Prospective study of heart disease in untreated maturity onset diabetics

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SUMMARY Frequent abnormalities of left ventricular function were demonstrated by systolic time intervals and M-mode echocardiography in 69 maturity onset diabetics without clinical heart disease before and during standard hypoglycaemic treatment.

The response of the ratio of pre-ejection period (PEP) to left ventricular ejection time (LVET) during the first two months of treatment identified two groups of patients. Group A had a normal or slightly raised ratio which fell with treatment. In group B the ratio was significantly higher and did not change even after four months treatment. The change in group A was thought to be a result of the improvement in blood glucose, as the correlation between the random blood glucose before treatment and PEP/LVET ratio was lost with reduction of hyperglycaemia. The persistently raised PEP/LVET in group B suggested significant left ventricular dysfunction.

Abnormalities of the diastolic closure rate and isovolumic relaxation time were frequently detected and in only nine of 69 patients were both within 2 SD from normal. They were more pronounced in group B and were significantly different from group A and normal subjects.

Group B could be subdivided into six patients (group B1) with outward wall motion in isovolumic relaxation and delayed aortic valve closure caused by incoordination and nine (group B2) who did not show these changes. An exercise electrocardiogram was positive in two of five group B1 patients and negative in the seven tested in group B2. Three patients in group B2 and one in group A had clinically apparent diabetic microvascular disease.

Coronary artery disease was common and seven patients (six in group B1 and one in group A) demonstrated left ventricular wall dyskinesis in the absence of symptoms; 11 of the original group of 110 were excluded because of symptomatic disease. A smaller group had slow ejection and relaxation, probably a result of increased left ventricular stiffness from myocardial involvement by diabetic microvascular disease.

Cardiovascular disease is a major cause of morbidity and mortality in patients with maturity onset diabetes.1 2 Coronary artery disease is common1 but diabetics can develop abnormalities of myocardial function with patent main coronary arteries,3 4 which may progress to cardiomyopathy and chronic heart failure. This may be part of the generalised microvascular disease which causes retinopathy, neuropathy, and nephropathy.5 9 Histological studies of myocardium have shown that abnormalities of small vessels6 8 and capillary basement membrane10 are common. No information is available on whether the duration of diabetes is important in the development of left ventricular dysfunction and chronic heart failure or if the progression of heart disease can be influenced by hypoglycaemic therapy.

Systolic left ventricular function can be measured by systolic time intervals and M-mode echocardiographic indices of ejection. Abnormalities of these have been shown in both diabetics without clinical heart disease7 8 (especially those with proliferative retinopathy and nephropathy) and patients with coronary artery disease,13 in whom it indicates a poor prognosis.13 Changes in systolic time intervals have been noted with treatment of recently diagnosed diabetics.14 Diastolic left ventricular function
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can be evaluated by measuring the time relations of various events in the cardiac cycle (aortic valve closure, mitral valve opening, and minimal dimension) and the associated left ventricular wall motion. Disturbed ventricular filling in young asymptomatic diabetics and patients with hypertension can be differentiated from the segmental abnormalities which are the cause of impaired left ventricular function in coronary artery disease.

This study was designed to investigate by simple non-invasive methods untreated maturity onset diabetics to determine the prevalence of left ventricular dysfunction and whether it is influenced by standard hypoglycaemic therapy and can be differentiated from coronary artery disease.

Patients

Consecutive patients between 30 and 65 years who presented to the Dudley Road Hospital Diabetic Clinic with clinical symptoms of diabetes and a random blood glucose greater than 11.1 mmol/l, a fasting glucose greater than 6.1 mmol/l, or a blood glucose greater than 11.1 mmol/l two hours after a 50 g oral glucose tolerance test and who had received no hypoglycaemic therapy previously were considered for inclusion in the study.

Initial assessment included clinical examination, electrocardiogram, chest radiography, and routine biochemistry (urea and electrolytes, liver function tests, and cholesterol), and patients with the following conditions were excluded:

1. Coronary artery disease, that is angina of effort or previous myocardial infarction. Resting electrocardiographic abnormalities suggestive of ischaemic heart disease including infarction, bundle-branch block, and ST segment abnormalities.

2. Presence of a disease known to influence left ventricular function (thyroid disease, alcoholism, hypertrophic obstructive cardiomyopathy, and hypertension (BP > 145/95 mmHg)).

3. Chronic heart failure, clinical heart disease (peripheral oedema, gallop rhythm, auscultatory abnormalities), and a cardiothoracic ratio > 55 per cent or other chest x-ray abnormalities.

4. Peripheral vascular disease.

5. Heavy cigarette smokers > 20/day.

6. Hypercholesterolaemia (serum cholesterol > 7.0 mmol/l).

Methods

Systolic time intervals were obtained (after Weissler et al.17) in the early afternoon on a Cambridge multichannel photographic recorder at speed 100 mm/s. The Q - A2 (time interval from Q wave of the electrocardiogram to the onset of the aortic second heart sound) and left ventricular ejection time (LVET) were measured in ms (Fig. 1) and the following were derived:

Pre-ejection period (PEP) = (Q - A2) - LVET
and ratio of PEP/LVET

The latter ratio was used and not the heart rate corrected indices because of the wide range of resting heart rates in the diabetic subjects.

Echophonocardiography was performed with simultaneous electrocardiogram (standard lead II) in the partial left lateral position using an Ekoline SK20 Ultrasonoscope at paper speed 100 mm/s. The early diastolic closure rate was determined in mm/s from the slope E - Fo of the mitral valve at its point of maximal excursion. The isovolumic relaxation time was determined in ms from the
onset of the aortic sound to the point of rapid anterior motion of the anterior mitral valve cusp. Left ventricular dimensions in diastole (DD) (at R wave of electrocardiogram), minimal dimension (DS), and at the point of mitral valve opening were determined. The time interval between the aortic second sound and minimal dimension was measured (Fig. 2). The following were derived:

\[
\% \text{ fractional shortening} = \frac{DD - DS}{DD} \times 100
\]

\[
\% \text{ dimension change during isovolumic period} = \frac{\text{dimension at mitral valve opening} - DS}{DD - DS} \times 100
\]

When required, a continuous multistage exercise electrocardiogram was performed using a graded bicycle ergometer with an initial workload of 300 kpm/min rising by increments of 300 kpm at three minute intervals. The electrocardiogram was continuously monitored and sampled at three minute intervals until 85 per cent predicted maximal heart rate was achieved, and during nine minutes rest.

All patients while on treatment had a reassess-

ment of clinical features, blood glucose, electrocardiogram, and systolic time intervals at approximately two months, and a selected group at four months.

Echocardiography and the determination of systolic time intervals were also performed in two age- and sex-matched control groups (Table 1): (1) 50 normal subjects; (2) 25 patients with typical angina of effort without clinical or electrocardiographic evidence of myocardial infarction or cardiomegaly on radiography.

The echocardiograms and systolic time intervals were numerically coded by an independent observer and interpreted blind by LMS.

Pearson's correlation coefficient and paired and Student's t tests were used to analyse the differences between the incremental and prevalence scores.

Results

One-hundred-and-ten patients presented during the course of the study of whom 41 were excluded (11 with coronary artery disease, nine with hypertension, three with peripheral vascular disease, four with previous thyroid disease, three heavy smokers, one with acromegaly, one with chronic heart failure, eight poor echocardiographic quality, and one with a calcified bicuspid aortic valve). Among those included in the study, two patients had background retinopathy, one had significant proteinuria, and one had a sensory peripheral neuropathy. The values quoted are mean ± one standard deviation.

In the untreated group PEP/LVET (0.36 ± 0.06) was significantly different from the normal subjects (0.31 ± 0.004, p < 0.001). The wide range (0.26–0.50) of values correlated with the random blood glucose (Fig. 3) (r = ±0.72 p < 0.001). After two months of treatment the correlation coefficient fell to 0.36 (not significant) with a reduction in blood glucose values.

The distribution of PEP/LVET values before treatment was slightly positively skewed. Though there was only an insignificant change of PEP/ LVET ratio in the total group (0.36 ± 0.09 to 0.34 ± 0.07) during initial treatment, a bimodal distribution within the sample became evident and

Table 1  Age and sex of groups (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>All untreated diabetics</th>
<th>Group A</th>
<th>Group B</th>
<th>Normal</th>
<th>Angina</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=69</td>
<td>n=54</td>
<td>n=15</td>
<td>n=50</td>
<td>n=25</td>
</tr>
<tr>
<td>Age (y)</td>
<td>54 ± 5</td>
<td>55 ± 3</td>
<td>53 ± 2</td>
<td>56 ± 3</td>
<td>58 ± 4</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>37</td>
<td>29</td>
<td>8</td>
<td>30</td>
<td>14</td>
</tr>
<tr>
<td>M</td>
<td>32</td>
<td>25</td>
<td>7</td>
<td>20</td>
<td>11</td>
</tr>
</tbody>
</table>

Fig. 2  Left ventricular echocardiogram of normal subject with simultaneous electrocardiogram (ECG) and phonocardiogram (PCG). DD, diastolic dimension; DS, systolic dimension; DMVO, dimension at mitral valve opening; Y, isovolumic relaxation time; X, interval from aortic second sound to minimal dimension.
identified two subgroups of patients with no overlap of values, designated groups A and B. Group A (n=54) had a PEP/LVET ratio either within the range of the control group or which became normal at the two month review (pretreatment 0.34 ±0.04 and review 0.30 ±0.02); the change is significant (p<0.01). Group B (n=15) had a higher pretreatment PEP/LVET ratio which did not significantly change with treatment (pretreatment 0.43 ±0.04, review 0.46 ±0.02). Both values were significantly different from the control group and group A (p<0.001). After four months’ treatment the PEP/LVET ratios were unchanged (0.45 ±0.03) (Fig. 4). The diastolic closure rate was reduced in 42 of 69 of the diabetic patients (more than 2 SD from normal) and the isovolumic relaxation time was prolonged in 58 of 69; both were significantly different from normal (p<0.001) and there was no change with treatment. The diastolic closure rate and isovolumic relaxation time were significantly different in groups A and B (p<0.001) (Table 2). It was possible to subdivide group B into those with a significant dimension change during isovolumic relaxation and associated delayed aortic valve closure, group B₁ (n=6), and those without, group B₂ (n=9) (Table 3). One patient in group A demonstrated significant dimension change.

The left ventricular dimensions and fractional shortening were normal in all but five patients. In three (one each in groups A, B₁, and B₂) the diastolic dimension was greater than 60 mm (2 SD from normal); in the patient in group B₁ there was reverse septal motion and reduced fractional shortening. Two other patients showed a reduction in fractional shortening from the normal of 33 ±5 per cent to 14 per cent (patient in group B₂) and 16 per cent (patient in group A).

Resting electrocardiographic abnormalities were present in ten patients: five had a mean frontal plane QRS axis greater than minus 30 degrees (two patients in B₁, three in A), one patient in B₁ had poor progression of praeordial R waves, and four had inferior or lateral lead T wave inversion (two in A, one each in B₁ and B₂).

An exercise electrocardiogram was performed on 12 group B patients four months after presentation; none developed chest pain but two showed 2 mm ST depression in the lateral leads after achieving 85 per cent of the maximal predicted heart rate; both were in subgroup B₁.

A significant fall in blood glucose (p<0.001) and relief of diabetic symptoms was achieved in both groups by treatment. Initial random blood glucose in group B (14 ±3 mmol/l) was greater than group A (11 ±0 mmol/l, p<0.05) but there was no difference at review (9 ±3 and 8 ±2 mmol/l, respectively). A similar proportion of group A (28 of 54) and group B (eight of 15) were assigned to oral hypoglycaemic agents, there was one patient on insulin in each group and the remainder required diet alone. Group B₂ contained all patients with clinically apparent microvascular disease except one with proteinuria who was in group A.

Discussion

Approximately three-quarters of diabetics in Great Britain are of maturity onset type and diabetes affects at least 1 per cent of the population. Heart
Table 2  Systolic time intervals, diastolic closure rate, and isovolumic relaxation time in control and diabetic groups (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal n=50</td>
<td>Angina n=25</td>
</tr>
<tr>
<td></td>
<td>Pre- treatment</td>
<td>Post- treatment</td>
</tr>
<tr>
<td>PEP/LVET (ms)</td>
<td>0.31 ± 0.004</td>
<td>0.34 ± 0.06</td>
</tr>
<tr>
<td>Diastolic closure rate (mm/s)</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Isovolumic relaxation time (ms)</td>
<td>58 ± 9</td>
<td>75 ± 23</td>
</tr>
</tbody>
</table>

a. Difference from normal, p < 0.001.  b. Difference pre- and post-treatment in group A, p < 0.01.  c. Difference from angina group, p < 0.001.  d. Difference between groups A and B, p < 0.001.  e. Difference from normal, p < 0.01.  f. Difference from angina group, p < 0.01.

disease is a major cause of morbidity and mortality in this group. We have studied 69 maturity onset diabetics before and during treatment and have shown frequent abnormalities of left ventricular function by non-invasive techniques.

Systolic time intervals are a non-specific indicator of left ventricular systolic function. The response of PEP/LVET identified two groups of patients: in group A PEP/LVET was slightly raised or normal and fell with treatment, in group B it was significantly higher at presentation and did not change. These results confirm the presence of abnormal systolic time intervals previously reported in diabetics before and during initial treatment, but the specific changes were different from the latter study probably because of the dissimilar sample investigated. Though unexpected because of the wide daily fluctuations in blood glucose, the correlation between the PEP/LVET and random blood glucose before treatment indicates a relation between the degree of glucose intolerance and left ventricular dysfunction particularly as it was lost with treatment. We suggest the changes in group A are directly the result of the metabolic effects of hyperglycaemia and are similar to the improvements in abnormal motor conduction velocities and platelet function that have been noted with the initial control of diabetes. The persistently raised PEP/LVET in group B is evidence of significant left ventricular dysfunction which was confirmed by analysis of the diastolic function.

The diastolic closure rate and isovolumic relaxation time have a complex underlying mechanism and show the presence of a non-specific abnormality in early diastole related to filling and relaxation; they are abnormal in many conditions which affect the left ventricle, such as coronary artery disease, hypertrophic obstructive cardiomyopathy, and hypertension. We demonstrated a correlation between these variables (r = -0.73, p < 0.001) in the wide range of values. Group B was significantly different from group A and the normals (p < 0.001) which confirms the presence of abnormal left ventricular diastolic function.

Coronary artery disease usually produced abnormalities of left ventricular function because of the segmental nature of myocardial ischaemia. Contraction loses its co-ordinate mechanism and

Table 3  Diastolic abnormalities in untreated maturity onset diabetes (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Normal n=50</th>
<th>Angina n=25</th>
<th>Group A n=54</th>
<th>Group B n=15</th>
<th>Group B1 n=6</th>
<th>Group B2 n=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relation of aortic valve closure to minimal dimension (ms)</td>
<td>-40 ± 12</td>
<td>a</td>
<td>a, b</td>
<td>a</td>
<td>a</td>
<td>c, d</td>
</tr>
<tr>
<td>Outward wall motion in isovolumic period as percentage total dimension change</td>
<td>0</td>
<td>16 ± 11</td>
<td>7 ± 12</td>
<td>12 ± 15</td>
<td>25 ± 7</td>
<td>4 ± 2</td>
</tr>
</tbody>
</table>

a. Difference from normal, p < 0.001.  b. Difference from angina, p < 0.01.  c. Difference from angina, p < 0.001.  d. Difference group B1 from B2, p < 0.001.

* If negative aortic valve closure precedes minimal left ventricular dimension.
this delays aortic valve closure to the time of minimal left ventricular dimension, prolongs the PEP (index), and increases PEP/LVET. A similar incoordinate mechanism in diastole produces a dimension change between minimal left ventricular dimension and the delayed mitral valve opening and, though specific, is an insensitive method of detecting coronary artery disease. Significant outward motion with delayed aortic valve closure was seen in group B, and in one patient in group A. Patients in group B also had persistently abnormal PEP/LVET and one had reverse septal motion and reduced fractional shortening. There were resting electrocardiographic abnormalities in four, and in two of the five patients tested there was lateral ST depression on an exercise electrocardiogram. There seems no doubt that this group has asymptomatic coronary artery disease and the abnormalities are a result of left ventricular wall dyskinesis; this fairly gross form of coronary artery disease probably indicates a poor prognosis. The absence of a history of angina or myocardial infarction tends to corroborate the epidemiological and necropsy evidence which suggests that diabetics have a high incidence of unreported myocardial infarctions.

In contrast, group B2 had similar abnormalities of PEP/LVET, diastolic closure rate, and isovolumic relaxation time but aortic valve closure always preceded minimal left ventricular dimension, and though mitral valve opening was delayed there was no outward wall motion. These abnormalities, which are similar to those described in hypertension and young diabetics, are significantly different from group B1 and the anginal control group. Thus the patients in group B2 demonstrated slow ejection and relaxation without the incoordination associated with coronary artery disease. This diffuse left ventricular involvement was present in 13 per cent (nine of 69) of maturity onset diabetics at presentation and was not influenced by hypoglycaemic treatment. It is not possible to exclude the presence of coronary artery disease without coronary arteriography which we could not ethically justify, but seven of the group were exercise tested and none had a positive test. Myocardial histology in diabetics often shows extravascular connective tissue infiltration and small vessel abnormalities as a manifestation of microvascular disease. These abnormalities would be expected to increase left ventricular stiffness and produce the slow ejection and relaxation that we have shown. Three of the nine patients had clinically obvious microvascular disease, and it is well known that microvascular disease can be detected by fluorescein angiography and renal biopsy in the absence of clinical evidence of disease. It seems likely that the abnormalities in group B2 are a result of myocardial involvement by diabetic microvascular disease.

Diastolic abnormalities were more frequent than those in systole, and 60 of 69 patients had either the diastolic closure rate or isovolumic relaxation time outside two standard deviations from the normal. There is a spectrum of abnormality from slight prolongation of isovolumic relaxation time and reduced diastolic closure rate with normal wall motion to the more pronounced abnormalities suggestive of coronary artery disease and asymptomatic cardiomyopathy. Whether the diastolic abnormalities in group A which are at the lower end of the range are the result of either or both of these disease processes is speculative, but there was no clear differentiation between the two groups and in only one patient was there any evidence of incoordinate relaxation. Maturity onset diabetes often has an insidious onset with persistent hyperglycaemia and this is a risk factor for coronary artery disease, but the patients were selected because of normal serum cholesterol and blood pressure and moderate smoking habits, and though there were seven patients with asymptomatic coronary artery disease the probability of significant coronary artery disease in group A is low in the absence of clinical symptoms. Therefore many diabetics may have lesser degrees of myocardial involvement of the type discussed above.

We have shown a range of abnormalities of left ventricular function in diabetics at presentation. Incoordinate left ventricular function was detected in seven and there was symptomatic coronary artery disease in 11 of the original sample. Therefore coronary artery disease occurred frequently, i.e. 16 per cent or 18 of 110, of whom seven had no chest pain, and as incoordination, clinical history, and resting electrocardiogram are insensitive methods of detecting coronary artery disease, this is an underestimate of its true incidence and emphasises the frequent association of diabetes and coronary artery disease. Group A showed frequent non-specific diastolic abnormalities, the cause of which is unknown. Nine patients had diffuse left ventricular disease with slow ejection and relaxation with no evidence of coronary artery disease, which is suggestive of a myopathic process related to diabetic microvascular disease. Long-term follow-up is in progress to determine the prognosis of group B1 patients and whether group B2 patients will develop clinically apparent microvascular disease earlier than other patients or progress to chronic heart failure as predicted from the Framingham study.
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Requests for reprints to Dr L M Shapiro, Department of Cardiology, Dudley Road Hospital, Birmingham B18 7QH.

References
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