Malignant hypertension: cardiac structure and function at presentation and during therapy

L M SHAPIRO, D G BEEVERS

From the University of Birmingham, Department of Medicine, Dudley Road Hospital, Birmingham

SUMMARY We have studied electrocardiograms, chest radiographs, and digitised apex echocardiograms in 16 patients with malignant hypertension before and after up to six months of antihypertensive treatment and compared them with those of eight patients with severe benign hypertension.

Adequate blood pressure reduction was obtained in 14 with resolution of retinopathy, but one patient died and another had poor blood pressure control. Nine had electrocardiographic criteria of left ventricular hypertrophy which did not change with treatment and 10 had lateral ischaemia which resolved in seven.

The malignant hypertensives were divided into seven with and nine without a previous hypertensive history. Both groups had normal echocardiographic cavity dimensions, but the former group tended to have hypertrophy (similar to that in benign hypertensives) and the latter did not. After adequate reduction of blood pressure, no change in wall and septal thickness occurred (except in one patient with poor blood pressure control).

At entry, malignant hypertensives showed delayed mitral valve opening with significant cavity dimension increase during prolonged isovolumic relaxation, reduced peak rate, and prolonged duration of cavity dimension increase and cavity shape change (inward wall motion) during the upstroke of the apexcardiogram which showed a tall "a" wave. After reduction of blood pressure, though the delay in mitral valve opening persisted, the timing of A₁ returned towards normal and the dimension change during the upstroke of the apexcardiogram and the relative height of the "a" wave were reduced but remained significantly different from normal.

Some patients without a previous hypertensive history may develop a malignant phase without left ventricular hypertrophy on the electrocardiogram or echocardiogram. They maintain their pump function even with radiological pulmonary oedema, have incoordinate relaxation and contraction, and have abnormal filling. Similar functional abnormalities were found in malignant hypertensives with hypertrophy. Treatment to reduce blood pressure reduces incoordinate contraction, but impaired diastolic function persists as in benign hypertension, suggesting that these abnormalities are the result of altered myocardial properties that may occur without hypertrophy.

Malignant hypertension is a rare disorder with a high but declining mortality and morbidity from renal, cerebral, and cardiac complications.^{1,2}

Echocardiographic features in non-malignant hypertension may include left ventricular wall thickening, even with a normal electrocardiogram.³ This degree of hypertrophy is probably related to the severity of hypertension and is reduced by successful blood pressure control.^{4,5} We have previously shown that in

some untreated patients with malignant hypertension, left ventricular wall thickness, cavity dimensions, and systolic function are normal, while diastolic function is disturbed.^{6,7} We concluded that in some patients, the malignant phase is of relatively rapid onset and not preceded by prolonged hypertension which would result in hypertrophy. The purpose of the present study is to extend the previous investigation and study 16 malignant hypertensives by echocardiography before and after six months of treatment with anti-hypertensives.

Patients and methods

Four groups of patients were studied.

- (a) **Normal:** twelve normal subjects (two women, 10 men) aged 29 to 59, mean age 42 years. All had a diastolic blood pressure (Vth phase) below 85 mmHg.
- (b) **Hypertensive:** all were untreated before presentation to hospital. The malignant phase of hypertension was diagnosed by the presence of grade III or IV hypertensive retinopathy, that is retinal exudates and haemorrhages with or without papilloedema. All patients were initially treated with 100 mg oral atenolol to ensure controlled blood pressure reduction.⁸ Echocardiography was performed within 24 hours of starting treatment when blood pressure had fallen on average 10% from the peak values. After the initial phase of therapy patients were treated with various drug combinations, including beta adrenergic blocking agents, diuretics, and vasodilators including hydralazine, minoxidil, and methyl-dopa. The subgroups of patients with hypertension were as follows.
 - (i) **Severe benign hypertension:** eight patients (three women, five men) aged 26 to 43, mean age 37 years. Blood pressure at presentation ranged from 180/125 to 240/155 mmHg (mean 195/130 mmHg).
 - (ii) **Malignant hypertension:** seven patients (two women, five men) with a previous history of hypertension (Table 1).
 - (iii) **Malignant hypertension:** nine patients (one woman, eight men) with no previous history of hypertension (Table 1).

ELECTROCARDIOGRAPHY

A standard 12 lead electrocardiogram was recorded at presentation and at intervals during treatment and the sum of the deflections of the S wave in lead V1 plus the maximum R wave in V5 or V6 was noted. Left ventricular hypertrophy was assumed if this figure exceeded 3.5 cm. The presence of ST-T changes was also noted. No subject had electrocardiographic evidence of a myocardial infarction.

CHEST RADIOGRAPHY

A standard 2 metre posteroanterior chest radiograph was taken at presentation and at intervals during treatment. The cardiothoracic ratio was determined by dividing the cardiac transverse diameter by the internal thoracic diameter, expressed as a percentage; cardiomegaly was assumed if this exceeded 50%. Pulmonary oedema was recorded when Kerley's "B" lines, or interstitial or alveolar oedema were present.

ESTIMATION OF LEFT VENTRICULAR DIMENSIONS AND FUNCTION

Patients were studied before or within 24 hours of starting antihypertensive treatment and at intervals during treatment. Echophonocardiography with simultaneous apexcardiogram and electrocardiogram (standard lead II) was performed in the partial left lateral position with an SK20 ultrasonoscope and a Cambridge multichannel photographic recorder with a paper speed of 10 cm/s. A left ventricular echocardiogram at the level of the tips of the mitral valve (to define onset of opening), showing clear continuous echoes from both the septum and posterior wall, was used for further analysis. The thicknesses of the interventricular septum and posterior wall were

Table 1 Clinical features, electrocardiogram, and chest radiograph in hypertensives (number with abnormal feature)

	Treatment	No.	Blood pressure	Retinopathy			Electrocardiogram		Chest radiograph	
			Mean (range) (mmHg)	Ex	Haem	Pap	LVH (voltage)	ST-T depression or T inversion	Cardiomegaly	Pulmonary oedema
Malignant hypertension with previous history of hypertension	Before	7	250 (250 - 300) 155 (130 - 175)	6	6	5	5	4	6	3
	After	6	156 (142 - 196) 98 (86 - 126)	2	1	1	5	1	5	0
Malignant hypertension with no previous history of hypertension	Before	9	245 (230 - 290) 157 (130 - 180)	8	9	8	4	6	1	3
	After	9	158 (138 - 175) 97 (88 - 115)	2	0	1	4	2	1	0

Ex, exudates; Haem, haemorrhages; Pap, papilloedema; LVH, left ventricular hypertrophy (see methods); Cardiomegaly, cardiothoracic ratio greater than 50%.

measured at end-diastole (R wave on the electrocardiogram) in cm. Left atrial dimension was measured in cm at end-systole from the anterior border of the posterior atrial wall to the posterior aortic wall and expressed as a ratio of aortic root dimension.

Echocardiograms were digitised as previously described by Gibson and Brown,⁹ using a Summagraphics digitiser and a Prime 300 computer system. From these records the following measurements were made: (i) end-systolic cavity dimension (cm); (ii) end-diastolic cavity dimension (cm); (iii) peak rate of increase in dimension during early diastole (cm/s); (iv) early diastolic filling period, defined as the period from minimal left ventricular dimension to the time of reduction in filling to 20% of its peak value (ms); (v) time intervals in ms from the Q wave of the electrocardiogram to the aortic second heart sound (A_2) (this was corrected for heart rate as described by Weissler *et al.*¹⁰ and expressed as QA_2 index); time from A_2 to minimum dimension, which was taken as negative if minimum dimension followed and positive if it preceded A_2 ; time from minimum dimension to mitral valve opening; (vi) change in dimension during isovolumic relaxation expressed as a percentage of the total dimension change during the cardiac cycle; (vii) change in left ventricular dimension during the time of inscription of the upstroke of the apexcardiogram (isovolumic contraction), expressed as a percentage of the total dimension change during the cardiac cycle.¹¹

The ratio of the apexcardiogram "a" wave to the total deflection (H) was calculated and was assumed to be raised if the a/H ratio exceeded 0.15 (2 standard deviation from normal).¹²

Fig. 1 Electrocardiogram of a man with malignant hypertension (previous four year history of benign essential hypertension) showing severe left ventricular hypertrophy.

STATISTICAL METHOD

Values are quoted as mean $\pm$ one standard deviation. Student's *t* test was used to test differences between normally distributed variables and χ^2 between variables with a skewed distribution.

Results

CLINICAL (Table 1)

The mean blood pressure before treatment was 250/155 and 245/157 mmHg, respectively, in patients with and without a previous history of hypertension, and fell during treatment to means of 156/98 and 158/97 mmHg, respectively. One patient with an apparently good reduction in blood pressure (last record 166/95 mmHg) died from a stroke three weeks after presentation. Ten patients had satisfactory reductions in blood pressure (below 145/100 mmHg), four had moderate reductions in blood pressure (below 165/115 mmHg), and one man with no previous hypertensive history remained severely hypertensive (196/125 mmHg) after five months, possibly because of poor compliance. Blood pressure reduction resulted in a regression of retinopathy in all but this last patient.

ELECTROCARDIOGRAPHY (Table 1; Fig. 1 and 2)

The voltage criteria for left ventricular hypertrophy were present in nine of 16 patients with malignant hypertension and all patients with benign hypertension. Lateral ST-T changes were present in 10 of 16 patients. There were wide variations, however, in the electrocardiogram at presentation from severe left ventricular hypertrophy (Fig. 1) to normal (Fig. 2). After treatment improvement in the ST-T changes was noted in some patients, suggesting resolution of subendocardial ischaemia. There was little change in electrocardiographic voltage criteria.

Fig. 2 Normal electrocardiogram from woman with malignant hypertension and no previous hypertensive history.

Fig. 3 Chest radiograph of man with malignant hypertension with a previous hypertensive history before treatment showing pulmonary oedema and increased heart size.

Fig. 4 Chest radiograph of malignant hypertensives without a previous history showing normal findings.

CHEST RADIOGRAPHY (Table 1, Fig. 3 and 4)

Before treatment the mean cardiothoracic ratio was 57% and 47%, respectively, in the malignant hypertensives with and without a previous history. Pulmonary oedema was present in six of 16 (two interstitial, two alveolar, and two with Kerley's "B" lines), and in addition a further two patients had pulmonary vascular redistribution to the upper lobe vessels. There was rapid improvement in the features of pulmonary oedema in all patients with treatment but little change in heart size.

LEFT VENTRICULAR STRUCTURE (Table 2)

The mean values for cavity dimensions were normal at presentation⁶ and no significant change occurred with treatment. Therefore, derived indices of ejection such as fractional shortening and ejection fraction were normal and are not quoted.

The wall and septal thicknesses at presentation and during treatment are shown (Fig. 5 and 6). Those with a previous history of hypertension (Fig. 7) tended to have left ventricular hypertrophy and those without a previous history did not (Fig. 8). After

Table 2 Changes in left ventricular function in hypertensives during treatment

	No.	Treatment	QA ₂ index (ms)	A ₂ to minimum dimension (ms)	Minimum dimension to MVO (ms)	Increase in cavity dimension		Dimension changes % of total		Apexcardiogram a/H ratio	Left atrial to aortic ratio
						Peak rate (cm/s)	Duration (ms)	During isovolumic relaxation	During upstroke apexcardiogram		
Normal	12		540±17	-46±14	10±3	19±3	166±40	0±3	3±3	0.07±0.04	1.0±0.2
Benign hypertension	8	Before	542±20	-27±35	70±15	12±3*	196±30	15±7	7±4	0.12±0.06	1.2±0.5
	8	After	541±19	-30±32	71±16	11±7§	182±36	12±6	4±7	0.09±0.05	1.2±0.3
Malignant hypertension with previous history	7	Before	533±34	-9±45	76±18	11±2*	191±35	20±11	19±15¶	0.36±0.16‡	1.3±0.2¶
	6	After	535±39	-21±40	73±17	11±4*	187±4	17±12	8±9	0.21±0.09‡	1.2±0.4
Malignant hypertension with no previous history	9	Before	505±30¶	-87±27‡	71±23	9±3*	220±43¶	16±15	27±16‡	0.40±0.11†	1.1±0.2
	9	After	537±36	-41±40¶¶	69±27	10±4*	210±41¶	15±9	9±10¶¶	0.17±0.08¶**	1.1±0.2

Difference from normal * p<0.001; § <0.005; ‡ <0.01; ¶ <0.05.

Difference before and after treatment †† p<0.001; ¶¶ p<0.05.

MVO, mitral valve opening.

Fig. 5 Graph of left ventricular posterior wall thicknesses before and during treatment in malignant hypertension. ●—● previous history of hypertension. ○—○ no previous history.

Fig. 7 Echocardiogram of patient with malignant hypertension (BP 230/146 mmHg) and previous hypertensive history. Note severe hypertrophy of posterior wall and septum, a tall apexcardiographic "a" wave with normal cavity dimensions and ejection.

treatment patients without left ventricular hypertrophy normally showed no change, except patient (a) (Fig. 5 and 6) who had poor blood pressure control (196/126 mmHg after five months) and who developed hypertrophy (from 0.9 to 1.3 cm). Cases with hypertrophy either showed no change or a tendency to a small reduction.

The left atrial/aortic root ratio was approximately unity in normotensives, but all hypertensives showed some increase and in untreated malignant hyperten-

Fig. 6 Graph of ventricular septal thickness before and during treatment in malignant hypertension.

Fig. 8 Echocardiogram of patient with malignant hypertension (BP 245/163 mmHg) with no previous hypertensive history. Note absence of hypertrophy and raised a/H ratio and normal cavity dimensions.

sives with a previous history the ratio was significantly greater than normal ($p < 0.05$). There were no significant changes with treatment.

LEFT VENTRICULAR FUNCTION (Table 2, Fig. 9 and 10)

Time intervals

The timing of A_1 was significantly early in the untreated patients, and returned to normal after treatment.

Fig. 9 Normal digitised M-mode echocardiogram showing (from the bottom upwards) the original data, continuous posterior wall thickness, and rate of change and an apex echo dimension loop. Two crosses on dimension trace represent aortic closure and mitral opening.

At presentation in all hypertensives there was significant delay in mitral valve opening and this did not change. Therefore, isovolumic relaxation time was reduced but remained outside the normal range because of a change in the relation of A_2 to minimum dimension and not because of a relative change in the timing of mitral valve opening.

Left ventricular filling

The peak rate of early diastolic filling was significantly reduced in all hypertensive groups and in some patients the duration of filling was prolonged. There were no significant changes with treatment even though the mean heart rate fell from 87 to 62 bpm because of beta adrenergic blockade.

Isovolumic relaxation and contraction

All hypertensives showed an increase in cavity dimension before mitral valve opening, suggesting the presence of incoordinate relaxation and there were no significant changes during treatment. Benign hyper-

Fig. 10 Digitised M mode echocardiogram of patient with malignant hypertension without a previous history of hypertension. This shows reduced peak rate and prolonged duration of cavity dimension increase, delayed mitral valve opening with dimension increase during isovolumic relaxation, and cavity dimension change during the upstroke and downstroke of the apexcardiogram.

tensives had no reduction in cavity dimension during the upstroke of the apexcardiogram but both malignant groups showed significant changes ($p < 0.05$), suggesting the presence of incoordinate contraction as well. After reduction of blood pressure, this was significantly reduced and was similar to that found in non-malignant hypertensive patients.

Apexcardiogram

Adequate traces were obtained in all but one hypertensive patient and in 10 of 12 normal subjects. Patients with benign hypertension had normal a/H ratios, whereas those with malignant hypertension had significantly abnormal values ($p < 0.01$), suggesting raised left ventricular end-diastolic pressure. During treatment the mean values for both of these groups fell and in those without a previous history the change was significant ($p < 0.05$). Neither value, however, returned to normal; they remained significantly different from normal ($p < 0.05$).

Discussion

We have shown that in patients presenting with malignant hypertension, the presence of a previous hypertensive history identifies two groups.^{6,7} Those with a known hypertensive history, either benign or malignant, tend to have ventricular hypertrophy and those presenting acutely without a previous history usually do not have hypertrophy. After a period of antihypertensive therapy, resolution of retinopathy and pulmonary oedema was noted, with no real changes in hypertrophy. Therefore, patients may have malignant phase hypertension and be successfully treated without developing ventricular hypertrophy.

Patients presenting with malignant hypertension form a heterogeneous group. One end of the spectrum was represented by a girl of 15 years with grade IV retinopathy with longstanding hypertension resulting from the Ask-Upmark kidney, who also had electrocardiographic and echocardiographic evidence of severe left ventricular hypertrophy without radiographic cardiomegaly or pulmonary oedema. At the other end was a middle-aged male smoker who presented for the first time with retinopathy, a normal electrocardiogram, no left ventricular hypertrophy, and x-ray evidence of pulmonary oedema. Presumably the first example resulted from a gradual increase in blood pressure and the second from a rapid rise, resulting in "left ventricular failure" not adaptation.

Left ventricular hypertrophy occurs in response to the peak systolic pressure in benign hypertension and is presumably an adaptive mechanism for maintaining relatively normal rate of contraction, peak systolic wall stress, and oxygen requirement.¹³ While the rate of development of cardiac hypertrophy is not known in man, it may occur in a few weeks after the application of a raised afterload in experimental animals.¹⁴ Good blood pressure reduction (below 145/100 mmHg) was obtained in 10 (66%) of our patients and either no change in wall thickness or a trend toward a reduction was noted. Moderate blood pressure reduction (below 165/115 mmHg) resulted in no change in wall thickness and in one man who had no previous hypertensive history and poor blood pressure control an increase in wall and septal thickness was noted. In some patients with malignant hypertension either pressure rise is rapid and does not allow sufficient time for hypertrophy, or some other factor (such as ischaemia from arteriolitis) prevents its development. The usual response of a failing left ventricle, either from ischaemia or increasing afterload, is ventricular dilatation and reduced ejection with a raised end-diastolic pressure. This was not observed in malignant hypertensives, even with pulmonary oedema. Cavity dimensions and ejection remained

relatively normal with raised end-diastolic pressure and abnormal filling relaxation, a similar situation to that found in hypertrophic cardiomyopathy.¹⁵ This may occur with excess catecholamine secretion, as we have described elsewhere in a woman with pheochromocytoma.¹⁶

While left ventricular ejection remains apparently normal in malignant phase hypertension (presumably normal pump function is required to maintain the blood pressure), in response to grossly raised afterload, contraction becomes incoordinate and aortic valve closure occurs early. Because of the timing of A_2 , isovolumic relaxation may be grossly prolonged. Delay in mitral valve opening was associated with outward wall motion reflecting incoordinate relaxation. Incoordinate contraction and relaxation are the result of abnormal myocardial properties or regional disturbances of function (such as in hypertrophic cardiomyopathy or ischaemic heart disease).^{11 15 17} In addition, there was reduction in the peak rate and prolonged duration of the initial rapid phase of ventricular filling. These are also non-specific abnormalities occurring in all forms of hypertrophy such as hypertrophic cardiomyopathy, aortic stenosis, and hypertension.¹⁵ After reduction in blood pressure, the abnormalities of function return to levels similar to those found in benign hypertension. These abnormalities persisted even in the absence of hypertrophy and it must be assumed that they are caused by diffuse fibrosis disrupting myocardial relaxation.

Left atrial enlargement is sometimes found in benign hypertension,³ and in the malignant phase it was relatively common. While the abnormalities of atrial size were subtle, the apexcardiographic a/H ratio was grossly raised.¹⁸ The highest values were found in malignant hypertensives without a previous history and those with radiological evidence of pulmonary oedema. After a reduction in blood pressure, the a/H ratio fell significantly but remained abnormal. Its reversible nature suggests that the mechanism is similar to that found in the transiently ischaemic ventricle in coronary disease and that the reduction in afterload in our hypertensives improves myocardial perfusion. There was improvement in lateral ST segment and T wave abnormalities in seven of 10 patients.

The high level of mortality in malignant hypertension is well known. Keith *et al.*¹⁹ in 1939 showed that the average survival time for untreated grade IV hypertensive retinopathy was 10.5 months, and as recently as 1952 to 1959 the five year mortality was 75%. It was reduced to 66% only in the period 1960 to 1967.²⁰⁻²² It is interesting to speculate on the cause of increased mortality in malignant hypertensives. While the absolute blood pressure levels are quantitatively greater than in benign hypertension, this cannot be

the only factor. There may be a specific circulating humoral factor responsible for tissue damage,²³ though immunological mechanisms may be important.²¹ We and others have shown, however, that cigarette smoking is strongly associated with the malignant phase and 13 of the 16 cases in this series were smokers.²⁴ We suggest that in some patients with malignant hypertension blood pressure rises too rapidly for normal adaptive processes. In a 40 year follow-up of 1038 untreated hypertensives, approximately 1% were initially in the malignant phase, and no patient with benign hypertension developed malignant hypertension.²⁵ Malignant hypertension may be a heterogeneous disorder, probably with different pathological mechanisms resulting in a similar clinical picture.

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Requests for reprints to Dr L M Shapiro, Cardiology Department, Dudley Road Hospital, Birmingham B18 7QH.