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The development and feasibility of a composite score of echocardiographic indices that may stratify outcome in patients with diabetes mellitus

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ABSTRACT

Background: Early detection of changes in cardiac structure and function associated with type 2 diabetes (T2DM) is important. However when multiple abnormalities are present, combining individual measurements can be subjective. This study sought to create a simple echo score that summarises measurements that may detect early and prognostically important changes in cardiac function.
Methods: Standard echocardiography was performed on 849 people with T2DM (median age 65 years, 40% female, median duration of diabetes 5.5 years). Principal components analysis was performed on measurements of LV mass, LA volume, E:e′, and s′, to create an objective summary score. The score was included in two Cox proportional hazard models adjusted for CV risk factors: one estimated the development of heart failure (HF) and the second estimated any CV event.
Results: The first two principal components represented 75% of the variation between the four echo measurements. A continuous score that represents the residual difference between these two components was derived that only requires measurement of medial E:e′ and s′. The score was significantly associated with the development of HF within four years (hazard ratio 1.34; 95% CI 1.15, 1.56).
Conclusions: We have developed a simple, objective score that enhances the use of echocardiography in the detection of sub-clinical cardiac disease in people with T2DM. Initial findings suggest that it may help identify those at increased risk of developing HF within four years.

1. Introduction

Abnormalities of cardiac function occur among people with type 2 diabetes mellitus (T2DM) [1,2]. Whilst many people with diabetes have co-existing hypertension and coronary artery disease, cardiac abnormalities can occur due to diabetes alone, resulting in a "diabetic cardiomyopathy" [3]. Diabetic cardiomyopathy is increasingly recognised [3] and is often present before clinical manifestations are apparent. On echocardiography, diabetic cardiomyopathy is characterised by an increase in left ventricular mass (LVM), increased left atrial (LA) volume, raised E:e′ (related to LV diastolic function), and reduced systolic function (s′) [3]. Ejection fraction and end-systolic volume have been shown to be powerful predictors of outcome among patients with heart failure (HF) [4,5]. However people with diabetes may be regarded as being in a pre-clinical phase of HF [6] and subtle or early abnormalities in LV systolic function may be more relevant [7]. The four measurements selected for use in this work are well validated markers of differing facets of cardiac structural and functional abnormalities. Individually, these parameters have been associated with increased cardiovascular (CV) risk, as well as incident or recurrent HF [8–13].

For an individual patient, the challenge is to integrate several indices of cardiac function derived from echocardiography. Some measurements may be classified as normal and others as abnormal, and the final decision about cardiac function becomes increasingly subjective. Therefore, we sought to create a simple echocardiographic score that would objectively combine information from these measures of cardiac structure and function, and so be suitable for clinical use. We then gauged if the score could identify people more likely to develop clinical

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disease by assessing the ability of the score to stratify future a) decompensated HF and b) major CV events.

2. Methods

2.1. Study population

Data from two cohorts of people with T2DM were combined for this study. The NPCII cohort (n = 294) has been described previously [14]. In brief, community-based patients with T2DM (diagnosis >5 years and/or receiving treatment for diabetes) without known CV, cerebrovascular or peripheral arterial disease were recruited. The ADVANCE cohort (n = 555) is a subset of patients from a multi-centre randomised controlled trial [15]. Subjects were required to have ≥1 risk factor for CV disease or have experienced a CV event. One hundred and seventy two patients in the ADVANCE cohort (31%) had experienced a CV event, of whom six had been hospitalised for HF. The total 849 subjects represent a broad range of people with varying duration of diabetes, with and without a history of CV events. The studies complied with the Declaration of Helsinki, ethics approval was obtained for each study, and informed consent was obtained from all subjects.

2.2. Echocardiography

All patients underwent transthoracic 2D echocardiography (Philips HDI 5000 or Philips iE33, Bothell, WA) performed by experienced sonographers to the same research protocol. Images were measured at a single core laboratory. At least three representative cardiac cycles of each image were measured and averaged. Left atrial areas were measured in the 2- and 4-chamber apical long-axis views, optimised for LA measurement, and volume calculated using the modified Simpson's method. If images in the 2-chamber view were inadequate, single plane estimation of LA volume from the 4-chamber view was used. Left ventricular mass was estimated from m-mode images, measured using the leading edge convention from the parasternal long-axis view [16]. In the apical 4-chamber view, peak transmitral velocities of the early (E) and late (A) filling waves were measured with the sample volume at the leaflet tips during diastole; and peak tissue velocities of the early (e′), late (a′) and systolic (s′) waves of the medial and lateral mitral annulus were assessed with pulsed wave tissue Doppler, to maximise the peak velocity whilst ensuring the entire frame was captured.

2.3. Principal components analysis

Principal components analysis (PCA) was used to create the score. This technique creates uncorrelated variables that are weighted averages of the original variables. The new composite variables (principal components) successively capture as much variability remaining in the data as possible. An advantage of PCA is that it doesn't require a dependent variable and so is not limited to the relationship with a specific outcome. The first one or two principal components can form the basis of a score that is an objective summary of the original data, provided the proportion of variation explained is sufficiently high.

The echo parameters included in the score were selected a priori based on clinical relevance and expert opinion. Each are measured on different scales (LVM, g; LA volume, mL; E:e′, no units; s′, cm/s) therefore the analysis was performed on the correlation matrix, where the data is centred (by subtracting the variable mean) and standardised (dividing by the standard deviation of the variable) so the attributes can be compared directly with each other.

The primary analysis was performed using non-indexed values of LA volume and LVM, and medial measurement of e′ and s′. To investigate the effect of alternative forms, the analysis was repeated using LA volume and LVM indexed by body surface area (BSA), and by height$^{2.7}$; and repeated with lateral, or both medial and lateral measurements of e′ and s′. Models were compared on the basis of the proportion of variance explained by the first two principal components, then by the scores that were derived.

The goal was to create a simple summary score that is easily calculated and for which measurements can be readily obtained. Initial review of the components analysis showed the coefficients of some measurements to be similar. Therefore the first two principal components were combined algebraically to reduce the number of measurements required.

Median values by study, and by outcome, were compared using the Mann–Whitney U test. Count data were compared using a test of proportions. R statistical software v2.12.0 was used throughout [17].

2.4. Relationship of score to outcome

Two outcomes were defined. Any CV event was defined as the first of: CV death (n = 18), myocardial infarction (n = 28), stroke or transient ischaemic attack (n = 25), or HF (n = 15). The second outcome was the development of HF only (n = 20). In the ADVANCE study, non-fatal HF was reported clinically, and all other CV events were independently adjudicated using source documents; in the NPCII study, endpoints were obtained from medical records.

The relationships between the outcome and the score, as well as each of the echo measurements, were initially visualised using density plots. Multivariable Cox proportional hazard models were then created to assess the independent significance of the echo score or individual echo measurements in the presence of standard CV risk factors (age, gender, smoking, systolic blood pressure (SBP), total:HDL cholesterol). Variables specifically associated with HF were not available for inclusion as a) prior HF was an exclusion criterion for NPCII, and b) the prevalence of clinical HF was low in the ADVANCE cohort (1% had a prior hospitalisation for HF). The association with outcome was statistically significant when the 95% confidence interval of the hazard ratio excluded one.

3. Results

Patient characteristics are shown in Table 1: 40% were female, median age 65 years (IQR 58–70 years), and median duration of diabetes 5.5 years (IQR 3–10 years). One third of the dataset are from the NPCII cohort, which is younger (57 vs 67 years, $p < 0.001$) and includes more women than the ADVANCE study (49% vs 34%, $p < 0.001$), which may explain the lower LVM in NPCII (199 g vs 236 g, $p < 0.001$). Otherwise the two cohorts have very similar clinical and echocardiographic characteristics except the median albumin creatinine ratio is lower in NPCII than ADVANCE (1.1 vs 12.4, $p < 0.001$).

3.1. Principal components analysis

Three-quarters of the variation in the echo measurements is represented by the first two principal components (Supplementary Table 1). The first and second components (PC1, PC2) account for 44% and 31% respectively of the total variation.

The same percentage of variation was represented in the first two principal components when LA volume and LVM were indexed to height$^{2.7}$ (variation = 75%), and a smaller percentage when indexed to BSA (variation = 73%). As performing an additional measurement (height) does not improve on the score, the simpler version using non-indexed values will be used. Similarly, <75% of the variation is summarised in the first two principal components with lateral measurements of e′ and s′ either in place of, or in combination with, medial measurements (variation = 73% and 67%). Therefore the final score requires medial measurements only.

Table 1
Patient characteristics.

	Whole group	NPCII	ADVANCE
N	849	294	555
Age, years	65 (58–70)	57 (50–64)	67 (63–71)
Female	336 (40)	145 (49)	191 (34)
Duration of diabetes, years	5.5 (3–10)	6 (3–10)	5 (2–10)
Height, m	1.68 (1.6–1.75)	1.67 (1.59–1.74)	1.69 (1.61–1.76)
Weight, kg	85 (74–98)	87 (72–103)	84 (75–96)
Waist:hip ratio	0.94 (0.89–0.99)	0.95 (0.9–1.01)	0.94 (0.89–0.97)
Total cholesterol, mmol/L	4.7 (4.0–5.5)	4.5 (3.9–5.3)	4.9 (4.1–5.6)
HDL, mmol/L	1.2 (1.0–1.4)	1.3 (1.1–1.5)	1.2 (0.96–1.4)
LDL, mmol/L	2.6 (2.0–3.3)	2.2 (1.6–2.9)	2.8 (2.2–3.4)
Triglycerides, mmol/L	1.7 (1.2–2.4)	1.9 (1.4–2.9)	1.6 (1.2–2.2)
Alb:cr	7.1 (2.0–21.7)	1.1 (0.4–4.0)	12.4 (5.3–33.2)
HbA1c, %	6.9 (6.4–7.8)	7.0 (6.3–8.1)	6.9 (6.4–7.7)
Glucose, mmol/L	7.6 (6.1–9.4)	7.3 (5.4–10)	7.7 (6.3–9.1)
MAP, mm Hg	95 (88–104)	97 (90–106)	94 (88–102)
Echocardiography			
LV mass, g	221 (181–279)	199 (160–246)	236 (193–297)
LV mass/BSA, g/m^2	112 (95–136)	103 (85–119)	120 (101–144)
LA volume, mL	66 (53–84)	64 (48–79)	68 (54–86)
LA volume/BSA, mL/m^2	34 (27–42)	33 (26–39)	35 (28–43)
E:e′ medial	10.3 (8.2–12.6)	10.1 (8.3–12.1)	10.4 (8.1–13.0)
E:e′ lateral	7.3 (5.8–9.2)	7.3 (5.7–8.9)	7.3 (5.8–9.4)
s′ medial, cm/s	7.3 (6.2–8.3)	7.4 (6.5–8.2)	7.1 (6.1–8.4)
s′ lateral, cm/s	8.4 (7.2–10.1)	8.5 (7.3–16.4)	8.3 (7.0–10.1)

Values are median (interquartile range) or n (%).
HDL = high-density lipoprotein; LDL = low-density lipoprotein; Alb:cr = albumin creatinine ratio; HbA1c = glycated haemoglobin; MAP = mean arterial pressure, BSA = body surface area.