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Left Ventricular Diastolic Function in Type 2 Diabetes Mellitus

Prevalence and Association With Myocardial and Vascular Disease

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Background—Although type 2 diabetes mellitus is a risk factor for developing congestive heart failure, the mechanism leading to heart failure is unclear. We examined the prevalence of left ventricular (LV) systolic and diastolic dysfunction in patients with type 2 diabetes mellitus in relation to vascular function and myocardial perfusion.

Methods and Results—A prospective observational study of 305 patients with type 2 diabetes mellitus (diabetes duration, 4.5±5.3 years) referred consecutively to a diabetes clinic were screened for LV systolic and diastolic function by echocardiography. Vascular function was estimated using noninvasive estimation of pulse pressure, carotid arterial compliance, total arterial compliance, and valvulo-arterial impedance. The prevalences of LV diastolic dysfunction and left atrial (LA) volume index >32 mL/m^2 were 40% and 32%, respectively. The prevalence of myocardial ischemia on myocardial perfusion scintigraphy was more frequent in patients with grade 2 diastolic dysfunction and LA volume index >32 mL/m^2 compared with those having normal or grade 1 diastolic dysfunction (P=0.002) or LA volume index ≤32 mL/m^2 (P<0.001), respectively. Predictors of grade 2 diastolic dysfunction and LA dilation were summed stress score on myocardial perfusion scintigraphy, total arterial compliance, and valvulo-arterial impedance, whereas pulse pressure and carotid arterial compliance were not, after adjusting for age, sex, and diabetes duration. On multivariable modeling, summed stress score (P<0.001) and valvulo-arterial impedance (P=0.027) remained predictors of grade 2 diastolic dysfunction, and only summed stress score (P<0.001) was a predictor of LA dilation.

Conclusions—Abnormal LV filling is closely associated with abnormal myocardial perfusion on myocardial perfusion scintigraphy, whereas the association of LV filling with vascular function is less prominent.

Clinical Trial Registration—The trial has been registered at www.clinicaltrial.gov with Identifier: NCT00298844.

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Key Words: left ventricular diastolic dysfunction ■ left atrial volume index ■ myocardial perfusion ■ vascular function ■ type 2 diabetes mellitus

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In the past decade, patients with signs and symptoms of heart failure despite a near normal left ventricular (LV) systolic function has received growing attention, for which the term LV diastolic heart failure or heart failure with normal ejection fraction (HFNEF) has been introduced. It has been demonstrated that there exists an important association between HFNEF and type 2 diabetes mellitus (T2DM),[1–3] in which the prevalence of abnormal LV diastolic function has been reported to be 43% to 75% in these patients.[4–6] In addition, several studies have consistently demonstrated increased mortality rates in patients with HFNEF.[7] LV diastolic function can be evaluated noninvasively by Doppler echocardiography, and, in the recent European Consensus Statement on Diagnosis of HFNEF, Doppler echocardiography has a central position in establishing the diagnosis.[8] Whether HFNEF is caused by an intrinsic myocardial disorder or related to vascular disease with abnormal ventriculo-arterial coupling is, however, still controversial. Better understanding of this is imperative for implementation of therapeutic interventions to improve the prognosis of this large patient group.

Clinical Perspective on p 31

To investigate the association between myocardial function and vascular function in patients with T2DM, we assessed the

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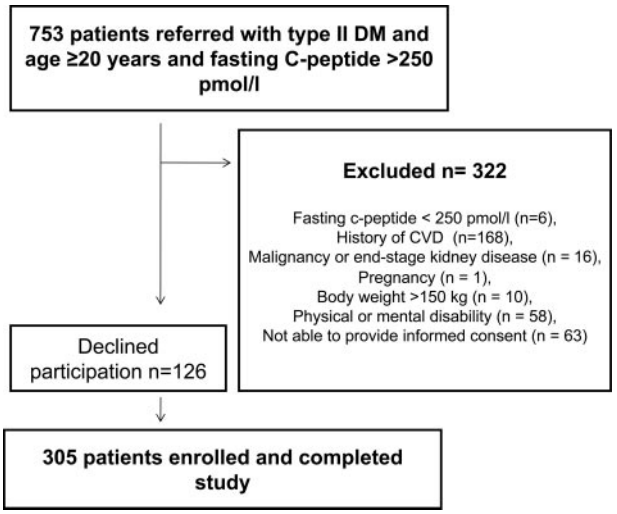

Figure 1. Enrollment of patients.

association between vascular disease, arterial compliance, and myocardial perfusion with the presence of moderate or severe LV diastolic dysfunction and left atrial (LA) dilation in a T2DM population with no history of cardiovascular disease.

Methods

Population

In a prospective observational design, 753 patients with T2DM referred for the first time to the Diabetes Clinic at Odense University Hospital, Denmark, from January 2006 to December 2007, were evaluated. Reasons for referral were (1) diabetes education or (2) glycemic regulation of poorly regulated diabetes. We enrolled patients ages ≥20 years with a fasting C-peptide >250 pmol/L. Of the 753 patients, 431 were eligible and 126 patients declined to participate; thus, the remaining 305 T2DM patients were enrolled in the study (Figure 1). The study was carried out according to Good Clinical Practice, was approved by the Regional Ethics Committee, and registered at www.clinicaltrials.gov. All participants gave written informed consent.

Each patient underwent a single-day program including a cardiovascular risk factor evaluation; a comprehensive Doppler echocardiogram; myocardial perfusion scintigraphy (MPS); B-mode ultrasound of the carotid arteries; measurements of brachial, ankle, and toe systolic blood pressures; and measurement of plasma N-terminal pro–brain natriuretic peptide (NT-proBNP). Glomerular filtration rate was determined using a 1-point ^{51}Cr-EDTA clearance procedure.[9]

Echocardiography

The echocardiograms were obtained on a Vivid 5 GE medical ultrasound machine with a 2.5-MHz transducer and were stored digitally for later blinded analysis. For all Doppler recordings, a horizontal sweep of 100 mm/s was used, and for all Doppler variables, the average of 5 consecutive beats was measured.

LV Systolic Function

LV ejection fraction (LVEF) and LV volumes were estimated using the biplane modified Simpson method.[8,10] LV systolic dysfunction was defined as LVEF <50%. Pulsed-wave Doppler was used in the apical 5-chamber view or apical long-axis view with the cursor placed in the LV outflow tract. Stroke volume (SV) and cardiac output (CO) were calculated using the LV outflow tract area and stroke length from a pulsed-wave Doppler recording of outflow tract flow. CO was calculated as SV multiplied by heart rate. Based on continuous-wave Doppler recording of LV outflow, the mean pressure gradient across the aortic valve was measured.

LV dimension were obtained from the parasternal long-axis view. LV mass index was calculated using the formula $(0.8 \cdot [1.04 \cdot (LVDd + IVSd + PWd)^3 - (LVDd)^3]) + 0.6$ g)/body surface area.[10] LV hypertrophy was considered moderate to severe if LV mass index was >108 g/m^2 (women) and >131 g/m^2 (men).[10] Relative wall thickness was calculated using the formula $(2 \cdot PWd)/LVDd$.[10]

LV Diastolic Function

Mitral inflow was assessed with pulsed-wave Doppler obtained with the transducer in the apical 4-chamber view, with the Doppler beam aligned perpendicular to the plane of the mitral annulus. The Doppler sample volume was placed between the tips of the mitral leaflets during diastole. Color M-mode Doppler echocardiography was done in the apical 4-chamber view, with the M-mode cursor aligned parallel with LV inflow. The M-mode cursor was positioned through the center of inflow, avoiding boundary regions. The propagation velocity (Vp) was measured as the slope of the first aliasing velocity from the mitral annulus in early diastole to 4 cm distally into the LV cavity. Tissue Doppler was used at the septal and lateral mitral annulus to measure the mitral plane movement. LV filling was divided into 4 distinct filling patterns, based on a combination of mitral inflow, tissue Doppler measurements of the mitral plane movement, and mitral inflow assessed with color M-mode.[11] Normal LV diastolic function was defined as mitral deceleration time: 140 to 240 ms, E/A flow velocity ratio: 0.7 to 1.5, Vp >45 cm/s, and $e_{septum}' \geq 8$ cm/s; grade 1 diastolic dysfunction: mitral deceleration time >240 ms, E/A flow velocity ratio <0.7, Vp ≤45 cm/s, and $e'_{septum} < 8$ cm/s; grade 2 diastolic dysfunction: mitral deceleration time: 140 to 240 ms, E/A flow velocity ratio: 0.7 to 1.5, Vp ≤45 cm/s, and $e'_{septum} < 8$ cm/s; grade 3 diastolic dysfunction: mitral deceleration time <140 ms, E/A flow velocity ratio >1.5, Vp ≤45 cm/s, and $e'_{septum} < 8$ cm/s.

LA Volume Index

LA volume was estimated by the biplane area-length method, using measurements at the apical 4- and 2-chamber views at end-systole (maximum LA size).[10] LA volume index was calculated as LA volume divided with the body surface area. LA volume index was considered moderate or severely increased if it was >32 mL/m^2.

The absolute interobserver agreement between 2 observers obtained in 20 randomly selected patients on LV diastolic filling pattern and LA volume index over or below 32 mL/m^2 was 95% (κ=0.91) and 85% (κ=0.70), respectively.

Myocardial Perfusion Scintigraphy

The MPS examinations were performed in concordance with standards of the American Society of Nuclear Cardiology using ECG-gated single-photon emission computed tomography with ^{99m}technetium sestamibi.[12] Whenever a potential stress-induced perfusion defect was observed, an additional rest study was carried out to evaluate the degree of reversibility. In 269 patients, adenosine stress (140 μg/kg/min) was used, in 26 bicycle exercise stress using the Bruce protocol, and in 10 dobutamine stress tests. A semiquantitative visual interpretation was made by 2 observers using a 20-segment model. A summed stress score (SSS) was calculated. The final result was decided by consensus. Myocardial ischemia was defined as a regional perfusion abnormality with a total SSS ≥4 and at least 1 segment with an SSS ≥2. Four perfusion patterns were registered: normal, reversible, mixed, and fixed defects according to the standards of the American Society of Nuclear Cardiology.[12] The 2 observers' diagnostic accuracy has been reported previously.[13]

Vascular Function

Total arterial compliance was estimated by calculating the stroke volume index pulse-pressure ratio (SVi/PP).[14] Arterial impedance was estimated using the valvulo-arterial impedance (Zva) calculated by the formula (systolic blood pressure+mean gradient over the aortic valve)/stroke volume index.[14] Regional vascular compliance was assessed as carotid arterial compliance ($CCA_{compliance}$), using B-mode ultrasound

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Table 1. Characteristics

	Total (n=305)	LAVI ≤32 mL/m^2 (n=206)	LAVI >32 mL/m^2 (n=99)	P
Age, y	58.6±11.3	56.4±11.3	63.0±10.0	<0.001
Male sex	166 (54)	109 (53)	57 (58)	0.444
Diabetes duration, y	4.5±5.3	4.2±5.1	5.0±5.6	0.192
BMI, kg/m^2	32.2±5.8	32.2±5.8	32.2±5.9	0.985
Systolic blood pressure, mm Hg	138.7±18.1	136.5±17.3	143.1±19.1	0.003
Diastolic blood pressure, mm Hg	79.5±10.9	78.8±10.1	80.8±12.4	0.132
Pulse pressure, mm Hg	59.2±13.2	57.7±13.2	62.2±12.8	0.005
HbA1c, %	7.3±1.3	7.4±1.4	7.1±1.1	0.047
Fasting C-peptide conc, pmol/L	1146±644	1109±661	1224±604	0.145
Fasting insulin conc, pmol/L	106±104	99±88	120±131	0.107
Total cholesterol conc, mmol/L	4.4±1.0	4.4±1.1	4.2±0.9	0.099
Creatinine, μmol/L	90±24	87±18	96±33	0.001
NT-proBNP, pg/mL*	61 (31–105)	51 (29–87)	85 (37–266)	<0.001
Hypertension	197 (64)	127 (62)	69 (70)	0.170
Current smoker	82 (27)	65 (32)	16 (16)	0.004
Atrial fibrillation†	12 (4)	3 (1)	9 (9)	0.003

Data are presented as mean±SD or n (%). BMI indicates body mass index; conc, concentration.
*Median with interquartile range; †tested with Fisher exact test.

scans of the common carotid arteries and calculated by the formula (carotid diameter$_{max}^2$−carotid diameter$_{min}^2$)/pulse pressure.[15]

Brachial pulse pressure ≤50 mm Hg, CCA$_{compliance}$ ≥0.25 mm^2/kPa, SVi/PP >0.6 mL/m^2/mm Hg, and Zva ≤4 mm Hg/mL/m^2 were considered normal.[14]

Peripheral Arterial Disease

Carotid intima media thickness (CIMT) was measured semiautomatically as the mean of minimum 200 measurements per location site (the bulbus region and the proximal end of the common carotid artery) from digitally stored images using B-mode ultrasound scans of the posterior wall bilaterally at end-diastole (10-MHz linear transducer). Each image was also investigated for plaques using the ARIC study plaque definition.[16] The 95% limits of agreement between 2 observers in 20 randomly selected patients on mean CIMT was −0.158 to 0.081 mm. The absolute interobserver agreement on presence of plaques was 98% (κ=0.74). Carotid arterial disease was defined as mean CIMT >1.00 mm and/or the presence of a plaque at any carotid artery location.

Ankle and toe systolic blood pressure measurements were performed using the strain-gauge technique.[17] After 20 minutes, rest cuffs were placed around the ankles and proximal phalanges of the big toe. Strain gauges were placed around the distal phalanges of the big toe. Duplicate measurements of ankle and toe systolic blood pressures were obtained. Arm systolic and diastolic blood pressures were measured. The ankle-brachial-index (ABI) and the toe systolic blood pressure index (TSPI) were calculated as the systolic blood pressure at each level, respectively, divided by the brachial systolic blood pressure. Peripheral arterial disease (PAD) was defined as ABI <0.90 and/or TSPI <0.64.[18]

Statistical Analysis

Continuous variables are presented as mean and standard deviations and categorical variables as numbers and percentages. We used the Student *t* test to test for differences between independent continuous variables and the χ^2 test or Fisher exact test to test for differences between categorical variables. Because of a well-known nongaussian distribution of NT-proBNP, this parameter was presented as median and interquartile range, and a Mann–Whitney test was used to compare groups. We analyzed the association between each outcome variable (grade 2 diastolic dysfunction and LA volume index >32 mL/m^2), and the predefined indicators of vascular function (pulse pressure, CCA$_{compliance}$, SVi/PP-ratio, and Zva), renal function (GFR), and indicators of LV function (NT-proBNP, LV mass index, and SSS) using a logistic regression analysis with forced entry of the confounders: age, male sex, and diabetes duration. Because of colinearity of the vascular function covariables, these were tested separately. Each model was analyzed for each separate vascular function covariable, together with SSS and the above-mentioned confounders. Results are reported as odds ratios (ORs) with 95% CIs and corresponding probability values. A probability value <0.05 was considered statistically significant. STATA version 9.2 was used for calculations.

Results

Characteristics of the 305 patients with T2DM are summarized in Table 1. No patients had a history of cardiovascular disease. In only 27 patients (9%), LVEF was ≤50%. LV diastolic function was abnormal in 121 patients (40%): 67 patients (22%) had grade 1 diastolic dysfunction, 54 patients (18%) had grade 2 diastolic dysfunction, and no patients had grade 3 diastolic dysfunction (Table 2). Patients with grade 2 diastolic dysfunction were characterized by higher age (62±9 versus 57±12 years, P=0.01), higher NT-proBNP (median, 83; interquartile range, 33 to 789 versus median, 51; interquartile range, 31 to 94 pg/mL; P=0.02), higher frequencies of New York Heart Association (NYHA) class II-IV (37% versus 18%, P=0.001), and lower GFR (81±26 versus 92±22 mL/min/m^2, P=0.002). Measures of vascular function (CCA$_{compliance}$, SVi/PP, PP, and Zva) were significantly correlated, whereas only weak correlation with SSS existed (Table 2.) Vascular function and LV function are summarized in Table 3.

Vascular Function, Myocardial Perfusion, and Grade 2 Diastolic Dysfunction

There were no differences in pulse pressure between patients with normal or grade 1 diastolic function versus grade 2 diastolic dysfunction (59±13 versus 61±12 mm Hg, P=0.18). A normal

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Table 2. Bivariate Correlation Matrix Among Study Measures

	SSS	Pulse Pressure	$CCA_{compliance}$	SVi/PP Ratio	Zva	GFR	NT-proBNP
Pulse pressure	0.05						
$CCA_{compliance}$	−0.07	0.47					
SVi/PP ratio	−0.11	−0.63	0.4				
Zva	0.11	0.25	0.22	−0.79			
GFR	0.05	−0.19	0.15	0.07	0.05		
NT-proBNP	0.17	0.12	−0.08	−0.05	0.04	−0.39	
LVMI	0.02	0.16	0.02	−0.03	0.01	−0.14	0.28

pulse pressure (≤50 mm Hg) was observed in 82 patients (27%). In 9 patients (11%) with normal pulse pressure, grade 2 diastolic dysfunction was found. In contrast, 45 patients (20%) with an abnormal pulse pressure had grade 2 diastolic dysfunction. In addition, $CCA_{compliance}$ (1.07±0.35 versus 1.24±0.47 mm^2/kPa, P=0.02) and total arterial compliance (SVi/PP) (0.58±0.14 versus 0.64±0.19 mL/m^2/mm Hg, P=0.03) were decreased, and valvulo-arterial impedance (Zva) increased (4.40±1.11 versus 4.06±0.94 mm Hg/mL/m^2, P=0.02) in patients with grade 2 diastolic dysfunction compared with patients having normal or grade 1 diastolic dysfunction. This association remained significant for SVi/PP and Zva after adjustment for age, male sex, and diabetes duration (Table 4).

Abnormal myocardial perfusion was seen in 92 patients (30%); most often these perfusion defects were reversible and suggested single coronary vessel disease (Table 3). In 49 patients, the location of perfusion abnormality suggested disease in the left anterior descending, in 25 the left circumflex, and in 43 the right coronary artery. Abnormal perfusion was seen in 48% with grade 2 diastolic dysfunction compared with 26% with normal or grade 1 diastolic dysfunction (P=0.002). Furthermore, SSS remained an independent predictor of grade 2 diastolic dysfunction when pulse pressure, $CCA_{compliance}$, SVi/PP, or Zva was included in the model separately, whereas only Zva remained an independent predictor (Table 5).

Vascular Function, Myocardial Perfusion, and Moderate or Severe LA Dilation

In 99 patients (32%), LA volume index was moderate or severely increased (LA volume index >32 mL/m^2). Characteristics of patients with LA volume index >32 mL/m^2 are summarized in Tables 1 and 3.

In multivariable logistic regression, the predictors of LA volume index >32 mL/m^2 were SVi/PP ratio, Zva, NT-proBNP, LV mass index, and SSS (Table 3).

SSS remained an independent predictor of moderate or severe LA dilation when pulse pressure, $CCA_{compliance}$, SVi/PP, or Zva was included in the model separately, whereas none of these variables remained significant (Table 5).

Vascular Disease

To assess the association with vascular complications, 3 groups were established. Group I had normal or grade 1 diastolic dysfunction and LA volume index ≤32 mL/m^2 (n=205); group II, normal or grade 1 diastolic dysfunction and LA volume index >32 mL/m^2 (n=47); and group III, grade 2 diastolic dysfunction and LA volume index >32 mL/m^2 (n=53). T2DM patients in group 3 had significantly higher prevalence of myocardial ischemia on MPS and impaired renal function on 1-point ^{51}Cr-EDTA clearance procedure compared with patients in group 1 (P<0.001 and P=0.009). In contrast, these patients did not have a higher prevalence of carotid arterial disease (P=0.25) or PAD (P=0.86) (Figure 2).

Discussion

The present study demonstrated in a large population of patients with T2DM with no history of cardiovascular disease a low prevalence of LV systolic dysfunction (9%) similar to the prevalence observed in the general population[5]; however, the study confirms a high prevalence of LV diastolic dysfunction (40%) in these patients. Importantly, the study suggested a close association between the presence of moderate or severe LV diastolic dysfunction and abnormal myocardial perfusion, whereas the association with vascular function was considerably weaker. Thus, our findings support that moderate or severe LV diastolic dysfunction in the early phase of T2DM is closely associated with intrinsic LV dysfunction. However, such LV diastolic dysfunction is not closely related to vascular disease with arterial stiffening and abnormal ventriculo-arterial coupling.

The cardiovascular system can be regarded as a continuous system of a reservoir, a pump, and vessels. Thus, an abnormality in one component will affect the others. Based on this, the coupling between the LV and the arteries may play an important role in the development of heart failure. Increasing arterial stiffness causes premature return of reflected pulse waves in late systole leading to increasing systolic blood pressure and pulse pressure.[15] This will cause increased myocardial oxygen demand, LV hypertrophy, increased wall stress, and myocardial ischemia, which may cause or aggravate abnormal LV diastolic function and eventually overt heart failure. This mechanism has been suggested to be importantly involved in the development of HFNEF, based on increased pulse pressure, pulse wave velocity, and abnormal ventriculo-arterial coupling.[8,19] Although it is recognized that T2DM also is associated with increased risk of heart failure, it is not clear whether this is related to abnormal ventriculo-arterial coupling or due to a direct effect of hyperglycemia or hyperinsulinemia on the myocardium, or both. Studies in patients with diabetes compared with nondiabetic subjects have demonstrated increased myocardial fibrosis,[20,21] and, importantly, the amount of myocardial fibrosis in diabetes patients has been suggested further increased in those with an

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Table 3. Echocardiography: Cardiovascular and Microvascular Disease

	Total (n=305)	LAVI ≤32 mL/m^2 (n=206)	LAVI >32 mL/m^2 (n=99)	*P*
Echocardiography				
LV structure				
End-systolic volume, mL	41.5±15.3	40.1±12.9	44.4±19.0	0.025
End-diastolic volume, mL	102.4±21.1	102.0±20.2	103.3±23.0	0.635
LV systolic function				
LV ejection fraction, %	60.3±8.0	61.3±6.9	58.2±9.6	0.002
S'_{septum}, cm/s	7.9±1.3	8.1±1.1	7.4±1.4	<0.001
$S'_{lateral}$, cm/s	8.7±4.6	9.0±5.4	8.1±1.9	0.117
Stroke volume index, mL/m^2	36.0±7.6	36.1±7.7	36.0±7.4	0.949
Cardiac index, L/min/m^2	2.68±0.60	2.66±0.58	2.72±0.65	0.417
LV mass index, g/m^2	98.8±21.0	95.2±18.5	106.8±23.6	<0.001
Relative wall thickness	0.45±0.08	0.45±0.07	0.46±0.09	0.321
LV hypertrophy, moderate to severe	40 (13)	18 (9)	22 (22)	0.002
LV diastolic function and grade				
Peak E-wave velocity, m/s	0.80±0.16	0.80±0.16	0.80±0.17	0.930
Peak A-wave velocity, m/s	0.85±0.19	0.82±0.17	0.93±0.21	<0.001
E/A ratio	0.96±0.25	1.00±0.23	0.88±0.26	<0.001
DT, ms	220±48	216±42	227±55	0.057
Vp, cm/s	52.0±16.9	55.6±15.3	43.1±16.1	<0.001
e'_{septum}, cm/s	8.3±1.9	8.9±1.7	7.1±1.7	<0.001
$e'_{lateral}$, cm/s	10.5±1.7	10.7±2.5	9.5±2,7	<0.001
E/e'_{septum} ratio	10.0±2.7	9.2±2.0	11.7±3.0	<0.001
Normal diastolic function	184 (60)	167 (81)	17 (17)	<0.001
Grade 1 diastolic dysfunction	67 (22)	38 (18)	29 (29)	0.042
Grade 2 diastolic dysfunction	54 (18)	1 (1)	53 (54)	<0.001
Grade 3 diastolic dysfunction	0	0	0	
LAVI, mL/m^2	28.8±7.4	25.2±4.0	37.7±4.9	<0.001
Vascular function				
$CCA_{compliance}$, mm^2/kPa	1.21±0.45	1.25±0.47	1.12±0.41	0.023
SVi/PP ratio, mL/m^2/mm Hg	0.63±0.18	0.65±0.19	0.60±0.16	0.019
Zva, mm Hg/mL/m^2	4.12±0.98	4.05±0.95	4.24±1.03	0.116
Myocardial perfusion scintigraphy				
Myocardial ischemia	92 (30)	49 (24)	43 (43)	<0.001
Perfusion defect size				
SSS 4–8	78 (26)	49 (24)	29 (29)	0.349
SSS 9–13*	9 (3)	0	9 (9)	<0.001
SSS >13*	5 (2)	0	5 (5)	0.003
Reversibility of perfusion defects				
Reversible defects	58 (19)	30 (15)	28 (28)	0.005
Mixed defects*	13 (4)	5 (2)	8 (8)	0.763
Fixed defects*	21 (7)	14 (7)	7 (7)	0.929
No. of involved coronary arteries				
1-vessel disease	68 (22)	45 (22)	23 (23)	0.785
2-vessel disease*	23 (8)	4 (2)	19 (19)	0.027
3-vessel disease*	1 (1)	0	1 (1)	0.999
B-mode ultrasound scan of the carotid arteries				
$CIMT_{mean}$, mm	0.82±0.14	0.81±0.14	0.85±0.13	0.009
Carotid arterial disease	129 (42)	76 (37)	53 (54)	0.006

(*Continued*)

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Table 3. Continued

	Total (n=305)	LAVI ≤32 mL/m^2 (n=206)	LAVI >32 mL/m^2 (n=99)	P
Ankle and toe systolic blood pressure				
Ankle systolic blood pressure, mm Hg	162.5±26.1	162.0±22.5	163.6±32.3	0.613
Toe systolic blood pressure, mm Hg	125.7±29.5	125.7±26.8	125.7±34.6	0.995
PAD	45 (15)	25 (12)	20 (20)	0.063
1-Point ^{51}Cr-EDTA clearance procedure				
GFR, mL/min/m^2	89.6±23.0	92.4±22.3	83.6±23.3	0.001
Impaired renal function	29 (10)	17 (8)	12 (12)	0.281

Data are presented as mean±SD or n (%).
*Tested with Fisher exact test.

abnormal MPS.[22] In accordance with this, the present study suggests that advanced diastolic dysfunction, which is often associated with increased LV stiffness, was related to SSS, NT-proBNP, LV mass index, total arterial compliance, and valvulo-arterial impedance. When, myocardial perfusion and vascular function were assessed, only SSS and valvulo-arterial impedance provided independent information.

In the case of chronic LA volume or pressure overload, the size of the LA will increase. Thus, in absence of significant mitral valve disease, intracardiac shunts, or chronic anemia, LA volume will reflect "chronic" LA pressure overload. The present study is the first to systematically evaluate LA volume in a large population of T2DM patients and suggests that moderate or severe LA dilation is seen in almost one third of the patients. In the study population, moderate or severe mitral valve disease was not present, and no patients had chronic anemia; thus, the most likely cause of LA dilation was pressure overload. We found a statistically significant association with LA volume index >32 mL/m^2 and SSS, NT-proBNP, LV mass index, total arterial compliance, and valvulo-arterial impedance in multivariable analysis. However, when myocardial perfusion and vascular function were included in the same model, only SSS was an independent predictor of LA volume index >32 mL/m^2.

Table 4. Predictors of Grade 2 Diastolic Dysfunction and LAVI >32 mL/m^2

Grade 2 Diastolic Dysfunction	Adjusted OR per SD (95% CI)	P
Covariables		
Pulse pressure	1.10 (0.81–1.50)	0.528
$CCA_{compliance}$	0.72 (0.51–1.01)	0.060
SVi/PP ratio	0.69 (0.48–0.98)	0.039
Zva	1.49 (1.11–2.02)	0.009
GFR	0.67 (0.47–0.95)	0.027
NT-proBNP	1.61 (1.16–2.24)	0.005
LVMI	1.37 (1.01–1.86)	0.046
SSS	2.31 (1.57–3.39)	<0.001
LAVI >32 mL/m^2	**Adjusted OR per SD (95% CI)**	**P**
Covariables		
Pulse pressure	1.21 (0.94–1.57)	0.142
$CCA_{compliance}$	0.86 (0.65–1.13)	0.266
SVi/PP ratio	0.74 (0.56–0.99)	0.040
Zva	1.35 (1.04–1.75)	0.023
GFR	0.88 (0.65–1.18)	0.388
NT-proBNP	2.06 (1.32–3.21)	0.001
LVMI	1.65 (1.26–2.17)	<0.001
SSS	2.80 (1.89–4.14)	<0.001

Separate regression models were run for all participants for grade 2 diastolic dysfunction and LAVI >32 mL/m^2. All listed covariables were tested separately after forced entry of age, male sex, and diabetes duration in the regression models. Outcome variables are grade 2 diastolic dysfunction and LAVI >32 mL/m^2.

These results suggest that the cause of advanced LV diastolic dysfunction and LA dilation in patients with T2DM is linked to ischemic myocardium and intrinsic LV dysfunction and to a lesser degree arterial stiffening with abnormal ventriculo-arterial coupling. However, as LV diastolic dysfunction was uncommon in the subgroup with normal pulse pressure, and valvulo-arterial impedance remained predictive of LV diastolic dysfunction, a component of vascular dysfunction in the development of LV diastolic stiffening cannot be excluded in this study. Because the majority of perfusion defects on MPS were reversible and regional, we consider it likely that the defects were caused by epicardial disease, although microvascular disease cannot be ruled out. Future studies should address this issue in detail.

In the present study, we found a prevalence of myocardial ischemia on MPS of 30%. This is in agreement with previous studies of T2DM patients without known coronary artery disease, in which the prevalence has varied from 14% to 32%.[23–25]

Study Limitations

Despite great effort, almost one third of eligible patients refused to participate in the study. Although no statistical differences were present between the study group and the nonparticipants with regard to age and diabetes duration (data not shown), selection bias cannot be ruled out.

When planning and conducing the present study, no ASE/EAE consensus existed on grading LV diastolic dysfunction. This was, however, introduced by ASE/EAE in February 2009.[26] Although the grading of LV diastolic function in the present study and the new recommendations are very alike there are minor differences in the cut off of E/A ratio and mitral deceleration time. Specifically, our definition of grade 1 diastolic dysfunction is more restrictive than the

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Table 5. Association Between Myocardial Perfusion, Vascular Function, and Grade 2 Diastolic Dysfunction/LAVI >32 mL/m^2 After Adjustment for Age, Male Sex, and Diabetes Duration

Grade 2 Diastolic Dysfunction	Adjusted OR per SD (95% CI)	*P*
Covariables		
Pulse pressure	1.03 (0.75–1.41)	0.853
SSS	2.30 (1.56–3.39)	<0.001
$CCA_{compliance}$	0.79 (0.55–1.12)	0.188
SSS	2.26 (1.53–3.34)	<0.001
SVi/PP ratio	0.75 (0.52–1.09)	0.127
SSS	2.25 (1.52–3.32)	<0.001
Zva	1.45 (1.04–2.01)	0.027
SSS	2.26 (1.53–3.36)	<0.001
GFR	0.62 (0.42–0.91)	0.014
SSS	2.50 (1.65–3.79)	<0.001
NT-proBNP	1.50 (1.07–2.11)	0.019
SSS	2.36 (1.51–3.32)	<0.001
LVMI	1.39 (1.01–1.90)	0.044
SSS	2.35 (1.58–3.48)	<0.001
LAVI >32 mL/m^2	**Adjusted OR per SD (95% CI)**	***P***
Covariables		
Pulse pressure	1.15 (0.88–1.51)	0.313
SSS	2.77 (1.87–4.10)	<0.001
$CCA_{compliance}$	0.94 (0.70–1.26)	0.672
SSS	2.78 (1.87–4.12)	<0.001
SVi/PP ratio	0.80 (0.59–1.08)	0.149
SSS	2.80 (1.87–4.18)	<0.001
Zva	1.29 (0.97–1.72)	0.076
SSS	2.82 (1.88–4.22)	<0.001
GFR	0.80 (0.58–1.11)	0.188
SSS	2.90 (1.94–4.33)	<0.001
NT-proBNP	1.90 (1.23–2.95)	0.004
SSS	2.75 (1.84–4.10)	<0.001
LVMI	1.81 (1.34–2.43)	<0.001
SSS	3.08 (2.03–4.69)	<0.001

Outcome variables are grade 2 diastolic dysfunction and LAVI >32 mL/m^2.

published guideline. This was chosen because many patients were middle-aged or elderly, and it is well known that even among healthy subjects ages >60 years, E/A ratios <1.0 and mitral deceleration times >200 ms are frequently seen and considered normal.[26] However, we did perform a post hoc reanalysis of our data based on the new definition (data not presented), which led to the same overall conclusions as presented.

Although there was clear overweight of patients with shortness of breath on exertion (NYHA class ≥II), it must be emphasized that the population identified in this study with diastolic dysfunction did not strictly represent patients with HFNEF.

We chose a cutoff point of CIMT >1.00 mm. We recognize that this in a young person may be abnormal and in an elderly subject normal. However, most patients in our study were ages 50 to 70 years, where a cutoff of 1.00 mm seems reasonable.[27] In addition, this cutoff aids comparison with the large epidemiological study in which this cutoff point has been used.[27]

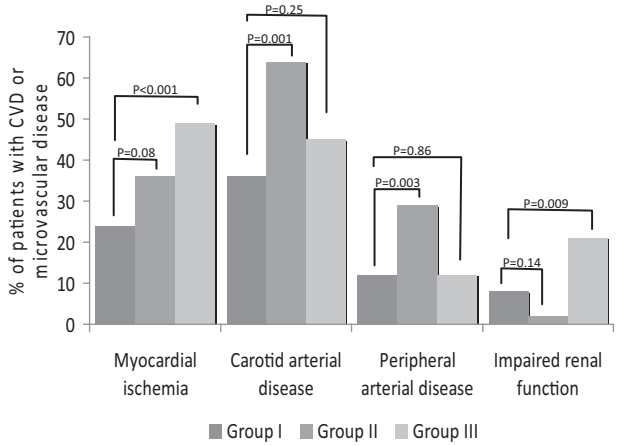

Figure 2. LV diastolic function: comparisons between groups with respect to myocardial ischemia, carotid arterial disease, PAD, and impaired renal function. Group 1 had normal or grade I diastolic dysfunction and LAVI ≤32 mL/m^2; group 2, normal or grade I diastolic dysfunction and LAVI >32 mL/m^2; and group 3, grade II diastolic dysfunction and LAVI >32 mL/m^2.

The gold standard for assessment of ventricular and arterial elastance is invasive assessment of end-diastolic pressure and cardiac output. Because the number of participants was large (n=305) and the patients did not have a clinical indication for an invasive study, we did not consider it justified or ethical to perform invasive assessment of effective arterial elastance. In addition, all chosen noninvasive estimates have been validated invasively.

Conclusion

The prevalence of LV diastolic dysfunction was high in patients with T2DM with no history of cardiovascular disease. The study suggested a close association between the presence of advanced LV diastolic dysfunction and abnormal myocardial perfusion on MPS. In contrast, the association with abnormal vascular function was considerably less prominent. Thus, our findings support that moderate or severe LV diastolic dysfunction and LA dilation in the early phase of T2DM is closely associated with intrinsic LV dysfunction. However, such LV diastolic dysfunction and LA dilation are not closely related to vascular disease with arterial stiffening and abnormal ventriculo-arterial coupling.

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Disclosures

None.

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CLINICAL PERSPECTIVE

In the past decade, the term left ventricular (LV) diastolic heart failure or heart failure with normal ejection fraction has been introduced. The symptoms of heart failure are believed to be caused by abnormalities in LV filling, which are frequently seen in patients with type 2 diabetes mellitus. Whether LV diastolic dysfunction in patients with type 2 diabetes mellitus is caused by an intrinsic myocardial disorder or related to vascular disease is, however, still controversial. Better understanding of this is imperative for implementation of therapeutic interventions to improve the prognosis of these patients. In the present study, patients with type 2 diabetes mellitus with no history of heart failure or coronary artery disease referred to a diabetes clinic for the first time (n=305) were studied. The present study demonstrated a low prevalence of LV systolic dysfunction (9%); however, the study confirmed a high prevalence of LV diastolic dysfunction (40%). Importantly, the study suggested a close association between the presence of moderate or severe LV diastolic dysfunction and abnormal myocardial perfusion on myocardial perfusion scintigraphy, whereas the association with vascular function was considerably less prominent. Thus, our findings support the hypothesis that moderate or severe LV diastolic dysfunction and left atrial dilation in the early phase of type 2 diabetes mellitus are closely associated with intrinsic LV ischemic dysfunction. However, such LV diastolic dysfunction and left atrial dilation are not closely related to vascular disease with arterial stiffening and abnormal ventriculo-arterial coupling.

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Left Ventricular Diastolic Function in Type 2 Diabetes Mellitus: Prevalence and Association With Myocardial and Vascular Disease

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