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Review



# Epicardial Adipose Tissue and Cardiac Arrhythmias

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Obesity is associated with an increased risk of atrial and ventricular arrhythmias, including life-threatening ones. Epicardial adipose tissue (EAT) is located deep under the visceral pericardium (epicardium) and is therefore in direct contact with the underlying myocardium. In pathological conditions, EAT undergoes a phenotypic transition from a “neighbor” with protective properties to a substrate that secretes many substances that change the electrophysiology of cardiomyocytes by modulating ion currents that disrupt intercellular electrical connections and stimulate fibrosis. An excess of EAT can cause atrial and ventricular conduction disturbances, which are already evident with standard electrocardiography, predispose to the occurrence of the re-entry phenomenon and cardiac arrhythmias. Among the mechanisms of arrhythmogenesis under the influence of EAT, modulation of ion channels and gap junctions, fibrous remodeling and fatty infiltration are more often considered. However, most of these mechanisms have been studied in experimental studies and cannot easily be extrapolated to humans. There is convincing evidence of a direct relationship between EAT volume and the severity of atrial fibrillation, as well as the clinical benefit obtained from weight loss in patients with this arrhythmia. It is likely that the benefits of weight loss may extend to ventricular arrhythmias.

**Keywords:** obesity; epicardial adipose tissue; cardiac arrhythmias; inflammation.

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Обзорная статья

## Эпикардиальная жировая ткань и аритмии сердца

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Ожирение связано с повышенным риском предсердных и желудочковых аритмий, в том числе угрожающих жизни. Эпикардиальная жировая ткань (ЭЖТ) локализуется глубоко под висцеральным перикардом (эпикардом) и, следовательно, находится в непосредственном контакте с нижележащим миокардом. При патологических состояниях ЭЖТ претерпевает фенотипический переход от «соседа» с защитными свойствами к субстрату, секретирующему множество веществ, которые изменяют электрофизиологию кардиомиоцитов путем модуляции ионных токов, нарушающих межклеточные электрические связи пациентов стимулирующих фиброз. Избыток ЭЖТ способен вызывать нарушения предсердной и желудочковой проводимости, которые очевидны уже при стандартной электрокардиографии, предрасполагать к возникновению феномена re-entry и аритмиям сердца. Среди механизмов аритмогенеза под влиянием ЭЖТ чаще рассматриваются модуляция ионных каналов и щелевых контактов, фиброзное ремоделирование и жировая инфильтрация. Однако большинство этих механизмов изучены в экспериментальных исследованиях и не могут быть легко экстраполированы на человека. Убедительно доказана прямая связь между объемом ЭЖТ и тяжестью течения фибрилляции предсердий, а также клиническая выгода, получаемая при снижении массы тела у пациентов с этой аритмией. Вполне вероятно, что польза от потери веса может распространяться и на желудочковые аритмии.

**Ключевые слова:** ожирение; эпикардиальная жировая ткань; аритмии сердца; воспаление.

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## BACKGROUND

The prevalence of obesity and the number of associated diseases are increasing worldwide [1, 2]. More than 650 million obese people on our planet (body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>) [3], according to the World Health Organization, are associated with an increased risk of type 2 diabetes mellitus, cardiovascular and oncological diseases, chronic kidney disease, pathology of the musculoskeletal system, and infections, resulting in a 1.3-fold increase in the probability of early death compared with people with normal weight [4]. In the human body, white, brown, and beige adipose tissues are extensive, and they perform important physiological functions [5]. BMI higher than 25 kg/m<sup>2</sup> is associated with a higher risk of sudden cardiac death [6] and atrial fibrillation (AF) [7]. In addition, high BMI and obesity correlate with QTc prolongation and QRS complex duration [8], which are independent risk factors for cardiac arrhythmias. Therefore, obesity may be significant in causing life-threatening cardiac arrhythmias.

Visceral adipose tissue tends to accumulate in the abdominal cavity around the internal organs and the heart [9]. BMI and the volume of visceral, including epicardial adipose tissue (EAT), have a significant relationship [10]. Due to its proximity to the heart, EAT is considered to have a potential proarrhythmic effect [11]. The volume of EAT is directly related to the occurrence, duration, and recurrence of AF [12]. In addition, the EAT volume on free ventricle walls correlates with the incidence of ventricular extrasystole [13], and the volume of fat surrounding the parietal pericardium and EAT is directly related with the development of ventricular tachyarrhythmia in patients with cardiac failure [14]. Despite an increasing number of publications on the effect of EAT on the risk of cardiac arrhythmias, its electrophysiological mechanisms are still unspecified.

This study aimed to summarize the literature data on the proposed mechanisms of EAT arrhythmogenicity to determine guidelines for its correction in clinical practice. In the furtherance of this aim, a search and analysis of literary sources in English and Russian languages were performed in the MEDLINE/PubMed database for the keywords “epicardial adipose tissue”, “epicardial fat”, “electrophysiological remodeling”, “cardiac arrhythmias”, as well as in the eLIBRARY database for keywords “epicardial adipose tissue” and “cardiac arrhythmias”. The filters “clinical trial”, “meta-analysis”, “randomized controlled trial”, “review”, “systematic review”, and “10 yr” were used. For inclusion in the review, studies of any design, presenting modern outlooks of the relationship between EAT and cardiac arrhythmias, were considered. When choosing publications, full-text articles in peer-reviewed journals with a high impact factor were preferable. After screening 260 literature sources, 124 of the most significant full-text articles were selected and analyzed, and 91 most cited ones of them were included in the review.

## Epicardial adipose tissue: From physiology to pathology

There are three types of adipose tissue: white, brown, and beige. White adipose tissue is extensive throughout the body in the form of subcutaneous or visceral fat. Its main function is an energy storage site, and adipocytes consist of individual lipid droplets of triglycerides, which impart the characteristic yellow color to the tissue, with minimal space for mitochondria [15]. In addition, white adipose tissue secretes a number of hormones, cytokines, complement, and growth factors with both endocrine and paracrine activity that affect adjacent and distant tissues [16]. In relation to white adipose tissue, brown adipose tissue dissipates energy through thermogenesis and is found in the cervical, supraclavicular, axillary, paravertebral, mediastinal regions, and upper abdomen, and is antagonistic [15, 17]. Based on its function, brown adipose tissue is characterized by an abundance of mitochondria, which imparts a brown tint to adipocytes, and triglycerides are stored there in the form of small vacuoles. Brown adipose tissue also has a denser network of vascular microcirculation and sympathetic innervation due to a greater need for oxygen and the need to respond to thermogenesis [15]. Beige adipose tissue is an intermediate phenotype that has the functions of white and brown adipose tissues; it regulates energy balance and thermogenesis [18].

EAT represents a depot of white visceral fat that uniquely exhibits the characteristics of beige adipose tissue. Due to the absence of a fascial boundary, EAT is localized deep under the visceral pericardium (epicardium) and thus in direct contact with the underlying myocardium. EAT is mainly localized along the atrioventricular and interventricular sulci, circumflex artery, and left anterior descending coronary artery, around the atria, and is located in the right ventricle, as well as free wall and apex of the left ventricle [19]. EAT can cover up to 80% of the heart surface and reach 20% of the entire cardiac mass.

EAT protects the myocardium and coronary arteries from mechanical influences because of its elasticity and compressibility. Unlike other fat depots, EAT has an extraordinarily high rate of lipogenesis and lipolysis, functions as a local energy store of free fatty acids (FFAs) and a buffer against the lipotoxic effects of their excess [5, 20]. EAT also functions as an endocrine organ that secretes a number of adipokines [21], is a source of catecholamine biosynthesis, including noradrenaline [22], modulates the proliferation and contractility of vascular wall smooth muscle, and has antiapoptotic and antioxidant effects [5, 20].

The release of FFA from EAT adipocytes into plasma can take place locally and be a rapidly mobilized source of energy supply to the heart given the proximity between EAT and cardiomyocytes. Although mitochondrial FFA oxidation represents 60%–90% of the metabolic substrate of cardiomyocytes, lipid overload is toxic [23]. If the absorption of FFA by cardiomyocytes exceeds the oxidative capacity

of mitochondria, toxic lipids accumulate, which leads to mitochondrial and endoplasmic reticulum dysfunction, dysregulation of calcium movement, and increased production of reactive oxygen species [24]. The resulting calcium overload of the cytosol and spontaneous calcium release are significant in arrhythmogenesis through late post-depolarization and trigger activity [25]. Reactive oxygen species induce early post-depolarization, facilitate the onset of ventricular arrhythmias in rats, and alter the electrical connection between cardiomyocytes, leading potentially to conduction delay and increased risk of arrhythmias [26].

FFAs can be stored in the form of myocardial cytosolic lipid droplets [24], which can serve as an energy reservoir and prevent lipotoxicity. They can also be used to perform lipid signaling functions and to construct membranes [27]. However, this might result in an excessive production of reactive oxygen species and contribute to arrhythmia when the capacity of lipid droplets in cells is exhausted or their function is impaired [28].

The anatomical proximity of EAT to the myocardium and their common blood supply from the coronary arteries have induced scientific interest and promoted research with accumulating evidence of the paracrine role of EAT in the development of cardiovascular diseases.

### **Inflammation and products of secretion of epicardial adipose tissue**

EAT undergoes a phenotypic transition from a “neighbor” with protective properties to an inflammatory substrate in pathological conditions. For example, a higher pro-inflammatory activity of EAT was noted in patients with coronary heart disease than in people without it [29]. Matrix ribonucleic acid expression is activated. Levels of pro-inflammatory cytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), and monocyte chemotactic protein-1 are increased, while the formation of anti-inflammatory adiponectin is suppressed [30]. In type 2 diabetes mellitus, there was also a shift toward pro-inflammatory secretome (i.e., all secretion products) of EAT, as well as decreased levels of adiponectin, and increased cell expression of Monocyte Chemotactic Protein 1 and CD68+ compared with people without diabetes [31]. Pharmacotherapy of coronary heart disease and type 2 diabetes mellitus has been shown to contribute to the regression of the inflammatory phenotype of EAT, a less inflammatory profile of its secretome [32, 33].

The cause-and-effect relationships of the processes documented remain controversial despite the evidence for the transition of EAT to a pro-inflammatory state in cardiometabolic disorders and its reversibility with pharmacotherapy. EAT is known to significantly differ from subcutaneous adipose tissue in its pronounced pro-inflammatory profile, in particular higher concentrations of matrix ribonucleic acid, levels of IL-1b, IL-6 and TNF- $\alpha$ , leptin, resistin, CD45, macrophages, mast cells and T lymphocytes, and so forth, as well as a drastically reduced

level of adiponectin [34]. Meanwhile, the inflammatory nature of EAT has a genetic basis, being detected in overweight and obese people, regardless of the presence of cardiovascular diseases [35].

### **Obesity, epicardial adipose tissue, and risk of cardiac arrhythmias**

Obesity is characterized by excessive fat deposition and represents a chronic, mild, systemic pro-inflammatory condition. Hypertrophy of adipocytes with an increase in the volume of adipose tissue creates a hypoxic environment and induces genetic mutations, which leads to an increase in levels of pro-inflammatory mediators and a decrease in anti-inflammatory mediators, respectively [36]. Obesity is associated with an increased risk of atrial and ventricular arrhythmias [37], similar to another pathology that is characterized by a pro-inflammatory condition. For example, compared with people with normal BMI values (18.5–24.9 kg/m<sup>2</sup>), the risk of AF can be increased by 65% in people with a BMI higher than 30 kg/m<sup>2</sup>, corresponding to a 4% increased risk for each unit of BMI gain. This predisposition to AF may be due to electrophysiological remodeling caused by an increase in atrial volume, conduction disorders, and an increase in the expression of profibrotic mediators that contribute to the formation of an arrhythmogenic substrate [38]. Such changes are reversible with weight loss, as shown in a model of obese sheep, where a 30% weight loss reduced atrial pressure and fibrosis, while also improving conductivity by means of increase in connexin expression [39]. In addition to systemic obesity, it was revealed that electrical and structural remodeling is modulated by localized obesity, resulting in the most pronounced pathological changes in areas adjacent to EAT, which was associated with arrhythmogenesis [38].

Taking into consideration that EAT is a metabolically active depot in direct contact with the myocardium, several variants of its connection with arrhythmogenesis are suggested. G. Thanassoulis et al. [40] demonstrated in the Framingham Heart study that the risk of AF increased with an increase in pericardial fat volume. The mass of epicardial fat, determined using computed tomography, was significantly higher in patients with paroxysmal AF compared with examined patients with sinus rhythm [41]. The volume of pericardial fat correlates with the severity of AF; in persistent AF, it is significantly higher than in paroxysmal AF [42]. According to a meta-analysis of 63 observational studies involving 352.275 participants, an increase in EAT volume was associated with a predominantly increased risk of persistent AF rather than paroxysmal AF. In addition, EAT volume was a better predictor of AF risk than other indicators of obesity, such as BMI, body surface area, waist circumference, waist-to-hip ratio, as well as intrathoracic fat and abdominal fat volumes [43]. EAT is an independent predictor of AF recurrence after catheter ablation [44]. In patients with recurrent AF, EAT volume and serum C-reactive protein levels are directly correlated, suggesting

inflammation as a mediator between EAT and arrhythmic risk [45]. These data confirm that adipose tissue, being in direct contact with the myocardium, contributes to the development of the arrhythmia substrate, possibly through paracrine mechanisms.

There is inconsistent data linking EAT volume to ventricular arrhythmias. Thus, EAT thickness has been reported to correlate directly with the frequency of ventricular extrasystoles [46] and is a prognostic factor for significant prolongation of the QT interval (> 450 ms), the risk of ventricular tachycardia or ventricular fibrillation in heart failure, and relapse of ventricular tachycardia after ablation [8, 47, 48]. However, other authors have not noted a relationship between EAT volume and QTc interval duration [49] and have reported that EAT thickness correlates better with increased PR interval [50] and P wave length, but not with QT variance [51].

### **Electrophysiological changes induced by epicardial adipose tissue**

Traditionally, abnormal generation and abnormal conduction of an electrical impulse are considered as mechanisms of cardiac arrhythmias. Abnormalities in the generation of impulses are due to pacemaker and trigger activity, with the latter depending on the action potential duration (APD) or an increase in the concentration of  $\text{Ca}^{2+}$  ions in the cytosol due to exit from the sarcoplasmic reticulum. Impulse conduction abnormalities can result in anatomically or functionally determined re-entry cardiac arrhythmias. The basis for unidirectional block and re-entry is provided by the spatial heterogeneity of repolarization timing. The standard surface electrocardiogram contains information about APD, automatic behavior, and delay in conduction and, therefore, can provide mechanistic information about arrhythmogenesis in the most accessible way.

An increase in the P wave duration on the electrocardiogram indicates atrial conduction delay. The volume of EAT correlates positively with the P wave duration and atrial conduction delay [52]. At the same time, in patients with morbid obesity, the increase in the P wave duration indicates at least partially the atrial dilatation [53]. The P wave dispersion is determined as the difference between the maximum and minimum duration in several superficial leads of the electrocardiogram. It serves as a marker for anatomical remodeling and heterogeneous distribution of atrial activation. In healthy individuals, P wave dispersion is associated with EAT thickness [54]. The degree of infiltration of the interatrial septum with adipose tissue is independently related to the number of P wave fragmentations (a marker of heterogeneous conduction) in patients with paroxysmal AF and people at risk of developing this arrhythmia [55]. Overall, this demonstrates an association between infiltration of interatrial septum with adipose tissue and atrial conduction delay and discontinuity.

The P-R interval is the total time required to conduct impulses through the right atrium, atrio-ventricular node,

bundle of His, and its branches. After adjusting for the effects of variables, EAT volume correlates linearly with longer P-R interval [52]. It has been revealed that in examined patients with the highest EAT volume, the P-R interval duration is 10–16 ms longer than in people with the lowest EAT volume [56]. According to observational studies, an association between P-R interval prolongation and increased incidence of AF, heart failure, and mortality [57]. Since the P-R interval includes conduction through various structures, it is not clear whether EAT affects the conduction velocity in each of them or whether there is an area of its preferential effect.

An increase in the duration of the QRS complex may be caused by myocardial hypertrophy or a delay in intraventricular conduction. A study with the participation of 3,087 healthy subjects revealed that EAT volume was directly related to longer QRS complex duration after adjusting for several variables [56]. In addition, the presence of a fragmented QRS complex was associated with an increase in the volume of EAT both in healthy people and in patients with arterial hypertension [58, 59]. Inhomogeneous anisotropic ventricular conduction may be the root cause of ventricular re-entry arrhythmias.

The QT interval, which indicates the time required for ventricular depolarization and repolarization, is usually corrected (corrected QT interval, QTc) using the H.C. Bazett's equation taking into account heart rate. Significant prolongation of the QTc interval can cause ventricular tachyarrhythmias, such as torsades de pointes [60]. There have only been a few studies on the relationship between EAT volume and QT interval and its variance, and their results are unpersuasive [52, 54]. Therefore, the relationship between EAT and ventricular repolarization remains unclear.

The heterogeneity of ventricular repolarization is shown by changes in the shape or duration of the T wave. A longer time interval between the peak and the end of the T wave indicates the repolarization heterogeneity, is a predictor of the risk of sudden cardiac death and death from all causes [61]. In an observational study, this interval increased in subjects with higher EAT volumes. In this study, high EAT volume was associated with increased QT interval dispersion, which indicated increased repolarization heterogeneity [62], as well as the risk of ventricular re-entry arrhythmias and sudden cardiac death.

### **Possible mechanisms of arrhythmogenesis under the influence of epicardial adipose tissue on the heart**

#### *Ion-channel modulation*

Local and systemic inflammation can induce a proarrhythmic substrate in the heart by modulating ion channels mediated by cytokines IL-1b, TNF- $\alpha$ , and IL-6, which are actively secreted by EAT [63]. As a result, an increase in the current of  $\text{Ca}^{2+}$  ions with a decrease in their concentration in the sarcoplasmic reticulum, a decrease in the current of  $\text{K}^{+}$  ions lengthen the APD, increase the tendency

to spontaneous diastolic depolarization and trigger activity, as well as a functional block of conduction [64]. However, most of the evidence for cytokine-mediated modulation of ion channels was obtained in experiments in mice. Although the currents of Na<sup>+</sup> and K<sup>+</sup> ions that promote rapid depolarization (phase 0) and the resting membrane potential (phase 4) are similar in mice and humans, the current of Ca<sup>2+</sup> ions in mice is much weaker, which leads to the almost complete absence of the plateau phase (phase 2) [65], and repolarization is differently regulated by currents of K<sup>+</sup> ions. This means that the effect of EAT on the function of ion channels that has been established in experiments cannot be extrapolated to humans. FFAs secreted by EAT are also capable of exerting an arrhythmogenic effect on the myocardium through direct modulation of APD and predisposing to late post-depolarizations. However, reports on the direction of such an effect are contradictory [34, 66]. Cytokines and FFAs derived from EAT prolong APD, facilitate re-entry and late post-depolarizations, probably contributing to the spatial heterogeneity of repolarization, but these concepts require further confirmation.

#### *Gap junction modulation*

Specialized cell surface structures, known as gap junctions, guarantee the direct transfer of ions and small molecules between adjacent cells. Gap junctions between myocardial cells also provide the electrical impulse required for the heart muscle contraction. They consist of two semi-canals, or connexons, each formed by six ion-channel proteins called connexins. Connexin-40 (K40), Connexin-43 (K43), and Connexin-45 (K45) are most abundant in the human heart, revealed in the gap junctions of the atria, ventricles, and specialized conductive tissue. A relationship has been established between reduced connexin expression and a tendency to atrial or ventricular arrhythmias [67]. In obesity, the level of K43 in the atria decreases, which may predispose to AF [68]. In an experiment with obese sheep, it was found that weight loss of 30% was associated with an increased expression of K43 and a simultaneous improvement in conductivity with a decrease in its heterogeneity, a decrease in vulnerability to AF [39]. BMI correlates with EAT volume [69], while weight gain and an increase in EAT volume with a high-calorie diet were associated with suppression of K43 production, a decrease in impulse conduction velocity, and greater inducibility of ventricular arrhythmias [70].

The cytokines IL-6 and TNF- $\alpha$  secreted by EAT are able to widen gap junctions by suppressing the formation of K40 and K43, which leads to slow conduction and an increased risk of re-entry [71, 72]. At the same time, it was revealed that the width of the gaps between adjacent cardiomyocytes is greater in AF patients [73].

#### *Fibrotic tissue remodeling*

Fibrotic tissue remodeling in the myocardium creates a substrate for re-entry, forming tortuous conduction pathways

and simultaneously delaying macroscopic myocardial conduction. A number of authors have demonstrated that atrial fibrosis increases with the progression of obesity, and the increasing volume of EAT is associated with an increase in the secretion of profibrotic cytokines (IL-1b, IL-6, TNF- $\alpha$ , and monocytic chemotactic protein-1) responsible for local inflammation, collagen deposition, and fibrosis (structural remodeling) [74, 75]. Local concentrations of matrix metalloproteinases-2, metalloproteinases-7, and metalloproteinases-9 are directly correlated with the level of atrial collagen and fibrosis [75], the former being directly related to the volume of EAT and the severity of AF [76]. Connective tissue growth factor and activin A are more actively expressed by EAT in AF patients compared with people with sinus rhythm, closely correlated with fibrosis and atrial remodeling [77].

#### *Adipose infiltration*

Along with the paracrine effects of EAT, infiltration of epicardial adipocytes into the myocardium can separate myocardial fibers, resulting in slow conduction or block, contributing to re-entry arrhythmias. This process does not differ from the fibroadipose infiltration noted in hereditary cardiomyopathies [78]. A global decrease in conduction velocity, greater electrogram fractionation, and a decrease in voltage were observed in obese individuals as EAT volume and atrial fat infiltration increased, which were more dependent on EAT volume than on global indices of obesity, such as BMI. These changes were more pronounced in areas adjacent to epicardial fat depots, suggesting their role in the development of the AF substrate [38]. Vulnerability to AF due to epicardial adipose filtration has been demonstrated in obese dogs with or without frequent atrial pacing to induce AF. It is noteworthy that epicardial adipose infiltration was detected after frequent atrial pacing to induce AF even in non-obese animals and correlated with interstitial fibrosis [79]. Lower negative resting membrane potential, lower action potential amplitude, and longer repolarization time due to disturbance of potassium and calcium transmembrane currents in cardiomyocytes, associated with EAT, may explain the predisposition to arrhythmias due to fatty infiltration [80].

Decrease in weight and volume of epicardial adipose tissue for the control of cardiac arrhythmias in humans

Given the evidence for the role of EAT as a source of secretome with a proarrhythmic effect, it is hypothesized that its regression can reduce the risk of arrhythmia. It has been established that the volume of EAT decreases with weight loss achieved through lifestyle modification or surgical intervention. The Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research registry demonstrated an association between weight loss and EAT volume among participants who achieved body weight loss by more than 5% [81]. However, a decrease in body weight by less than 5% was not accompanied by significant changes in EAT volume [82]. Specific weight loss programs using low-calorie diets in obese patients have demonstrated a similar

pattern of EAT changes [83, 84]. As a result, a 6-month diet with an energy value of 900 kcal/day induced a decrease in body weight by an average of 20% and a decrease in EAT thickness by 32% [83]. Restriction of caloric intake to 1,547 kcal/day for 12 weeks was sufficient for the regression of visceral abdominal obesity, a significant (by 11.0%) decrease in body weight, and a decrease in EAT thickness (by 17.2%). In obese individuals, aerobic exercise lasting an hour achieving 60%–70% of the maximum heart rate three times per week for 12 weeks resulted in a decrease in EAT thickness by 9% [84]. It was established that weight loss after bariatric surgery reduced the volume of EAT by an average of 24%, although the effect varied depending on the method of intervention (only 14.6% after creation of Roux-en-Y gastric bypass and only 5.3% after sleeve gastrectomy) [85].

A decrease in the tendency toward cardiac arrhythmias as a result of weight loss has been established. In a randomized controlled trial, caloric restriction and low-intensity physical exercises led to greater weight loss than lifestyle recommendations with a 15-month follow-up (14.3 kg vs. 3.6 kg). It is noteworthy that patients who restricted calorie intake and exercised had a lower burden and severity of AF symptoms than in the control group [86]. A decrease in the burden of arrhythmia has been reported with follow-up for up to 2 yr after catheter ablation of AF. For example, aggressive correction of cardiometabolic risk factors was associated with arrhythmia-free survival rate in 32.9% and 87% of patients with a history of single and repeated ablations, respectively, compared with 9.7% and 17.8% of patients who received standard treatment [87].

In the LEGACY study, in patients with a baseline BMI of 27 kg/m<sup>2</sup> or higher, the relationship between weight loss and arrhythmia-free survival during a 5-yr follow-up of AF patients was noted. Compared with loss of less

than 10% of body weight, loss of more than 10% of body weight was associated with a six-fold higher probability of arrhythmia-free survival. Patients who consistently and gradually lost weight experience the greatest improvement, while body weight fluctuations of more than 5% after lifestyle changes created a 2-fold higher risk of AF [88]. In order to assess the progression and possibility of reversal of AF with sustained weight loss, a group of the LEGACY project patients was further examined in the REVERSE-AF project. It turned out that in 88% of patients with weight loss of more than 10%, persistent AF transformed into paroxysmal AF, compared with 49% and 26% in groups that achieved weight loss of 3%–9% and less than 3%, respectively [89]. Given that EAT volume regresses with weight loss, lifestyle modification is a noninvasive and inexpensive intervention that enables to control cardiac arrhythmias.

Although there is convincing evidence for the benefit of weight loss in AF patients, it is not clear whether patients with ventricular arrhythmias will receive similar benefits. A meta-analysis involving 7,197 patients demonstrated QT interval prolongation and greater QT variance in overweight and obese patients compared with normal weight individuals, but these values decreased on average by 25.77 ms and 13.47 ms, respectively, with weight loss [90]. Given that the QT interval and QT variance are indices of risk for ventricular arrhythmia [91], the benefit of weight loss may probably extend to ventricular arrhythmias, although this remains to be established.

## ADDITIONAL INFORMATION

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