Published in final edited form as:

Diabetes Res Clin Pract. 2010 May ; 88(2): 189–195. doi:10.1016/j.diabres.2009.12.007.

Predictors of diastolic dysfunction among minority patients with newly diagnosed type 2 diabetes

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Abstract

Aim—To determine mutable risk factors for asymptomatic diastolic dysfunction in ethnic minority patients newly diagnosed with type 2 diabetes.

Methods—We recruited consecutive adults with newly diagnosed diabetes who had no signs or symptoms or history of heart disease. All patients received standardized evaluation including interview, physical examination, laboratory tests and echocardiogram with tissue Doppler studies. We used logistic regression models to identify mutable risk factors for diastolic dysfunction.

Results—Among 126 study subjects (52% women, age 45 ± 10 years, BMI 33 ± 7 , 42% with hypertension, 100% ejection fraction $> 50\%$), evidence of diastolic dysfunction was present in 64 (51%). After controlling for age, heart rate and blood pressure, independent predictors of diastolic dysfunction included physical inactivity (OR: 2.3; 95% CI: 0.9–6.1; $P = 0.08$) and glucose (OR: 4.9; 95% CI: 1.4–17.8; $P = 0.02$). Physical inactivity was associated with early diastolic dysfunction (impaired relaxation), whereas epicardial fat thickness and glucose levels were associated with late diastolic dysfunction (impaired compliance). The hs-CRP and BNP levels were not associated with diastolic dysfunction.

Conclusions—Asymptomatic diastolic dysfunction was prevalent among urban minority patients newly diagnosed with diabetes. Important differences exist among factors that affect early and late diastolic function that may have prognostic and therapeutic implications.

Keywords

Heart failure; Prevention; Metabolic syndrome; Complications

Conflict of interest

There are no conflicts of interest.

1. Introduction

Diabetes is a well-recognized causal risk factor for heart failure, the leading cause of hospital admissions in the U.S. [1]. Diabetes has known adverse macro- and micro-vascular effects, causing myocardial infarction, ischemic cardiomyopathy and poor systolic function. However, the role of diabetes in diastolic heart failure is less appreciated but rapidly gaining attention [2,3] because the prevalence of and the morbidity and mortality from diastolic heart failure rivals, and may soon exceed, that of systolic heart failure [4].

Although the systolic function of the heart has garnered the most clinical and research attention, left ventricular relaxation and compliance – diastolic function – is clinically important and equally complex. Thus, we need to identify the etiologic risk factors, define the most efficient screening tests and determine the most effective treatment strategies for non-ischemic diastolic dysfunction among patients with diabetes.

As the process of myocardial remodeling starts before the onset of symptoms, heart failure guidelines [1] emphasize detection of subclinical left ventricular function and identification of patients at risk. Given the increased risk of heart failure in diabetes, the American College of Cardiology and the American Heart Association have listed diabetes as sufficient criteria for diagnosing stage A heart failure – equivalent to “pre-heart failure” – which identifies a person at high risk for heart failure in the absence of structural heart disease or symptoms [1]. The progression to stage B – structural heart disease but still without symptoms – is associated with increased mortality, but the risk of dying increases 5-fold when symptoms of heart failure occur (stages C and D) [5]. As studies in Olmsted County suggest, approximately half of patients with early grades of diastolic dysfunction progress to more advanced grades after 5–6 years [6]. Diastolic dysfunction, even low-grade dysfunction, is associated with lower functional capacity and quality of life [7,8].

Both diabetes and heart failure are more common among patients from minority ethnic groups. We sought to determine the prevalence of diastolic dysfunction (stage B heart failure) among patients from ethnic minorities who are newly diagnosed with type 2 diabetes but have no symptoms or signs suggestive of heart disease. Our aim was to identify potentially mutable risk factors for diastolic dysfunction.

2. Subjects, design and methods

2.1. Design and subjects

We conducted a cross-sectional study of consecutive adults newly diagnosed with type 2 diabetes attending a diabetes clinic at a large urban public hospital in Chicago from 2004 to 2006. Patients were eligible if diabetes was diagnosed using American Diabetic Association criteria [9] within 6 months of enrollment, there was evidence for the metabolic syndrome [10], functional status was normal (equivalent to 7 metabolic equivalents of energy expenditure according to Goldman SAS scale [11]), and there was no history, symptoms, clinical or ECG signs suggestive of cardiovascular disease after a thorough standardized evaluation by a physician investigator. Patients were ineligible if their serum creatinine was 141 $\mu\text{mol/L}$ or greater (as kidney dysfunction may induce heart dysfunction [12]); there was any current or chronic infectious disease, other than moniliasis; or if there was a history of prolonged cocaine or heroin use or alcoholism (CAGE score of 2–4) [13], selecting a highly sensitive but non-specific threshold for alcoholism to avoid confounding, as the effects of alcohol and drugs on the heart can be complex. This study was approved by the hospital's Institutional Review Board, and all subjects provided written informed consent.

2.2. Measurements

Each patient had a standardized medical interview and physical examination by one of the physician investigators, a standardized laboratory evaluation, a 12-lead electrocardiogram, and an echocardiogram. Blood pressure was measured using standard techniques [14]. Electrocardiographic left ventricular hypertrophy was defined by Cornell criteria [15]. Laboratory measurements included serum creatinine, hemoglobin A_{1c}, B-type natriuretic peptide (BNP) (Advia Centaur Immunoassay Systems, Bayer Diagnostics, New York), and highly sensitive C-reactive protein (hs-CRP) (Immulin 2000 immunometric assay, DPC, California). Values of BNP and hs-CRP below the lowest measurable result (<5 pg/L for BNP; <0.2 mg/L for hs-CRP) were considered equivalent to zero. The highest serum glucose, measured at the diagnosis of diabetes was recorded after review of patient's medical record.

We classified patients as physically active if they reported being physically active at work (eg, delivering the mail or heavier physical activity) or if they reported exercising at least 15–30 min at least 3 times per week. Otherwise, they were classified as physically inactive.

2.3. Echocardiography

Transthoracic echocardiograms using M-mode, 2D, Doppler and tissue Doppler imaging (TDI) were conducted using standard equipment (Vivid 7, GE Healthcare, Wauwatosa, WI) and techniques [16] by a registered sonographer and interpreted by an experienced cardiologist (B.M.) who was blinded to the subjects' anthropometric and clinical characteristics.

Measurements of interventricular septal thickness, posterior wall thickness and left ventricular internal diameter were made at end-diastole and end-systole. Left ventricular mass index was then calculated using the American Society of Echocardiography formula and Devereux's correction for obesity [17]. Ejection fraction and wall motion abnormalities were assessed visually. Epicardial fat thickness on the free wall of the right ventricle was measured at the thickest point in parasternal short and long axis views and the largest value was recorded [18].

We used pulsed wave Doppler images to measure the inflow at the tips of the mitral valve leaflets before (average of five measurements) and after Valsalva maneuver in order to calculate early (E) and late (A) diastolic mitral flow velocities and deceleration time (interval from peak E velocity to time when velocity was extrapolated to zero). We used tissue Doppler images to measure early (e') and late (a') peak displacement velocities of the lateral mitral valve annulus. The left ventricular end-diastolic pressure was estimated using the E: e' ratio. Pulsed wave Doppler of pulmonary vein flow was used as an adjunct to other parameters in the assessment of diastolic function. Inferior vena cava diameter measured in the subcostal echocardiographic view was used by cardiologist to assess patient's volume status and its implication on diastolic parameters.

2.4. Primary outcome variables

Mild (abnormal relaxation, grade I) and advanced (pseudonormal and restrictive patterns—grades II–IV) diastolic dysfunction were defined using established criteria [16]. Specifically, the diagnosis of grade I diastolic dysfunction was established by an experienced cardiologist using the following criteria: E:A > 0.75, deceleration time (DT) greater than 240 ms, IVRT greater than 90 ms in the absence of intravascular volume depletion (ie, in absence of inferior vena cava collapse), taking into account pulmonary vein flow patterns. Grade II diastolic dysfunction (pseudonormal filling) was defined as impaired relaxation associated with moderate elevation in filling pressures: $0.75 \text{ ms} < \text{E:A} < 1.5$, $\text{DT} > 140 \text{ ms}$, and $\text{E:e}'$

10, taking into account pulmonary vein flow patterns. We evaluated diastolic dysfunction as a dichotomous variable, defined by the presence of any grade diastolic dysfunction (although none of the subjects had grade III or IV diastolic dysfunction) and also as a continuous variable, using $E:e'$ ratio, excluding subjects with grade II diastolic dysfunction from the latter analysis.

2.5. Secondary outcome variables

Early diastolic function, which is an active process of left ventricular wall relaxation, was assessed using the tissue Doppler parameter e' . Late diastolic function, which depends on the compliance of the left ventricle in response to blood flow generated by atrial contraction, was assessed by measuring lateral mitral valve annulus peak displacement velocity, presumably reflecting left ventricular wall stretch (strain), using the tissue Doppler imaging parameter a' . We attempted to adjust for the effects of blood volume on ventricular stretch by measuring the effects of a' while controlling for late diastolic filling velocity, A in the multivariable-adjusted analysis.

In mild (grade I) diastolic dysfunction, the increase in late mitral inflow velocity (A) is typically proportionate to the increase in rate of left ventricular wall expansion (stretch) and mitral annulus excursion velocity at end-diastole (a') [16]. Hypothetically, in moderate (pseudonormal or grade II) diastolic dysfunction, however, the left ventricular compliance is limited, as increasing left ventricular end-diastolic pressure leads to a diminution of the mitral inflow velocity during atrial contraction (A), despite maximal compensatory expansion of stiff left ventricle, reflected by a' . In late phases of diastolic dysfunction (grades III and IV), left ventricular stretching is reduced and left ventricular end-diastolic pressure is elevated, indicating a restrictive pattern, further compromising left ventricular compliance, reflected by a reduction in both A and a' [16].

Since a' has a non-linear relationship with severity of diastolic dysfunction, we excluded the 6 patients with pseudonormal filling from the regression analyses when e' and a' were the outcome variables.

2.6. Statistical analysis

We used logistic regression to assess the relationship between diastolic dysfunction and each potential predictor variable. For ordinal or continuous predictor variables, we first verified the model assumption of a linear monotonic relationship between the predictor and the log-odds of the outcome. Variables that did not meet this assumption were appropriately transformed (glucose, triglycerides, microalbuminuria, BNP, hs-CRP).

We used multivariable logistic models to identify independent predictors of diastolic dysfunction, while adjusting in each model for age, heart rate and blood pressure, well-recognized causes (confounders) of diastolic dysfunction. Blood pressure was controlled using 7 variables: diagnosis or therapy for hypertension (dichotomous), systolic blood pressure (continuous, mm Hg), diastolic blood pressure (continuous, mm Hg) and the squared and cubed values of systolic and diastolic blood pressure.

Finally, we used separate linear regression models to assess independent risk factors for the components of diastolic function (e' , a' , $E:A$ ratio, and $E:e'$ ratio) as continuous outcome variables, adjusting for age, heart rate and blood pressure. Because an increased left ventricular mass is often associated with the development of diastolic dysfunction, we also tested whether left ventricular mass index was a principal mediator of diastolic dysfunction in early diabetes.

To identify efficient screening tests for early diastolic dysfunction, we used logistic regression models but expanded our list of potential predictor variables to include not only potential causes of diastolic heart failure but also factors that can be the effects of heart failure, such as BNP.

We used Stata software (Version 10.1, StataCorp, College Station, TX) for all statistical analyses.

3. Results

Among the 612 consecutive patients with newly diagnosed type 2 diabetes during the study period, 100 were excluded because of evidence of cardiovascular disease, 177 because of alcohol or drug abuse, and 79 for other reasons (an additional 140 patients refused to participate). Thus, 126 patients were eligible for study. Most patients were between 30 and 60 years of age and from African/American (31%), Hispanic/Latino (46%) and other immigrant (23%) ethnic groups. Over 50% reported a physically inactive lifestyle, over 60% were obese, and all had metabolic syndrome (combination of three or more of the following factors: hypertension, obesity, diabetes, hypertriglyceridemia, or low HDL).

Although all patients were asymptomatic, diastolic dysfunction was evident by echocardiographic criteria in 64 (51%) of the 126 patients. Nearly all patients with diastolic dysfunction were classified as mild (relaxation abnormality), except 6 who had evidence of a pseudonormal filling pattern. None of the participants had restrictive physiology. Since a' has non-linear responses with increasing severity of diastolic dysfunction, we excluded the 6 patients with pseudonormal filling from the regression analyses when e' and a' were the outcome variables. Table 1 describes the relationship between patient characteristics and diastolic dysfunction.

3.1. Diastolic dysfunction

Table 2 describes the significant relationships between diastolic dysfunction and clinical and echocardiographic characteristics analysed separately. As expected, age and hypertension were strong univariable clinical predictors of diastolic dysfunction.

Table 3 describes the best multivariable model of clinical variables for predicting diastolic dysfunction, while adjusting for age, heart rate and blood pressure. Independent predictors of diastolic dysfunction included random serum glucose level and physical inactivity. The multivariable model displayed good discrimination (area under the ROC curve: 0.84; 95% CI: 0.78–0.91) and good calibration (Hosmer–Lemeshow goodness of fit test: $P=0.99$). The odds of diastolic dysfunction were over 2-fold higher among those who reported a physically inactive lifestyle compared to those who reported a physically active lifestyle (OR: 2.3; 95% CI: 0.9–6.1), after adjusting for the other variables in the model. Thus, 3 mutable clinical variables – blood pressure, glucose control and physical inactivity – appear to be independent causal risk factors for asymptomatic diastolic dysfunction. Of note, body mass index, lipid measures, BNP and hs-CRP were not significantly associated with diastolic dysfunction in our sample of asymptomatic patients.

The ECG changes were not helpful in identifying patients who may benefit from echocardiographic evaluation for diastolic dysfunction (OR = 1.2 with 95% CI: 0.5–2.9 and $P=0.63$).

3.2. Left ventricular end-diastolic pressure

We also assessed diastolic dysfunction as a continuous variable using the $E:e'$ ratio, which reflects left ventricular end-diastolic pressure. This outcome measure was significantly

associated with physical inactivity ($P = 0.04$), even after controlling for age ($P = 0.01$), heart rate ($P = 0.6$) and blood pressure parameters ($P = 0.04$ for systolic blood pressure), as well as left ventricular mass index ($P = 0.02$).

3.3. Left ventricular relaxation

Left ventricular wall relaxation during early diastole (e') is an active, energy-dependent process. The strongest clinical predictor of impaired relaxation was physical inactivity (Table 3), which remained significant after adjusting for age or early diastolic filling velocity (E). Serum glucose levels, hemoglobin A_{1c}, lipid levels, BMI and epicardial fat were not associated with ventricular wall relaxation.

3.4. Left ventricular compliance

Left ventricular wall compliance during late diastole (a') reflects the ability of the left ventricle to passively expand (stretch) in response to the inflow of blood after atrial contraction. The strongest independent predictors were random serum glucose and epicardial fat pad thickness (Table 3). These predictors remained significant after adjusting for left ventricular wall relaxation (e') or late diastolic filling velocity (A). Also, epicardial fat pad thickness remained significant after adjusting for body mass index and cholesterol and triglyceride levels. Physical inactivity, a strong predictor of impaired ventricular relaxation in early diastole, was not associated with ventricular compliance in late diastole ($P = 0.72$).

3.5. E:A ratio

The ratio of early to late mitral flow velocity (E:A) was associated with random glucose ($P = 0.008$), after controlling for age, heart rate and blood pressure parameters.

3.6. Left ventricular mass index

An increased left ventricular mass is presumed to be one mechanism for impaired diastolic function. Although no participant met electrocardiographic or echocardiographic criteria for left ventricular hypertrophy, the independent clinical predictors of left ventricular mass index were age (for each decade, $\beta = 2.6$, $P = 0.001$), body mass index (for each 10 kg/m², $\beta = 5$, $P < 0.001$) and ethnicity ($P = 0.001$), in a model that also controlled for diagnosed/treated hypertension ($\beta = 1.8$, $P = 0.30$).

4. Discussion

Half of our sample of asymptomatic patients with newly diagnosed type 2 diabetes had diastolic dysfunction. The prevalence was high even among those who were normotensive (40%) or younger than age 50 years (34%). Four variables were independently associated with diastolic dysfunction: age, hypertension, serum glucose and physical inactivity. The 4 variable model was accurate – well calibrated with good discrimination (area under ROC curve 0.84) – and performed well in risk-stratifying patients. For example, according to the model, a 40-year old, normotensive, physically active patient with well-controlled (normal) blood glucose would have a 9% likelihood of having asymptomatic diastolic dysfunction. On the other hand, a 55-year old, inactive, hypertensive patient with a blood glucose of 11.1 mmol/L would have an 89% likelihood of diastolic dysfunction. The finding that physical inactivity was also strongly associated with the continuous parameter of diastolic dysfunction (E: e') was additional support for its role as an important predictor. Despite a positive association between B-type natriuretic peptide and left ventricular end-diastolic pressure, the relationship was not statistically significant in our sample. Our exclusion of patients with signs or symptoms of heart disease and the small number of cases with pseudonormal filling might explain why our findings differ from studies reporting significantly higher BNP levels among those with diastolic dysfunction [7,19]. High

sensitivity C-reactive protein was not helpful in identifying patients with diastolic dysfunction in our cohort. The lack of a strong association between diastolic dysfunction and triglycerides, high-density lipoprotein cholesterol, hypertension and weight [20] likely is due to the spectrum of these variables was limited by enrolling only patients with the metabolic syndrome.

The biological plausibility of diabetes as a causal risk factor for diastolic dysfunction has substantial research support. Diabetes affects cardiomyocyte resting tension and thus left ventricular compliance [21]. However, a recent study failed to demonstrate an improvement in diastolic function after 4 months of intensive glycemic control [22]. These negative results might be due to the relatively mild hyperglycemia at baseline or the short duration of the intervention.

Our results suggest that in grade 1 diastolic dysfunction, factors affecting left ventricular relaxation and compliance are different. Early diastolic relaxation, an active process, was associated with physical inactivity, but not with metabolic parameters. In contrast, late diastolic ventricular compliance (stretch), a passive process, was associated with metabolic parameters (blood glucose and epicardial fat pad thickness), but not physical inactivity. The mechanism for the metabolic effects on late diastolic function cannot be attributed solely to hyperglycemia-induced reduction in intravascular volume because there was no association between hyperglycemia and mitral inflow velocity (A), which is a volume-dependent parameter of late diastole.

In mild diastolic dysfunction, it is typically thought that the decreased left ventricular relaxation in early diastole (e') causes a compensatory increase in left ventricular stretch in late diastole (a'). However, our results suggest that for any given e' , there is greater ventricular stretch (a') when glucose is higher and epicardial fat is thicker. Although the compensatory increase in left ventricular stretch can have beneficial effects on cardiac function, these benefits might only be evident in the short run. We hypothesize that over time, persistent overstretching may result in cardiomyocyte microtrauma, which can lead to inflammation and fibrosis, causing the increased stiffness seen with grades II–IV diastolic dysfunction [21].

The distinction we draw between early and late diastolic dysfunctions may have implications for clinical interventions. Loimaala et al. [23] were unable to demonstrate a change in left ventricular relaxation (e') among men with diabetes who participated in a 12-month exercise training program. However, they did show an improvement in a' , probably related to patients' improved metabolic profiles (A_{1c}, lipids, weight), illustrating that different factors affect ventricular relaxation and compliance, and that the metabolic abnormalities in diabetes have their greatest effects on compliance.

Although the decline in ventricular relaxation (e') with age is well characterized [24], to our knowledge this is the first report documenting a link between physical inactivity and left ventricular relaxation, independent of age. Whether physical inactivity plays a causal role in diastolic dysfunction remains uncertain, however, given our cross-sectional study design and the absence of corroborating evidence from studies using rigorous methods [23]. Definitive evidence about the cause–effect relationship will likely require a carefully crafted longitudinal design and a study of the effects of increasing physical activity on myocardial function.

The association we found between epicardial fat and parameters of diastolic dysfunction is also novel. Epicardial fat thickness correlates with visceral fat depot and diminishes as patients lose weight [25]. Epicardial fat releases large amounts of fatty acids, inflammatory factors and adipokines, which may contribute to diastolic dysfunction [25,26]. The

adipokines may act in a paracrine fashion because of their close proximity to cardiac myocytes and their shared blood supply [25]. Therefore we hypothesize that the epicardial fat pad, in effect, may marinate the cardiomyocytes with its metabolic and inflammatory paracrine byproducts.

One potential role of our predictive model is to more efficiently identify the subset of patients who may need an echocardiogram to verify subclinical heart disease. The clinical recommendations, regardless of echocardiographic findings, will always include healthy lifestyle modifications and optimal control of hypertension, hyperglycemia and hyperlipidemia, but patient adherence to a self-management program might improve if patients were aware of early heart disease. Recent research demonstrated that substantial weight loss (23%) in obese patients improved diastolic parameters by reducing intramyocardial triglyceride content [20]. Therefore, the predictive model might help identify patients who would benefit from a very intensive weight loss intervention—for treating stage B heart failure, in addition to inducing diabetes remission.

The main limitation of our study is its cross-sectional design, which prevents ascribing a causal role for significant predictor variables (physical inactivity, glucose, epicardial fat). We also relied on patients' self-report, and did not perform formal metabolic fitness evaluations, which can detect subtle impairments [23]. Finally, although none of the patients had evidence suggesting coronary heart disease as a cause of diastolic dysfunction, this could not be ruled out without more extensive testing.

In summary, asymptomatic diastolic dysfunction is prevalent among urban minority patients newly diagnosed with type 2 diabetes. Important differences exist among factors that affect early and late diastolic function that may have implications when evaluating therapies for diastolic dysfunction. Physical inactivity appears to be an important risk factor, especially for impaired ventricular relaxation during early diastole. Epicardial fat thickness and hyperglycemia, on the other hand, are associated with increased left ventricular stretch during late diastole, independent of hypertension and age. Further studies will be necessary to verify whether these are causal risk factors and whether early detection and intervention have clinical benefit.

Acknowledgments

We thank Geraldine Holt, Marvin Alviso, Avinder Mehta, Gustavo Jurado for help in patient recruitment; Leonard Boral and Parhat Quadri for laboratory testing. This study was funded from internal institutional funds.

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Table 1

Sample characteristics by diastolic dysfunction.

Characteristic	Normal diastolic function (<i>n</i> = 62)	Diastolic dysfunction (<i>n</i> = 64)	<i>P</i> value
Age, years (mean ± SD)	40 ± 9	51 ± 9	<0.001
Women, <i>n</i> (%)	29 (47)	36 (56)	0.29
Ethnic group, <i>n</i> (%)			0.46
African American	17 (27)	22 (34)	
Hispanic/Latino	32 (52)	26 (41)	
Other	13 (21)	16 (25)	
Hypertension, diagnosis or treatment, <i>n</i> (%)	18 (29)	35 (55)	0.004
Systolic blood pressure, mm Hg (mean ± SD)	131 ± 20	138 ± 18	0.02
Diastolic blood pressure, mm Hg (mean ± SD)	73 ± 12	78 ± 12	0.01
Heart rate, beats/minute (mean ± SD)	74 ± 12	77 ± 14	0.017
Physical inactivity, <i>n</i> (%)	25 (41)	39 (62)	0.02
Body mass index, kg m ² (mean ± SD)	33 ± 7	33 ± 7	0.94
Glucose, mmol/L median (10–90 percentile)	10.2 (6.1–17.1)	12.3 (7.6–19.2)	0.01
Hemoglobin A _{1c} , % (mean ± SD)	10.5 ± 2	11.2 ± 2	0.05
Total cholesterol, mmol/L (mean ± SD)	5.1 ± 1.3	5.4 ± 1.3	0.25
High density lipoprotein cholesterol, mmol/L (mean ± SD)	1.1 ± 0.3	1.2 ± 0.3	0.39
Triglycerides, mmol/L median (10–90 percentile)	1.7 (0.9–4.5)	2.3 (1.0–4.5)	0.58
Microalbuminuria, mg/g Cr median (10–90 percentile)	15 (4–74)	20 (5–111)	0.17
High sensitivity CRP, mg/L median (10–90 percentile)	6 (1–30)	7 (2–23)	0.71
B-type natriuretic peptide, pg/L median (10–90 percentile)	117 (20–611)	93 (20–353)	0.14
Echocardiographic characteristics			
Left ventricular mass, g median (10–90 percentile)	134 (104–182)	148 (107–207)	0.06
Left ventricular mass index, gm ^{-2.7} (mean ± SD)	35 ± 8	41 ± 11	0.004
Epicardial fat pad thickness, mm (mean ± SD)	1.7 ± 0.9	2.3 ± 1.0	0.002
Late diastolic velocity (<i>a'</i>), cm/s (mean ± SD)	7.1 ± 1.7	8.3 ± 1.7	<0.001
Early diastolic velocity (<i>e'</i>), cm/s (mean ± SD)	10 ± 7	6 ± 1	<0.001
Left ventricular end-diastolic pressure (E: <i>e'</i>)	8.4 ± 2.3	11.4 ± 3.6	<0.001
Deceleration time (DT), s (mean ± SD)	196 ± 28	255 ± 43	<0.001
Late diastolic filling velocity (A), cm/s (mean ± SD)	58 ± 14	75 ± 18	<0.001
Early diastolic filling velocity (E), cm/s (mean ± SD)	77 ± 16	65 ± 16	<0.001

The last 5 echocardiographic parameters were used in evaluating diastolic function.

Table 2

Univariable predictors of diastolic dysfunction.

Variables	OR (95% CI)	P value
Clinical		
Age (for 10 years)	3.4 (2.1–5.4)	<0.001
Hypertension	3.0 (1.4–6.2)	0.004
Systolic blood pressure (per 10 mm Hg)	1.2 (1.0–1.5)	0.03
Diastolic blood pressure (per 5 mm Hg)	1.2 (1.1–1.5)	0.02
Physical inactivity	2.4 (1.1–4.7)	0.02
Glucose (ln(glucose))	3.2 (1.3–8.1)	0.02
Hemoglobin A _{1c} (for 1%)	1.2 (1.0–1.4)	<0.05
Echocardiographic		
Epicardial fat pad thickness (for 1 mm)	1.9 (1.3–2.9)	0.002
Left ventricular mass index (per 10 g m ^{-2.7})	1.8 (1.2–2.7)	0.006

Table 3

Multivariable mutable predictors of diastolic dysfunction and of its components (left ventricular (LV) relaxation I and compliance), controlled for age, heart rate and blood pressure^a.

Predictor	Diastolic dysfunction		LV relaxation (early diastolic mitral annular velocity, e') ^b $r^2 = 0.20, P < 0.001$		LV compliance (late diastolic mitral annular velocity, a') ^c $r^2 = 0.21, P < 0.001$	
	OR	P value	β coefficient	P value	β coefficient	P value
Physical inactivity	2.3 (0.9–6.1)	0.08	–0.79 (–1.53–0.04)	0.04	–	–
Glucose (after logarithmic transformation)	4.9 (1.4–17.8)	0.02	–	–	0.87 (0.07–1.67)	0.03
Epicardial fat pad thickness (for 1 mm)	–	–	–	–	0.37 (0.01–0.73)	0.04

^aBlood pressure was controlled using 7 variables: diagnosis or therapy for hypertension (dichotomous), systolic blood pressure (continuous, mm Hg), diastolic blood pressure (continuous, mm Hg) and the squared and cubed values of systolic and diastolic blood pressure. Other control variables included age and heart rate.

^bPatients with pseudonormal filling pattern were excluded from this analysis.

^cModel was controlled for late diastolic filling velocity (A).