Novel cardiac imaging technologies : implications in clinical decision making

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Chapter 2

Findings from left ventricular strain and strain rate imaging in asymptomatic patients with type 2 diabetes mellitus

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ABSTRACT

Background: Regional left ventricular (LV) myocardial functional changes in early diabetic cardiomyopathy are not well documented.

Methods: LV multidirectional strain and strain rate (SR) analyses by 2D speckle tracking were utilized to detect subtle myocardial dysfunction in 47 asymptomatic, male patients (57±6years) with type 2 diabetes mellitus. Results were compared to 53 male controls matched by age, body mass index and body surface area.

Results: There were no differences in LV end-diastolic volume index (40.7±8.9 vs 44.1±7.8mL/m^2, p=ns), end-systolic volume index (16.0±4.8 vs 17.8±4.3mL/m^2, p=ns), ejection fraction (61.0±5.5 vs 59.8±5.3%, p=ns). Transmitral E/A (0.95±0.21 vs 1.12±0.32, p=0.007) and pulmonary S/D ratios (1.45±0.28 vs 1.25±0.27, p=0.001) were more impaired in diabetic patients. Importantly, diabetic patients had impaired longitudinal but preserved circumferential and radial systolic and diastolic function. Diabetes mellitus was an independent predictor for longitudinal strain, systolic SR and early diastolic SR on multiple linear regression analysis (all $p<0.001$).

Conclusions: LV longitudinal systolic and diastolic functions were impaired but circumferential and radial functions were preserved in uncomplicated type 2 diabetic patients.

INTRODUCTION

Diabetic cardiomyopathy is defined as left ventricular (LV) dysfunction that occurs independently of coronary artery disease and hypertension.[1] The pathogenesis of diabetic cardiomyopathy is likely to be multifactorial, including microvascular disease, altered myocardial metabolism, and altered myocardial structure with fibrosis. Patients with early diabetic cardiomyopathy often have evidence of global diastolic dysfunction but preserved systolic function as reflected by a normal LV ejection fraction (EF).[2] Compared to LVEF, myocardial velocity, strain and strain rate (SR) analyses are more sensitive indices of LV function and have been demonstrated to be abnormal in diabetic patients.[3-8] However, these studies often included patients with diabetic complications or associated co-morbidities which may introduce important biases on LV functional evaluation. [3-8] Currently, there is no extensive information on the effects of diabetes mellitus on LV mechanics. Thus, we evaluated multidirectional LV myocardial systolic and diastolic functions in a group of truly uncomplicated, normotensive, diabetic patients using 2-dimensional (2D) speckle tracking echocardiography.

METHODS

Study population

Forty-seven patients with type 2 diabetes mellitus were recruited in this study. The inclusion and exclusion criteria for all the diabetic patients have previously been reported.[2] Briefly, women were not recruited to avoid possible confounding influences of gender and plasma estrogen levels on lipid metabolism and myocardial triglyceride accumulation. Inclusion criteria for all diabetic patients included: 1) Type 2 diabetes mellitus diagnosed according to World Health Organization criteria[9] and treated with sulfonylurea derivatives in stable doses, 2) HbA1c below 8.5%, and 3) resting blood pressure <150/85 mmHg, with or without antihypertensive medication. In addition, as an inclusion criterion, the presence of myocardial ischemia was excluded in all patients by a negative high-dose dobutamine stress echocardiogram.[2] Exclusion criteria included known cardiovascular disease or diabetes related complications including proliferative retinopathy, autonomic neuropathy as excluded by Ewing's tests[10], and microalbuminuria as excluded by measurements of albumin/creatinine ratio in a urine sample.

Fifty-three male control subjects recruited were frequency matched for age, body mass index and body surface area (BSA). All control subjects had normal physical examinations and normal echocardiograms. Exclusion criteria for the control subjects included history of diabetes mellitus, smoking, hypertension and cardiomyopathy. The institutional ethics review board of the hospital approved the study and all subjects gave informed consent.

Echocardiography

Transthoracic echocardiography was performed with the subjects at rest using commercially available ultrasound transducer and equipment (M3S probe, Vivid 7, GE-Vingmed, Horten, Norway). All

images were digitally stored on hard disks for offline analysis (EchoPAC version 07.00, GE-Vingmed, Horten, Norway). A complete 2D, color, pulsed and continuous-wave Doppler echocardiogram was performed according to standard techniques.[11,12] Left ventricular mass index was calculated from 2D echocardiographic measurements using the area-length formula at end-diastole [13], and corrected for BSA.[14] LV end-diastolic volume index (EDVI) and end-systolic volume index (ESVI) were calculated using Simpson's biplane method of discs and corrected for BSA. LVEF was calculated and expressed as a percentage.

Mitral inflow and pulmonary venous velocities were recorded using conventional pulsed-wave Doppler echocardiography in the apical 4 chamber view using a 2 mm sample volume. Transmitral early (E wave) and late (A wave) diastolic velocities as well as deceleration time were recorded at the mitral leaflet tips. LV isovolumic relaxation time was also recorded. The pulmonary venous peak systolic (S) and diastolic (D) velocities were recorded with the sample volume positioned 1 cm below the orifice of the right superior pulmonary vein in the left atrium. Septal E/E' ratio was determined using color-coded tissue Doppler imaging (frame rates > 100 frames/sec) with the sample volume placed in the basal septum.

Two-dimensional speckle tracking analysis

2D speckle tracking analyses were performed on grey scale images of the LV obtained in the apical 2-, 3- and 4-chamber views and short-axis mid-ventricular views. Left ventricular radial and circumferential functions were determined in the mid-ventricular short-axis view, and longitudinal function was determined in the 3 apical views. During analysis, the endocardial border was manually traced at end-systole and the region of interest width adjusted to include the entire myocardium. The software then automatically tracks and accepts segments of good tracking quality and rejects poorly tracked segments, while allowing the observer to manually override its decisions based on visual assessments of tracking quality. Peak systolic strain, peak systolic SR (SR Sm) and peak early diastolic SR (SR Em) for the 3 orthogonal myocardial functions were determined. Mean global longitudinal strain/SR were calculated from the 3 individual apical global longitudinal strain/SR curves respectively whereas mean global circumferential strain/SR and mean radial strain/SR were obtained from the mid-ventricular short-axis view. All strain and SR measurements were exported to a spreadsheet (Microsoft ® Excel 2002, Microsoft Corporation, Redmond, WA).

To define intra- and inter-observer variability, strain and SR measurements were repeated for 10 randomly selected patients at least 4 weeks apart by the same observer on the same echocardiographic images, and by a second independent observer.

Statistical analysis

Continuous variables were presented as mean ± 1 SD unless otherwise stated. Unpaired Student's t test and Mann-Whitney U test were used to compare 2 groups of unpaired data of Gaussian and non-Gaussian distribution respectively. Multivariate linear regression analysis (enter method) was used to identify independent clinical determinants of LV strain/SR. To avoid multicolinearity between the univariate predictors, a tolerance of > 0.5 was set. Intra- and inter-observer variability of

strain and SR measurements by 2D speckle tracking were expressed as mean absolute differences and assessed by Bland-Altman analysis.[15] A 2-tailed p value of < 0.05 was considered significant. All statistical analyses were performed using SPSS for Windows (SPSS Inc, Chicago), version 16.

RESULTS

The mean age, body mass index and body surface area were 57.1 ± 6.2 years, 27.0 ± 3.1 kg/m^2, and 2.07 ± 0.18 m^2 respectively, and there were no significant differences between diabetic patients and controls (Table 1).

Table 1. Clinical Parameters in Patients with Diabetes and Healthy Subjects

Variable	Patients with diabetes (n = 47)	Healthy subjects (n = 53)	p value
Demographics			
Age (years)	58.0 ± 5.5	56.2 ± 6.6	NS
Body mass index (kg/m^2)	27.6 ± 3.2	26.4 ± 3.0	NS
Body surface area (m^2)	2.10 ± 0.18	2.05 ± 0.18	NS
Mean heart rate (beats/min)	72.5 ± 10.5	65.8 ± 8.2	0.001
Systolic blood pressure (mmHg)	137 ± 11	128 ± 13	< 0.001
Medications			
Beta blockers (%)	2.1	-	-
Calcium channel antagonist (%)	6.4	-	-
Angiotensin converting enzyme inhibitors (%)	27.7	-	-
Angiotensin receptor blocker (%)	12.8	-	-

The median diabetes mellitus diagnosis duration was 4 years (range 1 to 11 years), and the mean HbA1c level was 6.4 ± 0.7%. Although there was no evidence of autonomic neuropathy in the patients as documented by Ewing's test, the mean heart rate and systolic blood pressure of the diabetic patients was increased relative to the controls.

Table 2 outlines the echocardiographic parameters. There were no significant differences in the indexed LV volumes and EF between the diabetic patients and healthy controls. Transmitral E/A and pulmonary S/D ratios were significantly impaired in diabetic patients as compared to controls. There was also no significant difference in septal E/E' ratio between diabetic patients and healthy controls.

Myocardial strain and strain rate analysis

The mean frame rates for the apical and short-axis views were 82.3 ± 18.2 and 90.0 ± 19.5 frames/s respectively. Compared to healthy controls, diabetic patients had significantly impaired longitudinal systolic and diastolic strain and SR, but preserved circumferential and radial strains and SR (Table 2).

Table 2. Echocardiographic Parameters Between Patients with Diabetes Mellitus and Healthy Subjects

Variable	Patients with diabetes mellitus (n = 47)	Healthy subjects (n = 53)	p value
LV mass index (g/m2)	87.4 ± 13.8	83.9 ± 15.6	NS
LV end-diastolic volume index (mL/m2)	40.7 ± 8.9	44.1 ± 7.8	NS
LV end-systolic volume index (mL/m2)	16.0 ± 4.8	17.8 ± 4.3	NS
LV ejection fraction (%)	61.0 ± 5.5	59.8 ± 5.3	NS
Doppler			
Transmitral E/A ratio	0.95 ± 0.21	1.12 ± 0.32	0.007
Deceleration time (msec)	192.2 ± 37.5	196.1 ± 39.3	NS
Isovolumic relaxation time (msec)	83.3 ± 13.9	84.6 ± 19.9	NS
Pulmonary S/D ratio	1.45 ± 0.28	1.25 ± 0.27	0.001
Longitudinal function			
Mean global strain (%)	-18.3 ± 2.2	-19.9 ± 1.9	< 0.001
Mean global systolic SR (s^{-1})	-0.99 ± 0.17	-1.07 ± 0.13	0.009
Mean global early diastolic SR (s^{-1})	1.04 ± 0.25	1.26 ± 0.26	< 0.001
Circumferential function			
Global strain (%)	-22.7 ± 2.9	-23.0 ± 3.2	NS
Global systolic SR (s^{-1})	-1.40 ± 0.28	-1.37 ± 0.23	NS
Global early diastolic SR (s^{-1})	1.79 ± 0.46	1.99 ± 0.61	NS
Radial function			
Mean strain (%)	40.6 ± 11.1	42.7 ± 12.1	NS
Mean systolic SR (s^{-1})	1.71 ± 0.45	1.80 ± 0.48	NS
Mean early diastolic SR (s^{-1})	-1.98 ± 0.57	-2.14 ± 0.70	NS

LV: left ventricular; SR: strain rate

Determinants of longitudinal myocardial function

To investigate the independent clinical determinants of LV longitudinal strain, SR Sm and SR Em, multivariate linear regression analyses were performed with age, body mass index, mean heart rate, systolic blood pressure and presence of diabetes mellitus entered as covariates (Table 3). The presence of diabetes mellitus was an independent correlate of longitudinal strain (multiple R = 0.496, p = 0.001), SR Sm (multiple R = 0.612, p < 0.001) and SR Em (multiple R = 0.552, p < 0.001) on all the linear regression models.

Intra- and inter-observer variability

Intra- and inter-observer variabilities for the myocardial strain and SR measurement were evaluated (Table 4). Assessments of LV longitudinal strain/SR had the lowest intra- and inter-observer measurement variability compared to assessments of circumferential and radial strains/SR. Bland and Altman analysis showed small biases with no significant trend for all the intra- and inter-observer strain and strain rate measurements.

Table 3. Independent Correlates of Global Longitudinal Strain, Global Longitudinal Systolic Strain Rate, and Global Longitudinal Diastolic Strain Rate

Variable	Global Longitudinal Strain		Global Longitudinal Systolic SR		Global Longitudinal Diastolic SR	
	β	p value	β	p value	β	p value
Age (yrs)	-0.216	0.052	-0.095	0.341	-0.129	0.223
Body mass index (kg/m^2)	0.118	0.272	0.129	0.189	-0.153	0.140
Mean heart rate (beats/min)	-0.232	0.038	-0.551	< 0.001	0.167	0.118
Systolic BP (mmHg)	-0.055	0.638	-0.084	0.429	-0.053	0.637
Presence of diabetes mellitus	0.508	< 0.001	0.513	< 0.001	-0.477	< 0.001

BP: blood pressure; SR: strain rate

Table 4. Intra-observer and Inter-observer Variability of Left Ventricular Strain and Strain Rate Measurements

Variable	Intra-observer Absolute Difference	Inter-observer Absolute Difference
Longitudinal function		
Mean global strain (%)	1.2 ± 0.5	0.9 ± 1.0
Mean global systolic strain rate (s^{-1})	0.10 ± 0.06	0.09 ± 0.08
Mean global early diastolic strain rate (s^{-1})	0.08 ± 0.05	0.13 ± 0.09
Circumferential function		
Global strain (%)	1.2 ± 1.0	2.3 ± 2.4
Global systolic strain rate (s^{-1})	0.08 ± 0.08	0.16 ± 0.09
Global early diastolic strain rate (s^{-1})	0.31 ± 0.27	0.39 ± 0.45
Radial function		
Mean strain (%)	4.3 ± 2.3	6.5 ± 5.4
Mean systolic strain rate (s^{-1})	0.27 ± 0.18	0.34 ± 0.24
Mean early diastolic strain rate (s^{-1})	0.37 ± 0.34	0.39 ± 0.23

DISCUSSION

The present study demonstrated the presence of subclinical myocardial systolic and diastolic dysfunctions in type 2 diabetic patients with no diabetic related complications and good glycemic control. Despite normal LV mass, volumes and EF, the diabetic population showed impairments of LV longitudinal strain and SR but preserved circumferential and radial strain and SR. The presence of

diabetes mellitus was an independent predictor of LV longitudinal strain, systolic SR and diastolic SR on multiple linear regression analysis.

Pathogenesis of diabetic cardiomyopathy

The pathogenesis of diabetic cardiomyopathy is likely to be multifactorial, ranging from microvascular disease, altered myocardial metabolism, and structural changes in the myocardium with increased fibrosis. Increasingly, evidence is emerging on the role of myocardial lipotoxic injury from lipid oversupply. Visceral adipose tissue insulin resistance leads to increased myocardial fatty acid delivery and uptake with associated myocardial triglyceride accumulation.[16, 17] It is assumed that the subsequent accumulation of fatty acid intermediates is associated with mitochondrial dysfunction, leading to cell damage, apoptosis, replacement with fibrosis and myocardial contractile dysfunction.[17] Recent studies have evaluated the relationship between increased myocardial steatosis and LV dysfunction in patients with type 2 diabetes mellitus.[2, 18] Rijzewijk et al demonstrated diastolic dysfunction in a group of uncomplicated diabetic patients with documented myocardial steatosis on magnetic resonance spectroscopy.[2] In contrast, McGavock et al showed no association between myocardial triglyceride accumulation and LV function in a heterogeneous group of diabetic patients.[18] Of note, their results could be influenced by the use of insulin (a lipogenic agent) and the presence of undiagnosed coronary artery disease in their patient population, whereas Rijzewijk et al excluded patients with potential confounding comorbid conditions such as hypertension and coronary artery disease (excluded by dobutamine stress echocardiography). [2, 18] Both studies demonstrated normal global systolic function as reflected by a normal LVEF. Similarly, the present study demonstrated the presence of diastolic dysfunction (indicated by significantly greater impairments of transmitral E/A and pulmonary S/D ratios) but preserved global LVEF in diabetic patients compared to normal controls.

Changes in myocardial function

Previous epidemiological studies have demonstrated increased prevalence of diabetes mellitus in heart failure populations, and this increased prevalence is seen particularly in heart failure patients with normal LVEF.[19] However, LVEF is a relatively insensitive measure of LV systolic function compared to strain and strain rate imaging, especially in the context of subclinical LV systolic dysfunction.[3-8] As the LV myocardial architecture is a complex array of longitudinally and circumferentially orientated fibres located predominately in the epicardium/endocardium and mid-wall respectively[20], multidirectional analyses of longitudinal, circumferential and radial function allow understanding of regional LV myocardial functional changes in subclinical diabetic heart disease.

Both Fang et al and Vinereanu et al demonstrated decreased LV longitudinal function but compensatory increase in radial function in diabetic patients.[3, 4] However, due to the angle limitations associated with tissue Doppler imaging, both studies could only assess the impact of diabetes mellitus on LV longitudinal and radial functions in a few limited myocardial segments, and circumferential myocardial function was not evaluated. Using 2D speckle tracking to assess all myocardial segments, the present study demonstrated reduced longitudinal strain and SR (predominantly derived from

epicardial/endocardial fibre contraction) but preserved circumferential and radial strains and SR (predominantly derived from mid-wall circumferential fibres contraction) in diabetic patients. This finding suggests that myocardial dysfunction in early diabetic cardiomyopathy may start in the subendocardium. On multivariate analysis, the presence of diabetes mellitus was an independent predictor of impaired longitudinal strain and SR in this unique group of truly uncomplicated type 2 diabetic patients.

Clinical implications

The novel aspect of the current study is the multidirectional strain and SR analysis by 2D speckle tracking in patients with uncomplicated type 2 diabetes mellitus. The associated myocardial systolic and diastolic dysfunction detected on echocardiography was independent of age, body mass index and blood pressure. Current 2D speckle tracking analysis cannot take into account "through plane" cardiac motion and that may influence the absolute strain/SR values. The exclusion of women in the study limits its generalizability. However, the widespread availability of echocardiography and ease of use with 2D speckle tracking may allow serial assessments of patients with diabetic heart disease and monitor disease progression.

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