Prevalence and predictors of cardiac hypertrophy and dysfunction in patients with Type 2 diabetes

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ABSTRACT

The aim of the present study was to determine the prevalence and predictors of an abnormal echocardiogram in patients with Type 2 diabetes. Cardiac function and structure were rigorously assessed by comprehensive transthoracic echocardiographic techniques in 229 patients with Type 2 diabetes. Cardiovascular risk factors and diabetic complications were assessed, and predictors of an abnormal echocardiogram were identified using multivariate logistic regression analysis. An abnormal echocardiogram was present in 166 patients (72 %). LVH (left ventricular hypertrophy) occurred in 116 patients (51 %), and cardiac dysfunction was found in 146 patients (64 %), of whom 109 had diastolic dysfunction alone and 37 had systolic ± diastolic dysfunction. Independent predictors of an abnormal echocardiogram were obesity, age, the number of antihypertensive drugs used (all \( P < 0.001 \)) and creatinine clearance (\( P < 0.05 \)). The risk of an abnormal echocardiogram increased by 9 % for each year over 50 years of age \{OR (odds ratio), 1.09 [95 % CI (confidence interval), 1.04–1.15]\}, 3-fold if obesity was present [BMI (body mass index) > 30; OR, 4.2 (95 % CI, 1.9–9.0)] and by 80 % for each antihypertensive agent used [OR, 1.8 (95 % CI, 1.3–2.4) per agent]. In conclusion, an abnormal cardiac echocardiogram is common in patients with Type 2 diabetes. Importantly, although cardiac abnormalities can be predicted by traditional risk factors, such as age, obesity and renal function, the absence of micro- or macro-vascular complications does not predict a normal echocardiogram. We suggest that an echocardiogram identifies those with Type 2 diabetes at increased cardiovascular risk due to occult LVH and diastolic dysfunction, and this information may lead to more aggressive management of known risk factors in the clinic.

INTRODUCTION

Type 2 diabetes mellitus is a CHD (coronary heart disease) risk equivalent [1] associated with a significant cardiovascular disease burden [2,3], which includes a 2–3-fold increase in cardiac death [4] and an increased risk of CHF (congestive heart failure) [5]. Diabetes also directly contributes to the development of LVH [LV (left...
ventricular) hypertrophy [6], which in itself is a predictor of cardiac morbidity and mortality. Systolic dysfunction is associated with macrovascular disease, but, early in the course of diabetes, cardiac fibrosis and hypertrophy [7,8] cause impaired relaxation and diastolic dysfunction [9].

Cardiac function can be assessed non-invasively using cardiac echocardiography. With the advent of the newer echocardiographic modalities of TDI (tissue Doppler imaging) and colour M-mode echocardiography measuring \( V_p \) (flow propagation velocity), it is now possible to more accurately classify diastolic dysfunction into progressively worsening grades that include the abnormal relaxation pattern (mild), the intermediate or pseudonormal pattern (moderate) and the restrictive physiology pattern (severe) [10–15]. Conventional echocardiographic methods exhibit a U-shaped parabolic pattern when progressing from normal to worsening degrees of diastolic dysfunction, and thus the ‘pseudonormal’ pattern has not always been distinguished from the true ‘normal’ group. The distinction is important, as diastolic dysfunction has adverse prognostic implications [16,17] and is an independent risk factor for all-cause mortality [11].

Current guidelines for patients with diabetes recommend preventative strategies to minimize the risk of cardiovascular events [18,19]. To this end, the accurate and non-invasive identification of occult cardiac dysfunction should form a routine part of the management [20]. Screening via a 12-lead ECG lacks sufficient sensitivity and specificity for the detection of cardiac disease in asymptomatic patients with diabetes [21]. To date, it is unclear whether routine echocardiography in asymptomatic patients has any clinical utility in the general diabetic population seen in the outpatient setting. The present study examines the prevalence and clinical predictors of cardiac functional and structural abnormalities in a cross-sectional survey of 229 patients with Type 2 diabetes, using conventional Doppler echocardiography and the newer modalities of TDI and colour M-mode echocardiography.

**MATERIALS AND METHODS**

**Study population**

A total of 251 with Type 2 diabetes were studied prospectively. An echocardiogram is part of a routine complications surveillance programme at the Diabetic Clinic at Austin Health, Melbourne, Australia. As our primary referral base (80%) is from general practitioners, with only 20% referred from within the hospital, the cohort is representative of patients with Type 2 diabetes seen in the wider community. The research was carried out according to the Declaration of Helsinki (2000) of the World Medical Association, and was approved by the Human Research Ethics Committee at Austin Health. All subjects provided written consent.

Each patient completed a questionnaire, cross-checked by a review of the medical record, on cardiac risk, including a history of hypertension, presence of dyslipidaemia, duration of diabetes, and the presence of microvascular disease (nephropathy, retinopathy and neuropathy), cardiac disease [MI (myocardial infarction), angina, CHF, previous angioplasty and/or bypass surgery] and other macrovascular complications [stroke, TIA (transient ischaemic attack) and PVD (peripheral vascular disease)]. Systolic and diastolic BPs (blood pressures) were measured after 5 min of recumbency, using the appearance and disappearance of the Korotkoff sounds. Height and weight were measured for determination of BMI (body mass index), and BSA (body surface area) was measured using the formula (weight\(^2\times425\times\)height\(^2\times725\)×71.84/10000. Urine and plasma electrolytes were measured on a Hitachi 911 automatic analyser (Roche Diagnostics). Plasma high-sensitivity CRP (C-reactive protein) levels were measured using the SYNCHRON LX\textsuperscript{®} system on a Beckman Coulter analyser. HbA\(_1c\) (glycated haemoglobin) was measured by automated HPLC (Bio–Rad Laboratories). Fasting lipids were measured by enzymatic colorimetry. Total cholesterol was measured by enzymatic colorimetric methods, and LDL (low-density lipoprotein)-cholesterol was calculated using the Friedewald equation. Urinary albumin excretion was estimated by immunoturbidimetry (Dade-Behring) from a 24-h urine collection. The level of albuminuria was defined categorically according to standard guidelines. Creatinine clearance was determined using the Cockroft–Gault formula and was expressed per 1.73 m\(^2\) of BSA.

**Definitions**

Hypertension was defined as present if patients were on antihypertensive medication, had a history of hypertension and/or had evidence of hypertension (BP > 130/85 mmHg). Patients were considered to have microalbuminuria if two out of three consecutive urine samples had an AER (albumin excretion rate) of \( \geq 20 \mu g/min \) but \( \leq 200 \mu g/min \), and macroalbuminuria if two out of three consecutive urine samples revealed an AER of \( > 200 \mu g/min \). Retinopathy was assessed after examination of a dilated fundus by an ophthalmologist or if the subject had a history of laser photocoagulation. Peripheral neuropathy was determined upon examination and chart review at the Diabetic Clinic. The presence of macrovascular disease was defined by a positive history of cardiac, cerebral or PVD.

**Echocardiography**

Transthoracic echocardiography examination was performed as described previously by our group [13–15] using an Acuson Sequoia ultrasound system, with measurements made according to the guidelines from the American Society of Echocardiography. M-mode echocardiography [22] was used to measure LV EF.
RESULTS

Patient characteristics

Investigations were performed in 251 patients with Type 2 diabetes. As 22 patients were excluded due to significant valvular heart disease, mechanical valve prostheses or non-diagnostic imaging, 229 patients remained in the final study group. The total group studied included 145 men and 84 women with a mean age of 62 ± 1 years, and a median duration of diabetes of 10 years. Most patients had established microvascular complications of diabetes (64 %), including retinopathy (29 %), elevated albuminuria (AER > 20 µg/min; 40 %) or peripheral neuropathy (28 %). At the time of review, over 78 % of patients were hypertensive, 33 % of patients had a history of ischaemic heart disease and 12 % of patients had established macrovascular disease at other sites (peripheral or cerebrovascular disease), meaning that over one-third of patients had established macrovascular disease. Table 1 shows the clinical characteristics of patients with a completely normal cardiac echocardiogram compared with those with an abnormal echocardiogram (LVH alone, diastolic dysfunction and/or systolic dysfunction).

Echocardiography

A normal echocardiogram was present in 28 % of patients (n = 63), and abnormalities were detected in 72 % (n = 166) (Table 2). A total of 20 in patients had LVH alone (9 %), 109 subjects had diastolic dysfunction alone (48 %), 11 had systolic dysfunction (5 %) and 26 had both systolic and diastolic dysfunction (11 %). Subjects with diastolic dysfunction only were classified into those with an abnormal relaxation (n = 51) or a pseudonormal pattern (n = 57). There was one patient with a restrictive physiology pattern (results not shown).

Structural abnormalities

Patients with an abnormal echocardiogram had higher rates of LVH, with raised LVMI (P < 0.001) and significantly lower E’. Those with any LV dysfunction (systolic ± diastolic dysfunction) had higher LA (left atrial) areas (P < 0.001) than those with normal functional parameters (normal and LVH alone) (Table 2).

Functional abnormalities

By definition, subjects with systolic dysfunction (n = 37) had lower EFs (P < 0.001) than those with a normal echocardiogram. An abnormal echocardiogram was associated with lower E/A ratios (P < 0.05) and, as expected, the conventional Doppler (DT and IVRT) results exhibited a parabolic pattern (Table 2). By contrast, the newer modalities of TDI and colour M-mode exhibited linear properties. Thus subjects with LV dysfunction (systolic ± diastolic dysfunction) had higher E/E’ and E/Vp ratios (P < 0.001; Table 1) and lower S’ (TDI-derived systolic myocardial velocity)
and $V_h \ (P < 0.001)$ compared with normal, confirming the utility of the newer modalities in the differentiation of normal from pseudonormal diastolic function.

**Clinical predictors of cardiac dysfunction on echocardiography**

On univariate analysis, subjects with an abnormal echocardiogram were approx. 10 years older, had a longer duration of diabetes and were more likely to be obese (Table 1, and Figure 1 and Figure 2). They also had poorly controlled hypertension with a higher BP, despite the use of more antihypertensive agents, and established micro- and macro-vascular complications ($P < 0.01$) (Table 1 and Figure 1). Total cholesterol and LDL-cholesterol were significantly lower in patients with an abnormal echocardiogram ($P < 0.05$), reflecting the greater use of statins ($P < 0.05$). However, neither glycaemic control nor the mode of hypoglycaemic therapy were significantly different between groups. In addition, there were no differences in gender, smoking status, systemic inflammation (as measured by CRP) or a family history of CHD.

Subjects with systolic dysfunction were twice as likely to have established macrovascular disease than those with diastolic dysfunction. Over 70% of patients with systolic dysfunction had an established cardiac history compared to those with diastolic dysfunction ($P < 0.01$ and 21% of subjects with a normal echocardiogram ($P < 0.01$ compared with systolic dysfunction; $P = 0.2$ compared with diastolic dysfunction). Microvascular disease was also more common in systolic dysfunction than those with isolated diastolic disease (Table 1).

Patients with LVH but no dysfunction were clinically different from those with a completely normal echocardiogram. In particular, these patients were more likely to have microvascular complications ($P = 0.03$),...
Echocardiographic findings in patients with Type 2 diabetes with a normal or abnormal echocardiogram compared with patients with a normal echocardiogram.

By contrast, the presence of systolic dysfunction was assumed in patients without established complications. This effect was statistically independent of the longer duration of diabetes seen in older patients. The presence of obesity was also a strong risk factor for an abnormal echocardiogram, with an over 3-fold increase in risk if BMI was in the obese range [BMI > 30; OR, 4.2 (95 % CI, 1.9–9.0)]. In addition, the presence of hypertension was strongly associated with abnormal findings on echocardiography. Furthermore, the greater the number of agents required to control BP levels, the more likely that an abnormal echocardiogram was present [OR, 1.8 (95 % CI, 1.3–2.4) per agent]. Notably, this effect was independent of both renal function and the duration of diabetes.

DISCUSSION
Cardiac dysfunction is common in patients with Type 2 diabetes. Using a combination of myocardial TDI and colour M-mode Vp, as well as conventional Doppler profiles, cardiac abnormalities were present in 72 % of adults with Type 2 diabetes; up to 35 % of these abnormalities would not have been diagnosed without rigorous echocardiographic assessment. The independent predictors of an abnormal echocardiogram were obesity, age, the number of antihypertensive agents used and creatinine clearance. Glycaemic control, dyslipidaemia, smoking status and a family history of CHD did not predict an abnormal echocardiogram. Most importantly, we found no independent association of an abnormal echocardiogram with clinical evidence of micro- and macro-vascular complications. This result indicates that normal cardiac findings cannot be assumed in patients without established diabetic complications.
LVH

As in the Framingham Heart Study [6], LVH was present in 70% (116/166) of patients with an abnormal echocardiogram, many of whom also had hypertension, diabetic complications and diastolic dysfunction. LVH was present in 21% (20 out of 94 patients) of those with normal diastolic function and in 65% (88 out of 135 patients) with diastolic dysfunction. Epidemiological studies show the prevalence of LVH is 6% in normal diastolic function and increases to 29% in those with diastolic dysfunction, but these studies contain few subjects with diabetes (45 out of 1274 patients, or 3.5%) [23]. Our present results confirm that diabetes accelerates the development of LVH [24] and the subsequent development of diastolic dysfunction.

Cardiac dysfunction

In the present study, we found a surprisingly low rate of impaired systolic function (16%), despite high rates of diastolic abnormalities (59%) and CHD. It is unlikely that the results reflect a sampling bias, as echocardiograms were not ordered according to clinical indication. However, in keeping with the increased mortality rate in patients with diabetes after MI, it is possible that the occurrence of coronary ischaemia in a cardiac milieu of fibrosis, hypertrophy and diastolic dysfunction is more likely to result in death and, consequently, less patients with systolic dysfunction.

In the present study, the rate of diastolic dysfunction was 59%, which is higher than in a population-based survey that reported a prevalence of 28% [11]. Most studies in diabetes have involved relatively small numbers of patients without cardiac risk factors (other than diabetes itself) or complications. Furthermore, many studies were performed before the newer echocardiographic techniques were available and, therefore, under-diagnosed diastolic abnormalities. More rigorous assessment of cardiac function to unmask the pseudonormal pattern results in approx. 25% more cases of diastolic dysfunction.

Predictors of cardiac abnormalities in diabetes

The independent predictors of an abnormal heart echocardiogram were obesity, age, the number of antihypertensive agents used and creatinine clearance. Age was the strongest predictor of an abnormal
Cardiac hypertrophy and dysfunction in patients with Type 2 diabetes

Although the presence of impaired systolic function was reliably predicted by a past history of cardiac disease, normal cardiac function cannot be assumed in those without established diabetic complications. The importance of diagnosing diastolic dysfunction has only recently been recognized, and its presence provides important prognostic information [11,17,29]. Whether the abnormalities we observed in the present study will have prognostic significance is the subject of on-going research in our centre.

Our present findings reinforce the need to aggressively treat hypertension at the earliest possible opportunity in patients with diabetes. The benefit of BP lowering in diabetics with ECG-defined LVH is clear [30] and, although the optimal treatment of diastolic dysfunction in diabetes is unknown, improved BP control will improve diastolic parameters in hypertensive subjects [31]. Guidelines set arbitrary BP levels at which treatment should be initiated, but a recent study suggests the need to lower BP in diabetes, whatever the initial BP [32]. In the ADVANCE trial, administration of a fixed combination of perindopril and indapamide to patients with Type 2 diabetes, irrespective of baseline BP or the use of other antihypertensives, including renin–angiotensin system blockade, reduced BP (5.6/2.2 mmHg) and the risk of major vascular deaths [32].

Early detection and treatment of cardiac disease is paramount in improving health outcomes in Type 2 diabetes. Our present results suggest an echocardiogram may serve to more precisely identify those subjects with diabetes at increased cardiovascular risk due not only to impaired systolic function, but also to occult LVH and diastolic dysfunction. If such information were available to the physician, it may lead to more aggressive management of known risk factors, such as hypertension in the clinic.

ACKNOWLEDGMENTS

This work was supported by educational grants from the National Health and Medical Research Council of Australia, Servier Laboratories, Australia, and a Pfizer CardioVascular Lipid award to P.M.S.

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