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Electrocardiograph Alteration Correlated to Epicardial Fat Tissue Thickness: A Systematic Review

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ABSTRACT

Epicardial adipose tissue (EAT) or epicardial fat tissue (EFT) affect cardiac electrical impulse through chemical secretion. Change of electrical cardiac impulse may lead into cardiac arrhythmia. Measurement of EAT correlates to the prognosis of cardiac arrhythmia cases caused by inflammatory and fibrotic properties which facilitate arrhythmogenesis. The aim of this study is to review the change of cardiac impulses and arrythmias correlation to EAT. Epicardial Adipose Tissue, Epicardial Fat, Electrocardiography, and Arrhythmia were used as keywords. Studies that we include were published between 2015 and 2021. We use inclusion and exclusion criteria to select included studies. We included five observational studies. This review includes 644 patients with predominant male younger than 65 years old. Epicardial fat tissue thickness more than 5,35 mm and 9 mm correlates to increased P-wave dispersion and increased T peak-end (Tp-e)/QT ratio, and Tp-e/QTc duration. Thicker EAT also correlates to the presence of fragmented QRS (fQRS). We found no cut-off point to determine-increased EAT. Epicardial fat tissue thickness correlates to P-wave dispersion, Tp-e/QT, Tp-e/QTc ratio, and fQRS. Evaluation of these parameters in echocardiography examination might have beneficial value to predict arrythmia in patients, especially those with overweight or obesity.

1. INTRODUCTION

Body mass index (BMI), which used to diagnose- obesity, is known to be positively correlated with visceral adiposity, including subcutaneous adipose tissue and epicardial adipose tissue (EAT) or epicardial fat tissue (EFT) [1], [2]. On the other side, BMI is also previously described as an independent risk factor for atrial fibrillation (AF) [3]. The mechanism of BMI correlation with AF is predicted to have a correlation with EAT but not with subcutaneous adipose tissue [2].

As any other visceral adipose tissue, EAT is 'an organ' with endocrine and paracrine effects and can secret inflammatory cytokines [4]. Inflammation around myocardium might produce arrhythmia [5]. However, EAT might produce electrocardiograph alteration before arrythmia is detected. The aim of this study is to review electrocardiograph alteration which correlates with EAT.

2. Material and Methods

We conducted online-based literature search on online databases, such as PubMed, ScienceDirect, SpringerLink and others. Epicardial Adipose Tissue, Epicardial Fat, Electrocardiography, and Arrhythmia were used as keywords. Studies that we include were published between 2015 and 2020 and the subjects were >18 years old, did not have any documented past illness of: CAD, congestive heart failure, left ventricular ejection fraction < 45%, valvular dysfunction, pericardial disease, cardiac pacemaker, chronic infective and/or inflammatory disease, malignancy, chronic kidney disease, chronic hepatic disease, abnormal thyroid function test, electrolyte imbalance, or drug intake that could affect ECG.

Epicardial fat tissue/ epicardial adipose tissue thickness were measured using parasternal long axis view, measuring hypoechoic space between outer wall of right ventricle and visceral pericardial, and was done blindly by a cardiologist. Electrocardiography was also interpreted blindly by minimum one cardiologist. Literatures that were not written in English and cannot be obtain in full text were excluded. Other data such as body mass index, sex, age, etc. were used as demographic data.

Table 1. PICO for review

Components	
Population	Patient without
Interventions	Epicardial Fat Tissue
Comparator	None
Outcome	Electrocardiogram
Type of study	Observational studies

3. RESULT

Our primary search on online databases found 252 studies. After removing duplication, studies that do not meet the inclusion criterias, and not eligible in full-text studies, we include five studies in this review, consist of observational studies. Full-texted articles that we have screened were summarized in Table 3.

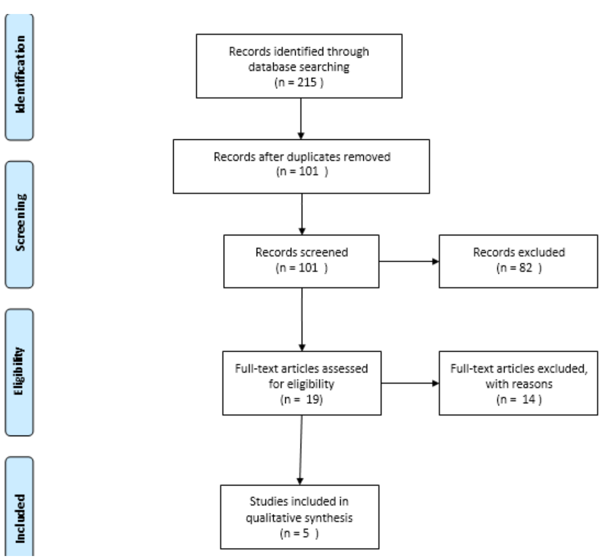

Figure 1. Algorithm studies reviewed

Total subjects that were included in this study are 644 patients with predominance of male - and age younger than 65 years old. Body mass index varied, from overweight to morbid obesity. Other demographic data were summarized in Table 2

Table 2. Baseline characteristics

	[6] (n=216)	[7] (n=40)	[8] (n=70)	[9] (n=90)	[10] (n=228)
Age (years old)	56,1	36,35	50,9	61,6	58,2
Male	90	4	34	40	157
BMI (Kg/m^2)	28,3	46,97	26,0	28,5	25,2
Left ventricle ejection fraction(%)	62	63	Not measured	56,1	61,94
Left atrial diameter(mm)	33,5	36,12	36	35,2	37,9

Table 3. Full-texted article obtained and reviewed

No	Title	Authors	Objectives	Methods	Results	Conclusion	
1	Left atrial epicardial adipose tissue radiodensity is associated with electrophysiological properties of atrial myocardium in patients with atrial fibrillation	[13]	To evaluate EAT phenotype is associated with the electrophysiological properties of adjacent atrial myocardium in patients with atrial fibrillation (AF).	Assess pre-procedural amount and radiodensity of left atrial EAT using CT scan and voltage mapping before ablation for AF patients	Patients with LA-low Voltage Zone presented significantly lower LA-EAT radiodensity than patients with no LA-LVZ (− 101.8 ± 12.5 HU vs. − 90.4 ± 6.3 HU, p = 0.004).	Low LA-EAT radiodensity is associated with presence of LVZ	Excluded Measurement using CT-scan
2	The relationship between echocardiographic epicardial adipose tissue, P-wave dispersion, and corrected QT interval	Alaa Quisi et. Al	to evaluate the association between EAT thickness and both P-wave dispersion (Pd) and corrected QT interval (QTc),	Assess EAT using echocardiography and measure Pd and QTc using ECG, then compare groups with low and high EAT	Pd was significantly greater in the EAT high group (p=0,001), QTc was significantly greater in the latter group (p=0,004)	EAT thickness was associated with Pd and QTc	Included
3	The association of the amounts of epicardial fat, P wave duration, and PR	Shih-jie jhuo et. Al	to elucidate the association between the amounts of epicardial fat and the	Amount of EAT in was measured using MDCT and P-wave duration, QTc, and	PR interval P wave duration and inter-atrial conduction block was associated with amounts of EAT. RA	PR interval, P wave duration, inter-atrial conduction block was associated with amount	Excluded, measurement using CT

	interval in electrocardiogram		characteristics of ECG.	QT dispersion was assessed using ECG	epicardial fat was most significantly associated with PR interval, and P wave duration	of epicardial fat	
4	Effect of the Epicardial Adipose Tissue Volume on the Prevalence of Paroxysmal and Persistent Atrial Fibrillation	[14]	Evaluated the effect of the EATV on the prevalence of paroxysmal AF (PAF) and persistent AF (PeAF) and the relationships with cardiac structure and functional remodeling	Patients underwent MDCT were divided into sinus rhythm, PAF, and PeAF groups.	The cutoff value of the EATV index for the prevalence was higher in PeAF than in PAF (64 vs. 55 mL/m2, P<0.01)	The EATV index is associated with the prevalence of PAF and PeAF, and its cutoff values are predictive for PAF and PeAF development independently of other AF risk factors.	Excluded, use CT scan
5	Left Atrial Epicardial Fat Volume Is Associated With Atrial Fibrillation: A Prospective Cardiovascular Magnetic Resonance 3D Dixon Study	[5]	Assess whether epicardial fat volume around the LA is associated with AF	Patients with AF and no history AF were measured of EAT using magnetic resonance	LA-EAT significant and an increase per mL was associated with 42% in odds of AF	Magnetic resonance-based LA EAT significantly increased in AF patients	Excluded, measurement using MR
6	Human Epicardial Adipose Tissue cTGF Expression is an Independent Risk Factor for Atrial Fibrillation and Highly Associated with Atrial Fibrosis	[4]	To evaluate precise role that EAT plays in the pathogenesis of AF is not yet been completely understood	Use PCR to determine cTGF and Galectin. EAT measured with echo	Quantitative real-time PCR showed that connective tissue growth factor (cTGF) expression was significantly higher in EAT than in subcutaneous adipose tissue (SAT) or paracardial adipose tissue (PAT) from patients with AF, and in EAT from patients with SR (P < 0.001).	Highly expressed in EAT, cTGF is associated with atrial fibrosis, and can be an important risk factor for AF.	Excluded, no ECG evaluation

7	Influence of Sex on the Association Between Epicardial Adipose Tissue and Left Atrial Transport Function in Patients With Atrial Fibrillation: A Multislice Computed Tomography Study	[9]	To evaluate the influence of sex on the association between EAT and left atrial (LA) transport function	Patients with atrial fibrillation ablation procedure was assessed for EAT with CT scan	The ratio of periatrial to total EAT volume correlated significantly with LA emptying fraction and LA voltage in both sexes, whereas total EAT volume and serum adiponectin level did not	Compared with matched men, postmenopausal women with atrial fibrillation had higher periatrial adiposity, which was independently correlated with decreased LA voltage and LA transport function	Excluded, ECG parameters were not described
8	Epicardial fat thickness correlates with P-wave duration, left atrial size and decreased left ventricular systolic function in morbid obesity	A Fernandes-Cardoso	To evaluate influence of EF on atrial remodeling and cardiac Function on morbidly obese without these comorbidities	Patients with obese and non-obese. EAT was measured using echo and P wave duration analyzed using ECG	Positive correlation was found between EFT and PWD (r=0,70, p=0,001)	Excess of EAT significantly impact on atrial remodeling and cardiac function	Included
9	Differences in the structural characteristics and distribution of epicardial adipose tissue between left and right atrial fibrillation	Hideyuki Hasebe	We investigated structural characteristics of the bi-atria and epicardial adipose tissue (EAT) volume in patients with RAF	Patients underwent CT examination for EAT and divided into RAF and LAF	Both the LA-EAT and RA-EAT volumes were smaller in the RAF group than the LAF group (4.2 [2.8–5.6] vs. 9.1 [7.8–10.4] mL/m2; P < 0.001 and 5.3 [4.3–6.3] vs. 9.5 [8.4–10.6] mL/m2; P < 0.001, respectively	RAF was structurally characterized by predominant RAA enlargement, small left atrium, and less EAT surrounding the atria.	Excluded, measurement using CT scan
10	Inflammation of left atrial epicardial adipose tissue is associated with	Takashi Kusayama et al	To investigate the association between AF and inflammation of the EAT around the LA.	retrospectively identified regions of EAT around the LA and measured the density of these	a higher EAT density was significantly associated with the presence of PAF after adjusting for other risk factors (odds ratio: 1.25;	inflammation of EAT around the LA, but not SAT, is related to the presence of PAF	Excluded, measurement use CT scan

	paroxysmal atrial fibrillation			areas using computed tomography	95% confidence interval: 1.08–1.45, p = 0.003)		
11	Association of Left Atrial Epicardial Adipose Tissue with Electrogram Bipolar Voltage and Fractionation: Electrophysiologic Substrates for Atrial Fibrillation	Tarek Zghaib et al	To investigate the association of EAdT with adjacent myocardial substrate	Patients who underwent cardiac computed tomography as well as electro-anatomical mapping in sinus rhythm prior to an initial AF ablation procedure	EAdT (−0.29) were associated with log bipolar voltage as well as low-voltage zones (<0.5 mV).	presence of overlaying EAdT was associated with lower bipolar voltage and electrogram fractionation as electrophysiologic substrates for AF.	Excluded, measurement CT scan
12	The relationship between epicardial adipose tissue and P wave and QT dispersions	Yuksel Cicek et. al	the influence of EAT on QT and P wave dispersions (QTd, PWd), as simple, non-invasive tools of proarrhythmia on surface ECG.	Normal coronary arteries subjects underwent ECG to evaluate QTd, PWd and underwent echo to evaluate EAT	EAT was significantly related to P wave dispersion (r=0,265; p=0,026)	A significant association between EAT and PWd was demonstrated in this study	Included
13	Evaluation of Electrocardiographic T-peak to T-end Interval in Subjects with Increased Epicardial Fat Tissue Thickness	Ozgur Kaplan et. Al	to evaluate the association of EFT thickness with indices of ventricular repolarization by using T-peak to T-end (Tp-e) interval and Tp-e/QT ratio.	Patients with EFT >= 9mm and less than 9mm were evaluated using echocardiograph and ECG	Significant positive correlations were found between EFT thickness and Tp-e interval (r = 0.548, p < 0.001), cTp-e interval (r = 0.259, p = 0.01), and Tp-e/QT (r = 0.662, p < 0.001) and Tp-e/QTc ratios (r = 0.560, p < 0.001)	Tp-e and cTp-e interval, Tp-e/QT and Tp-e/QTc ratios were increased in subjects with increased EFT,	included
14	The relationship between epicardial fat tissue thickness and frequent	Abdulkadir et al	To evaluate the possible relationship between EFT thickness and frequent VPBs.	50 patients with VPB and 50 controls enrolled and evaluate	EFT thickness was significantly associated with VPB frequency	EFT thickness was independently associated with frequent VPBs.	Excluded, measurement only use echo

	ventricular premature beats			using transthoracal echocardiograph and 24-h holter echocardiography			
15	Is epicardial fat depot associated with atrial fibrillation? A systematic review and meta-analysis	Maddalena Gaeta	to verify the relationship between AF and EF depot, performing a meta-analysis of observational case series studies.	7 studies consist of observational case series were analyed	significant difference of EF was observed when comparing both persistent and paroxysmal AF subtypes with respect to healthy participants (EF difference 48.0 ml (95% CI = 25.2, 70.8) and 15.7 ml (95% CI = 10.1, 21.4) for persistent and paroxysmal, respectively	The present work expands the strength of previously reported association between EF amount and atrial arrhythmia.	Excluded, meta-analysis. Use CT and MRI
16	Epicardial Fat Volume and the Risk of Atrial Fibrillation in the General Population Free of Cardiovascular Disease	Daniel bos et al	to improve our understanding of the potentially causal role of epicardial fat in the development of AF	Subjects were underwent CT scan for EAT and ECG used to follow for AF	Larger amounts of epicardial fat were associated with an increased risk of AF (hazard ratio [HR] per 1-SD increase: 1.31; 95% CI: 1.05 to 1.65)	There is association of EAT with AF	Excluded, no ECG parameter was described
17	The effect of Dapagliflozin treatment on epicardial adipose tissue volume and P-wave indices an Ad-hoc analysis of the previous randomized clinical trial	Takao Sato et al	To investigate the effect of dapagliflozin on EAT volume and P wave indices	Patients with T2DM and coronary artery disease divided into 2 groups, treated with dapagliflozin and not, EAT was measured with echo and P wave indices measured with ECG	In multivariate analysis, the change in EAT volume was independent determinant of the change in P-wave dispersion	Dapagliflozin reduce EAT volume and P-wave indices. P wave indices were especially associated with changes in EAT volume	Excluded, there is intervention using dapagliflozin

18	Increased epicardial adipose tissue volume is associated with PR interval prolongation	Wei-chin Hung et al	investigate the association between epicardial adipose tissue (EAT) volume and PR-interval prolongation as assessed by computed tomography (CT) and Twelve-lead ECGs.	Patients underwent CT for EAT examination and ECG to be evaluated	Statistically significant correlations were observed between the EAT volume and the PR interval (p = 0.183, p = 0.003), and QRS duration (p = 0.144, p = 0.018)	EAT volume is highly associated with PR interval prolongation	Excluded, use CT scan
19	The presence of fragmented QRS is associated with increased epicardial adipose tissue and subclinical myocardial dysfunction in healthy individuals	Mehmet Yaman et al	to measure epicardial adipose tissue (EAT) and to assess left ventricular (LV) systolic and diastolic function in a healthy population grouped according to the presence of fragmented QRS (fQRS)	Patients with fQRS and not was evaluated forEAT using echocardiograph	EAT thickness was significantly increased in fQRS(+) individuals (0.59 vs. 0.44 mm, p<0.001).	presence of fQRS on the admission ECG is associated with increased EAT	Included

Epicardial fat tissue/ epicardial adipose tissue thickness, which measured by echocardiography varied from 0,59 to more than 10 mm. Some studies also divided EAT thickness into two groups. However, this groups were not similarly classified, one study uses cut-off point 5,35mm and the other one use 9 mm. There was a correlation between body mass index and EAT thickness. Epicardial fat tissue was found to be correlated to P-wave dispersion, Tp-e/QT ratio, Tp-e/QTc ratio, and the presence of fragmented QRS. Studies that were included and their results were summarized in Table 4.

Table 4. Studies included

Author (year)	Result
[6]	P-wave dispersion was significantly greater in the EAT high group (p=0,001). Odds ratio for P-wave dispersion correlated with EAT thickness is 1,1026(p=0,002)
[7]	Positive correlation was found between EFT and P-wave dispersion (r=0,70; p=0,001)
[8]	EAT was significantly associated with P-wave duration (r=0,265; p-0,026)
[9]	Significant possitve correlations were found between EFT thickness and Tp-e interval (r=0,548; p<0,001), c-Tp-e (r=0,259; p=0,01), Tp-e/QT ratio (r=0,662; p<0,001) and Tp-e/QTc ratio (r=0,56; p<0,001)
[10]	EAT was found to be correlated to presence of fragmented QRS (r=0,205; p<0,001)

4. DISCUSSION

Our study shows thicker EAT in patients with higher BMI. This finding is similar to previous study, which described that BMI is a method of measurement of overall adiposity [3]. Several studies had different cut-off value to define- increased or high EAT. Patients with metabolic syndrome was described to have increased EAT when the thickness is >9,5mm for men and 7,5 mm for women [6]. In terms of insulin resistance, both men and women were described to have increased EAT when the thickness is more than 9,5 mm [7]. Patients with subclinical atherosclerosis and coronary artery disease defined to have increased EAT with cut-off point 7 mm and 5,2 mm, respectively, in both sexes. A meta-analysis shows normal population can have EAT thickness around 2,5-7,1 mm in European ethnicity. There's no guideline or consensus that stated about this cut-off value [8]. Previous study shows that women have less EAT [9], therefore women might have ECG alteration with lesser EAT thickness compared to men.

4.1 EAT, P-wave and atrial fibrillation

P-wave dispersion is an ECG parameter that is defined as the difference between widest and narrowest P-wave duration. It represents inhomogeneous propagation of sinus impulse in the atria, delay atrial depolarization, and diminished voltage. These conditions can be a predictor of recurrent and paroxysmal atrial fibrillation [10], [11]. Our review shows that EAT correlates with the increase of P-wave dispersion. Thickness of EAT more than 5,35 have significant higher P-wave dispersion. The mechanism of this correlation might happen due to EAT promotes structural remodeling through adipocytokines in atrial myocardium. Therefore, increment of EAT is not only accompanied with P-wave dispersion but also with LAD [10- 12].

P-wave duration was previously described to have significant correlation with right atrium EAT measured with CT-scan [13]. Moreover, measurement using CT-scan was also found that EAT correlates with interatrial block and longer PR interval. Hence, left atrial EAT measured by 3D magnetic resonance showed that left atrial EAT promotes left atrial remodeling, which shown as increased left atrial volume, and correlates to atrial fibrillation [5]. The remodeling effect of EAT was also confirmed with EATV (EAT divided by body surface area), and positively correlates with increase of left atrial diameter and persistent AF [14]. This finding is similar to our review. Therefore, this study also provides supportive findings for previous meta-analysis that stated EAT associated with AF [15].

4.2 Ventricular changes

Ventricular arrythmia predictor can be obtained with QT interval, corrected QT interval, and QT dispersion. Some studies showed that these parameters were affected by heart rate and body weight. Other parameters that suggested to be more accurate for ventricular repolarization are Tp-e/QT and Tp-e/QTc ratio. One study that we conclude in this review shows that EAT do not affect QT interval dispersion. However, it is found that EAT thickness, moreover, more than 9 mm, was significantly correlated with Tp-e/QT and Tp-e/QTc ratios. This finding might suggest that a thicker EAT may have higher probability to get ventricular arrhythmia [8]. Exact pathomechanism of this finding has not been known. However, previous study which observed ECG on patients with ventricular premature beats, found out that higher EAT might promote structural changes such as left ventricular mass, atrial and right ventricular size. These changes might cause increased fibrosis, electrophysiological changes, and calcium handling of myocardium, which then promote ventricular premature beats [16].

Another important ECG parameter for myocardial scaring and fibrosis is fragmented QRS. This wave may be found in some cardiac diseases such as myocardial infarction and sarcoidosis. Our review found that EAT thickness was also significantly correlates to fragmented QRS and may suggest that higher EAT might correlates to wider and more extensive myocardial fibrosis [17]. Moreover, in correlation with myocardial infarction, previous studies found that EAT correlated to acute coronary syndrome patient's outcome [18-20]. This study might strengthen this correlation.

4.3 Limitation

Our study used inclusion and exclusion criterias for subjects, ECG and echocardiography examinations, therefore we believe that our study gives a homogenous subjects and reliable echocardiography intepretation. This review also have several limitations. We have not directly proof that EAT thickness correlates to inflamation cytokines and myocardial alteration. Direct correlation between EAT and cytokines or myocardial strain might have a better way to describe our findings. Moreover, measurement of EAT might also better and more precise using an advanced device such as magnetic resonance. Cut-off point for increased EAT can not be clearly stated. Our review covered only 644 subjects, which may need further

5. Conclusion

Epicardial fat tissue thickness correlates to P-wave dispersion, Tp-e/QT, Tp-e/QTc ratio, and fQRS. Evaluation of these parameters in echocardiography examination might have beneficial value to predict arrythmia in patients, especially those with overweight or obesity. Further studies are needed to confirm the pathophysiology and to increase the accuracy of EAT measurements.

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