Epicardial Adipose Tissue Thickness as an Independent Predictor of Ventricular Tachycardia Recurrence following Ablation

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List of Abbreviations

AVGs	Atrioventricular grooves
BMI	Body mass index
CT	Computed tomography
EAT	Epicardial adipose tissue
ICD	Implantable cardioverter-defibrillator
IL	Interleukins
IVGs	Interventricular grooves
LA	Left atrium
LDL	Low-density lipoprotein
MCP-1	Monocyte chemoattractive protein-1
MRI	Magnetic resonance imaging
PAT	Pericardial adipose tissue
RV	Right ventricle
TNF	Tumor necrosis factor
VF	Ventricular fibrillation
VT	Ventricular tachycardia

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Epicardial Adipose Tissue

Introduction

Fat tissue is a complex organ with endocrine and metabolic properties. It secretes numerous bioactive molecules with profound local and systemic effects. Based on available evidence, the differentiation of adipose tissue based on its regional distribution is becoming increasingly important. Recent studies have shown that the distributaion and anatomical position of adipose tissue can have a role in the pathophysiology of some cardiometabolic and endocrinological diseases. The epicardial adipose tissue (EAT) with its paracrine influences on the myocardium and coronary arteries due to its anatomical proximity arouses special scientific interest. In the following, the most important aspects are outlined in their short form.

Anatomy

EAT is a fat tissue between the myocardium and the visceral leaf of the pericardium (1) (Figure 1). EAT surrounds approximately 80% of the myocardium accounts for 15% of myocardial weight (2, 3). EAT is usually located on the free wall of the right ventricle (RV) and the left ventricular apex. However, it is not evenly distributed over the cardiac surface. There are also large accumulations around the branches of the large coronary arteries, around the atria and atrial tubes (4). In some cases, a small amount of epicardial fat moves directly from the epicardium to the myocardium, following the adventitia of the coronary vessels (5). EAT shares blood supply with the underlying myocardium, and there is no separation of fatty tissue from the myocardium, as is the case with skeletal muscle (6, 7). Therefore, both the myocardium and EAT are supplied by the coronary arteries.

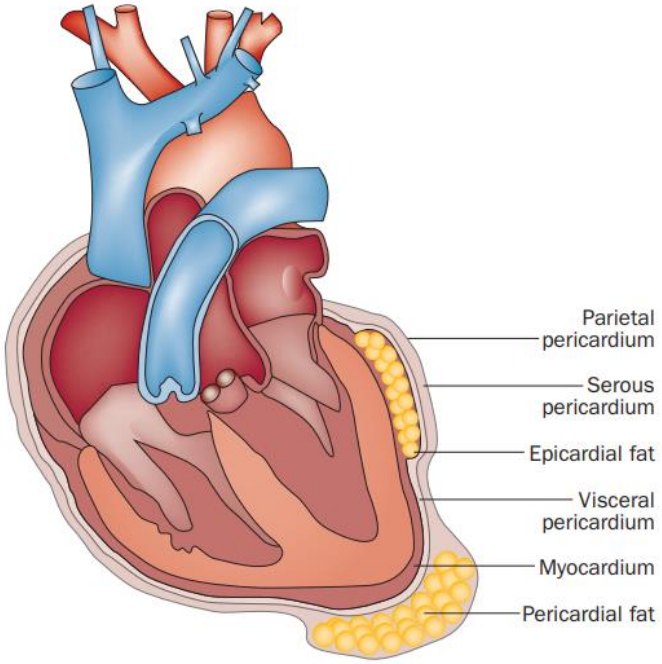

Figure 1. Localization of epicardial and pericardial adipose tissue -Adapted from Gianluca Iacobellis. Nat Rev Endocrinol 2015 (8)

Embryology

Embryologically, EAT is derived from the splanchopleural mesoderm. It is therefore related to visceral adipose tissue, which has the same origin, and also has a similar metabolic profile (9). Histologically, EAT is mainly composed of adipocytes. It also includes stromal vascular cells, macrophages, ganglions and nerve cells (10, 11). Interestingly, EAT is considered beige adipose tissue because, like brown adipose tissue, it expresses uncoupling protein 1, which is responsible for thermogenesis in brown adipose tissue (12, 13).

Physiology and Pathophysiology

Due to its paracrine, autocrine and systemic effects, EAT is considered an endocrine organ that is believed to have both protective and damaging effects (4). Protective effects include:

1) Its ability to act as a buffer between the myocardium and the vascular bed,
2) Its function as an anatomical guide for the cardiac/sympathetic nerves (fibers), and
3) Its role in fat metabolism.

Fatty acids

EAT is rich in saturated fatty acids, has a high protein content and the highest capacity for the release of free fatty acids compared to other visceral fat deposits. The release of free fatty acids is particularly important because under physiological conditions, the myocardium mainly uses these fatty acids for energy production (14). EAT protects against excess free fatty acids, because EAT stores the triglycerides and releases on demand (14-17).

Thermogenetic properties

The potential thermogenetic properties of EAT to protect against hypothermia, similar to brown adipose tissue, have become the focus of scientific attention. Therefore, protection of the coronary arteries and underlying myocardium from cold is also another function of EAT (18). The fact that hibernating animals have large cardiac fat deposits supports this hypothesis. On the other hand, studies in animal models postulate that the myocardium generates enough heat with each contraction, so that a thermogenetic dependency cannot exist (19).

Secretory properties

The main harmful effects of EAT are paracrine effects on the coronary and myocardium and systemic inflammatory effects (20, 21). These effects are caused by the release of various active pro-atherogenic or pro-inflammatory cytokines such as interleukins (IL) (especially IL-6, IL-18), monocyte chemoattractive protein-1 (MCP-1), tumor necrosis factor (TNF), endothelial growth factors, plasminogen activator inhibitor 1, leptin and adiponectin (22). On the other hand, adipocytokines can change the membrane potential, e.g. by reducing the cardiac output of K+ ions (23), which may cause arrhythmias despite the protective effect of epicardial fat reduction of free fatty acids.

Measurement of EAT

In general, there is no agreement on the examination modality to be used and the measurement method to be applied for each modality for EAT assessment.

Echocardiography

Echocardiographically, EAT over the free wall of the RV is measured transthoracically in the parasternal short and long axis (24). By definition, the relative echo-free space between the myocardium and the visceral layer of the pericardium is determined. Due to the compressibility, measurements are preferably taken at the end of systole. An average of the measured values of at least 3 cycles should be calculated. This is the most common echocardiographic procedure, however, end diastolic determination of EAT has also been recommended by other groups (25, 26). However, it should be noted that echocardiography often makes it difficult to distinguish EAT from pericardial adipose tissue (PAT). Therefore, for further differentiation in some cases cardiac, other imaging modalities may be helpful (27).

Magnetic resonance imaging

Cardiac magnetic resonance imaging (MRI) is regarded as the gold standard for the determination of the EAT volume, particularly due to the possibility of tissue-specific imaging using T1 and T2 weighting (28). The method of determination of EAT has been stablished by Flüchter [(29). This method is based on volumetry using a modified Simpson method in the short axis sections (29). Due to the universal choice of sectional plane, volumetry of PAT or analysis of regional fat accumulations around the coronary arteries is also possible in MRI. In addition to the usual T1/T2 images, differentiation of molecules, especially of water and fat, can be achieved in MRI with separate procedures (30).

Computed tomography

Measurement of the EAT is also possible using computed tomography (CT) (28). In a recent validation study by Elming, EAT and EAT were combined and a volumetric comparison with cardiac MRI was performed, which were comparable with MRI findings (28).

EAT and heart disorders

Coronary artery disease

Findings of different studies support the role of EAT as a promoter of atherosclerotic plaque formation and progression (31). EAT correlates significantly with the extent and severity of coronary artery disease (CAD). This relationship has been reported in different clinical studies and meta-analyses (32). Furthermore, a correlation with fatal and non-fatal myocardial infarction in the general population, regardless of traditional risk factors has been also reported (32-34). A doubling of the volume of EAC tissue has been associated with around 2.5-fold increase in the risk of cardiovascular events (33). Observational studies have also been associated with risk for CAD regardless of body mass index (BMI) and the presence of coronary calcifications (35). A possible influence on the early stages of atherosclerotic plaque formation is also discussed (8). This hypothesis is supported by an animal model study that has shown that EAT resection can slow down atherosclerosis (36).

Cardiac arrhythmias

Different studies have shown that patients with atrial fibrillation (AF) have a higher amount of EAT in comparison to the healthy individuals (Table 1). In a recently published meta-analysis, EAT was associated with AF development. We have also shown in our recent meta-anlysis, EAT volume/thickness is higher in patients with AF recurrence after catheter ablation in comparison to those without recurrence (Table 2) (37). Reports, regarding the association between EAT and other arrhythmias are still limited (38). However, a higher thickness of EAT was observed in patients with premature ventricular contraction ablation failure

(39). Besides, in another study on 50 patients with heart failure, an association between PAT and development of ventricular fibrillation/tachycardia (VF/VT) was noticed (40). In this study, baseline PAT was significantly higher in patients who developed VF/VT during the follow-up (40).

Table 1. Studies reporting an association between EAT and AF

Reference	year	Country	Healthy subjects EAT volume		AF patients EAT volume		Imaging
			n	Mean±SD (ml)	n	Mean±SD (ml)	
Nagashima (41)	2011	Japan	37	138.3±45.2	40	185.6±76.1	CT
Mahabadi (34)	2014	Germany	3809	92.7±46.1	46	147.1±64.4	CT
Kanazawa (42)	2014	Japan	120	113.9±32.5	120	148.8±46.1	CT
Al-Chekakie (43)	2010	USA	76	76.1±36.3	197	101.6±44.1	CT
Greif (44)	2013	Germany	934	255.7±127.2	354	284.8±139.2	CT
Shin (45)	2011	Korea	80	67.2±23.1	80	83.8±26.8	CT
Wong (46)	2011	Australia	20	168.8±130.4	102	299.9±192.2	MRI

AF: atrial fibrillation, CT: computed tomography; EAT: epicardial adipose tissue; MRI: Magnetic resonance imaging

Table 2. Studies reporting an association between EAT and AF recurrence after catheter ablation

Reference	Year	AF Recurrence		No AF recurrence		Type of EAT	Imaging
		n	Mean±SD*	n	Mean±SD*		
Tsao (47)	2011	24	35.2±12.5	44	26.8±11.1	LA-EFT volume	CT
Nagashima (41)	2011	15	239±90.2	25	153.5±42.7	Total EFT volume	CT
		15	69.6±35.5	25	40.7±13.9	LA-EFT volume	CT

Murakami (48)	2012	12	200±62	26	145±37	Total EFT volume	CT
Chao (49)	2013	64	6.3±0.6	149	5.7±0.6	RV wall EFT Thickness	Echocardiography
		31	7.3±0.6	25	6.7±0.7	RV wall EFT Thickness	Echocardiography
Kawakami (50)	2013	34	147.3±35.8	61	109.5±34.9	Total EFT volume	CT
Soucek (51)	2014	27	115.8±38.2	75	86.6±38.2	Total EFT volume	CT
Nakahara (52)	2014	47	33.2±10.7	13	25.1±11	LA-EFT volume	CT
Masuda (53)	2015	24	35.1±13.1	29	25.0±9.5	LA-EFT volume	CT
Kocyigit (54)	2015	60	4.4±2.1	189	4.3±1.6	RV wall EFT Thickness	CT
Canpolat (55)	2016	45	7.79±2.2	189	5.79±1.38	RV wall EFT Thickness	Echocardiography

AF: atrial fibrillation, CT: computed tomography; EAT: epicardial adipose tissue; LA: left atrium; RV: right ventricle

* Notice: Unit of the volume and thickness variables are milliliter (ml) and millimeter (mm), respectively

Heart Failure

Although some reports have shown a positive correlation between EAT amount and myocardial fibrosis, and left ventricular dysfunction; still controversial data exist (31). However, it is believed that ETA contributes in the fibrotic transformation occurring in patients with chronic heart failure (56). In some studies, EAT could predict the cardiovascular death in this specific population (56, 57).

Metabolic syndrome

EAT thickness correlates with metabolic syndrome and its components including high levels of low-density lipoprotein (LDL) cholesterol, hypertension, diabetes/insulin resistance (26). However, appropriate cutoff

points of EAT thickness/volume in association with risk of metabolic syndrome are still unclear. The relation between EAT and type 2 of diabetes mellitus has been recently confirmed (58). Moreover, a positive association between EAT and visceral adiposity, BMI, and waist circumference has been observed (59). In another study a strong correlation was reported between fasting plasma glucose and elevated level of EAT (60).

Future direction

EAT as an independent metabolic or endocrine organ is increasingly moving into the focus of clinical studies. Although the above-mentioned studies have not yet revealed any direct clinical implications, research in this area is making a substantial contribution to the understanding of atherogenesis. Indeed, exact mechanism and roles of dysfunctional EAT in cardiovascular diseases development still needs to be confirmed in further studies. Thus, the metabolic processes in EAT appear to be an attractive research area for the identification of previously unknown proatherogenic processes, not least because of the anatomical proximity to coronary arteries. In conclusion, further research is still needed to address unanswered questions in this fascinating field of research.

VT Catheter Ablation

Introduction

VT is a life-threatening tachycardic arrhythmia that originates from the ventricles of the heart. Management has changed significantly over the last decades. Catheter ablation of VT is becoming increasingly important, and nowadays is considered as a standard therapy for patients affected with sustained recurrent monomorphic VT (61). In the therapy and thus the prevention of further VT episodes, catheter ablation is currently taking on an increasingly important role independent of the underlying etiology.

History of VT ablation

In 1981, open-heart VT ablation during cardiac surgery was described (62). Although this technique was highly effective, a high risk of complications with a relevant perioperative mortality rate of 8-17 % was problematic. Therefore, alternatives to lesion generation with a better safety profile were quickly sought. In 1982, the application of myocardial ablation using direct current shocks was then described, which was a logical step in the development of VT ablation (63). Then, development of radiofrequency ablation with lower and controllable energy transmission led to a significant reduction of complication rates in VT ablations. After first studies in the early 1990s, RF ablation became the standard therapy for patients with VT (64).

Catheter ablation for VT in structural and non-structural heart disease

Idiopathic VT is defined as VT in patients without structural heart disease or ion channel disease (65). This includes in particular VT from the right or left ventricular outflow tract. Since most idiopathic VT is characterized by a focal mechanism (triggered activity or increased automatism), punctual catheter ablation is often possible and successful. In contrast to idiopathic VT, VT in structural heart disease is usually caused by a macro-reentry related to a myocardial scar (66). Here, the compact scar without surviving cardiomyocytes is not considered arrhythmogenic. Rather, surviving cardiomyocytes (gray zone area) with regions of slow conduction velocity are held responsible for the development of a reentry (67). This is based

on a central isthmus through the scar with sometimes several "entry" and "exit" points. Therefore, the ablation of this central isthmus is the basis for the catheter ablation of VT in existing myocardial scars.

Outcome of VT catheter ablation

In ischemic cardiomyopathy, the larger studies have reported recurrence rates of between 12 and 47% after 6 to 23 months (68, 69). In patients with non-ischemic cardiomyopathy, a smaller number of studies are available and no randomized study exists. The available observational and retrospective studies describe recurrence rates of 23-53% after 22 to 53 months (70-72). Although VT ablation seems effective in terms of reducing the number of implantable cardioverter-defibrillator (ICD) discharges and mortality; recurrent VTs are still commonly seen in many patients, depending on the follow-up duration (72, 73). Post ablation VT recurrence is usually reported in 25-50% of the cases, and is associated with an increased risk of mortality (74).

Predictors of VT recurrence after catheter ablation

Different studies have attempted to recognize predictors of adverse outcomes, mainly VT recurrence after catheter ablation. In a meta-analysis on 24 studies, VT inducibility after ablation in patients with non-ischemic cardiomyopathy and non-ischemic dilated cardiomyopathy was associated with an increased risk of VT recurrence (odds ratio=5.83 and 3.92; respectively, both $P<0.00001$)(75). Moreover, this study revealed that combined endo-epicardial VT ablation was associated with a reduced risk of VT recurrence in comparison with endocardial-only ablation approach (OR=2.02, P=0.009) (75). In another meta-analysis on three studies, early referral for VT ablation was a predictor of less VT recurrence event in patients with structural heart disease (relative risk=0.69, $p<0.0001$) (76). In a study on 144 patients with ischemic cardiomyopathy who underwent VT catheter ablation, anti-arrhythmic drug therapy failure, left ventricular ejection fraction less than 40%, and total revascularization were the predictors of post ablation VT recurrence (77). Besides, reduced left ventricular ejection fraction, a history of previous ablation and implantation of cardiac devices such as implantable cardioverter defibrillator (ICD) or cardiac resynchronization device were identified as best predictors of VT recurrence in another study (78).

Objectives of the thesis

Though the relationship between EAT and AF occurrence and its post-ablation recurrence has been highlighted in several recent studies (79), the association between EAT and VT recurrence is unknown. Since increased cardiac adipose tissue is associated with an ascending trend in fatty infiltration of ventricular myocardium (40, 80), it is reasonable to hypothesize that EAT might facilitate the creation of an anatomical substrate for VT.

We aimed to assess the association between pre-procedural EAT thickness measurement by means of cardiac MRI and post-ablation VT recurrence.

Epicardial adipose tissue thickness as an independent predictor of ventricular tachycardia recurrence following ablation

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BACKGROUND Although several investigations have shown a relationship between increased epicardial adipose tissue (EAT) and atrial fibrillation (AF), the association between EAT and ventricular tachycardia (VT) has not been evaluated.

OBJECTIVE We investigated the association between EAT and postablation VT recurrence.

METHODS Sixty-one consecutive patients (mean age = 62.0 ± 13.9 years) undergoing VT ablation with preprocedural cardiovascular magnetic resonance imaging (CMR) were recruited. EAT thickness was measured using CMR in the right and left atrioventricular grooves (AVGs), right ventricular free wall, and anterior, inferior, and superior interventricular grooves.

RESULTS During a mean follow-up period of 392.9 ± 180.2 days, postablation VT recurrence occurred in 15 (24.6%) patients. EAT thickness was significantly higher in the VT recurrence group than in the nonrecurrent VT group at the right (18.7 ± 5.7 mm vs 14.1 ± 4.4 mm; $P = .012$) and left (13.3 ± 3.9 mm vs 10.4 ± 4.1 mm; $P = .020$) AVGs. The best cut-off points for predicting VT recurrence were calculated as 15.5 mm for the right AVG (area under receiver operating characteristic [ROC] curve = 0.74) and 11.5 mm for the left AVG (area under ROC curve = 0.72). Multivariate Cox regression analysis showed that preprocedural right AVG-EAT (hazard ratio: 1.2; 95% confidence interval: [1.06–1.39], $P = .004$) was the only independent predictor of VT recurrence after adjustment for covariates. Kaplan-Meier analysis showed a difference for postablation VT recurrence between the 2 groups, with right AVG-EAT thickness cut-off value of <15.5 mm vs ≥15.5 mm (log-rank, $P = .003$).

CONCLUSIONS We suggested a new possible imaging marker for risk stratification of postablation VT recurrence. A higher EAT may be associated with VT recurrence after catheter ablation of VTs.

KEYWORDS Adipose tissue; Catheter ablation; Epicardial fat; Morbidity; Risk assessment; Recurrence; Ventricular tachycardia

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Introduction

Catheter ablation has been considered as a standard therapy for patients affected with sustained recurrent monomorphic ventricular tachycardia (VT).[1] Although VT ablation seems effective in terms of reducing the number of implantable cardioverter-defibrillator (ICD) discharges and mortality, recurrent VTs are still commonly seen in many patients, depending on the follow-up duration.[2,3]

Epicardial adipose tissue (EAT), a specialized visceral fat tissue, has been recently suggested to play a significant role in promoting arrhythmogenesis owing to its proinflammatory properties and anatomical proximity to myocardium.[4] It is believed that leptin, adipocytokines, interleukin-6, and tumor necrosis factor alpha, which are produced by EAT, can promote initiation and development of coronary artery disease (CAD) and arrhythmias such as atrial fibrillation (AF).[5] Moreover, it has been reported that EAT can modulate different metabolic and biochemical triggers, leading to AF.[6] Though the relationship between EAT and AF occurrence and its postablation recurrence has been highlighted in several recent studies,[7] the association between EAT and VT recurrence is unknown. Since increased cardiac adipose tissue is associated with an ascending trend in fatty infiltration of ventricular myocardium,[8,9] it is reasonable to hypothesize that EAT might facilitate the creation of an anatomical substrate for

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VT. We aimed to assess the association between preprocedural EAT thickness measurement by means of cardiovascular magnetic resonance imaging (CMR) and postablation VT recurrence.

Methods

Study design and setting

This retrospective cohort study was conducted between January and December 2016 at our department, as part of the Leipzig VT Ablation Cohort. The study is in compliance with the principles outlined in the Declaration of Helsinki, and it was also approved by the Institutional Ethics Committee. All consecutive patients scheduled for VT ablation procedure with preprocedural CMR were included in this study.

Cardiac magnetic resonance imaging

All preprocedural high-resolution CMR examinations were performed using 1.5T MRI system (Philips Ingenia, Best, the Netherlands), 10 minutes after the application of 0.2 mmol/kg intravenous contrast (gadolinium-DTPA). Full details of the CMR protocol have been previously described in detail.[10] Briefly, the CMR protocol contained standard cine and late-gadolinium enhancement imaging in all standard cardiac geometries. Steady-state free precession sequences were similarly employed in patients without an ICD for cine imaging, whereas 3-dimensional inversion-prepared spoiled gradient echo sequences were used in all patients with an ICD using a standardized CMR protocol. All the image analyses were further performed off-line via a dedicated software package (Automatic Detection of Arrhythmic Substrate, ADAS-VT, Galgo Medical SL, Barcelona, Spain). Two independent readers blinded to the ablation outcomes performed the measurements, and any disagreements $\geq$1 mm were discussed and revised.

Epicardial adipose tissue measurement

EAT was defined as the adipose tissue located between the visceral layer of the pericardium and outer surface of the myocardium.[11] Methods of EAT measurement have been previously described elsewhere.[12] Briefly, EAT was measured on the horizontal long-axis plane in end-diastolic phase in right and left atrioventricular grooves (AVGs), as well as anterior interventricular groove (IVG) (Figure 1A). Additionally, EAT was measured in inferior and superior IVGs, as well as right ventricular (RV) free wall on basal short-axis plane (at the level of the papillary muscles' tip) in end-diastolic phase (Figure 1B).

Ventricular tachyarrhythmia ablation

Our detailed ablation procedure is described in detail elsewhere.[3] Briefly, antiarrhythmic medications were withheld for a time period of 5 half-lives prior to ablation whenever possible. The procedure was then performed under deep sedation and monitoring direct arterial blood pressure and oxygen saturation. The left ventricular cavity could be reached through a transseptal puncture. A steerable sheath (Agilis, St. Jude Medical, St. Paul, MN) was used for transseptal puncture. Before transseptal puncture, heparin was administered to maintain an activated clotting time of >250 seconds. A multichannel recording system (Prucka CardioLab, GE Healthcare, Waukesha, WI) was used to record the data. Programmed electric stimulation from the RV apex and outflow tract using 4 different drive cycle lengths (500, 430, 370, and 330 ms) and up to 3 extrastimuli was done to induce VT. Further stimulation in the left ventricle was also performed if VT was not inducible. The same induction protocol was similarly done to reinduce the postablation VT. In 11 patients epicardial ablation was done after subxyphoid puncture using a Tuohy needle. A steerable sheath (Agilis-EPI, St. Jude Medical, St. Paul, MN) was used to facilitate the catheter maneuverability and stability.

Mapping was done in sinus rhythm and/or during RV stimulation with an electroanatomic 3-dimensional mapping system (Carto 3 System, V6, Biosense Webster Inc, Diamond Bar, CA) and fluoroscopy. Limited activation and pace mapping were used to direct the ablation. Activation and entrainment mapping were also performed in some patients with hemodynamically stable VTs. Ablation of late potentials and dechanneling were done in all patients. Furthermore, radiofrequency energy was employed for ablation using open irrigated-tip ablation catheters with power settings of up to 50 W and an irrigation rate up to 30 mL/min (Thermocool, Biosense Webster Inc, Diamond Bar, CA) or 50 W and a flow rate of 15 mL/min (Carto-3-System, Thermocool SF, Biosense Webster Inc). The endpoint of the catheter ablation was noninducibility of any VT.

Follow-up visits

Follow-up visits were performed at every 3 months or earlier if the patients had developed symptoms consistent with VT recurrence in our pacemaker/ICD outpatient clinic. Primary endpoints of the study were defined as follows: (1) the sustained VT as documented by electrocardiogram, ICD interrogation, or VT below detection; and (2) the occurrence of cardiac-related death. Acute success and procedure-related complications were assumed as the secondary endpoints.

Statistical analysis

The normal distribution of the data was examined using the 1-sample Kolmogorov-Smirnov test. Comparison of the continuous variables was fulfilled via independent-samples t test (for normally distributed data), and Mann-Whitney U test (for nonnormally distributed data). Pearson χ^2 test was used for comparing the categorical data in both groups. In cases wherein more than 20% of cells had the expected frequency less than 5, Fisher exact test was implemented. Moreover, correlations between body mass index (BMI) and EAT thicknesses were assessed using Pearson correlation test. The continuous variables were further expressed as mean $\pm$ standard deviation once the data were found to be normally distributed, or in the form of median [25th–75th percentile] when the data

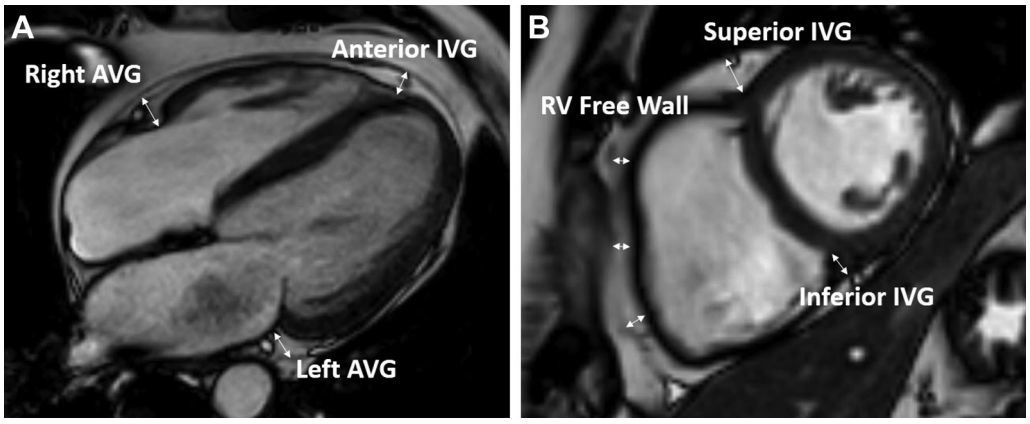

Figure 1 Examples of echocardiographic measurement of epicardial adipose tissue (EAT) thickness on cardiac magnetic resonance imaging (CMR) at different locations, including right and left atrioventricular grooves (AVGs), as well as anterior, inferior, and superior interventricular grooves (IVGs), and also right ventricular (RV) free wall. **A:** True fast imaging with steady-state precession (TrueFISP) image of horizontal long-axis view in end-diastole. **B:** TrueFISP image of short-axis view in end-diastole. The EAT thickness of RV free wall was recorded through averaging the measurement of 3 different levels.

were not normally distributed. The categorical variables were also reported as frequencies (%). The receiver operating characteristic (ROC) curve was also plotted to determine the optimal cut-off points of preprocedural EAT thickness in order to predict postablation VT recurrence during follow-up. Cox (proportional hazards) regression was used to test the effect of explanatory variables on postablation VT recurrence, adjusted for other variables. VT recurrence-free survival was then estimated by Kaplan-Meier estimator and log-rank test owing to a cut-off point of 15.5 mm for the right AVG-EAT thickness. IBM SPSS Statistics for Windows (version 25.0, IBM Corp, Armonk, NY) was used and $P < .05$ was considered statistically significant.

Results

Baseline characteristics

A total of 63 patients were studied; among them, 2 patients were excluded owing to noninterpretable CMR. Therefore,

Table 1 Baseline characteristics of patients with and without postablation ventricular tachycardia recurrence

Variables, n (%)	Nonrecurrent VT (n = 46)	Recurrent VT (n = 15)	*P*
Age	60.5 ± 14.9	66.7 ± 9.2	.080
Sex, male	42 (91.3)	13 (86.7)	.600
Body mass index, kg/m^2	27.6 ± 4.1	29.2 ± 3.7	.190
Coronary artery disease	23 (50.0)	3 (20.0)	.041
Atrial arrhythmia	15 (32.6)	6 (40.0)	.601
Coronary artery bypass grafting	8 (17.4)	1 (6.7)	.533
Hypertension	26 (56.5)	7 (46.7)	.506
Diabetes	10 (21.7)	3 (20.0)	.886
Prior stroke	5 (10.9)	1 (6.7)	.635
Chronic obstructive pulmonary disease	3 (6.5)	1 (6.7)	.984
Chronic renal failure*	15 (32.6)	6 (33.3)	.959
NYHA score	1.9 ± 0.6	2.0 ± 0.7	.745
Beta blocker	40 (87.0)	12 (80.0)	.509
Amiodarone	16 (34.8)	7 (46.7)	.401
Mexiletine	2 (4.3)	0 (0)	.412
Sotalol	2 (4.3)	1 (6.7)	.718
Flecainide	0 (0)	0 (0)	-
ACE inhibitor	28 (60.9)	10 (66.7)	.687
Aldosterone antagonists	17 (37.0)	7 (46.7)	.504
Statin	28 (60.9)	4 (26.7)	.021†
ICD	32 (69.6)	13 (86.7)	.191
ICD shocks/ATP/external defibrillation	27 (58.7)	9 (60.0)	.929
Electrical storm >3 per 24 hours	12 (26.1)	2 (13.3)	.308
Prior VT ablation	12 (26.1)	7 (46.7)	.135
Left ventricular ejection fraction (%)	38.9 ± 12.8	29.3 ± 12.7	.052

ACE = angiotensin-converting enzyme; ATP = antitachycardia pacing; ICD = implantable cardioverter-defibrillator; VT = ventricular tachycardia.
Data are presented as n (%) or mean ± standard deviation.
*Glomerular filtration rate less than 60 mL per minute / 1.73 m^2.
†Statistically significant.

Table 2 Procedural characteristics and long-term outcomes of patients with and without postablation ventricular tachycardia recurrence

Variables	Nonrecurrent VT (n = 46)	Recurrent VT (n = 15)	*P*
Total procedure time (min)*	147.5 [120.0–191.0]	165.0 [135.0–200.0]	.283
Radiation time (min)*	14.6 [8.8–23.1]	18.2 [9.0–30.4]	.621
Radiation dose (μGy)*	1149.1 [441.6–1832.5]	1449.5 [573.0–3536.0]	.487
Total ablation duration (s)*	1244.5 [801.7–2392.2]	2151.0 [635.0–3619.0]	.327
Ablation approach, n (%)			
Endocardial	39 (84.8)	11 (73.3)	.317
Epicardial /endo-epicarial	7 (15.2)	4 (26.7)	
Acute ablation success (electrophysiological testing after ablation), n (%)			
Successful	40 (87.0)	15 (100.0)	.338
Unsuccessful	1 (2.2)	0 (0)	
Not inducible VT	5 (10.9)	0 (0)	

VT = ventricular tachycardia.
*Median [25th–75th percentile].

61 patients (55 male, 6 female) with a mean age of 62.0 ± 13.9 years were finally studied. During a mean follow-up period of 392.9 ± 180.2 days, postablation VT recurrence occurred in 15 (24.6%) patients (6 of them had recurrence of at least 1 previously induced VT during the index procedure). Patients' baseline characteristics are summarized in Table 1.

Procedure-related characteristics

The two study groups showed no significant difference regarding total procedure time (P = .283), total ablation duration (P = .327), radiation time (P = .621), and radiation dose (P = .487) (Table 2). Moreover, no significant difference was reported between both study groups in terms of acute VT success rate (nonrecurrent VT vs recurrent VT, 87.0% vs 100%, P = .338). Procedure-related complications and pericardial effusion during pericardial access catheterization also occurred in only 1 patient (2.2%) of the nonrecurrent VT group (P = .656).

Follow-up

Follow-up duration was similar in both nonrecurrent VT (387.8 ± 183.1 days) and recurrent VT (408.3 ± 176.4 days) groups (P = .706). The median time for first postablation VT recurrence was 118.4 [17.0–189.0] days.

Epicardial adipose thickness

The EAT was higher in the recurrent VT group than in the nonrecurrent VT one, at the right and left AVGs, anterior and inferior IVGs, and also the RV free wall; however, these differences were statistically significant only at right and left AVGs (Table 3). The best cut-off point for the prediction of VT recurrence was calculated as 15.5 mm for the right AVG-EAT thickness (95% confidence interval [CI] [0.57–0.89], P = .013, area under ROC = 0.74) and 11.5 mm for the left AVG-EAT thickness (95% CI [0.56–0.89], P = .020, area under ROC = 0.72) (Figure 2). The sensitivity of the right and the left AVG cut-off points were, respectively, 83.3% and 75.0% and cut-off point specificity of right and left AVGs were 66.7% and 69.0%, respectively (Figure 2).

Further analysis on EAT

Variables for which univariate analysis yielded a P value of <.10 (Table 1) were included in a multivariate Cox regression model. Regression analysis showed that the preprocedural right AVG-EAT thickness (hazard ratio: 1.2; 95% CI: [1.06–1.39], P = .004) was the only independent predictor of postablation VT recurrence after being adjusted for all other variables, including age (P = .305), statin (P = .108), CAD (P = .250), left ventricular ejection fraction (P = .297), and the left AVG-EAT thickness (P = .297). Figure 3 represents

Table 3 Different sites of thickness measurements of epicardial adipose tissue in patients with and without postablation ventricular tachycardia recurrence

Site	Exact location of EAT measurement	Nonrecurrent VT (n = 46)	Recurrent VT (n = 15)	*P*
Atrioventricular groove	Right	14.1 ± 4.4	18.7 ± 5.7	.012*
	Left	10.4 ± 4.1	13.3 ± 3.9	.020*
Interventricular groove	Anterior	6.4 ± 2.7	7.2 ± 3.2	.516
	Superior	9.9 ± 3.9	8.3 ± 3.1	.390
	Inferior	6.2 ± 2.2	6.4 ± 2.6	.839
Right ventricular	Free wall	4.9 ± 2.1	5.1 ± 1.8	.863

EAT = epicardial adipose tissue; VT = ventricular tachycardia.
Data (in mm) are presented as mean ± standard deviation.
*Statistically significant.

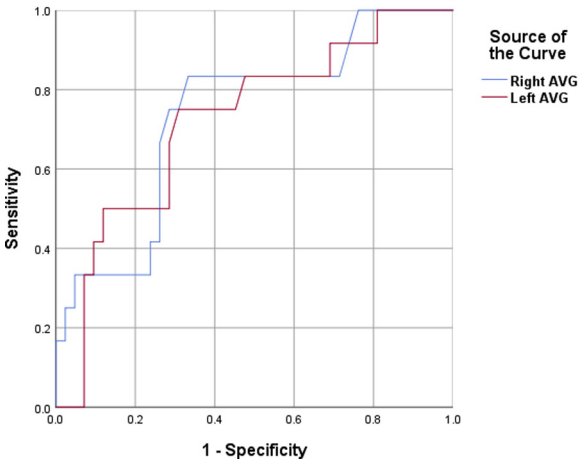

Figure 2 Receiver operating characteristic curve illustrating the accuracy of right and left atrioventricular groove (AVG) thickness of epicardial adipose tissue for predicting postablation ventricular tachycardia recurrence.

the Kaplan-Meier curves for freedom from postablation VT recurrence according to the right AVG-EAT. No significant correlation was observed between BMI and right (r = 0.197, P = .162) or left AVG-EAT thickness (r = 0.244, P = .084). In addition, no relationship was reported between EAT thickness and the status of statin therapy (Table 4).

Discussion

Main findings

To the best of our knowledge, the present study is the first report on the association between EAT and VT recurrence, which showed a significant association between increased EAT thickness and VT recurrence after catheter ablation. It is interesting to note that EAT thickness within almost all the measurable locations was higher in patients with VT recurrence; however, increases in the right and the left AVG-EAT thicknesses were statistically significant. Moreover, the long-term VT recurrence-free survival was better in patients with lower amounts of EAT in comparison to those with higher amounts. Finally, the AVG-EAT thickness was not related to BMI and/or statin therapy, and the right AVG-EAT thickness remained to be the only predictor of VT recurrence in the regression model.

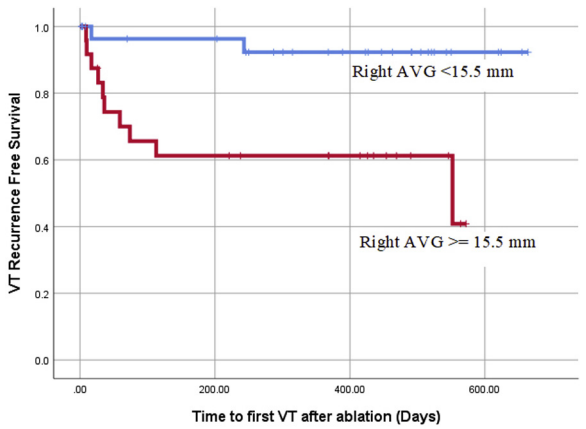

Figure 3 Kaplan-Meier analysis showed a significant difference for the overall postablation ventricular tachycardia (VT) recurrence between the 2 groups of patients with right atrioventricular groove (AVG) epicardial adipose tissue thickness cut-off value of <15.5 mm vs ≥15.5 mm (log-rank, P = .003).

Cardiac adipose tissue and cardiac arrhythmia

Although a close relationship has been suggested between increased EAT and significant CAD. Nowadays, an increasing number of studies are attempting to assess the association between EAT and cardiac arrhythmia.[13,14] An association was reported between pericardial adipose tissue and development of ventricular fibrillation / VT in patients with systolic heart failure.[9] Wu and colleagues[9] reported that in 50 patients with heart failure, baseline pericardial fat volume was significantly higher in those with ventricular fibrillation / VT than those without this condition (36.3 [32.8–43.1] mL/m^2 vs 24.1 [20.2–27.6] mL/m^2) during a median follow-up of 694 days.[9] In our study the EAT had been evaluated; and the study populations were different from those reported by Wu and colleagues. Recently, two published meta-analyses evaluated the association between increased EAT and AF incidence and also AF recurrence.[7,15] Though these studies have helped to find another piece of the puzzle of association between EAT and cardiac arrhythmia, we believe direct evidence evaluating the association between EAT and VT is still inadequate.

Potential mechanisms linking EAT to VT

While the mechanism underlying increased EAT in patients with recurrent VT is uncertain, the present data implied that EAT might contribute to the progression of underlying mechanisms that could result in VT development. First and foremost, EAT can have higher ability to absorb and secrete free fatty acids (FFAs) in comparison with other visceral adipose tissues, and FFAs have also been shown to be associated with ventricular arrhythmias.[16] Since FFAs are the main substrates for myocardial cells under normal physiologic conditions, increased FFA metabolism can reduce the ventricular arrhythmia threshold.[17] In human studies, a positive correlation has been observed between ventricular arrhythmia prevalence and serum FFA in patients with myocardial infarction.[18] Kankaanpaa and colleagues[19] reported that EAT assessed by CMR was related to FFA exposure, and these changes could precede left ventricular overload and hypertrophy, and consequently lead to higher incidence of arrhythmias. Therefore, considering the anatomical and functional proximity of the myocardium to its surrounding adipose tissue, it seems probable that the FFA produced by EAT can be considered as a cause of higher rate of ventricular arrhythmias. Although the exact mechanism through which higher FFA levels in ischemic myocardial cells may lead to arrhythmias is still unclear, FFA may conceivably affect ventricular arrhythmia of epicardial source due to its anatomical proximity and of endocardial source due to indirect effects.[16,17]

Table 4 Epicardial adipose tissue thickness in patients with and without statin therapy who underwent ventricular tachycardia ablation

Site	Exact location of EAT measurement	Without statin (n = 29)	With statin (n = 32)	*P*
Atrioventricular groove	Right	16.0 ± 5.7	14.3 ± 4.3	.232
	Left	11.6 ± 4.9	10.7 ± 3.7	.441
Interventricular groove	Anterior	6.5 ± 3.4	6.7 ± 2.3	.810
	Superior	8.2 ± 3.7	10.7 ± 3.6	.060
	Inferior	6.6 ± 2.4	6.0 ± 2.2	.435
Right ventricular	Free wall	5.2 ± 2.9	4.8 ± 1.2	.496

EAT = epicardial adipose tissue.
Data (in mm) are presented as mean ± standard deviation.

The other hypothesis linking EAT to VT is related to adipose cells, known as lipomatous metaplasia. Different studies have shown that infarcted myocardium can be infiltrated by lipomatous metaplasia, which can facilitate reentry in scar areas.[20] Mordi and colleagues[21] showed that lipomatous metaplasia (with a hazard ratio of 2.67) remained a significant predictor of sustained VT, heart failure hospitalizations, and also all-cause mortality in a multivariate model including other strong predictors.[21] This study revealed the importance of increased cardiac adipose tissue in the development of ventricular arrhythmias.

Another proposed hypothesis is the association between cardiac adipose tissue, gap junction, and connexin remodeling, which have been shown to contribute to ventricular arrhythmias in patients with ischemic heart disease.[22] Interestingly, a strong association between ventricular arrhythmias and fibro-fatty replacement and accumulation of glycosphingolipids has also been observed in patients with myotonic dystrophy and Fabry disease, which puts more emphasis on the importance of cardiac adipose tissue with regard to ventricular arrhythmias.[23,24] It has been shown that EAT can lead to expression of numerous inflammatory markers, which have been similarly observed to be involved in VT pathogenesis.[6,25] In comparison with subcutaneous fat, it has been revealed that EAT is associated with higher levels of inflammatory cytokines, and a higher inflammatory state can subsequently lead to a higher structural and electrical remodeling of the heart, and finally a higher incidence of arrhythmia.[26]

Obesity and EAT

Although obesity can be associated with increased EAT, this phenomenon occurs in a condition named lipotoxic cardiomyopathy, when the normal storage sites of fat, including subcutaneous adipose tissue and visceral adipose tissue, are saturated.[18] Currently, more studies show the efficacy of total body weight loss on EAT reduction[27]; however, our findings, in line with the results reported by Wu and colleagues,[9] showed that systemic adiposity was not a significant predictor for ventricular arrhythmias. This finding may indirectly imply the importance of EAT reduction through a targeted therapy strategy as a part of strategic planning for VT recurrence prevention, and not necessarily total body weight reduction. Nevertheless, the effect of EAT reduction on the outcome of VT ablation requires additional clinical trials and studies. Rowe and colleagues[28] showed that lowering FFA and maintaining it in the normal range throughout the treatment period via administration of nicotinic acid analogue had resulted in a significant reduction of the incidence of VTs following myocardial infarction. Currently, statin therapy and weight loss are the only recommended strategies for EAT reduction.[27,29] However, surgical removal of EAT, and use of botulinum toxin, are on their initial phases of clinical trials and are not fully approved regarding their safety and efficacy.[30,31] Although our findings highlighted a higher proportion of statin therapy in the nonrecurrent VT group, EAT was not related to the usage of statins, and statin did not lead to a significant lower amount of EAT in nonrecurrent patients, which may indicate the importance of finding more specific treatments for EAT reduction.

Limitations

The first limitation was associated with the relatively small sample size, which might have influenced the results of the statistical analyses. Besides, there were some important differences in baseline characteristics between the 2 groups. To adjust for the potential effect from these potential confounding factors, we included all these variables, including left ventricular ejection fraction and type of cardiomyopathy, which have been previously shown to be independent prognosticators of higher postablation VT recurrence, in our multivariate analyses. Moreover, we measured right and left AVG-EAT, which are not usually sites for VT ablation; therefore, we were not able to assess the potential association between local EAT and the scar area and/or VT origin. Further studies using more detailed 3-dimensional EAT imaging might be necessary to address this issue.

There were no available data regarding biomarkers, including C-reactive protein and interleukins, so the association between EAT and these factors was not assessed. Moreover, other components of body fat, including total body fat, abdominal fat, and waist circumference, were not measured; however, we believe that these measurements may highlight further information on the difference of systemic vs local adiposity.

Conclusion

The current study presented a new possible imaging marker for risk stratification of postablation VT recurrence. This study showed that the right and left AVG-EAT thickness were higher in patients affected with VT recurrence

compared with those without VT recurrence after ablation. Further studies are warranted to compare the efficacy of possible therapeutic options for EAT reduction and their potential impacts on the VT recurrence prevention.

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Summary

Dissertation zur Erlangung des akademischen Grades
Dr. med.

Titel:	Epicardial Adipose Tissue Thickness as an Independent Predictor of Ventricular Tachycardia Recurrence following Ablation
eingereicht von:	Alireza Sepehri Shamloo, geb. 11.09.1990 in Mashhad
angefertigt an:	Herzzentrum Leipzig – Universitätsklinik, Abteilung für Rhythmologie
Direktor:	Prof. Dr. med. Gerhard Hindricks
Betreuer:	Prof. Dr. med. Gerhard Hindricks PD Dr. med. habil. Arash Arya

Monat und Jahr (der Einreichung):

Although several investigations have shown a relationship between increased epicardial adipose tissue (EAT) and atrial fibrillation (AF), the association between EAT and ventricular tachycardia (VT) has not been evaluated. We investigated the association between EAT and post-ablation VT recurrence. In this study, sixty-one consecutive patients (mean age=62.0±13.9) undergoing VT ablation with pre-procedural cardiac magnetic resonance imaging (MRI) were recruited. EAT thickness was measured using cardiac MRI in the right and left atrioventricular grooves (AVGs), RV free wall, anterior, inferior, and superior interventricular grooves (IVGs). During a mean follow-up period of 392.9±180.2 days, post-ablation VT recurrence occurred in 15 (24.6%) patients. EAT thickness was significantly higher in the VT recurrence group than that in the non-recurrent VT at the right (18.7±5.7 vs. 14.1±4.4 mm; p=0.012) and left (13.3±3.9 vs. 10.4±4.1; p=0.020) AVGs. The best cut-off points for predicting VT recurrence were calculated as 15.5 mm for the right AVG (area under ROC curve=0.74) and 11.5 mm for the left AVG (area under ROC curve=0.72). Multivariate Cox regression analysis showed that pre procedural right AVG-EAT (HR: 1.2; 95% CI: [1.06-1.39], p=0.004) was the only independent predictor of VT recurrence after adjustment for covariates. Kaplan–Meier analysis showed a difference for post-ablation VT recurrence between the two groups with right AVG-EAT thickness cut-off value of <15.5 mm versus ≥15.5 mm (log-rank, p=0.003). Based on the finding of this study, we suggested a new possible imaging marker for risk stratification of post-ablation VT recurrence. A higher EAT may be associated with VT recurrence after catheter ablation of VTs.

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