

Original Article

Effect of Echocardiographic Epicardial Adipose Tissue Thickness on Success Rates of Premature Ventricular Contraction Ablation

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Background: Idiopathic premature ventricular contractions are frequently seen ventricular arrhythmias. Radiofrequency ablation is an effective treatment to improve symptoms and eliminate premature ventricular contractions. Epicardial adipose tissue is a true visceral adipose depot of the heart. A relation between an elevated epicardial adipose tissue thickness and myocardial structural pathologies. However, an association of EAT thickness with success rates for premature ventricular contractions ablation has not been investigated yet.
Aims: To assess the relation between the epicardial adipose tissue thickness and success rates for premature ventricular contraction ablation.

Study Design: Retrospective case-control study.

Methods: A total 106 consecutive patients who have had high premature ventricular contraction burden of >10,000/24-h using ambulatory Holter monitorization and underwent catheter ablation were enrolled in this study. A frequency of premature ventricular contractions of more than 10000 per day was defined as frequent premature ventricular contractions. Epicardial adipose tissue thickness was measured by using 2-D transthoracic echocardiography. A successful ablation was termed as over 80 % decrease in pre-procedural premature ventricular contraction attacks with the same morphology in 24-h Holter monitorization after 1-month follow-up visit from an ablation procedure.

Results: Successful premature ventricular contractions ablation was achieved in 87 (82.1%) patient. Epicardial adipose tissue thickness was importantly higher in unsuccessful ablation patients ($p < 0.001$). Procedure time, total fluoroscopy time and radiofrequency ablation time were statistically higher in unsuccessful group ($p < 0.001$). In stepwise multivariate logistic regression analyze, epicardial adipose tissue thickness and pseudodelta were independently associated with procedural success (both p values < 0.001). In receiver operating curve (ROC) analysis, epicardial adipose tissue thickness was found to be an important predictor for procedural success ($AUC = 0.85$, $p = 0.001$), with a cut-off value of 7.7 mm and sensitivity of 92% and specificity of 68%.

Conclusion: Our study findings suggested that epicardial adipose tissue thickness was greater in patients with premature ventricular contraction ablation failure, which was also found as a significant predictor of procedural success.

Keywords: Premature ventricular complexes, ablation, epicardial adipose tissue

Idiopathic premature ventricular contractions (PVCs) are frequently seen ventricular arrhythmias. Assessment and treatment of PVCs is complex, and is highly dependent on the clinical scenario (1). The outflow tracts (OT), both right and left (RVOT and LVOT) are the best known origin of idiopathic PVCs. Idiopathic ventricular tachycardia (VT) or frequent PVCs from the right ventricular outflow tract usually occur in structural cardiac disease. Other sites for PVCs include the His-Purkinje system, the annuli of the aortic, pulmonary, and both atrioventricular (AV) valves, endocavitary structures, moderator band and false tendons (2). Frequent PVCs are generally symptomatic and they have also been known to cause arrhythmia induced CMP. The frequency of PVCs/24hour that is related with decreased left ventricular (LV) function has been presented at attacks above 10–25% of the sum of cardiac beats (3–4). Radiofrequency ablation (RFA) is an effective treatment to improve symptoms and eliminate PVCs (5). An indication for ablation was having a markedly symptoms with very frequent PVCs under medical therapy (6). Moreover, the presence of PVC induced CMP with or without symptoms another indication for catheter ablation.

Epicardial adipose tissue (EAT) thickness is the true visceral adipose deposit of the heart (7). The EAT is not only adjacent to atria but also is associated with autonomic ganglia and it is the probable mechanism leading to arrhythmia (8). Many studies have shown that EAT thickness is related with some common disorders such as increased LV mass, atherosclerosis, arterial stiffness, hypertension and atrial fibrillation (9). Currently, more studies show the relationship between EAT thickness and AF existence and its post-ablation recurrence has been emphasized.(10) In addition, the first report on the association between EAT and structural heart disease associated VT recurrence, which showed a significant association between increased EAT thickness and VT recurrence after catheter ablation.(11) However, the association between EAT thickness and success rates for idiopathic PVCs ablation is unknown. Therefore; the goal of present study was to assess the association between PVCs ablation success and EAT thickness.

METHODS

Patient selection and study protocol

A total of 106 consecutive patients who underwent catheter ablation for idiopathic PVCs in between January 2015 and July 2018 were enrolled in this study. Inclusion criteria of the present study were as follows: 1) frequent PVC, as indicated by the total PVC count of > 10,000 beats during the 24-h Holter ECG monitoring; 2) patients having a symptoms or patients with symptomatic PVC-CMP; 3) resistancy with anti-arrhythmic drugs (AADs), beta blockers or nondihydropyridine calcium channel blockers (at least 3 months) 4) >18 years old. 24-hour Holter recording were done again after one month follow-up. Over 80 % decline in PVCs with the same morphology in 24-hour Holter monitorization after 1-month from the procedure was reported as successful ablation procedure. Exclusion criteria of the present study were: Coronary artery disease including previous myocardial infarction, percutaneous coronary intervention, and coronary artery by-pass surgery history, structural cardiac disease, which were detected by exercise stress testing, coronary angiography, cardiac multi-detector computed tomography and/or radionuclide scans after proper indications, dilated or hypertrophic cardiomyopathy, valvular heart diseases (except mild form).

Demographic, clinic and laboratory characteristics of the study patients were recorded from patient files. Furthermore, ECG or 24-hour Holter recordings ECG were obtained from the entire study population. The study protocol was approved by the Local Institutional Ethics Committee.

Echocardiographic examination

Transthoracic echocardiogram was performed using commercially available equipment (Philips iE33 2006 (USA) with 2D guided M-mode features. Echocardiographic examination was applied in the left lateral decubitus position. Parasternal long- and short-axis views and apical views were used as standard imaging windows. Baseline parameters such as both LV end-diastolic and end-systolic volumes, LV ejection fraction (calculated by modified Simpson's method) were measured in the apical four-chamber view. All echocardiographic examinations were made by physician, who was unaware of the results of the study.

Measurement of EAT. Parasternal longitudinal and transverse parasternal views were used to measure of EAT thickness on the right ventricular free wall. And the mean value of both measurements was calculated. An echo-free space between the outer wall of the myocardium and the visceral layer of pericardium was defined as an epicardial fat tissue. It's thickness was measured perpendicularly on the free wall of the right ventricle at end-systole in three cardiac cycles according to a predefined method (12). The 106 patients data were evaluated by two experienced cardiologists. Intra- and inter-observer variabilities for EAT thickness were 4.6% and 5.7%, respectively. Epicardial fat measurement from both long and short- axis was concordant.

Electrophysiological study and radiofrequency catheter ablation (RFCA) procedure.

All antiarrhythmic drugs, except amiodarone, were discontinued for 5 half lives before the procedure. A decapolar mapping catheter (6F, 110 cm, Inquiry™, St. Jude Medical, St. Paul, Minnesota, USA) was inserted through the right femoral vein and placed in the coronary sinus by using fluoroscopic guidance. A standard transvenous 6-F quadripolar catheter (6F, 110 cm, Mariner® SC Series, Medtronic, Minneapolis, MN, USA) was placed at the right

ventricular apex. Endocardial signal and surface ECG were recorded using the EP Tracer device (Medtronic, Inc., USA). 3D electro-anatomic map is performed with CARTO 3 D Mapping System, (Biosense Webster, CA, USA), NAVX (St Jude Medical, MN, USA) or noncontact mapping (Ensite Array, St Jude Medical). Ablation was performed with irrigated-tip catheter contact sense catheter (Thermo-cool-SmartTouch, Biosense-Webster, Inc., CA, USA), open irrigated non-contact sense catheters (3.5 mm tip Thermocool or Thermocool SF, Biosense-Webster) and FlexAbility catheter (Endosense/ Abbott, St Paul, Minnesota, USA). Activation mapping or pace mapping were used to identify potential sites for ablation. If no PVCs were seen or only rare PVCs, intravenous isoproterenol was administered to facilitate the presence of PVCs. Acute procedural success defined as no occurrence of spontaneous or inducible PVCs using an isoproterenol infusion for a 30-minute observation period after last ablation lesion and absence of the predominant PVC in the 24 hours post-ablation.

Statistical Analysis

One-sample Kolmogorov-Smirnov test was used for assessing whether the variables distribution normal or not. Variables were indicated as mean±standard deviation (minimum:maximum) or median (minimum:maximum) values. According to normality test result, independent samples t test or Mann Whitney U test were used for comparing the study groups. Categorical variables were compared by Chi square test or Fisher's exact test. In order to estimate the sensitivity and specificity of EAT levels for predicting procedure success rate, receiver-operating characteristic curve (ROC) analysis was done. Area under the roc curve (AUC) value with 95% CI (confidence intervals) were reported. The relationship among continuous variables were examined by using correlation analysis and Spearman correlation coefficient was computed. Logistic regression analysis was used to examine associations between procedural success, EAT and other variables. Variables with a *p* value of < 0.1 in univariate logistic regression analysis were included in a multivariate logistic regression analysis. SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MedCalc for Windows (version 12.5 (MedCalc Software, Ostend, Belgium) softwares were used for performing statistical analysis and the level of significance was set at *p*<0.05. Power analysis were done by using a software program (IBMM SPSS Sample Power, 2010, Chicago,USA) with power (1 - β) set at 0.80 and α = 05, two-tailed.

RESULTS

A comparison of baseline demographic characteristics including past history of ablation between successful PVCs ablation patients and those with unsuccessful ablation group were reported in Table 1. Successful PVCs ablation was achieved in 87 (82.1%) patients. In the remaining 19 (17.9%) cases, ablation was unsuccessful according to previously mentioned criteria. There was no difference between the study groups according to baseline characteristics. The electrocardiographic and echocardiographic findings of the study participants were presented in Table 2. Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter LVEDV, LVESV and EF were not different between two groups. Average duration of maximum deflection index and PVCs maximum QRS duration were higher in unsuccessful ablation group (*p*= 0.045 and 0.034, respectively). EAT thickness was importantly elevated in unsuccessful ablation group (*p*<0.001). Activation mapping showed that the PVCs originated at the right ventricular outflow tracts of 43 (40.5%), aortic cusps of 37 (35%), papillary muscles of 7 (6.6%), left ventricular summit (LVS) of 12 (11.3%), multi of 3 (1.9%) and other locations of 3 (2.8%) patients (Table 3). Procedure-related complications occurred in 6 patients as follows: cardiac tamponade in 1 patient from both groups, 1 transient ischemic attack and 3 hematomas in the successful ablation group. The effusion was self-limiting and was managed conservatively in successful ablation patients. In other patient, pericardial effusion and consequent tamponade were managed with timely by using pericardiocentesis technique. The suspected site of localization was includes only an epicardial summit region in this patient. Transient ischemic attack, which becomes evident as a visual impairment right after the procedure in a patient, was managed conservatively and clinical picture was self-limiting with complete recovery. The suspected site of localization was a left ventricular papillary muscle in this patient. Procedure duration time, total fluoroscopy time and the net duration of radiofrequency time were statistically higher in unsuccessful group as expected (*p*: <0.001).

Epicardial fat thickness and fluoroscopy duration was importantly positively correlated between each other for all cases (*r*_s=0.31; *p*=0.008) (Table 4). In stepwise multivariate logistic regression analyze, EAT thickness and pseudo-delta wave time were independently associated with procedural success (both *p* values <0.001) (Table 6). In ROC analysis, EAT thickness achieves an AUC 0.85 (*p* = 0.001) for the prediction for procedural success. A cut-off value for EAT thickness of 7.7 mm predicted procedure success with sensitivity of 92% and specificity of 68% (Table 5 - Figure 1).

DISCUSSION

In the present study; EAT thickness and fluoroscopy duration were found to be significantly higher in unsuccessful ablation group. Forty two percentage of the PVCs were from the RVOT, with 32% from the aortic cusps. Catheter ablation proved to be highly effective in eliminating these PVCs. Similar to the patient group in our study, the 3-month success rate in ablation involving all idiopathic PVC was reported to be 80%. (13) This finding is similar to the success rate of our study. Finally, it was shown that EAT thickness was a strong predictor of procedure success in PVCs ablation patients.

The success rate of ablation was found to be lower in patients originating from the left ventricular summit (LVS) region. [6 (31.58%) versus 6(6.70%) *p*=0.024] Electrocardiographic and electrophysiological features were taken into consideration in determining that premature ventricular complexes were summit-folded. (14-15)

Cheng Z. et al. demonstrated that for LV summit VAs, the prolonged pseudo-delta wave time ($PdW > 53 \text{msn}$) and intrinsicoid deflection time ($IDT > 74 \text{msn}$) and maximum deflection index ($MDI > 0.45$) indicated an epicardial origin. PVCs originating from this region can be eliminated by RFCA applied within the great cardiac vein (GCV) or by using a subxiphoid transpericardial access. Similar to the results of our study, Yamada T. et al. shown that radiofrequency catheter ablation success is lower because LVS is close to coronary arteries and / or epicardial adipose tissue.(16)

PVCs are common causes of palpitations. The presence of rare PVCs during 24 hour ambulatory holter monitoring is very frequent and generally accepted as usual findings. The main indications for catheter ablation of PVCs are being symptomatic under medical therapy and having a LV dysfunction. (6) Radiofrequency catheter ablation of the frequent idiopathic PVCs has been accepted as convenient, beneficial and effective treatment method for symptomatic frequent PVCs and suspected PVC induced cardiomyopathy. Zhong et al demonstrated in their recent study that, a mean decrease in PVC burden was importantly higher in the ablation group as compared to the medical therapy group ($-21,779$ per 24-hour mean PVC decrease in the ablation group compared to -8376 per 24-hour in the medical therapy group, $P < 0.001$). (16)

It is well established that EAT can be considered as a form of visceral adipose tissue(17). In addition to systemic effects, EAT has paracrine effects. It releases proinflammatory cytokines such as tumor necrosis factor alpha ($TNF-\alpha$), interleukin-1- beta ($IL1-\beta$), and IL-6, which can cause variable irreversible changes in myocardium structure including myocardial fibrosis (18). The association between EAT and atherosclerosis, hypertension, impaired coronary flow reserve, arterial stiffness and atrial fibrillation was reported in some studies (19-23). Wong et al. studied epicardial fat by means of cardiac magnetic resonance (MR) in 130 patients, and demonstrated that arterial pericardial fat volumes are associated with the prevalence and severity of AF and recurrence after radiofrequency ablation (24) It is known that EAT is associated with higher levels of inflammatory cytokines, and a higher inflammatory state can subsequently lead to a higher structural and electrical remodeling of the heart, and finally a higher incidence of serious ventricular arrhythmias and sudden cardiac death. (18) Wu et al. reported that on 50 patients with systolic heart failure (HF), pericardial adipose tissue and development of ventricular fibrillation (VF)/VT in patients with HF.(25) Recently, Shamloo et al., also reported that MR-measured epicardial fat volumes (right and left atrioventricular grooves, as well as anterior interventricular groove) was significantly higher in the VT recurrence group than that in the non-recurrent VT (11) However, unlike our study, sustained monomorphic ventricular tachycardia in patients with structural heart disease were discussed in this study.

Several mechanisms may play roles to establish an association between PVCs ablation success and EAT thickness. The mechanism of PVCs may be structural and ultrastructural changes which is caused by EAT. Myocardial structural impairment such as advanced remodelling and resulting fibrosis may lead to alterations in action potential characteristics, which triggers the heart to PVCs (26). Kiris et al (27) reported an elevated EAT thickness in the setting of PVCs. An independent association between EAT thickness and frequent PVCs was also shown in this study. Akyuz et al (28) found an elevated epicardial fat thickness in patients with fragmented QRS compared to controls, which had been considered as an indicator for myocardial fibrosis or scarring in variety of diseases. Voulgari et al. (29) reported a relation of LV arrhythmogenicity with low level of inflammation in metabolic syndrome. The association between EAT thickness and ablation success may also depend on other mechanisms. The effects of adipose tissue on impedance and even the role of autonomic nervous system in the EAT are other possible mechanisms. EAT, the visceral fat repository in the heart, contains intrinsic cholinergic and adrenergic nerves, which interact with the extrinsic cardiac parasympathetic and sympathetic nervous systems. These EAT nerves represent a significant source of norepinephrine and epinephrine. Ian A. White reported that an increase in EAT volume correlates with a hyperactive adrenergic signaling resulting from an increased catecholamine biosynthesis. (30) EAT is associated with higher levels of inflammatory cytokines, and a higher inflammatory state can subsequently lead to a higher structural and electrical remodeling of the heart, and finally a higher incidence of arrhythmia. As a result, an increased adrenergic activity may augment the frequency of PVCs that may lead to a more resistant to ablation therapy.

Study Limitations

The present study had some limitations. Firstly, we had a small study population, which arose from single center. Moreover, advanced imaging techniques such as magnetic resonance imaging (MRI) or computed tomography (CT) were not used to detect EFT. Although two-dimensional echocardiography is a useful imaging modality for the evaluation of EFT thickness, which is importantly correlated with MRI and CT, they are not useful for routine clinical practice for their lack of cost-effectiveness and time consuming feature and radioactive effect respectively. Third, a correlation between EFT thickness and inflammatory marker or cytokines was lacking in our study. Last, a specificity of EFT for predicting success of ablation procedure, which was detected by ROC analysis is low. Results of an ablation procedure may depend on several factors, which are related with some inflammatory markers or structural changes of the heart such as EFT. However, limited numbers of patients may decrease specificity of EFT in some disease settings. In addition, other factors affecting procedural success effect sensitivity and specificity of the EFT.

Our study is the first to demonstrate a useful effect transthoracic echocardiography-derived EAT thickness in identifying PVCs ablation success. EAT thickness was found to be increased in unsuccessful ablation group. It was also reported that EAT thickness was a good independent predictor of procedure success in PVCs ablation. The causal relationship between EAT and pathogenesis of PVCs requires further studies with a larger population.

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Uncorrected Proof

TABLES

Table 1. Baseline characteristics

	Procedure success		p-value
	No(n=19)	Yes (n=87)	
Age	51.17±9.49	43.54±12.55	0.054 ^a
Gender (F/M)	11(57.90%)/8(42.10%)	43(49.40%)/44(50.60%)	0.562 ^b
BMI	27.58±2.48	25.72±3.85	0.114 ^a
Risk Factors			
DM	3(15.80%)	8(9.19%)	0.615 ^c
HT	4(21.05%)	12(13.79%)	0.582 ^c
HL	3(15.80%)	13(14.90%)	0.860 ^c
Smoking	6(31.50%)	36(41.38%)	0.750 ^c
Prior ablation	3(15.80%)	12(13.79%)	0.673 ^c

Data were presented as mean±st.deviation(min.:max.), median(min.:max.) and n(%), a:Independent samples t test, b: Pearson chi-square test, c:Fisher's exact test. BMI: body mass index, DM: diabetes mellitus, HT: hypertension, HL: hyperlipidemia

Table 2. Echocardiographic parameters and ECG findings

	Procedure success		p-value
	No (n=19)	Yes (n=87)	
Echocardiographic parameters			
LVEDD (mm)	47.50(44:58)	50(44:61)	0.068 ^c
LVESD (mm)	31(27:46)	33(27:47)	0.135 ^c
LVEDV (ml)	106(83:130)	108(83:139)	0.489 ^c
LVESV (ml)	48.50(35:71)	48(35:88)	0.296 ^c
EF(%)	53.75(42:64)	55(25:67.70)	0.667 ^c
EAT thickness (mm)	9.07±1.32(7.4:11.6)	7.34±10.1(4.5:10.1)	<0.001 ^a
ECG Findings			
Intrinscoid deflection time (msec)	71.50±11.59(48:92)	64.61±12.16(43:96)	0.076 ^a
Max deflection index (%)	0.53±0.09(0.40:0.68)	0.48±0.08(0.30:0.68)	0.045 ^a
Pseudo-delta n (%)	9 (47)	9 (10)	<0.001 ^b
Heart rate	74.92±9.82(63:90)	74.40±9.19(55:95)	0.863 ^a
Max QRS duration (msec)	142(122:160)	134(121:150)	0.034 ^b
PVC frequency (%)	16(10:28)	20(9:33)	0.142 ^b

Data were presented as mean±st.deviation(min.:max.), median(min.:max.) and n(%). a:Independent samples t test, b:Fisher's exact test, c: Mann Whitney U test. LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, LVEDV: left ventricular end diastolic volume, LVESV: left ventricular end systolic volume, EF: Ejection fraction, EAT: Epicardial adipose tissue

Table 3. Details and Complications of Ablation Procedures

	Procedure success		p-value
	No (n=19)	Yes (n=87)	
Catheter Ablation Techniques			
Carto	11(57.90)	51(57.30)	1.00 ^c
Ensite Presicion/Nav X	8(42.10)	36(43.70)	

Procedural duration (min)	169.50±27.46(135:222)	95.44±35.76(45:214)	<0.001 ^a
Fluoroscopy time (min)	21.75(17:36)	11.90(3:25)	<0.001 ^d
Duration of radiofrequency energy delivery (min)	15.25±3.74(9.50:22.10)	7.91±3.80(2.60:18.20)	<0.001 ^a
Complications			
Cardiac tamponade	1(5.26%)	1(1.15%)	0.311 ^c
Cerebrovascular events	0	1(1.15%)	1.00 ^c
Hematoma	0	3(3.49%)	1.00 ^c
Site of origin			
RVOT	3(15.79%)	40(45.98%)	0.049 ^b
Coronary Cusp	6(31.58%)	31(35.63%)	0.739 ^c
Papillary muscle	1(5.26%)	6(6.70%)	1.00 ^c
Left Ventricular Summit	6(31.58%)	6(6.70%)	0.024 ^c
Multiple	2(10.52%)	2(2.30%)	0.111 ^c
Other	1(5.26%)	2(2.30%)	0.431 ^c

Data were presented as mean±st.deviation(min.:max.), median(min.:max.) and n(%)

a:Independent samples t test, b: Pearson chi-square test, c:Fisher's exact test, d: Mann Whitney U test

Table 4. Correlation between EAT thickness and procedural details

EAT thickness	Unsuccessful procedure (n=19)		Successful procedure (n=87)		Total (n=106)	
	rs	P	rs	p	Rs	p
Fluoroscopy time (min)	-0.13	0.696	0.06	0.663	0.31	0.008
Duration of Radiofrequency energy delivery (min)	-0.55	0.063	-0.01	0.933	0.23	0.053
Procedural duration (min)	0.20	0.541	-0.09	0.500	0.21	0.085
PVCs frequency	-0.40	0.214	0.10	0.452	-0.02	0.843

rs: Spearman correlation coefficient

Table 5. Receiver-operating characteristic (ROC) curve for the prediction of procedural success using EAT thickness.

AUC Value	p-değeri	Cutoff	Sensitivity	Specificity	+PV	-PV	
		0.85	<0.001	>7.70	91.67%	67.80%	36.70% 97.60%

AUC: Area under the ROC curve; +PV: Positive predictive value; -PD: Negative predictive value

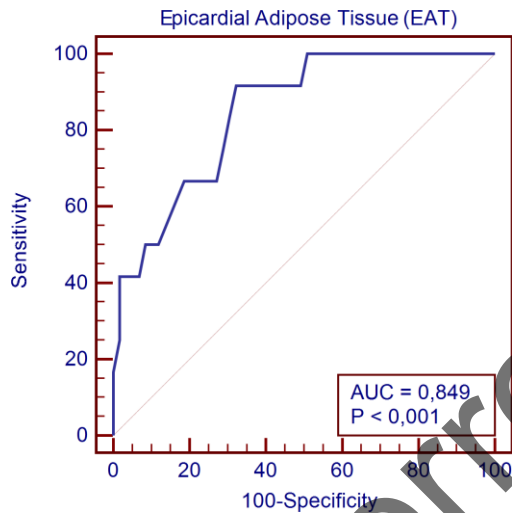


Figure-1. Receiver-operating characteristic (ROC) curve for the prediction of procedural success using Epicardial Adipose Tissue (EAT). The area under the curve (AUC) for EAT is 0.85(95%CI:0.74-0.92) with $p < 0.001$.

Table-6. Association of procedural success with Multiple Variables in Univariate and Multivariate Logistic Regression Analyses.

Variables	Univariate OR (95% CI)	P value	Multivariate OR (95% CI)*	P value
EAT thickness	0.92 (0.97-0.99)	<0.001	0.92 (0.97-0.99)	<0.001
Max QRS duration	0.98 (0.93-1.03)	0.35	-	-
Intrinscoid deflection time	0.95 (0.91-0.99)	0.02	0.98 (0.92-1.03)	0.41
Pseudo-delta	7.8 (2.5-24.3)	<0.001	6.6 (1.5-29.4)	0.01

EAT, epicardial adipose tissue; CI, confidence interval; OR, odds ratio

*Adjusted for: Epicardial adipose tissue, Intrinscoid deflection time and pseudo-delta