Epicardial fat tissue can predict subclinical left ventricular dysfunction in patients with erectile dysfunction

Hayati Eren, Muhammed Bahadir Omar, Ulker Kaya, Ertugrul Gazi Ozbey, and Lutfi Ocal

Introduction

Erectile dysfunction (ED) is not a simple sexual activity disorder by itself, but by definition is an early form of atherosclerosis [1]. Similar to atherosclerotic diseases, ED patients have risk factors such as diabetes mellitus (DM), hypertension (HT), dyslipidemia, smoking, and metabolic syndrome [1,2]. Endothelial cell damage and endothelial dysfunction caused by oxidative stress constitute the basic pathogenesis of the disease [1,2]. The emergence of symptoms of ED approximately 2–5 years before the onset of various cardiovascular diseases, and the determination of a relationship between the severity of ED and the severity of cardiovascular events, shows that ED is a leading condition for the development of atherosclerosis [3,4]. However, ED has recently been recognized as an independent indicator of cardiovascular disease risk. Therefore, the presence of ED may provide an opportunity for early detection of cardiovascular disease risk in men without overt cardiovascular disease [3,4].

Epicardial fat tissue (EFT) is a metabolically active tissue surrounded by the visceral pericardium that also produces inflammatory, atherogenic cytokines, and is considered to be an indicator of increased cardiovascular risk in many clinical situations [5–7]. Studies have reported that the increase in EFT thickness is associated with subclinical atherosclerosis, coronary artery disease (CAD), left ventricular (LV) dysfunction, and metabolic syndrome [8–11].

Previous studies have shown that increased EFT is associated with impaired LV function, even in the absence of cardiovascular disease [12–14]. At the same time, increased EFT thickness has begun to be accepted as a cardioembolic risk factor [5,6,8]. Studies conducted with ED patients have found a relationship between ED and EFT thickness, and it has been shown that the thickness of EFT in these patients is proportional to the current cardiovascular risk status [15,16].

Two-dimensional speckle tracking echocardiography (2D-STE) is a new imaging method used to evaluate...
cardiac mechanics [17]. Myocardial function analysis with 2D-STE is superior to many other conventional imaging techniques [17]. It is extremely valuable in defining subclinical myocardial dysfunction in various clinical situations, and early detection of these subclinical changes in myocardial tissue will provide an opportunity for early diagnosis and treatment of cardiovascular complications [18]. Further evaluation of cardiovascular risk is recommended for men diagnosed with ED using non-invasive methods to detect subclinical cardiovascular disease [3,4]. Therefore, the aim of this study is to investigate the value of EFT in predicting LV subclinical dysfunction in patients with ED with normal LV ejection fraction in conventional 2D echocardiography and without overt cardiovascular disease, using 2D-STE method.

**Methods**

**Study population**

A total of 126 consecutive patients admitted to the urology outpatient clinic with a diagnosis of ED and planned to determine cardiovascular risk were included in the study. A total of 132 age and gender-matched volunteers were selected as the control group. Those with LV segmental motion defects, history of CAD (history of percutaneous coronary intervention and coronary bypass), DM, LV ejection fraction <55%, previous cerebrovascular disease, peripheral artery disease, conduction abnormalities, atrial fibrillation, valvular heart disease more than mild, any cardiac surgery history of pacemaker, polyneuropathy due to surgical trauma (radical retropubic prostatectomy, cystectomy, etc.), neurological diseases, poor echocardiographic image and positive cardiovascular stress test, phosphodiesterase inhibitors and the patients taking beta blockers were not included in the study. Traditional risk factors such as HT, age, smoking, and family history of CAD of all participants was recorded. Cardiovascular stress test was applied to all participants using Bruce Protocol to investigate ischemia. A 12-lead ECG with a filter range of 0.5-150 Hz (25 mm/s, 10 mm/mV) was performed in all patients. Blood samples were taken to evaluate routine biochemical and hematological parameters after 12 h of fasting. A systolic blood pressure value of 140 mm Hg and/or a diastolic blood pressure value of ≥90 mmHg was defined as HT. Informed consent was obtained from all participants and the study was approved by the local ethics committee.

Transthoracic echocardiogram (TTE) examination of all participants was performed in left lateral lying position using 2.5–3.5 MHz ultrasound probe (Philips Affiniti 50, Amsterdam, Netherlands). Standard echocardiographic measurements such as left atrium length, LV systolic and diastolic diameters, LV wall thicknesses and LV ejection fraction (LVEF) were performed in accordance with the European Society of Cardiology Echocardiography guidelines [19].

**Imaging and measurement of epicardial fat tissue**

Echocardiographic assessment of EFT thickness was performed as described by Iacobellis and Willens [5]. The measurement of EFT thickness was performed by TTE from a parasternal long-axis view on the right ventricle’s free wall at end-diastole, and the greatest perpendicular distance to the aortic annulus was achieved and averaged over three cardiac cycles [5]. In the parasternal long-axis window, hypoechoic space on the right ventricular free wall was defined as EFT (Figure 1) [5]. EFT was detected as an area of relatively low echogenicity located between the right ventricle and the inner leaf of the pericardium. In order to detect intra-observer variability, 25 individuals were randomly selected, and the EFT thickness of these 25 individuals was measured once every week. Accordingly, the repeatability of EFT thickness measurement was calculated with the intraclass correlation coefficient analysis. It was observed that the repeatability of EFT thickness measurement was quite good (intra-class correlation coefficient = 0.915; p<.001) [3]. The diagnosis of ED was made according to the answers given to five questions in the International Index of Erectile Function (IIIEF-5) and was categorized according to the total score as stated previously [20]. Those with a total score of 22–25 were determined as

![Figure 1. Transthoracic echocardiography parasternal long-axis view demonstrating the epicardial fat tissue as the hypoechoic space on the right ventricular free wall at end-diastole.](image-url)
non-ED, those with a total score of 17–21 as mild ED, those with a total score of 12–16 as mild-moderate ED, those with a total score of 8–11 as moderate-ED and those between 1 and 7 as severe ED [20].

**Speckle tracking echocardiography**

STE and GLS were assessed from standard two-dimensional, gray-scale images derived from apical two-three and four-chamber views. GCS was evaluated using the parasternal short-axis images in LV basal, mid, and apical levels. The images were obtained during an end-expiratory breath-hold at a frame rate of 60–80 frames/s. For further offline analysis, all images were transferred to a workstation and automated software QLAB quantification software version 7.1 (Philips, the Netherlands) was used. Automated tracking of myocardial speckles was then reviewed and manually adjusted as minimally as possible. The endocardial border was manually traced in the end-systolic frame for each view. The entire circumference of the LV was divided into six equal segments by the software. Myocardial strain curves were then generated via the software by frame-by-frame tracking of the natural acoustic markers throughout the cardiac cycle. Longitudinal strain was calculated from the apical two-chamber, three-chamber, and four-chamber views, whereas circumferential strain was derived from the three short-axis views. Fifteen patients with inadequate image quality for GLS and GCS analysis were excluded from the study. Also, global systolic strain rate (GSRs), the global diastolic strain rate during the early (GSRe), and late (GSRa) phase of diastole were analyzed.

**Statistical analysis**

All measurements were evaluated by Kolmogorov–Smirnov test in terms of compliance with normal distribution. Continuous variables were given as mean± standard deviation, and categorical variables as frequency (percentage). In comparison of groups, student-t or Mann–Whitney U test was used for continuous variables, and chi-square test for categorical variables. Spearman correlation analysis was performed to determine the correlation between values. Multiple linear regression analysis was used to determine independent predictors of LV systolic functions. Statistical significance was defined as p<.05. SPSS version 22.0 (SPSS 22.0 for Windows, Inc., Chicago, IL) was used for all statistical calculations.

**Results**

The demographic, clinical characteristics and laboratory parameters of the patients and the control group are given in Table 1. There was no difference in the frequency of HT, smoking, and family CAD in both groups. In addition, there was no difference between the two groups in values such as glomerular filtration rate (GFR), body mass index (BMI), and age. For laboratory values other than LDL, there was no difference between the two groups, while the LDL value was significantly higher in the ED group.

Among conventional echocardiography parameters, no difference was observed between LVEF, left atrium diameter, LV wall thickness, left ventricular mass index (LVMI), ventricular systolic and diastolic diameters (Table 2). While the E/A ratio was similar in both groups, E/e’ was higher in the ED group (6.8±2.2 vs. 8.4±2.6, p=.012). EFT thickness was observed to be significantly higher in the group with ED (p<0.001) (Table 2). When Spearman correlation analysis was performed, a significant correlation was observed between EFT thickness and IIEF-5 score (r=−0.485, p<.001) (Figure 2).

Comparison of LV strain and strain rate between groups is shown in Table 3. GLS and GCS are negative
Table 2. The conventional echocardiographic findings of study patients.

| Variables       | Control (n=145) | ED (n = 129) | p Value |
|-----------------|-----------------|--------------|---------|
| LVMI (g/m²)     | 111.2 ± 21.6    | 112.3 ± 23.4 | .324    |
| IVSd (cm)       | 0.96 ± 0.13     | 0.97 ± 0.11  | .146    |
| PWd (cm)        | 0.92 ± 0.12     | 0.93 ± 0.10  | .537    |
| LVEDD (cm)      | 4.83 ± 0.32     | 4.79 ± 0.31  | .234    |
| LVEF (%)        | 62.2 ± 3.7      | 63.1 ± 4.5   | .271    |
| E/e             | 1.72 ± 0.24     | 1.81 ± 0.22  | .001    |
| E/A             | 0.26 ± 0.11     | 0.29 ± 0.13  | .121    |
| Eft             | 1.22 ± 0.25     | 1.27 ± 0.29  | .242    |
| Eft/e           | 6.8 ± 2.2       | 8.4 ± 2.6    | .012    |

ED: erectile dysfunction; ED: erectile dysfunction; E/A: ratio between diastolic early (E) and late diastolic mitral inflow (A) velocities; E/E': ratio between early diastolic mitral inflow velocity and early diastolic aortic root velocity; IVSd: interventricular septum thickness; LAa: left atrial diameter; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVMI: left ventricular mass index; PWd: posterior wall diastolic thickness

Table 4. Independent predictors of LV-GLS in multiple linear regression analysis.

| Variables                          | Univariate analysis | Multivariate analysis |
|------------------------------------|---------------------|-----------------------|
|                                    | R       | p Value | B coefficient | 95cl p Value |
| EFT thickness                      | −0.504  | <.001   | −3.071        | (−6.289)(−1.162) | <.001 |
| Age                               | −0.463  | .003    | −0.973        | (−1.711)(−0.175) | <.017 |
| LDL                               | −0.132  | .125    | —             | —              | .123    |
| HT                                | −0.170  | .004    | −0.620        | (−1.521)(−0.013) | .003    |
| IIEF-5 score                      | 0.513   | <.001   | 1.746         | (1.034)(3.143) | .003    |
| E/E'                              | −0.314  | .045    | —             | —              | .243    |
| values due to shortening of a myocardial segment in each direction. GLS and GCS were revealed to be more deterioration in the ED group compared to controls (−18.2 ± 2.7 vs. −21.1 ± 3.9, p < .01; −19.5 ± 4.1 vs. −21.9 ± 3.9, p < .01, respectively) (Table 3).

Discussion

In this study, for the first time, we investigated the association between EFT and subclinical myocardial systolic dysfunction in patients with ED by 2D-STE method. Our results showed that ED is associated with subclinical deterioration on the left ventricle systolic function. Even if the absence of overt cardiovascular disease and risk factors, GLS and GCS were detected to be lower in patients with ED and also there was a strong correlation between ED severity and GLS and GCS. It also showed that EFT thickness was higher in ED patients than the control group and that there was a relationship between the severity of ED and EFT thickness. In addition, we found that EFT was independently associated with both GLS and GCS in ED patients. These findings clearly demonstrated that EFT thickness in ED patients is associated with subclinical LV systolic dysfunction.
ED is a common health problem that is increasing in frequency today and affects quality of life [20]. It has been shown that ED is no longer a simple sexual disease, but an early predictor of cardiovascular diseases and mortality [21]. Previous studies focused particularly on the fact that ED is a predictor of CAD [21]. It has been shown that cardiovascular events generally occur 2-5 years after the diagnosis of ED [22]. In a study, it was shown that 57% of patients with a history of coronary bypass had ED in their history [23]. It has been shown that the presence of ED may also be the first sign of systemic vascular disease [24,25].

Previously, ED was considered to be a result of systemic disorders such as HT, DM and other vascular diseases, but now the common view is that ED is an early sign of early atherosclerosis and thus systemic vascular diseases [25]. The above studies support this view. Subclinical endothelial dysfunction and inflammation are thought to be the main pathophysiological factors in the occurrence of cardiovascular diseases in ED patients [26,27]. Low-grade subclinical inflammation in ED may lead to an atherosclerotic process by causing deterioration in endothelial function [26,27]. It has been clearly demonstrated that damage to the penile artery occurs before the development of clinically significant atherosclerotic disease [26]. Recently, Gandaglia et al. stated that ED and cardiovascular diseases should be seen as two different symptoms of the same systemic condition, and that ED is an early marker of symptomatic cardiovascular diseases [27]. In support of the hypothesis that ED may serve as a marker of silent cardiovascular disease, Jackson et al. detected CAD by computed tomographic coronary angiography in approximately half of men presenting with ED but without cardiac symptoms [28]. The Third Princeton Consensus Conference suggested further cardiac evaluations, pointing out that ED patients without known cardiovascular disease should be considered at increased risk of cardiovascular disease [29].

In this study, for the first time, we aimed to determine the role of EFT in predicting subclinical myocardial systolic dysfunction in ED patients with normal conventional echocardiograms, with 2D-STE method.

Two-dimensional speckle tracking echocardiography (2D-STE) is an effective method used to assess myocardial systolic and diastolic function in detail [30]. Moreover, it is a useful method to evaluate Two-dimensional speckle tracking echocardiography (2D-STE) and is an effective method used to assess myocardial systolic and diastolic function in detail [30]. Moreover, it is a useful method to evaluate subclinical LV systolic dysfunction in patients with normal ejection fraction on conventional echocardiography [30].

In our current study, we found that although EF was normal in conventional ECHO, there was a decrease in GLS and GCS values measured with 2D-STE and subclinical LV systolic dysfunction in patients with ED. Similarly, previous studies have shown that LV systolic dysfunction is more common in ED patients compared to control groups [31]. In a recent study, Zehir et al. found that while EF was normal in ED patients, GLS and GCS values decreased [32]. In addition, Karaqöz et al. found decreased GLC and GLS values in ED patients even after excluding cardiovascular risk factors in their study [31]. Our study is also considerable in terms of showing the relationship between LV systolic dysfunction and ED degree. In our study, as the ED level increased, we observed a decrease in the GLS and GCS values. As the ED level increases, the increase in endothelial dysfunction at the same degree may explain these results. Uslu et al. showed that endothelial dysfunction is associated with the progression of myocardial systolic dysfunction, suggesting that endothelial dysfunction developing in ED patients may play a role in myocardial deterioration [33]. However, microvascular dysfunction due to cumulative coronary risk factors leading to endothelial dysfunction may occur without significant coronary stenosis and may cause contractile abnormalities [33]. Another recent study showed that the LV function and endothelial dysfunction deteriorate in patients with ED without evident CAD [34]. These findings can help explain the deterioration of GLS and GCS values, even in the absence of overt DM and CAD. The fact that it is possible to detect these subclinical changes in the ventricle with global deformation analysis shows the importance of the test [33].

EFT is a metabolically active tissue surrounded by the visceral pericardium that also produces pro-inflammatory, pro-atherogenic cytokines, and is considered to be an indicator of increased cardiovascular risk in
microvascular dysfunction is an independent marker of ED in men without CAD [28]. Similarly, a relationship was found between increased EFT and microvascular dysfunction developing in coronary arteries [38]. Therefore, it has been revealed that the developing microvascular disorder can play an important role both in the presence of increased EFT and in the development of ED [28]. In conclusion, it is not surprising that the presence of increased EFT in ED patients predicts deterioration in ventricular functions. In our study, it is not difficult to explain the high EFT thickness and impaired LV systolic functions in ED patients with the above mechanisms.

In addition, diabetic patients and in patients with CAD or peripheral artery disease were not included in our study to show the absolute effects of ED on LV function. Therefore, we think that the presence of ED may cause subclinical impairment in LV systolic function. These findings suggest that, even in the presence of normal LV systolic function in conventional echocardiographic evaluation, ED patients should be made more strait cardiovascular risk stratification using more advanced imaging methods, and the hypothesis that a more detailed assessment of cardiovascular disease is required in the presence of ED in men over 50 years old seems to be confirmed by the results of our study [39]. Therefore, it seems reasonable to note the higher EFT thickness in the echocardiography of patients with ED. Our results showed that high EFT thickness may have affected LV systolic function in patients with ED. In light of these findings, we suggest that EFT can be used to detect individuals with increased cardiovascular risk in ED patients.

**Limitations**

Our findings should be considered in the light of potential study limitations. The first limitation can be considered as the low number of patients, especially the small number of patients in subgroups. In our study, we excluded major cardiovascular risk factors such as overt CAD, DM, and peripheral vascular disease, but there may be silent CAD in study subjects, since there are studies of ED patients without cardiac symptoms but with CAD detected by CT. Although there is a significant relationship between increased EFT thickness and LV dysfunction, this cause-effect relationship cannot be fully explained. Although epicardial fat accumulation can be measured most accurately using MRI or CT imaging, it was observed that the results in studies performed with echocardiography coincided with CT or MRI studies and it was stated that echocardiographic EFT measurement could...
be used [3]. Finally, we did not have follow up data of patients.

Conclusions
Our study results revealed that there is a decrease in GLS and GCS values in patients with ED, that is, impairment in LV systolic functions. In patients with ED, a more comprehensive cardiovascular risk classification is required even in the absence of main major cardiovascular risk factors or overt cardiovascular disease. The STE parameters can identify subtle changes before clinical signs of a cardiovascular disorder occur. STE parameters can identify ED patients at high risk of developing cardiovascular disease before clinical signs of a cardiovascular disease occur. The EFT thickness was higher in the patients with ED. The ED patients with higher EFT thickness had more subclinical LV deterioration. We suggest that EFT thickness may be used to predict future cardiovascular events in patients with ED.

Acknowledgments
The authors gratefully acknowledge all the volunteers who accepted to participate in this study.

Author contributions
Doctors Eren, Kaya, Omar, Öcal and Özbeý were involved in the conception and design, data collection, as well as analysis and interpretation of data. All coauthors have revised the manuscript critically and have approved it for submission.

Disclosure statement
All of the authors have no conflict of interest.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID
Hayati Eren http://orcid.org/0000-0002-2159-064X

References
[1] Azadzoi KM, Goldstein I. Erectile dysfunction due to atherosclerotic vascular disease: the development of an animal model. J Urol. 1992;147(6):1675–1681.
[2] Montorsì F, Briganti A, Salonia A, et al. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. Eur Urol. 2003;44(3):360–364.
[3] Shambloul R, Ghanem H. Erectile dysfunction. Lancet. 2013;381(9861):153–165.
[4] Hackett G, Kirby M, Wylie K, et al. British society for sexual medicine guidelines on the management of erectile dysfunction in men-2017. J Sex Med. 2018;15(4):430–457.
[5] Jacobelli G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. J Am Soc Echocardiogr. 2009;22(12):1311–1319.
[6] Tok D, Kadife I, Turak O, et al. Increased epicardial fat thickness is associated with low grade systemic inflammation in metabolic syndrome. Arch Turk Soc Cardiol. 2012;40(8):690–695.
[7] Mazurek T, Zhang L, Zalewski A, et al. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation. 2003;108(20):2460–2466.
[8] Jacobelli G, Gao YJ, Sharma AM. Do cardiac and perivascular adipose tissue play a role in atherosclerosis? Curr Diab Rep. 2008;8(1):20–24.
[9] Ahn SG, Lim HS, Joe DY, et al. Relationship of epicardial adipose tissue by echocardiography to coronary artery disease. Heart. 2008;94(3):e7–e7.
[10] Konishi M, Sugiyama S, Sugamura K, et al. Accumulation of pericardial fat correlates with left ventricular diastolic dysfunction in patients with normal ejection fraction. J Cardiol. 2012;59(3):344–351.
[11] Fontes-Cardalho R, Fontes-Oliveira M, Sampaio F, et al. Influence of epicardial and visceral fat on left ventricular diastolic and systolic functions in patients after myocardial infarction. Am J Cardiol. 2014;114(11):1663–1669.
[12] Rado SD, Lorbeer R, Gatisid S, et al. MRI-based assessment and characterization of epicardial and paracardial fat depots in the context of impaired glucose metabolism and subclinical left-ventricular alterations. Br J Radiol. 2019;92(1096):20180562.
[13] Zhu L, Gu S, Wang Q, et al. Left ventricular myocardial deformation: a study on diastolic function in the Chinese male population and its relationship with fat distribution. Quant Imaging Med Surg. 2020;10(3):634–645.
[14] Maurice F, Gaborit B, Vincentelli C, et al. Cushing syndrome is associated with subclinical LV dysfunction and increased epicardial adipose tissue. J Am Coll Cardiol. 2018;72(18):2276–2277.
[15] Dursun M, Besiroğlu H, Çakir SS, et al. Increased visceral adiposity index associated with sexual dysfunction in men. Aging Male. 2018;21(3):187–192.
[16] . Tanik S, Sarıkaya S, Zengin K, et al. Cardiometabolic risk factors in patients with erectile dysfunction. ScientificWorldJournal. 2014;2014:892091.
[17] Mondillo S, Galdieri M, Mele D, et al. Echocardiography study group of the Italian society of cardiology (Rome, Italy). Speckle-tracking echocardiography: a new technique for assessing myocardial function. J Ultrasound Med. 2011;30(1):71–83.
Biering-Sørensen T, Hoffmann S, Mogelvang R, et al. Myocardial strain analysis by 2-dimensional speckle tracking echocardiography improves diagnostics of coronary artery stenosis in stable angina pectoris. Circ Cardiovasc Imaging. 2014;7(1):58–65.

Lang RM, Bierig M, Devereux RB, et al. Chamber Quantification Writing Group; American Society of Echocardiography’s Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18(12):1440–1463.

Cappelleri JC, Siegel RL, Glasser DB, et al. Relationship between patient self-assessment of erectile dysfunction and the sexual health inventory for men. Clin Ther. 2001;23(10):1707–1719.

Schouten BW, Bohnen AM, Bosch JL, et al. Erectile dysfunction prospectively associated with cardiovascular disease in the Dutch general population: results from the Krimpen Study. Int J Impot Res. 2008;20(1):92–99.

Araujo AB, Hall SA, Ganz P, et al. Does erectile dysfunction contribute to cardiovascular disease risk prediction beyond the Framingham risk score? J Am Coll Cardiol. 2010;55(4):350–356.

Levine LA, Kloner RA. Importance of asking questions about erectile dysfunction. Am J Cardiol. 2000;86(11):1210–3. A5.

Araujo AB, Travison TG, Ganz P, et al. Erectile dysfunction: cardiovascular risk and the role of the cardiologist. Int J Clin Pract. 2003;57(2):96–99.

Solomon H, Man J, Wierzbicki AS, et al. Impaired brachial artery endothelium-dependent and -independent vasodilation in men with erectile dysfunction and no other clinical cardiovascular disease. J Am Coll Cardiol. 2004;43(2):179–184.

Gandaglia G, Briganti A, Jackson G, et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urol. 2014;65(5):968–978.