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Left ventricular function in diabetes mellitus
I: Methodology, and prevalence and spectrum of abnormalities

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SUMMARY Frequent abnormalities of left ventricular function were detected in 212 established diabetic patients using non-invasive techniques.

Diabetics without angina or heart failure (n=185) were significantly different from normal subjects (n=50) in beat-to-beat variation, ratio of pre-ejection period to left ventricular ejection time, pre-ejection period index, isovolumic relaxation time, and interval from minimal dimension to mitral valve opening.

Diabetics with angina (n=18) were similar to control subjects with angina (n=25); they showed a significant dimension change during the isovolumic period as compared with other diabetics and normals. Sixteen diabetics without angina also showed outward motion during the isovolumic period (incoordinate relaxation) and 13 had abnormal systolic time intervals. Four diabetics suffered a myocardial infarction during the study period; all had previously shown incoordination.

Comparison of diabetics with a diastolic blood pressure below 100 mmHg and between 100 and 125 mmHg showed that the latter had a thicker posterior wall; the enlarged systolic dimension and reduced fractional shortening were the result of the inclusion of five of the 11 diabetic subjects with heart failure in the hypertensive group. Insulin-dependent diabetics tend to have more pronounced abnormalities of left ventricular function than those not requiring insulin.

Patients selected from a diabetic clinic frequently have impaired left ventricular function, and ventricular hypertrophy, when present, in primarily caused by hypertension.

There is increasing evidence that diabetics have abnormalities of left ventricular function in the absence of clinical heart disease.[1–6] Whether this results from small vessel disease of the myocardium, the metabolic effects of diabetes, or coronary artery disease is unknown, but the Framingham study[7] showed that diabetics suffered an incidence of heart failure in excess of that predicted from atherogenic risk factors.

A wide range of abnormalities in systolic and diastolic left ventricular function has been shown in diabetics but the number of patients in each group tends to be small and usually only one clinical type is included. For example, patients without microvascular disease have been shown to have normal[6] and abnormal[1] systolic time intervals, and those with severe microvascular disease (proliferative retinopathy and nephropathy) abnormal systolic time intervals[3] and echocardiograms.[4]

The purpose of our study was to investigate left ventricular function in a representative sample of patients attending a diabetic clinic using established, non-invasive techniques. We report here the prevalence and spectrum of abnormalities we have found.

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Patients and methods

We selected 212 subjects from a total of 473 diabetic patients whose disease had been present at least three months, attending the Dudley Road Hospital Diabetic Clinic between October 1978 and January 1980. All patients between the ages of 16 and 60 years were considered for inclusion. Exclusion of over half of the possible subjects occurred for the following reasons:

(1) Eighty in whom a suitable high quality echocardiogram could not be recorded; in most a second attempt on a separate occasion was made before exclusion.
(2) Ninety-six who declined investigation.
(3) Eighty-five who suffered from conditions known to affect the echocardiographic measurements or directly to influence left ventricular function, such as a diastolic blood pressure greater than 125 mmHg (26), previous myocardial infarction (21), thyroid disease (20), alcoholism (9), chronic renal failure (3), left bundle-branch block (4), and atrial fibrillation (2).

The mean age of the 212 patients was 44 ± 12 years and there were 119 men and 93 women. Fifty-three patients were treated with oral hypoglycaemic agents, 69 with once daily and 39 with twice daily insulin, and 51 by diet alone.

Fifty-two patients had severe microvascular complications (proliferative retinopathy and/or heavy proteinuria), 84 had mild complications (mild background retinopathy and/or proteinuria), and 76 had no complications. Twenty-seven had clinical heart disease, 18 complaining of angina and 11 having heart failure (two patients had both). Two patients with angina and eight with heart failure had severe microvascular complications.

Two groups of non-diabetic patients were selected as controls:

(i) 50 normal subjects, 30 men and 20 women (mean age 47 ± 14 years), either members of hospital staff or patients undergoing investigation of atypical chest pain who had normal coronary and left ventricular angiograms.
(ii) 25 patients with typical angina of exertion, 14 men and 11 women (mean age 52 ± 9 years), undergoing investigation. All had significant coronary artery atherosclerosis on angiography and none had had a myocardial infarct or was taking beta-blocking agents.

Assessment included clinical history and examination using a standardised questionnaire. Angina of exertion and left ventricular failure were recorded as present or absent.

Estimation of beat-to-beat variation[8] was performed after at least 15 minutes of supine rest by measuring the RR intervals in standard lead II on the electrocardiogram during three cycles of inspiration and expiration. The minimum RR intervals were subtracted from the maximum and the result expressed as a change in heart rate (beats per minute). The mean of three cycles was used in the analysis of beat-to-beat variation.

Systolic time intervals were obtained (after Weissler *et al.*[9]) in the early afternoon on a Cambridge-multichannel photographic recorder at paper speed 100 mm/s. The QA_2 (time interval from Q wave on the electrocardiogram to onset of aortic second heart sound) and left ventricular ejection time were measured in ms in 10 cardiac cycles and the following were derived (Fig. 1):

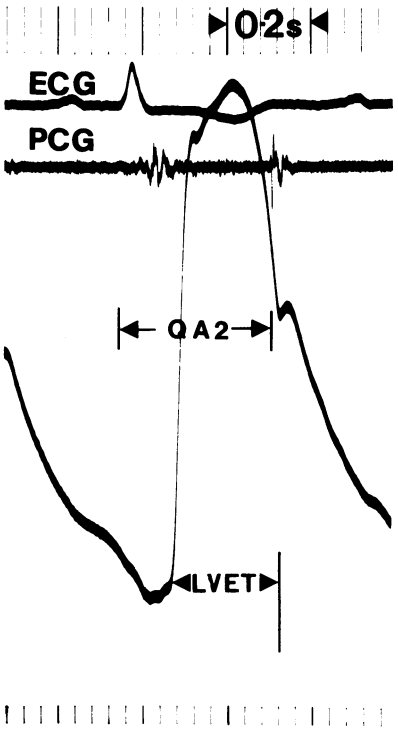

Fig. 1 *Measurement of systolic time intervals. Simultaneous electrocardiogram (ECG), phonocardiogram (PCG), and right carotid pulse. Left ventricular ejection time (LVET). Total electromechanical systole (QA_2).*

Pre-ejection period (PEP) $= (QA_2) - LVET$.
Ratio of PEP/LVET $\times 100$.
PEP index $= PEP + (0{\cdot}4 \times \text{heart rate})$[9].

Echophonocardiography was performed with a simultaneous electrocardiogram (standard lead II) in the partial left lateral position using a SK20 Ultrasonoscope. The isovolumic relaxation time was determined in ms from the onset of the aortic sound to the point of separation of the anterior and posterior mitral valve cusps. Left ventricular dimensions at end-diastole (DD) (at R wave electrocardiogram), minimal dimension (DS), and at the point of mitral valve opening were determined, and the time interval between the two latter points measured (Fig. 2). The following were derived from five cardiac cycles:

$$\text{Percentage fractional shortening} = \frac{DD - DS}{DD} \times 100$$

Percentage dimensional change during isovolumic relaxation =

$$\frac{\text{dimension at mitral valve opening} - DS}{DD - DS} \times 100$$

Posterior left ventricular wall and interventricular septal thickness were measured at end-diastole (Fig. 2).

All systolic time interval and echocardiographic measurements were made in ignorance of the clinical details. A random 10 per cent sample (n=21) of tracings from diabetics was remeasured, as a test of reproducibility, using re-test reliability coefficients.

Frequencies were reported for all variables. Student's t tests were used to analyse mean differences between control and diabetic groups.

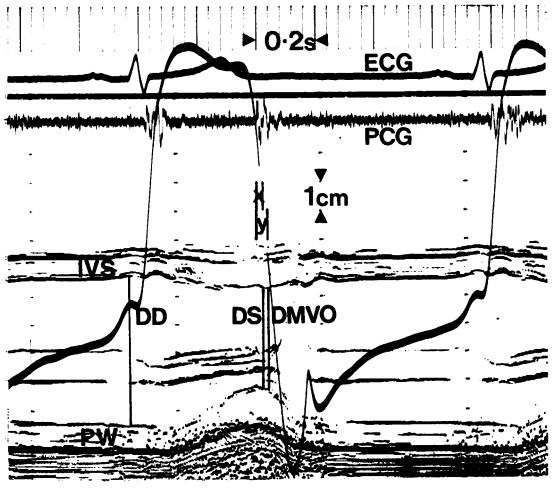

Fig. 2 *Echocardiographic measurements. Echocardiogram of normal subject with simultaneous electrocardiogram (ECG) and phonocardiogram (PCG). Diastolic dimension (DD). Systolic dimension (DS). Dimension of mitral valve opening (DMVO). Posterior wall thickness (PW). Interventricular septum (IVS). Interval from minimal dimension to mitral valve opening (x). Isovolumic relaxation time (y).*

Results

The re-test reliability coefficients were: beat-to-beat variation 0·74, PEP/LVET 0·96, PEP index 0·97, isovolumic relaxation time 0·98, interval from minimal dimension to mitral valve opening 0·93, cavity dimensions and wall thicknesses 0·96 to 0·98.

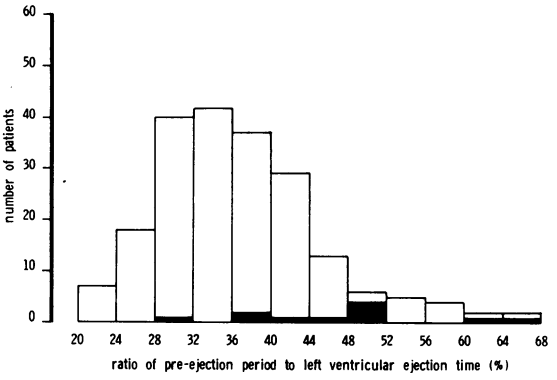

Fig. 3 *Frequency distribution of ratio of pre-ejection period to left ventricular ejection time. The shaded areas represent patients with heart failure.*

(1) DIABETICS WITHOUT CLINICAL HEART DISEASE V NORMAL SUBJECTS (Table 1A)

The beat-to-beat variation in diabetics was 13 ±10 which was significantly different from normal (27 ±14, $p < 0.001$). There was a wide range of PEP/LVET values, but the mean of 35 ±8 per cent also differed significantly from normal ($p < 0.001$) (Fig. 3). The PEP index too showed a wide range but the mean differed from normal ($p < 0.01$) (Fig. 4). The upper part of the range of both PEP/LVET and PEP index was partially occupied by diabetics in left ventricular failure.

The isovolumic relaxation time was 75 ±21 (normal 58 ±9, $p < 0.001$) and 48 per cent of the sample was outside 2 SD from normal (greater than

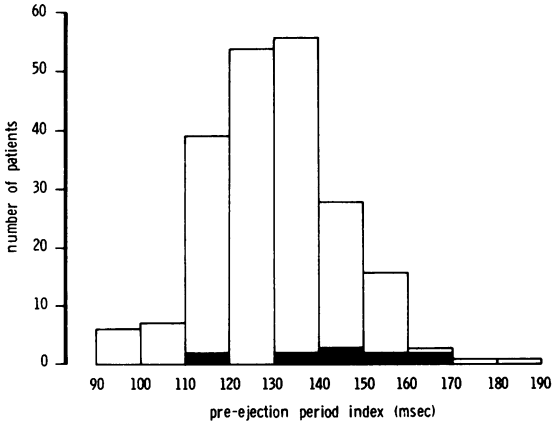

Fig. 4 *Frequency distribution of pre-ejection period index. The shaded areas represent patients with heart failure.*

76 ms) (Fig. 5). The interval from minimal dimension to mitral valve opening was 32 ±34 ms (normal 12 ±3 ms, $p < 0.001$) and 54 per cent of the sample was outside 2 SD from normal (greater than 18 ms) (Fig. 6).

Left ventricular dimensions were normal in all subjects without clinical heart failure. In the 11 diabetics in heart failure, diastolic dimension (53 ±9 mm), systolic dimension (42 ±9 mm), and fractional shortening (21 ±7%) were all significantly different from normal ($p < 0.001$).

(2) DIABETICS V SUBJECTS WITH ANGINA (Table 1B)

In 184 (87%) diabetic subjects aortic valve closure preceded minimal left ventricular dimension and in 179 (84%) this was within 2 SD from normal (−46 ±12 ms): of the 34 (16%) who were abnormal, 18 had angina of exertion. Sixty per cent of diabetic patients had no dimension change during the isovolumic phase and in 182 (86%) the change was less than 2 SD from normal. The 18 diabetics with angina of exertion had a dimension change of 21 ±17 per cent which was significantly different from the non-anginal diabetics (4 ±3%, $p < 0.001$) and similar to the anginal control group (16 ±11%) (Table 1B). Sixteen diabetics who were free from chest pain showed both a disturbed relation of aortic valve closure to minimal dimension and significant dimension change during isovolumic relaxation.

During the study period four diabetics were admitted to hospital with a definite myocardial infarction. One woman had previously had angina and all four had shown incoordinate relaxation and abnormal systolic time intervals.

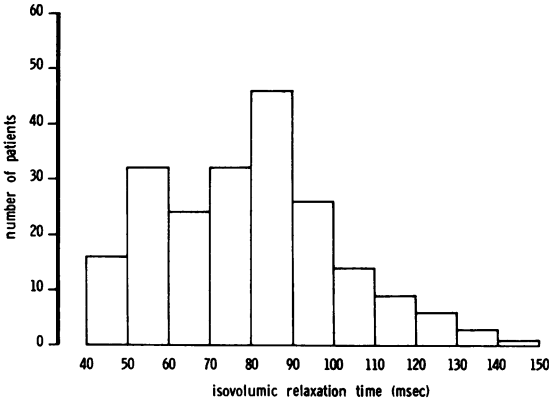

Fig. 5 *Frequency distribution of the isovolumic relaxation time.*

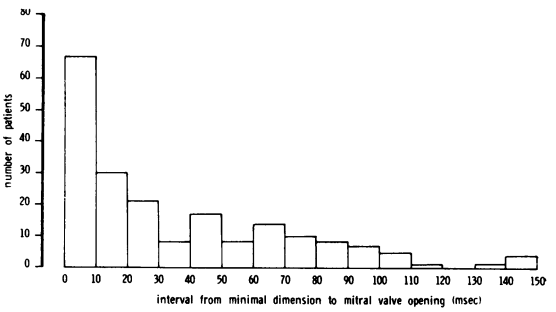

Fig. 6 *Frequency distribution of the interval from minimal dimension to mitral opening.*

Table *Measurements of left ventricular function in diabetic patients and control subjects*

	No.	*Beat-to-beat variation*	*PEP/LVET* (%)	*PEP index* (ms)	*Isovolumic relaxation time* (ms)	*Minimal dimension to mitral valve opening* (ms)	*Diastolic dimension* (mm)	*Systolic dimension* (mm)	*Fractional shortening* (%)	*Dimension change during isovolumic period* (%)	*Diastolic wall thickness* (mm)	*Septal thickness* (mm)
(A) Subjects with no heart disease												
Diabetics	185	13 ±10	35 ±8	129 ±15	75 ±21	32 ±34	45 ±4	28 ±4	37 ±8	4 ±3	8 ±4	9 ±3
Non-diabetics	50	27 ±14*	31 ±4*	124 ±10*	58 ±9*	12 ±3*	45 ±3	29 ±5	36 ±4	1 ±3	8 ±1	8 ±3
(B) Subjects with angina												
Diabetics	18	11 ±9	38 ±12	130 ±22	84 ±21	90 ±35	43 ±6	29 ±7	33 ±8	21 ±17	8 ±2	8 ±3
Non-diabetics	25	24 ±10*	34 ±6	126 ±8	75 ±23	74 ±15	44 ±4	28 ±6	36 ±7	16 ±11	8 ±3	8 ±3
(C) Diabetic subjects												
Normotension	194	12 ±9	34 ±6	127 ±14	75 ±21	31 ±35	44 ±6	29 ±6	36 ±8	5 ±9	8 ±3	9 ±3
Hypertension	18	8 ±8	44 ±9*	145 ±18**	82 ±18	43 ±35	49 ±9	36 ±9**	27 ±10**	7 ±17	11 ±3**	11 ±3
(D) Diabetic subjects												
Insulin-dependent	108	11 ±10	36 ±6	130 ±19	82 ±24	39 ±30	44 ±6	29 ±4	34 ±8	4 ±7	8 ±3	9 ±3
Non-insulin-dependent	104	14 ±11	34 ±7	126 ±14	70 ±19**	27 ±32	45 ±5	29 ±5	36 ±7	6 ±6	8 ±3	8 ±3

Differences between groups: *$p < 0.001$; **$p < 0.01$.

(3) NORMOTENSIVE V HYPERTENSIVE DIABETICS (Table 1C)
Diabetics with a diastolic blood pressure below 99 mmHg (normotensive) and between 100 and 125 mmHg (hypertensive) were compared. All normotensive diabetics had normal posterior wall and interventricular septal thickness regardless of the presence of diabetic complications, angina, or heart failure. Hypertensive diabetics (n=18) were older, 50 ±9 compared with 43 ±12 years, and had greater posterior wall and interventricular septal thicknesses. The hypertensive group contained five and the normotensive group six of the patients with heart failure. Because 28 per cent of the hypertensives were in heart failure as a group they showed significantly enlarged left ventricular dimensions, reduced fractional shortening, and abnormal systolic time intervals.

(4) INSULIN-DEPENDENT V NON-INSULIN DEPENDENT DIABETICS (Table 1D)
Comparison of diabetics who at the time of investigation required insulin (n=108) with those taking oral hypoglycaemic agents or diet (n=104) shows that the former was a younger group (39 ±7 compared with 48 ±10 years) and tended to have more abnormal function, but only the isovolumic relaxation time and interval from minimum dimension to mitral valve opening reached significant values (both $p < 0.01$).

Discussion

To determine the prevalence of a disorder or its complications it is necessary to examine a representative sample of the population likely to be affected. Hospital clinics often do not reflect the prevalence and type of disorder in the community. Mild and borderline diabetics are the most common type[10] and often remain undiagnosed for long periods or are treated by general practitioners. Diabetic clinics tend to have a preponderance of insulin-dependent diabetics, those with complications, and those recently diagnosed. A study of the left ventricular function in the latter group has previously been reported.[11]

From a total of 473 patients 212 were investigated; though the former figure represented the majority of the clinic we do not know how our sample compared with a diabetic population in the community. Therefore, the incidence of complications and abnormalities of left ventricular function reflects a diabetic clinic population and the results might be different if based on a community study.

We found a very high prevalence of abnormalities of left ventricular function, especially in diastole. The most common abnormality was delay in mitral valve opening relative to aortic valve closure and/or minimal dimension. The frequency distributions were positively skewed and in 85 (40%) of the diabetics both values were prolonged. These are non-specific abnormalities and have been described in various disorders of impaired left ventricular function including hypertension[12] and coronary artery disease.[12 13] Similarly, abnormal systolic time intervals, either a raised PEP/LVET and/or prolonged PEP index, suggested impaired ejection[14] but did not define a cause.

In a previous study[11] we showed that it was possible to differentiate patients with impaired left ventricular function caused by coronary artery disease and by diabetes (in some patients with coronary artery disease, left ventricular function may be normal[13]). The patchy nature of coronary atherosclerosis renders some segments of the myocardium ischaemic which move paradoxically and leaves others well perfused which move normally. The synchronous mechanism of left ventricular contraction and relaxation is lost and this disturbs the normal relations of the isovolumic period, where aortic valve closure precedes minimal dimension by 40 to 50 ms and there is no dimension change before mitral valve opening.[12 14] In the anginal groups (both controls and diabetics) minimal dimension occurred early (around the time of aortic valve closure) and the dimension change during the isovolumic period was the result of a change of shape, not of volume, before the mitral valve opened. Sixteen asymptomatic diabetics showed incoordinate relaxation. The absence of chest pain may have been the result of visceral neuropathy, and they were assumed to have asymptomatic but significant coronary artery disease. This was supported by the subsequent course of four patients who suffered a myocardial infarction.

We have shown previously that covert heart disease, as determined by abnormal left ventricular function, is common among newly diagnosed, maturity-onset diabetics.[11] In the present sample of established diabetics, the high incidence of heart disease was confirmed. Clinical disease occurred in 13 per cent and seriously disturbed left ventricular function in 30 per cent. As 21 patients with myocardial infarction were excluded and the methods used were insensitive in the detection of coronary artery disease, this was probably an underestimate of the true prevalence of heart disease. It is not possible, however, to compare its occurrence with that in the controls as they were selected to be normal.

Necropsy studies[15 16] of diabetic patients with severe complications and heart failure show myo-

cardial hypertrophy and increased heart weights. In 194 of our normotensive diabetics there was no increase in posterior wall or interventricular septal thickness, regardless of the degree of impairment of left ventricular function. In 18 diabetics with a diastolic blood pressure between 100 and 125 mmHg there was a modest increase in wall thickness. This group contained five of the 11 patients with heart failure; therefore as a group they showed increased left ventricular dimensions and reduced fractional shortening. This suggests that myocardial involvement in diabetes is non-hypertrophic, that myocardial hypertrophy is primarily associated with hypertension, and that in our sample left ventricular failure was frequently associated with both severe microvascular complications and hypertension.[17]

Impaired left ventricular function was not confined to insulin-dependent diabetics but was relatively more common than in non-insulin-dependent patients. This may be a result of the dissimilar composition of the groups; the insulin-dependent diabetics included proportionately more young patients and those with severe complications, and the non-insulin-dependent patients predominantly middle-aged subjects.

There is good evidence from this and other studies[1–6 11] that left ventricular function in diabetes is frequently abnormal. This is not unexpected as there is both accelerated extra- and intramural coronary artery atherosclerosis,[18] and arteriolar[15 16] and capillary[19] involvement by diabetic microvascular disease. Scar formation from myocardial infarctions which may be painless, and diffuse fibrosis[20] from the generalised ischaemia related to small vessel involvement could impair left ventricular function. In diabetes blood viscosity,[21] platelet adhesion,[22] and erythrocyte deformability[23] are abnormal; these rheological disturbances may reduce local tissue perfusion and further compromise the coronary circulation. A spectrum of abnormality of left ventricular function exists in diabetes ranging from the normal, to incoordinate or delayed relaxation, to heart failure. Whether they are the result of one disorder with a common aetiology or of unrelated disorders with differing pathogenesis is unknown, though it seems likely that they are multifactorial. The role of impaired left ventricular function in the increased morbidity and mortality from heart disease in diabetes is unknown but it may make an important contribution.

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