RESEARCH

Evolution of subclinical myocardial dysfunction detected by two-dimensional and three-dimensional speckle tracking in asymptomatic type 1 diabetic patients: a long-term follow-up study

Anne Ringle MD\textsuperscript{1,2}, Anne Dornhorst FRCP\textsuperscript{2}, Michaela B Rehman MD\textsuperscript{2,4}, Cristina Ruisanchez MD\textsuperscript{2,5} and Petros Nihoyannopoulos MD FRCP FACC FESC FAHA\textsuperscript{2}

\textsuperscript{1}Department of Cardiology, Hôpital Saint Philibert, GHICL, Lille, France
\textsuperscript{2}Department of Cardiology, Hammersmith Hospital, Imperial College NHS Trust, London, UK
\textsuperscript{3}Department of Diabetes and Endocrinology, Hammersmith Hospital, Imperial College NHS Trust, London, UK
\textsuperscript{4}Department of Cardiology, Centre Hospitalier Universitaire de Poitiers, Poitiers, France
\textsuperscript{5}Hospital Universitario Marques de Valdecilla, Santander, Cantabria, Spain

Abstract

\textbf{Background:} We sought to assess the long-term evolution of left ventricular (LV) function using two-dimensional (2D) and three-dimensional (3D) speckle tracking echocardiography (STE) for the detection of preclinical diabetic cardiomyopathy, in asymptomatic type 1 diabetic patients, over a 6-year follow-up.

\textbf{Design and methods:} Sixty-six asymptomatic type 1 diabetic patients with no cardiovascular risk factors were compared to 26 matched healthy controls. Conventional, 2D and 3D-STE were performed at baseline. A subgroup of 14 patients underwent a 6-year follow-up evaluation.

\textbf{Results:} At baseline, diabetic patients had similar LV ejection fraction (60 vs 61%; \( P = \text{NS} \)), but impaired longitudinal function, as assessed by 2D-global longitudinal strain (GLS) \((-18.9 \pm 2 \text{ vs } -20.5 \pm 2; \ P = 0.0002 \)) and 3D-GLS \((-17.5 \pm 2 \text{ vs } -19 \pm 2; \ P = 0.003 \)). At follow-up, diabetic patients had worsened longitudinal function compared to baseline (2D-GLS: \(-18.4 \pm 1 \text{ vs } -19.2 \pm 1; \ P = 0.03 \)). Global circumferential (GCS) and radial (GRS) strains were unchanged at baseline and during follow-up. Metabolic status did not correlate with GLS, whereas GCS and GRS showed a good correlation, suggestive of a compensatory increase of circumferential and radial functions in advanced stages of the disease – long-term diabetes (GCS: \(-26.3 \pm 3 \text{ vs } -23.3 \pm 3; \ P = 0.008 \)) and in the presence of microvascular complications (GRS: \(38.8 \pm 9 \text{ vs } 34.3 \pm 8; \ P = 0.04 \)).

\textbf{Conclusions:} Subclinical myocardial dysfunction can be detected by 2D and 3D-STE in type 1 diabetic patients, independently of any other cardiovascular risk factors. Diabetic cardiomyopathy progression was suggested by a mild decrease in longitudinal function at the follow-up, but did not extend to a clinical expression of the disease, as no death or over heart failure was reported.

Key Words
- diabetes mellitus
- diabetic cardiomyopathy
- speckle tracking
- three-dimensional echocardiography
- left ventricular function
Introduction

Cardiovascular disease is the major complication of diabetes, accounting for 50% of all diabetes mortality (1). This is not only due to coronary artery disease and associated hypertension, but also to the direct adverse effect of diabetes on the heart, irrespective of other cardiovascular risk factors, called diabetic cardiomyopathy (2, 3, 4). The mechanisms that lead to the development of diabetic cardiomyopathy are multifactorial and likely to act synergistically. These include hyperglycaemia, inducing increased oxidative stress and diversion to alternative metabolic pathways, increased free fatty acid leading to cardiac steatosis, insulin resistance, activation of the renin–angiotensin system, microvascular disease and cardiac autonomic dysfunction. The combination of these mechanisms results in myocardial hypertrophy and fibrosis. Previous studies have demonstrated subclinical impairment of diastolic and systolic longitudinal functions (5, 6, 7, 8) in diabetic patients. Findings on radial function were controversial, with either a decreased, preserved or even increased radial function (9, 10).

However, there is paucity of data relating to global and regional left ventricular (LV) function in type 1 diabetic patients over a prolonged follow-up period (11, 12). Indeed, most studies included type 2 diabetic patients with a significant proportion of other cardiovascular risk factors, which may represent confounding factors when trying to establish a link between diabetes and myocardial dysfunction. In addition, very few studies have assessed the progression of these changes over the years using deformation imaging (13). Deformation imaging has advanced rapidly, and two-dimensional (2D) and three-dimensional (3D) (14, 15, 16) speckle tracking echocardiography (STE) are probably more sensitive measures than ejection fraction (LVEF) to assess global myocardial function.

In this study, we sought to assess global LV function using 2D and 3D-STE, to detect subclinical myocardial dysfunction in a cohort of asymptomatic type 1 diabetic patients with no cardiovascular risk factors or coronary artery disease. We also assessed the progression of preclinical LV dysfunction by conducting a 6-year follow-up evaluation in a subgroup of patients.

Methods

Patient population

Patients aged older than 18 years with isolated type 1 diabetes were recruited from the diabetes outpatient clinic at Charing Cross Hospital (London). Exclusion criteria were recent diagnosis of diabetes (<1 year), documented cardiac disease, diabetic nephropathy, cardiovascular risk factors (hypertension, hypercholesterolemia, active smoking, obesity, age over 60 years).

Sixty-six patients were recruited, 22 of whom were initially studied in 2008 when an early pilot study had been undertaken, with a further 44 prospectively enrolled between June and September 2014. Each patient underwent an interview and a clinical examination to rule out any cardiovascular signs or symptoms, blood and urine laboratory tests, as well as 2D and 3D echocardiography.

They were subsequently compared with a control group of age- and gender-matched healthy subjects recruited between June and September 2014 among outpatients who presented for a routine echocardiography, providing they met the following criteria: no cardiovascular risk factors, no personal history of heart disease, no clinical history of chronic disease or chronic medication and normal transthoracic echocardiography.

A 6-year follow-up examination consisting of clinical, biological and echocardiographic assessment was performed on the initial subgroup of patients recruited in 2008. Follow-up was only completed in 14. The rest were either lost to follow-up or refused (N=3) to participate. One patient who had developed 3-vessel ischaemic heart disease was excluded from the analysis.

Patients’ characteristics and treatments (insulin) were similar in 2008 and 2014.

The local ethics committee approved the research protocol and informed consent was obtained from all subjects.

Echocardiography

A transthoracic echocardiography was performed using an IE33 ultrasound machine (Philips) according to standardised protocol. Standard 2D and Doppler measurements were performed according to the current guidelines of the European Association of Cardiovascular Imaging (17).

Additional images for 2D-STE were acquired at a frame-rate of 60–90 frames/s, during three cardiac cycles, and analysed using a semi-automated, vendor-independent software (2D-CPA, TomTec Imaging Systems). Endocardial border was manually traced at end-diastole, tracked throughout the cardiac cycle and divided into six equal segments. Tracking quality was visually verified and adjusted where necessary. Global longitudinal strain (GLS) and strain rate (GLSR)
were obtained from apical 2-, 3- and 4-chamber views. Global radial and circumferential strain (GCS and GRS) and strain rates (GCSR and GRSR) were obtained from parasternal short-axis views at basal, mid-papillary and apical levels. Diastolic function was assessed using peak strain rate at early diastole (SRE) and the ratio of E wave and SRE (E/SRE), as it was suggested to be a better predictor of LV filling pressure in patients with preserved LVEF (18).

3D full volume of the LV was obtained from a single acquisition of 4 cardiac cycles, during breath-hold, at a volume rate of 20–40 volumes/s and analysed using TomTec 4D-LV function to assess 3D-GLS, 3D-LV volumes and 3D-LVEF. After adjusting the orientation of 2D planes, the software tracked the endocardial border. The observer adjusted the trace according to a visual assessment of tracking quality. 3D-LV strains were assessed and displayed as global and regional curves. Rotational motion was studied by twist (difference in rotation between base and apex) and torsion (twist divided by vertical distance between base and apex).

All studies (from 2008 to 2014) were performed using the same ultrasound machines and standardised protocol. All initial studies from 2008 were re-analysed in 2014 using the same software, by the same operators.

**Statistical analysis**

Statistical analyses were performed using SPSS Statistics, version 22.0 (SPSS) and reviewed by the Department of Statistics of Lille University Hospital. Quantitative variables are expressed as mean ± s.d. if normally distributed (as assessed using Shapiro–Wilk test) or median (interquartile range) otherwise. Qualitative variables are expressed as frequencies and percentages.

Bivariate comparisons between the two groups (patients vs controls) were made using Student’s t-test for quantitative variables (or Mann–Whitney U test when non-normally distributed) and Chi-square or Fisher’s exact tests for qualitative variables. To study the evolution between baseline and follow-up, paired t-test or Wilcoxon signed-rank test was used as appropriate. The associations between 2D-STE, 3D-STE, standard echocardiography and metabolic status were determined by Pearson correlation coefficient, t-test or chi-square test according to the nature of data studied.

To assess intraobserver and interobserver variability, measurements were repeated in 55 randomly selected patients ≥1-week apart by the same observer, and in 20 randomly selected patients by a second independent observer. Variability was expressed as percentage and intra-class correlation coefficients (ICC). Percentage intraobserver and interobserver variabilities were calculated as the absolute difference divided by the average of the two measurements. Statistical testing was done at the two-tailed α level of 0.05.

**Results**

**Baseline**

**Clinical and biological characteristics at baseline** The final population consisted of 66 asymptomatic type 1 diabetic patients. Table 1 summarises clinical and biological data of diabetic and control populations at baseline (no significant difference, all P values >0.05). All patients were free from cardiovascular diseases or risk factors other than diabetes.

**Echocardiographic characteristics at baseline** No statistical difference between patients and controls was found in LV mass, dimensions or systolic function based on conventional echocardiography (all P values >0.05, Table 1). Diastolic dysfunction was more frequent in the diabetic group (11% vs 0%).

2D-STE analyses were conducted in all patients and controls (Table 1). Only longitudinal function was significantly reduced, with lower absolute values of GLS in the diabetic group. All other parameters of systolic myocardial deformation were not different in diabetic patients and controls (GCS, GRS, GLSR, GCSR, GRSR; Table 1).

E/SRE ratios were higher in the diabetic group, while SRE showed a non-significant downward trend.

Two patients and 3 controls were excluded from 3D-STE analyses due to inadequate image quality. 3D data were not available for the subgroup of patients recruited in 2008. The assessment of 3D myocardial deformation was then carried out on 71% of the population (42 patients and 23 controls) and confirmed similar LV volumes and systolic function but significant impairment of longitudinal function in diabetic patients, as demonstrated by a decreased 3D-GLS in diabetic patients (Fig. 1 and Table 1). 3D Twist and Torsion were similar in patients and controls.

3D-GLS showed a good correlation with 2D-GLS (ICC=0.592 (0.117–0.791)) and with 3D-LVEF (r = −0.54; P<0.0001).
Correlation between STE and metabolic status

Metabolic status was studied through 3 parameters: the presence of microvascular complications of diabetes (microalbuminuria, neuropathy and/or retinopathy); diabetes control using HbA1c >53 mmol/mol as a cut-off value for uncontrolled diabetes and diabetes duration, expressed in years and by dividing the population into two duration-based groups ('short-term diabetes' <10 years, 'long-term diabetes' >10 years).

No link was found between GLS and the coexistence of other microvascular complications of diabetes (2D-GLS: $-19.3 \pm 2$ vs $-18.8 \pm 1$; $P=0.21$ and 3D-GLS: $-17.2 \pm 2$ vs $-17.8 \pm 2$; $P=0.31$), between GLS and uncontrolled diabetes (2D-GLS: $-18.9 \pm 2$ vs $-18.9 \pm 1$; $P=0.99$ and 3D-GLS: $-17.2 \pm 1$ vs $-17.3 \pm 2$; $P=0.52$) or between GLS and diabetes duration – when expressed in years: 2D-GLS ($r=0.024; P=0.85$), 3D-GLS ($r=0.27; P=0.08$) or when dividing the population into two duration-based
Figure 1
Three-dimensional (3D) speckle tracking echocardiography assessment. (A) 38-year-old female diabetic patient with normal 3D-left ventricular volumes and ejection fraction, but decreased 3D-GLS. (B) Age-matched female control with normal 3D-left ventricular volumes, ejection fraction and 3D-GLS. EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; GLS, global longitudinal strain; SV, stroke volume.
groups (<10 and >10 years: $P=0.82$ for 2D-GLS, $P=0.47$ for 3D-GLS).

In contrast, circumferential and radial strains showed a good correlation and increased with the progression of the disease: GCS and GRS were higher when diabetes duration was >10 years (significant for GCS: $-26.05 \pm 3\text{ vs } -23.3 \pm 3$; $P=0.009$, borderline for GRS: $37.05 \pm 32$; $P=0.05$), also, GRS was higher in the presence of microvascular complications ($38.8 \pm 9 \text{ vs } 34.3 \pm 8$; $P=0.04$).

Rotational parameters non-significantly increased in long-term diabetes (Twist: 9.4 ± 5 vs 8.2 ± 5; $P=0.5$, Torsion: 1.2 ± 0.6 vs 1 ± 0.6; $P=0.5$).

**Observer variabilities**  Intraobserver and interobserver reproducibility were excellent for 2D-GLS (intraobserver: ICC (95% confidence interval (CI)) 0.974 (0.955–0.985), 2.5% variability; interobserver: ICC 0.927 (0.818–0.971), 3.8% variability), 3D-GLS (0.967 (0.944–0.981), 4.9%); 0.893 (0.728–0.958), 5.1%) and 2D-GCS (0.951 (0.916–0.971), 3.9%); 0.899 (0.734–0.961), 4.8%) and good for 2D-GRS (0.824 (0.699–0.897), 14.6%); 0.815 (0.533–0.927), 12.3%).

**Follow-up**

Fourteen patients completed the 6-year follow-up assessment (50% female). None had developed overt heart failure. No cardiac or extra-cardiac death was reported. Clinical and echocardiographic characteristics at follow-up are summarised in Table 2.

LV volumes and ejection fraction remained unchanged at follow-up, while LV mass and relative wall thickness increased. Diastolic dysfunction (5 at follow-up (36%) vs 0 at baseline, $P=0.025$) and LA dilation (4 (29%) vs 0, $P=0.046$) were more frequent (Table 2).

Longitudinal function was modestly reduced at follow-up (decreased GLS, GLSR and S’ velocities), while GCS and GRS showed a non-significant increase (Table 2).

**Discussion**

In this study, we have shown that longitudinal function in type 1 diabetic patients is impaired compared to controls, independently of any other cardiovascular risk factor, despite having a normal ejection fraction. These findings were consistent regardless of the speckle tracking technique used and were confirmed in a 6-year follow-up evaluation conducted in a subgroup of patients: 2D-GLS at baseline, 3D-GLS at baseline and 2D-GLS at follow-up were all reduced. Conversely, GCS and GRS remained unchanged at baseline but increased during long-term follow-up in type 1 diabetics suggestive of a compensatory mechanism.

**Subclinical myocardial dysfunction in asymptomatic type 1 diabetic patients**

The population in this study differs from previous data available, as it was only focused on isolated type 1 diabetes. Patients with other cardiovascular risk factors were excluded as our aim was to identify direct adverse effects of diabetes on the heart, in the absence of other confounding factors.
Although experimental (19, 20, 21) and clinical (22, 23, 24) evidence is growing, the existence of a specific diabetic cardiomyopathy is still a matter of debate in this population (4, 25). The majority of previous studies (10, 13, 26) involved type 2 diabetic patients, with coexistence of hypertension (38–64%), hypercholesterolemia and obesity, relatively advanced mean age (up to 60 years) and a short diabetes duration (less than 10 years). Our population was younger (mean age 37) and the duration of diabetes was longer (21 years). Study population at baseline showed a higher proportion of female as lower-risk populations may show a female predominance (usual male to female sex ratio in diabetes mellitus 1:1–1.5:1). Recent studies have focused on type 1 diabetes (11) but did not strictly exclude patients with additional risk factors (more than half of patients were smokers in the large study by Jensen and coworkers (11). We therefore demonstrated that in this diabetic population with isolated type 1 diabetes, subclinical myocardial dysfunction can be identified using STE.

Changes in systolic and diastolic function assessed by 2D and 3D-STE

Whether diastolic function highlights an early stage of diabetic cardiomyopathy before progressing to more significant systolic dysfunction has been controversial (5, 25). The prevalence ranges from 23 to 75% depending on the methods used and populations studied (46% in a study based on the current guidelines) (5). In the present study, diastolic dysfunction was more frequent in diabetic patients at baseline and worsened during follow-up (11% at baseline, 36% at follow-up). It was detected both by standard and STE parameters.

LV longitudinal function was impaired in diabetic patients at baseline and continued after a 6-year follow-up. This was detected by both 2D and 3D-STE, while standard echocardiography failed to detect any changes. These findings are consistent with previous studies (6, 7, 10, 26), suggesting that longitudinal fibres are the first affected by diabetic cardiomyopathy. Changes in the other components of myocardial deformation are less well established and vary across studies (9, 10, 12, 13, 27, 28).

Baseline evaluation showed no significant changes in circumferential or radial function. In the 6-year follow-up group consisting of long-term (27 ± 10 years) and older (45 ± 7 years) diabetic patients, both GCS and GRS showed a non-significant upward trend. Rotational function was unchanged. Previous reports based on TDI, 2D-STE or magnetic resonance imaging also found preserved or increased twist and torsion in diabetic cardiomyopathy (29, 30).

Over the 6-year follow-up, systolic and diastolic parameters deteriorated. Despite these echocardiographic changes, no patient developed signs of overt heart failure at that point in time. Hence, the progression of preclinical diabetic cardiomyopathy seems to go through a long subclinical, asymptomatic phase and the hypothesis of diabetic cardiomyopathy leading to heart failure has not yet been clearly demonstrated in type-1 diabetics. It may be that a longer follow-up may be necessary or that more patients may be necessary.

Correlation with metabolic status

No correlation was found between longitudinal strain and metabolic status, whether assessed by glycaemic control, duration of diabetes or coexistence of microvascular complications. This is not in keeping with previous studies that reported a correlation between reduced longitudinal strain and uncontrolled diabetes (26, 31), diabetes duration (6) or microalbuminuria (11).

In contrast, circumferential and radial strain increased in more advanced stages of the disease, for long durations of diabetes (>10 years) and when other complications of diabetes were present. These findings are in agreement with recent paediatric studies (27, 32) as well as previous studies (6, 7, 9), in which circumferential and radial functions were preserved or paradoxically increased. A recent study in paediatric patients (31) with short-term type 1 diabetes reported increased GCS but not GLS in patients with higher blood sugar levels and suggested that hyperglycaemia-induced increased energy turnover may lead at first to hyperdynamic cardiac mechanics which on the long term might contribute to the development of diabetic cardiomyopathy. Other reports (10, 12, 28) demonstrated a decrease of systolic strain in all directions, that could be interpreted as further progression of the disease. To balance reduced longitudinal function, compensatory mechanisms arise, with increased circumferential and radial contraction. Then, as the disease progresses, global myocardial dysfunction sets in, resulting in overt LV dysfunction. Fang and coworkers (9) analysed this phenomenon in terms of myocardial fibre orientation, suggesting that myocardial dysfunction starts in the endocardium (i.e. reduced longitudinal contraction) as opposed to preserved mid-wall fibres (i.e. circumferential and radial contraction).
Comparison of speckle tracking techniques
As previously reported (33), 3D-STE was faster to acquire and to analyse compared to 2D-STE (one full-volume image for 3D-STE vs 6 for 2D-STE), but required high-quality images to obtain accurate analyses. Both techniques showed a good reproducibility; as expected, it was slightly lower for GRS.

Limitations
The main limitation of this study was that follow-up was performed on a small number of patients. This was due to the fact that many patients were lost to follow-up and other refused to re-attend. However, we could demonstrate a significant worsening in longitudinal function over a 6-year period.

Even though the two groups were comparable at baseline, the limited number of volunteers did not allow for strict matching of patients and controls.

Study population may not be representative of the general diabetic population as it was specifically selected in type-1 diabetics in order to identify direct adverse effects of diabetes on the heart independently of confounding factors.

The study protocol did not include a systematic stress test or coronary angiogram at baseline or at follow-up because it was not clinically indicated in this population. As in routine practice, we relied on a detailed interview, clinical examination and resting echocardiography, and excluded all patients presenting a history of cardiac disease or any cardiovascular sign or symptom. Diabetic patients were considered at very low probability of coronary artery disease based on clinical grounds and normal resting echocardiography.

We identified subclinical systolic and diastolic dysfunction in the diabetic group, but did not identify real cut-off values for an adverse prognosis. Clinical implications in terms of individual patient management remain to be determined.

Conclusions
Subclinical diastolic and systolic dysfunction can be detected by 2D and 3D-STE in type 1 diabetic patients, independently of any other cardiovascular risk factors. The progression of diabetic cardiomyopathy was suggested by a mild echocardiographic deterioration in longitudinal function after 6 years of follow-up in a smaller subgroup.

It did not extend to a clinical expression of the disease, as no death or overt heart failure was reported.

Further longitudinal investigations on larger populations need to be conducted to explore the exact course of the disease and determine the indications for and specific nature of therapies to be prescribed.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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