Cardiac function and coronary arteriography in asymptomatic Type 1 (insulin-dependent) diabetic patients: evidence for a specific diabetic heart disease

B. M. Fisher¹, G. Gillen³, G. B. M. Lindop⁴, H. J. Dargie² and B. M. Frier¹

Departments of ¹ Diabetes, ² Cardiology, ³ Clinical Physics and ⁴ Pathology, Western Infirmary and Gartnavel General Hospital, Glasgow, Scotland, UK

Summary. Cardiac function was examined in 63 asymptomatic Type 1 (insulin-dependent) diabetic patients, aged 30–50 years, using radionuclide ventriculography and exercise electrocardiography to investigate the possible existence of a specific diabetic heart disease. Comparisons were made with 45 age- and sex-matched non-diabetic controls. Radionuclide ventriculography was performed at rest and during the physiological stresses of isometric exercise, cold-pressor testing and dynamic exercise. Scans were technically satisfactory in 56 of the diabetic patients and 38 of the control subjects. The resting left ventricular ejection fractions and the responses to isometric exercise and cold-pressor testing were similar in the diabetic patients and controls. A smaller rise in the left ventricular ejection fraction during dynamic exercise was observed in male diabetic patients compared with male control subjects ($9 \pm 1\%$ (mean $\pm$ SEM) vs $14 \pm 1\%$ ($p < 0.005$)). A similar trend was observed in female diabetic patients,

with a rise of $5 \pm 1\%$ on dynamic exercise compared with a rise of $8 \pm 1\%$ in the control group. Sixteen diabetic patients (29%) demonstrated an abnormal response to dynamic exercise, and 5 of these had an abnormal exercise electrocardiogram. Cardiac catheterisation and coronary arteriography were performed in eight of these 16 patients, and all 8 had normal coronary arteries. Endomyocardial biopsy revealed arteriolar thickening and interstitial fibrosis in 5 patients, and in 2 patients basement membrane thickening was conspicuous. Thus, in diabetic patients cardiac function may be abnormal without evidence of coronary heart disease, and some patients appear to have the histological changes consistent with a diabetic microangiopathy involving the heart.

Key words: Diabetic heart disease, radionuclide ventriculography, coronary arteriography, endomyocardial biopsy, diabetic microangiopathy.

Cardiovascular disease is the most common cause of death in patients with diabetes mellitus over the age of 30 years [1]. Variable evidence has implied the existence of a specific cardiac disease of diabetes [2–5], termed variously as “diabetic cardiopathy” [3] or “diabetic cardiomyopathy” [2, 5], which might contribute to the increased mortality of diabetes. This evidence has accumulated from non-invasive cardiac testing and has incorporated pathological abnormalities, mainly from post-mortem material. The cardiac function of young Type 1 (insulin-dependent) diabetic patients aged less than 30 years is similar to that of non-diabetic subjects when assessed by radionuclide ventriculography [6]. The left ventricular function of asymptomatic, middle-aged Type 1 diabetic patients has now been compared with asymptomatic non-diabetic subjects using the same technique. Because the cardiac responses to the applied physiological stresses of males and females may differ [7], the responses of each sex have been examined separately. Invasive studies were undertaken to ex-

amine the possible pathophysiological causes of the abnormal function in some patients in whom abnormal cardiac function was demonstrated initially by non-invasive investigation. Coronary arteriography and endomyocardial biopsy permitted an examination of the relative contribution of asymptomatic coronary heart disease and microangiopathy to functional abnormalities of the diabetic heart.

Subjects and methods

The study was approved by the local Medical Ethical Committee, and was performed in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants.

A group of 63 patients (35 male, 28 female) with Type 1 diabetes, aged between 30 and 50 years (Table 1), was recruited at random from the Diabetic Clinic at Gartnavel General Hospital, Glasgow, and comprised a representative population of this age group attending the clinic. The duration of diabetes ranged from 6–26 years for males, and from 8–28 years for females. No patient complained of chest pain, exertional dyspnoea, palpitations, ankle swelling or any other symptom

Table 1. Clinical details of Type 1 diabetic patients and normal subjects

	Male		Female	
	Diabetic patients (n=35)	Control subjects (n=25)	Diabetic patients (n=28)	Control subjects (n=20)
Age (years) (mean $\pm$ SD)	40 $\pm$ 5	41 $\pm$ 4	43 $\pm$ 5	44 $\pm$ 4
Duration of diabetes (years) (mean $\pm$ SD)	17 $\pm$ 6	–	18 $\pm$ 5	–
Total insulin dose (U/day) (mean $\pm$ SD)	52 $\pm$ 17	–	42 $\pm$ 11	–
Glycosylated haemoglobin (%) (mean $\pm$ SEM)	9.7 $\pm$ 0.2	6.2 $\pm$ 0.1	10.1 $\pm$ 0.4	6.0 $\pm$ 0.2

of cardiac disease, and all patients had a normal body mass index. Hypertensive patients were not studied, thus excluding two patients in whom hypertension was undiagnosed previously (diastolic blood pressure >95 mmHg) and 9 patients with treated hypertension. One patient with treated thyrotoxicosis was excluded, and no patient was studied within 3 months of diabetic ketoacidosis to avoid any effect of severe metabolic disturbance on cardiac function. Glycosylated haemoglobin (HbA_{1c}) was measured by gel electrophoresis, the upper limit of normal for our laboratory being 8%. Values less than 10% were assumed to indicate reasonable glycaemic control in diabetic patients, but various degrees of glycaemic control were represented within the diabetic group.

Autonomic neural function was assessed by the heart rate responses to the Valsalva manoeuvre, to deep breathing and to standing, and by the blood pressure responses to standing and isometric exercise [8]. Ophthalmological evaluation was performed by a single observer within 3 months of the cardiac assessment. After dilatation of the pupils, the fundi were examined by both direct and indirect ophthalmoscopy, fundal colour photographs were taken, and fluorescein angiography was performed. The fundal appearances for each eye were graded according to a modification of the method described by Dahl Jorgensen et al. [9]: Grade 1 – no retinopathy; Grade 2 – 1–3 microaneurysms per fundus; Grade 3 – >3 microaneurysms or haemorrhages or both; Grade 4 – hard exudates; Grade 5 – capillary shutdown, vessel wall staining, cotton wool spots (i.e. signs of pre-proliferative retinopathy); Grade 6 – new vessels, or previous photo-coagulation. Six patients declined detailed ophthalmological assessment other than ophthalmoscopy.

Renal function was assessed by testing urine with Albustix. In Albustix-negative patients, excretion of albumin was measured on a timed 24 hour collection of urine. Albumin was assayed with a competitive binding radioimmunoassay using a liquid-phase second antibody separation. The detection limit of the assay is 20 μ g/l. The intra-assay coefficient of variation is 7.2% and the inter-assay coefficient of variation is 8.4% across the working range. We were unable to assess renal function by this method in six patients who declined further assessment. The renal function was then graded as follows: Grade 1 – no nephropathy; Grade 2 – microalbuminuria (albumin excretion >27 mg/24 h); Grade 3 – Albustix positive proteinuria.

The control group comprised 45 age- and sex-matched, non-diabetic subjects (25 male, 20 female) recruited from friends and relatives of the patients and from hospital staff (Table 1). The regularity of exercise of the diabetic and control groups were similar. Of the 35 male diabetic patients, 13 were currently cigarette smokers, 5 were pipe smokers, and 2 had stopped smoking within the last 3 years. A positive family history of ischaemic heart disease was obtained in 10 pa-

tients, and fasting hyperlipidaemia (Serum triglyceride >1.8 mmol/l, Serum cholesterol >7.5 mmol/l) was found in 3 patients. Of the 25 male controls, 8 were cigarette smokers with one pipe smoker and one ex-smoker, 8 had a positive family history of ischaemic heart disease, and 1 had hyperlipidaemia. In the female diabetic patient group, 14 of the 28 patients were currently smokers, 14 gave a positive family history, and 2 showed fasting hyperlipidaemia. Similar risk factors for ischaemic heart disease were found in the 20 female control subjects, 10 of whom were currently smokers with a positive family history in 11 subjects and fasting hyperlipidaemia in 3 subjects.

Non-invasive investigation

Exercise electrocardiography and radionuclide ventriculography were performed on consecutive mornings between 09.00 and 11.00 hours. Treadmill exercise electrocardiography was carried out using the Bruce protocol [10] on the Marquette computer-assisted system of exercise (Marquette Electronics Inc, Milwaukee, Wisc, USA), and analyses were performed blindly by two observers. Radionuclide ventriculography was performed using the multiple gated technique with the isotope Technetium 99m. Erythrocytes were labelled *in vivo* by the injection of the isotope 30 min after the intravenous injection of stannous pyrophosphate.

Subjects were studied supine, using the Siemens Lem mobile gamma camera (Siemens Limited, Des Plaines, Ill, USA) which was positioned to give the best separation of the left and right ventricles. This was usually at an angle of 30°–45° in the left anterior oblique position with a 15° cranio-caudal tilt to separate the atria from the ventricles. Data was obtained at a rate of 20 frames/cycle at rest and during the following physiological stresses:

- Isometric exercise* – handgrip exercise using a dynamometer (Tephco-electronics Ltd, Edinburgh, UK) at 30% of maximum voluntary contraction by the dominant hand for 3 min.
- Cold-pressor testing* – immersion of the right hand to the wrist in cold water for 3 min.
- Dynamic exercise* on the bicycle ergometer commencing with 25 watts at 60 rpm and increasing by 25 W increments until exhaustion, with acquisition of data during the last 3 min of exercise.

The left ventricular ejection fraction (LVEF) was determined by standard methods using the formula:

$$\text{LVEF} = \frac{\text{end diastolic counts} - \text{end systolic counts}}{\text{end diastolic counts} - \text{background counts}}.$$

A single fixed region of interest was used. This technique leads to slight underestimation of the ejection fraction, but is more reproducible than using a variable region of interest [11, 12]. The reproducibility for this technique in our laboratory is $r=0.98$. The technique has been validated against contrast angiography in 50 patients, and the correlation coefficient for the comparison of ejection fraction values is 0.88. Regional wall motion was assessed blindly by creating parametric images of regional stroke volume and regional ejection fraction.

Invasive investigation

This was offered to all subjects found to have abnormal function on non-invasive testing. Clinical details and the results of non-invasive investigation of the subgroup of patients who were studied by invasive techniques are shown in Table 2. Informed consent for these procedures was obtained from every subject. Coronary arteriography was performed to determine if the subjects had coronary heart disease which was surgically remedial but asymptomatic. At cardiac catheterisation, left ventriculography and coronary arteriography were performed using the Judkins technique with standard cineangiographic views. Angiographic data were analysed by two independent observ-

Table 2. Clinical characteristics of eight Type 1 diabetic patients investigated by invasive techniques

Age (years)	Sex (M/F)	Duration of diabetes (years)	Complications	Exercise electro-cardiograph	Ejection fraction (%)	
					Rest	Exercise
39	F	13	Background retinopathy (Grade 4)	Normal	55	43
49	F	22	Nil	Abnormal	56	54
46	F	16	Background retinopathy (Grade 4)	Normal	49	42
49	F	33	Background retinopathy (Grade 4)	Normal	46	44
44	F	23	Nil	Normal	42	40
41	F	14	Background retinopathy (Grade 3)	Abnormal	52	50
42	M	18	Proliferative retinopathy (Grade 6), Diabetic nephropathy (Grade 3)	Normal	40	41
42	M	11	Nil	Abnormal	55	57

Fig. 1. Changes in left ventricular ejection fraction during the physiological stresses in male subjects (mean $\pm$ SEM). The difference during dynamic exercise was significant ($p < 0.005$), but no significant differences were present during isometric exercise or cold pressor testing. ■ diabetic patients; □ control subjects **Fig. 2.** Changes in ejection fraction during the physiological stresses in female subjects (mean $\pm$ SEM). None of the differences were statistically significant. ■ diabetic patients; □ control subjects

ers. Endomyocardial biopsy was taken using a Cordis biptome through a 7 F long venous access sheath positioned in the right ventricle under fluoroscopic and pressure control. Typically, biopsies were obtained without difficulty from the septum and body of the right ventricle. No complications occurred during or after these procedures.

Histological methods

A minimum of three biopsies were taken. One was snap-frozen in liquid nitrogen for cryostat sections and the others were fixed in 2% glutaraldehyde. One of these was embedded in Araldite and 1- μ m sections were cut for light microscopy; 90-nm ultrasections were then mounted on grids for electron microscopy. The remaining pieces were embedded in paraffin wax and 2- μ m sections were cut serially through the entire biopsy. All sections were stained with a battery of routine histological stains.

Statistical analysis

Statistical comparisons were made using Student's *t*-test for unpaired data, and results are expressed as mean $\pm$ SEM except where stated otherwise. Associations between diabetic complications, metabolic control and ventricular function were examined by analysis of variance.

Results

Exercise electrocardiography was abnormal in 14 diabetic patients (6 male, 8 female) and in 4 controls (2 male, 2 female), with the development of downsloping or horizontal ST segment depression of 1 mm or more 0.08 s after the onset of the ST segment (J point).

Radionuclide ventriculography: Satisfactory scans were obtained in 56 diabetic patients (32 male, 24 female) and in 38 controls (22 male, 16 female). The resting left ventricular ejection fractions were similar in the male patients and controls, with values of $50 \pm 2\%$ and $47 \pm 2\%$ respectively (NS), and also in the female patients and controls, who had respective values of $50 \pm 2\%$ and $52 \pm 2\%$ (NS). The responses of the ejection fraction to the various physiological stresses are shown in Figures 1 (male subjects) and 2 (female subjects).

During *isometric exercise* the mean left ventricular ejection fraction in male subjects fell by $1 \pm 1\%$ in the diabetic group (range -10% to $+6\%$) and by $2 \pm 1\%$ in the controls (range -12% to $+6\%$) (NS). The mean left ventricular ejection fraction in the female subjects fell by $0.7 \pm 0.7\%$ in the diabetic patients (range -7% to

Fig. 3. An electron micrograph showing a capillary in the right ventricular myocardium. There is a gross excess of basement membrane material in its wall, with obvious reduplication of the basal lamina. Magnification $\times 13,200$

+7%) and by $2 \pm 1\%$ in the controls (range -6% to $+3\%$) (NS).

During *cold-pressor testing* the mean left ventricular ejection fraction in male subjects fell by $0.5 \pm 0.6\%$ in the diabetic patients (range -8% to $+6\%$) and by $0.9 \pm 0.8\%$ in the controls (range -7% to $+5\%$) (NS). In female subjects the mean left ventricular ejection fraction fell by $0.8 \pm 0.8\%$ in the diabetic patients (range -8% to $+8\%$) and by $0.5 \pm 0.6\%$ in the controls (range -5% to $+8\%$) (NS).

On *supine dynamic exercise* the rise in mean left ventricular ejection fraction in male subjects was less in patients than in controls, being $9 \pm 1\%$ in the diabetic group (range $+1$ to $+19\%$) compared with a rise of $14 \pm 1\%$ in the control group (range $+4\%$ to $+24\%$) ($p < 0.005$). In female subjects a similar trend was apparent, with a rise in the diabetic group of $5 \pm 1\%$ (range -12 to $+17\%$), and in the control group of $8 \pm 1\%$ (range -2 to $+17\%$), although this did not achieve statistical significance. No abnormalities of regional wall motion of the heart were observed either at rest or in response to the various physiological stresses in any of the subjects.

A failure to increase the ejection fraction by more than 5% occurred in 9 of the 35 male diabetic patients and in 1 non-diabetic male control. Only 2 of these 9 diabetic males had an abnormal exercise electrocardiogram (ECG). In the 2 groups of female subjects, the ejection fraction increased by less than 5% on dynamic exercise in 11 diabetic patients and in 7 controls. Seven female patients and 2 female controls either demonstrated no change or a fall in ejection fraction on dynamic exercise. Three of these 7 female patients also had an abnormal exercise ECG.

The changes in ejection fraction on dynamic exercise did not correlate with either the duration of diabetes, the glycaemic status as assessed by HbA_{1c} or with the prevailing blood glucose during radionuclide ventriculography. There was no association between the rise in left ventricular ejection fraction and the grade of autonomic neuropathy, retinopathy or nephropathy.

Coronary arteriography and myocardial biopsy

No significant obstructive disease of the coronary arteries was demonstrated in any of the 8 diabetic patients studied by coronary arteriography, nor were any abnormalities observed with left ventricular angiography.

Preliminary histological examination of the endomyocardial biopsies revealed an increase in interstitial fibrous tissue in 3 individual subjects. There was some thickening of the walls of occasional arterioles in 5 patients, one of whom showed early hyalinisation. Electron microscopy showed conspicuous basement membrane thickening with reduplication of the basal lamina in cardiac tissue from 2 subjects (Fig. 3). Detailed measurements are currently being made on the dimensions of basement membrane in specimens from all subjects, and will be described in a subsequent communication when the results are available.

Discussion

The existence of a specific diabetic heart disease, distinct from coronary artery disease, has been suspected for several years, and is supported by some pathological evidence in man [13, 14] and by experimental studies in

animals [15, 16]. The development of safe, non-invasive methods to evaluate cardiac function has allowed a detailed examination of the heart in asymptomatic diabetic patients. Studies have included measurements of systolic time intervals [17–19] and echocardiography [20–23], the results of which have inferred the presence of a “diabetic cardiomyopathy”. However, the changes found in the above studies were non-specific, and could be coronary artery disease. We have shown previously that abnormalities detected by radionuclide ventriculography are uncommon in young Type 1 diabetic patients under 30 years of age [6]. In the present study cardiac investigation was undertaken in an older group of patients, in whom cardiovascular disease is the most common cause of death [1]. Radionuclide ventriculography is an accurate method of assessing cardiac function. In contrast to the measurements of systolic time intervals and echocardiography, where differences can be identified in the mean response of a group but individual abnormalities cannot be identified, radionuclide ventriculography can identify individual patients with abnormal ventricular function. This has allowed a detailed invasive investigation of diabetic patients, confirming that these abnormalities are not associated with coronary heart disease. Furthermore, endomyocardial biopsy in these subjects has enabled a correlation between functional abnormalities, and measurement of pathological changes which have been studied previously only at post-mortem [13, 14].

In the present study the resting ventricular function, and the responses to isometric exercise and to cold-pressor testing in diabetic patients of either sex, did not differ from the control groups. These stress tests have been suggested as an alternative to dynamic exercise to detect both coronary heart disease and congestive cardiomyopathy [24, 25]. However, wide variations in the normal responses to these stimuli have been reported, and the value of stress tests of this type has been challenged [26]. In the present study these particular tests did not demonstrate abnormalities of cardiac function in the diabetic subjects. By contrast, radionuclide ventriculography during dynamic exercise is a sensitive test for the detection of abnormalities of left ventricular function [27], and a normal response to dynamic exercise has been defined as a rise of the ejection fraction of more than 5% from the resting value [28]. One-third of the male diabetic patients in the present study responded abnormally, which is similar to the percentage of abnormal responders in a study of male diabetic patients aged 21–35 years [29]. However, that study [29] included patients with Type 2 (non-insulin-dependent) diabetes and did not examine a homogeneous population; it should therefore be interpreted with caution, as oral hypoglycaemic agents may affect cardiac function [30].

There are several possible explanations for this abnormal function in male diabetic patients. It may primarily be caused by a specific heart disease of diabetes,

as has been inferred from the results of other non-invasive studies. The abnormalities could represent early, asymptomatic coronary heart disease, but in most cases the abnormal ventricular function was not associated with an abnormal exercise electrocardiogram, and the regional wall motion during radionuclide ventriculography was normal in all subjects. Exercise electrocardiography using the Marquette system does not provide total sensitivity and may sometimes mask positive ST changes compared with other ECG techniques. However, if asymptomatic coronary heart disease does make a significant contribution, the exercise electrocardiogram should be abnormal more frequently in those patients with abnormal ventricular function, which was not demonstrated in the present study. Furthermore, in those patients in whom invasive investigations were performed no abnormalities were found during coronary arteriography, excluding coronary heart disease as the underlying pathogenesis. Autonomic neuropathy has been shown to impair the cardiovascular responses to exercise in diabetic patients [31]. In the present study autonomic neuropathy was graded using a series of tests of cardiovascular reflexes, but no association was identified between the severity of autonomic dysfunction and impaired ventricular function. None of the patients who were catheterised had significant autonomic neuropathy. Finally, it has been suggested that the abnormal ventricular function found in patients with diabetes is associated with defective energy metabolism of the heart [32]. None of the patients had poor glycaemic control at the time of study as assessed by glycosylated haemoglobin or a random blood glucose before the supine exercise, but the contribution of metabolic factors to cardiac function is ill-defined. In the individual diabetic patient the ventricular response to exercise may be determined by the interaction of multiple factors including the presence or absence of a specific heart disease, coronary heart disease, autonomic neuropathy and the prevailing metabolic milieu.

Epidemiological analysis has indicated that diabetic women have an increased frequency of heart disease compared with a non-diabetic female population. In the Framingham study, Type 1 diabetic women had an increased incidence of congestive cardiac failure which could not be attributed to ischaemic or valvular heart disease [33]. The increased mortality of diabetic women could be associated with a specific diabetic heart disease, but their cardiac function has seldom been examined. The female patients in the present study had a smaller rise in their mean ejection fraction in response to dynamic exercise compared with the female controls, but because of the wide range of responses observed in non-diabetic women this difference was not statistically significant. An increase in the ejection fraction of less than 5% should not be regarded as abnormal in the female diabetic subjects, as almost half of the female control subjects did not produce a rise of this magnitude. In the present study abnormal ventricular function in fe-

male subjects has been defined either as a failure to rise or as a fall in ejection fraction on dynamic exercise [7]. Using this definition, abnormal ventricular function was observed in one-third of the female diabetic patients in the present study. Because of the variability of the measurement of ejection fraction, invasive investigations were performed only in female patients with a fall in ejection fraction. This sex difference may explain the abnormal cardiac function reported in a group of patients aged 20–40 years in whom a reduced cardiac response to dynamic exercise was observed [34]. That study examined 10 male and 10 female diabetic patients, while only 4 of the 18 control subjects were female [34]. If our proposed criteria for normal responses were applied, the rise in ejection fraction would be less than 5% in half of the male diabetic patients, while one-third of the female diabetic patients would have either no rise or a fall in ejection fraction, providing results similar to the present study.

Cardiac catheterisation of diabetic patients with symptoms of chest pain or dyspnoea has demonstrated abnormalities of ventricular function in the absence of coronary artery disease [35], but non-invasive investigation of cardiac function was not reported in these patients. Similar studies have not been reported previously in asymptomatic diabetic individuals, except in patients assessed before renal transplantation [36]. Abnormal myocardial function during cardiac catheterisation in the absence of coronary artery disease was demonstrated in one-third of a group of diabetic patients with end-stage renal failure, while one-third of the patients had normal myocardial function and one-third had demonstrable coronary artery disease [36]; histological examination was not performed. In the present study, preliminary histological examination of endomyocardial biopsy specimens suggested the presence of a diabetic microangiopathy involving the heart in some patients, and more detailed quantitative analysis is currently being undertaken. It is possible that similar histological changes may be present in patients who have normal cardiac function, but it is impossible in this study to prove that a microangiopathy involving the diabetic heart is the cause of the functional abnormality. Nor is it possible to ascertain which pathological process could be responsible for the abnormal ventricular function. The primary abnormality may be a disturbance of the coronary microcirculation, or the development of myocardial fibrosis may directly reduce ventricular contractility, with secondary changes in the microcirculation. The myocardial specimens were small, which can encourage errors of interpretation, and histological artefacts of myocardial biopsies are recognised to occur. While the thickening of the vessel walls may simply be artefactual, this does not explain the replacement of the myocardium by fibrous tissue, and if this fibrotic process is widespread within the myocardium of long-standing diabetic patients, then impairment of ventricular function would be anticipated. We submit that our

observations support the concept of a specific heart disease which develops as a long-term complication of diabetes.

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Dr. B. M. Fisher
Department of Diabetes
Gartnavel General Hospital
1053 Great Western Road
Glasgow G12 0YN
UK