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Original Article

Diastolic function in patients with heart failure with preserved ejection fraction and atrial fibrillation: impact of diabetes

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Abstract: Introduction: The objective of our study was to evaluate the severity of diastolic dysfunction in patients with heart failure with preserved ejection fraction (HFpEF), atrial fibrillation (AF) and type 2 diabetes mellitus (T2DM) compared to those with HFpEF and AF without DM. Material and methods: This is an observational, prospective, case-control study. We selected 720 patients with heart failure consecutively admitted between March 2019-December 2020, of whom 253 patients with AF. After applying the inclusion/exclusion criteria, 105 subjects remained in the study. The patients were divided into two groups, according to the presence of T2DM: group A (39 patients with T2DM, 37.14%), group B (66 patients without T2DM, 62.85%). 2D transthoracic echocardiography was performed in all patients. The study was approved by the Ethics Committee of the hospital. Statistical analysis was performed using R software, version 4.0.2. Results: Patients with HFpEF, AF, and T2DM had higher LV filling pressures compared to those without DM (OR = 5.00, 95% CI: 1.77-15.19). Moreover, patients with insulin-requiring T2DM (OR = 6.25, 95% CI: 1.50-25.98) had higher LV filling pressures than those treated with oral antidiabetic drugs (OR = 4.44, 95% CI: 1.37-15.17). We demonstrated that patients with T2DM had higher E/e' ratio (difference -2.78, P 0.0003, 95% CI: -4.24 to -1.31) and lower deceleration time (DT) (difference 23.04, P 0.0002, 95% CI: 11.10-34.97) than those without T2DM. Conclusions: Patients with HFpEF, AF and T2DM have higher LV filling pressures than those without T2DM, suggesting that the presence of T2DM leads to a more severe diastolic dysfunction.

Keywords: Heart failure with preserved ejection fraction, atrial fibrillation, diabetes mellitus, diastolic dysfunction, left ventricular filling pressures

Introduction

Patients with type 2 diabetes mellitus (T2DM) have an increased risk of cardiovascular complications, with a 4 to 5-fold higher risk to develop heart failure (HF) [1-4]. T2DM is more common in patients with heart failure with preserved ejection fraction (HFpEF) than in those with reduced ejection fraction (HFrEF) [5-7]. Approximately 30-40% of patients with HFpEF have T2DM [8, 9]. The association of T2DM and HFpEF leads to a worse prognosis, with a 70-80% higher risk of hospitalization and mortality [10-16].

T2DM may lead to myocardial hypertrophy, increased extracellular collagen deposits with fibrosis, microangiopathy caused by accumulation of mucopolysaccharides in the small vessels of the heart, disturbances of myocytes' metabolism, and myocardial dysfunction [17-23]. All these alterations are known as diabetic cardiomyopathy.

In patients with HFpEF, T2DM leads to a systemic proinflammatory state and increased oxidative stress in the endothelium of coronary microcirculation [24]. These pathological changes are associated with a decreased release of nitric oxide, reduced activity of protein kinase G in the cardiomyocytes, and myocardial stiffness [24].

T2DM, especially when associated with a poor glycaemic control, is a risk factor for diastolic dysfunction [25-28]. In patients with asymp-

tomatic diastolic dysfunction, T2DM is a predictor of progression to chronic HF [29]. According to Poirier et al., patients with T2DM initially develop diastolic dysfunction and in more advanced stages systolic dysfunction appears [30]. Approximately 75% of patients with T2DM and diastolic dysfunction may be asymptomatic [31].

HFpEF is more frequent in women with T2DM and comorbidities, such as obesity, arterial hypertension, atrial fibrillation (AF). At echocardiography, these patients have normal LVEF and LV cavity dimensions, but a dilated left atrium and increased stiffness of the LV walls, causing elevated LV filling pressures [32, 33].

There are several pathophysiological mechanisms in T2DM that induce myocardial remodelling and dysfunction, such as hyperglycaemia, glucotoxicity, lipotoxicity, mitochondrial dysfunction, autoimmunity, inflammation, activation of renin-angiotensin-aldosterone system, myocardial fibrosis, impaired myocardial calcium metabolism, insulin resistance and hyperinsulinaemia [17, 34, 35]. T2DM also determines increased oxidative stress because of high levels of glycation products, free fatty acids, leptin and glucose auto-oxidation [36].

The Candesartan in Heart Failure-Assessment of MoRtality and Morbidity (CHARM) study included 7,599 patients with symptomatic HF, with or without T2DM, and concluded that the risk of cardiovascular mortality and hospitalization for HF was 2-fold higher in patients with LVEF >40% and T2DM than in those without T2DM [13].

Patients with HFpEF frequently associate AF, which is the most common sustained cardiac arrhythmia in clinical practice, with significant morbidity and mortality [37, 38]. Patients with T2DM have a 34% higher risk of developing AF compared to non-diabetic patients [39, 40]. Thus, HFpEF, AF and T2DM often coexist.

The ultrasound evaluation of diastolic function in patients with AF is more difficult than in those with sinus rhythm, and more advanced ultrasound techniques, such as tissue Doppler, are needed. The ratio between early passive transmitral inflow velocity (E) and the mean pulsed tissue Doppler velocity of the mitral annulus-e' (the media between septal e' and lateral e') represents an accurate method of measuring LV filling pressures in patients with sinus rhythm or AF [41]. Consequently, the E/e' ratio can be a useful indicator of the severity of diastolic dysfunction in patients with HFpEF, with or without AF. The deceleration time (DT) value of the E wave is another parameter that may be used for assessing diastolic function in patients with AF.

The objective of our study was to determine if there is a link between the presence of T2DM, treated with oral antidiabetics drugs (OAD) or insulin, and the severity of diastolic dysfunction in patients with HFpEF and chronic AF. We hypothesized that patients with HFpEF and chronic AF who associate T2DM have a more severe diastolic dysfunction and an increased E/e' ratio compared to those without T2DM. The primary endpoint of this study was to evaluate LV filling pressures in patients with HFpEF, chronic AF, and T2DM compared to those without T2DM. The secondary endpoint was to determine if there are other factors that may influence the LV filling pressures in the study group.

Material and methods

Study population

This is an observational, prospective, case-control study. We recruited 702 consecutively admitted patients with the diagnosis of chronic HF, hospitalized in the Internal Medicine Clinic of the Clinical Emergency Hospital of Bucharest, Romania, between March 2019 and December 2020. Of these patients, we selected the patients with permanent AF, respectively 253 patients.

The inclusion criteria in the study were age more than 18 years old, diagnosis of HFpEF and chronic AF, absence of regional LV motion abnormalities, signed written informed consent to participate in the study.

The exclusion criteria were LVEF <50%, a suboptimal ultrasound view, recent myocardial infarction or unstable angina (less than four weeks before enrollment), other cardiac rhythms than AF, type 1 DM, diet-controlled T2DM, psychiatric disorders, corona virus disease 2019 (COVID-19). The study protocol is shown in **Figure 1**.

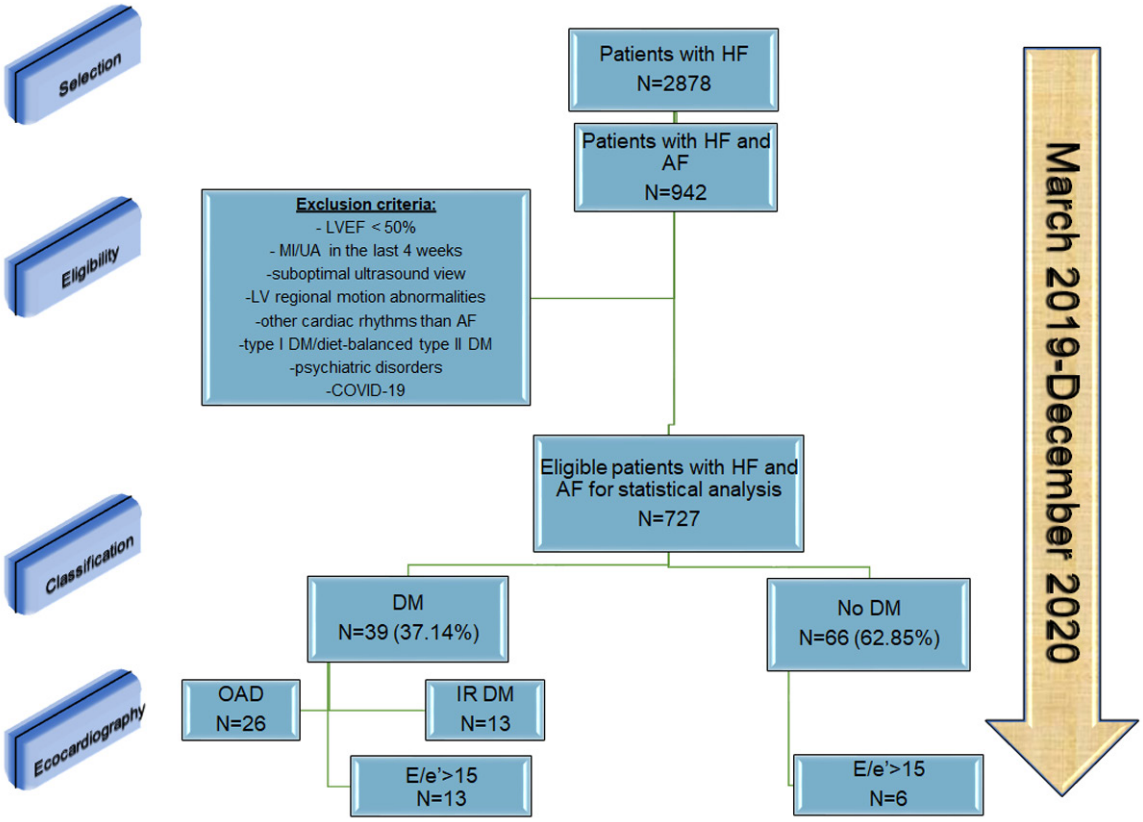

Figure 1. Selection of the patients included in the study. Note: HF-heart failure; AF-atrial fibrillation; LVEF-left ventricular ejection fraction; LV-left ventricular; MI-myocardial infarction; UA-unstable angina; T2DM-type 2 diabetes mellitus; HFpEF-heart failure with preserved ejection fraction; OAD-oral antidiabetic drugs; IR-insulin-requiring.

After applying the inclusion and exclusion criteria, 105 patients with HFpEF and AF remained in the study. This sample is representative for the general population of patients with HFpEF and AF.

The diagnosis of HFpEF was based on the presence of signs and symptoms of heart failure, LVEF ≥50%, elevated levels of natriuretic peptides and at least one additional criterion of relevant structural changes such as LV hypertrophy and/or left atrial enlargement or diastolic dysfunction [42].

The diagnosis of AF was made using a standard 12-lead electrocardiogram or automated continuous monitoring of cardiac rhythm for 24-72 hours.

The diagnosis of T2DM was based on plasma glucose level >126 mg/dL or haemoglobin A1c ≥6.5% and oral glucose tolerance test, if the diagnosis was not clear [43]. Most of the patients were already diagnosed with T2DM before enrollment, but if T2DM was newly diagnosed, we reffered the patients to the diabetologist for investigations and confirmation of diagnosis.

The patients were divided in two subgroups, according to the presence of T2DM: subgroup A included 39 patients with T2DM (37.14%); subgroup B included 66 patients without T2DM (62.85%). From the 39 patients included in subgroup A, 26 were treated with OAD and 13 were treated with insulin. Baseline demographics were obtained at inclusion in the study.

The study respected the ethical standards of the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. The study was approved by the Ethics Committee of the Clinical Emergency Hospital of Bucharest, Romania (approval no 4714/24.05.2019). All patients included in the study provided their

Table 1. Baseline characteristics of patients with HFpEF and AF

	No T2DM (N = 66)	T2DM (N = 39)	All (N = 105)
Age			
Mean ± SD	75.61 ± 12.70	73.85 ± 9.61	74.95 ± 11.63
Median (IQR)	78.50 (19.00)	73.00 (15.50)	77.00 (19.00)
Min-Max	47.00 to 94.00	64.00 to 93.00	47.00 to 94.00
Sex			
M-number (%)	23/66 (34.84)	10/39 (25.64)	33/105 (31.42)
F-number (%)	43/66 (65.16)	29/39 (74.36)	72/105 (68.58)
Obesity			
No-number (%)	38/66 (57.57)	20/39 (51.28)	58/105 (55.23)
Yes-number (%)	28/66 (42.43)	19/39 (48.72)	47/105 (44.77)
Mitral regurgitation			
No-number (%)	6/66 (9.09)	3/39 (7.69)	9/105 (8.57)
Yes-number (%)	26/66 (39.39)	17/39 (43.58)	43/105 (40.95)
Mitral stenosis			
No-number (%)	32/66 (48.48)	18/39 (46.15)	50/105 (47.61)
Yes-number (%)	0/66 (0.00)	2/39 (5.12)	2/105 (1.9)
Aortic regurgitation			
No-number (%)	24/66 (36.36)	10/39 (25.64)	34/105 (32.38)
Yes-number (%)	8/66 (12.12)	10/39 (25.64)	18/105 (17.14)
Aortic stenosis			
No-number (%)	29/66 (43.93)	16/39 (41.02)	45/105 (42.85)
Yes-number (%)	3/66 (4.54)	4/39 (10.25)	7/105 (6.66)
Hypertension			
No-number (%)	5/66 (7.57)	2/39 (5.12)	7/105 (6.66)
Yes-number (%)	27/66 (40.9)	18/39 (46.15)	45/105 (42.85)
Coronary artery disease			
No-number (%)	22/66 (33.33)	10/39 (25.64)	32/105 (30.47)
Yes-number (%)	10/66 (15.15)	10/39 (25.64)	20/105 (19.04)
Chronic kidney disease			
No-number (%)	23/66 (34.84)	11/39 (28.2)	34/105 (32.38)
Yes-number (%)	9/66 (13.63)	9/39 (23.07)	18/105 (17.14)

Note: T2DM-type 2 diabetes mellitus; SD-standard deviation; IQR-inter quartile range; Min-minimum; Max-maximum; M-males; F-females.

written informed consent to participate in this study.

Laboratory tests

Blood tests were performed in all patients enrolled in the study: complete cell blood count (leukocytes 4,000-9,000/μL; haemoglobin 12.6-17.2 g/dL; platelets 150.000-350.000/μL), creatinine (0.7-1.4 mg/dL), blood ureea nitrogen (19-43 mg/dL), serum sodium (137-145 mmol/L), serum potassium (3.5-5 mmol/L), aminotransferases (aspartate aminotransferase 14-50 U/L; alanine aminotransferase 10-50 U/L), glycaemia (75-110 mg/dL), troponin I (<5 ng/mL), creatine kinase (55-170 U/L), creatine kinase-MB (10-16 U/L), total cholesterol (140-200 mg/dL), triglycerides (30-150 mg/dL).

Echocardiography

2D transthoracic echocardiography was performed in all patients, using commercially available ultrasound systems, Phillips CX50 or Vivid 9 machine. Conventional measurements, such as LV end-diastolic and end-systolic diameters and volumes, left atrial diameter and volume, right atrium diameter and area, right ventricle diameter, were obtained. LVEF was calculated in the apical 4- and 2-views, using the modified Simpson's biplane method. Valvular pathologies were evaluated using color, pulse and continuous Doppler.

For evaluating the diastolic dysfunction, E/e' ratio and deceleration time of the E wave (DT) were used. Pulse Doppler was used to measure E wave velocity and DT, and tissue Doppler to determine e' velocity, in order to evaluate the E/e' ratio, that correlates well with intracardiac pressure. Therefore, LV filling pressures increase proportionally with the increase of the E/e' ratio. E/e' ratio >15 and and DT <130 milliseconds were considered abnormal [41, 44].

Statistical analysis

Statistical analysis was performed using R software, version 4.0.2. To evaluate the influence of T2DM and other clinical and demographic variables on the LV filling pressures, a simple binomial univariate logistic regression was used to assess the independent predictors for increased LV filling pressure. The dependent

Table 2. Predictors of increased LV filling pressure in patients with HFpEF and AF ± T2DM

	Coefficient (β)	*p*-value	OR [95% CI]
No T2DM	REFERENCE	-	-
T2DM OAD	1.49	0.0134	4.44 [1.37 to 15.17]
T2DM IR	1.83	0.0102	6.25 [1.50 to 25.98]
T2DM			
No	REFERENCE	-	-
Yes	1.60	0.0032	5.00 [1.77 to 15.59]
Age	0.02	0.2247	1.02 [0.98 to 1.07]
Sex			
F	REFERENCE	-	-
M	0.008	0.9880	1.008 [0.32 to 2.85]
Obesity			
No	REFERENCE	-	-
Yes	0.38	0.4470	1.47 [0.54 to 4.05]
Mitral regurgitation			
No	REFERENCE	-	-
Yes	-0.70	0.2810	0.49 [0.14 to 1.98]
Mitral stenosis			
No	REFERENCE	-	-
Yes	0.84	0.4990	2.33 [0.10 to 25.65]
Aortic regurgitation			
No	REFERENCE	-	-
Yes	0.84	0.1040	2.32 [0.83 to 6.48]
Aortic stenosis			
No	REFERENCE	-	-
Yes			0.58 [0.18 to 1.71]
Hypertension			
No	REFERENCE	-	-
Yes	-0.47	0.5122	0.62 [0.16 to 3.03]
Coronary artery disease			
No	REFERENCE	-	-
Yes	1.51	0.0043	4.53 [1.62 to 13.26]
Chronic kidney disease			
No	REFERENCE	-	-
Yes	1.58	0.0032	4.86 [1.70 to 14.24]

Note: OR-odds ratio; CI-confidence interval; T2DM-diabetes mellitus; OAD-oral antidiabetics; IR-insulin-requiring.

variable ("output") was the presence or absence of increased LV filling pressure and the independent variables ("input") were the clinical and demographic individual factors of the patients. Normally distributed data were expressed as mean ± standard deviation. Data deviating from normal range were expressed as median. The individual values of E/e' ratio and DT were also compared in patients with T2DM versus non-diabetics. The Two Sample Welch T test two-sided was used to determine the differences of E/e' ratio and DT between the two subgroups of patients, respectively with or without T2DM. A value of $P<0.05$ was considered to be statistically significant.

Results

The baseline characteristics of the patients are shown in **Table 1**, including age, sex and co-morbidities.

Evaluation of the predictors of increased LV filling pressure

Patients with HFpEF, AF, and T2DM had higher LV filling pressures compared to those without T2DM (OR = 5.00, 95% CI: 1.77-15.19). Moreover, in subgroup A, patients with insulin-requiring T2DM (OR = 6.25, 95% CI: 1.50-25.98) had higher LV filling pressures than those treated with OAD (OR = 4.44, 95% CI: 1.37-15.17) (**Table 2**). The predictors of increased LV filling pressure are summarized in **Figure 2**.

The multiple logistic regression with backward selection algorithm demonstrated that independent predictors for increased LV filling pressures are T2DM under treatment with OAD compared to the absence of T2DM (OR = 5.40, 95% CI: 1.53-20.57), and insulin-requiring T2DM compared to the absence of T2DM (OR = 7.56, 95% CI: 1.62-37.58) (**Table 3**).

Other factors that lead to increased LV filling pressure were coronary artery disease (OR = 4.53, 95% CI: 1.62-13.26) and chronic kidney disease (OR = 4.86, 95% CI: 1.70-14.24) (**Table 2**).

Evaluation of echocardiographic data in patients with T2DM

Comparing the E/e' ratio and DT of E wave in patients with T2DM versus non-diabetics, we observed higher values for E/e' (**Table 4**) and respectively lower values for DT (**Table 5**) in

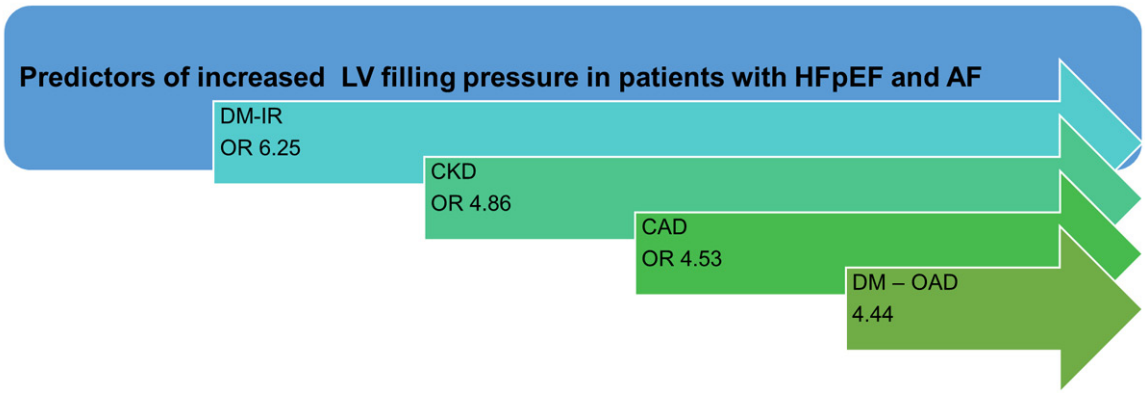

Figure 2. Predictors for increased LV filling pressure in patients with HFpEF and AF. Note: LV-left ventricular; HFpEF-heart failure with preserved ejection fraction; AF-atrial fibrillation; DM-IR-insulin-requiring diabetes mellitus; CKD-chronic kidney disease; CAD-coronary artery disease; OAD-oral antidiabetic drugs.

Table 3. Multiple logistic regression with backward selection algorithm in patients with HFpEF and AF

	Coefficient (β)	*p*-value	OR [95% CI]
No T2DM	REFERENCE	-	-
T2DM OAD	1.68	0.0097	5.40 [1.53 to 20.57]
T2DM IR	2.02	0.0101	7.56 [1.62 to 37.58]

Note: OR-odds ratio; CI-confidence interval; T2DM-type 2 diabetes mellitus; OAD-oral antidiabetic drugs; IR-insulin-requiring.

Table 4. Comparison of E/e' ratio values between patients with HFpEF and AF ± T2DM

E/e'	No T2DM (n = 66)	T2DM (n = 39)
Mean ± SD	10.35 ± 3.62	13.13 ± 3.65
Median (IQR)	8.50 (7.00)	15.00 (7.50)
Min to Max	6.00 to 17.00	6.00 to 17.00

Note: E/e' ratio-ration between early passive transmitral inflow velocity (E) and the pulsed tissue Doppler velocity of the mitral annulus (e'); T2DM-type 2 diabetes mellitus; SD-standard deviation; IQR-inter quartile range; Min-minimum; Max-maximum.

Table 5. Comparison of DT values between patients with HFpEF and AF ± T2DM

DT	No T2DM (n = 66)	T2DM (n = 39)
Mean ± SD	200.35 ± 26.95	177.31 ± 31.13
Median (IQR)	203.00 (13.75)	196.00 (58.00)
Min to Max	132.00 to 251.00	130.00 to 220.00

Note: DT-deceleration time of E wave; T2DM-type 2 diabetes mellitus; SD-standard deviation; IQR-inter quartile range; Min-minimum; Max-maximum.

patients with T2DM compared to non-diabetics. Moreover, patients with still normal LV filling pressures and T2DM had elevated values than non-diabetics.

Using a Two Sample Welch T test two-sided, statistically significant differences were obtained between E/e' ratio (difference -2.78, P 0.0003, 95% CI: -4.24 to -1.31) and DT values (difference 23.04, P 0.0002, 95% CI: 11.10 to 34.97) in patients with HFpEF and AF ± T2DM.

Discussion

The primary and secondary endpoints of this study were hypothesized on the basis of the well-known relationship between HFpEF, AF and T2DM. Taking into account that several previous trials revealed that diabetic patients with HFpEF have a more severe diastolic dysfunction [1, 13, 14, 45], our study focused on patients with HFpEF and AF, with the purpose to investigate the impact of T2DM on diastolic function in these patients. Our results show that patients with insulin-requiring T2DM have even higher LV filling pressures than those treated with OAD, suggesting that the severity of diastolic dysfunction is related to the severity of T2DM.

In patients with HFpEF and sinus rhythm, E/A ratio was used to determine the stage of diastolic dysfunction, and additionally E/e' ratio was used for evaluating LV filling pressure. In patients with AF, E/A ratio cannot be used and the evaluation of diastolic dysfunction is more challenging. In our study, E/e' ratio was applied, as an accurate indicator of LV filling pressure, even in patients with AF, and correlates well with LV filling pressure determined by invasive methods [46].

The present study demonstrated that patients with HFpEF and AF plus T2DM have a greater E/e' ratio than those without T2DM, correlating with higher LV filling pressures and a more advanced diastolic dysfunction. DT of the E wave, as another ultrasound indicator of higher LV filling pressures, was determined, and proved to be lower in diabetic patients.

Also, we demonstrated that among patients who have still normal LV filling pressures, those with T2DM have higher E/e' ratio than those without T2DM. T2DM may be considered a risk factor for diastolic dysfunction progression.

The impact of T2DM in patients with HF was evaluated in several other studies. According to a study by Aguilar et al., that included 987 patients with HF and LVEF >45%, of whom 285 (28.9%) with T2DM, diabetic patients have an increased LV and arterial stiffness, and higher rated of diastolic dysfunction with impaired relaxation, with a very important role in the pathophysiology of HFpEF [14]. Myocardial fibrosis, increased levels of extracellular collagen, neurohormonal and calcium disturbances seem to be some of the pathophysiological mechanisms leading to diastolic dysfunction in diabetic patients [17-23].

The trial of MacDonald et al. included 7,599 patients with HF (HFrEF or HFpEF) and concluded that patients with HFpEF and T2DM have a high risk of hospitalization for HF, even higher than those with HFrEF [13]. The hypothesis proposed in this study was that T2DM may represent the primary cause of cardiac dysfunction in some patients with HFpEF or, in those who already had HFpEF before developing T2DM, the pathophysiological processes may be more deleterious for diastolic function than for systolic function [13]. Thus, as our results have also revealed, T2DM has an important impact on the evolution of HFpEF.

From et al. studied 1,760 patients with T2DM, of whom 411 patients (23%) had preclinical diastolic dysfunction, defined as an E/e' ratio >15, without a previous diagnosis of HF [46]. The diabetic patients with diastolic dysfunction included in this study were more frequent females, older and with comorbidities, such as arterial hypertension or coronary artery disease, had more frequently left atrium dilation and increased LV mass than those with normal diastolic function [46]. These authors revealed that diastolic dysfunction with an elevated E/e' ratio in diabetic patients is related with HF development: for every unit increase in E/e' ratio, the risk of developing HF increased by 3%. Also, diastolic dysfunction was associated with higher risk of AF development and mortality [46].

According to Kristensen et al., patients with HFpEF and T2DM have a more advanced diastolic dysfunction, with higher LV filling and E/e' ratio, in addition to more pronounced signs of congestion, higher NT-proBNP levels, worse quality of life and prognosis [5]. This study enrolled 4,128 patients with HFpEF, of whom 27% had T2DM (1,134 patients) [5]. Among patients with HFpEF, those with T2DM had a higher risk of hospitalization for HF and a greater rate of overall and cardiovascular mortality compared to those without T2DM [5].

The Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) study included 216 stable patients with HFpEF, of whom 93 with T2DM [1]. Although patients included in this study had similar systolic and diastolic function, no matter the T2DM status, patients with T2DM had higher LV filling pressures compared to non-diabetics [1].

The study realized by Van Heerebeek et al. focused on the pathophysiological changes that appear in the myocardium of diabetic patients [47]. These authors analyzed the LV endomyocardial biopsy samples of 28 patients with HFpEF, of whom 16 with T2DM, and 36 with reduced LVEF, of whom 10 with T2DM, all without coronary artery disease [47]. The study determined that patients with HFpEF and T2DM have increased LV stiffness because of higher cardiomyocyte resting tension compared to patients with HFpEF without T2DM [47]. Furthermore, this study demonstrated that the increased cardiomyocyte resting tension is caused by a deficit of phosphorylation of the cytoskeletal or myofilamentary proteins, that could be corrected by protein kinase A administration [47].

Fontes-Carvalho et al. enrolled 1,063 adults aged over 45 years old, without prior myocardial infarction or myocardial revascularization, significant valvular disease or type 1 DM, of whom 23.7% with diastolic dysfunction [48].

Patients with metabolic syndrome or T2DM had lower e' velocity and higher E/e' ratio compared to those with normal glucose metabolism [48]. The prevalence of diastolic dysfunction was progressively increasing, as follows: 16.3% in patients without metabolic syndrome, 32.6% in patients with metabolic syndrome, 36.6% in patients with metabolic syndrome and T2DM [48]. It was also noticed a trend for progressively lower e' velocity and E/A ratio and higher E/e' ratio in patients with metabolic syndrome and T2DM compared to those with metabolic syndrome without diabetes, and to individuals without metabolic syndrome [48].

The majority of the studies mentioned above included patients with diastolic dysfunction, with or without T2DM, and revealed that those with T2DM have a more advanced diastolic dysfunction, with higher LV filling pressures than those without T2DM. Our study included a special category of patients with HFpEF and AF, excluding those with other cardiac rhythms, and the results showed that the association of T2DM in these patients leads to higher LV filling pressures compared to patients without T2DM.

In our study, the secondary endpoint consisted of the identification of other factors or comorbidities that may increase LV filling pressure. The results revealed that coronary artery disease and chronic kidney disease are independent contributors to elevated LV filling pressures in the study population.

Coronary artery disease is present in about 40-55% of patients with HFpEF [49]. Myocardial ischemia may be the cause of HFpEF and its optimal treatment may improve the outcome in patients with coronary artery disease and HFpEF [49]. Patients with HFpEF may even have detectable blood levels of cardiac troponin, thus, although they do not have an acute coronary syndrome, they may have subclinical cardiomyocytes injury and coronary microvascular dysfunction [50] that can be evaluated by measuring the coronary flow reserve (CFR).

Taqueti et al. analyzed 201 patients without prior history of coronary artery disease, who were tested for suspected coronary artery disease by serum cardiac troponin level, transthoracic echocardiography and stress cardiac positron emission tomography [50]. The study demonstrated that in patients with symptoms of myocardial ischaemia, without obstructive epicardial disease, reduced CFR is related with diastolic dysfunction [50]. A CFR <2 and a E/e' septal >15 were associated with a 5-fold higher risk of hospitalization for HFpEF [50].

Patients with chronic kidney disease are at high risk of cardiovascular death because of coronary artery disease and HF, especially patients undergoing hemodialysis [51]. Diastolic dysfunction is common in patients with chronic kidney disease and is associated to an increased risk of mortality [52]. Moreover, diastolic dysfunction appears prior to systolic dysfunction, both in patients with early stage kidney disease and hemodialysis [53]. The study of Franczyk-Skora et al. enrolled 118 patients with chronic kidney disease and showed that the severity of diastolic dysfunction varies proportionally with the severity of the renal disease [54].

An important finding of our study is that patients with HFpEF, AF and T2DM, even if they may still have a normal LV filling pressure, have a higher LV filling pressure compared to those without T2DM. Moreover, our results show that patients with insulin-requiring T2DM have greater LV filling pressure than those under treatment with OAD, suggesting that the severity of T2DM correlates with the severity of the diastolic dysfunction. Moreover, we identified coronary artery disease and chronic kidney disease as independent predictors of high LV filling pressure.

The limitations of our study are the relatively small number of patients included, and the echocardiographical examination, that was performed by several examiners, with possible inter-individual differences in appreciating the ultrasound data.

Future research may be focused on evaluating the relationship between the duration of T2DM and the severity of diastolic dysfunction in patients with HFpEF and AF, and on determining if an earlier diagnosis of diastolic dysfunction in patients with T2DM may lead to a more intensive treatment of T2DM, that may limit the progression of diastolic dysfunction.

Conclusions

The current study demonstrated that patients with HFpEF and AF plus T2DM have higher E/e'

ratio and lower DT, even if still in the normal range, than those without T2DM. Consequently, we determined that patients with HFpEF, AF plus T2DM have higher LV filling pressures and a more severe diastolic dysfunction compared to patients with HFpEF, AF without T2DM. Furthermore, our results show that patients with insulin-requiring T2DM have even higher LV filling pressures than those treated with OAD, suggesting that the severity of diastolic dysfunction in T2DM is related to worse control of T2DM.

Disclosure of conflict of interest

None.

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