Factors influencing cardiac hypertrophy in hypertensive patients

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Summary

1. Seventeen male patients with essential hypertension were studied after 4 weeks of placebo and after 8 weeks of β-adrenoceptor-blockade therapy with atenolol (100 mg/day).
2. The influence of the following factors on left ventricular wall thickness and left ventricular mass index as determined by echocardiography was examined: patient's age, duration of hypertension, arterial pressure, blood pressure variability, supine heart rate, maximal exercise heart rate, left ventricular wall stress and 24 h urinary catecholamines.
3. Left ventricular mass index was related to systolic blood pressure ($r = 0.54$, $P < 0.05$) and to extent of increase in heart rate with maximal exercise ($r = 0.62$, $P < 0.05$). No significant correlation was present between mass index and other variables.
4. After atenolol therapy, left ventricular mass index decreased by $14 \text{ g/m}^2$ (12%). Changes in mass were related to its initial value ($r = 0.69$, $P < 0.01$) and to % change in wall stress ($r = 0.64$, $P < 0.05$). Patients who had a decrease in mass index of 10% or greater had an initially lower diastolic pressure ($P < 0.001$). Other factors did not appear to influence significantly the regression of hypertensive left ventricular hypertrophy.

Key words: atenolol, cardiac hypertrophy, echocardiography, hypertension.

Abbreviations: BP, blood pressure (DBP, diastolic; SBP, systolic); LV, left ventricle; LVM, left ventricular mass; LVMI, left ventricular mass index; PWT, posterior wall thickness; VST, ventricular septum thickness.

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Introduction

Factors influencing the development and regression of left ventricular hypertrophy in hypertensive disease have not been fully defined. Animal studies showed that factors other than elevated blood pressure may evoke cardiac hypertrophy. Hypertrophy was prevented or its regression achieved by treatment with α-methyldopa but not with hydralazine [1]. Such results were obtained in spite of the fact that blood pressure levels were lower in spontaneously hypertensive rats (SHR) treated with hydralazine than in those treated with α-methyldopa. The absence of a close correlation between anatomical and clinical aspects of left ventricular hypertrophy on one side, and arterial hypertension on the other, implicates other factors in the genesis of cardiac hypertrophy in hypertensive patients.

The purpose of this work was to examine the relationship of arterial pressure, heart rate, age, adrenergic factors and left ventricular wall stress to left ventricular wall thickness and mass in hypertensive patients. Since β-adrenoceptors have recently been implicated in hypertrophy, the effect of cardioselective β-adrenoceptor-blockade therapy on left ventricular mass was also investigated.

Methods

Seventeen male patients with essential hypertension were studied as outpatients. Secondary hypertension was excluded by the usual routine procedures as described previously [2].

Each patient was followed initially for 4 weeks, all previous antihypertensive medication was discontinued and a placebo was given. Blood pressure and heart rate were checked at weekly intervals. Patients were included in the study if at
the end of the 4 weeks on placebo they had a diastolic arterial pressure persistently greater than 95 mmHg. The study then comprised a further 8 weeks' treatment period during which patients were asked to take 100 mg of atenolol (Tenormin, I.C.I.) once daily in the morning. Patients' ages ranged from 30 to 61 years, with a mean of 48.7 years. The duration of well-documented hypertension ranged from a recently discovered to 11 years' duration with a mean value of 5-07 years.

A maximal exercise test, echocardiographic studies, measurements of urinary catecholamine excretion and 24 h endogenous urinary creatinine clearance were performed at the end of placebo period and during the last week of atenolol treatment.

The details of echocardiographic examination have been described previously [3, 4]. The Penn Convention [5] was used for measurements of wall and septal thickness and estimated left ventricular mass (LVM). An average of septal (VST) and posterior wall thickness (PWT) was used to calculate mean wall thickness (h). The LV internal radius (r) at end-diastole (ED) was derived as $r = \frac{ED \text{ diameter}}{2}$. Values derived from the measurements included, besides the estimated LVM, peak systolic stress and ratio of LV mean wall thickness to internal LV cavity radius ($h/r$). Corrections were made to account for changes in body surface area and the left ventricular mass index (LVMI) was obtained by dividing the LVM by the body surface area.

Coefficient of blood pressure variability during the placebo period was determined as the percentage of standard deviation/mean of pressure readings.

The relationship was examined between PWT, VST and LVMI and the patient's age, duration of hypertension, systolic blood pressure (SBP), diastolic BP (DBP), coefficient of SBP variability, supine heart rate, maximal exercise heart rate, extent of increase in heart rate with maximal exercise, urinary catecholamine excretion and peak systolic stress.

The correlation between changes in wall thickness and LVMI with atenolol therapy and the previous variables was also investigated.

**Results**

**Relationship between wall thickness, LVMI and other variables before β-adrenoceptor-blockade therapy**

The only significant correlation was present between the LVMI and systolic blood pressure ($r = 0.54, P < 0.05$), the LVMI and the degree of cardiac acceleration after maximal exercise ($r = 0.62, P < 0.05$). Non-significant correlation was present between LVMI and diastolic blood pressure ($r = 0.38$) and urinary catecholamines ($r = 0.45$). No relationship was present between LVMI and supine heart rate ($r = 0.27$) or peak systolic stress ($r = 0.09$). The ventricular septal thickness and $h/r$ ratios were poorly related to SBP ($r = 0.46$ and 0.36 respectively), and they were not related to DBP ($r = 0.27$ and 0.15). Similarly, age, duration of hypertension and SBP variability were not related to LVMI and wall thickness.

Measurements of peak systolic stress were inversely related to the wall thickness to internal cavity radius ratio ($h/r$) ($r = -0.75, P < 0.01$). Thus patients with thick ventricular walls and larger mass to cavity ratio had the lowest wall stress.

**Effect of cardio-selective β-adrenoceptor-blockade therapy**

After atenolol treatment (100 mg/day for 8 weeks) mean blood pressure decreased from 197/119 $\pm$ 5.7/3.9 mmHg to 160/98 $\pm$ 2.9/2.3 mmHg ($P < 0.001$), supine heart rate from 83 $\pm$ 2.64 to 74 $\pm$ 1.78 beats/min ($P < 0.005$) and the exercise heart rate from 122 $\pm$ 3.17 to 92 $\pm$ 2.11 beats/min ($P < 0.001$). Ventricular septal thickness decreased from 11.1 $\pm$ 0.5 to 10.4 $\pm$ 0.4 mm ($P < 0.05$) and LVMI from 126 $\pm$ 10.1 to 112 $\pm$ 8.5 g/m$^2$ ($P < 0.005$).

Urinary catecholamines decreased from 149 $\pm$ 9.6 $\mu$g/24 h (1.2 $\mu$g 24 h$^{-1}$ mg$^{-1}$ of creatinine) to 91 $\pm$ 4.39 $\mu$g/24 h (0.77 $\mu$g 24 h$^{-1}$ mg$^{-1}$ of creatinine) ($P < 0.001$). Peak systolic stress decreased from 290 $\pm$ 19.43 to 231 $\pm$ 14.95 $\times$ 10$^3$ dyn/cm$^2$ ($P < 0.001$).

Posterior wall thickness and $h/r$ did not change.

Patients were classified into two groups, A and B, according to the extent of decrease in LVMI. Patients in group A had a decrease in LVMI of less than 10%, and patients in group B had a decrease of 10% or greater.

When comparing the clinical, echocardiographic and other characteristics of the two groups, the only significant difference was in the diastolic blood pressure, which was more elevated in patient group A (130 $\pm$ 4.56 vs 115 $\pm$ 2.03 mmHg, $P < 0.001$).

**Relationship between changes in LVMI and different variables**

The change in LVMI was significantly related to the initial (pre-treatment) LVMI ($r = 0.69$,
Cardiac hypertrophy in hypertension

\[ P < 0.01 \) and ventricular septal thickness \((r = 0.73, P < 0.01)\). Correlation was absent or poor with exercise heart rate \((r = 0.22)\) and urinary catecholamines \((r = -0.43)\). Patient's age, duration of hypertension and the variability of SBP as determined by coefficient of variation did not appear to influence the change in LVMI after \( \beta \)-adrenoceptor-blockade therapy.

Regression in LVMI was related to the percentage change in peak systolic stress \((r = 0.64, P < 0.05)\). Poor or no correlation was present between the change in LVMI and the changes in arterial pressure or heart rate.

Discussion

The use of radiological and electrocardiographic criteria in previous studies for assessment of left ventricular hypertrophy was of limited value as these do not provide information about wall thickness and cavity dimensions. The latter information is not usually available in life unless the patient has been subjected to left ventricular angiography. M-mode echocardiography has been used in the present study as it allows accurate and non-invasive measurement of the thickness of the wall and the diameter of the left ventricular cavity. As it is safe, simple and reproducible, serial readings can be made and the effects of interventions can be studied. Echocardiographic estimation of left ventricular mass may have some limitations since it is derived from indirect calculations and from assumptions still requiring validation. However, the use of the Penn Convention [5] in the present study allowed an accurate estimate of left ventricular mass, which compares favourably with biplane angiographic determinations. When correlated with autopsy findings, this procedure gave a highly significant correlation \((r = 0.96)\).

In this study an attempt has been made to correlate echocardiographic indexes of wall thickness and derived left ventricular mass index (LVMI) with arterial pressure and other factors which might influence left ventricular hypertrophy in hypertensive patients. Two factors only proved to be correlated significantly with LVMI: systolic blood pressure and the increase in heart rate after maximal exercise. The closer relationship of LVMI with systolic rather than the diastolic pressure was in agreement with our previous observations [6] and with those of others [7, 8], including post-mortem studies, and reflects the special importance of systolic pressure in determining cardiac work and oxygen consumption. However, the correlation of hypertrophy with hypertension was less close than could be expected. Furthermore, we found no relationship between the change in LVMI and the degree of reduction of arterial pressure with \( \beta \)-adrenoceptor-blockade therapy. The discrepancies between the level of arterial pressure and the occurrence of signs of cardiac hypertrophy or their reversal by therapy have been reported both in human and animal studies. Many explanations have been suggested. Badeer [9] has emphasized the role of heart rate in the development of cardiac hypertrophy. We did not find any correlation between the resting supine or maximal exercise heart rate with LVMI in the pretreated patients nor a relationship between the changes in these parameters and the regression of left ventricular hypertrophy. The duration of hypertension might be another factor. In our study, patients with long-standing hypertension did not appear to have a greater increase in LVMI compared with patients of similar age and pressure but with shorter duration of hypertension. Also the regression of LVMI with antihypertensive therapy was not related to duration of previous hypertension. However, since it is difficult to determine the exact time of onset of hypertension and because of the small number of patients investigated, it is difficult to reach a definite conclusion.

Aging has been claimed to produce a progressive increase in myocardial mass. However, no relationship was found between patient's age and the LVMI or its regression with treatment.

The permissive or aggravating role of adrenergic influences on cardiac hypertrophy was suggested many years ago and is supported by the recent experiments in spontaneous hypertensive rats [1]. Exogenous catecholamines will provoke a hypertrophic response, whereas administration of guanethidine will prevent myocardial hypertrophy in rats in response to exercise [10]. Both propranolol and practolol administration have been shown to decrease ventricular weight in the rabbit and implicate the \( \beta \)-adrenoceptors in hypertrophy. The only evidence of a possible adrenergic role in our study is the presence of a significant correlation between the LVMI and the extent of increase in heart rate after maximal exercise. However, there was no relationship between urinary catecholamine excretion and left ventricular hypertrophy. Furthermore, the reduction in urinary catecholamines after \( \beta \)-adrenoceptor-blockade therapy did not correlate with the degree of regression in LVMI.

Study of changes in left ventricular wall thickness with therapy showed only a decrease in VST; PWT did not change and it was shown that changes in LVMI correlated with decrease in
peak systolic stress. These findings are in agreement with previous suggestions [11], that if wall tension, the stimulus to myocardial hypertrophy, is increased, the stimulus strength will vary with the radius of curvature of the ventricular cavity as predicted by Laplace's law. This stimulus will be greater at the level of the septum, whose radius of curvature is greater, than that portion of the posterior wall which is explored by M-mode echocardiography. The latter region, lying just below the A–V groove, may be affected by geometric forces that prevent it from thickening or thinning as much as other portions of the left ventricle. Changes in wall stress would thus appear to influence the ventricular septum more than the posterior wall.

The present study does not explain how β-adrenoceptor blockade produces regression of left ventricular hypertrophy since the reduction in arterial pressure and urinary catecholamines with treatment did not correlate with changes in LVMi. Other factors must be implicated. Possible causes such as the renin–angiotensin system, genetic predisposition and altered myocardial composition have to be investigated.

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References