-term increase in afterload.[1] Indeed, the dominant factor contributing to the development of cardiac hypertrophy is increased end-systolic stress.[2] According to the Laplace law, end-systolic stress is influenced not only by the geometric properties of the ventricle but also by the level of systolic blood pressure. Systolic blood pressure results from the interaction between cardiac performance and the physical properties of the arterial system. Studies of impedance spectra have shown that the physical properties of the arterial system involve three components[3]: an inertial component, a resistive component, and a capacitive component. In most studies[4] only vascular resistance is considered. Hence the degree of cardiac hypertrophy is related to the level of blood pressure and the degree of constriction of the small arteries. However, the capacitive properties of the arterial system are also involved in the development of cardiac hypertrophy as suggested by several lines of evidence. First, in cross-sectional studies, the correlation coefficient relating cardiac hypertrophy to blood pressure is relatively low,[4] which indicates that factors other than vascular resistance play a role in the development of cardiac hypertrophy. Second, cardiac hypertrophy is better correlated with systolic than with diastolic pressure,[4] and the level of systolic pressure is largely influenced by modifications in aortic compliance. Finally, during systole the heart "feels" a load that is mainly produced by the aortic chamber, an observation suggesting that a reduction in aortic compliance might cause a predominant increase in systolic pressure and end-systolic stress, thus promoting cardiac hypertrophy.[5] In the present review we discuss some evidence of the relationships between arterial distensibility and cardiac hypertrophy, with implications for cardiovascular risk and antihypertensive therapy.

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ARTERIAL DISTENSIBILITY AND CARDIAC HYPERTROPHY IN ESSENTIAL HYPERTENSION

In a previous study we observed strong correlations between cardiac hypertrophy and arterial distensibility[6] using left ventricular mass index and pulse-wave velocity (PWV) as representative indexes,

respectively. In that study, performed in 10 normotensive patients (126 ± 3/78 ± 2 mm Hg; mean ± SEM) and 10 hypertensive patients (169 ± 3/104 ± 3 mm Hg), left ventricular mass (LVM) was calculated according to the formula: $[(LVIDd + 2\ LVPWTd)^3 - (LVIDd)^3] \times 1.05$, where LVIDd was left ventricular internal end-diastolic diameter and LVPWTd was left ventricular posterior wall end-diastolic thickness.[7-9] LVM was converted to LVM index (LVMI) by dividing by the body surface area and was expressed in gm/m^2. The ratio between LVM and left ventricular end-diastolic volume (M/V) was also calculated as an index to better evaluate the severity of concentric hypertrophy; M/V ratio was significantly correlated to carotid-femoral pulse-wave velocity (PWV_{CF}) (Fig. 1).[10, 11] PWV_{CF} was measured to estimate arterial distensibility according to the equation of Bramwell and Hill.[12] In this equation $PWV = \sqrt{VdP/\rho dV}$, where V = arterial volume, dV = change in volume, dP = change in pressure, and ρ = blood density. In 10 normotensive and 10 essential hypertensive patients of the same age and sex ratio, a strong correlation was observed between the M/V ratio and PWV_{CF} ($r = 0.61$; $p < 0.001$), suggesting that decreased distensibility had an effect on the degree of cardiac hypertrophy. In addition, end-systolic stress, calculated with the use of echocardiography dimensions and cuff blood pressure,[9] was positively correlated ($r = 0.73$; $p < 0.001$) with PWV_{CF}, even for a constant age ($r = 0.73$).

However, cardiac hypertrophy may be influenced by arterial distensibility through the indirect effect of elevated distending pressures that mechanically reduce arterial compliance.[13] Indeed, the correlation between M/V ratio and PWV_{CF} disappeared at a constant systolic pressure, suggesting that the observed relationship was mediated by the increase in systolic arterial pressure, which increased end-systolic stress.

Therefore it was important to demonstrate that a reduction in arterial compliance may influence "per se" the degree of cardiac hypertrophy independent of blood pressure level. Invasive studies of vascular impedance have shown that in both normal subjects and hypertensive patients, the degree of cardiac hypertrophy is closely related to the physical properties of the large arteries system. In these studies the properties of the arterial system were evaluated with characteristic impedance values.[14] In the 20 normotensive and hypertensive patients of the previously discussed study,[6] there was a significant negative correlation ($r = -0.70$; $p < 0.001$) between brachial artery compliance and M/V ratio. Brachial artery compliance was calculated according to the

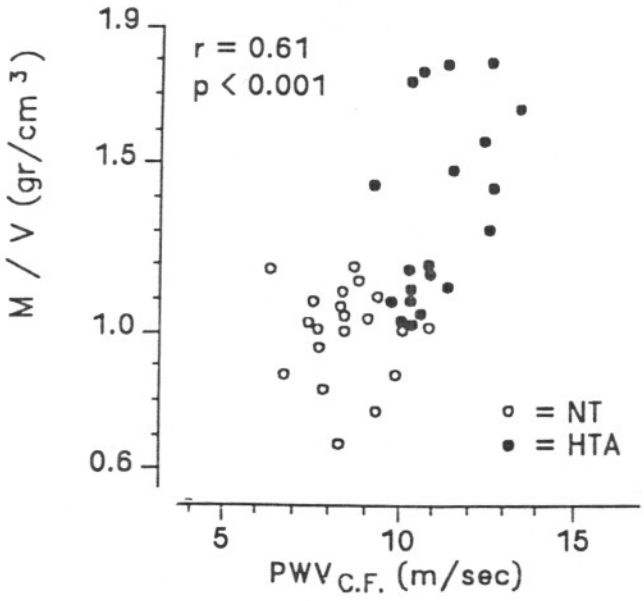

Fig. 1. PWV_{CF} is directly correlated with left ventricular mass/volume ratio *(M/V)* in normotensive and hypertensive subjects ($r = 0.61$; $p < 0.001$). For normal subjects $r = 0.20$ (NS) and for hypertensive subjects $r = 0.45$ ($p < 0.02$). (From Bouthier JD, DeLuca N, Safar ME, Simon ACh. AM HEART J 1985;109:1345-52.)

equation of Bramwell and Hill. From this equation brachial artery compliance was calculated as $BAC = dV/dP = V/\rho\ PWV^2$, where BAC = brachial artery compliance. Because V can be expressed in radius per unit length, $dV/dP = 3.14\ R^2/\rho\ PWV^2$, where R is the inner radius of the artery. In this equation dV/dP is expressed in cm^4/dynes 10^{-7}, with R in centimeters, PWV in centimeters per second, and ρ equals 1.06.[15, 16] In contrast to the correlation between PWV_{CF} and M/V ratio, the correlation between BAC and M/V ratio remained significant at a constant systolic ($r = -0.61$; $p < 0.05$) or diastolic blood pressure ($r = -0.57$; $p < 0.05$).

Another way to estimate arterial distensibility yielded similar results at the level of the aortic arch. A noninvasive determination of aortic arch diameter was performed in 16 patients with sustained essential hypertension and in 15 normal subjects with their age, sex, and body surface area in the same range.[17] In all subjects, brachial mean arterial pressure and pulse pressure (PP), cardiac mass (measured by echocardiography), and PWV_{CF} were measured together with ultrasonic determinations of aortic-arch diastolic (DD) and systolic (SD) diameter (suprasternal window). For each subject, the pulsatile change in aortic diameter (dD = SD − DD), strain (dD/DD), and aortic arch elastic modulus Ep (PP × DD/dD) were calculated. Compared with normal subjects, hypertensive subjects showed characteristically an

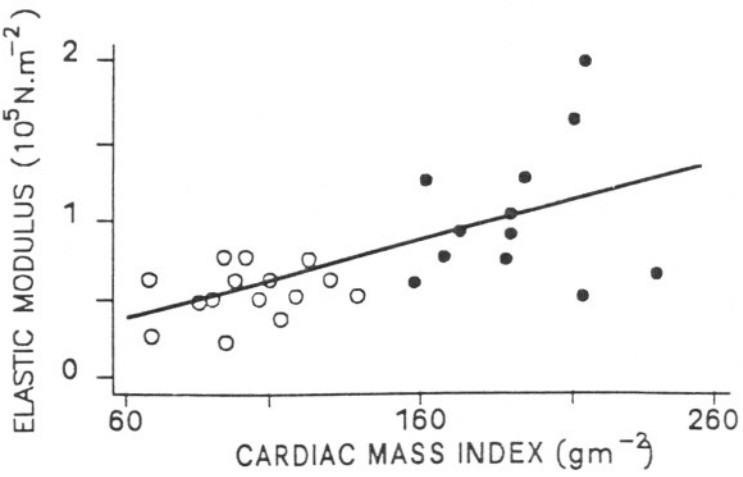

Fig. 2. Positive relationship between elastic modulus and cardiac mass index in normotensive and hypertensive subjects ($r = 0.60$; $p < 0.01$). *Open circles*, normotensive subjects; *solid circles*, hypertensive subjects. (Reprinted with permission from the American College of Cardiology [J Am Coll Cardiol 1989; 13:399-405.])

increase in aortic arch diameter (DD: 29.6 ± 1.0 vs 25.4 ± 1.0 mm; $p < 0.01$), in Ep (1.07 ± 0.13 vs 0.53 ± 0.04 10^5 N · m^{-2}; $p < 0.001$) and in PWV (11.8 ± 0.5 vs 8.9 ± 0.3 m/sec; $p < 0.001$). In the studied population, a positive correlation was observed not only between PWV_{CF} and cardiac mass index ($r = 0.62$; $p < 0.01$), but also between Ep and cardiac mass index ($r = 0.60$; $p < 0.01$) (Fig. 2), even after adjustment for blood pressure, suggesting that an increase in aortic elastic modulus contributes to the development of cardiac hypertrophy in subjects with sustained essential hypertension.

The ability of the heart to generate external power depends not only on myocardial performance but also on the physical properties of the arterial tree and the contained intravascular volume.[13] There are two components of external ventricular hydraulic power. The first is steady power, which is associated with mean arterial pressure and peripheral resistance and is dissipated in the arterioles. The second is pulsatile power, which is associated with the phasic contraction of the ventricle and depends on large-artery distensibility and wave reflections. Normally pulsatile power accounts for 10% to 17% of total power in humans.[13] In hypertensive patients, both components of power are significantly increased, with an increased proportion of pulsatile power to total power.[13, 14] The magnitude of pulsatile power depends on the relationship between ascending aortic impedance and the harmonic content of the left ventricular ejection wave. The findings of the described studies[6, 14, 17, 18] strongly suggest that the increased pulse pressure observed in hypertensive subjects at a given mean arterial pressure reflects a disturbance of the normal relationship between the components of the ventricular ejection and the impedance presented to the ventricle. This results in increased pulsatile energy losses in vascular pulsation with a further increase in cardiac work and mass.

CLINICAL AND THERAPEUTIC IMPLICATIONS

The point that decreased aortic compliance might favor the development of cardiac hypertrophy through increases in systolic and pulse pressures (and hence in end-systolic stress) may have several clinical and therapeutic implications, as suggested by the following observations.

Cardiac mass measured from echocardiography was evaluated in 11 normal subjects and 36 patients of similar age with sustained essential hypertension.[18] The hypertensive patients were divided into two groups of similar age, weight, height, and mean arterial pressure according to pulse pressure values. Patients in the first group (group I) had a pulse pressure less than 60 mm Hg, whereas the second group (group II) had a pulse pressure equal or superior to this value. Group II patients had significantly higher values for cardiac mass (148.8 ± 44.3 vs 116.3 ± 19.8 gm/m^2; $p < 0.01$) (mean ± SD) than group I, whereas mean arterial pressure was similar in the two groups. Such findings suggest that a therapeutic approach selectively improving pulse pressure might potentially better reverse cardiac hypertrophy in those hypertensive subjects with higher levels of pulse pressure.

Subsequently, 60 patients with sustained systolic-diastolic hypertension were submitted to a stepped care approach treatment to obtain an adequate con-

trol of blood pressure with classic antihypertensive drugs.[19] After 24 months of follow-up, 30 patients had adequate control of both systolic and diastolic pressures (group A), whereas in 30 other patients (group B), diastolic pressure was controlled, but systolic pressure remained elevated. The distribution of antihypertensive treatment in group A and group B patients was not significantly different: diuretic or β-blocker or association (23 vs 18 patients); diuretic + β-blocker + vasodilator (6 vs 6 patients); others including calcium channel blockers with various associations (1 vs 6 patients). For the same age and mean arterial pressure as patients of group A, patients of group B were characterized by higher values in PWV_{CF} than those in group A, indicating decreased aortic distensibility. The elevated values of PWV could not be explained on the basis of differences in therapeutic regimen or associated clinical atherosclerotic diseases. Left ventricular hypertrophy, which was assessed from ECG parameters, was significantly higher in Group B patients than in Group A patients, suggesting that cardiac mass was increased in Group B patients, despite insignificantly different levels of mean arterial pressure. Thus it appears that the increase in systolic pressure in group B indicates an enhanced rigidity of the arterial wall despite antihypertensive therapy and could have consequences with regard to the degree of cardiac hypertrophy.

More specifically, antihypertensive drugs may or may not increase arterial distensibility and reverse cardiac hypertrophy for the same degree of blood pressure reduction. The first observations were obtained from a study of vasodilators, which showed that for the same antihypertensive effect, dihydralazine constricted brachial artery diameter, whereas diltiazem enlarged it.[20] Similarly, dihydralazine did not modify systemic arterial compliance, whereas captopril and nitroglycerin increased it.[21]

We recently extended these observations to the study of PWV_{CF} before and after the administration of several types of vasodilating antihypertensive drugs,[6, 22, 23] including a dihydralazine-like substance (cadralazine), calcium-entry blockers (nicardipine, nitrendipine), and a converting-enzyme inhibitor (captopril). The drugs were administered orally in a short-term, single-dose design to effect the same blood pressure reduction in groups of hypertensive patients who were matched for age and baseline blood pressure.[6] Whereas cadralazine was unable to modify PWV, this parameter decreased after the administration of converting-enzyme inhibitors[22, 24] or a calcium-entry blocker.[6] Because PWV_{CF} is an adequate index of aortic distensibility,[16] it was therefore suggested that only converting-enzyme inhibitors and calcium-entry blockers could improve the increased aortic rigidity of patients with essential hypertension.

The modifications in the buffering function of large arteries, observed in short-term conditions may also occur with long-term treatment with nicardipine, enalapril, and perindopril.[24-26] It is remarkable that these modifications parallel those observed with the reversal of cardiac hypertrophy, as previously studied in the literature.[27] With the administration of dihydralazine, the hemodynamic pattern is one of decreased vascular resistance and unchanged arterial compliance, and there is no regression of cardiac hypertrophy.[28, 29] However, with administration of calcium-entry blockers and converting-enzyme inhibitors, the hemodynamic pattern is one of decreased vascular resistance and increased vascular compliance, and a regression of cardiac hypertrophy may be observed.[26, 28] This apparent coherence between the presence or absence of regression of cardiac hypertrophy and the presence or absence of an increase in arterial compliance must be attenuated by the observation that some β-blocking drugs such as propranolol, which induce regression of cardiac hypertrophy,[27, 28] do not increase arterial compliance.[24] Such observations call into question the parallel or disparate origins of cardiac and vascular alterations after long-term antihypertensive therapy in patients with essential hypertension[28] and need further investigation.

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