

Detection of clinically significant coronary artery disease in hypertensive patients

Echocardiographic study

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SUMMARY Simultaneous echocardiograms and phonocardiograms were recorded and digitised in 29 normal control subjects and 88 unselected hypertensive patients. Left ventricular wall thickness and isovolumic relaxation time were measured. The time relations between valvular events and endocardial movement were examined. Dimension change during the period of isovolumic relaxation was measured.

Left ventricular wall thickness ranged from normal values to massive hypertrophy in hypertensive patients. Isovolumic relaxation time was prolonged (85 ± 25 ms) and related to increasing left ventricular wall thickness. When indices of the co-ordination of left ventricular wall movement were studied (time relation of aortic valve closure to minimum cavity dimension, dimension change during isovolumic relaxation), two separate groups of hypertensive patients were identified. Group 1 (60 patients) had normal time relations between valvular events and endocardial movement, with only small dimension changes during isovolumic relaxation, implying co-ordinate wall motion. Group 2 (28 patients) had abnormal time relations and large dimension changes during isovolumic relaxation implying incoordinate wall motion.

All patients in group 1 had normal electrocardiograms. Fifty-eight were asymptomatic, while two patients with chest pain were shown to have non-significant coronary artery disease. In group 2, 25 of 28 patients had abnormal electrocardiograms. Ten patients had previously been shown to have significant coronary artery disease, while of the remaining 18, seven had angina and 11 were asymptomatic. In a 14-month follow-up seven of these 18 patients from group 2 (three with angina, four who were asymptomatic) had a major cardiac event (five myocardial infarctions, two sudden deaths) whereas no cardiac events occurred in the patients in group 1. The echocardiographic recognition of incoordinate left ventricular wall motion in a hypertensive population identifies a group of patients with a high incidence of clinically significant coronary artery disease.

Prolonged systemic arterial hypertension may result in left ventricular hypertrophy which can be identified by echocardiography before any abnormality is seen on the electrocardiogram.¹ The effect of hypertrophy secondary to systemic hypertension on left ventricular performance is not clearly established. Animal experiments suggest that in the absence of failure the performance of the pressure-loaded ventricle is unimpaired.²⁻⁴

Information on left ventricular performance in hypertensive human subjects is sparse; it is mostly derived from echocardiographic studies and confined to an assessment of systolic function. The findings

have been conflicting.^{5,6} Both these latter papers describe normal left ventricular function in patients with left ventricular hypertrophy, while other authors^{1,7} find evidence for depression of function.

M-mode echocardiography is an ideal non-invasive method for investigating cardiac structure, but is less applicable in the study of cardiac function when segmental abnormalities of wall motion occur, as in patients with coronary heart disease.⁸ If M-mode echocardiography is combined with phonocardiography, however, and the results processed using a simple digitising technique, it is possible to identify changes both in the timing of events during the cardiac cycle and in left ventricular dimensions during

isovolumic relaxation. Chen and Gibson⁹ have shown that in patients with coronary artery disease there is a strong association between shortening of the interval between aortic valve closure (A_2) and minimum left ventricular cavity dimension and incoordinate wall movement. It has also been¹⁰ shown that significant changes in dimension during isovolumic relaxation reflect incoordinate function of the ventricle, defined as angiographically visible abnormalities of wall motion, irrespective whether the part of the ventricle visualised by the echocardiographic beam is normal or abnormal.

In an attempt to obtain further information on left ventricular performance in an unselected group of hypertensive patients, we studied patients both by conventional echocardiographic analysis of left ventricular dimension and wall thickness, and also by the digitising technique, paying particular attention to early diastolic events. The results were compared with normal controls. The study findings were correlated with a retrospective clinical analysis and a further follow-up over a one-year period.

Patients and methods

Combined echocardiographic and phonocardiographic studies were made over a six-month period in 136 patients with hypertension (systemic arterial diastolic pressure persistently above 100 mmHg before treatment) and 35 normotensive subjects without clinical, radiological, or electrocardiographic evidence of cardiac disease. Tracings of sufficient quality for further analysis were obtained in 29 normal subjects (27 men, two women, mean age 38, range 21 to 63) and 88 hypertensive patients (60 men, 28 women, mean age 51, range 24 to 73) who comprise the study series. Thirty-seven of the hypertensive patients were untreated at the time of study, the remainder were taking either a beta-adrenergic blocking agent (36 patients) or other hypotensive drugs (15 patients).

Patients were studied in the left semilateral position using a Cambridge Instruments ultrasonoscope and 2.25 MHz focused transducer. An electrocardiogram and phonocardiogram were recorded simultaneously. Tracings were made using a Cambridge Instruments photographic recorder at a paper speed of 100 mm/s; only those records which clearly showed mitral valve opening and which had well defined continuous septal endocardial and left ventricular posterior wall endocardial and epicardial echoes were accepted for further analysis (Fig. 1). Records were digitised.¹¹

Plots were generated over one cardiac cycle to show the original data, left ventricular cavity dimension, the rate of change of dimension, the rate of change of dimension normalised to refer to unit length of dimension, left ventricular posterior wall thickness,

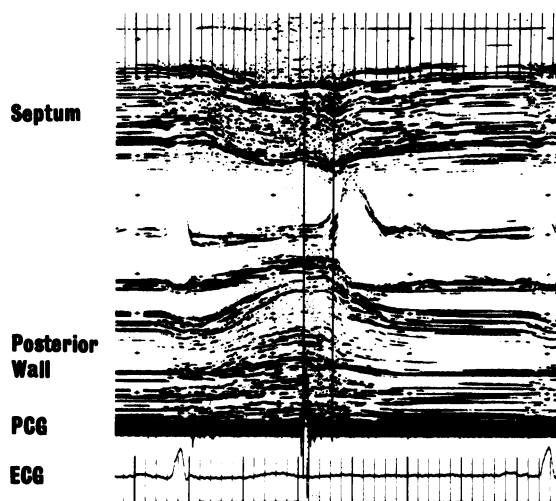


Fig. 1 Echocardiogram from a hypertensive patient (group 1) showing the septum and left ventricular posterior wall recorded with an electrocardiogram (ECG) and phonocardiogram (PCG). The vertical lines represent from left to right (i) aortic valve closure and (ii) mitral valve opening.

and septal thickness. Superimposed on the plots were the timing of aortic valve closure (taken as the first high frequency vibration of the aortic component of the second heart sound), and the timing of mitral valve opening (taken as the initial separation of the mitral valve cusps) (Fig. 2). For each patient, the average measurements for two cardiac cycles were taken. Measurements were made of:

- (1) Left ventricular maximum and minimum dimension.
- (2) Maximum and minimum thickness of septum and left ventricular posterior wall.
- (3) Normalised peak rate of dimension change during ejection (peak VCF) and during diastole (peak rate of dimension increase).
- (4) Time intervals (expressed to the nearest 5 ms) of:
 - (a) Cycle length, the interval between successive Q waves.
 - (b) $Q-A_2$ corrected using the regression equation to a heart rate of 60/min.¹²
 - (c) Isovolumic relaxation time (A_2 to mitral valve opening).
 - (d) A_2 to minimum left ventricular cavity dimension (the point where the derivative of cavity dimension alters from negative to positive).
 - (e) Minimum cavity dimension to mitral valve opening.
- (5) Changes in left ventricular dimension during isovolumic relaxation, expressed as a percentage of total change in dimension.

Patients with hypertension were initially considered

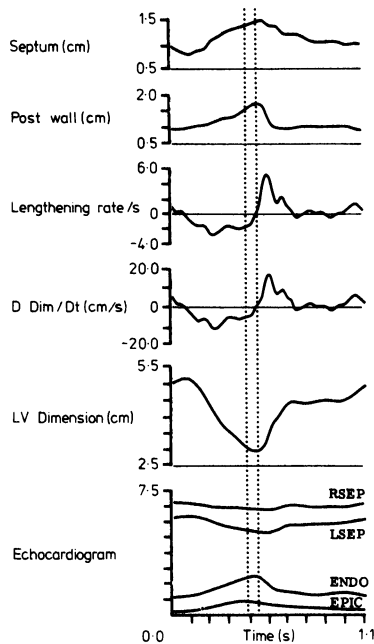


Fig. 2 Digitised echocardiogram from a normal control. Illustrated from the bottom are the original data, left ventricular dimension, rate of change of dimension, rate of change of dimension normalised to refer to unit lengths of dimension, posterior wall thickness, and (top) septal thickness. The vertical lines represent from left to right (i) aortic valve closure and (ii) mitral valve opening. Minimum cavity dimension is the point where the derivative of cavity dimension changes from positive to negative.

as a single group. Later two separate groups were identified based on whether or not there was evidence of incoordinate wall motion defined as shortening of the interval between A₂ and minimum left ventricular cavity dimension to less than 20 ms or an abnormal dimension change during isovolumic relaxation greater than 12%. Group 1 (60 patients comprising 37 men, 23 women, mean age 49, range 24 to 73) had values within the normal range with respect to these measurements. Group 2 (28 patients comprising 23 men, five women, mean age 55, range 39 to 70) had values for either one (nine patients) or both (19 patients) of these measurements outside the normal range.

Results are expressed as mean ± 1 SD. Normal values were taken as those lying within a range of two standard deviations of the corresponding mean value of the normal group. Differences between means were compared using Student's t test. Linear regression analysis was used to measure correlation between variables.

Results

These are given in detail in the Table.

NORMAL SUBJECTS

Maximum and minimum left ventricular cavity dimensions were 5.0±0.5 cm and 3.1±0.5 cm, respectively. Maximum septal and left ventricular posterior wall thicknesses were 1.5±0.2 cm and 1.7±0.2 cm, respectively. Minimum septal and left ventricular posterior wall thicknesses were 1.0±0.1 cm and 0.8±0.1 cm, respectively. Peak VCF was 2.5±0.6 and peak rate of dimension increase during diastole was 5.7±1.7. Isovolumic relaxation time (65±15 ms) corresponded well with the value (60±20

Table All measured and calculated variables for normal controls (n=29) and hypertensive patients in group 1 (n=60) and group 2 (n=28)

Measurement	Normal subjects	Group 1	Group 2
Maximum left ventricular dimension (cm)	5.0±0.5	5.0±0.5	5.1±1.0
Minimum left ventricular dimension (cm)	3.1±0.5	3.0±0.5	3.2±1.2
Maximum septal thickness (cm)	1.5±0.2	1.7±0.3*	2.0±0.3**
Minimum septal thickness (cm)	1.0±0.1	1.2±0.2**	1.5±0.4**
Maximum posterior wall thickness (cm)	1.7±0.2	1.9±0.3**	2.1±0.3**
Minimum posterior wall thickness (cm)	0.8±0.1	1.0±0.2**	1.2±0.2**
Peak VCF/s	2.5±0.6	2.6±0.7	2.7±1.0
Peak rate of dimension increase/s	5.7±1.7	5.5±2.2	4.4±1.4*
Cycle length (ms)	855±200	885±195	870±205
Q to aortic valve closure (index)	540±16	522±22	540±20
Isovolumic relaxation time (ms)	65±15	80±20*	100±30*
A ₂ to minimum cavity dimension (ms)	50±15	60±15	15±30**
Minimum dimension to mitral valve opening (ms)	15±20	20±15	85±30**
Dimension change during isovolumic relaxation (%)	-4±8	0±7	28±18*

* p<0.01 ** p<0.001

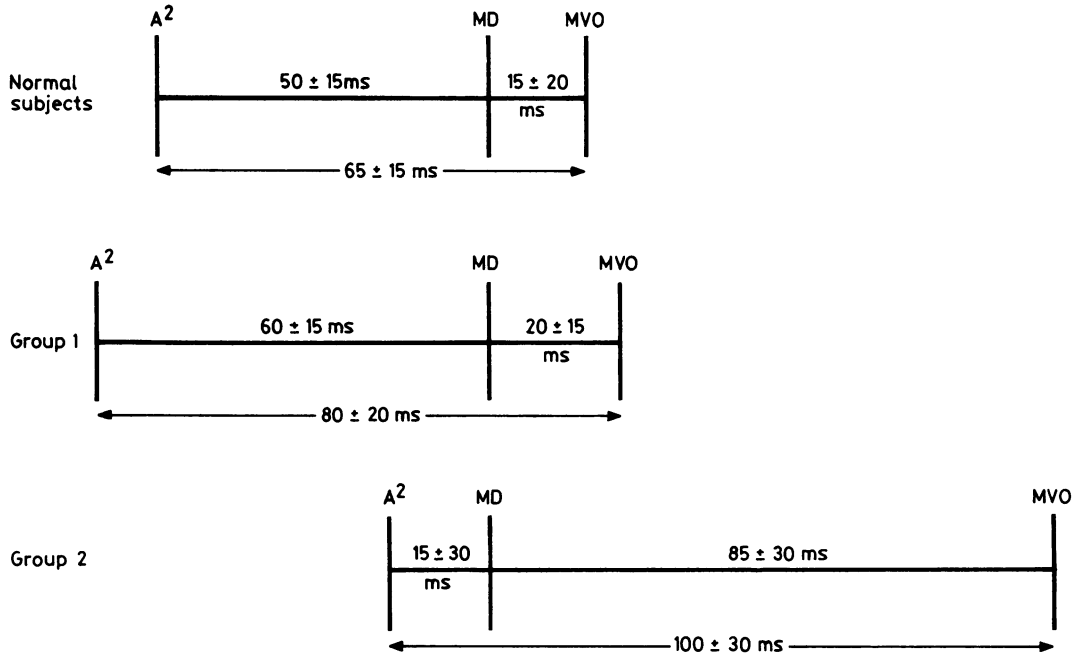


Fig. 3 Schematic representation of time relations between aortic valve closure (A₂), minimum cavity dimension (MD) and mitral valve opening (MVO) in (top) normal controls, hypertensive patients in group 1, and (bottom) hypertensive patients in group 2.

ms) obtained by Chen and Gibson⁹ using the same technique. A constant relation was observed in the timings of A₂, minimum cavity dimension, and mitral valve opening relative to each other (Fig. 3). A₂ preceded minimum cavity dimension by 50 ± 15 ms while mitral valve opening followed minimum cavity dimension by 15 ± 20 ms. Only small changes were observed in left ventricular cavity dimension during the isovolumic relaxation period (-4 ± 8%).

HYPERTENSIVE PATIENTS (ALL SUBJECTS)

Left ventricular posterior wall minimum thickness was increased (1.1 ± 0.2 cm, p < 0.001) and unimodally distributed in the hypertensive population (Fig. 4). Isovolumic relaxation time was prolonged (85 ± 25 ms, p < 0.001) and also unimodally distributed (Fig. 4). Isovolumic relaxation time was correlated with left ventricular posterior wall thickness (Fig. 5, r = 0.66, p < 0.001). The previously defined indices of the

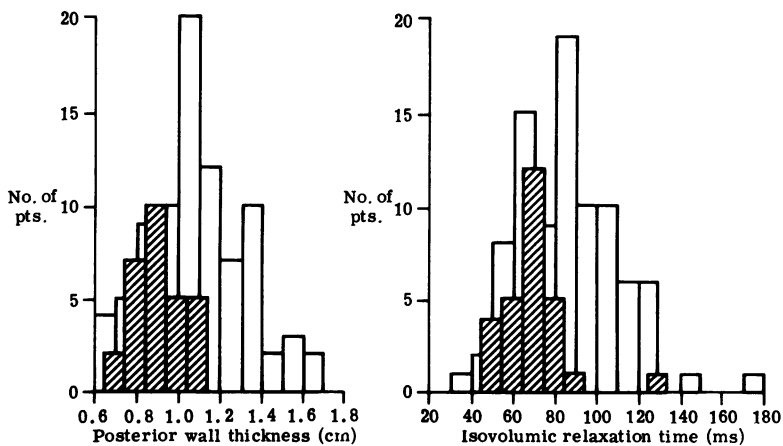


Fig. 4 Histograms showing the distribution of values of posterior wall thickness (left-hand panel) and isovolumic relaxation time in hypertensive patients (open columns) and normal controls (hatched columns). The normal controls distribution is slightly offset.

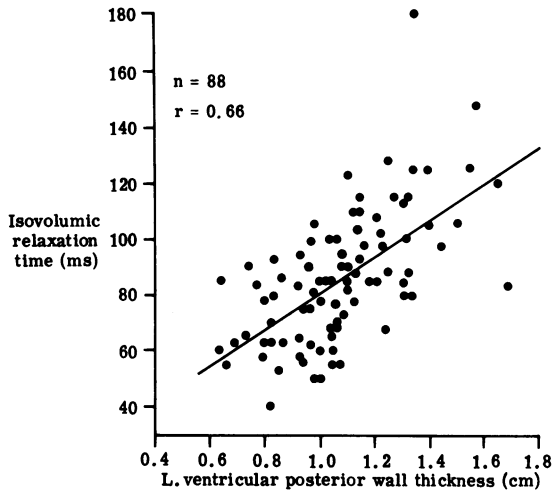


Fig. 5 Relation of duration of isovolumic relaxation and left ventricular posterior wall thickness.

co-ordination of left ventricular wall motion (the timing of A_2 relative to minimum cavity dimension and dimension change during isovolumic relaxation) were distributed bimodally (Fig. 6) enabling two groups of hypertensive patients to be defined.

GROUP 1 (HYPERTENSIVE PATIENTS WITH COORDINATE WALL MOTION)

By comparison with normal subjects, maximum septal and posterior wall thicknesses in these patients were increased (1.7 ± 0.3 cm and 1.9 ± 0.3 cm, respectively), as were minimum thickness of septum (1.2 ± 0.2 cm) and posterior wall (1.0 ± 0.2 cm). Isovolumic relaxation time was prolonged (80 ± 20 ms). The time relations between A_2 , minimum cavity dimension, and mitral valve opening were preserved (Fig. 3). Aortic valve closure preceded minimum cavity dimension by 60 ± 15 ms and mitral valve opening followed minimum cavity dimension by 20 ± 15 ms, neither value being significantly different from normal. Dimension change during isovolumic relaxation period also remained within the normal range ($0 \pm 7\%$).

GROUP 2 (HYPERTENSIVE PATIENTS WITH INCOORDINATE WALL MOTION)

Maximum septal and posterior wall thicknesses were increased, being 2.0 ± 0.3 cm and 2.1 ± 0.3 cm, respectively. Minimum septal and posterior wall thicknesses were increased being 1.5 ± 0.4 cm and 1.2 ± 0.2 cm, respectively. Isovolumic relaxation time was lengthened (100 ± 30 ms). In contrast to group 1 the normal time relations between A_2 , minimum cavity dimension, and mitral valve opening were

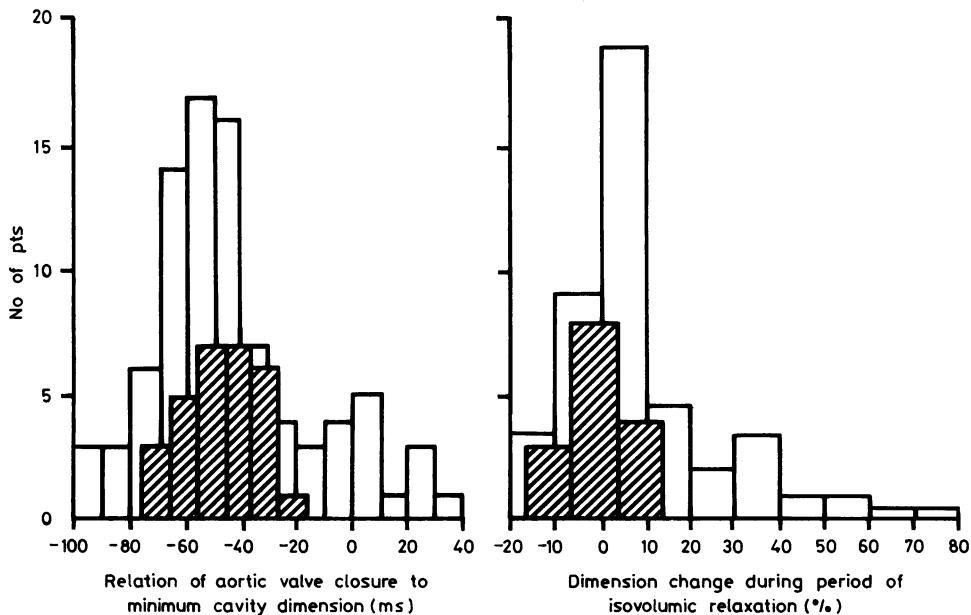


Fig. 6 Histograms showing the distribution of values of the time interval A_2 to minimum cavity dimension (left hand panel) and dimension change during isovolumic relaxation in hypertensive patients and in normal controls. Layout as in Fig. 4.

disturbed (Fig. 3). Aortic valve closure preceded minimum cavity dimension by only 15 ± 30 ms while mitral valve opening followed it by 85 ± 30 ms. Associated with these changes was an abnormally increased dimension change during the isovolumic relaxation period ($28 \pm 18\%$) (Fig. 7).

EFFECTS OF BETA-BLOCKING DRUGS

Of the 88 hypertensive patients studied, 37 were being treated with a beta-adrenergic blocking drug at the time of study (19 in group 1, 18 in group 2). No differences were observed within the groups in the measured variables between those patients taking beta-blockers and those who were not.

CLINICAL ANALYSIS

Group 1

Of the 60 patients in this group, 58 were asymptomatic with normal electrocardiograms. The remaining two patients had normal electrocardiograms, but had atypical chest pain. Both these patients were shown to have normal left ventricular function in the presence of minor coronary artery disease (less than 50% narrowing) by cardiac catheterisation.

Group 2

At the time of study, 10 had documented significant coronary artery disease, five by cardiac catheterisation (greater than 50% coronary artery narrowing and segmental abnormalities of wall motion) and five by previous myocardial infarction as shown by a typical history and associated electrocardiographic and enzyme changes. The remaining 18 patients all had

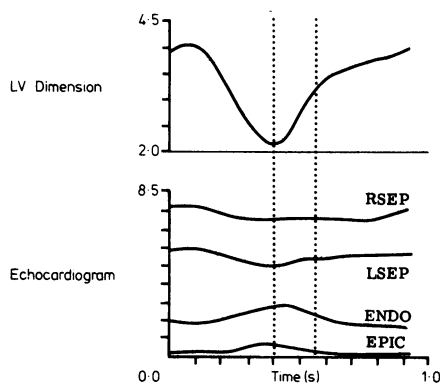


Fig. 7 Digitised echocardiogram from a hypertensive patient in group 2. The panels illustrate (bottom) the original data and (top) left ventricular dimension. The vertical lines represent from left to right aortic valve closure and mitral valve opening. A considerable change in dimension occurs during isovolumic relaxation.

abnormal electrocardiograms with T wave inversion in the left ventricular leads suggesting either left ventricular hypertrophy or myocardial ischaemia. Seven of these 18 had a typical history of angina pectoris while 11 were asymptomatic. In a mean follow-up period of 14 months (range nine to 18 months) seven of these 18 patients (three with angina, four who were asymptomatic) had a major cardiac event (five developed myocardial infarction while two died suddenly). In group 1, no cardiac events occurred during this follow-up period ($p < 0.001$, Fisher's exact probability test).

Discussion

The analysis of echocardiograms and phonocardiograms using the technique of digitisation allows the time relations between valvular events and endocardial motion to be clarified, and dimension change during the period of isovolumic relaxation to be identified. Our results confirm those of Chen and Gibson⁹ in showing a constant relation in normal subjects between aortic valve closure (A_2) and minimum cavity dimension. In patients with asynchronous left ventricular contraction this relationship is disturbed by shortening of the time interval Q to minimum cavity dimension while Q to A_2 remains constant.¹³ In normal subjects dimension changes during the isovolumic relaxation period are small. In patients with segmental abnormalities of wall motion caused by coronary artery disease considerable changes can be identified. In the period of isovolumic relaxation a dimension change in one segment of the ventricle implies an equal and opposite change elsewhere in the ventricle; therefore the presence of abnormalities of wall motion can be identified whether or not the part of the left ventricle in the plane being studied has normal function.^{14 15}

Our results show that in a hypertensive population left ventricular wall thickness ranges from normal values to massive hypertrophy. This consequence of chronic pressure overload can be identified by echocardiography without other evidence of hypertrophy being apparent. A prolonged isovolumic relaxation time was observed in many of the hypertensive patients the degree of which was related to increasing left ventricular wall thickness. Prolonged isovolumic relaxation (possibly reflecting a slow onset of relaxation) may be an intrinsic property of hypertrophy.

The patients in group 1 differed from normal subjects only in having increased left ventricular wall thickness and prolonged isovolumic relaxation. Wall motion abnormalities as detected by shortened A_2 to minimum cavity dimension and increased dimension change during isovolumic relaxation were not present.

This suggests that ventricular hypertrophy *per se* is a benign process in which the co-ordination of left ventricular wall motion is preserved. By contrast the patients in group 2 had evidence of incoordinate left ventricular wall motion with either shortened A_2 to minimum cavity dimension or increased dimension change during isovolumic relaxation or both. Though these abnormalities of wall motion have been demonstrated using a sophisticated technique, in practice they can be easily recognised on the echocardiogram without recourse to complex analysis (Fig. 8).

In group 1 all the patients had normal electrocardiograms and 58 were asymptomatic. By contrast, all but three of the patients in group 2 had abnormal electrocardiograms. Ten had been shown to have important coronary artery disease at the time of study, while of the remaining 18, seven had angina and 11 were asymptomatic. In a mean follow-up period of 14 months, seven patients from this group of 18 (three with angina, four who were asymptomatic) had a major cardiac event (five myocardial infarctions, two sudden deaths) whereas no cardiac events occurred in the patients in group 1. These clinical correlates strongly suggest that in hypertensive patients the echocardiographic recognition of incoordinate wall motion distinguishes those patients with a high incidence of clinically significant coronary artery disease.

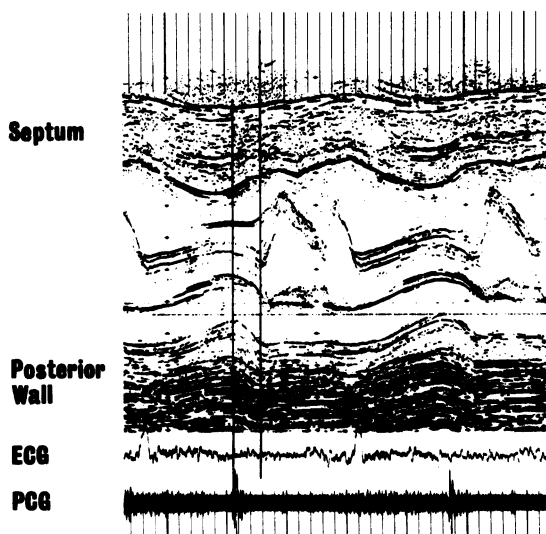


Fig. 8 Echocardiogram from a hypertensive patient in group 2 showing the septum and left ventricular posterior wall recorded with an electrocardiogram (ECG) and phonocardiogram (PCG). The vertical lines represent from left to right aortic valve closure and mitral valve opening. Simple inspection shows a change in left ventricular dimension during isovolumic relaxation.

In those patients with electrocardiographic abnormalities echocardiographic features of incoordinate wall motion were universally present. This suggests that the electrocardiographic changes in hypertensive heart disease are not simply the result of hypertrophy (a number of patients in group 1 had massive hypertrophy without electrocardiographic changes), but reflect incoordinate wall motion during relaxation most probably the result of significant coronary artery disease.

This study shows that in a hypertensive population echocardiography can identify prospectively a group of patients with a high incidence of important coronary artery disease. We suggest that this group deserves further study to determine if any intervention could alter prognosis.

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