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The role of epicardial obesity in the development of left ventricular diastolic dysfunction

Aim	To study the effect of epicardial adipose tissue on risk of left ventricular (LV) diastolic dysfunction (DD) in patients with visceral obesity.
Material and methods	Obesity leads to the development of LV DD and is a major cause of heart failure with preserved LV ejection fraction (HFpEF). However, the contribution of epicardial adipose tissue to DD is understudied. This study included 101 men with general obesity (body weight index, 32.9±3.6 kg/m^2). Based on severity of epicardial obesity (EO), two groups were formed: group 1, patients with an epicardial adipose tissue thickness (EATt) >7 mm (n=70), and group 2, patients with EATt <7 mm (n=31). Arterial hypertension, diabetes mellitus, coronary atherosclerosis, and disorders of LV diastolic function according to echocardiography (EchoCG) were the exclusion criteria. Diastolic function and LV mechanics were evaluated by speckle-tracking EchoCG for all patients at the start of the study and again at 4.7±0.3 years.
Results	At baseline, none of the patients of either group had significant differences in EchoCG characteristics of LV diastolic function (left atrial volume index, LV early diastolic longitudinal lengthening velocity, peak tricuspid regurgitation velocity, and the ratio of diastolic transmitral flow velocity to mean mitral annular velocity (E/e'). However, there were significant increases in the LV untwisting velocity to –122.11 [–142.0; –116.0 degrees/s^{-1}] degrees/s and the time to LV peak untwisting velocity to 472.3 ms. Repeated EchoCG showed an increase in left atrial volume index in group 1 to 35.04 [33.0; 39.7] ml/m^2. Repeated evaluation of the LV mechanics revealed increases in the times to LV peak untwisting and twisting and decreases in the LV twisting and untwisting velocities. The logistic regression analysis showed that EATt was a risk factor for LV DD in obesity. Furthermore, the ROC analysis determined the optimal EATt cut-off threshold of ≥9 mm as a predictor for LV DD development.
Conclusion	EO facilitates the development of LV DD and, thus, represents a major cause for HFpEF. An EATt value of ≥9 mm can be considered as a risk factor for LV DD development in patients with EO.

Keywords	Epicardial obesity; diastolic dysfunction; myocardial fibrosis
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The prevalence of heart failure with preserved ejection fraction (HFpEF) of the left ventricle (LV) has increased significantly over the past 20 years in Europe and the United States by 10–20% in comparison to systolic heart failure (HF) [1]. There are several factors contributing to the increasing number of patients with HF – the aging of the population, the high incidence of concomitant disorders that contribute to the development and progression of HF, and advancements in HF diagnosis techniques are among them [2]. Thus, it is relevant to study left ventricular diastolic dysfunction (LVDD), which is the basis for HFpEF. However, as there are no early pathognomonic signs and patients seek medical attention when a severe clinical picture develops; there are some challenges in the early diagnosis of LVDD [3]. The high prevalence of such a risk factor (RF) as obesity cannot but affect the prevalence of HFpEF [4]. Obesity is listed as one of the significant etiological RFs for the development of HF in one of the most recent guidelines on the definition and classification of HF [5]. Visceral obesity (VO) plays an important part in the development of obesity-related diseases. Cardiomyocyte apoptosis is one of the main mechanisms underlying myocardial dysfunction in obesity. It is followed by myocardial fibrosis, which is regarded the primary morphological mechanism of the development and progression of HF [6]. The available evidence suggests that the degree

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of myocardial fibrosis is associated with the degree of LVDD [7]. However, the accepted algorithms for diagnosing indirect indicators of increased myocardial stiffness due to LV fibrosis cannot be used to determine the presence of myocardial fibrosis due to blind spots that prevent a precise identification of LVDD [8, 9]. In this regard, efforts are made to find non-invasive techniques for the diagnosis of asymptomatic LVDD. These methods include speckle tracking echocardiography, which examines the LV mechanics. The effect of obesity (including VO) on the risk of HF is still not fully understood, and it is important to find non-invasive diagnostic tools that can identify asymptomatic LVDD to prevent the progression of HF.

Objective

Evaluate the effect of epicardial adipose tissue on the risk of LVDD in patients with VO.

Material and Methods

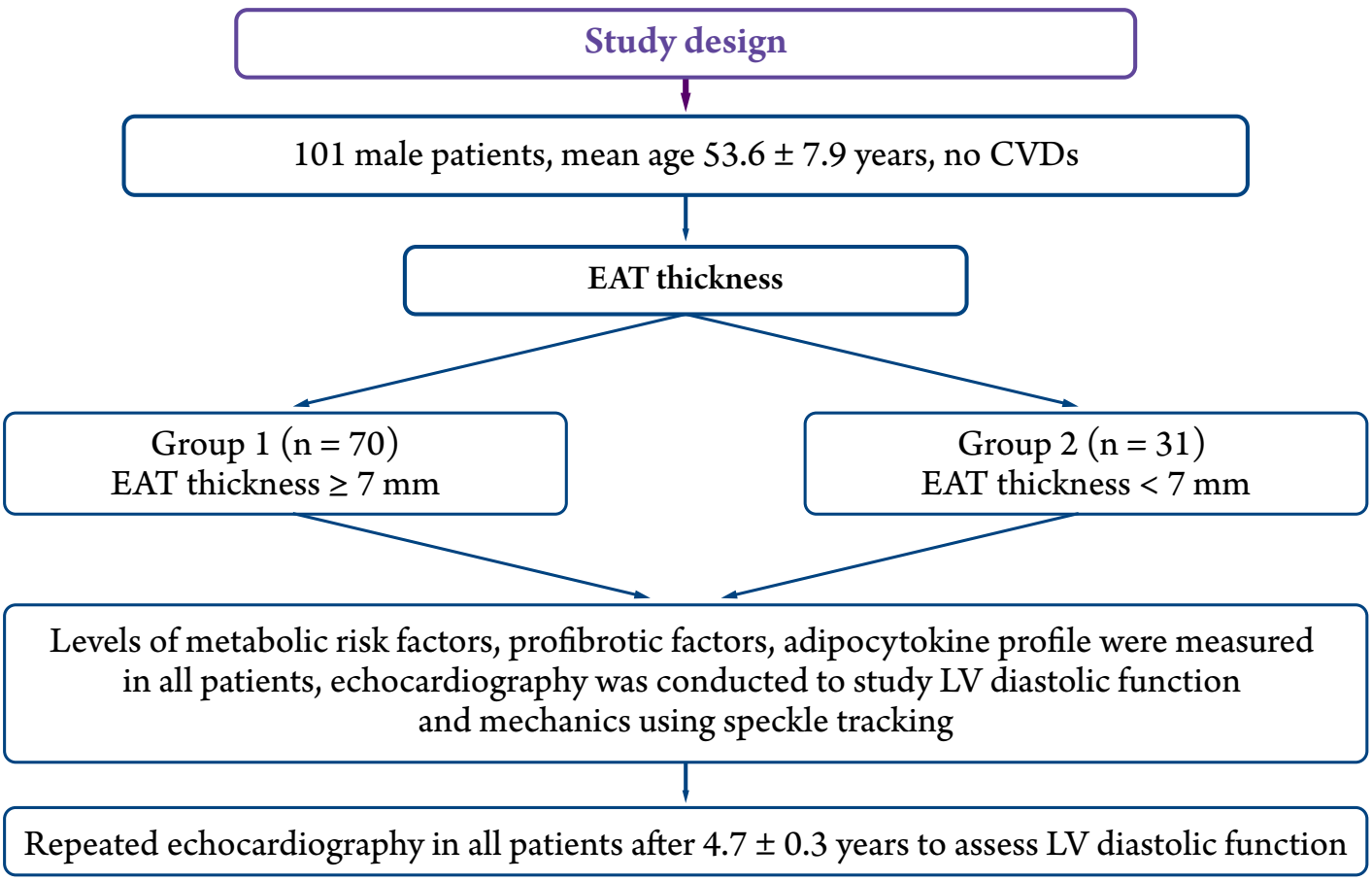
Between 2016 and 2017, 101 male patients were included in the study. Patients went to the Altai Regional Cardiology Dispensary with complaints of chest pain. Patients had no cardiovascular diseases (CVDs) according to a comprehensive examination. The mean age of the study subjects was 53.6 ± 7.9 years.

The study was approved by the local ethics committee at the Altai Regional Cardiology Dispensary. All patients signed the informed consent before being included in the study.

Grade I–III general obesity was the main inclusion criterion. Body mass index (BMI) was calculated by the formula: weight (kg)/height (m^2). The mean BMI was 32.9±3.6 kg/m^2. General obesity was established with BMI ≥ 30 kg/m^2.

Arterial hypertension (AH), coronary atherosclerosis, type 2 diabetes mellitus, and LVDD according to transthoracic echocardiography, were the exclusion criteria. Patients underwent multispiral computed tomography (MSCT) of coronary arteries or coronary artery angiography, as indicated, in order to exclude coronary artery atherosclerosis. Coronary artery MSCT was performed using a 64 slice CT scanner with data processing on the VITREA workstation and Integris 3000 angiography system. 24-hour monitoring of blood pressure was carried out using a MD-01M

Figure 1. Study design



BMI, body mass index; EAT, epicardial adipose tissue.

device (Russia) to exclude AH including masked forms.

Two groups were formed depending on the degree of epicardial obesity (EO), which was determined by the thickness of the epicardial adipose tissue (EAT): Group 1 included patients with EAT thickness of ≥7 mm (n=70) and Group 2 included patients with EAT thickness of <7 mm (n=31). In previous studies, EAT thickness of ≥7 mm was associated with the risk of developing metabolic disorders [10].

In 2021, a study was performed to assess LV diastolic function and mechanics using echocardiography. The mean follow-up period was 4.7±0.3 years. The study design is shown in Figure 1.

Echocardiography was performed following the standard procedure on the VIVID E95 scanner with an M5Sc probe (1.5–4.5 MHz). EAT thickness was measured in systole in the right ventricular (RV) free wall projection along the long axis. The landmark was a perpendicular line drawn to the aortic annulus [11].

The 2016 EAE/ASE guidelines were used to assess the LVDD in patients with preserved LVEF. The following indicators were determined: lateral and medial (septal) mitral annulus diastolic velocity (e', m/s) in the pulse-wave tissue Doppler mode, mitral peak early diastolic filling velocity in the pulse-wave Doppler mode (E, m/s), the E/e' ratio, left atrial volume index (LAVI; mL/m^2), peak tricuspid regurgitation velocity (m/s) [4].

To assess the LV mechanics, the parasternal LV view was obtained along the short axis at the mitral valve (MV) level and the LV apex in at least three cardiac cycles.

The data obtained were processed on the EchopacPC workstation using the speckle tracking technique. To assess LV rotation, rotation curves were obtained in degrees at the MV level (RotMV) and apical segments (Rotapex) at end systole. LV twist was calculated in degrees as the difference between the apex rotation and the basal rotation (Rotapex–RotMV) [12].

The untwist rate (in early diastole, deg/s^{-1}) and the time to peak LV untwist (as the first negative peak after the AV closure, ms), the LV twist rate (deg/s^{-1}), the time to peak LV twist (as the first positive peak after the R wave on the electrocardiogram, ms) were registered [11].

The baseline mean EAT thickness was 1.8 times higher in Group 1 than in Group 2: 8.66 [7.0; 9.0] mm and 5.02 [4.0; 6.0] mm, respectively (p = 0.001).

Statistical analysis of the data was carried out in the Biostatistics Research Center. The SAS 9.3, STATISTICA 13.0, and SPSS 26.0 statistical suites were used. The distribution of variables was tested using the Shapiro-Wilk, Kolmogorov-Smirnov, Kramer-von Mises, and Anderson-Darling methods for each indicator. Each of the normally distributed continuous variables is expressed as the mean (M) and standard deviation (SD), and non-normally distributed variables are presented as the medians (Me) and interquartile ranges [Q1; Q3]. The statistical significance threshold for the null hypothesis was p=0.05. The relationship between a qualitative attribute acting as a dependent resulting indicator and a subset of quantitative and qualitative attributes was analyzed using a logistic regression model with step-by-step inclusion and exclusion of predictors. The results of the logistic regression equations are represented by a set of regression coefficients, the achieved significance levels for each coefficient, a concordant of the patient's actual membership in one of the groups, and the theoretical membership according to the logit regression equation. A total of several dozen logit regression equations were obtained, from which the equations with the highest values (> 80%) of the indicator were selected. The selected predictors were ranked according to the strength of their relationships with the dependent variable by classifying the predictors by absolute values of standardized regression coefficients. The results of the conjugation table analysis and the results of the comparison of the central measures for the dependent attribute groups were used to interpret the equation structures. This analysis is one of the main statistical tools that allows determining the presence and nature of the relationship between the dependent variable or response (the presence or absence of LVDD the dependent variable was in our study) and independent variables or predictors (each EAT thickness value was a predictor in our analysis). It can also be used to predict the response using the predictor values. The relative contribution of the predictor was expressed by the Wald chi-square statistics.

The equation of the dependence of the LVDD probability on the EAT thickness was as follows:

$$P=\frac{\exp(-10{,}3692+0{,}9805\cdot X)}{1+\exp(-10{,}3692+0{,}9805\cdot X)},$$

where p is the theoretical probability of LVDD; the presence and the absence of the risk of LVDD was stated at $p \geq 0.5$ and $p < 0.5$, respectively; X is EAT thickness; – 10.3692 is an absolute term of the equation.

Results

LV diastolic function was evaluated following the 2016 EAE/ASE guidelines and the parameters of

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LV mechanics were determined in all patients at baseline. The results of this analysis are provided in Table 1.

According to Table 1, the compared groups did not differ statistically significantly in the echocardiographic parameters of the LV diastolic function. However, statistically significant changes in the LV mechanics (LV untwist rate and time to peak LV untwist) were detected in Group 1.

In 4.7 ± 0.3 years, all patients (n = 101) were subjected to echocardiography to re-evaluate LV diastolic function and mechanics. It was found that 20 (19.8%) patients had LVDD – 18 (90%) patients in Group 1 and 2 (10%) patients in Group 2. Some patients had various combinations of changes in LVDD. However, as seen in Table 2, there was a statistically significant increase only in LAVI to 35.04 mL/m^2 (p=0.0003) and no statistically significant differences in such indicators as e′, E/e′, and peak tricuspid regurgitation velocity. Patients with EO had a decrease in LV twist and untwist rate and an increase in time to peak LV twist and untwist.

A logistic regression analysis was performed to study the prognostic effect of EAT thickness on the risk of LVDD (Table 3).

The concordance (percent of correct prediction) was 70.4%. This supports that the equation accurately describes the grouping of patients depending on the combination of values of the attribute included in the equation. Thus, this logit regression equation correctly predicted the presence of LVDD in 70.4% of cases. The Somers' D test was used as a concordance measure of the real distribution of observations by individual grades of an attribute and prognosis based on the logistic regression equation, i.e. the strength of relationship between the presence

Table 1. Comparative characteristics of echocardiographic parameters in patients with and without epicardial adiposity

Parameter	Group 1 (n = 70)	Group 2 (n = 31)	p
E, m/s	0.89 [1.18; 0.35]	0.87 [1.03; 0.58]	0.426
e′, cm/s	0.09 [0.14; 0.07]	0.10 [0.12; 0.08]	0.251
E/e′ mean, units	7.74 [8.89; 6.42]	8.51 [9.70; 7.12]	0.078
Left atrial volume index, mL/m^2	28.52 [31.25; 24.17]	28.01 [30.21; 26.24]	0.549
Peak tricuspid regurgitation velocity, m/s	2.71 [2.9; 2.41]	2.67 [2.87; 2.41]	0.134
Twist, degrees	19.89 [22.0; 18.01]	16.89 [21.0; 12.47]	0.158
Twist rate, deg/s^{-1}	119.25 [126.3; 101.70]	99.25 [118.0; 85.0]	0.182
Time to peak twist, ms	192.41 [226.0; 142.0]	184.30 [216.0; 140.0]	0.850
Untwist rate, deg/s^{-1}	-122.11 [-142.0; -116.0]	-82.14 [-89.0; -74.1]	0.001
Time to peak untwist, ms	472.3 [510.0; 421.0]	410.0 [375.0; 415.0]	0.016
E/A, units	1.25 [1.58; 1.01]	1.26 [1.52; 1.01]	0.934

The data are presented as the medians and interquartile ranges (Me [Q1; Q3]). E, early diastolic filling velocity; e′, lateral-medial mitral annular velocity; E/e′, ratio of the mean early diastolic filling velocity to the mean lateral-medial mitral annular velocity; E/A, ratio of the early to late early diastolic filling velocity.

Table 2. Comparative characteristics of echocardiographic indicators of LVDD and LV mechanics over time in patients with and without epicardial obesity

Parameter	Group 1 (n = 70)	Group 2 (n = 31)	p
E, m/s	0.89 [0.98; 0.84]	0.89 [0.99; 0.85]	0.201
e′, cm/s	0.09 [0.09; 0.11]	0.10 [0.11; 0.09]	0.669
E/e′ mean, units	9.19 [10.0; 8.18]	7.74 [8.89; 6.42]	0.911
Left atrial volume index, mL/m^2	35.04 [33.0; 39.7]	28.52 [31.25; 24.17]	< 0.001
Peak tricuspid regurgitation velocity, m/s	2.66 [2.35; 2.88]	2.71 [2.89; 2.54]	0.376
Twist, degrees	14.79 [8.70; 18.50]	19.89 [22.0; 18.01]	0.188
Twist rate, deg/s^{-1}	92.85 [66.70; 102.80]	114.71 [124.70; 98.70]	0.011
Time to peak twist, ms	223.0 [165.0; 269.0]	192.41 [226.0; 142.0]	0.013
Untwist rate, deg/s^{-1}	-83.88 [-94.0; -63.0]	-112.79 [-135.0; -87.0]	< 0.001
Time to peak untwist, ms	499.0 [512.0; 427.0]	459.0 [489.0; 419.0]	0.049

The data are presented as the medians and interquartile ranges (Me [Q1; Q3]). LVDD, left ventricular diastolic dysfunction; E, early diastolic filling velocity; e′, lateral-medial mitral annular velocity; E/e′, ratio of the mean early diastolic filling velocity to the mean lateral-medial mitral annular velocity; E/A, ratio of the early to late early diastolic filling velocity.

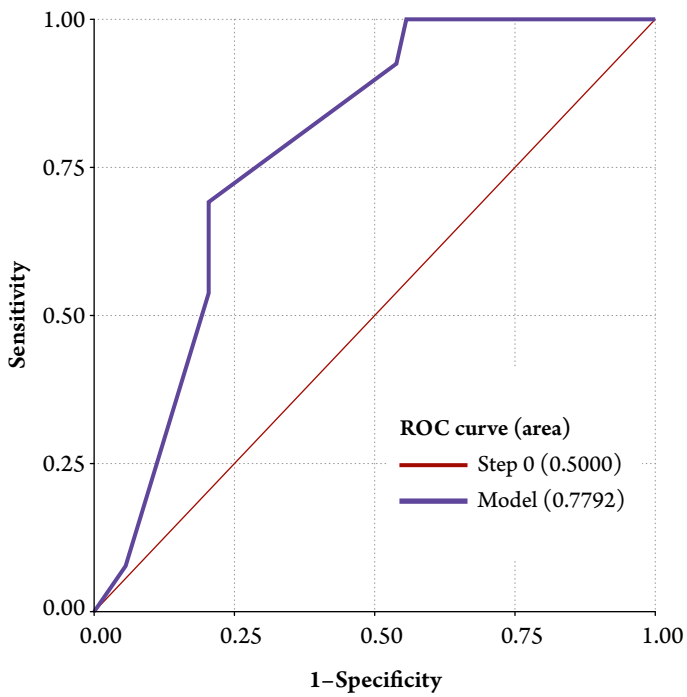
of LVDD and the prognosis. This test varies from 0 (a complete mismatch) to 1 (a complete match). It is equal to 0.558 for the logit regression equation with one predictor of EAT thickness. A ROC-curve was generated to evaluate the quality of the model. The area under the curve was 0.7792; the Gini test was 55.8%, which indicates the good quality of the model (Figure 2).

Moreover, during this analysis, the optimal cut-off value for EAT thickness ≥ 9 mm was determined as a predictor of LVDD. In this case, the percent of true positive classification results (sensitivity), i.e. the presence of LVDD, is 81%, and the percent of true negative classification results (specificity), i.e. the absence of LVDD, is 85%.

Discussion

LVDD develops at the early stages of CVDs. The need for timely detection of asymptomatic LVDD and risk factors for HF is increasingly being discussed. Experts propose to determine such parameters as e', E/e', LAVI, peak tricuspid regurgitation velocity on echocardiography to identify LVDD. We evaluated these indicators and observed no statistically significant differences in the study groups. Echocardiography with estimation of the parameters characterizing LV diastolic function detected LVDD in 20% of cases in 4.7±0.3 years. Our findings are consistent with the published works. In a prospective study, LVDD was detected in 19% of 588 obese patients. In another study, LV diastolic function was estimated in obese patients after 20 years of follow-up, LVDD was found in 26.2% of patients [13].

Figure 2. ROC curve for LVDD prediction model for EAT thickness



LVDD, left ventricular diastolic dysfunction; EAT, epicardial adipose tissue.

Moreover, we made an attempt study the effect of EAT thickness on the risk of developing LVDD. And it was found that EAT thickness can be considered as a RF for LVDD. The obesity pandemic has a significant impact on the prevalence of HF, as the two conditions are now often combined. Treatment of HF in obesity is becoming a major clinical challenge. At the same time, most obese patients have preserved LVEF, and only relatively severe diastolic dysfunction has symptoms [14]. There is an understanding that VO is accompanied by lipotoxicity to organs and tissues including the myocardium. In case of lipotoxic condition, the processes of myocardial dysfunction and myocyte apoptosis are activated, which leads to fibrosis that serves as the pathophysiological basis of LVDD. A prospective study analyzed the correlation between metabolic features and LVDD in healthy 30–60-year-old individuals who were included in the population-based STANISLAS cohort. The subjects were examined 20 years later in accordance with current international guidelines. Those who had elevated BMI and triglyceride levels were at a higher risk of LVDD [14].

It should be noted that in our study, the groups had a statistically significant difference only in EAT thickness. There were no statistically significant differences in traditional indicators of obesity (waist circumference, hip circumference, BMI, waist-to-hip ratio). It might be difficult to prove the effects of traditional obesity indicators on the development and progression of LVDD, while EO allowed identifying such effects.

The identified changes in the LV mechanics can be explained by the onset and progression of LVDD. It was shown in a study conducted in patients with documented LVDD using transmitral flow indices, that time to peak LV untwist and LV untwist rate are increased at the initial stage of LVDD. As LVDD progresses, LV untwist rate decreases, time to peak untwist is slightly reduced, and twist rate and time peak twist increase. Our findings are consistent with the data obtained by Ahmed et al. [15]. They showed that at the early stage of LVDD accompanied by violated LV relaxation, LV untwist rate and time to peak LV untwist increase; as LVDD progresses, these indicators decrease, and the values of LV untwist

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indicators normalize or decrease with E/A >1.5 [15]. Several trials that studied LV untwist using speckle-tracking echocardiography in patients with LVDD shown by transmitral Doppler indices, showed the relationship between LV untwist and LVDD indices [15], which allows assuming that patients with VO have asymptomatic LVDD. Currently, two major multi-ethnic trials are carried out: Multi-Ethnic Study of Atherosclerosis and Framingham Heart Study identified the presence of fatty deposits around the heart as an independent risk factor for CVDs [16].

Conclusion

Thus, epicardial obesity contributes to the development of left ventricular diastolic dysfunction and is therefore one of the leading causes of heart failure with preserved left ventricular ejection fraction. The threshold value of epicardial adipose tissue thickness of ≥ 9 mm was identified in this study as a risk factor for the development of left ventricular diastolic dysfunction in patients with epicardial obesity.

Limitations

Potential limitations of the assessment of echocardiography epicardial adipose tissue include difficulties in differentiating between epicardial adipose tissue and pericardial adipose tissue, and changes in the speed of sound in adipose tissue.

Limitations of the study are mainly associated with a small sample of male patients only and single-center design.

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