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Effect of therapy on left ventricular function in hypertension

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Summary

1. Twelve untreated hypertensive patients whose blood pressure was 171·8 ± 5·5 mmHg systolic and 119·7 ± 3·4 mmHg diastolic (mean ± SEM) were treated aggressively with diuretics plus other antihypertensive agents. Echocardiograms were performed before, and 2 weeks, 3 months and 6 months after therapy. Blood pressures were lowered to an average of 142/98 mmHg over the 6 month period.

2. Mean velocity of circumferential fibre shortening rose from 1·1 ± 0·09 to 1·3 ± 0·06 diameters/s at 2 weeks and remained elevated at the end of 3 months (1·3 ± 0·03 diameters/s) ($P < 0·025$), but returned to the control level in 6 months. Similarly, ejection fraction increased significantly during the same period from a control value of 65·1 ± 4·4 to 73·4 ± 1·8% ($P < 0·025$) and persisted in this range at 3 months. At 6 months the ejection fraction had returned to pretreatment levels. There were significant reductions in left ventricular end-systolic and end-diastolic dimensions. Left ventricular mass index decreased from 182·3 ± 18·3 to 163·8 ± 12·4 g/m^2 after 6 months of therapy.

3. These results indicate that in the early stages of blood pressure reduction there is a temporary increase in ejection phase indices, probably related to afterload reduction. The reduction in the left ventricular mass index suggests that increased cardiac muscle mass due to elevated blood pressure may be partially reversible after long-term reduction in blood pressure.

Key words: echocardiogram, hypertension, left ventricle.

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Introduction

Left ventricular hypertrophy accompanies sustained elevation of arterial pressure (McKee, Castelli, McNamara & Kannel, 1971). It represents a normal response of a muscle subjected to an increased work load. The process of compensation by hypertrophy is limited, however, and eventually in many patients left ventricular performance deteriorates, resulting in congestive heart failure. Chronic reduction of arterial pressure prevents congestive heart failure in spite of the fact that some of the drugs used have negative inotropic effects. For example, ganglion-blocking drugs which inhibit both α- and β-adrenergic functions produce dramatic reversal of hypertensive congestive heart failure (Freis, Rose, Partenope, Higgins, Kelley, Schnaper & Johnson, 1953). Left ventricular function in the hypertensive heart would appear to be not dependent only on the inotropic state of the ventricle.

There is controversy regarding the status of left ventricular performance during the phase of hypertrophy before any gross dysfunction is apparent. Some investigators have found in animals and in human subjects that the contractility of the hypertrophied heart is depressed (Spann, Buccino, Sonnenblick & Braunwald, 1967; Frohlich, Tarazi & Dustan, 1971; Gunning, Cooper, Harrison & Coleman, 1973) whereas others have shown no change in the inotropic state of the myocardium (Gamble, Phornphutkul, Kumar, Sanders, Manasek & Monroe, 1973; Williams & Potter, 1974). A study (Karliner, Williams, Gorwitt, Crawford & O'Rourke, 1977) using the echocardiogram has indicated that the inotropic state of the left ventricle is within the normal range in patients with hypertensive heart disease who do not exhibit any evidence of congestive heart failure or coronary artery disease. The present study was designed to examine left ventricular function in

hypertensive patients free of congestive heart failure or evident coronary artery disease both in the untreated state and after reduction of arterial pressure with antihypertensive agents.

Methods

Subjects

After giving their informed consent 12 patients with established essential hypertension were recruited into the study. Their average age was 49 years with a range of 38–60 years. In all but one patient, hypertension was newly discovered and they had received no previous drug therapy. The remaining patient had received antihypertensive therapy for a period of 4 months but had discontinued treatment 6 months before entering the study. For all patients systolic and diastolic blood pressure averaged 172 and 120 mmHg respectively. None of the patients had a history of congestive heart failure and there was no clinical or electrocardiographic evidence of coronary artery disease.

Procedure

Echocardiograms were performed with the SKF 20A Ekoline ultrasonoscope with a 2·25 MHz, 1·25 cm transducer focused at 10 cm with a repetitive rate of 1000 impulses/s. A Honeywell strip-chart recorder was used to record the echocardiogram at a speed of 50–100 mm/s. Only patients with technically satisfactory echocardiograms were included in the study.

The echocardiograms were recorded with the patients supine and in the postabsorptive state. The transducer was placed in the third or fourth left intercostal space parasternally and the ultrasound beam was directed posteromedially until the characteristic motion of the anterior mitral leaflet was seen. The transducer was then tilted towards the inflow tract of the left ventricle just below the free edges of the mitral valve leaflets. At this level tracings were recorded for the measurements of left ventricular dimensions and ejection phase indices.

After the baseline recordings, treatment was initiated with the administration of hydrochlorothiazide, 50 mg twice daily. The patients were seen two to three times per week and other antihypertensive drugs were added as required in order to lower the diastolic pressure to at least 20% below the control value and/or to 99 mmHg or lower within 2 weeks of starting therapy. In eight of 12 patients blood pressure was lowered to below 100 mmHg diastolic during this interval but in four patients the diastolic pressure remained between 100–110 mmHg. However, these latter patients exhibited an average initial diastolic pressure greater than 120 mmHg during the control period. Echocardiography was repeated 2 weeks, 3 months and 6 months after treatment. The effective drug regimens consisted of hydrochlorothiazide alone in five patients, diuretic plus reserpine in three patients, diuretic plus hydrallazine in one patient and diuretic plus reserpine plus hydrallazine in two patients. One patient received diuretic plus hydrallazine and another diuretic with α-methyldopa plus guanethidine.

Echocardiographic measurements

The left ventricular end-diastolic dimension was taken as the distance between the left surface of the interventricular septum and the endocardium of the posterior wall at the time of the R wave of the electrocardiogram. The left ventricular end-systolic dimension was taken as the peak inward motion of the interventricular septum. Left ventricular posterior wall thickness was measured as the distance between the endocardium and epicardium before atrial systole. Left ventricular volumes were determined by a method previously described (Troy, Pombo & Rackley, 1972). Stroke volume was obtained by subtracting end-systolic volume from end-diastolic volume.

Left ventricular mass was calculated by multiplying left ventricular shell volume by 1·1 (the specific gravity of cardiac muscle) with the formula: left ventricular mass = (end-diastolic diameter + 2 × left ventricular posterior wall thickness)^2 − end-diastolic volume × 1·1. The left ventricular mass index was obtained by dividing left ventricular mass by the surface area of the patient. The mean rate of circumferential fibre shortening was calculated from the formula:

$$\frac{\text{end-diastolic diameter} - \text{end-systolic diameter}}{\text{end-diastolic diameter}} \times \frac{1}{\Delta t}$$

where Δt is the duration of minor axis shortening. The duration of minor axis shortening was determined directly from inspection of posterior left ventricular wall motion. Ejection fraction was obtained by dividing left ventricular stroke volume by left ventricular diastolic volume. Left ventricular wall stress was calculated by multiplying the peak systolic blood pressure by one-half the systolic diameter. The product thus obtained was divided by twice the left ventricular wall thickness during systole (Fortuin, 1975).

Blood pressure was measured by sphygmomanometry; heart rate was calculated from the electrocardiogram. The significances of the differences of the means were tested by using Student's *t*-test for paired observations.

Results

Blood pressure and heart rate

Blood pressure fell significantly ($P < 0.05$) during the first 2 weeks of therapy. Systolic blood pressure fell from 171.8 ± 5.5 mmHg (mean $\pm$ SEM, $n = 12$) during the control period to 142.6 ± 4.6 mmHg (Table 1). The diastolic blood pressure fell from 119.7 ± 3.4 to 98.8 ± 2.9 mmHg. These mean values included the four patients who had initial diastolic pressures over 120 mmHg which fell to between 100 and 110 mmHg. During the subsequent 6 months of follow-up, blood pressure decreased further to 141.7 ± 4.8 mmHg systolic and 96 mmHg diastolic, including the four patients whose diastolic pressure was over 100 mmHg, although this additional reduction beyond 2 weeks was not significant. Heart rate did not change significantly compared with control values during the entire period of treatment.

Left ventricular dimensions and wall thickness

A significant reduction in systolic as well as diastolic dimensions was observed 2 weeks after the blood pressure was lowered. Both dimensions reached their lowest values at the 3 month examination, and at the end of 6 months there was a slight but insignificant rise in both systolic and diastolic dimensions (Table 1). Left ventricular wall thickness, however, remained unchanged from the control value during this period of treatment. Left ventricular mass index declined significantly after therapy, reaching its lowest value at 3 months and remaining significantly below the pretreatment value (Table 1).

Ejection-phase indices

Mean rate of circumferential fibre shortening in the control period averaged 1.1 ± 0.9 diameters/s. After reduction of blood pressure it rose significantly to 1.3 ± 0.06 diameters/s at 2 weeks and remained elevated at that level at 3 months. At the end of 6 months mean rate of circumferential fibre shortening returned to the control level (Table 1). Similarly, ejection fraction increased significantly from 65.1 ± 2.4 to $73.4 \pm 1.6\%$ ($P < 0.01$). At the end of 6 months it had fallen

TABLE 1. *Changes in clinical and echocardiographic data after treatment with antihypertensive agents*

Mean results $\pm$ SE are shown.

	Blood pressure (mmHg)		End-systolic diameter (mm)	End-diastolic diameter (mm)	Posterior wall thickness (mm)	Left ventricular mass index (g/m²)	Mean velocity of circumferential fibre shortening (diameters/s)	Left ventricular wall stress (g/cm²)	Ejection fraction (%)
	Systolic	Diastolic							
Pretreatment control	171·8 ± 5·5	119·7 ± 3·4	33 ± 1·4	50 ± 1·3	14 ± 0·9	182·3 ± 18·3	1·1 ± 0·9	74·8 ± 4·4	65·1 ± 2·4
Post-treatment									
2 weeks	142·6 ± 4·6	98·8 ± 2·9	31 ± 1·2	47 ± 1·2	14 ± 1·1	170·7 ± 17·6	1·3 ± 0·06	54·8 ± 2·9	73·4 ± 1·8
3 months	138·3 ± 4·6	98·3 ± 3·3	28 ± 0·1	45 ± 1·5	14 ± 0·9	155·9 ± 14·5	1·3 ± 0·03	51·3 ± 1·9	73·8 ± 1·6
6 months	141·7 ± 4·8	96·8 ± 2·8	31 ± 1·2	47 ± 1·3	14 ± 0·9	163·8 ± 12·4	1·1 ± 0·09	55·6 ± 3·5	68·6 ± 1·8

to 68·6 ± 1·8% (Table 1). Left ventricular wall stress decreased significantly ($P < 0.0005$) when the blood pressure was reduced at the end of 2 weeks and remained at approximately the same level thereafter.

Discussion

The results of the present study indicate that left ventricular function in untreated hypertensive patients without any clinical evidence of heart failure is not abnormally depressed. These data are consistent with the result of a previous study (Karliner *et al.*, 1977) which showed that hypertensive patients who were under antihypertensive therapy demonstrated normal left ventricular function.

Increase in left ventricular mass is an important adaptive mechanism to sustained pressure overload in hypertension and there has been great interest in its effects on the overall function of the left ventricle. The information regarding the functional ability of the hypertrophied myocardium has been studied in both laboratory animals and in human subjects. The results obtained in animal studies have been conflicting. In studies on papillary muscle (Spann *et al.*, 1967; Bing, Matsushita, Fanburg & Levine, 1971; Alpert, Hamrell & Halpern, 1974) a depressed inotropic state of hypertrophied muscle has been demonstrated. However, studies in young rats with left ventricular hypertrophy produced by chronic aortic constriction (Gamble *et al.*, 1973) showed there was no evidence of depressed left ventricular function. Furthermore studies on awake dogs (Sesayama, Franklin & Ross, 1977) showed that left ventricular hypertrophy did not impair the inotropic state of the left ventricle. Studies in humans have been limited because of the lack of reliable non-invasive methods. Now availability of non-invasive techniques such as echocardiography and radionuclide imaging may provide a clearer definition of left ventricular function.

In the present study all data were obtained with the patient at rest. The possibility is therefore not excluded that evidence of impaired left ventricular performance, which was not evident in the resting state, might have become evident during the stress of exercise.

The reduction of blood pressure obtained with antihypertensive drug treatment was associated with an increase in left ventricular contractile force and ejection fraction. This response may well have been secondary to the fall in blood pressure and consequent reduction in mean left ventricular wall stress. Similar responses have been observed after acute administration of antihypertensive agents (Imperial, Levy & Zieske, 1961), with an inverse relationship between the myocardial ejection-phase indices and outflow resistance. In the present study left ventricular mean rate of circumferential fibre shortening and ejection fraction remained elevated until 3 months of treatment but returned to pretreatment levels after 6 months. These differences between subacute and chronic responses to afterload reduction suggest that, in the non-failing heart at least, a shortening of ejection-phase indices after blood pressure reduction may not be a long-lasting phenomenon. It is possible that a gradual readjustment may take place in the left ventricle when the afterload has been reduced for long periods although the mechanism by which this might occur cannot be determined from this present study.

Although there was a reduction in left ventricular mass index after therapy this was not accompanied by significant changes in left ventricular wall thickness. This may reflect preservation of wall thickness by changes in myocardial architecture despite effects of afterload reduction in decreasing protein synthesis and hence left ventricular mass.

The present data further support the beneficial effects of antihypertensive therapy on myocardial performance. Although the drug therapy in a few patients included sympathetic inhibiting agents, principally reserpine, there was no evidence of a depressive effect of such treatment on left ventricular performance. On the contrary, chronically reducing left ventricular workload was associated with overall reduction in left ventricular dimension and left ventricular mass index without changes in left ventricular performance. It is possible, however, that other antihypertensive agents which were not tested in the present study such as the β-adrenoreceptor-blocking drugs might exert a more definite depressive effect on left ventricular function.

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