REGRESSION OF LEFT VENTRICULAR HYPERTROPHY DURING TREATMENT WITH ANTIHYPERTENSIVE AGENTS

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- 1 Echocardiography showed 14 of 24 patients with essential hypertension to have hypertrophy of their left ventricular walls. In eight of these 14 patients the left ventricular configuration initially fulfilled the criteria for asymmetric septal hypertrophy (ASH) and six were symmetrically hypertrophied, the remaining ten being normal.
- 2 Following 12 weeks' treatment of hypertension with the object of reducing the supine BP to 150/90 mmHg or below, there was a reduction of wall thickness so that only two of the eight continued to show ASH.
- 3 The six patients with symmetrical left ventricular hypertrophy also showed a significant reduction in the thickness of the septum and the posterior wall. Those with normal echocardiograms did not change.
- 4 This reduction of wall thickness produced by antihypertensive therapy may represent regression of left ventricular hypertrophy.

Introduction

It has been established that antihypertensive therapy has markedly reduced the risks to the patient of stroke and renal failure (Veterans Cooperative Study, 1967). Treatment of hypertension has not yet been shown to improve coronary mortality to a similar degree, but a recent report (Berglund *et al.*, 1978) has shown that there may be some benefit. Left ventricular hypertrophy commonly occurs in hypertension and it has previously been most accurately assessed from pathological specimens. At necropsy it is concentric and both the interventricular septum (IVS) and the posterior left ventricular wall (PLVW) can be seen to have become thickened in a uniform manner (Muir, 1976). Electrocardiograms and chest radiographs are of limited value in the assessment of hypertrophy and will not measure left ventricular wall thickness nor cavity dimensions. This latter information is not usually available in life unless the patient has been subjected to left ventricular angiography. As this procedure is only indicated if there is clinical evidence of a serious cardiac abnormality it is rarely carried out, and information about wall and cavity sizes may be complicated by co-existing pathology. Furthermore, serial observations have rarely been made and control groups are difficult to justify ethically for research purposes.

M mode echocardiography allows accurate and non-invasive measurement of the thickness of the

walls and the diameters of the left ventricular cavity. As it is safe, simple and reproducible serial recordings can be made and the effects of interventions can be studied (von Bibra & Richardson, 1978). In addition, echocardiography is superior to left ventricular angiography in the detection of asymmetric septal hypertrophy (ASH). This latter condition is defined as left ventricular hypertrophy with a ratio of IVS and PLVW of 1.3 : 1 or greater (Henry *et al.*, 1973). ASH is thought by many to be part of the spectrum of hypertrophic obstructive cardiomyopathy, as it is often to be found in the first degree relatives of patients with this condition (Clarke *et al.*, 1973).

To assess the response of the left ventricular dimensions to hypertension and to antihypertensive therapy we studied serially 25 patients with essential hypertension using echocardiography while they were participating in a formal hypertension trial.

Methods

Twenty-five patients with essential hypertension (12 male, 13 female; mean age 55.4 yr; range 25-71 yr) were selected. Hypertension was defined as a supine diastolic BP of at least 95 mmHg recorded on a minimum of four occasions during the previous 2 months with a random zero sphygmomanometer which was used throughout the study. Exclusion

criteria included a history of myocardial infarction in the previous 6 months or angina (more than two attacks per week), clinical evidence of heart failure, aortic or mitral valve disease, heart block, renal insufficiency or secondary hypertension, recent diuretic therapy, and psychosis or the use of psychotropic agents.

Written informed consent was obtained. The patients were slowly withdrawn from any previous antihypertensive medication and observed for a 4-week washout period on no therapy, followed by a 3-week placebo period. At monthly intervals thereafter the patients were fully re-assessed by a complete physical examination and routine biochemistry. A chest X-ray, a full blood count, an electrocardiogram and a midstream urine examination were also carried out. The patients were excluded from the trial if the supine diastolic BP fell below 95 mmHg or increased above 130 mmHg during the washout or placebo periods.

At the end of the placebo period the patients were randomly allocated to one of two blind treatment periods with either nadolol or propranolol. The dose of β -blocker was increased at each visit until there was either control of hypertension, defined as two consecutive weekly supine diastolic BP readings below 90 mmHg, or until there were unacceptable side-effects, or the maximum dosage had been reached. The patients were reviewed weekly until week 12 of treatment.

Echocardiographic examination was carried out on the last day of the placebo period and again after 12 weeks of antihypertensive treatment. Recordings were made with a Smith-Kline Echoline 20 echocardiogram interfaced with a Cambridge multi-channel fibre optic recorder using a 2.25 MHz medium focus transducer with a repetition rate of 1000 impulses/second. Echocardiographs were printed on Kodak light-sensitive paper run at 50 mm/second. The technique of recording the echocardiograph was that described by Feigenbaum (1976). All patients were examined in the left lateral position at about 30° to

provide clear views of the IVS as described by Henry *et al.* (1973). The echoes from the IVS were recognized by their location and characteristic motion with reference to the electrocardiogram, and echoes from the anterior and posterior surfaces of the septum were identified as almost parallel and continual lines throughout the cardiac cycle. To obtain comparable serial recordings, each patient had his recording made through the same rib interspace at a fixed distance from the sternum, and the beam was directed through the widest diameter of the left ventricular cavity at the point of the maximum excursion of the leaflets of the mitral valve (Figure 1).

All echocardiographs were examined blind using an MM code on completion of the study before the treatment code was broken, and measurements of septal thickness and cavity diameter were made on the point of the R wave of the electrocardiogram, the mean of five consecutive beats being taken as the final value.

Statistical analysis

Statistical analysis of the antihypertensive effect of the drugs was carried out on an IBM 370 computer using an analysis of covariance programme BMDP2V developed at the Health Sciences Computer Facility at the University of California at Los Angeles. The mean of observations made during the last 2 weeks of active therapy were compared with the mean of measurements taken during the last 2 weeks of the placebo period and expressed as percentage changes from the placebo level.

Analysis of the changes observed on the echocardiographs was made using Students paired *t* test, and subgroup comparison was carried out using Scheffé's multiple comparison test (Cochran & Cox, 1957).

Table 1 Mean placebo level and percentage change with treatment

	<i>n</i>	Placebo	Change with propranolol*	<i>n</i>	Placebo	Change with nadolol*	<i>t</i> value	<i>P</i> value
Resting heart rate (beats/min)	10	83.3	-23.6%	15	81.4	-28.5%	1.10	NS
Supine BP (mmHg)	10	172.0	-9.7%	15	186.8	-12.1%	0.59	NS
Standing BP (mmHg)	10	107.00	-20.9%	15	111.9	-19.0%	0.77	NS
		169.2	-9.0%	15	173.4	-11.3%	0.52	NS
		111.6	-10.4%		116.1	-15.2%	1.82	NS

* Adjusted for final daily dose and differences in mean placebo period levels.

Figure 1 A representative pair of echocardiographs taken before (a) and after 12 weeks' antihypertensive therapy (b) with β -blocker (patient 24). CW, Chest wall; IVS, interventricular septum; RV and LV, right and left ventricles; PLVW, posterior left ventricular wall. A marked reduction in thickness of the IVS is seen between the two tracings.

Results

There was a reduction in supine diastolic BP of approximately 20% with both nadolol and propranolol (Table 1). There were no statistically significant differences in the antihypertensive effects of the two drugs. Critical analysis produced 24 satisfactory pairs of echocardiographs and one example is shown in Figure 1.

The patients were classified into three subgroups on the basis of their left ventricular echocardiographic findings before treatment (Table 2).

Normal

In the ten patients who initially had normal echocardiographs, paired *t* tests showed that there were

no significant changes over the 12-week treatment period. Before treatment the IVS and PLVW measured 1.18 ± 0.04 cm and 1.05 ± 0.04 cm and after treatment they measured 1.09 ± 0.04 cm and 1.03 ± 0.02 cm, respectively.

Asymmetric septal hypertrophy

The eight patients with ASH showed a highly significant reduction in the thickness of the septum from 1.86 ± 0.05 cm before treatment to 1.36 ± 0.10 cm after treatment ($P < 0.001$). There was, however, only minor reduction in the thickness of the PLVW from 1.06 ± 0.03 cm to 0.98 ± 0.03 cm ($P = 0.05$) in this group.

Figure 2 Changes in left ventricular wall thickness according to echocardiographic classification. —, Septum; - - - - - , PLVW. PL, Observations prior to active therapy; 3/12, observations after 12 weeks' therapy.

Symmetrical hypertrophy

The six patients with symmetrical hypertrophy showed a highly significant reduction in the thickness of both the IVS and PLVW during treatment. The septum initially measured 1.55 ± 0.05 cm and thinned to 1.25 ± 0.12 cm after treatment ($P < 0.001$), and the PLVW thinned from 1.22 ± 0.08 cm to 0.95 ± 0.03 cm ($P < 0.001$).

Covariance analysis did not show a relationship of wall thickness to either systolic or diastolic BP, to severity of hypertension, or to electrocardiogram voltages. These results are displayed graphically in Figure 2. In no case was there an increase in wall thickness during treatment. The end diastolic diameter which measured 4.83 ± 0.12 cm before treatment was unchanged afterwards 4.83 ± 0.17 cm.

Scheffé's multiple group comparison test indicates that before treatment there are three entirely separate populations corresponding to the three subgroups. After treatment this difference is lost and the two hypertrophy groups become indistinguishable from the normal group (Figure 2).

Table 2 Echocardiographic classification of hypertensive heart disease

	IVS + PLVW	IVS:PLVW
Normal	<2.5 cm	<1.5:1.0
ASH	>2.5 cm	>1.5:1.0
Symmetric hypertrophy	>2.5 cm	<1.5:1.0

IVS, Interventricular septal thickness; PLVW, posterior left ventricular wall thickness.

Discussion

Echocardiography provides an excellent non-invasive technique for measuring the left ventricular wall thickness (Troy *et al.*, 1972) and cavity diameters (Feigenbaum, 1972). It has recently been claimed to be superior to left ventricular angiography, as it has a 1 mm resolution of depth and a repetition frequency of 1000 impulses/second (Traill *et al.*, 1978).

An earlier echocardiographic report demonstrated ASH to occur in 12 out of 40 patients (Toshima *et al.*, 1975). However, this is not a universal finding and indeed an echocardiographic study of left ventricular performance showed only concentric hypertrophy and no evidence of ASH in treated hypertensives (Karlner *et al.*, 1977). Our study has demonstrated an incidence of septal hypertrophy similar to that of Toshima *et al.* (1975) but we have found no case of hypertrophic cardiomyopathy. It is known that there is an association between hypertrophic cardiomyopathy and hypertension (Moreyra *et al.*, 1970; Hamby *et al.*, 1971); and although the finding of an increased septal to posterior left ventricular wall ratio was not unexpected, we were surprised to find that following antihypertensive therapy there was a highly significant reduction of the septal thickness and indeed also a reduction of the posterior left ventricular wall thickness. Following treatment of hypertension no change in left ventricular diastolic dimensions was found, excluding the possibility that the apparent thinning of the ventricular walls was related to dilation with a redistribution of muscle mass.

Alterations in the wall thickness imply a concomitant reduction in left ventricular mass. The presence of ASH and the fact that only a limited area of the ventricle can be studied using M mode echocardiography makes calculation of changes of ventricular mass complicated and open to misinterpretation.

From our preliminary echocardiographic studies it seems that the left ventricle may respond to hypertension in three different ways. Firstly, the ventricle may remain normal with no hypertrophy of either the septum or posterior left ventricular wall. Secondly, there can be marked septal hypertrophy even though the posterior left ventricular wall remains within normal limits; and thirdly, there is not only septal hypertrophy but also marked hypertrophy of the posterior left ventricular wall. These three groups could be clearly differentiated statistically before antihypertensive therapy, but following treatment this separation was no longer possible. In the group with ASH only two patients continued to fulfill those criteria after treatment. In the group with symmetrical hypertrophy two patients also continued to show hypertrophy following treatment but the septum to posterior wall ratio

changed so that they now fall into the ASH group. The remaining patients had normal wall thickness after treatment. There did not seem to be a statistical relationship between the degree of BP reduction and the change in wall thickness.

If the alterations in wall thickness which have been demonstrated echocardiographically represent reduction of hypertrophy, this is the first occasion on which reduction of hypertrophy has been demonstrated in man. Experimental evidence has been produced by Sen *et al.* (1977) to indicate that methyldopa will reduce hypertrophy of the hypertensive ventricle. However, they did not show

that a marked reversal of hypertrophy occurred as a result of β -blockade and it is of particular interest in this study that all patients were treated with β -adrenoceptor antagonists. One might speculate at this stage that the reduction of hypertrophy in the hypertensive heart will reverse the tendency of ventricular muscle to become ischaemic under stress. The reduction of coronary mortality in treated hypertensive patients reported by Berglund *et al.* (1978) might thus be explained not by a direct effect on coronary arterial disease, but at least in part by a reduction of ventricular hypertrophy so that a less efficient coronary circulation can be tolerated.

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DR HOLLENBERG (Chairman): During your introduction, Dr Hill, I thought I heard you say that left ventricular hypertrophy *per se* made therapy more difficult in hypertension and increased the risk of hypertension; those statements surprised me.

DR HILL (London): No, left ventricular hypertrophy is associated with greater risk to the patient for the reasons that Dr Richardson described previously. It has been my experience — perhaps I was being a bit controversial and not using hard facts — but in my own experience, I found it rather more

difficult to control patients with a left ventricular hypertrophy because they seem to have much higher blood pressures as a group. We noticed this in our Camberwell population of West Indians: a lot of them have very severe left ventricular hypertrophy and as a group they tend to be very difficult to treat.

DR HOLLENBERG: All you are saying is that patients who have severe hypertension are both more difficult to treat and have a greater risk, and that left ventricular hypertrophy is really a manifestation of that.

DR HILL: That's correct. Yes.

DR FINNERTY (Washington): I would just like to find out from Dr Hill whether he's saying that the decrease in the size of the left ventricle is due to a decrease in BP or is due to the β -blockers and your data was comparing β -blocker and β -blocker. Wouldn't the same thing happen just as a direct result of decrease in BP?

DR HILL: Well, it could well do so and in fact there

is another study going on at the moment which has not yet been published, which shows the reverse effect. A group of patients who have been on various antihypertensive treatments have had their echocardiographs taken and their ventricular measurements made; the treatment has been stopped and they have been observed; and it can be seen that the walls then thicken up to give exactly the reverse of what I described. These patients were on a variety of treatments, including methyldopa, thiazides and β -blockers.