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Review

Genetic Implications of Fatty Tissue for the Development of Ventricular Arrhythmias

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Abstract: Ventricular arrhythmias are a common disorder, and sometimes the etiology remains unclear. Present data support cardiac fatty tissue's potential role as a substrate for ventricular arrhythmias. Diagnosing fatty tissue based on imaging markers and histopathological evidence is often challenging. Data about the influence of individual and multiple genetic variants on epicardial adipose tissue volume remain limited. In this review, we aimed to provide a comprehensive overview of the current understanding of the genetic basis of fatty tissue and its contribution to the pathogenesis of ventricular arrhythmias and to discuss the relationship between certain genetic variants and the development of ventricular arrhythmia.

Keywords: genetics; fatty tissue; ventricular arrhythmias

1. Introduction

Strong data suggest that obesity-related comorbidities contribute to the arrhythmogenic substrates. Lately, there has been an increased interest in evaluating the impact of excessive adipose tissue on arrhythmia occurrence, in the absence of other risk factors [1]. Body mass index (BMI) is an established marker for quantifying obesity and the relationship between weight and cardiovascular diseases (CVDs). Also, there is significant interest in evaluating the impact of adipose deposits and CVD [2].

Epicardial adipose tissue (EAT), as presented in Figure 1, represents a type of visceral fat located between the myocardial surface and the visceral layer of the pericardium. Because of i common embryologic origin with visceral fat deposits [3], EAT is often confused with pericardial fat. Data obtained from genome-wide association studies show various single-nucleotide polymorphisms (SNPs) involved in biological processes such as oxidation, diabetes/obesity, the reninangiotensin system, and dyslipidemia, but associated with certain phenotypes, cardiovascular risk, and CVD [4]. Several polygenic risk scores have been created to evaluate the burden of these genetic variants as well as individual susceptibility [5].

Even though the fatty tissue disposed around the cardiac vessels seems to play a supportive action by reducing vascular tension and torsion [6], it is also responsible for releasing several cytokines and hormones into circulation, which play an important role in the myocardial tissue. EAT exhibits a wide range of thermogenic and mechanical functions through the released cytokines. Next, based on these cytokines' pro- and anti-inflammatory effects, the ventricular myocardium and coronary arteries are affected, as the myocytes are closely situated near the zones with adipocytes and peri-cellular fibrosis. Even though the adipocytes express ion channels and gap junctional channels [7], there is scarce data on adipocyte–myocyte electrical coupling.

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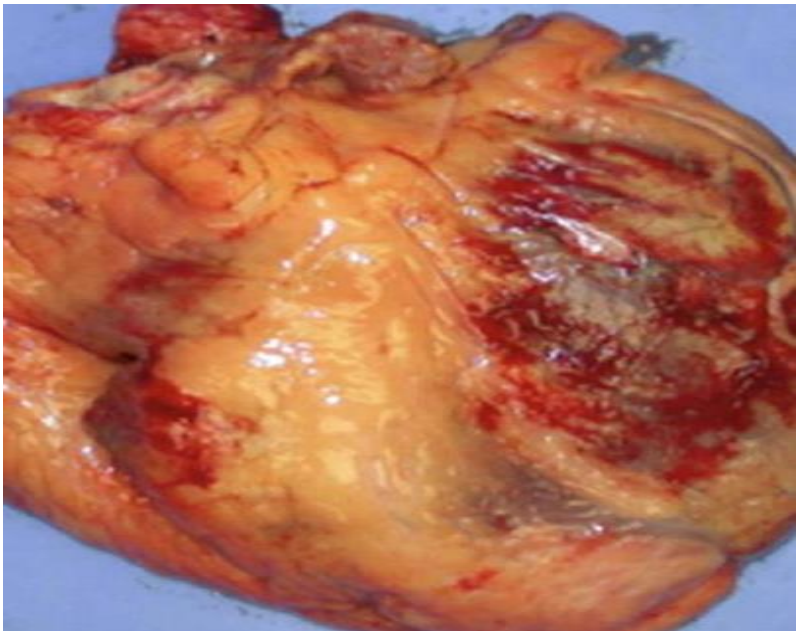


Figure 1. Image of an explanted human heart (anterior view) with the epicardial adipose tissue colored in yellow. EAT is visceral fat localized between the myocardial surface and the visceral layer of the pericardium, most often observed on both atria, the free wall of the right ventricle and the left ventricle's apex. EAT should be considered a biologically active structure connecting obesity and cardiovascular diseases, as well as a risk factor for the atherosclerotic process. EAT exhibits a heterogeneous distribution throughout the heart. Every EAT deposit presents a different transcriptome and proteome, leading to different effects on the adjacent heart structures.

Cardiac diseases such as arrhythmogenic right ventricular cardiomyopathy (ARVC), myotonic dystrophy, and Anderson—Fabry disease frequently present extensive adipose tissue deposits and increased EAT [8]. Patients with ischemic cardiomyopathy and left ventricular (LV) hypertrophy present a constant fatty tissue/muscle ratio, compared to the pathologies mentioned above, where the fatty tissue/muscle ratio seems to increase [9].

Epicardial adipose tissue plays a unique role in the occurrence and development of CVD, as well as cardiac arrhythmia occurrence. This review summarizes the relationship between genetics and EAT and the impact on the occurrence of ventricular arrhythmias. From our knowledge, this is the first review concerning this issue. Arrhythmias, either atrial or ventricular, are multifactorial, so establishing the exact mechanism that leads to arrhythmia requires further work.

2. Fatty Tissue

2.1. General Data on Fatty Tissue Infiltration

Adipose tissue is represented by either white fatty tissue, the predominant type, responsible for fat storage, or brown fatty tissue, involved in thermogenesis. Intramyocardial adipose tissue (IAT) is a normal finding and consists of fatty tissue stored within the cardiomyocytes, representing less than 1% of the total organ mass. Human evidence shows that intramyocardial adipose deposits are related to triglyceride storage and seem to be increased in conditions such as type 2 diabetes, obesity, or impaired glucose tolerance. IAT is mostly located in the right ventricle (RV), starting from the epicardium and extending to the endocardium. Adipose cells are usually spread among the myocardial fibers without involving processes such as fibrosis, inflammation, or cardiomyocyte replacement.

EAT represents the adipose tissue deposits located between the myocardium and the visceral layer of the pericardium [10]. EAT is considered white adipose tissue and includes

mainly adipocytes, smaller than those from visceral or subcutaneous adipose deposits. EAT exhibits different anatomical and physiological properties when compared to other fat deposits, so it may offer protection for the adjacent myocardium via brown fat-like thermogenic function, or it can be harmful through para or vasocrine secretion of various cytokines involved in inflammation and fibrosis.

Visceral adipose tissue (VAT) can be found around the main coronary arteries, in the atrioventricular or interventricular grooves, and around the RV [11]. Paracardial fatty tissue is located between the pericardium layers and the external area of the parietal pericardium (Figure 2).

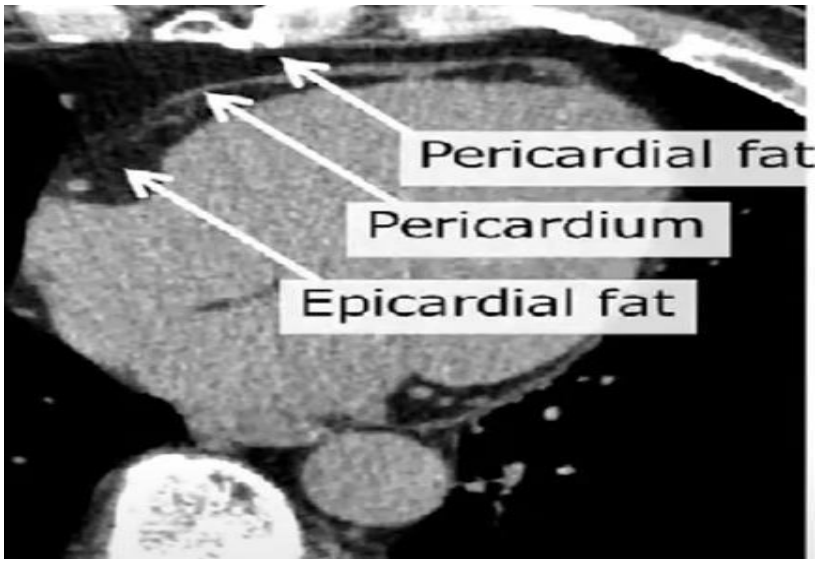


Figure 2. Cardiac CT view highlighting the epicardial adipose tissue, localized between the myocardium and the visceral layer of the pericardium, and the pericardial adipose tissue, localized outside the parietal pericardium.

Even though pericardial and the epicardial fatty tissue evolve from brown fatty tissue as well as intra-abdominal visceral adipose tissue, they exhibit different embryological origins [12]. Paracardial fatty tissue originates in the primitive thoracic mesenchyme, while epicardial tissue originates from the splanchnopleuric mesoderm.

While white adipose tissue is involved in accumulating triglycerides in large lipid droplets and then in the hydrolyzation process when energy is needed, brown adipose tissue participates in the lipid oxidation process responsible for thermogenesis. White adipose tissue undergoes various changes in obese individuals as it increases, becomes dysfunctional, and is more prone to developing an inflammatory status. At the same time, brown adipose tissue volume and activity decline because of the conversion from brown- to white-like adipocytes, a process named "whitening" [13].

Obesity is associated with an increased arrhythmic risk. Obesity coexists with hypertension, obstructive sleep apnea, and diseases that are also pro—arrhythmogenic. At the same time, there is strong evidence linking adipose tissue volume to arrhythmias and also weight-loss to arrhythmia-free survival [14].

2.2. Pathogenesis

The distribution of cardiac adipose tissue is highly heterogeneous. Although adipose infiltration is frequently observed and it is considered a normal finding, data also show a pro-arrhythmogenic effect, as several cardiac pathologies are associated with an increase in adipose infiltration, especially at the epicardium level.

Studies have shown that 80% of the myocardial area is covered by adipose tissue and up to 20% of the cardiac weight is represented by fatty tissue [3,15]. At the level of the ventricular myocardium, the fatty deposits are located on the free wall of the RV and at the left ventricle's (LV) apex. Data show that the amount of adipose tissue is similar for both LV and RV, although the total LV mass is superior to the RV mass [16]. The proposed cut-off for EAT thickness is 5 mm and EAT volume is 125 mL [17].

With aging, the EAT adipocytes become more prone to hemodynamic, metabolic and environmental changes, switching the EAT role of thermogenesis to energy storage [18]. Also, with aging, the proportion of EAT brown adipocytes tends to decrease in favor of white adipocytes.

Heart failure (HF) is a known cause of mortality and morbidity. Nowadays, HF with preserved ejection fraction (HFpEF) presents a significant increase in incidence and prevalence, especially in obese patients. Various studies have shown an association between HFpEF and increased EAT [19].

It is established that EAT is involved in arrhythmia mechanisms through automaticity or triggered or reentrant activity [20]. Adipocytes and other intra-myocardial cell types represent almost 70% of the cardiac cellular population. Myocardial infiltration mediated by proliferating cells leads to electrophysiological changes responsible for micro fibrosis. Myocyte remodeling may occur due to abnormal activity or crosstalk between myocytes and adjacent cells [21]. The subsequent imbalance created by the fatty tissue deposits, related to obesity and or inflammation, leads to significant remodeling of the electrical and structural properties of the myocytes. Next, changes in electrical propagation occur, either anisotropy or slowing of the electrical impulse conduction. Adipose deposits may also be responsible for an anatomical block of electrical impulse propagation, leading further to reentry-related arrhythmias.

The increase in EAT is also responsible for abnormal gene expression, myocyte activity, and nervous system activity through processes that involve cytokines, adipose infiltration, and oxidative stress (Table 1).

It is paramount to precisely locate the cardiac adipose deposits to perform further investigations into the link between adiposity andarrhythmic risk. Several receptor types, such as inflammation Toll-like receptors, play a significant role in signaling other factors, but further studies are needed.

First, EAT was presented as a marker of coronary atherosclerosis in the early 2000s. The EAT-atherosclerosis mechanisms are complex and based on inflammation, adipocyte stress, oxidative stress, endothelial damage, immunity response, lipid accumulation, and glucotoxicity [22]. The EAT surrounding the coronary arteries presents an enhanced expression of genes encoding factors regulating glucose and lipid metabolism, as well as pro-inflammatory adipokines. The coronary epicardial adipose tissue seems to be involved in the atherosclerosis process through the pro-inflammatory M1 macrophage infiltration from the EAT to the surrounding myocardium, through the release of inflammation factors such as CCL2, IL-6, and TNF, several adipokines as chemerin, resistin, intelectin 1, and serglycin, and the activation of immune response factors such as JUN N-terminal kinase (JNK), nuclear factor-κB (NF-κB) and Toll-like receptors (TLRs) [23].

The EAT from the left atrial level presents an enhanced expression of genes encoding pro-arrhythmogenic factors and participates in atrial fibrillation development by secreting profibrotic factors such as transforming growth factors like TGF -β1 and TGFβ2, pro-inflammatory cytokines such as IL-6 and tumor necrosis factor (TNF), connective tissue growth factor (cTGF), profibrotic factors such as matrix metalloproteinases (MMPs), free fatty acid infiltrations, and enhanced autonomic activity mediated through the ganglionated plexi.

Table 1. EAT activity [24].

Properties	Actions	Diseases
1. Metabolic activity [25,26] - increased lipolysis - decreased glycolysis - heat production	excess of free fatty acids myocardial protection against hypothermia	Coronary artery disease valvular diseases, diabetes metabolic syndrome
2. Angiogenic factors [27] - angiogenin - endostatin - VEGF - thrombospondin-2 - angiopoietin	cell adhesion proliferation migration angiogenesis	CAD
3. Growth and remodeling factors [28] - Activin A - follistatin - TGF 1, 2, 3 - MMP 1, 2, 3, 8, 9, 13	fibrosis myocyte calcium signaling extracellular matrix remodeling	HF diabetes
4. Adipocytokines [28–33] - adiponectin - leptin - resistin - visfatin - omentin - FABP4	increased insulin sensitivity anti-inflammatory properties inflammation atherosclerosis negative inotropic effect	Obesity Metabolic syndrome
5. Inflammatory cytokines and chemokines [33–36] - IL-6-1β - IL-6 and IL-7 receptor - PAI-1 - TNF-α - monocyte chemotactic protein-1 - chemokine ligands - adrenomedullin - phospholipase A2	atherosclerosis vasodilator anti-inflammatory effects	Obesity CAD

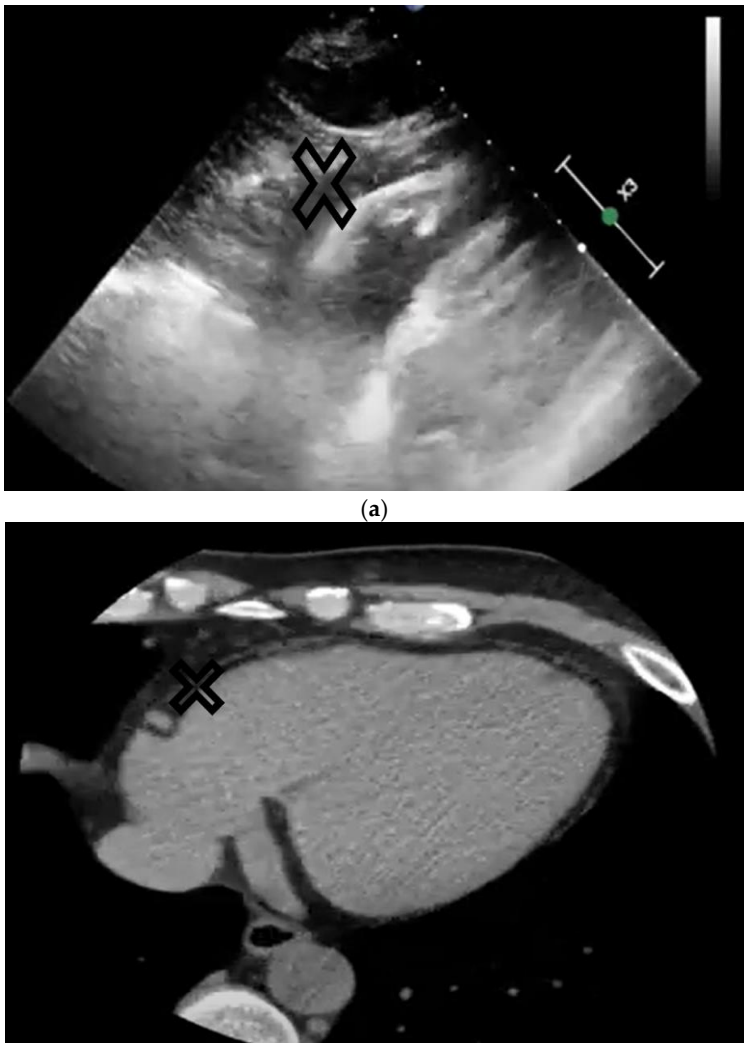
Monocyte chemotactic protein-1 (MCP 1), fatty acid-binding proteins (FABP4), coronary artery disease (CAD), tumor growth factor (TGF).

2.3. Adipose Tissue Diagnosis

Cardiac imaging such as echocardiography (TTE), computer tomography (CT), and magnetic resonance (MRI) are frequently used for describing cardiac fatty tissue, each one presenting advantages and disadvantages [37] (Table 2). Echocardiography allows the evaluation of adipose tissue based on thickness, is not expensive, and is widely spread. EAT is described as an echo-free and sometimes as an echo-dense space in patients with inflammation, between the myocardium and the visceral layer of the pericardium (Figure 3a). EAT is usually measured at end-systole, either in parasternal long- or short-axis view.

Conversely, CT and MRI allow volume, area, and thickness measurements, but are more expensive, and have radiation complications and obesity-related limitations. Cardiac CT allows high spatial and temporal resolution and 3-D cardiac views (Figure 3b). Several software programs allow a semi-automated quantification of the EAT dependent on the attenuation thresholds. Based on 3-D reconstruction, the EAT volume is calculated automatically. Cardiac MRI allows EAT measurements as well as focal EAT deposits and may provide data concerning intramyocardial adipose infiltration. When compared to cardiac CT, MRI has a decreased spatial resolution, but a higher soft tissue contrast, allowing

a precise delineation of the EAT from the other adipose layers. Overall, these imaging techniques improve the ability to localize fatty tissue deposits and infiltrations.



(**a**)

(**b**)

Figure 3. The upper image (**a**) represents a subxiphoid echo view of the heart, and the lower image (**b**) represents a CT view of the heart. The epicardial adipose tissue is marked on both images with X.

Table 2. Relationship between imaging measures of cardiac adipose tissue and VA.

Disease	Echocardiography	Cardiac CT	Cardiac MRI
ARVC		MAI is related to right ventricular (RV) dysfunction and the ventricular tachycardia substrate (conduction and repolarization disturbances) [38–40].	MAI is related to the severity of the right ventricular structural disease, impaired RV function, and impaired LV systolic function. LV fat infiltration is a predictor of ventricular arrhythmias such as VT or VF, and sudden cardiac death, and allows a reclassification of 5-year risk of events [41–45].

Table 2. *Cont.*

Disease	Echocardiography	Cardiac CT	Cardiac MRI
Myocardial infarction		MAI is correlated with scar age and size, as well as decreased amplitude of the bi and unipolar EGM, fragmented EGM, increased post-ablation VT recurrence, and all-cause mortality [46,47].	MAI is related to the size of the infarcted area, adverse LV remodeling, sustained VT, the number of HF hospitalizations, and all-causemortality [48].
Heart failure	EAT is a predictor of arrhythmic events such as VT or VF and AF [49].	In patients with dilated cardiomyopathy, MAI is associated with LV global function and the fibrosis volume [50].	
Other conditions	EAT is correlated with the burden of VPB and VPB ablation failure [51].		

Myocardial adipose infiltration—MAI; ventricular premature beats—VPB.

3. Ventricular Arrhythmias

Adipose tissue includes adipocytes, as well as pre-adipocytes, endothelial and stromal cells, macrophages, and lymphocytes. This type of population is responsible for releasing a variety of chemokines, cytokines, and other pro-inflammatory factors. These inflammatory settings create a substrate for arrhythmia development. Studies performed on coronary artery disease patients revealed increased levels of pro-inflammatory markers such as angiotensinogen, monocyte chemotactic protein (MCP1), IL1β, IL6, sIL6R, NFκB, and IKKβ when compared to the subcutaneous adipose tissue from the same individual [35,52]. EAT also exhibits a pro-fibrotic effect, as secretome analysis suggests through the detection of adipocytokines such as activin A, a member of the TGF-β family [28].

Studies also revealed contractile dysfunction, decreased insulin-mediated Akt Ser 473 phosphorylation, and enhanced SMAD 2 phosphorylation, suggesting that EAT can interfere with cardiomyocyte function and cardiac remodeling [29]. Also, there is an enhanced production of mitochondrial reactive oxygen species in the fatty tissue, which are promotors of inflammation. Meanwhile, oxidative stress plays a role in arrhythmia pathogenesis [52]. SERCA protein dysfunction leading to decreased or increased cytoplasmic calcium levels has also been related to arrhythmias [53].

The evidence concerning the link between EAT and ventricular arrhythmias is weak, but there is a strong correlation between adipose myocardial infiltration and cardiomyopathies. This group of patients presents localized or diffuse fibrosis, a pro-inflammatory status, and other comorbidities linked to arrhythmias. Studies have shown that intramyocardial fat is related to ventricular arrhythmias (VAs) in obese subjects or to some genetic disorders such as ARVC, myotonic dystrophy (MD), Fabry's disease, myocardial infarction, and heart failure [54].

For ARVC patients, the intramyocardial adipose burden is correlated with the level of RV dysfunction and the VT substrate [39]. Studies have shown that most of the local abnormal ventricular electrograms are located around the border of the RV adipose tissue, suggesting that superimposing the cardiac CT on the 3-D electroanatomic mapping may help to localize ablation targets. The evaluation of ARVC patients for LV infiltrations is

useful for predicting the risk of ventricular tachycardia or ventricular fibrillation, sudden cardiac death, or cardiac arrest, allowing a 5-year risk of events estimation [45].

Based on clinical and mapping/ablation studies, advances in understanding the arrhythmogenic process in ischemic heart disease have been noticed. Most ventricular arrhythmias in ischemic heart disease are initiated by a triggering premature ventricular beat (PVB), due to automaticity, particularly in acute ischemia episodes, micro reentry within the border zone, or triggered activity. Spontaneously occurring PVBs, couplets, and VT in patients with ischemic cardiomyopathy might be initiated and maintained by focal mechanisms without macro reentry evidence. The border zone plays a central role in arrhythmias perpetuation through the structural obstacles that induce conduction slowing and zig-zag conduction in the border zone, allowing the development of reentry circuits.

Acute myocardial ischemia and reperfusion involve metabolic, ionic, and neurohumoral mechanisms, causing mechanical and electrical complications, including cardiac death. Endocardial macro-reentry represents the main mechanism involved in the initiation and maintenance of VT, leading to VF during myocardial ischemia, usually involving multiple activation sites from or around the border region of the ischemic zone, although non-reentrant mechanisms originating from the subendocardium or subepicardium may also contribute.

Acute ischemia is responsible for opening the K(ATP) channels, leading to acidosis and hypoxia of myocardial cells and dispersion in repolarization across the border zone. Abnormalities of intracellular Ca2+ handling represent another possible cause of arrhythmias in patients with coronary artery disease. The substrate transforms triggers into VF and serves to perpetuate this through the fragmentation of waves in the ischemic zone.

The VF occurrence in myocardial ischemia is mainly caused by intramural reentry, mostly in the subendocardium and rarely in the subepicardium, with subsequent acceleration and then rapid recovery of excitability, causing conduction delay and an enhanced functional block. The ischemic substrate transforms triggers such as stretch, catecholamine, genetic predisposition, thrombin, etc. into VF and allows the maintenance of the fragmented waves in the ischemic area [55].

Data regarding patients with myocardial infarction show that intramyocardial adipose deposits are mostly located in the post-infarcted myocardium during lipomatous metaplasia [54]. Several studies performed in animals and humans have confirmed the association between this metaplasia and the electrophysiological changes in the myocardium [56], and with scar age and size, with low-amplitude intracardiac electrograms (both unipolar and bipolar) in ischemic cardiomyopathy patients, revealing this way the significant role of scarrelated VA in this setting [57]. Fragmented intracardiac electrograms seem to be more frequent in the areas with adipose tissue, especially in the subendocardial layer of the scar [47]. Data show that EAT is an independent predictor of VA recurrence and mortality post-ablation, suggesting the importance of this marker in risk stratification post-ventricular ablation [49].

Studies performed in patients with heart failure (HF) have revealed that LV hypertrophy, diastolic dysfunction, and mid or preserved ejection fraction HF are related to increased EAT [58]. The presence of EAT is associated with VA in patients with reduced ejection fraction HF. For patients with dilated cardiomyopathy, intramyocardial adipose tissue is related to LV global function and fibrosis volume, thus making intramyocardial adipose tissue a marker of the disease prognosis [50]. Data show that EAT is correlated with a prolonged QTc and an increased burden of ventricular ectopies, suggesting the arrhythmogenic potential of cardiac fatty tissue. Also, EAT thickness measured by echography was increased in patients with failed ventricular ectopy ablation [59]. Several studies did not re-

port a relationship between EAT and QTc interval [60], but rather withPR prolongation [61], P wave [62], and QT dispersion [63].

Some studies reveal a positive relationship between elevated EAT and VA burden, as well as the efficacy of VA ablation [64] and the recurrence after ablation [65], fragmented QRS, or increased QRS duration through the reentry mechanism [66]. The most frequent VA mechanism is represented by reentry, while triggered activity due to early or delayed afterdepolarizations might also be involved [67]. Structural, mechanical, or neurohormonal factors and ischemia may cause imbalances in the electrophysiological status, with enhanced automaticity through issues with conduction and refractoriness [68].

4. Genetics and Adipose Tissue

In a study performed by Ramo et al. (2023) [69], with more than 44 000 Biobank UK participants included, pericardial adipose tissue was positively correlated with male sex, age, and BMI. 5 novel genetic loci for pericardial adipose tissue were identified near *CDCA2, C5orf67/ANKRD55, WARS2, IP6K1*, and *PEPD*, as well as two previously reported foci near *TRIB2* and *EBF1*. This study detected a link between pericardial adipose tissue and coronary artery disease, as well as atrial fibrillation. To detect the causal genes in the seven associated loci, the Polygenic Priority Score (PoPs) was used. Transcriptional regulators of adipocyte morphology and brown adipogenesis, such as *EBF1, EBF2*, and *CEBPA*, as well as regulators of visceral adiposity (*WARS2* and *TRIB2*) were prioritized by the PoPS, in this way sharing determinants with abdominal adiposity.

Another study published by Sousa et al. [70] included 996 participants who were prospectively enrolled. The epicardial adipose tissue was evaluated by cardiac CT and, based on the genotyped and linked SNPs, a multiplicative genetic risk score (mGRS) was created. This study revealed the fact the subjects with above-median EAT were older and presented a higher BMI as well as other cardiac risk factors such as hypertension, diabetes, hypercholesterolemia, and metabolic syndrome. This higher EAT was also associated with a higher GRS, and this was considered an independent predictor of higher EAT volumes. Among the 33 variants, only 1 was strongly associated with EAT volume, but only in the univariate analysis, *rs1333049 (CDKN2B-AS1*) at the *9p21* locus. The variant *rs1801133* of *MTHFR677* was significantly and independently associated with an EAT volume above the median. This gene variant is involved in regulating plasma homocysteine levels.

The Sousa study revealed an increased number of different mutations linked to EAT volume compared to the studies previously published so far. Most of the previous studies evaluated the expression of the EAT genes on in vivo samples from patients undergoing CABG surgery, resulting in a limited number of participants [71]. Another study including coronary artery disease patients was published by Vacca et al. [72], and revealed the role of miRNA in the crosstalk between EAT and the coronary arteries. M-RNAs are small non–coding RNAs modulating gene expression. The study published by Tan et al. [73] showed that pro-inflammatory and immunological genes are upregulated in EAT coronary artery disease patients and play an important role in the coronary atherosclerosis process.

Data regarding the impact between sex and EAT volume are still under debate. Some studies have shown increased EAT volume in females [74] and some in men [75].

5. Correlation Between Genetics, Adipose Infiltration, and Cardiac Diseases

It seems that ARVC and myotonic dystrophy are correlated with fatty infiltration and VA [16]. This observation supports the involvement of fatty tissue in the pathogenesis of cardiac arrhythmias.

Up to 30% of patients diagnosed with myotonic dystrophy type 1 develop cardiac complications, related to the number of CTG repeats [76]. Usually, conduction disturbances are most frequent, but ventricular arrhythmias and ventricular systolic dysfunction are also reported. Three-dimensional mapping in patients with DM1 revealed low-voltage areas spread around both the right atria and ventricle [77], while myocardial biopsies showed extensive fibrosis, adipose deposits, inflammation, and myocardial hypertrophy [78].

ARVC represents an inherited cardiomyopathy with autosomal transmission and low penetrance, based on RV enlargement and dysfunction, fibro-fatty replacement of myocytes in the right ventricle, ECG abnormalities, and arrhythmias originating from the RV. Adipose infiltrations are correlated with advanced right ventricular structural disease in patients associated with the highest arrhythmic risk [41].

Almost 50% of the symptomatic patients present a mutation in one of the five major components of the cardiac desmosome [79], comprising *PKP2* (*encoding plakophilin-2*), *DSP* (*encoding desmoplakin*), *DSC2* (*encoding desmocollin-2*), *DSG2* (*encoding desmoglein-2*), and *JUP* (*encoding junctional plakoglobin*). Genetic testing is advised for patients with ARVC or ARVD as well as their family members. In cases where the affected individual (proband) with ARVC or ARVD does not present a genetic defect, it will not be present in other family members [59].

Fabry disease represents a X-linked lysosomal storage disease caused by reduced activity of alpha-galactosidase A, leading to lysosomal accumulations of neutral glycosphingolipids and globotriaosylceramide GL-3. Studies have identified hundreds of mutations involved in Fabry disease. Milder types associated with missense mutation are linked to cardiac involvement [80,81]. Ventricular tachycardia and ventricular fibrillation are the most frequent VAs described in Fabry disease. The prevalence of these arrhythmias is between 13 and 18% [82]. α-GAL A deficiency together with the accumulation of glycosphingolipid interferes with the expression of sodium and calcium ion channels, modifying in this way the cellular electrophysiological properties, which are responsible for Fabry disease-related VAs [83].

In the study performed by Sahasrabuddhe [84], 43 patients undergoing cardiac surgery were included, 27 patients for coronary artery bypass graft (CABG) and 16 for valvular surgery. After analyzing the gene expression obtained from the EAT samples, they observed an upregulation and higher expression of pro-inflammatory chemokines such as monocyte chemoattractant protein-1 (MCP-1), vascular cell adhesion molecule-1 (VCAM-1), and tumor necrosis factor-alpha (TNF-α) for the CABG group compared to non-CABG group, as was observed in other studies [35,85,86]. Downregulation was noted for anti-inflammatory chemokines such as uncoupling protein-1, adiponectin, and the adenosine A1 receptor (ADORA-1) [87,88]. In this way, EAT might be involved in the development of coronary artery diseases.

MCP-1 is responsible for macrophage infiltration infatty tissue, as described in previous studies. A higher expression of MCP-1 from epicardial fatty tissue when compared to subcutaneous fatty tissue and omental fat was observed in several studies [89,90]. EBF1 is involved in the regulation of the adipose cell morphology and lipolysis process [91], and decreased levels of *EBF1* are associated with white adipose tissue hypertrophy. Meanwhile, *EBF2* is involved in brown-like/beige adipose cell differentiation [92]. *CEBPA* encodes the transcription factor CCAAT/enhancer binding protein alpha (C/EBPα). The last one shares binding sites with Peroxisome proliferator-activated receptor gamma (*PPARγ*) and acts as a co-stimulator of adipogenesis and adipocyte differentiation. *TRIB2* is a promoter of CCAAT/enhancer binding protein beta, which transactivates the expression of both *C/EBPα* and *PPARγ* [93], whereas *WARS2* is responsible for encoding mitochondrial tryptophan-tRNA synthetase [94].

A total of 41 studies were evaluated in the literature review, but only 23 were considered relevant and included in this review (Table 3).

Table 3. Studies from the literature regarding patients with cardiac diseases and the histopathologic and genetic observations.

Study	
Nguyen et al., 1988 [78]	Patients: 12 patients with DM1, Histopathologic observations: Fibrosis, fatty infiltration, and atrophy. General observations Adipose infiltration was noticed in the ventricular myocardium (9), the sinus node (2), the AV node (2), the AV bundle (6), and in bundle branches (1). The size and the location of the conduction system lesions correspond to the ECG abnormalities, such as prolonged PR interval, intraventricular conduction delay, and bundle branch block. Cardiac involvement by MD might have contributed to sudden death in 4 cases.
Ahmad et al., 1988 [95]	Patients: >200 members with ARVD. Genetic observations: Genetic linkage excluded previously reported loci for ARVD, but detected a novel locus at 3p23. The haplotype analysis detected a common region between markers D3S3610 and D3S3659 of 9.3 cM.
Melberg et al., 1999 [96]	Patients: 27 ARVC patients. Genetic observations: 4 marker loci, D10S201, D10S2327, D10S1752, and D10S1432, were linked with ARVC.
Nava et al., 2000 [97]	Patients: 37 ARVC families. Histopathologic observations: ARVC was diagnosed at autopsy in 19 families or endomyocardial biopsy in 18 families. Genetic observations: In the linkage analysis, chromosomes 14q23-q24, 1q42-q43, and 2q32.1-q32.3 were detected. For 4 families, no linkage to known genes was observed, and for 10 families, no relevant results were detected.
Mckoy et al., 2000 [98]	Patients: 19 individuals with Naxos disease. Genetic observations: A homozygous 2-base-pair deletion of the plakoglobin gene was detected.
Protonotarius et al., 2001 [99]	Patients: 12 families with Naxos disease. Genetic observations: The analysis showed 28 homozygous and 40 heterozygous for the mutation. All homozygous adult patients (26) fulfilled the criteria of ARVC diagnosis, with the youngest at the age of 13. Genetic observations: In 8 heterozygous patients, minor ECG and/or echo abnormalities were detected. Among the 26 homozygotes patients, 92% presented ECG abnormalities, 92% presented ventricular arrhythmias, and all patients had RV structural alterations, but only 27% LV impairment.
Iacobellis et al., 2005 [100]	Patients: 16 patients undergoing CABG, 5 valvular diseases, 1 AD. Histopathologic observations: Adiponectin protein value, from the epicardial adipose tissue, was significantly decreased in patients with severe coronary artery disease compared to those without.
Dalal et al., 2005 [101]	SPatients: 100 patients diagnosed with ARVD. Histopathologic observations: Adipose infiltration of the RV with strands of cardiomyocytes was detected at the biopsy in 12 patients and at autopsy for 17 patients.
Den Haan et al., 2005 [102]	Patients: 82 patients with ARVD/C and 18 with suspected ARVD/C. Genetic observations: 52% presented a desmosome mutation, especially in PKP2. N 3 patients presented a mutation in more than 1 gene. A mutation was observed in 5 of 18 patients (28%).
Dello Russo et al., 2006 [77]	Patients: 13 DM1 patients. Genetic observations: A strong relationship was observed between CTG triplets and the percentage of Bi-v <0.5 mV in the atrial myocardium. General observations: The amplitude of the unipolar voltage (UNI-v) and bipolar voltage (BI-v), the bipolar potential duration, and the atrial propagation time were evaluated. UNI-v and BI-v in the inter-atrial septum, anterolateral atrial wall, and RV outflow tract were lower in MD1 patients compared to controls.

Table 3. *Cont.*

Study	
Kirchhof et al., 2006 [103]	Patients: 10-month-old plakoglobin-deficient mice. Genetic observations: Heterozygous plakoglobin deficiency is involved in ARVC. The manifestation of this phenotype is accelerated by endurance training, suggesting a functional role for plakoglobin and training in the development of ARVC.
Merner et al., 2008 [104]	Patients: 15 unrelated ARVC families with a disease-associated haplotype on chromosome 3p (ARVD 5). Genetic observations: The function of the TMEM43 gene contains a response element for PPAR gamma, which may explain the fibro-adipose replacement of the myocardium. General observations: ARVC at locus ARVD 5 is a fully penetrant, sex-influenced morbid disturbance.
Christensen et al., 2008 [105]	Patients: Dystrophia myotonica 1 (1 patient). Histopathologic observations: Fibro-fatty replacement. Genetic observations: Increased number of CTG repeats in the DM protein kinase gene.
Otten et al., 2010 [106]	Study: Patients: 2 families with 2 DES mutations. One family developed biventricular cardiomyopathy and for the other one, DRM with an ARVC(-like) phenotype was diagnosed in one patient. Genetic observations: DES mutations such as p.N342D and p.R454 were detected. Immunohistochemistry revealed desmin aggregates and a decreased amount of desmoplakin and plakophilin-2 in p.R454W mutation carriers.
Klauke et al., 2010 [107]	Patients: 22 ARVC patients. Genetic observations: In 43% of patients, disease-associated sequence variants such as JUP, DSG2, DSC2, DSP, PKP2 were detected. A desmin mutation p.N116S in one ARVC patient with ARVC and terminal heart failure was identified and located in segment 1A of the desmin rod domain.
Hedberg et al., 2012 [108]	Patients: 17 patients from an ARVC family. Genetic observations: Sanger sequencing detected the heterozygous *DES* mutation c.1255C>T, p. Pro 419Ser in exon 7 on chromosome 2 in 7 patients. The locus of ARVC 7 was detected in the *DES* on chromosome 2q35.
Jacob et al., 2012 [109]	Patients: 28 studies on the prevalence of mutations in desmosomal protein-encoding genes. Genetic observations: Mutations in PKP2 are the most frequent. Mutation prevalence in DSP, DSG2, and DSC2 varies among the geographic zones. Mutations in JUP are rarely detected, being more frequent in Denmark, Greece, and Cyprus.
Chen et al., 2014 [110]	Patients: Both AC patients and mouse AC models. Genetic observations: Anomalies in the expression of desmosomal proteins and the signaling pathway.
Samanta et al., 2016 [111]	Genetic observations: Remodeling of the gap junctional Connexin 43 channels in the scar area of myocytes.
Deshpande et al., 2016 [112]	Patients: 16 ARVC/D pediatric patients. Histopathologic observations: 6 autopsies, 6 explanted hearts, and 3 biopsies revealed massive fibro-fatty infiltration in the RV. Genetic observations: Two patients presented mutations previously reported and only one had a novel mutation of a known ARVC/D gene.
Sen-Chowdhry et al., 2016 [113]	Patients: ARVC. Histopathologic observations: Myocyte loss, inflammation, and fibro-adiposis were observed. Genetic observations: 40% of cases presented rare variants in genes encoding desmosome components. General observations: The desmosome components involved in the intercellular junctions are responsible for cardiac mechanical strength, and may also participate in signaling networks.
Sahasrabuddhe et al., 2020 [84]	Patients: Ischemic cardiomyopathy (27), valvular diseases (16). Histopathologic observations: Adiponectin showed downregulation in CABG patients. Genetic observations: *MCP-1*, *VCAM-1*, and, *TNF-α* are upregulated in the CABG group.

6. Future Directions

EAT volume is the result of a complex interaction between environmental, genetic, and epigenetic factors, which we started to uncover. Furthermore, EAT represents more than fat deposits: it represents a biologically active structure and an association between obesity and cardiovascular diseases.

EAT has attracted special interest lately as an important player in the pathophysiology of cardiovascular disease and is considered a risk factor for the atherosclerotic process. More important seems to be the earlier identification of the disease and its complications at a subclinical stage, preventing further progression. Many loci associated with adipose tissue are a targeted subset of drivers of unhealthy adiposity, unlike many loci linked with BMI which may exert their effects via neuronal pathways and hunger regulation [114]. Even though EAT can be a risk factor for the beginning of atherosclerotic development, its usefulness could lie in the detection of the disease at a subclinical stage, preventing future progression through preventive and even therapeutic measures.

It is well known that EAT is a source of free fatty acids, adipokines, and cytokines. In the presence of various inflammatory disorders, EAT participates in the atherosclerosis process, as well as myocardial fibrosis, and then contributes to arrhythmias and heart failure development. The relationship between adipose tissue and arrhythmia is not strictly related to obesity, but to the activation of multiple pathways, so for treating this matter, there is a need for a multidisciplinary approach including weight reduction, risk factors, and lifestyle modification. Investigating all the pro-arrhythmogenic mechanisms enhanced by obesity requires further research, as arrhythmias are multifactorial. In this regard, possible targets that need to be investigated to prevent or treat arrhythmias are EAT activity, mitochondrial reactive oxygen species, TGF- β 1, and SERCA proteins.

Beyond its utility as a flexible and modifiable risk marker, epicardial adipose tissue is also a therapeutic target for preventing atherosclerotic plaque growth and cardiovascular events. Despite the positive effects of lifestyle modification and bariatric surgery on EAT, there are no specific pharmacological drugs developed for EAT reduction. High-dose statin therapy seems to have a positive dose-dependent effect on EAT lowering. Studies performed with pro-protein convertase subtilisin/kexin 9 (PSCK9) inhibitors revealed reduction in EAT [115].

Glucose-lowering drugs, such as SGLT2 inhibitors and GLP-1 RA, exhibit cardioprotective effects and can target both atrial and coronary EAT for the treatment and prevention of AF and coronary artery disease by lowering EAT inflammation and increasing free fatty acid oxidation. GLP-1 receptor agonists are a type of glucose-lowering drug that lowers HbA1c, and modestly improves blood lipids and body weight while decreasing the risk of hypoglycemia by stimulating insulin secretion and lowering glucagon secretion, delaying gastric emptying, and reducing appetite [116]. Studies involving GLP1 RA showed the positive effect of this drug in reducing cardiovascular mortality, non-fatal stroke, and non-fatal myocardial infarction [117]. Preclinical studies revealed that GLP1 RA can reduce atrial fibrosis and atrial arrhythmias in rat models with myocardial infarction [118], as well as reduce the risk of development of ventricular arrhythmias after myocardial ischemia, the incidence of VF, and the number of VT and VF episodes [119]. The presence of GLP 1 receptors in the ventricular myocardium is still a matter of debate, as well as the effects of GLP-1RAs on arrhythmia development. The studies showed either no effects [120], or reduced risk for atrial arrhythmias [121], or efficient opposing of the β-adrenoceptor stimulation, thus reducing ventricular arrhythmic potential [122]. These results seem to be mediated through the release of acetylcholine and NO from the cardiac vagal neurons [123].

7. Conclusions

There is variability in the strength of the causative relationship between EAT and VA, mainly caused by the different populations studied, the different disease stages and adipose tissue locations (atrial, ventricular, and vascular), and the indexes used, such as volume and thickness. Research is needed to evaluate the connection between adipose tissue and arrhythmias, as various factors such as oxidative stress, autonomic tone, autophagy, variability of adipose tissue deposits, propagation of abnormal signals, development of reentry circuits, and myocyte death are involved. Next, possible therapeutic targets can be investigated.

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