

Peer Review File

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Reviewer A

The authors should be congratulated on an excellent study. The manuscript was well written and easy to follow.

Reply: Thank you for your work and for your recognition of this article.

Reviewer B

General comments

Thank you for the opportunity to review this interesting manuscript. In this study, Wang et al. examined the influence of epicardial adipose tissue volume on the risk of idiopathic ventricular tachycardia. They showed that patients with idiopathic ventricular tachycardia have increased EAT volumes compared to the control group. Overall, the results are exciting. However, it would be interesting if the authors could explain more details of the results, especially about the EAT volumes.

Specific points

General:

- Please check for English grammar (line 54, 59, 116, 130, 145, 150)

Reply: Thank you for your positive comments and valuable suggestions to improve the quality of our manuscript. We revised the English grammar (line 54, 59, 116, 130, 145, 150). Additionally, sorry for the language problem. We tried our best to improve the language. And a thorough revision has been made to address the language issues with the help of AJE English Language Editing Service. We hope you will find this revised version satisfactory.

This document certifies that the manuscript

The Relationship between Epicardial Adipose Tissue Volume on Coronary Computed Tomography Angiography and Idiopathic Ventricular Tachycardia

prepared by the authors

Zhe Wang, Jiawei Chen, Hehe Guo, Jiaju Li, Lichen Ren, Xiaojie Chen, Liping Sun, Yingwei Chen

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Abstract/Title:

- Please include the study design in the abstract or title

Reply: Thank you for your comment. We agreed and done. We were really sorry for our careless mistakes. We made major changes to the abstract section. This was a retrospective case-control study running from January 2020 to September 2022. We have modified our text as advised (see Page 1, line 11-12).

Introduction:

- The purpose of this study was to examine the association between EAT and IVT. I would suggest adding a hypothesis.

Reply: Thank you for your comment. We agreed and done. We were really sorry for our careless mistakes. We made major changes to the abstract section. At present, the role of EAT in IVT remains unclear. We hypothesized that greater EAT volume is associated with the presence of IVT In this retrospective study. We have modified our text as advised (see Page 3, line 51-54).

Methods:

- What is the study design of this paper?

- Line 71: please explain the abbreviation CCCT

- The control group consisted of hospitalised patients. What was the reason for admission of these patients? And in which department? Were these patients only from the department of cardiology? (if so, what are the implications for the generalizability of the results?)

- EAT was quantified using semiautomatic software. Different definitions of EAT have been described in multiple studies. Could you define the specific location of EAT? (In other words; did you include adipose tissue external to the pericardium?)

- Could you describe a sample size calculation or power analysis?

Reply: Thank you for your comment. We agreed and done. We made major changes to the manuscript. We have tried our best to modify our manuscript to meet the reviewer's requirements. If there are any other modifications we could make, we would like very much to modify them. We sincerely hope that our manuscript could be considered for publication. We extend our sincere gratitude for your time and dedication to managing our manuscript.

(1) This was a retrospective case-control study running from January 2020 to September 2022. We have modified our text as advised (see Page 1, line 11-12).

(2) We were really sorry for our careless mistakes. We corrected CCCT to CCTA.

(3) We performed a control group of hospitalized patients without IVT undergoing CCTA during the same time period. The patients in the control group were all hospitalized patients for different reasons, such as chest tightness, shortness of breath, chest pain, and so on. In our institution, CCTA was performed for hospitalized patients who screened for coronary heart disease. (see Page 4, line 66-72). Additionally, patients enrolled in our study rarely underwent cardiac magnetic resonance imaging, which may have resulted in patients with cardiomyopathy being missed. Further prospective studies are needed to confirm the findings (page 10, lines 204-207).

(4) EAT is defined as adipocytes between the visceral epicardium and the myocardium (see Page 6, line 101).

(5) We used the PASS software with α of 0.05 and β set to 0.1 for Type I error, the ratio of experimental to control group was 1:1, and according to previous literature (Cosson E, Nguyen MT, Rezgani I, Berkane N, Pinto S, Bihan H, Tatulashvili S, Taher M, Sal M, Soussan M, Brillet PY, Valensi P. Epicardial adipose tissue volume and myocardial ischemia in asymptomatic people living with diabetes: a cross-sectional study. *Cardiovasc Diabetol*. 2021 Nov 24;20(1):224. doi: 10.1186/s12933-021-01420-5. PMID: 34819079; PMCID: PMC8613918), the mean volume of EAT in the control group was 94, the mean volume of EAT in the experimental group was 110, the standard deviation of difference between the two groups was 0, and the final sample size required was 92 patients, 46 patients in the experimental group, and 46 patients in the control group. Therefore, the sample size of the study satisfies the requirement.

Results:

- Line 145 and 158-159: PSM and PS-adjusted are both used in the text. In my opinion, this can be confusing. Please use one of these two definitions. Moreover, the abbreviation "PS" is explained, while "PSM" is not.

- Patients with diagnosed with IVT had larger EAT volumes compared to the control group. What was this difference? You mentioned that this difference was statistically significant. Could you include the p-values? Line 155: Please provide the volumes.

Reply: We sincerely thank the reviewer for careful reading. Thank you for your good comments. We agreed and done. We have added some content to the article.

(1) We were really sorry for our careless mistakes. In this paper, we unified PS-adjusted and replaced PSM with PS-adjusted.

(2) The volume of EAT distribution is described in Figure 2. Patients with IVT had

significantly larger EAT volume compared with control patients in the unadjusted cohort (169.2 ± 48.2 ml vs. 92.7 ± 35.8 ml, $p < 0.001$). IVT patients had also significantly larger EAT volumes compared with control patients in the PS-adjusted cohort (171.1 ± 50.0 ml vs. 109.6 ± 37.1 ml, $p < 0.001$), (see Page 10, line 181-189).

Discussion:

- In my opinion, it is not clear why this is a cross-sectional study. This study included a case and control group and compared EAT in these two groups. Patients were retrospectively included, based on outcome (IVT). Cross-sectional studies are often used to examine prevalence.

- Line 189: please add what other risk factors are meant in this sentence.

- Line 237-239: Could you explain this sentence? In other words, how might EAT guide this treatment? Should we increase the dosage of these medications when patients have high volumes of EAT?

- Line 237-241: Did you adjust for these drugs in your statistical analysis?

Reply: We sincerely thank the reviewer for careful reading. Thank you for your good comments. We agreed and done. We have added some content to the article.

(1) We were really sorry for our careless mistakes. This is a retrospective cohort study from January 2020 to September 2022. We have modified our text as advised (see Page 3, line 34-35).

(2) Let's further clarify what are the other risk factors. Variables with $p < 0.10$ in the univariable analysis and important factors were included in the multivariable analysis model, including BMI, LVEF, E/A ratios < 1 , EAT attenuation, and EAT volume (per increase 10 ml). The multivariable logistic analysis found that EAT volume (per increase 10 ml, OR: 1.29, 95% CI: 1.17-1.41, $p < 0.001$) was an independent risk factor for IVT patients in the unadjusted cohort, as shown in Table 2. In the PS-adjusted cohort, EAT volume (per increase 10 ml, OR: 1.43, 95% CI: 1.25-1.64, $p < 0.001$) and EAT attenuation (OR: 1.13, 95% CI: 1.01-1.27, $p = 0.035$) were independently related to IVT, as depicted in Table 3 (see Page 11-12, line 207-214).

(3) New evidence suggests that physical activity and low-calorie diets may be effective non-pharmacological strategies for reducing EAT (see Page 14, line 266-268). Additionally, EAT may guide treatment decisions in patients with diabetes because drugs such as metformin, sodium glucose cotransporter 2 inhibitors, and glucagon-like peptide-1 receptor agonists are associated with reduced EAT. Some anti-inflammatory drugs such as colchicine and methotrexate may also have indirect effects on reduce EAT. However, we should note that whether reduction of EAT can confer benefits for patients' clinical outcomes requires further demonstration. When patients have a large EAT volume, whether drug treatment is needed should also be further confirmed (see Page 14, line 273-277).

(4) Our study did not include drugs such as hypoglycemia, which may have biased the results. We added these in the limitations section (see Page 15, line 287-288). If there are any other modifications we could make, we would like very much to modify them.

Reviewer C

Congrats to the authors for the huge job that they have done. The paper is well written and reads well. The results were clearly presented, the statistical methods used are corrects and the authors were fair specifying all the limitation of the study.

Just two minor comments:

-The introduction should provide more background regarding EAT and its pathophysiological functions

Reply: We sincerely thank the reviewer for careful reading. Thank you for your comment. We agree and done. Under physiological conditions, EAT is 20% of heart mass. EAT can be considered as an endocrine organ, which promotes the occurrence and development of arrhythmia through the vasocrine or paracrine secretion of pro-inflammatory and pro-fibrotic factors (see Page 5, line 67-70).

-The authors should add, in the text, the numerical values with SD showed in figure 4.

Reply: Thank you for your comment. We agreed and done. The median EAT volume was 147.3 ml in patients with IVT. There was a non-statistically significant increase of QTc in IVT patients with large EAT volume (≥ 147.3 ml) compared to low EAT volume (<147.3 ml) in IVT patients (437.7 ± 26.8 ms vs. 425.7 ± 29.0 ms, $p=0.058$). The large EAT volume (≥ 147.3 ml) patients had significantly longer Tp-e, and Tp-e/QTc, compared with low EAT volume (<147.3 ml) in IVT patients (114.1 ± 12.8 ms vs. 108.0 ± 13.0 ms, $p=0.034$; 0.26 ± 0.03 vs. 0.24 ± 0.04 , $p=0.020$; respectively), (see Page 11-12, line 207-214).

Reviewer D

The article by Dr. Z Wang et al describes the association between Epicardial Adipose Tissue (EAT) and Idiopathic ventricular Tachycardia (ITV). The study involved a total of 300 patients (100 ITV and 200 controls) undergoing CCTA retrospectively recruited between 2020 and 2022.

The authors observed that ITV patients had higher EAT volume compared to control subjects. Thus, they concluded that larger EAT volume is associated with an extended repolarization process in ITV patients.

Authors are to be praised for evaluating EAT volume by using a 3-D imaging technique (CT) that not only thickness or diameter. They identified adipose tissue based on Hounsfield units. Methodology is adequate, the results are mostly solid, the discussion is balanced, the conclusions are supported by the data and the manuscript reads well

Concerns.-

One of the major problems is the novelty of the observations. The authors have previously reported (Z Wang et al 2023) the association between EAT volume patients with ITV recurrence after catheter ablation, have larger EAT volume is associated with. Now they described the association between ITV patients and EAT volume compared with patients without ITV. Interesting but quite expected.

I assume that the study involved mostly Chinese subjects. Thus, this info should be clearly stated in the title.

Based on the figure 1. I assume that EAT covering both ventricles, atrioventricular groove and both atria were included? Distinction is important since the manuscript is focusing on idiopathic ventricular tachycardia (IVT). Impact of EAT has been postulated to be local. EAT covering atria is associated with atrial fibrillation and EAT covering ventricles with ventricular arrhythmias. It would be interesting to know the association in this manuscript between ventricular EAT and IVT. Otherwise, this should be mentioned in limitations.

Reply: Thank you for your comment. We agreed and done. The EAT quantitative software we used was unable to quantify the periventricular EAT volume. The effect of periventricular EAT volume on IVT needs to be further studied. We have modified our manuscript in the limitation section (see Page 15, line 291-294).

Also, it shows a 4-chamber view of the heart, but which was the upper anatomical limit to evaluate EAT? Most previous studies use pulmonary artery bifurcation as upper limit (with ventricular apex as lower anatomical limit). However, this is not explained in the manuscript.

Reply: Thank you for your comment. We agreed and done. We used the pulmonary artery bifurcation as the superior limit of the heart and the end of the left ventricular apex as the inferior limit. We added these contents in the method section (see Page 8, line130-132).

Table 1 showing the demographic characteristics of the patients involved in the study (Table 1) indicates significantly higher incidence of obesity among the IVT group vs the control. But there is no indication on any medication being taken by the groups. This info should be included in the article.

Reply: Thank you for your comments. Your advice makes our manuscript more stringent. Our article describes statin use in two groups. There were no significantly difference in statin use between two groups, as shown in Table 1. Our study did not include drugs such as hypoglycemia, which may have biased the results. We added these contents in the limitation section (see Page 15, line 287-288).

Reviewer E

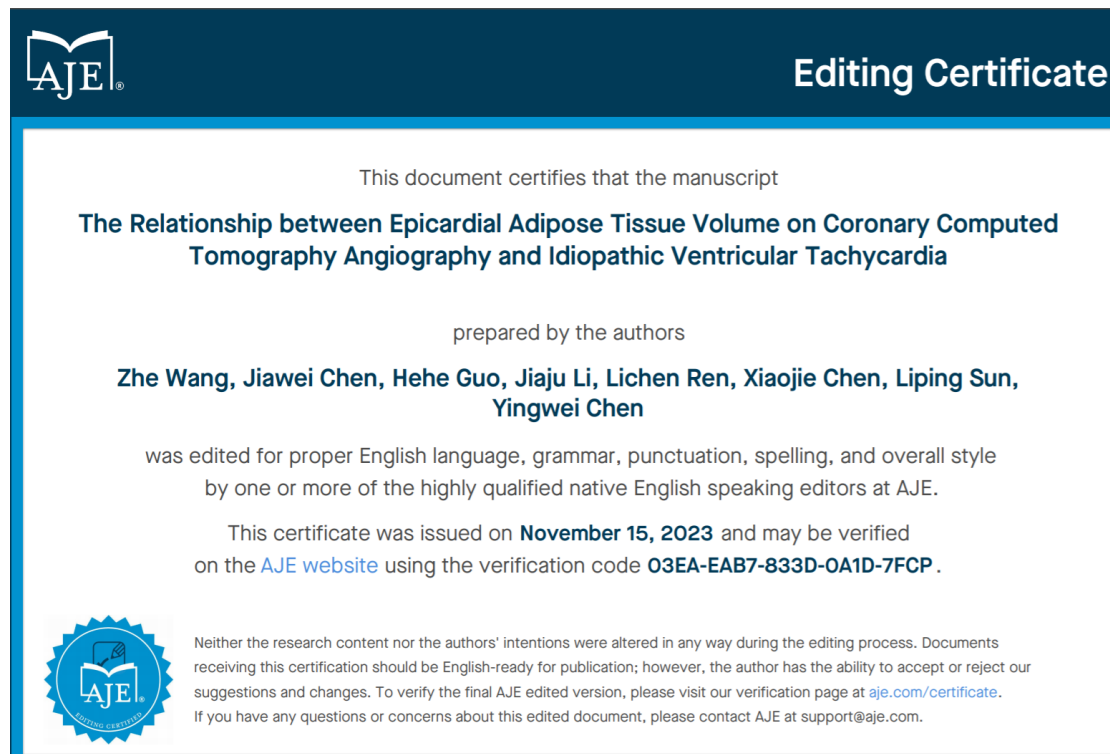
The authors perform a very interesting study in idiopathic ventricular tachycardia. However, this is an exclusion criteria once other entities have been ruled out. In this case, although structural heart disease was an exclusion criteria, some patients showed low ejection fraction in the CCTA. Therefore, we cannot assume that these patients didn't suffer from non-ischemic cardiomyopathy and in that case the tachycardia could be secondary and not idiopathic. Authors should clarify this point.

Reply: Thank you for your comment. We agreed and done. We have tried our best to modify our manuscript to meet the reviewer's requirements. Although structural heart disease is an exclusion criterion, some patients show low left ventricular ejection fraction. We cannot assume that these patients do not have non-ischemic cardiomyopathy, and ventricular tachycardia may be secondary, thus affecting the results. We added these contents in the limitation section (see Page 15, line 280-288).

If there are any other modifications we could make, we would like very much to modify

them. We sincerely hope that our manuscript could be considered for publication. We extend our sincere gratitude for your time and dedication to managing our manuscript. Also, there are some minor spelling mistakes to review.

Reply: Thank you for your positive comments and valuable suggestions to improve the quality of our manuscript. We are sorry for the language problem. We tried our best to improve the language. And a thorough revision has been made to address the language issues with the help of AJE English Language Editing Service. We hope you will find this revised version satisfactory.



Reviewer F

The authors examined the impact of EAT volume and idiopathic VT in a case-control study.

1. The abstract states 100 IVT patients and 200 controls, but the body of the manuscript do not have those numbers.

Reply: Thank you for your comment. We agreed and done. We were really sorry for our careless mistakes. The abstract section is written incorrectly, we have revised it to keep it consistent with the manuscript. This was a retrospective case-control study running from January 2020 to September 2022. IVT patients (n=81) and control patients (n=162) undergoing coronary computed tomography angiography (CCTA) were enrolled. (see Page 3, line 34-35).

2. Could details on the method of propensity matching be provided?

Reply: Thank you for your comment. We agreed and done. The 1:1 propensity score

(PS)-adjusted method was applied in the observational case-control study to reduce the bias in selecting the case controls, using a greedy and nearest neighbor matching algorithm with a caliper distance equal to 0.2. This process was done with the R package “MatchIt” (R Project for Statistical Computing),(see Page 8-9, line 142-147).

3. Are EAT volumes indexed for BSA?

Reply: We sincerely thank the reviewer for careful reading. Thank you for your comment. We study the EAT volume rather than the EAT volume index for BSA. However, we used multivariate logistic analysis to explore the correlation between EAT volume and IVT after adjusting other risk factors (BMI, LVEF, E/A ratios < 1, and EAT attenuation). EAT volume was independently related to IVT.

4. Do the authors have data on total EAT vs periventricular EAT?

Reply: Thank you for your comment. The EAT quantitative software we used was unable to quantify the periventricular EAT volume. The effect of periventricular EAT volume on IVT needs to be further studied. We have modified our manuscript in the limitation section (see Page 14, line 293-300)

We used well-dedicated semiautomatic software to measure EAT volume (syngo via Frontier Cardiac Risk Assessment, version 1.2.3, Siemens Healthineers, Germany). Previous studies have confirmed that EAT volume can be measured by CCTA (Europace. 2023 May 19;25(5):euad102. doi: 10.1093/europace/euad102; Japanese journal of radiology. 2018;36:528-536.doi:10.1007/s11604-018-0752-1; Eur J Radiol. 2015 Jun;84(6):1062-7. doi: 10.1016/j.ejrad.2015.03.018; European radiology. 2022;32:6028-6036.doi:10.1007/s00330-022-08781-9). We have tried our best to modify our manuscript to meet the reviewer’s requirements. If there are any other modifications we could make, we would like very much to modify them. We sincerely hope that our manuscript can be considered for publication. We extend our sincere gratitude for your time and dedication to managing our manuscript.