European Journal of Radiology 160 (2023) 110706

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Epicardial fat volume assessed with cardiac magnetic resonance imaging in patients with Takotsubo cardiomyopathy

Riccardo Cau [a], Pierpaolo Bassareo [b], Filippo Cademartiri [c], Christian Cadeddu [d], Antonella Balestrieri [a], Lorenzo Mannelli [c], Jasjit S. Suri [e], Luca Saba [a,*]

[a] Department of Radiology, Azienda Ospedaliero Universitaria (A.O.U.), di Cagliari – Polo di Monserrato, s.s. 554 Monserrato, Cagliari 09045, Italy
[b] Mater Misericordiae University Hospital and Our Lady's Children's Hospital, University College of Dublin, Crumlin, Dublin, Ireland
[c] IRCCS SDN, Naples, Italy
[d] Department of Cardiology, Azienda Ospedaliero Universitaria (A.O.U.), di Cagliari – Polo di Monserrato, s.s. 554 Monserrato, Cagliari 09045, Italy
[e] Stroke Monitoring and Diagnostic Division, AtheroPoint™, Roseville, CA, USA

ARTICLE INFO

Keywords:
Epicardial fat volume
Epicardial fat thickness
CMR
Takotsubo
Cardiomyopathy

ABSTRACT

Purpose: The aims of our study were to investigate with cardiovascular magnetic resonance (CMR) the role of Epicardial Fat Volume (EFV) and distribution in patients with Takotsubo cardiomyopathy (TTC). Moreover, we explored EFV in patients with TTC and related this to comorbidities, cardiac biomarkers, and cardiac function.
Methods: This retrospective study performed CMR scans in 30 consecutive TTC patients and 20 healthy controls. The absolute amount of EFV was quantified in consecutive short-axis cine stacks through the modified Simpson's rule. In addition, the left atrio-ventricular groove (LV) and right ventricle (RV) Epicardial Fat Thickness (EFT) were measured as well. Besides epicardial fat, LV myocardial strain parameters and T2 mapping measurements were obtained.
Results: TTC patients and controls were of comparable age, sex, and body mass index. Compared to healthy controls, patients with TTC demonstrated a significantly increased EFV, epicardial fat mass, and EFV indexed for body 7surface area ($p = 0.005$; $p = 0.003$; $p = 0.008$; respectively). In a multiple regression model including age, sex, BMI, atrial fibrillation, and dyslipidemia, TTC remained an independent association with EFV ($p = 0.008$). Global T2 mapping and Global longitudinal strain in patients with TTC were correlated with EFV ($r = 0.63$, $p = 0.001$, and $r = 0.44$, $p = 0.02$, respectively).
Conclusion: Patients with TTC have increased EFV compared to healthy controls, despite a similar body mass index. The amount of epicardial fat was associated with CMR markers of myocardial inflammation and subclinical contractile dysfunction.

1. Introduction

Epicardial fat is a deposit of visceral fat surrounding the myocardium. It has proved to be a metabolically active tissue that secretes adipokines with pro- and anti-inflammatory properties [1–3]. (see Fig. 1). In view of its close anatomical proximity to the myocardium without any separating fascia, epicardial fat may interact, affect, and interfere with cardiac function and physiology [4,5]. Recently, it has emerged that the communication between epicardial fat and the heart is a bidirectional pathway since the heart as well can affect epicardial fat via paracrine signaling, termed 'inside-to-outside' signaling [6].

In this scenario, several studies have investigated the role of epicardial fat in different cardiovascular diseases, including non-ischemic dilated cardiomyopathy, subclinical atherosclerosis, and coronary artery disease [7–10]. Recently, Gaibazzi et al. evaluated epicardial fat characteristics through *peri*-coronary fat attenuation index in patients with Takotsubo cardiomyopathy (TTC). The authors reported that *peri*-coronary fat attenuation index is higher in patients with TTC in

Abbreviations: **CMR**, cardiovascular magnetic resonance; **EFT**, Epicardial Fat Thickness; **EFV**, Epicardial Fat Volume; **EFM**, Epicardial Fat Mass; **LGE**, late gadolinium enhancement; **LV**, left ventricle; LVEF, left ventricle ejection fraction; **RV**, right ventricle; **SSFP**, steady-state free precession; **TTC**, Takotsubo cardiomyopathy.

* Corresponding author.
E-mail address: lucasaba@tiscali.it (L. Saba).

https://doi.org/10.1016/j.ejrad.2023.110706
Received 29 October 2022; Received in revised form 15 January 2023; Accepted 17 January 2023
Available online 21 January 2023

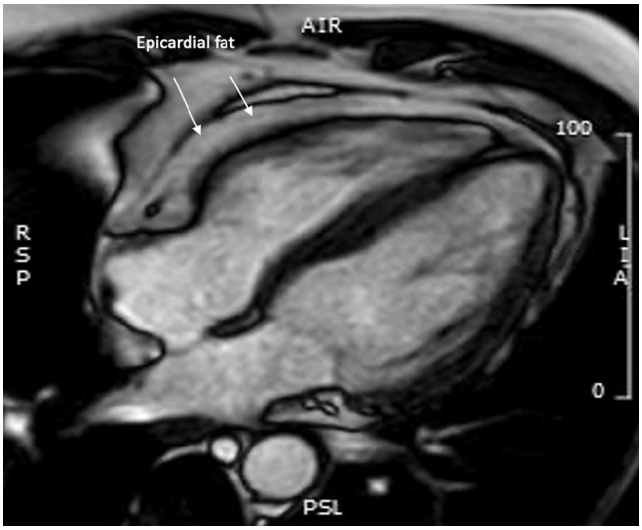

Fig. 1. The figure shows the four-chamber view of a patients with Takotsubo cardiomyopathy. The epicardial fat, located between the myocardium and pericardium, is indicated by the white arrows.

comparison with the control group, suggesting an underlying inflammation in the adipose tissue surrounding the myocardium [11]. Cardiovascular magnetic resonance (CMR) is considered the reference standard modality for myocardial tissue characterization [12,13]. T2 mapping is a specific CMR marker used as an index of myocardial edema and correlates with myocardial inflammation in endomyocardial biopsy samples [14]. CMR can also detect subclinical abnormalities of cardiac contractility using myocardial strain analysis independently of ejection fraction [15,16,17]. However, to date, there are scarce data about the volume and distribution of epicardial fat in TTC and its correlation with CMR markers.

Therefore, the first aim of the study was to investigate the presence of any possible significant difference in terms of Epicardial Fat Volume (EFV) and Epicardial Fat Thickness (EFT) between TTC patients and healthy controls. We also explored the association of epicardial fat with comorbidities, cardiac biomarkers, and cardiac function.

2. Material and method

2.1. Study population

In this retrospective, longitudinal, observational, single-center study, all consecutive patients with apical ballooning TS who underwent CMR between March 3rd, 2017, and August 7th, 2021 were included.

Inclusion criteria were based on the current definition reported in the Position Statement of the European Society of Cardiology Heart Failure Association [13]. The diagnostic criteria include regional wall motion abnormalities not limited to a single epicardial vascular distribution region, which are usually preceded by a stressful trigger, in the absence of culprit atherosclerotic disease as assessed by invasive catheterization; new ECG abnormalities; elevated serum natriuretic peptide and a small increase in cardiac troponin; and recovery of LV dysfunction at follow-up.

Exclusion criteria included: subjects <18 years; previous myocardial infarction; pre-existing cardiomyopathy; and suspected or known prior irreversible myocardial damage.

Controls were age-, sex- and body mass index (BMI)-matched and underwent CMR to rule out scar-related ventricular tachycardia. Controls were included if CMR showed no signs of structural heart defects. The Institutional Review Board approval for this retrospective, cross-sectional study was obtained, and patient's consent was waived because of the retrospective nature.

A flowchart demonstrating the application of inclusion and exclusion criteria is provided in Fig. 2.

2.2. Clinical parameters and cardiac biomarkers

Clinical parameters and cardiac biomarkers, including NT-proBNP, and troponin T were obtained from medical records within 10 days before CMR examination. Plasma biomarkers were not available for controls.

2.3. CMR acquisition

CMR scans were performed at 4.1 ± 2.6 days (median = 1 day, range = 1–10 days) after admission to the hospital by using a Philips Achieva dStream 1.5 T scanner system (*Philips Healthcare, Best, The Netherlands*). Anterior coil arrays were used. All cine-images were acquired using a balanced steady-state free precession and retrospective gating during an expiratory breath- hold manoeuvres (TE: 1.7mssec; TR: 3.4msec /flip-angle: 45°, section thickness = 8 mm) in both long-axis (two-, three- and four-chamber view) as well as short-axis plane with whole ventricular coverage from base to apex. Ten to fifteen short-axis views covering the whole Left and Right Ventricle (LV and RV, respectively) were obtained. T2 mapping was acquired on three representative short-axis slices (at the base, mid-ventricular, and apex, respectively) using a single-breath-hold, black-blood prepared ECG-triggered, spin-echo multiecho sequence. Details of the comprehensive CMR sequence parameters are included in the Supplementary Methods.

2.4. Evaluation of epicardial fat using CMR

A commercially available software platform (CVI42, Circle Cardiovascular Imaging Inc., Calgary, Canada) was used to evaluate EFV using the modified Simpson's rule on SSFP sequence [18]. The epicardial fat borders were manually delineated on consecutive end-diastolic short-axis slice covering the entire left and right ventricle from the level of mitral valve plane to the most inferior of epicardial fat was traced (Fig. 3). Total EFV was obtained after the summation of data from all slices. To obtain epicardial fat mass, the epicardial fat volume was multiplied by the specific density of fat (0.92 g/cm^3) [7].

EFT was measured at the end-diastolic phase in both left atrioventricular groove and right ventricle free wall. In particular, maximum epicardial fat thickness at the left atrioventricular groove was measured at end-diastolic phase on 4-chambers view, as previously mentioned in studies by other investigators [1]. On the other hand, the maximum epicardial fat thickness at the right ventricle free wall was measured in both 4-chamber view and in consecutive short-axis views covering the whole left ventricle. The latter measurements were obtained as an average of fat thickness in all short-axis images [18]. See Fig. 3. All CMR measurements were independently assessed by two radiologists (R.C. and M.P. with 4 and 6 years of experience in cardiovascular imaging, respectively) blinded to any clinical, echocardiography, and CMR data. After independent evaluation, final decisions were reached by consensus interpretation.

2.5. CMR image post-processing

We used the commercially available software Circle CVI42 (CVI42, Circle Cardiovascular Imaging Inc., Calgary, Canada) for cardiac MRI feature tracking (CMR-FT) data analysis. Offline CMR-FT analyses were conducted for the evaluation of peak global longitudinal strain (GLS), global radial strain (GRS), and global circumferential strain (GCS) in a 16-segment software-generated 2D model. Concerning GLS, data on myocardial strain were derived from two-, three- and four-chambers long-axis views. Regarding GRS and GCS, data on myocardial strain was derived from apical, mid-ventricular, and basal short-axis views in all the patients. On all images, the epi- and endocardial borders were

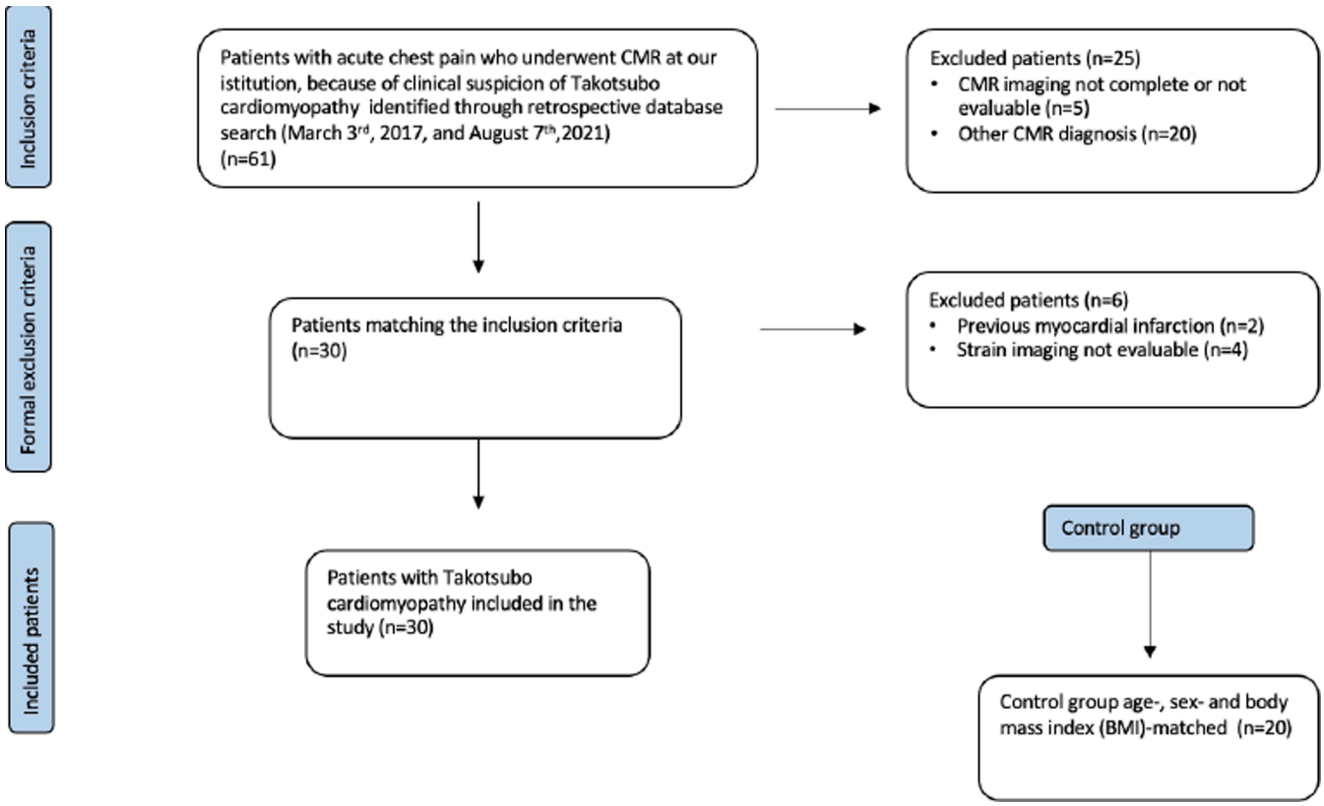

Fig. 2. . The figure demonstrated the outline of study protocol.

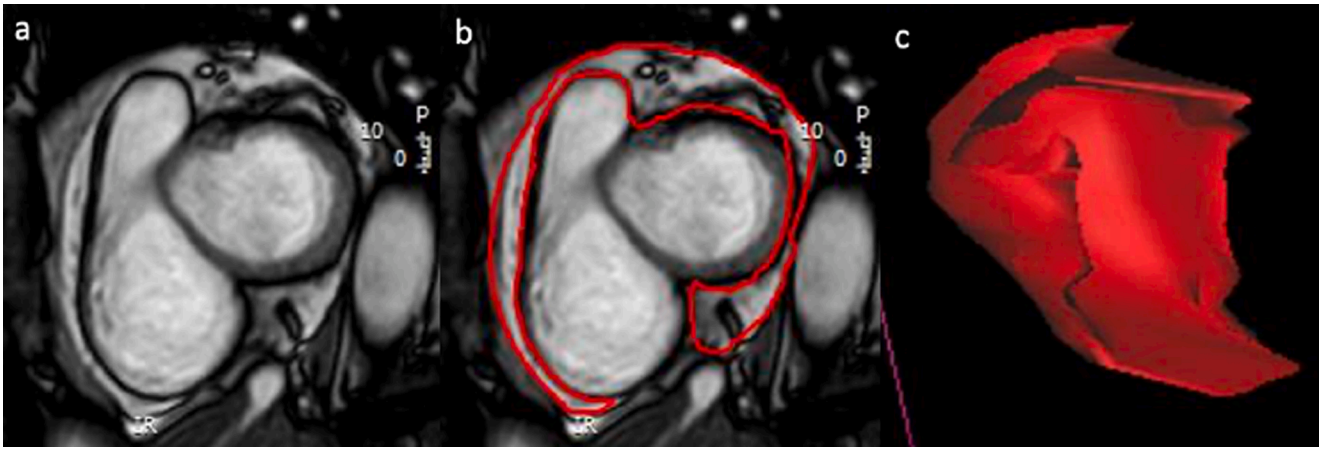

Fig. 3. Short-axis cine CMR image in end-diastolic phase in patients with Takotsubo cardiomyopathy (fig a). Example of epicardial Segmentation of epicardial fat outlining the contours of epicardial fat in end-diastolic images of short axis covering the left and right ventricles (fig b) with a 3-dimensional representation (fig c).

traced in end-diastole. After that, an automatic computation was triggered, by which the applied software algorithm automatically outlined the border throughout the cardiac cycle. The quality of the tracking and contouring was visually validated and manually corrected when needed by a radiologist with 6 years of experience in cardiovascular imaging.

T2 mapping values were generated off-line using the same dedicated CMR software (CVI42, Circle Cardiovascular Imaging Inc., Calgary, Canada). Epi- and endocardial borders were manually traced and propagated through the image stack and manually corrected when needed.

LGE extension was qualitatively and quantitatively evaluated. Briefly, the location of myocardial segment was evaluated and counted. The extension of LGE were obtained tracing the epicardial and endocardial contours in each short-axis image. A region of interest was manually placed in the myocardium without LGE. The LGE was defined as myocardium with mean signal intensity $>$ 5 SDs greater than the reference region of interest [19].

2.6. Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation. Comparisons of continuous data were performed using the independent samples *t*-test or Mann-Whitney *U* test; Kolmogorov-Smirnov tests were used to check continuous variables for normal distribution. Categorical variables were compared by using the chi-square test or Fisher's exact test, as appropriate. Correlation was assessed using the Pearson r and Spearman rho coefficient as appropriate. Association between epicardial fat volume, clinical parameters, and TTC were analyzed using multiple

linear regression.

A p-value < 0.05 was considered statistically significant. All statistical analysis was performed using IBM SPSS Statistics version 22 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient demographics and clinical data.

Thirty patients with TTC were included (27 females due to the gender-specific prevalence of TTC, mean age 70.62 ± 9.36 years.) and 20 healthy subjects (16 females, 68.73 ± 8.54 years). Most women were postmenopausal (27/30; 90%) with a documented stressful event in 66% of the cases.

Baseline characteristics of the enrolled patients are summarized in Table 1 and Table 2.

3.2. Epicardial fat in TTC patients

In comparison with healthy controls, patients with TTC demonstrated a significantly increased EFM, EFV and EFV indexed for body surface area (80.8 ± 34.6 g vs. 53.8 ± 17.7 g, p = 0.003; 85.2 ± 39.2 ml vs. 58.4 ± 19.2 ml, p = 0.005; 50.5 ± 18.8 ml/m2 vs. 33.7 ± 11.7 ml/m2, p = 0.008; respectively). Similarly, LV and RV EFT revealed significantly increased values in TTC patients (11.9 ± 3.67 mm vs. 8.1 ± 3,75 mm, p = 0.001; 13.3 ± 4.58 mm vs. 9.5 ± 3.2 mm, p = 0.002; respectively). See Table 2.

In a multiple regression model including age, sex, BMI, atrial fibrillation, and dyslipidemia TTC remained an independent association with EFV (p = 0.008).

3.3. Association between epicardial fat and comorbidities, cardiac biomarkers, and cardiac function

Body mass index and body surface were associated with EFV (r = 0.36; p = 0.015; r = 0.59; p = 0.004, respectively). In TTC patients, atrial fibrillation and dyslipidemia were associated with EFV (r = 0.45, p = 0.04; r = 0.38, p = 0.04). There were no other significant correlations between patient comorbidities and epicardial fat extension. Elevated plasma levels of Troponin were associated with EFV (r = 0.36, p = 0.015). In contrast, in TTC patients pro-BNP was not associated with EFV.

No associations were found between left and right ventricular dimensions and function. Global T2 mapping was positively associated with EFV (r = 0.63, p = 0.001). See Fig. 4. In addition, GLS was significantly associated with EFV (r = 0.44, p = 0.02; Fig. 4), whereas no association was found between GCS (r = 0.15, p = 0.42), GRS (r = 0.19, p = 0.33), LVEF (r = 0.10, p = 0.60) and EFV.

CMR imaging demonstrated LGE in 9 (30%) patients when using a threshold of 5 standard deviations, with a pattern of LGE that involved the full thickness of the myocardium segments affected by wall motion abnormalities. No association was found between LGE extension and EFV (r = 0.11, p = 0.54).

Fig. 5 demonstrated an example of T2 mapping and strain analysis in patients suffering from TTC and healthy control.

Table 1
Demographic and baseline clinical characteristics: healthy controls and patients with TTC.

	TTC patients	Healthy control	p
Age (years ± SD)	70.62 ± 9.36	68,73 ± 8,54	0.87
Female (n; %)	27 (90%)	16 (80%)	0.11
Body weight (kg ± SD)	64.9 ± 13.43	62.3 ± 11	0.68
BSA	1.66 ± 0.18	1.64 ± 0.13	0.51
BMI	24.75 ± 4.65	26.2 ± 4.71	0.85
Heart rate (bpm ± SD)	73.54 ± 14.63	72.1 ± 13.1	0.77
Duration of hospitalization (days ± SD)	10.76 ± 4.53	–	NA
Troponin	3706.11 ± 1881	–	NA
proBNP	4895 ± 6149	–	NA
Atrial fibrillation (n; %)	3 (10)	–	NA
Hypertension (n; %)	16 (53)	4 (25)	0.21
Dyslipidemia (n; %)	18 (60)	4 (25)	0,015
Current smoking (n; %)	4 (13)	2 (12)	0.83
Obesity (n; %)	2 (6)	1 (6)	0.76
Diabetes (n; %)	3 (10)	1 (6)	0.56
Stressful events (n; %)	20 (75)	–	NA

The data are presented as mean ± standard deviation (SD) for normally distributed quantitative variables and n (%) for qualitative variables.
Abbreviations: TTC = Takotsubo cardiomyopathy; BSA body surface area; BNP brain natriuretic peptide.

Table 2
CMR characteristics: healthy controls and patients with TTC.

	TTC patients	Healthy control	p
LVEF	46.92 ± 12.72	57.32 ± 5.6	0.41
LV EDV/BSA	68.39 ± 15.86	78.3 ± 11.1	0.54
LV ESV/BSA	30.46 ± 11.68	32 ± 6.5	0.63
LV SV/BSA	38.12 ± 12.19	46.8 ± 9.3	0.30
GLS	−12.18 ± 3.21	−17.8 ± 1.89	**0.001**
GRS	28.64 ± 9.59	−20.9 ± 1.8	**0.027**
GCS	−15.48 ± 7.9	37.5 ± 5	**0.024**
T2mapping (ms)	65.11 ± 5.36	54.2 ± 2.2	**0.001**
T1mapping (ms)	1121.58 ± 54.38	1021.13 ± 36.27	**0.001**
LGE (%)	7.8 ± 4.1	–	**NA**
Epicardial fat volume (ml)	85.20 ± 39.19	58.42 ± 19.21	**0.005**
Index Epicardial fat volume (ml/m^2)	50.45 ± 18.77	33.69 ± 11.71	**0.008**
Epicardial fat mass (g)	80.77 ± 34.6	53.8 ± 17.7	**0.003**
Left atrioventricular groove epicardial fat thickness (mm)	11.94 ± 3.67	8.13 ± 3.75	**0.001**
RV epicardial fat thickness (mm)	13.3 ± 4.58	9.25 ± 3.2	**0.002**

The data are presented as mean ± standard deviation (SD) for normally distributed quantitative variables and n (%) for qualitative variables.
Abbreviations: TTC = Takotsubo cardiomyopathy; EDV end-diastolic volume; ESV end-systolic volume; SV stroke volume; EF ejection fraction; BSA body surface area; GLS global longitudinal strain; GCS global circumferential strain; GRS global radial strain: LGE = late gadolinium enhancement.

4. Discussion

In this study, we found that EFV in TTC was significantly higher than in the control group independent of age, sex, BMI, and comorbidities. In addition, EFV in TTC was correlated with CMR markers of myocardial inflammation and subclinical contractile dysfunction.

CMR is on an upward trajectory concerning technological innovations in cardiovascular imaging [20–23]. Epicardial fat measurement in vivo can be performed using several imaging methods [24–26]. Among non-invasive techniques, CMR can be regarded as the reference modality for the estimation of total body fat, enabling easy evaluation and volumetric quantification of epicardial fat as well [18].

Epicardial fat is the metabolically active fat surrounding the myocardium. It has been shown to have both protective and unfavorable effects owing to the secretion of adipokines with pro- and anti-inflammatory properties [1–3]. Several papers have found a link between the amount of epicardial fat and different cardiovascular diseases [7,9,10,18,27]. In patients with dilated cardiomyopathy, it proved to be

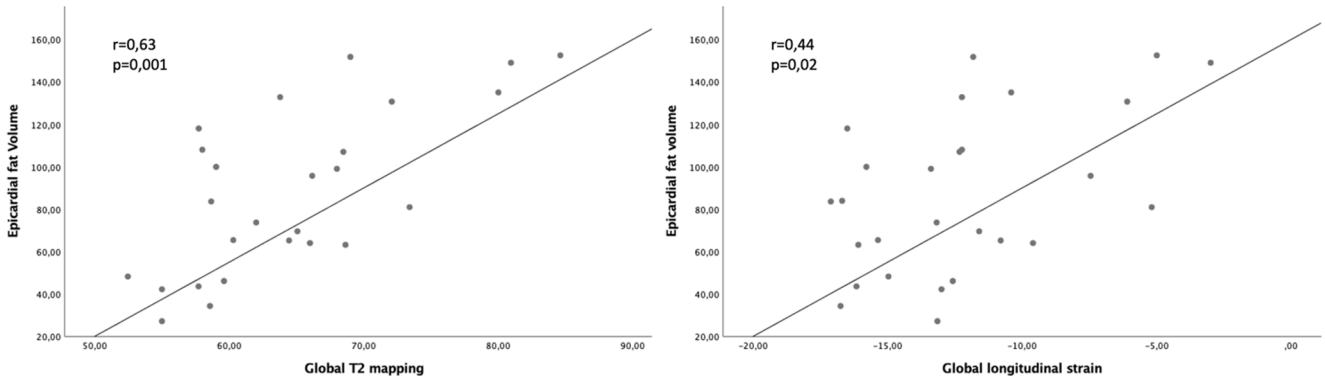

Fig. 4. . Correlation analysis between Epicardial fat volume and global T2 mapping and Global longitudinal strain.

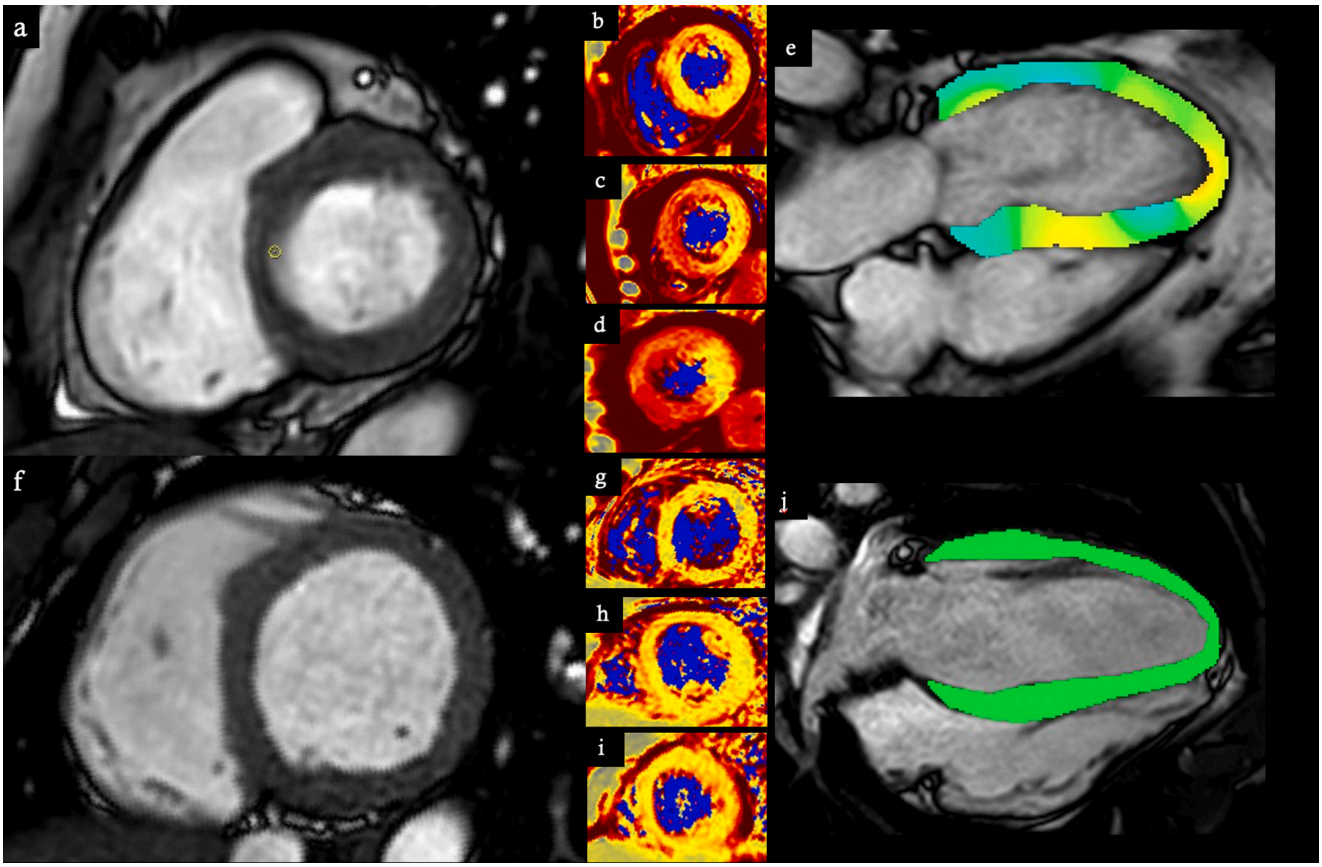

Fig. 5. Example of T2 mapping and strain analysis. Basal short-axis cine chamber view in end diastolic phase in patients with Takotsubo cardiomyopathy (fig a) demonstrating an epicardial fat thickness of the right ventricle free wall of about 12 mm and an epicardial fat volume of 130 ml (not shown). The analysis of T2 mapping showed an increase in signal at apical and mid-ventricular levels indicating edema (fig b–d). Figure f shows the pseudocolor maps of the left ventricle longitudinal strain at the end-diastolic phase in the same patient. Basal short-axis cine chamber view in end diastolic phase in healthy control (fig g) not showing the presence of epicardial fat in the right ventricle free wall and an epicardial fat volume of 43 ml (not shown). The analysis of T2 mapping showed normal values in all slices (fig g-i). Figure j shows the pseudocolor maps of left ventricle longitudinal strain at the end-diastolic phase in the same healthy control.

significantly decreased in comparison with healthy subjects [7]. Additionally, Mancio et Al. conducted a systematic review and metanalysis on the association between epicardial fat and coronary artery disease, demonstrating the significant association between epicardial fat volume and the onset of obstructive coronary stenosis, coronary artery calcification, and major adverse cardiac events [28].

To the best of our knowledge, this is the first work focused on the role of epicardial fat in TTC using CMR. In the present study, we investigated the amount of epicardial fat in TTC patients in comparison with the control group.

Patients with TTC showed significantly increased EFV, EFM, and EFT compared to the control group. Recently, El Shahawy et Al. investigated whether an increased EFV in women without obstructive coronary artery disease was related to significant microvascular dysfunction. They demonstrated that an excess in EFV is associated with cardiovascular structural and functional abnormalities, namely micro-arterial elasticity alterations, abnormal rise in systolic blood pressure, and microalbuminuria [29]. The authors suggested that the cytokines secreted by epicardial fat play a crucial role in the development of cardiac dysfunction, due to their pro-inflammatory properties [29]. Indeed, an

increase in epicardial fat depots results in an increased number of macrophages and T lymphocytes, and in turn it causes metabolic shift and secretion of proinflammatory cytokines, including interleukin-6 and vasoactive peptides leading to a chronic inflammatory state related to arterial stiffness and endothelial dysfunction [30]. The mechanism underlying the correlation between epicardial fat and reduced GLS may be explained by a direct cellular cross-talking between epicardial fat and myocardium via the paracrine action of epicardial fat-derived cytokines [31]. An in vitro study demonstrated increased expression of miR-208a secreted by epicardial fat that could influence mitochondrial β-oxidation changing the contractile myocardial function [32]. Conversely, the current study showed that EFV was not associated with GCS and GRS. This result agrees with a previous report [31]. The myocardium is composed of 3 layers of fibers, (1) subendocardial fibers contributing to longitudinal shortening, (2) subepicardial fibers contributing to circumferential shortening, and (3) transmural fibers contributing to radial shortening [15,31]. The subendocardial layer is more susceptible to ischemia, toxic, and metabolic factors [33–35]. It may be suggested that EFV may have an unequal effect on myocardium fibers in diverse directions and affect GLS, GCS, and GRS with different time courses. Along the same line, impaired GLS values, as a marker of subtle endocardial fibers compromise, may appear earlier than the global systolic dysfunction assessed by LVEF.

TTC is accompanied by myocardial and systemic inflammatory activation with elevated blood levels of pro-inflammatory cytokines, such as IL-6, that persist even over 5 months following the acute phase of the disease [36]. Furthermore, an increase in epicardial fat depots with augmented plasma free fatty acid levels may stimulate the cardiac autonomic nervous system [30]. The correlation of EFV and T2 mapping in TTC may be due to the activation of cellular and humoral inflammatory pathways.

The direct paracrine effect of epicardial fat-derived cytokines leads to an increase in myocardial inflammation [37,38].In this regard, CMR can non-invasively and quantitatively detect the presence of myocardial inflammation using T2 mapping [39].

One could speculate that the amount of epicardial fat with its pro-inflammatory substrate may be an underlying favoring factor in TTC pathophysiology. Another factor that could support this theory is the prevalence of TTC in postmenopausal women [40]. Indeed, estrogen is associated with decreased expression of pro-inflammatory adipokines, including interleukin. During menopause, estrogen levels decrease with a consequent relative hyperandrogenism that promote metabolically unfavorable fat redistribution and increase secretion of pro-inflammatory cytokines with consequent shift towards an inflammatory state [41]. Some authors speculated that reduced estrogen in menopause may predispose women to TTC [42,43].

The current study limitations should be acknowledged honestly. Firstly, the relatively small sample size and the retrospective nature of the study. However, we enrolled exclusively very homogenous TTC patients with the classic apical involvement. The promising results of our study could prompt further prospective trials including a larger number of patients to confirm our findings.

Second, TTC is markedly more common in women especially in postmenopausal period. This prevalence of TTC may influence the analysis of epicardial fat. Similarly, several cardiovascular risk factors, which are more represented in TTC cohort in our study, are associated with epicardial adipose tissue.

To avoid bias, we matched for age and sex the two groups under analysis and used a multiple regression model that included age and sex as well as atrial fibrillation and dyslipidemia to account for their potential confounding effect.

Third, there is no consensus regarding the limit of normality for epicardial fat with high variability among different patient populations [44]. The small sample size in our study may reduce the generalizability of epicardial fat values. However, we performed volumetric epicardial fat measurements with CMR that can be regarded as the reference standard for the estimation of total body fat, including epicardial adipose tissue [3,18,26].

Finally, the impairment in strain and parametric mapping measurements in patients with TTC would have been probably different if CMR had been performed within a shorter period of time, ideally the same day of hospital admission.

In conclusion, EFV was increased in TTC and was correlated with CMR markers of myocardial inflammation and subclinical contractile dysfunction. Such findings may provide new insight into the pathophysiology of TTC by suggesting the role of epicardial fat as an underlying favoring factor in TTC. Further longitudinal studies are warranted to confirm these results and to evaluate the prognostic role of EFV in TTC patients.

Disclosure

All authors agreed with the content and gave consent to submit.

All authors contributed equally to the work.

The authors state that this work is not under consideration elsewhere and none of its contents have been published previously.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

All authors read and approved the final manuscript.

The scientific guarantor of this publication is the corresponding author.

The authors declare that they have no competing interests.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejrad.2023.110706.

References

[1] H.M. Kim, K.J. Kim, H.-J. Lee, et al., Epicardial adipose tissue thickness is an indicator for coronary artery stenosis in asymptomatic type 2 diabetic patients: its assessment by cardiac magnetic resonance, Cardiovasc. Diabetol. 11 (1) (2012) 83, https://doi.org/10.1186/1475-2840-11-83.

[2] A.C.T. Ng, M. Strudwick, R.J. van der Geest, et al., Impact of epicardial adipose tissue, left ventricular myocardial fat content, and interstitial fibrosis on myocardial contractile function, Circ. Cardiovasc. Imag. 11 (8) (2018) e007372.

[3] A.J. Nelson, M.I. Worthley, P.J. Psaltis, et al., Validation of cardiovascular magnetic resonance assessment of pericardial adipose tissue volume, J. Cardiovasc. Magn. Reson. 11 (1) (2009) 15, https://doi.org/10.1186/1532-429X-11-15.

[4] G. Iacobellis, D. Corradi, A.M. Sharma, Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart, Nat. Clin. Pract. Cardiovasc. Med. 2 (10) (2005) 536–543, https://doi.org/10.1038/ncpcardio0319.

[5] G. Frühbeck, The adipose tissue as a source of vasoactive factors, Curr. Med. Chem. Cardiovasc. Hematol. Agents. 2 (3) (2004) 197–208, https://doi.org/10.2174/1568016043356255.

[6] A.S. Antonopoulos, C. Antoniades, The role of epicardial adipose tissue in cardiac biology: classic concepts and emerging roles, J. Physiol. 595 (12) (2017) 3907–3917, https://doi.org/10.1113/JP273049.

[7] C. Doesch, F. Streitner, S. Bellm, et al., Epicardial adipose tissue assessed by cardiac magnetic resonance imaging in patients with heart failure due to dilated cardiomyopathy, Obesity (Silver Spring) 21 (3) (2013) E253–E261, https://doi.org/10.1002/oby.20149.

[8] M.M. Tabakci, H.İ. Durmuş, A. Avci, et al., Relation of epicardial fat thickness to the severity of heart failure in patients with nonischemic dilated cardiomyopathy, Echocardiography 32 (5) (2015) 740–748, https://doi.org/10.1111/echo.12796.

[9] M. Petrini, M. Alì, P.M. Cannaò, et al., Epicardial adipose tissue volume in patients with coronary artery disease or non-ischaemic dilated cardiomyopathy: evaluation with cardiac magnetic resonance imaging, Clin. Radiol. 74 (1) (2019) 81.e1–81.e7, https://doi.org/10.1016/j.crad.2018.09.006.

[10] K. Iwasaki, N. Urabe, A. Kitagawa, T. Nagao, The association of epicardial fat volume with coronary characteristics and clinical outcome, Int. J. Cardiovasc. Imag. 34 (2) (2018) 301–309, https://doi.org/10.1007/s10554-017-1227-7.

[11] N. Gaibazzi, C. Martini, A. Botti, A. Pinazzi, B. Bottazzi, A.A. Palumbo, Coronary inflammation by computed tomography pericoronary fat attenuation in MINOCA

and Tako-Tsubo syndrome, J. Am. Heart Assoc. 8 (17) (2019), https://doi.org/10.1161/JAHA.119.013235.
[12] R. Cau, C. Solinas, P. De Silva, et al., Role of cardiac MRI in the diagnosis of immune checkpoint inhibitor-associated myocarditis, Int. J. Cancer (2022), https://doi.org/10.1002/ijc.34169. Published online.
[13] R. Cau, P. Bassareo, V. Cherchi, et al., Early diagnosis of chemotherapy-induced cardiotoxicity by cardiac MRI, Eur. J. Radiol. 130 (2020), 109158, https://doi.org/10.1016/j.ejrad.2020.109158.
[14] A.T. O'Brien, K.E. Gil, J. Varghese, O.P. Simonetti, K.M. Zareba, T2 mapping in myocardial disease: a comprehensive review, J. Cardiovasc. Magn. Reson. 24 (1) (2022) 33, https://doi.org/10.1186/s12968-022-00866-0.
[15] A. Scatteia, A. Baritussio, C. Bucciarelli-Ducci, Strain imaging using cardiac magnetic resonance, Heart Fail. Rev. 22 (4) (2017) 465–476, https://doi.org/10.1007/s10741-017-9621-8.
[16] R. Cau, P. Bassareo, J.S. Suri, G. Pontone, L. Saba, The emerging role of atrial strain assessed by cardiac MRI in different cardiovascular settings: an up-to-date review, Eur. Radiol. 32 (7) (2022) 4384–4394, https://doi.org/10.1007/s00330-022-08598-6.
[17] R. Cau, F. Pisu, M. Porcu, et al., Machine learning approach in diagnosing Takotsubo cardiomyopathy: the role of the combined evaluation of atrial and ventricular strain, and parametric mapping, Int. J. Cardiol. Published online (November 2022), https://doi.org/10.1016/j.ijcard.2022.11.021.
[18] S. Flüchter, D. Haghi, D. Dinter, et al., Volumetric assessment of epicardial adipose tissue with cardiovascular magnetic resonance imaging, Obesity (Silver Spring) 15 (4) (2007) 870–878, https://doi.org/10.1038/oby.2007.591.
[19] J. Schulz-Menger, D.A. Bluemke, J. Bremerich, et al., Standardized image interpretation and post-processing in cardiovascular magnetic resonance - 2020 update, J. Cardiovasc. Magn. Reson. 22 (1) (2020) 19, https://doi.org/10.1186/s12968-020-00610-6.
[20] V.M. Ferreira, J. Schulz-Menger, G. Holmvang, et al., Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations, J. Am. Coll Cardiol. 72 (24) (2018) 3158–3176, https://doi.org/10.1016/j.jacc.2018.09.072.
[21] Cau R, Bassareo P, Caredda G, Suri JS, Esposito A, Saba L. Atrial strain by feature-tracking cardiac magnetic resonance imaging in takotsubo cardiomyopathy. Features, feasibility, and reproducibility. Can. Assoc. Radiol. J. = J. l'Assoc. Can. des Radiol. Published online October 2021:8465371211042497. doi:10.1177/08465371211042497.
[22] Cau R, Bassareo P, Deidda M, et al. Could CMR tissue-tracking and parametric mapping distinguish between takotsubo syndrome and acute myocarditis? A pilot study. Acad. Radiol. Published online 2021. <http://www.sciencedirect.com/science/article/pii/S1076633221000155>.
[23] R. Cau, P.P. Bassareo, L. Mannelli, J.S. Suri, L. Saba, Imaging in COVID-19-related myocardial injury, Int. J. Cardiovasc. Imag. Published online (2020), https://doi.org/10.1007/s10554-020-02089-9.
[24] P.P. Bassareo, V. Fanos, M. Puddu, S. Marras, G. Mercuro, Epicardial fat thickness, an emerging cardiometabolic risk factor, is increased in young adults born preterm, J. Dev. Orig. Health Dis. 7 (4) (2016) 369–373, https://doi.org/10.1017/S2040174416000234.
[25] G. Milanese, M. Silva, L. Bruno, et al., Quantification of epicardial fat with cardiac CT angiography and association with cardiovascular risk factors in symptomatic patients: from the ALTER-BIO (Alternative Cardiovascular Bio-Imaging markers) registry, Diagn. Interv. Radiol. 25 (1) (2019) 35–41, https://doi.org/10.5152/dir.2018.18037.
[26] M. Guglielmo, A. Lin, D. Dey, et al., Epicardial fat and coronary artery disease: Role of cardiac imaging, Atherosclerosis 321 (2021) 30–38, https://doi.org/10.1016/j.atherosclerosis.2021.02.008.
[27] H. Nguyen, B. Tjoe, Epicardial adipose tissue in patients with takotsubo cardiomyopathy, J. Card. Fail. 25 (8) (2019) S41–S42, https://doi.org/10.1016/j.cardfail.2019.07.115.
[28] J. Mancio, D. Azevedo, F. Saraiva, et al., Epicardial adipose tissue volume assessed by computed tomography and coronary artery disease: a systematic review and meta-analysis, Eur. Hear J. – Cardiovasc. Imag. 19 (5) (2018) 490–497, https://doi.org/10.1093/ehjci/jex314.
[29] M. El Shahawy, S. Tucker, L. Izadi, A. Sabatini, S. Mohan, Excess epicardial fat volume in women is a novel risk marker for microvascular dysfunction, which may be a contributing factor in the atypical chest pain syndrome, Egypt Hear J. 73 (1) (2021) 37, https://doi.org/10.1186/s43044-021-00159-4.
[30] D. Austys, A. Dobrovolskij, V. Jablonskienė, V. Dobrovolskij, N. Valevičienė, R. Stukas, Epicardial adipose tissue accumulation and essential hypertension in non-obese adults, Medicina (Kaunas). 55 (8) (2019) 456, https://doi.org/10.3390/medicina55080456.
[31] G. Maimaituxun, K. Kusunose, H. Yamada, et al., Deleterious effects of epicardial adipose tissue volume on global longitudinal strain in patients with preserved left ventricular ejection fraction, Front Cardiovasc. Med. 7 (2020), 607825, https://doi.org/10.3389/fcvm.2020.607825.
[32] M. Blumensatt, P. Fahlbusch, R. Hilgers, et al., Secretory products from epicardial adipose tissue from patients with type 2 diabetes impair mitochondrial β-oxidation in cardiomyocytes via activation of the cardiac renin-angiotensin system and induction of miR-208a, Basic Res Cardiol. 112 (1) (2017) 2, https://doi.org/10.1007/s00395-016-0591-0.
[33] H. Geyer, G. Caracciolo, H. Abe, et al., Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications, J. Am. Soc. Echocardiogr. Off. Publ. Am. Soc. Echocardiogr. 23 (4) (2010) 351–355, https://doi.org/10.1016/j.echo.2010.02.015.
[34] E. Crendal, G. Walther, A. Vinet, et al., Myocardial deformation and twist mechanics in adults with metabolic syndrome: impact of cumulative metabolic burden, Obesity 21 (12) (2013) E679–E686.
[35] D. Algranati, G.S. Kassab, Y. Lanir, Why is the subendocardium more vulnerable to ischemia? A new paradigm, Am. J. Physiol. Heart Circ. Physiol. 300 (3) (2011) H1090–H1100, https://doi.org/10.1152/ajpheart.00473.2010.
[36] C. Scally, H. Abbas, T. Ahearn, et al., Myocardial and systemic inflammation in acute stress-induced (Takotsubo) cardiomyopathy, Circulation 139 (13) (2019) 1581–1592, https://doi.org/10.1161/CIRCULATIONAHA.118.037975.
[37] M. Nian, P. Lee, N. Khaper, P. Liu, Inflammatory cytokines and postmyocardial infarction remodeling, Circ Res. 94 (12) (2004) 1543–1553, https://doi.org/10.1161/01.RES.0000130526.20854.fa.
[38] M. Bartekova, J. Radosinska, M. Jelemensky, N.S. Dhalla, Role of cytokines and inflammation in heart function during health and disease, Heart Fail. Rev. 23 (5) (2018) 733–758, https://doi.org/10.1007/s10741-018-9716-x.
[39] M. Spieker, E. Katsianos, M. Gastl, et al., T2 mapping cardiovascular magnetic resonance identifies the presence of myocardial inflammation in patients with dilated cardiomyopathy as compared to endomyocardial biopsy, Eur. Hear J. Cardiovasc. Imag. 19 (5) (2018) 574–582, https://doi.org/10.1093/ehjci/jex230.
[40] J.-R. Ghadri, I.S. Wittstein, A. Prasad, et al., International expert consensus document on takotsubo syndrome (Part I): Clinical characteristics, diagnostic criteria, and pathophysiology, Eur Heart J. 39 (22) (2018) 2032–2046, https://doi.org/10.1093/eurheartj/ehy076.
[41] F. Lizcano, G. Guzmán, Estrogen deficiency and the origin of obesity during menopause, Biomed. Res. Int. 2014 (2014), 757461, https://doi.org/10.1155/2014/757461.
[42] B.T. Kuo, R. Choubey, G.M. Novaro, Reduced estrogen in menopause may predispose women to takotsubo cardiomyopathy, Gend. Med. 7 (1) (2010) 71–77, https://doi.org/10.1016/j.genm.2010.01.006.
[43] G. Pizzino, A. Bitto, P. Crea, et al., Takotsubo syndrome and estrogen receptor genes: partners in crime? J. Cardiovasc. Med. (Hagerstown). 18 (4) (2017) 268–276, https://doi.org/10.2459/JCM.0000000000000500.
[44] D. Davidovich, A. Gastaldelli, R. Sicari, Imaging cardiac fat, Eur. Hear J. – Cardiovasc. Imag. 14 (7) (2013) 625–630, https://doi.org/10.1093/ehjci/jet045.