CHAPTER 6

Changes in multidirectional LV strain in asymptomatic patients with type 2 diabetes mellitus: a 2-year follow-up study

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Abstract

Asymptomatic patients with diabetes mellitus (DM) and normal left ventricular (LV) ejection fraction (EF) may have LV dysfunction as assessed with speckle tracking echocardiography. Whether this subtle LV dysfunction may progress or not over time remains unknown. The present evaluation assessed changes in LV function with two-dimensional (2D) speckle tracking analysis in asymptomatic clinically stable patients with type 2 DM and normal LVEF after 2-year follow-up.

A total of 112 asymptomatic patients with type 2 DM and normal LVEF (53 ± 10 years, 59 % men) were evaluated. Patients remained clinically stable between baseline and follow-up echocardiography. Conventional and 2D speckle tracking echocardiographic measurements were performed. Circumferential (CS) and longitudinal strain (LS) were measured to assess systolic function and strain rate during isovolumic relaxation time (SR IVR) and peak transmitral early diastolic inflow strain rate (SR E) to asses diastolic function.

After 2-year follow-up, a significant increase in the LV mass index and significant decrease in the E/A ratio were observed. Left ventricular ejection fraction remained unchanged (59 % to 60 %, $p = 0.4$). In contrast, 2D speckle tracking analysis demonstrated a significant impairment in CS (-19.7 ± 4.0 % to -18.9 ± 3.8 %, $p < 0.001$), LS (-17.2 ± 2.3 % to -16.9 ± 2.7 %, $p = 0.022$) and SR E (1.02 ± 0.28 S^{-1} to 0.94 ± 0.25 S^{-1}, $p < 0.001$). After adjusting for changes in LV mass index, only changes in CS and SR E remained significant ($p < 0.001$ and $p = 0.013$, respectively).

Asymptomatic patients with type 2 DM and normal LVEF may show mild progression of subclinical LV dysfunction assessed with 2D speckle tracking echocardiography. The prognostic implications of these mild changes warrant prospective evaluation.

Introduction

Diabetes mellitus (DM) is an independent risk factor for the development of heart failure (HF).[1, 2] In addition, HF patients with DM have more severe disease and worse prognosis than patients without DM.[3] The increased prevalence of coronary artery disease (CAD) and hypertension in patients with DM contribute to the increased incidence of HF.[4, 5] Furthermore, diabetic cardiomyopathy has been proposed as a primary myocardial disease in DM patients without significant epicardial CAD, hypertension or valvular heart disease. This entity is characterized by microvascular disease, altered myocardial metabolism and increased myocardial fibrosis, that lead to gradual decline in left ventricular (LV) function with impairment in LV relaxation first, and then, followed by systolic dysfunction may progress over time to congestive HF.[6, 7] Therefore, before presenting with overt HF symptoms, diabetic patients may have long-standing subclinical myocardial dysfunction. Interestingly, whether progression of subclinical LV dysfunction towards overt HF symptoms occurs in DM patients is unknown. At present, there is a lack of longitudinal evaluations concerning the presence and development of structural and functional myocardial abnormalities in patients with DM.
Two-dimensional (2D) speckle tracking echocardiography has demonstrated that type 2 DM patients without cardiovascular complications and with preserved LV ejection fraction (EF) may exhibit LV systolic and diastolic dysfunction.[8] Further progression in LV dysfunction in asymptomatic clinically stable patients with type 2 DM has not been evaluated with this imaging technique. Therefore, the aim was to assess changes in LV function with 2D speckle tracking echocardiography in asymptomatic clinically stable patients with type 2 DM and normal LVEF.

Methods

Patient population

The population consisted of 112 asymptomatic patients with type 2 DM and complete clinical and echocardiographic follow-up at 2 years. This subgroup of patients was selected from an original cohort of patients previously described.[9] In brief, the original cohort included type 2 DM patients who were referred for cardiovascular risk assessment as part of regular patient care. All patients underwent a structured interview, physical examination, blood and urine laboratory testing and 2D transthoracic echocardiography. Type 2 DM was diagnosed according to the American Diabetes Association criteria in the absence of demonstrable auto-antibodies to islet cells, insulin and glutamic acid decarboxylase or low plasma C-peptide levels.[10] All patients were free of cardiovascular complaints as confirmed with the Rose questionnaire on chest pain.[11] Exclusion criteria were: angina or angina-equivalent symptoms, known CAD (defined as previous acute coronary syndrome, percutaneous or surgical coronary revascularization or angiographically documented coronary stenosis of ≥50 % luminal diameter), cardiomyopathy,

significant valvular heart disease, congenital heart disease, and heart rhythm other than sinus rhythm or conduction abnormalities.
In the present evaluation, consecutive patients with repeat echocardiography at 2-year follow-up, who remained clinically stable during the follow-up, were included. Patients who presented with major adverse cardiovascular events (acute coronary syndrome, myocardial infarction or coronary revascularization and cardiac surgery) during the follow-up were excluded. From the original 234 asymptomatic patients with type 2 diabetes mellitus, 121 patients had repeat echocardiogram at 2-year follow-up. Nine patients were excluded: 8 patients because of cardiovascular events and one because of inadequate image quality to ensure reliable speckle tracking analysis.
Clinical, demographic, and echocardiographic data were prospectively collected in the departmental electronic patient dossier information system (EPD-vision®; Leiden, The Netherlands) and retrospectively analyzed.

Echocardiography

Patients underwent 2D transthoracic echocardiography at baseline and at 2-year follow-up using a commercially available system (Vivid 7 and E9, General-Electric Vingmed, Horton, Norway) equipped with 3.5-MHz and M5S transducers. ECG-gated images were obtained in the parasternal, apical and subcostal views with the patient lying in the left lateral decubitus position. Standard M-mode, 2D, color, pulsed and continuous wave Doppler images were recorded during breath hold and saved in cine-loop format. Analyses of the images were performed offline with dedicated software (EchoPac version 112.0.1 General-Electric Vingmed).
Left ventricular end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were measured from the apical four- and two-chamber views and calculated using the Simpson's biplane method.[12] Thereafter, LVEF was calculated as [(LVEDV-LVESV)/LVEDV] x 100. LV mass was measured at end-diastole on M-mode recordings obtained in the parasternal long-axis view and calculated with the Devereux formula.[13] The intra- and interobserver reproducibility for the measurement of LV mass, assessed in 20 randomly selected patients, was 1.4 ± 13.2 g/m^2 and -1.2 ± 8.4 g/m^2, respectively. In addition, left atrial (LA) volume was calculated according to the ellipsoid method from three LA diameters measured in the apical four-chamber and parasternal long-axis views.[12] LV and LA dimensions were normalized for body surface area (BSA).
Parameters of LV diastolic function were determined from transmitral inflow velocities using pulsed wave Doppler recordings in the apical four-chamber view.[14] Early (E) and late (A) peak mitral inflow velocity of LV filling and deceleration time (DT) of the E-wave were measured and the E/A ratio was calculated. Isovolumic relaxation time (IVRT) was measured from pulsed wave Doppler spectral recordings obtained in the apical five-chamber view. Systolic and diastolic pulmonary vein flow velocities (PVs and PVd) were measured from pulsed wave Doppler recordings at the right superior pulmonary vein in the apical four-chamber view and the pulmonary vein PVs/PVd ratio was

calculated. Furthermore, peak mitral annular velocity (E') was measured using tissue Doppler imaging in the apical four-chamber view. E' was measured at the septal and lateral mitral annulus and the mean E' was calculated. Subsequently, the E/E' ratio was derived.[15]
The diastolic dysfunction grade was determined according to the criteria proposed by the European Association of Echocardiography:[14] 1. normal diastolic function when E' ≥9 cm/s and LA volume ≤34 mL/m^2, 2. mild diastolic dysfunction (grade I) when E/A ratio <0.8, DT >200 ms and E/E' ratio ≤8, 3. moderate diastolic dysfunction (grade II) when E/A ratio 0.8-1.5, DT between 160-200 ms and E/E' ratio between 9 and 12 and 4. severe diastolic dysfunction (grade III) when E/A ratio ≥2, DT <160 ms and E/E' ratio ≥13.[14]

2D Speckle tracking echocardiography

LV function was further assessed with 2D speckle tracking echocardiography using semi-automated software (EchoPac version 112.0.1 General-Electric Vingmed). 2D speckle tracking allows for angle-independent quantification of myocardial tissue deformation (strain) and the rate of deformation (strain rate) by analyzing frame to frame the movement of 'speckles' (myocardial acoustic markers) throughout the cardiac cycle.[16] 2D speckle tracking analysis was performed offline in standard grey-scale 2D images with a frame rate of at least 40 frames per minute. LV systolic function was assessed by measuring LV systolic circumferential and longitudinal strain. As previously described, circumferential strain (CS) evaluates the myocardial shortening along the curvature of the left ventricle in the short-axis view, whereas longitudinal strain (LS) assesses the magnitude of myocardial shortening in the longitudinal direction in the apical LV views.[17, 18] Furthermore, LV diastolic function was assessed measuring longitudinal strain rate during the IVRT (SR IVR) and at the peak early mitral inflow velocity (SR E) at the apical long-axis views.[19] These variables were measured as surrogates of LV pressure decay during the IVRT and LV relaxation, respectively.
Global LV circumferential peak systolic strain was measured using the LV short-axis view at the papillary muscle level. The endocardial border was manually traced on a single end-systolic frame. Subsequently, the software automatically generated a region of interest, which was manually adjusted to include the entire myocardial wall (Figure 1). Next, the software automatically divided the region of interest in six equal segments and indicated the tracking quality for each segment. If necessary, the region of interest was adjusted to improve tracking quality. Afterwards, the software provided strain and strain rate curves for the six myocardial segments (Figure 1). In addition, a 'global' curve was provided, representing the average strain, from which global LV circumferential peak systolic strain was derived.

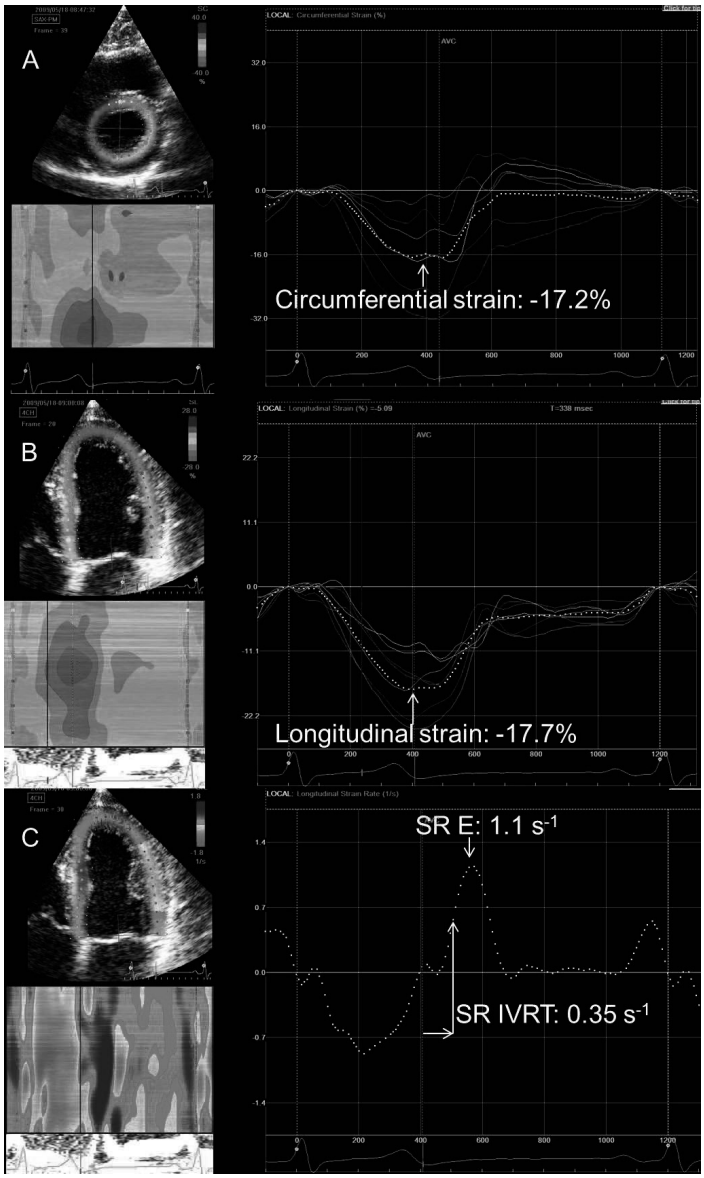

Figure 1 *Assessment of left ventricular myocardial strain (A, B) and strain rate (C) using 2D speckle tracking analysis. The upper left corner of each panel shows the region of interest including the entire myocardium. Regional strain curves are presented by the software as the colored lines (A, B) and a global strain curve (A and B) or strain rate curve (C) as the white dotted line. Circumferential strain (A) was measured from the LV short axis view. Longitudinal strain (B) was measured from the three standard apical views (apical long axis, two-chamber, and four-chamber view, respectively) and the average was calculated. Strain rate (C) during isovolumic relaxation time (calculated by adding the IVRT to the aortic valve closure time which is indicated by the vertical green dotted line in the strain rate curve) and at peak early diastolic inflow velocity (defined as the first peak in global longitudinal strain after aortic valve closure time) were measured from the three standard apical views and the average was calculated.*

Global LV longitudinal peak systolic strain was measured using the same method in the three standard apical views: the apical long-axis, two-chamber, and four-chamber views, respectively. The average global LV longitudinal peak systolic strain from the three apical views was calculated.
In addition, the longitudinal strain rate curves were used to assess SR IVR and SR E (Figure 1). SR IVR was defined as longitudinal strain rate during IVRT (calculated by adding the IVRT to the aortic valve closure time). SR E was defined as the first peak in global longitudinal strain rate after aortic valve closure. SR IVR and SR E were measured in the apical long-axis, two-, and four-chamber views and the average of these measurements was calculated.
Intra- and interobserver variabilities have been previously reported for global CS (1.2 ± 1.0 % and 2.3 ± 2.4 %) and for average global LS (1.2 ± 0.5 % and 0.9 ± 1.0 %).[8]

Statistical analysis

Continuous data are presented as mean ± standard deviation when normally distributed (as assessed with the Kolmogorov-Smirnov test) and as median (25^{th} and 75^{th} percentiles) when non-normally distributed. Categorical data are presented as frequencies and percentages.
Changes in conventional echocardiographic parameters at follow-up were determined using the paired t-test, Wilcoxon signed rank test and Friedman's test for repeated measurements, as appropriate. Changes in 2D speckle tracking strain parameters were evaluated with linear mixed models and adjusted for changes in the LV mass index during follow-up. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows (version 20.0, SPSS Inc., Chicago, IL, USA).

Results

Baseline clinical, demographic and echocardiographic characteristics

A total of 112 patients (mean age 53 ± 10 years, 66 (59%) men) were evaluated. By definition, all patients remained clinically stable and free of cardiovascular complaints during a median follow-up of 2.5 (2.3-2.8) years. The clinical characteristics of the patients are summarized in Table 1. Mean DM duration was almost 10 years and mean hemoglobin A1c was 7.6 ± 1.6 %. In addition, 72 (64 %) patients had hypertension (defined as blood pressure >140/90 or use of antihypertensive medication).
Echocardiographic parameters are presented in Table 2. Patients showed normal LV systolic function, based on the measurement of LVEF (59 ± 6 %) and LV volumes (mean indexed LVEDV and LVESV were 47 ± 9 mL/m^2 and 19 ± 5 mL/m^2, respectively).[12] Likewise, mean LV mass index and LA volume index were within normal range, 88 ± 18 g/m^2 and 18 ± 5 mL/m^2, respectively. In contrast, mean E/A ratio and E' were decreased and mean E/E' ratio was increased.[14] Classification in grades of LV diastolic dysfunction showed that 28 % of patients had normal LV diastolic filling pattern, 41 % had mild (grade I) and 31 % had moderate (grade II) diastolic dysfunction.
When LV systolic and diastolic functions were assessed with 2D speckle tracking echocardiography, patients showed impaired global LV CS and LS (Table 3).[8] In addition, LV diastolic dysfunction was confirmed with a reduced SR E, but normal SR IVR.[8, 20]

Changes in conventional and 2D speckle tracking echocardiographic data at follow-up

At follow-up, conventional echocardiography demonstrated no significant changes in LV systolic function (Table 2). Indexed LV volumes and LVEF remained unchanged. Interestingly, LV mass index significantly increased (from 88 ± 18 g/m^2 to 95 ± 18 g/m^2, p <0.01). In terms of LV diastolic function, the E/A ratio significantly decreased (from 1.04 ± 0.29 to 0.95 ± 0.28, p <0.01), indicating a decline in LV diastolic function. In contrast, mean E', E/E' ratio and LA volume index did not significantly change.
Changes in LV function as assessed with 2D speckle tracking echocardiography demonstrated deterioration in global LV systolic function (Table 3). Due to technical limitations, follow-up LV LS could not be assessed in one patient and LV CS analysis was not feasible in three patients. Global CS and global LS significantly impaired at follow-up (from -19.7 ± 4.0 % to -18.9 ± 3.8 %, p <0.001, and from -17.2 ± 2.3 % to -16.9 ± 2.7 %, p = 0.022, respectively). In addition, there was a progressive decline in LV diastolic function and particularly of LV relaxation with an impairment in SR E (from 1.02 ± 0.28 S^{-1} to 0.94 ± 0.25 S^{-1}, p <0.001). In contrast, SR IVR remained unchanged. When these changes were corrected for changes in LV mass index, changes in global LS were no longer significant (p = 0.051), whereas changes in CS and SR E remained significant (p <0.001 and p = 0.013, respectively) (Table 3).

Table 1 *Baseline clinical, demographic characteristics.*

Clinical variables	**n=112**
Age (years)	53 ± 10
Male gender, n (%)	66 (59%)
Diabetes duration (months)	115 ± 90
Hemoglobin A1c (%)	7.6 ± 1.6
Diabetes treatment, n (%)	
Diet only	3 (3%)
Oral glucose lowering agent	65 (58%)
Insulin	23 (21%)
Insulin and oral agent	21 (19%)
Body mass index (kg/m^2)	29 ± 5
Body surface area (m^2)	2.0 ± 0.2
Family history CAD, n (%)	60 (54%)
Smoking, n (%)	20 (18%)
Hypertension, n (%)	72 (64%)
Hypercholesterolemia, n (%)	88 (79%)
Total cholesterol (mmol/L)	4.9 ± 1.2
Triglycerides (mmol/L)	1.7 (1.2-2.6)
Creatinine (µmol/L)	78 ± 21
Glomerular filtration rate (mL/min/1.73m^2)	87 (75-106)
Urinary albumine/creatinine ratio (µg/µmol)	2.0 (0.9-7.0)
Microalbuminuria ≥3.5 µg/µmol	34 (30%)
Medication, n (%)	
Aspirin	21 (19%)
Angiotensin-converting enzyme inhibitor	38 (34%)
Angiotensin receptor antagonists	28 (25%)
Statins	61 (55%)

Abbreviations: CAD: coronary artery disease.
Family history of CAD was defined as a history of CAD in first degree family member before the age of 55 years in males or before 65 years in females. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of antihypertensive medication. Hypercholesterolemia was defined as a total cholesterol ≥5 mmol/L or statin use. Glomerular filtration rate (GFR) was calculated with the Modification of Diet in Renal Disease (MDRD) study equation. Patients were considered to have a normal renal function when GFR was ≥60 mL/min/1.73m2 and moderate renal dysfunction when GFR was 30-59 mL/min/1.73m2.

Table 2 *Changes in LV function as measured with conventional echocardiography at follow-up.*

Echocardiographic parameters	Baseline	Follow-up	*p*-value
LVEDV (mL/m^2)	47 ± 9	48 ± 10	0.5
LVESV (mL/m^2)	19 ± 5	20 ± 6	0.8
LVEF (%)	59 ± 6	60 ± 7	0.4
LV mass indexed by BSA (g/m^2)	88 ± 18	95 ± 18	<0.01
LA volume indexed by BSA (mL/m^2)	18 ± 5	18 ± 5	0.9
E (cm/s)	69 ± 15	69 ± 17	0.9
A (cm/s)	70 ± 18	75 ± 18	<0.01
E/A ratio	1.04 ± 0.29	0.95 ± 0.28	<0.01
DT (ms)	203 ± 36	217 ± 41	<0.01
IVRT (ms)	74 ± 10	74 ± 10	0.9
PVs (cm/s)	49 ± 12	48 ± 17	0.6
PVd (cm/s)	39 ± 10	37 ± 12	0.2
PVs/PVd ratio	1.31 ± 0.28	1.34 ± 0.31	0.5
E' (cm/s)	6.6 ± 2.1	6.6 ± 1.9	0.9
E/E' ratio	11.4 ± 5.1	11.3 ± 4.6	0.9
LV diastolic dysfunction			**0.4**
Normal function, n (%)	28%	25%	
Mild diastolic dysfunction, n (%)	41%	40%	
Moderate diastolic dysfunction, n (%)	31%	35%	

Abbreviations: A: peak transmitral late diastolic inflow velocity, BSA: body surface area, DT: deceleration time of E, E: peak transmitral early diastolic inflow velocity, E': peak early mitral annular velocity, IVRT: isovolumic relaxation time, LA: left atrium, LV: left ventricle, LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic volume.

Table 3 *Changes in left ventricular function as measured with 2D speckle tracking at follow-up.*

2D speckle tracking parameters	Baseline	Follow-up	*p*-value	*p*-value*
Global circumferential strain (%)	-19.7 ± 4.0	-18.9 ± 3.8	<0.001	<0.001
Global longitudinal strain (%)	-17.2 ± 2.3	-16.9 ± 2.7	0.022	0.051
Average SR IVR (S^{-1})	0.39 ± 0.21	0.38 ± 0.21	0.651	0.949
Average SR E (S^{-1})	1.02 ± 0.28	0.94 ± 0.25	<0.001	0.013

**p-value: adjusted for changes in LV mass index.*
Abbreviations: SR E: strain rate at peak transmitral early diastolic inflow velocity, SR IVR: strain rate during isovolumetric relaxation time.

Discussion

The present evaluation demonstrated a mild decline in LV function as assessed with 2D speckle tracking echocardiography in asymptomatic patients with type 2 DM and normal LVEF after a median follow-up of 2.5 years. At follow-up, deterioration of LV systolic function was shown by a significant decrease in CS and LS, whereas a decline in LV diastolic function was indicated by a significant decrease in SR E. Furthermore, a significant increase in LV mass was observed. Conversely, these changes in LV function were not detected by conventional echocardiography.

Increased prevalence of LV dysfunction in asymptomatic patients with DM

Contemporary population-based studies have shown that the incidence of congestive HF in patients with DM has increased by 3-15 times in the last years.[6, 21] Nichols et al. reported a 2.5-fold higher incidence of congestive HF in 8,231 DM patients compared with 8,845 non-DM patients who were followed-up for 5.5 years (30.9 vs. 12.4 cases per 1,000 person-years, $p < 0.001$).[21] The presence of CAD, renal dysfunction and hypertension are strong contributors to the increased incidence of congestive HF in DM patients.[21, 22] However, DM patients may remain asymptomatic for long time and early detection of changes in cardiac structure and function due to primary myocardial disease, hypertension or asymptomatic CAD may help to identify the patients with an increased risk for developing congestive HF. A wide range of prevalence of subclinical LV diastolic dysfunction has been reported in asymptomatic patients with DM ranging from 23 to 75 %.[6, 23] In a cohort of 1,760 asymptomatic DM patients, From et al. demonstrated that the prevalence of subclinical LV diastolic dysfunction, defined by an E/E' ratio >15, was 23 %.[6] During 5-years follow-up, DM patients with LV diastolic dysfunction doubled the cumulative probability of incident congestive HF of DM patients without LV diastolic dysfunction (36.9 % vs. 16.8 %, $p < 0.001$). The presence of LV diastolic dysfunction was independently associated with incident congestive HF after correcting for age, CAD, hypertension, LVEF, body mass index, LA volume, LV mass and E-wave deceleration time.[6] These findings underscore the need of sensitive diagnostic tools that permit early detection of subclinical LV dysfunction.

Prevalence of LV dysfunction assessed with speckle tracking echocardiography in asymptomatic DM patients

Conventional echocardiography is traditionally used to quantify LV systolic function by means of LVEF and diastolic function through assessment of mitral valve inflow velocity pattern and measurement of the E/A ratio and E-wave deceleration time.[12, 14] However, LVEF is an insensitive parameter to detect subtle LV dysfunction.[24, 25] In addition, the E/A ratio and E-wave deceleration time depend on preload conditions, LV relaxation and LV compliance, and cannot differentiate normal diastolic function from grade II diastol-

ic dysfunction without Valsalva manoeuvres. Accordingly, current recommendations include also the measurement of tissue Doppler imaging parameters such as the E' and the E/E' ratio, known markers of LV relaxation and LV filling pressures, respectively.[14] More recently, 2D speckle tracking echocardiography has allowed the detection of subclinical myocardial dysfunction by measuring multidirectional LV strain and strain rate. This modality overcomes important limitations of conventional echocardiography and tissue Doppler imaging. The assessment of LV strain and strain rate is a more sensitive marker of LV dysfunction and has a better reproducibility compared to LVEF.[8] In patients with DM and preserved LVEF, 2D speckle tracking echocardiography has demonstrated the presence of subtle LV systolic dysfunction.[8, 26] For example, the study by Nakai and coworkers showed that patients with type 2 DM and normal LVEF had impaired LV CS and LS when compared with healthy controls (LV CS: -22.6 % in type 2 DM patients vs. -24.4 % in controls, $p < 0.005$; and LV LS: -17.6 % in type 2 DM patients vs. -20.8 % in controls, $p < 0.001$).[26] However, studies evaluating changes in LV mechanics over time in type 2 DM patients who remain asymptomatic are sparse.

Progression of subclinical LV dysfunction

At present, only a few studies have investigated changes of LV dysfunction over time in patients with DM.[27] In 27 type 2 DM patients, Vintila et al. showed progression of subclinical LV dysfunction after 5-years follow-up by a significant reduction in longitudinal velocities measured with TDI echocardiography (mean longitudinal systolic velocity 4.9 cm/s vs. 5.6 cm/s, $p = 0.001$).[28] The present evaluation confirms and extends previous observations by measuring 2D speckle tracking echocardiography derived LV systolic and diastolic parameters. Asymptomatic patients with type 2 DM showed subclinical LV systolic and diastolic dysfunction as reflected by impaired CS and LS, and reduced SR E. More important, after 2-year follow-up and despite remaining clinically stable and asymptomatic, these patients showed progression of subclinical LV dysfunction with further impairment in CS and LS, and decline in SR E together with an increase in LV mass. In contrast, conventional echocardiographic measurements did not show significant changes in LV systolic and diastolic function. Therefore, 2D speckle tracking echocardiography may be a promising tool for identification and monitoring of subclinical LV dysfunction in patients with DM. Early identification of type 2 DM patients with subclinical LV dysfunction allows initiation of therapeutic strategies to prevent progression to HF and improve prognosis. Moreover, the current study demonstrated mild progression of subclinical LV dysfunction after 2-year follow-up, which supports the importance of regular echocardiographic surveillance of these patients.

Limitations

Some limitations should be acknowledged. First, the present evaluation is retrospective, includes a relatively small cohort of asymptomatic type 2 DM patients and some

patients had additional cardiovascular risk factors, such as hypertension or hypercholesterolemia, which may contribute to development and progression of LV dysfunction. However, as type 2 DM often is part of a clustering of cardiovascular risk factors, the current population is a better representation of the daily clinical practice. Second, to avoid the influence of myocardial ischemia on LV function, only patients who were clinically stable were included in the study. Exercise test was not systematically performed to exclude significant coronary stenosis. However, patients who presented with angina complaints or acute coronary syndromes during follow-up were excluded. Third, previous studies have demonstrated that strain and strain rate increase from base to apex, and therefore, heterogeneity in regional strain peaks was not further evaluated in the present study.[29] Fourth, N-terminal pro brain natriuretic peptide (NT-proBNP) was not systematically assessed. Finally, the prognostic implications of these mild changes in LV function were not evaluated. Additional prospective studies are needed in order to elucidate whether systematic echocardiographic surveillance should be recommended in order to improve the risk stratification of this subpopulation.

Conclusions

Asymptomatic patients with type 2 DM and normal LVEF may show mild progression of subclinical LV dysfunction assessed with 2D speckle tracking echocardiography. The prognostic implications of these mild changes in LV function and recommendations on systematic echocardiographic surveillance of this subpopulation need further prospective evaluation.

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