BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Diagnosis of left atrial appendage thrombus using cardiac computed tomography: new insights from thrombi locations

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-079876
Article Type:	Original research
Date Submitted by the Author:	14-Sep-2023
Complete List of Authors:	guo, chuxian; Guizhou Provincial People's Hospital, Cardiology Department; Guizhou Medical University Jiang, Zhi; Guizhou Provincial People's Hospital, Cardiology Department He, Jionghong; Guizhou Provincial People's Hospital, Cardiology Department; Guizhou Provincial People's Hospital, Echocardiography Department Ma, Haiyan; Guizhou Provincial People's Hospital, Radiology Department Wang, Yuquan; Guizhou Provincial People's Hospital, Radiology Department Tan, Jing; Guizhou Provincial People's Hospital, Cardiology Department; Guizhou Provincial People's Hospital, Echocardiography Department Ou, Qiaoqiao; Guizhou Provincial People's Hospital, Cardiology Department; Guizhou Medical University Tian, Ye; Guizhou Provincial People's Hospital, Cardiology Department Tian, Longhai; Guizhou Provincial People's Hospital, Cardiology Department Liu, Qifang; Guizhou Provincial People's Hospital, Cardiology Department Huang, Jing; Guizhou Provincial People's Hospital, Cardiology Department Yang, Long; Guizhou Provincial People's Hospital, Cardiology Department
Keywords:	Stroke < NEUROLOGY, Ultrasound < RADIOLOGY & IMAGING, Computed tomography < RADIOLOGY & IMAGING, Thromboembolism < CARDIOLOGY
Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.	
Supplementary material_Video S1.mp4	

SCHOLARONE™ Manuscripts

Article Title: Diagnosis of left atrial appendage thrombus using cardiac computed tomography: new insights from thrombi locations

Running Head: Detection of Left Atrial Appendage Thrombus Using Cardiac CT

Authors: Chuxian Guo [ad]*; Zhi Jiang [a]*; Jionghong He [ab]; Haiyan Ma [c]; Yuquan Wang [c]; Jing Tan [ab]; Qiaoqiao Ou [ad]; Ye Tian [a]; Longhai Tian [a]; Qifang Liu [a]; Jing Huang [a]; Long Yang [a]

Affiliations: From [a] Cardiology Department, Guizhou Provincial People's Hospital, Guiyang, China; [b] Echocardiography Department, Guizhou Provincial People's Hospital, Guiyang, China; [c] Radiology Department of Guizhou Provincial People's Hospital, Guiyang City, China; [d] Guizhou Medical University, Guiyang, China.

* Chuxian Guo and Zhi Jiang contributed equally to the study.

Corresponding author: Long Yang, Department of Cardiology, Guizhou Provincial People's Hospital, NO. 83 East Zhongshan Road, Guizhou Province, Guiyang City, 550002, China. E-mail: yanglong1001@outlook.com. Telephone: +86-18198169283. Fax: +86 0851- 85924943

Word count of the main part of the manuscript: 2081

Abstract

Background Cardiac computed tomography (CCT) is an emerging non-invasive modality for assessing left atrial appendage (LAA) thrombus, but the results were conflicting. Our study aims to evaluate the accuracy of CCT for detecting LAA thrombus in patients undergoing catheter ablation of atrial fibrillation (AF), using transesophageal echocardiography (TEE) as the reference standard.

Methods From May 2017 to December 2022, 726 patients (male: 60.2%, age: 61±11 years) who had both TEE and CCT before catheter ablation of AF were retrospectively included. The CCT protocol consisted of one angiographic phase and one delayed scan 30 seconds later. LAA thrombi were defined as solid masses on TEE or persistent defects on CCT. The thrombus dimension and location, the LAA filling and emptying flow velocity were assessed by TEE.

Results Of the 57(7.9%) patients with LAA thrombi identified by TEE, 29(50.9%) were located at the LAA ostium, and 28(49.1%) were in the LAA. The former showed higher motility following blood flow and heartbeats than the latter. The CCT detected 14(48.3%) of the LAA-ostium thrombi but 25(89.3%) of those in the LAA ($p = 0.001$). The LAA-ostium thrombi with the LAA mean flow velocity higher than 0.35m/s and maximum diameters shorter than 10mm were more prone to have CCT false-negative results.

Conclusion For patients undergoing catheter ablation for AF, CCT with a 30s delay scan is less sensitive to LAA thrombi than TEE, especially for LAA-ostium thrombi with smaller sizes and higher LAA flow velocity.

Keywords stroke; embolism; thrombosis; pulmonary vein isolation; cardiac imaging techniques; ultrasound.

Strengths and limitations of this study

1. A major strength of our study is based on a large cohort with high incidence of left atrial appendage thrombi.

2. We first report the impact of thrombus location on the sensitivity of CCT, using TEE as reference standard.

3. A limitation of this study is that it is a single-center and retrospective study.

4. The CCT protocol contained only one delayed-phase scan. Whether multiple delayed-phase scans reduce false-negative CCT results is unclear.

Title: Diagnosis of left atrial appendage thrombus using cardiac computed tomography: new insights from thrombi locations

Introduction

Transesophageal echocardiology (TEE) is currently the gold standard for the assessment of left atrial appendage (LAA) thrombi in patients undergoing catheter ablation of atrial fibrillation (AF)[1]. In the past decades, cardiac computed tomography (CCT) has been widely studied for detecting LAA thrombus[2-5]. Recently, the delayed contrast-enhanced CCT at 6 minutes was reported to reach 100% sensitivity and negative predictive value in detecting LAA thrombus[6]. For patients who are not tolerant of the discomfort associated with TEE, CCT is proposed as a reliable alternative[7]. However, the accuracy of CCT varied between studies[2-5, 8], raising the safety concern and limiting the routine use of CCT.

The left atrial thrombi were classified into a movable ball, fixed ball, and mountain according to their morphology[9]. Around 1/3 of the thrombi in the left atrium were movable. Although CCT is of high spatial resolution, its temporal resolution is 4~17Hz, and it takes 60ms ~ 250ms to acquire one slice[8, 10-12]. Compared to TEE, which allows live display with a high spatiotemporal resolution (<1mm, 20~30Hz)[13], CCT is theoretically inferior for identifying moving objects in the left atrium. In addition, the circulatory stasis and the fibrillation of the atrial wall during AF also increase the difficulty of detecting movable thrombi[14]. In previous studies, the presence of LAA thrombus was 2(0.24%) ~16(19.04%)[2-5, 15]. The high sensitivity and negative predictive value of CCT could be attributed to the low incidence of movable thrombus. Therefore, it is essential to investigate the diagnostic accuracy of CCT in a larger cohort with a higher incidence of LAA thrombus.

In the current study, we retrospectively included 726 patients who had both TEE and CCT before catheter ablation for AF. 57(7.9%) patients were diagnosed with LAA thrombi using TEE. We aimed to evaluate the sensitivity of CCT in detecting LAA thrombus and to analyze the risk factors of false-negative results.

Methods

Study population

From May 2017 to December 2022, patients were routinely scheduled for TEE and CCT before catheter ablation of AF in Guizhou Provincial People's Hospital. Those who had both examinations within a 12-hour interval on the same day were retrospectively included. All the patient characteristics and images were acquired from the clinical database. The CHA_2DS_2-VASc score was calculated following the 2020 ESC guideline[1]. The study was approved by the institutional ethics committee of Guizhou Provincial People's Hospital. The informed consent was waived due to the retrospective nature, and no identified information was collected.

CCT protocol

All patients were examined with a third-generation dual-source CT (SOMATOM Force, Siemens Healthineers, Forchheim, Germany). The imaging protocol included a standard

angiographic-phase acquisition to assess the anatomy of the left atrium and one delayed-phase acquisition at 30 s after contrast injection to detect thrombi. No electrocardiography gating was used. The tube voltage and current were automatically adjusted using the CARE kV or CARE DOSE 4D with the reference of 100kv and 250mA. The gantry rotation time was 250ms, and the detector collimator was 192×0.6 mm. The scanning image covers the range from the aortic arch to the cardiac base. The monitoring site was localized within the left atrium. The contrast material containing 350 mg/ml of iodine was administrated intravenously at 4-5 ml/s with a total dose of 35 ml by a double-barrel syringe, followed by the same amount of 0.9% saline. For the angiographic phase, the scanning was triggered when the monitoring site reached 90 HU. Then the delayed phase was acquired 30 s later. All images were reconstructed using the ADMIRE algorithm grade 3 with a layer thickness of 1 mm and interlayer spacing of 0.7 mm. The 3D left atrium and pulmonary veins were reconstructed using the Syngo.via software (Siemens Healthcare, Forchheim, Germany).

CCT image analysis

Images were transferred to an external workstation (Syngo VPCT body, Siemens Healthcare, Forchheim, Germany). Two independent radiologists with more than eight years of cardiovascular imaging, blinded to all patients' data, retrospectively evaluated the presence of LAA thrombus and LAA morphology. Thrombus was defined as a persistent filling defect in the 30s-delayed scans. The LAA morphology was classified into simple or complex according to their main and branching structures on the 3D reconstructions[16]. In case of disagreement, a final joint reading was performed to achieve consensus.

Transesophageal echocardiology

A PhilipsiEPIQ7C color Doppler ultrasound diagnostic instrument (Philips, Amsterdam, the Netherlands) and an X7-2t probe were used. The left atrium and LAA were scanned using a complete 2D, colored, pulsed, and continuous-wave Doppler echocardiogram according to the EACVI recommendations[17]. Thrombi were defined as circumscribed echogenic or echolucent masses distinct from the atrial wall. LAA ostium was defined as within the 5mm range of the junction between the smooth atrial wall and trabeculated LAA. The dimensions and locations of thrombi were assessed if present. The LAA filling and emptying velocity was averaged by ten consecutive measurements of the backward and forward flow rates using the pulsed wave Doppler. LAA mean flow velocity (LAAMFV) was calculated by halving the sum of the LAA filling and emptying velocity. Two independent cardiologists with more than five years of experience in echocardiology evaluated the presence of LAA thrombus and measured the flow velocity. Disagreements were resolved by consensus.

Statistical analysis

Continuous variables were expressed as mean ± SD deviation. The Student's t-test was used for comparison if normally distributed; otherwise, the Mann-Whitney U test was used. Categorical variables were expressed as frequency (percentage). The Chi-square test was used for comparison if the expected frequency is more than 5; otherwise, Fisher's exact test was used. A two-tailed p value of less than 0.05 was considered statistically significant. Using TEE as the reference standard, the diagnostic performance of CCT for LAA thrombi was calculated. All statistical analysis was performed using SPSS 26.0.

Results

Patient characteristics

A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study (Fig. 1). The patients with LAA thrombus had a higher incidence of previous stroke/transient ischemic attack (TIA) and congestive heart failure, larger left atrial size, worse left ventricular function and a higher rate of complex LAA morphology than those without LAA thrombus ($p < 0.05$) (Table 1).

Twenty-nine (50.9%) of the thrombi were located at the LAA ostium and 28(49.1%) were in the LAA. The clinical characteristics and maximum thrombus diameter were similar between the patients. The thrombi at the LAA ostium were accompanied by higher LAA filling and emptying velocities than those in the LAA (Supplementary material online, Table S1). The former also showed significantly higher mobility following the blood flow and cardiac motion than the latter (Supplementary material online, Video S1).

Diagnostic accuracy of CCT

The CCT had an overall sensitivity of 68.4% and a specificity of 99.4% to the LAA thrombi (Table 1). However, the CCT was less sensitive to the thrombi at LAA ostium than those in the LAA (48.3% vs. 89.3%, $p = 0.001$) (Supplementary material online, Table S1).

Representative images are shown in Fig. 2.

Given that high sensitivity is essential to exclude LAA thrombus, the CCT results of the LAA thrombi underwent further analysis. Compared with the CCT true-positive thrombi, the false-negative ones more frequently located at the LAA ostium (83.3% vs. 35.9%, $p = 0.001$), were shorter in the maximum diameters (8±2mm vs. 14±9mm, $p < 0.001$), and were accompanied by higher LAA filling and emptying velocities (0.53±0.15 m/s vs. 0.38±0.19 m/s, $p = 0.001$; 0.55±0.21 m/s vs. 0.37±0.14 m/s, $p < 0.001$) (Table 2). By scattering the CCT results on the 2-D plane that consisted of LAAMFV and thrombus maximum diameter, the thrombi at the LAA ostium with the LAAMFVs higher than 0.35m/s and maximum diameters shorter than 10mm were more prone to have CCT false-negative results (Fig. 3A). The CCT false-negative thrombi in the LAA had maximum diameters shorter than 8mm (Fig. 3B).

Discussion

Major findings

We reevaluated the accuracy of CCT for detecting LAA thrombus in the 726 patients undergoing catheter ablation for AF. TEE identified 57(7.9%) patients with LAA thrombi, of which 29(50.9%) were at the LAA ostium and 28(49.1%) in the LAA. The CCT was less sensitive in detecting LAA-ostium thrombi with smaller maximum diameters and higher LAAMFV.

Concordance

LAA thrombus is thought to form initially inside the LAA, where circulatory stasis is the greatest, and then extends towards the ostium. However, we found over half of the thrombi located at the LAA ostium. The result was concordant with a previous study that 46.3% of the thrombi were at the entrance section of LAA[9]. The presence of pits and troughs adjacent to the LAA orifice was reported in 57.7% of the human heart specimens[18]. It could be the anatomic basis for thrombosis. Another study using TEE discovered small recesses proximal to the entry of LAA in a significant number of patients, but no thrombus related to these structures was detected following LAA occlusion[19]. The discrepancy could be due to patient selection bias. Nonetheless, our findings raised concerns about the role of LAA-ostium recesses in thrombosis.

Although the third-generation 64-slice dual-source CT was employed in the current study, its sensitivity to LAA thrombi was not improved. The sensitivity of 89.3% to the thrombi in the LAA was comparable to the previous studies[2, 10, 11, 20-22]. However, the sensitivity significantly decreased for the LAA-ostium thrombi, which showed higher motility following blood flow and heartbeats than those in the LAA (Supplementary material online, Video S1). We further identified that the LAA-ostium thrombi with smaller sizes and higher LAA flow velocity were more prone to be missed using the CCT. As a higher temporal resolution is essential to detect movable objects[23], our findings suggested the impact of thrombus motility on CCT imaging. By calculating the gantry rotation time of 250ms, the CCT had a temporal resolution of 4Hz, significantly less than that of the TEE (20~40Hz). Thus, the low sensitivity of CCT in our study could be presumed to: (1) inadequate temporal resolution, (2) the high proportion of movable LAA-ostium thrombi, (3) the lack of ECG gating, (4) only one 30s delayed scan was used. The 4 CCT false-positive results in our study could be the misdiagnosis of thrombus due to circulatory stasis during AF[6, 24].

Discordance

Several studies reported that the CCT had 100% sensitivity in detecting LAA thrombi using ECG gating and single-segment reconstruction algorithm[25, 26], or multiple delayed-phase scans[3, 14, 27]. However, these studies have the following limitations: (1) Although the single-segment reconstruction algorithm increased the CCT's temporal resolution to 12Hz, the low incidence of LAA thrombus [2(0.24%) ~16(19.04%)] and the less variation of thrombus location could have overestimated the sensitivity of CCT for detecting LAA thrombi in a broader range of patients. (2) The multiple delayed-phase scans distinguished the thrombi from filling defects due to circulatory stasis. Still, the technique could not necessarily increase the sensitivity to smaller and movable thrombi located at the LAA ostium. We suggest that the CCT approach to detect LAA thrombi could differ according to their location. For static thrombi in LAA, persistent filling defects in multiple delayed-phase scans have been well established. For thrombi at LAA ostium, a temporal resolution comparable to TEE and even dynamic visualization could be necessary due to their higher motility.

Clinical implication

Our study found that the CCT with a 30s delayed scan did not reliably exclude LAA thrombus, especially those located at the LAA ostium. We did not find any clinical characteristics associated with the thrombus location. TEE is the only recommendation for stroke risk management for patients undergoing catheter ablation of AF in the 2020 ESC guideline[1]. For those who do not tolerate TEE, intracardiac echocardiography could be considered[28].

Limitations

Firstly, this retrospective single-center study included only patients undergoing catheter ablation for AF. The study's findings may not be generalizable to other patients with AF. Secondly, the CCT protocol contained only one delayed-phase scan. Whether multiple delayed-phase scans reduce false-negative CCT results is unclear. Thirdly, other factors unaccounted for in this analysis – heart rhythm, atrial/ventricular rate, and blood pressure during the TEE and CCT – could affect the conclusions. Fourthly, although the interval between the TEE and CCT was less than 12 hours, it is theoretically possible for thrombi to form or disappear within this timeframe. Lastly, the incidence of LAA thrombus was higher than that in previous studies (partially due to less adherence to anticoagulation treatment), which could have affected the thrombus location and motility.

Conclusions

In patients undergoing catheter ablation of AF, CCT with a 30s delay scan is less sensitive than TEE in detecting LAA thrombi, especially those located at LAA ostium with smaller sizes and higher LAA flow velocity.

Acknowledgments

We thank Nicholas Tan and Jason Tri from Mayo Clinic for their dedicated help in preparing the manuscript.

Data sharing statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

This study has received funding from the Science and Technology Support plan of Guizhou Province [No. (2017)2885 and (2018)2794] to L.Y. and Y.T., the Clinical Special Projects in Guizhou Province [NO. (2019)4430] to Q.L., and the Clinical Research Center Project of the Department of science and technology of Guizhou Province [NO. (2017)5405] to L.Y.

Ethical approval

This study received approval from the institutional ethics committee of Guizhou Provincial People's Hospital.

Contributors

Chuxian Guo and Zhi Jiang: Conceptualization, Methodology, Formal analysis, Writing-original draft, Writing – review & editing. Jionghong He, Haiyan Ma and Yuquan Wang: Conceptualization, Methodology, Formal analysis, Visualization, Writing – review & editing.

Jing Tan: Conceptualization, Methodology, Investigation, Writing – review & editing. Qiaoqiao Ou: Conceptualization, Investigation, Writing – review & editing. Ye Tian and Qifang Liu: Conceptualization, Writing – review & editing, Funding acquisition. Longhai Tian and Jing Huang: Conceptualization, Investigation, Writing – review & editing. Long Yang: Conceptualization, Methodology, Formal analysis, Writing – review & editing, Supervision, Funding acquisition. All authors read and approved the final manuscript.

Declaration of Competing Interest The authors declare that they have no competing interests.

Supplementary Material

Video S1 The online supplementary Video S1 showed LAA thrombi imaging of different location in TEE

A-C Thrombus located at the LAA ostium. D-F Thrombus located in the LAA.

Table S1 Patient characteristics between thrombus locations.

References

[1] Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021; **42**: 373-498.

[2] Dorenkamp M, Sohns C, Vollmann D, et al. Detection of left atrial thrombus during routine diagnostic work-up prior to pulmonary vein isolation for atrial fibrillation: Role of transesophageal echocardiography and multidetector computed tomography. *International Journal of Cardiology* 2013; **163**: 26-33.

[3] Zhai Z, Tang M, Zhang S, et al. Transoesophageal echocardiography prior to catheter ablation could be avoided in atrial fibrillation patients with a low risk of stroke and without filling defects in the late-phase MDCT scan: A retrospective analysis of 783 patients. *Eur Radiol* 2018; **28**: 1835-1843.

[4] Li W, Yu F, Zhu W, et al. Detection of left atrial appendage thrombi by third-generation dual-source dual-energy CT: Iodine concentration versus conventional enhancement measurements. *Int J Cardiol* 2019; **292**: 265-270.

[5] Guha A, Dunleavy MP, Hayes S, et al. Accuracy of contrast-enhanced computed tomography for thrombus detection prior to atrial fibrillation ablation and role of novel Left Atrial Appendage Enhancement Index in appendage flow assessment. *Int J Cardiol* 2020; **318**: 147-152.

[6] Spagnolo P, Giglio M, Di Marco D, et al. Diagnosis of left atrial appendage thrombus in patients with atrial fibrillation: delayed contrast-enhanced cardiac CT. *Eur Radiol* 2021; **31**: 1236-1244.

[7] Yu S, Zhang H, Li H. Cardiac Computed Tomography Versus Transesophageal Echocardiography for the Detection of Left Atrial Appendage Thrombus: A Systemic Review and Meta-Analysis. *J Am Heart Assoc* 2021; **10**: e022505.

[8] Kottmaier M, Jilek C, Berglar S, et al. Exclusion of left atrial thrombus by dual-source cardiac computed tomography prior to catheter ablation for atrial fibrillation. *Clin Res Cardiol* 2019; **108**: 150-156.

[9] Abe Y, Asakura T, Gotou J, et al. Prediction of embolism in atrial fibrillation: classification of left atrial thrombi by transesophageal echocardiography. *Jpn Circ J* 2000; **64**: 411-415.

[10] Kim YY, Klein AL, Halliburton SS, et al. Left atrial appendage filling defects identified by multidetector computed tomography in patients undergoing radiofrequency pulmonary vein antral isolation: a comparison with transesophageal echocardiography. *Am Heart J* 2007; **154**: 1199-1205.

[11] Tang RB, Dong JZ, Zhang ZQ, et al. Comparison of contrast enhanced 64-slice computed tomography and transesophageal echocardiography in detection of left atrial thrombus in patients with atrial fibrillation. *J Interv Card Electrophysiol* 2008; **22**: 199-203.

[12] Martinez MW, Kirsch J, Williamson EE, et al. Utility of Nongated Multidetector Computed Tomography for Detection of Left Atrial Thrombus in Patients Undergoing Catheter Ablation of Atrial Fibrillation. *JACC: Cardiovascular Imaging* 2009; **2**: 69-76.

[13] Vegas A. Three-dimensional transesophageal echocardiography: Principles and clinical applications. *Ann Card Anaesth* 2016; **19**: S35-S43.

[14] Maltagliati A, Pontone G, Annoni A, et al. Multidetector computed tomography vs multiplane transesophageal echocardiography in detecting atrial thrombi in patients candidate to radiofrequency ablation of atrial fibrillation. *Int J Cardiol* 2011; **152**: 251-254.

[15] Budoff MJ, Shittu A, Hacioglu Y, et al. Comparison of transesophageal echocardiography versus computed tomography for detection of left atrial appendage filling defect (thrombus). *Am J Cardiol* 2014; **113**: 173-177.

[16] He J, Fu Z, Yang L, et al. The predictive value of a concise classification of left atrial appendage morphology to thrombosis in non-valvular atrial fibrillation patients. *Clin Cardiol* 2020; **43**: 789-795.

[17] Flachskampf FA, Decoodt P, Fraser AG, et al. Guidelines from the Working Group. Recommendations for performing transesophageal echocardiography. *Eur J Echocardiogr* 2001; **2**: 8-21.

[18] Su P, McCarthy KP, Ho SY. Occluding the left atrial appendage: anatomical considerations. *Heart* 2008; **94**: 1166-1170.

[19] Meincke F, Schmidt-Salzmann M, Kreidel F, et al. New technical and anticoagulation aspects for left atrial appendage closure using the WATCHMAN device in patients not taking warfarin. *Eurointervention* 2013; **9**: 463-468.

[20] Homsi R, Nath B, Luetkens JA, et al. Can Contrast-Enhanced Multi-Detector Computed Tomography Replace Transesophageal Echocardiography for the Detection of Thrombogenic Milieu and Thrombi in the Left Atrial Appendage: A Prospective Study with 124 Patients.

Rofo 2016; **188**: 45-52.

[21] Shapiro MD, Neilan TG, Jassal DS, et al. Multidetector computed tomography for the detection of left atrial appendage thrombus: a comparative study with transesophageal echocardiography. *J Comput Assist Tomogr* 2007; **31**: 905-909.

[22] Hur J, Kim YJ, Lee HJ, et al. Dual-enhanced cardiac CT for detection of left atrial appendage thrombus in patients with stroke: a prospective comparison study with transesophageal echocardiography. *Stroke* 2011; **42**: 2471-2477.

[23] Jung B, Föll D, Böttler P, et al. Detailed analysis of myocardial motion in volunteers and patients using high-temporal-resolution MR tissue phase mapping. *J Magn Reson Imaging* 2006; **24**: 1033-1039.

[24] Fukushima K, Fukushima N, Kato K, et al. Correlation between left atrial appendage morphology and flow velocity in patients with paroxysmal atrial fibrillation. *Eur Heart J Cardiovasc Imaging* 2016; **17**: 59-66.

[25] Kapa S, Martinez MW, Williamson EE, et al. ECG-gated dual-source CT for detection of left atrial appendage thrombus in patients undergoing catheter ablation for atrial fibrillation. *J Interv Card Electrophysiol* 2010; **29**: 75-81.

[26] Kuronuma K, Matsumoto N, Suzuki Y, et al. Usefulness of Dual-Phase Snapshot 320-Detector Computed Tomography for the Detection of a Left Atrial Appendage Thrombus. *Int Heart J* 2019; **60**: 849-853.

[27] Wang L, Kadiyala M, Koss E, et al. CTA Detection of Left Atrial Stasis and Thrombus in Patients with Atrial Fibrillation. *Pacing Clin Electrophysiol* 2016; **39**: 1388-1393.

[28] He G, Liu H, Huang X, et al. Intracardiac versus transesophageal echocardiography for

diagnosis of left atrial appendage thrombosis in atrial fibrillation: A meta-analysis. *Clin Cardiol* 2021; **44**: 1416-1421.

Figure legends

Figure 1 Patient flowchart.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; LAA = left atrial appendage; TEE = transesophageal echocardiography.

Figure 2 Representative TEE and CCT images of the LAA thrombi.

The upper panel shows CCT images. The lower panel shows TEE images. A-B. Representative false-negative CCT result. The thrombus was located in the LAA. C-D. Representative false-negative CCT result. The thrombus was located at the LAA ostium. E-F. Representative true-positive CCT result. The thrombus was located in the LAA. G-H. Representative true-positive CCT result. The thrombus was located at the LAA ostium. White arrows denote the thrombi.

Figure 3 Scatter plots of CCT results of LAA thrombi.

Red dots denote the CCT false-negative thrombi. Green dots denote the CCT true-positive thrombi. The LAAMFV was calculated by halving the sum of the LAA emptying and filling velocity. A. The CCT false-positive thrombi at the LAA ostium had the LAAMFV over 0.35 m/s and the maximum diameters over 10 mm. B. The CCT false-positive thrombi in the LAA ostium had a maximum diameter over 8 mm.

Abbreviations: CCT = cardiac computed tomography; LAA = left atrial appendage; LAAMFV = left atrial appendage mean flow velocity.

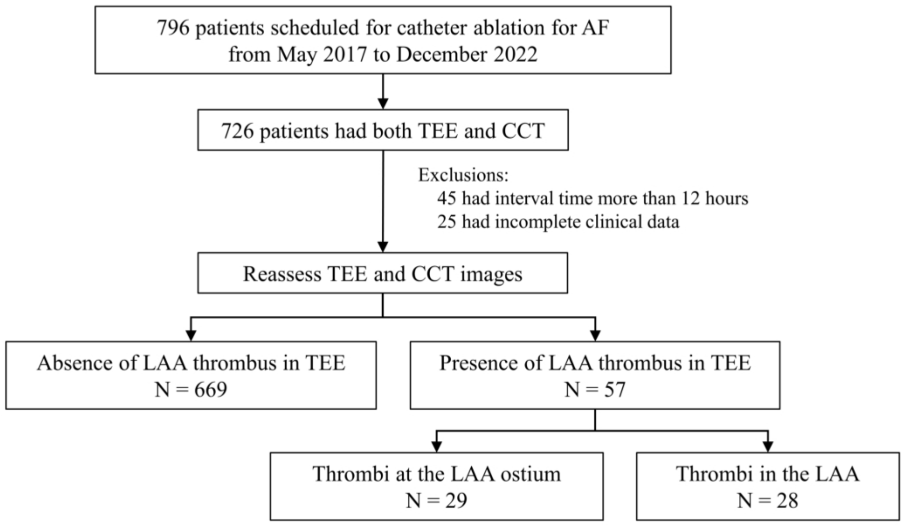


Figure 1 Patient flowchart.
Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; LAA = left atrial appendage; TEE = transesophageal echocardiography.

190x104mm (300 x 300 DPI)

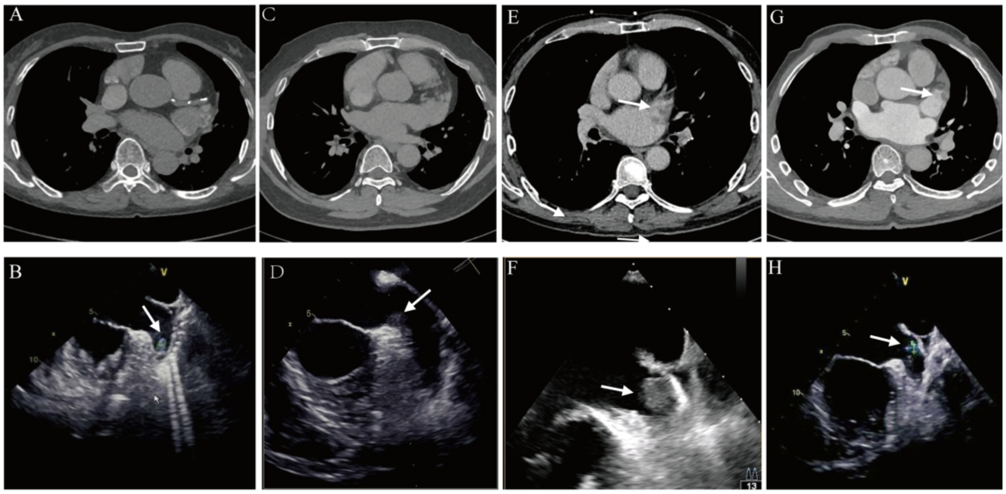


Figure 2 Representative TEE and CCT images of the LAA thrombi.
The upper panel shows CCT images. The lower panel shows TEE images. A-B. Representative false-negative CCT result. The thrombus was located in the LAA. C-D. Representative false-negative CCT result. The thrombus was located at the LAA ostium. E-F. Representative true-positive CCT result. The thrombus was located in the LAA. G-H. Representative true-positive CCT result. The thrombus was located at the LAA ostium. White arrows denote the thrombi.

190x98mm (300 x 300 DPI)

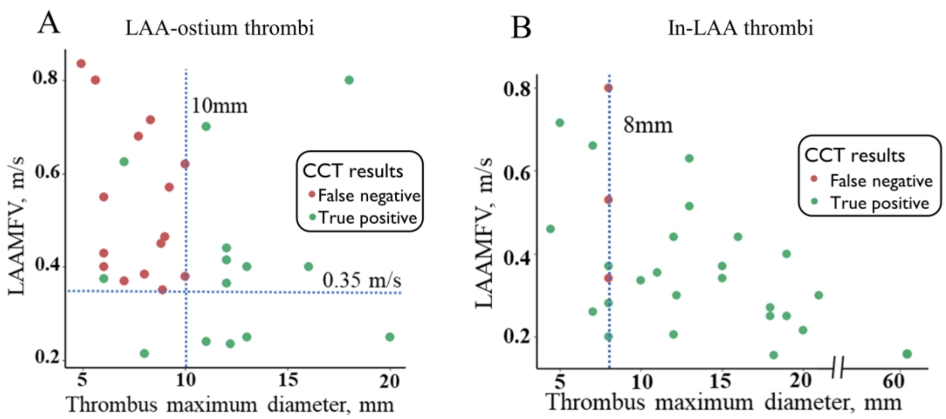


Figure 3 Scatter plots of CCT results of LAA thrombi.
Red dots denote the CCT false-negative thrombi. Green dots denote the CCT true-positive thrombi. The LAAMFV was calculated by halving the sum of the LAA emptying and filling velocity. A. The CCT false-positive thrombi at the LAA ostium had the LAAMFV over 0.35 m/s and the maximum diameters over 10 mm. B. The CCT false-positive thrombi in the LAA ostium had a maximum diameter over 8 mm.
Abbreviations: CCT = cardiac computed tomography; LAA = left atrial appendage; LAAMFV = left atrial appendage mean flow velocity.

190x89mm (300 x 300 DPI)

Table 1 Patient characteristics.

Characteristics	Overall (n=726)	LAA thrombus * Positive (n=57)	Negative (n=669)	*P* value
Age, year	61±11	64±10	61±11	0.129
Male	437(60.2)	36(63.2)	401(59.9)	0.634
Paroxysmal AF	436(60.1)	30(52.6)	406(60.7)	0.233
AF course, month	42±83	39±45	43±85	0.540
CHA_2DS_2-VASc score	2±2	3±2	2±2	0.089
Congestive heart failure	116(16.0)	18(31.6)	98(14.6)	0.001
Hypertension	346(47.7)	25(43.9)	321(48.0)	0.550
Diabetes mellitus	107(14.7)	10(17.5)	97(14.5)	0.534
Previous Stroke/TIA	91(12.5)	14(24.6)	77(11.5)	0.004
Vascular disease	292(40.2)	22(38.6)	270(40.4)	0.795
LAAPD, mm	36±7	41±9	36±7	＜0.001
LVEDD, mm	46±5	49±7	46±5	0.006
LVEF, %	60±8	56±11	60±7	0.005
Complex LAA morphology	289(39.8)	35(61.4)	254(38.0)	0.001
CCT results				
Filling defects	43(5.9)	39(68.4)	4(0.6)	＜0.001
No filling defects	683(94.1)	18(31.6)	665(99.4)	

Values are mean ± SD or n (%).

* The thrombi were detected using the TEE.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, previous stroke/transient ischemic attack/thromboembolism (doubled), vascular disease, age 65–74 years and sex category (female); LAA = left atrial appendage; LAAPD = left atrial anterior-posterior diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; TEE = transesophageal echocardiography; TIA = transient ischemic attack.

Table2 Patient characteristics between CCT true-positive and false-negative results.

Characteristics	LAA thrombus *		*P* value
	CCT false-negative result (n=18)	CCT true-positive result (n=39)	
Age, years	64±9	64±10	0.810
Male	11(61.1)	25(64.1)	0.828
Paroxysmal AF	12(66.7)	18(46.2)	0.149
AF course, month	42±54	38±40	0.952
CHA_2DS_2-VASc score	3±2	3±2	0.450
Congestive heart failure	5(27.8)	13(33.3)	0.675
Hypertension	10(55.6)	15(38.5)	0.227
Diabetes mellitus	5(27.8)	5(12.8)	0.168
Previous Stroke/TIA	5(27.8)	9(23.1)	0.702
Vascular disease	7(38.9)	15(38.5)	0.975
LAAPD, mm	41±9	41±9	0.770
LVEDD, mm	49±6	49±7	0.336
LVEF, %	59±9	55±12	0.331
Complex LAA	9(50.0)	26(66.7)	0.230
LAA filling velocity, m/s	0.53±0.15	0.38±0.19	0.002
LAA emptying velocity, m/s	0.55±0.21	0.37±0.14	0.001
Thrombi maximum diameter, mm	8±2	14±9	<0.001
Thrombus location			
LAA ostium	15(83.3)	14(35.9)	0.001
In LAA	3(16.7)	25(64.1)	

Values are mean ± SD or n (%).

* The thrombi were detected using the TEE.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, previous stroke/transient ischemic attack/thromboembolism (doubled), vascular disease, age 65–74 years and sex category (female); LAA = left atrial appendage; LAAPD = left atrial anterior-posterior diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; TEE = transesophageal echocardiography; TIA = transient ischemic attack.

Table S1 Patient characteristics between thrombus locations.

Characteristics	Thrombus location *		*P* value
	LAA ostium (n=29)	In LAA(n=28)	
Age, years	63±10	64±10	0.886
Male	20(69.0)	16(57.1)	0.355
Paroxysmal AF	18(62.1)	12(42.9)	0.146
AF course, month	40±52	39±35	0.648
CHA_2DS_2-VASc score	2±2	3±2	0.220
Congestive heart failure	9(31.0)	9(32.1)	0.928
Hypertension	10(34.5)	15(53.6)	0.147
Diabetes mellitus	5(17.2)	5(17.9)	1.000
Previous Stroke/TIA	7(24.1)	7(25.0)	0.940
Vascular disease	9(31.0)	13(46.4)	0.233
LAAPD, mm	41±10	40±8	0.873
LVEDD, mm	49±6	49±8	0.492
LVEF, %	57±11	55±11	0.424
Complex LAA	17(58.6)	18(64.3)	0.661
LAA filling velocity, m/s	0.48±0.19	0.37±0.19	0.021
LAA emptying velocity, m/s	0.47±0.20	0.38±0.16	0.050
Thrombus maximum diameter, mm	10±4	14±10	0.045
CCT results			
Filling defects	14(48.3)	25(89.3)	0.001
No filling defects	15(51.7)	3(10.7)	

Values are mean ± SD or n (%).

* The thrombus locations were determined using the TEE.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, previous stroke/transient ischemic attack/thromboembolism (doubled), vascular disease, age 65–74 years and sex category (female); LAA = left atrial appendage; LAAPD= left atrial anterior-posterior diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; TEE = transesophageal echocardiography; TIA = transient ischemic attack.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract		From May 2017 to December 2022, 726 patients (male: 60.2%, age: 61±11 years) who had both TEE and CCT before catheter ablation of AF were retrospectively included.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found		Our study aims to evaluate the accuracy of CCT for detecting LAA thrombus in patients undergoing catheter ablation of atrial fibrillation (AF), using transesophageal echocardiography (TEE) as the reference standard.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5	Transesophageal echocardiology (TEE) is currently the gold standard for the assessment of left atrial appendage (LAA) thrombi in patients undergoing catheter ablation of atrial fibrillation (AF)…
Objectives	3	State specific objectives, including any prespecified hypotheses	5	We aimed to evaluate the sensitivity of CCT in detecting LAA thrombus and to analyze the risk factors of false-negative

				results.
Methods				
Study design	4	Present key elements of study design early in the paper		All the patient characteristics and images were acquired from the clinical database. The CHA2DS2-VASc score was calculated following the 2020 ESC guideline.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		From May 2017 to December 2022, patients were routinely scheduled for TEE and CCT before catheter ablation of AF in Guizhou Provincial People's Hospital. Those who had both examinations within a 12-hour interval on the same day were retrospectively included.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants		In the current study, we retrospectively included 726 patients who had both TEE and CCT before catheter ablation for AF.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7	Thrombus was defined as a persistent filling defect in the 30s-delayed scans. The LAA morphology was classified into

			simple or complex according to their main and branching structures on the 3D reconstructions…
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	All patients were examined with a third-generation dual-source CT. The imaging protocol included a standard angiographic-phase acquisition to assess the anatomy of the left atrium and one delayed-phase acquisition at 30 s after contrast injection to detect thrombi…
Bias	9	Describe any efforts to address potential sources of bias	Two independent radiologists with more than eight years of cardiovascular imaging, blinded to all patients' data... Two independent cardiologists with more than five years of experience in echocardiology evaluated the presence of LAA thrombus and measured the flow velocity...
Study size	10	Explain how the study size was arrived at	In the current study, we retrospectively included 726 patients who had both TEE and CCT before catheter ablation for AF.

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8	Using TEE as the reference standard, the diagnostic performance of CCT for LAA thrombi was calculated.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7	Continuous variables were expressed as mean ± SD deviation…
		(*b*) Describe any methods used to examine subgroups and interactions	N/A	
		(*c*) Explain how missing data were addressed	N/A	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7	Using TEE as the reference standard, the diagnostic performance of CCT for LAA thrombi was calculated.
		(*e*) Describe any sensitivity analyses	N/A	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study…
		(b) Give reasons for non-participation at each stage	N/A	
		(c) Consider use of a flow diagram	8	A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study (Fig. 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8	A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study (Fig. 1)…

		(b) Indicate number of participants with missing data for each variable of interest		A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study (Fig. 1).
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		Twenty-nine (50.9%) of the thrombi were located at the LAA ostium and 28(49.1%) were in the LAA. Compared with the CCT true-positive thrombi, the false-negative ones more frequently located at the LAA ostium (83.3% vs. 35.9%, p = 0.001) …
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A	
		(*b*) Report category boundaries when continuous variables were categorized		Given that high sensitivity is essential to exclude LAA thrombus, the CCT results of the LAA thrombi underwent further analysis. By scattering the CCT results on the 2-D plane, the thrombi at the LAA ostium…
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9	The CCT had an overall sensitivity of 68.4% and a specificity of 99.4%... Given that high sensitivity is essential to exclude LAA thrombus, the CCT results of the LAA thrombi underwent further analysis…
Discussion				
Key results	18	Summarise key results with reference to study objectives		We reevaluated the accuracy of CCT for detecting LAA thrombus in the 726 patients undergoing catheter ablation for AF.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		Firstly, this retrospective single-center study included only patients undergoing catheter ablation for AF…
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,11	Thus, the low sensitivity of CCT in our study could be presumed to: (1) inadequate temporal resolution…
Generalisability	21	Discuss the generalisability (external validity) of the study results	12	This retrospective single-center study included only patients undergoing catheter ablation for AF. The study's findings may not be generalizable to other patients with AF…
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13	This study has received funding from the Science and Technology Support plan of Guizhou Province…

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Diagnosis of left atrial appendage thrombus using cardiac computed tomography: new insights from thrombi locations

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-079876.R1
Article Type:	Original research
Date Submitted by the Author:	12-Dec-2023
Complete List of Authors:	Guo, Chuxian; Guizhou Provincial People's Hospital, Cardiology Department; Guizhou Medical University Jiang, Zhi; Guizhou Provincial People's Hospital, Cardiology Department He, Jionghong; Guizhou Provincial People's Hospital, Cardiology Department; Guizhou Provincial People's Hospital, Echocardiography Department Ma, Haiyan; Guizhou Provincial People's Hospital, Radiology Department Wang, Yuquan; Guizhou Provincial People's Hospital, Radiology Department Tan, Jing; Guizhou Provincial People's Hospital, Cardiology Department; Guizhou Provincial People's Hospital, Echocardiography Department Ou, Qiaoqiao; Guizhou Provincial People's Hospital, Cardiology Department; Guizhou Medical University Tian, Ye; Guizhou Provincial People's Hospital, Cardiology Department Tian, Longhai; Guizhou Provincial People's Hospital, Cardiology Department Liu, Qifang; Guizhou Provincial People's Hospital, Cardiology Department Huang, Jing; Guizhou Provincial People's Hospital, Cardiology Department Yang, Long; Guizhou Provincial People's Hospital, Cardiology Department
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine, Radiology and imaging
Keywords:	Stroke < NEUROLOGY, Ultrasound < RADIOLOGY & IMAGING, Computed tomography < RADIOLOGY & IMAGING, Thromboembolism < CARDIOLOGY
Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.	
Supplementary material_Video S1.mp4	

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Article Title: Diagnosis of left atrial appendage thrombus using cardiac computed tomography: new insights from thrombi locations

Running Head: Detection of Left Atrial Appendage Thrombus Using Cardiac CT

Authors: Chuxian Guo [ad]*; Zhi Jiang [a]*; Jionghong He [ab]; Haiyan Ma [c]; Yuquan Wang [c]; Jing Tan [ab]; Qiaoqiao Ou [ad]; Ye Tian [a]; Longhai Tian [a]; Qifang Liu [a]; Jing Huang [a]; Long Yang [a]

Affiliations: From [a] Cardiology Department, Guizhou Provincial People's Hospital, Guiyang, China; [b] Echocardiography Department, Guizhou Provincial People's Hospital, Guiyang, China; [c] Radiology Department of Guizhou Provincial People's Hospital, Guiyang City, China; [d] Guizhou Medical University, Guiyang, China.

* Chuxian Guo and Zhi Jiang contributed equally to the study.

Corresponding author: Long Yang, Department of Cardiology, Guizhou Provincial People's Hospital, NO. 83 East Zhongshan Road, Guizhou Province, Guiyang City, 550002, China. E-mail: yanglong1001@outlook.com. Telephone: +86-18198169283. Fax: +86 0851- 85924943

Word count of the main part of the manuscript: 2243

Abstract

Background Cardiac computed tomography (CCT) is an emerging non-invasive modality for assessing left atrial appendage (LAA) thrombus, but the results were conflicting. Our study aims to evaluate the accuracy of CCT for detecting LAA thrombus in patients undergoing catheter ablation of atrial fibrillation (AF), using transesophageal echocardiography (TEE) as the reference standard.

Methods From May 2017 to December 2022, 726 patients (male: 60.2%, age: 61±11 years) who had both TEE and CCT before catheter ablation of AF were retrospectively included. The CCT protocol consisted of one angiographic phase and one delayed scan 30 seconds later. LAA thrombi were defined as solid masses on TEE or persistent defects on CCT. The thrombus dimension and location, the LAA filling and emptying flow velocity were assessed by TEE.

Results Of the 57(7.9%) patients with LAA thrombi identified by TEE, 29(50.9%) were located at the LAA ostium, and 28(49.1%) were in the LAA. The former showed higher motility following blood flow and heartbeats than the latter. The CCT detected 14(48.3%) of the LAA-ostium thrombi but 25(89.3%) of those in the LAA ($p = 0.001$). The LAA-ostium thrombi with the LAA mean flow velocity higher than 0.35m/s and maximum diameters shorter than 10mm were more prone to have CCT false-negative results.

Conclusion For patients undergoing catheter ablation for AF, CCT with a 30s delay scan is less sensitive to LAA thrombi than TEE, especially for LAA-ostium thrombi with smaller sizes and higher LAA flow velocity.

Keywords stroke; embolism; thrombosis; pulmonary vein isolation; cardiac imaging techniques; ultrasound.

Strengths and limitations of this study

1. A major strength of our study is based on a large cohort with high incidence of left atrial appendage thrombi.

2. We first report the impact of thrombus location on the sensitivity of CCT, using TEE as reference standard.

3. A limitation of this study is that it is a single-center and retrospective study.

4. The CCT protocol contained only one delayed-phase scan. Whether multiple delayed-phase scans reduce false-negative CCT results is unclear.

Title: Diagnosis of left atrial appendage thrombus using cardiac computed tomography: new insights from thrombi locations

Introduction

Transesophageal echocardiology (TEE) is currently the gold standard for the assessment of left atrial appendage (LAA) thrombi in patients undergoing catheter ablation of atrial fibrillation (AF)[1]. In the past decades, cardiac computed tomography (CCT) has been widely studied for detecting LAA thrombus[2-5]. Recently, the delayed contrast-enhanced CCT at 6 minutes was reported to reach 100% sensitivity and negative predictive value in detecting LAA thrombus[6]. For patients who are not tolerant of the discomfort associated with TEE, CCT is proposed as a reliable alternative[7]. However, the accuracy of CCT varied between studies[2-5, 8], raising the safety concern and limiting the routine use of CCT.

The left atrial thrombi were classified into a movable ball, fixed ball, and mountain according to their morphology[9]. Around 1/3 of the thrombi in the left atrium were movable. Although CCT is of high spatial resolution, its temporal resolution is 4~17Hz, and it takes 60ms ~ 250ms to acquire one slice[8, 10-12]. Compared to TEE, which allows live display with a high spatiotemporal resolution (<1mm, 20~30Hz)[13], CCT is theoretically inferior for identifying moving objects in the left atrium. In addition, the circulatory stasis and the fibrillation of the atrial wall during AF also increase the difficulty of detecting movable thrombi[14]. In previous studies, the presence of LAA thrombus was 2(0.24%) ~16(19.04%)[2-5, 15]. The high sensitivity and negative predictive value of CCT could be attributed to the low incidence of movable thrombus. Therefore, it is essential to investigate

the diagnostic accuracy of CCT in a larger cohort with a higher incidence of LAA thrombus.

In the current study, we retrospectively included 726 patients who had both TEE and CCT before catheter ablation for AF. 57(7.9%) patients were diagnosed with LAA thrombi using TEE. We aimed to evaluate the sensitivity of CCT in detecting LAA thrombus and to analyze the risk factors of false-negative results.

Methods

Study population

From May 2017 to December 2022, patients were routinely scheduled for TEE and CCT before catheter ablation of AF in Guizhou Provincial People's Hospital. Those who had both examinations within a 12-hour interval on the same day were retrospectively included. All the patient characteristics and images were acquired from the clinical database. The CHA_2DS_2-VASc score was calculated following the 2020 ESC guideline[1]. The study was approved by the institutional ethics committee of Guizhou Provincial People's Hospital. The informed consent was waived due to the retrospective nature, and no identified information was collected.

CCT protocol

All patients were examined with a third-generation dual-source CT (SOMATOM Force, Siemens Healthineers, Forchheim, Germany). The imaging protocol included a standard

angiographic-phase acquisition to assess the anatomy of the left atrium and one delayed-phase acquisition at 30 s after contrast injection to detect thrombi. No electrocardiography gating was used. The tube voltage and current were automatically adjusted using the CARE kV or CARE DOSE 4D with the reference of 100kv and 250mA. The gantry rotation time was 250ms, and the detector collimator was 192×0.6 mm. The scanning image covers the range from the aortic arch to the cardiac base. The monitoring site was localized within the left atrium. The contrast material containing 350 mg/ml of iodine was administrated intravenously at 4-5 ml/s with a total dose of 35 ml by a double-barrel syringe, followed by the same amount of 0.9% saline. For the angiographic phase, the scanning was triggered when the monitoring site reached 90 HU. Then the delayed phase was acquired 30 s later. All images were reconstructed using the ADMIRE algorithm grade 3 with a layer thickness of 1 mm and interlayer spacing of 0.7 mm. The 3D left atrium and pulmonary veins were reconstructed using the Syngo.via software (Siemens Healthcare, Forchheim, Germany).

CCT image analysis

Images were transferred to an external workstation (Syngo VPCT body, Siemens Healthcare, Forchheim, Germany). Two independent radiologists with more than eight years of cardiovascular imaging, blinded to all patients' data, retrospectively evaluated the presence of LAA thrombus and LAA morphology. Thrombus was defined as a persistent filling defect in the 30s-delayed scans. The LAA morphology was classified into simple or complex according to their main and branching structures on the 3D reconstructions[16]. In case of disagreement, a final joint reading was performed to achieve consensus.

Transesophageal echocardiology

A PhilipsiEPIQ7C color Doppler ultrasound diagnostic instrument (Philips, Amsterdam, the Netherlands) and an X7-2t probe were used. The left atrium and LAA were scanned using a complete 2D, colored, pulsed, and continuous-wave Doppler echocardiogram according to the EACVI recommendations[17]. Thrombi were defined as circumscribed echogenic or echolucent masses distinct from the atrial wall. LAA ostium was defined as within the 5mm range of the junction between the smooth atrial wall and trabeculated LAA. The dimensions and locations of thrombi were assessed if present. The LAA filling and emptying velocity was averaged by ten consecutive measurements of the backward and forward flow rates using the pulsed wave Doppler. LAA mean flow velocity (LAAMFV) was calculated by halving the sum of the LAA filling and emptying velocity. Two independent cardiologists with more than five years of experience in echocardiology evaluated the presence of LAA thrombus and measured the flow velocity. Disagreements were resolved by consensus.

Statistical analysis

Continuous variables were expressed as mean ± SD deviation. The Student's t-test was used for comparison if normally distributed; otherwise, the Mann-Whitney U test was used. Categorical variables were expressed as frequency (percentage). The Chi-square test was used for comparison if the expected frequency is more than 5; otherwise, Fisher's exact test was used. A two-tailed *p* value of less than 0.05 was considered statistically significant. Using TEE as the reference standard, the diagnostic performance of CCT for LAA thrombi was

calculated. Multivariate logistic regression analysis was conducted to determine the predictors of CCT false-negative results, and the validity was assessed using the receiver operating characteristics (ROC) curve. All statistical analysis was performed using SPSS 26.0.

Results

Patient characteristics

A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study (Figure 1). The patients with LAA thrombus had a higher incidence of previous stroke/transient ischemic attack (TIA) and congestive heart failure, larger left atrial size, worse left ventricular function, and a higher rate of complex LAA morphology than those without LAA thrombus ($p < 0.05$) (Table 1).

Twenty-nine (50.9%) of the thrombi were located at the LAA ostium and 28(49.1%) were in the LAA. The clinical characteristics and maximum thrombus diameter were similar between the patients. The thrombi at the LAA ostium were accompanied by higher LAA filling and emptying velocities than those in the LAA (Supplementary material online, Table S1). The former also showed significantly higher mobility following the blood flow and cardiac motion than the latter (Supplementary material online, Video S1).

Diagnostic accuracy of CCT

The CCT had an overall sensitivity of 68.4% and a specificity of 99.4% to the LAA thrombi (Table 1). However, the CCT was less sensitive to the thrombi at LAA ostium than those in the LAA (48.3% vs. 89.3%, $p = 0.001$) (Supplementary material online, Table S1). Representative images are shown in Figure 2.

Given that a high sensitivity is essential to exclude LAA thrombus, the CCT results of the LAA thrombi underwent further analysis. Compared with the CCT true-positive thrombi, the false-negative ones more frequently located at the LAA ostium (83.3% vs. 35.9%, $p = 0.001$), were shorter in the maximum diameters (8±2mm vs. 14±9mm, $p < 0.001$), and were accompanied by higher LAA filling and emptying velocities (0.53±0.15 m/s vs. 0.38±0.19 m/s, $p = 0.001$; 0.55±0.21 m/s vs. 0.37±0.14 m/s, $p < 0.001$) (Table 2). The result was also concordant in the LAA-ostium thrombi subgroup (Supplementary material online, Table S2). By scattering the CCT results on the 2-D plane that consisted of LAAMFV and thrombus maximum diameter, the thrombi at the LAA ostium with the LAAMFVs higher than 0.35m/s and maximum diameters shorter than 10mm were more prone to have CCT false-negative results (Figure 3A). For the thrombi in the LAA, the maximum diameter or LAAMFV did not impact the CCT results (Figure 3B). In the logistic regression model, the thrombus maximum diameter, location, and LAA mean flow velocity (LAAMFV) were independently associated with the CCT false-negative results (Supplementary material online, Table S3). The ROC curve (AUC 0.909, 95%CI: 0.834 ~ 0.984) is shown in Figure S1.

Discussion

Major findings

We reevaluated the accuracy of CCT for detecting LAA thrombus in the 726 patients undergoing catheter ablation for AF. TEE identified 57(7.9%) patients with LAA thrombi, of which 29(50.9%) were at the LAA ostium and 28(49.1%) in the LAA. The CCT was less sensitive in detecting LAA-ostium thrombi with smaller maximum diameters and higher LAAMFV.

Concordance

LAA thrombus is thought to form initially inside the LAA, where circulatory stasis is the greatest, and then extends towards the ostium. However, we found over half of the thrombi located at the LAA ostium. The result was concordant with a previous study in which 46.3% of the thrombi were at the entrance section of LAA[9]. The presence of pits and troughs adjacent to the LAA orifice was reported in 57.7% of the human heart specimens[18]. It could be the anatomic basis for thrombosis. Another study using TEE discovered small recesses proximal to the entry of LAA in a significant number of patients, but no thrombus related to these structures was detected following LAA occlusion[19]. The discrepancy could be due to patient selection bias. Nonetheless, our findings raised concerns about the role of LAA-ostium recesses in thrombosis.

Although the third-generation 64-slice dual-source CT was employed in the current study, its sensitivity to LAA thrombi was not improved. The sensitivity of 89.3% to the thrombi in the LAA was comparable to the previous studies[2, 10, 11, 20-22]. However, the sensitivity significantly decreased for the LAA-ostium thrombi, which showed higher motility following blood flow and heartbeats than those in the LAA (Supplementary material online, Video S1). We further identified that the LAA-ostium thrombi with smaller sizes and higher LAA flow velocity were more prone to be missed using the CCT. As a higher temporal resolution is essential to detect movable objects[23], our findings suggested the impact of thrombus motility on CCT imaging. By calculating the gantry rotation time of 250ms, the CCT had a temporal resolution of 4Hz, significantly less than that of the TEE (20~40Hz). Thus, the low sensitivity of CCT in our study could be presumed to: (1) inadequate temporal resolution, (2) the high proportion of movable LAA-ostium thrombi, (3) the lack of ECG gating, (4) only one 30s delayed scan was used. The 4 CCT false-positive results in our study could be the misdiagnosis of thrombus due to circulatory stasis during AF[6, 24].

Discordance

Several studies reported that the CCT had 100% sensitivity in detecting LAA thrombi using ECG gating, single-segment reconstruction algorithm[25, 26], or multiple delayed-phase scans[3, 14, 27]. However, these studies have the following limitations: (1) Although the single-segment reconstruction algorithm increased the CCT's temporal resolution to 12Hz, the low incidence of LAA thrombus [2(0.24%) ~16(19.04%)] and the less variation of thrombus location could have overestimated the sensitivity of CCT for detecting LAA thrombi in a broader range of patients. (2) The multiple delayed-phase scans distinguished the thrombi from filling defects due to circulatory stasis. Still, the technique could not necessarily increase the sensitivity to smaller and movable thrombi at the LAA ostium.

We suggest that the CCT approach to detect LAA thrombi could differ according to their location and motility. Persistent filling defects in multiple delayed-phase scans have been well established for static thrombi in LAA. However, LAA-ostium thrombi could be highly motile due to blood flow and myocardial contraction. In our study, the LAA flow velocity indirectly reflected the thrombus motility. The filling defects that indicate the presence of thrombi could still be enhanced as the thrombi swayed much faster than the duration required for scanning. Furthermore, the filling defect size also depended on the thrombi size. Therefore, smaller LAA-ostium thrombi with higher LAA flow velocity could be prone to be missed by CCT. A temporal resolution comparable to TEE (20~40Hz) could be necessary.

Clinical implication

Our study found that the CCT with a 30s delayed scan did not reliably exclude LAA thrombus, especially those located at the LAA ostium. We did not find any clinical characteristics associated with the thrombus location. TEE is the only recommendation for stroke risk management for patients undergoing catheter ablation of AF in the 2020 ESC guideline[1]. For those who do not tolerate TEE, intracardiac echocardiography could be considered[28].

Limitations

Firstly, this retrospective single-center study included only patients undergoing catheter ablation for AF. The study's findings may not be generalizable to other patients with AF. Secondly, the CCT protocol contained only one delayed-phase scan. Whether multiple delayed-phase scans reduce false-negative CCT results is unclear. Thirdly, other factors unaccounted for in this analysis – heart rhythm, atrial/ventricular rate, and blood pressure during the TEE and CCT – could affect the conclusions. Fourthly, although the interval between the TEE and CCT was less than 12 hours, it is theoretically possible for thrombi to form or disappear within this timeframe. Lastly, the incidence of LAA thrombus was higher than that in previous studies (partially due to less adherence to anticoagulation treatment), which could have affected the thrombus location and motility.

Conclusions

In patients undergoing catheter ablation of AF, CCT with a 30s delay scan is less sensitive than TEE in detecting LAA thrombi, especially those located at LAA ostium with smaller sizes and higher LAA flow velocity.

Acknowledgments

We thank Nicholas Tan and Jason Tri from the Mayo Clinic for their dedicated help in preparing the manuscript.

Data sharing statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

This study has received funding from the Science and Technology Support plan of

Guizhou Province [NO. (2017)2885 and (2018)2794] to L.Y. and Y.T., the Clinical Special Projects in Guizhou Province [NO. (2019)4430] to Q.L., and the Clinical Research Center Project of the Department of science and technology of Guizhou Province [NO. (2017)5405] to L.Y.

Ethical approval

This study received approval from the institutional ethics committee of Guizhou Provincial People's Hospital.

Contributors

Chuxian Guo and Zhi Jiang: Conceptualization, Methodology, Formal analysis, Writing-original draft, Writing – review & editing. Jionghong He, Haiyan Ma, and Yuquan Wang: Conceptualization, Methodology, Formal analysis, Visualization, Writing – review & editing. Jing Tan: Conceptualization, Methodology, Investigation, Writing – review & editing. Qiaoqiao Ou: Conceptualization, Investigation, Writing – review & editing. Ye Tian and Qifang Liu: Conceptualization, Writing – review & editing, Funding acquisition. Longhai Tian and Jing Huang: Conceptualization, Investigation, Writing – review & editing. Long Yang: Conceptualization, Methodology, Formal analysis, Writing – review & editing, Supervision, Funding acquisition. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Supplementary Materials

Video S1 Representative TEE video of the thrombi at LAA ostium (A-C) and those in the LAA (D-F).

Table S1 Patient characteristics between thrombus locations.

Table S2 Patient characteristics between true-positive and false-negative CCT results.

Table S3 Multivariate analysis of the predictors for false-negative CCT results.

Figure S1 The ROC curve of the logistic regression model for predicting false-negative CCT results.

Abbreviation: AUC= area under the curve; CCT = cardiac computer tomography; CI = confidence interval.

References

1. Hindricks G, Potpara T, Dagres N*, et al.* 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021 **42**:373-498.

2. Dorenkamp M, Sohns C, Vollmann D*, et al.* Detection of left atrial thrombus during routine diagnostic work-up prior to pulmonary vein isolation for atrial fibrillation: role of transesophageal echocardiography and multidetector computed tomography. *Int J Cardiol*. 2013 **163**:26-33.

3. Zhai Z, Tang M, Zhang S*, et al.* Transoesophageal echocardiography prior to catheter ablation could be avoided in atrial fibrillation patients with a low risk of stroke and without filling defects in the late-phase MDCT scan: A retrospective analysis of 783 patients. *Eur Radiol*. 2018 **28**:1835-1843.

4. Li W, Yu F, Zhu W, Zhang W, Jiang T. Detection of left atrial appendage thrombi by third-generation dual-source dual-energy CT: Iodine concentration versus conventional enhancement measurements. *Int J Cardiol*. 2019 **292**:265-270.

5. Guha A, Dunleavy MP, Hayes S*, et al.* Accuracy of contrast-enhanced computed tomography for thrombus detection prior to atrial fibrillation ablation and role of novel Left Atrial Appendage Enhancement Index in appendage flow assessment. *Int J Cardiol*. 2020 **318**:147-152.

6. Spagnolo P, Giglio M, Di Marco D*, et al.* Diagnosis of left atrial appendage thrombus in patients with atrial fibrillation: delayed contrast-enhanced cardiac CT. *Eur Radiol*. 2021 **31**:1236-1244.

7. Yu S, Zhang H, Li H. Cardiac Computed Tomography Versus Transesophageal Echocardiography for the Detection of Left Atrial Appendage Thrombus: A Systemic Review and Meta-Analysis. *J Am Heart Assoc*. 2021 **10**:e022505.

8. Kottmaier M, Jilek C, Berglar S*, et al.* Exclusion of left atrial thrombus by dual-source cardiac computed tomography prior to catheter ablation for atrial fibrillation. *Clin Res Cardiol*. 2019 **108**:150-156.

9. Abe Y, Asakura T, Gotou J*, et al.* Prediction of embolism in atrial fibrillation: classification of left atrial thrombi by transesophageal echocardiography. *Jpn Circ J*. 2000 **64**:411-5.

10. Kim YY, Klein AL, Halliburton SS*, et al.* Left atrial appendage filling defects identified by multidetector computed tomography in patients undergoing radiofrequency pulmonary vein antral isolation: a comparison with transesophageal echocardiography. *Am Heart J*. 2007 **154**:1199-205.

11. Tang RB, Dong JZ, Zhang ZQ*, et al.* Comparison of contrast enhanced 64-slice computed tomography and transesophageal echocardiography in detection of left atrial thrombus in patients with atrial fibrillation. *J Interv Card Electrophysiol*. 2008 **22**:199-203.

12. Martinez MW, Kirsch J, Williamson EE*, et al.* Utility of nongated multidetector computed tomography for detection of left atrial thrombus in patients undergoing

catheter ablation of atrial fibrillation. *JACC Cardiovasc Imaging*. 2009 **2**:69-76.

13. Vegas A. Three-dimensional transesophageal echocardiography: Principles and clinical applications. *Ann Card Anaesth*. 2016 **19**:S35-S43.

14. Maltagliati A, Pontone G, Annoni A*, et al.* Multidetector computed tomography vs multiplane transesophageal echocardiography in detecting atrial thrombi in patients candidate to radiofrequency ablation of atrial fibrillation. *Int J Cardiol*. 2011 **152**:251-4.

15. Budoff MJ, Shittu A, Hacioglu Y*, et al.* Comparison of transesophageal echocardiography versus computed tomography for detection of left atrial appendage filling defect (thrombus). *Am J Cardiol*. 2014 **113**:173-7.

16. He J, Fu Z, Yang L*, et al.* The predictive value of a concise classification of left atrial appendage morphology to thrombosis in non-valvular atrial fibrillation patients. *Clin Cardiol*. 2020 **43**:789-795.

17. Flachskampf FA, Decoodt P, Fraser AG, Daniel WG, Roelandt JR. Guidelines from the Working Group. Recommendations for performing transesophageal echocardiography. *Eur J Echocardiogr*. 2001 **2**:8-21.

18. Su P, McCarthy KP, Ho SY. Occluding the left atrial appendage: anatomical considerations. *Heart*. 2008 **94**:1166-70.

19. Meincke F, Schmidt-Salzmann M, Kreidel F, Kuck KH, Bergmann MW. New technical and anticoagulation aspects for left atrial appendage closure using the WATCHMAN® device in patients not taking warfarin. *EuroIntervention*. 2013 **9**:463-8.

20. Homsi R, Nath B, Luetkens JA, Schwab JO, Schild HH, Naehle CP. Can Contrast-Enhanced Multi-Detector Computed Tomography Replace Transesophageal Echocardiography for the Detection of Thrombogenic Milieu and Thrombi in the Left Atrial Appendage: A Prospective Study with 124 Patients. *Rofo*. 2016 **188**:45-52.

21. Shapiro MD, Neilan TG, Jassal DS*, et al.* Multidetector computed tomography for the detection of left atrial appendage thrombus: a comparative study with transesophageal echocardiography. *J Comput Assist Tomogr*. 2007 **31**:905-9.

22. Hur J, Kim YJ, Lee HJ*, et al.* Dual-enhanced cardiac CT for detection of left atrial appendage thrombus in patients with stroke: a prospective comparison study with transesophageal echocardiography. *Stroke*. 2011 **42**:2471-7.

23. Jung B, Föll D, Böttler P, Petersen S, Hennig J, Markl M. Detailed analysis of myocardial motion in volunteers and patients using high-temporal-resolution MR tissue phase mapping. *J Magn Reson Imaging*. 2006 **24**:1033-9.

24. Fukushima K, Fukushima N, Kato K*, et al.* Correlation between left atrial appendage morphology and flow velocity in patients with paroxysmal atrial fibrillation. *Eur Heart J Cardiovasc Imaging*. 2016 **17**:59-66.

25. Kapa S, Martinez MW, Williamson EE*, et al.* ECG-gated dual-source CT for detection of left atrial appendage thrombus in patients undergoing catheter ablation for atrial fibrillation. *J Interv Card Electrophysiol*. 2010 **29**:75-81.

26. Kuronuma K, Matsumoto N, Suzuki Y*, et al.* Usefulness of Dual-Phase Snapshot 320-Detector Computed Tomography for the Detection of a Left Atrial Appendage Thrombus. *Int Heart J*. 2019 **60**:849-853.

27. Wang L, Kadiyala M, Koss E*, et al.* CTA Detection of Left Atrial Stasis and Thrombus in Patients with Atrial Fibrillation. *Pacing Clin Electrophysiol*. 2016 **39**:1388-1393.

28. He G, Liu H, Huang X*, et al.* Intracardiac versus transesophageal echocardiography for diagnosis of left atrial appendage thrombosis in atrial fibrillation: A meta-analysis. *Clin Cardiol*. 2021 **44**:1416-1421.

Figure legends

Figure 1 Patient flowchart.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; LAA = left atrial appendage; TEE = transesophageal echocardiography.

Figure 2 Representative CCT and TEE images of the LAA thrombi.

The left and middle images are from the CCT angiographic and delayed phase. The right images are from the TEE. A-C. Representative false-negative CCT result of the thrombus in the LAA. D-F. Representative false-negative CCT result of the LAA-ostium thrombus. G-I. Representative true-positive CCT result of the thrombus in the LAA. J-L. Representative true-positive CCT result of the LAA-ostium thrombus. White arrows denote the thrombi.

Abbreviation: CCT = cardiac computer tomography; LAA = left atrial appendage.

Figure 3 Scatter plots of CCT results.

Red dots denote the CCT false-negative thrombi. Green dots denote the CCT true-positive thrombi. The LAAMFV was calculated by halving the sum of the LAA emptying and filling velocity. A. For the LAA-ostium thrombi, the CCT false-negative results had the LAAMFV higher than 0.35 m/s and maximum diameters less than 10 mm. B. For the thrombi in the LAA, the maximum diameter or LAAMFV did not significantly impact CCT results.

Abbreviations: CCT = cardiac computed tomography; LAA = left atrial appendage; LAAMFV = left atrial appendage mean flow velocity.

Table 1 Patient characteristics.

Characteristics	Overall (n=726)	LAA thrombus *		*P* value
		Positive (n=57)	Negative (n=669)	
Age, year	61±11	64±10	61±11	0.129
Male	437(60.2)	36(63.2)	401(59.9)	0.634
Paroxysmal AF	436(60.1)	30(52.6)	406(60.7)	0.233
AF course, month	42±83	39±45	43±85	0.540
CHA_2DS_2-VASc score	2±2	3±2	2±2	0.089
Congestive heart failure	116(16.0)	18(31.6)	98(14.6)	0.001
Hypertension	346(47.7)	25(43.9)	321(48.0)	0.550
Diabetes mellitus	107(14.7)	10(17.5)	97(14.5)	0.534
Previous Stroke/TIA	91(12.5)	14(24.6)	77(11.5)	0.004
Vascular disease	292(40.2)	22(38.6)	270(40.4)	0.795
LAAPD, mm	36±7	41±9	36±7	<0.001
LVEDD, mm	46±5	49±7	46±5	0.006
LVEF, %	60±8	56±11	60±7	0.005
Complex LAA morphology	289(39.8)	35(61.4)	254(38.0)	0.001
CCT results				
Filling defects	43(5.9)	39(68.4)	4(0.6)	<0.001
No filling defects	683(94.1)	18(31.6)	665(99.4)	

Values are mean ± SD or n (%).

* The thrombi were detected using the TEE.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, previous stroke/transient ischemic attack/thromboembolism (doubled), vascular disease, age 65–74 years and sex category (female); LAA = left atrial appendage; LAAPD = left atrial anterior-posterior diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; TEE = transesophageal echocardiography; TIA = transient ischemic attack.

Table 2 Patient characteristics between CCT true-positive and false-negative results.

Characteristics	LAA thrombus *		*P* value
	CCT false-negative result (n=18)	CCT true-positive result (n=39)	
Age, years	64±9	64±10	0.810
Male	11(61.1)	25(64.1)	0.828
Paroxysmal AF	12(66.7)	18(46.2)	0.149
AF course, month	42±54	38±40	0.952
CHA_2DS_2-VASc score	3±2	3±2	0.450
Congestive heart failure	5(27.8)	13(33.3)	0.675
Hypertension	10(55.6)	15(38.5)	0.227
Diabetes mellitus	5(27.8)	5(12.8)	0.168
Previous Stroke/TIA	5(27.8)	9(23.1)	0.702
Vascular disease	7(38.9)	15(38.5)	0.975
LAAPD, mm	41±9	41±9	0.770
LVEDD, mm	49±6	49±7	0.336
LVEF, %	59±9	55±12	0.331
Complex LAA	9(50.0)	26(66.7)	0.230
LAA filling velocity, m/s	0.53±0.15	0.38±0.19	0.002
LAA emptying velocity, m/s	0.55±0.21	0.37±0.14	0.001
Thrombi maximum diameter, mm	8±2	14±9	<0.001
Thrombus location			
LAA ostium	15(83.3)	14(35.9)	0.001
In LAA	3(16.7)	25(64.1)	

Values are mean ± SD or n (%).

* The thrombi were detected using the TEE.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, previous stroke/transient ischemic attack/thromboembolism (doubled), vascular disease, age 65–74 years and sex category (female); LAA = left atrial appendage; LAAPD = left atrial anterior-posterior diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; TEE = transesophageal echocardiography; TIA = transient ischemic attack.

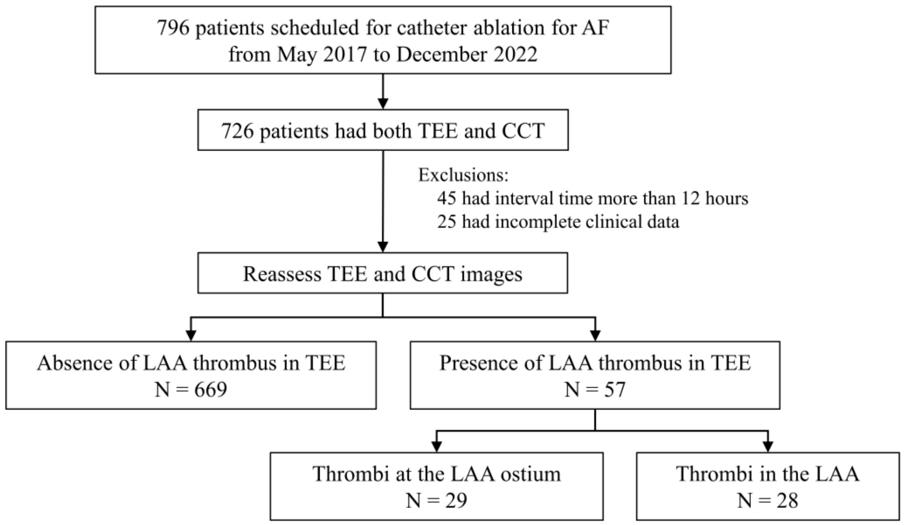


Figure 1 Patient flowchart.
Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; LAA = left atrial appendage; TEE = transesophageal echocardiography.

190x104mm (600 x 600 DPI)

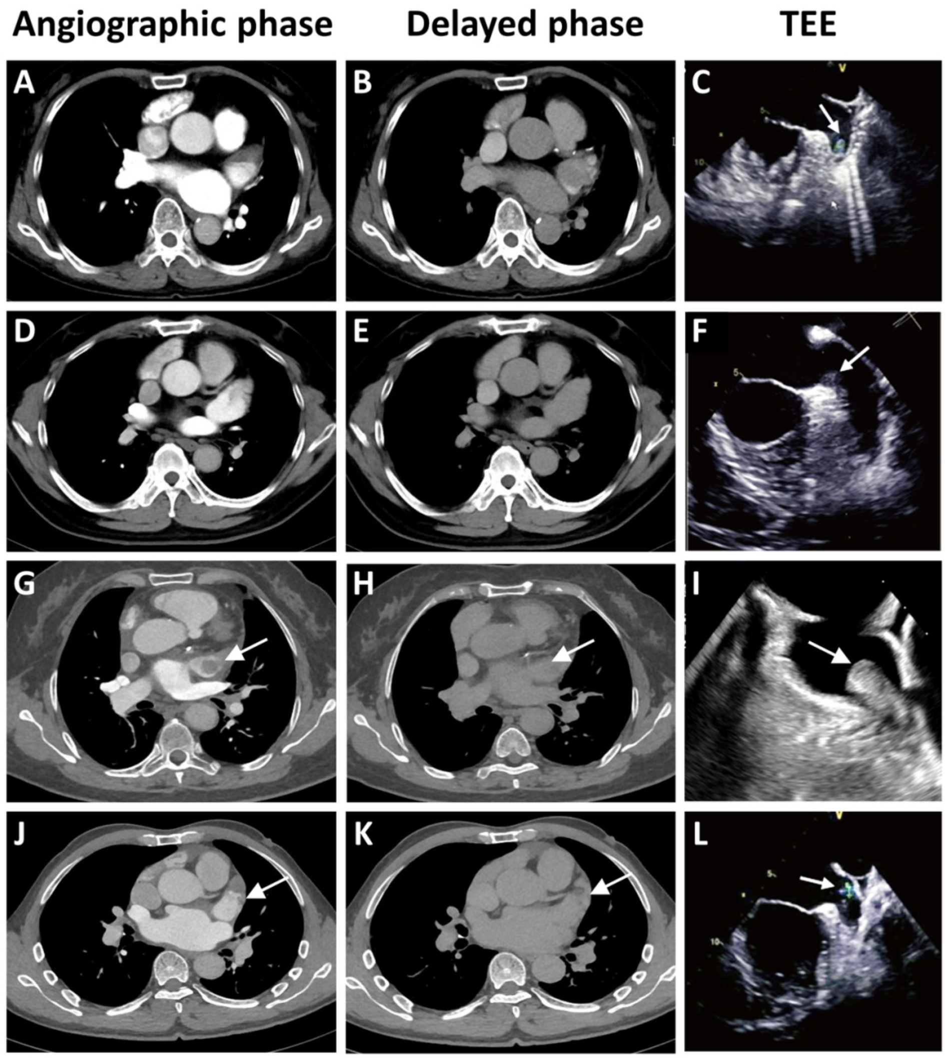


Figure 2 Representative CCT and TEE images of the LAA thrombi.
The left and middle images are from the CCT angiographic and delayed phase. The right images are from the TEE. A-C. Representative false-negative CCT result of the thrombus in the LAA. D-F. Representative false-negative CCT result of the LAA-ostium thrombus. G-I. Representative true-positive CCT result of the thrombus in the LAA. J-L. Representative true-positive CCT result of the LAA-ostium thrombus. White arrows denote the thrombi.
Abbreviation: CCT = cardiac computer tomography; LAA = left atrial appendage.

116x128mm (300 x 300 DPI)

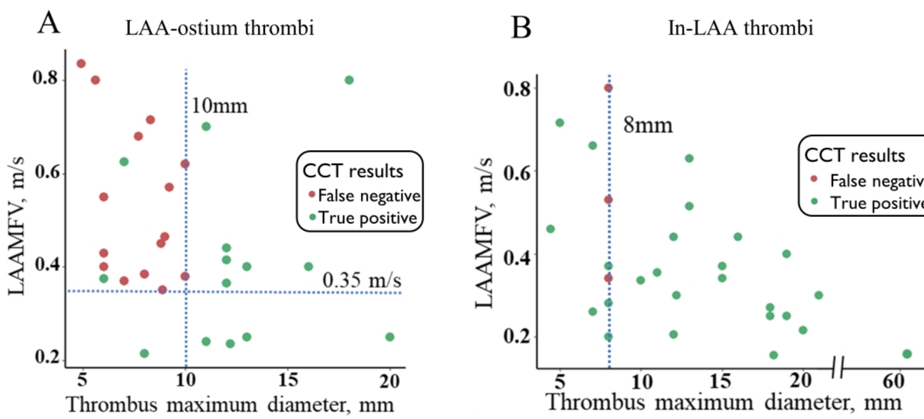


Figure 3 Scatter plots of CCT results.
Red dots denote the CCT false-negative thrombi. Green dots denote the CCT true-positive thrombi. The LAAMFV was calculated by halving the sum of the LAA emptying and filling velocity. A. For the LAA-ostium thrombi, the CCT false-negative results had the LAAMFV higher than 0.35 m/s and maximum diameters less than 10 mm. B. For the thrombi in the LAA, the maximum diameter or LAAMFV did not significantly impact CCT results.
Abbreviations: CCT = cardiac computed tomography; LAA = left atrial appendage; LAAMFV = left atrial appendage mean flow velocity.

190x89mm (600 x 600 DPI)

Table S1 Patient characteristics between thrombus locations.

Characteristics	Thrombus locations *		*P* value
	LAA ostium (n=29)	In LAA (n=28)	
Age, years	63±10	64±10	0.886
Male	20(69.0)	16(57.1)	0.355
Paroxysmal AF	18(62.1)	12(42.9)	0.146
AF course, month	40±52	39±35	0.648
CHA_2DS_2-VASc score	2±2	3±2	0.220
Congestive heart failure	9(31.0)	9(32.1)	0.928
Hypertension	10(34.5)	15(53.6)	0.147
Diabetes mellitus	5(17.2)	5(17.9)	1.000
Previous Stroke/TIA	7(24.1)	7(25.0)	0.940
Vascular disease	9(31.0)	13(46.4)	0.233
LAAPD, mm	41±10	40±8	0.873
LVEDD, mm	49±6	49±8	0.492
LVEF, %	57±11	55±11	0.424
Complex LAA	17(58.6)	18(64.3)	0.661
LAA filling velocity, m/s	0.48±0.19	0.37±0.19	0.021
LAA emptying velocity, m/s	0.47±0.20	0.38±0.16	0.050
LAAMFV, m/s	0.47±0.18	0.37±0.17	0.029
Thrombus maximum diameter, mm	10±4	14±10	0.045
CCT results			
Filling defects	14(48.3)	25(89.3)	0.001
No filling defects	15(51.7)	3(10.7)	

Values are mean ± SD or n (%).

* The thrombus locations were determined using the TEE.

The LAAMFV was calculated by halving the sum of the LAA emptying and filling velocity.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, previous stroke/transient ischemic attack/thromboembolism (doubled), vascular disease, age 65–74 years and sex category (female); LAA = left atrial appendage; LAAMFV = left atrial appendage mean flow velocity; LAAPD= left atrial anterior-posterior diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; TEE = transesophageal echocardiography; TIA = transient ischemic attack.

Table S2 Patient characteristics between true-positive and false-negative CCT results.

Characteristics	LAA-ostium thrombi*		P value
	CCT false-negative result (n=15)	CCT true-positive result (n=14)	
Age, years	63±10	64±10	0.726
Male	10(66.7)	10(71.4)	1.000
Paroxysmal AF	10(66.7)	8(57.1)	0.597
AF course, month	44±58	36±45	0.677
CHA_2DS_2-VASc score	3±2	2±2	0.288
Congestive heart failure	4(26.7)	5(35.7)	0.700
Hypertension	8(53.3)	2(14.3)	0.050
Diabetes mellitus	4(26.7)	1(7.1)	0.330
Previous Stroke/TIA	4(26.7)	3(21.4)	1.000
Vascular disease	6(40.0)	3(21.4)	0.427
LAAPD, mm	39±9	44±11	0.221
LVEDD, mm	49±6	48±5	0.370
LVEF, %	59±8	55±13	0.444
Complex LAA	7(46.7)	10(71.4)	0.264
LAA filling velocity, m/s	0.52±0.15	0.43±0.21	0.110
LAA emptying velocity, m/s	0.55±0.21	0.38±0.15	0.027
LAAMFV, m/s	0.53±0.16	0.41±0.18	0.047
Thrombus maximum diameter, mm	8±2	12±4	0.001

Values are mean ± SD or n (%).

* The LAA-ostium thrombi were determined using the TEE.

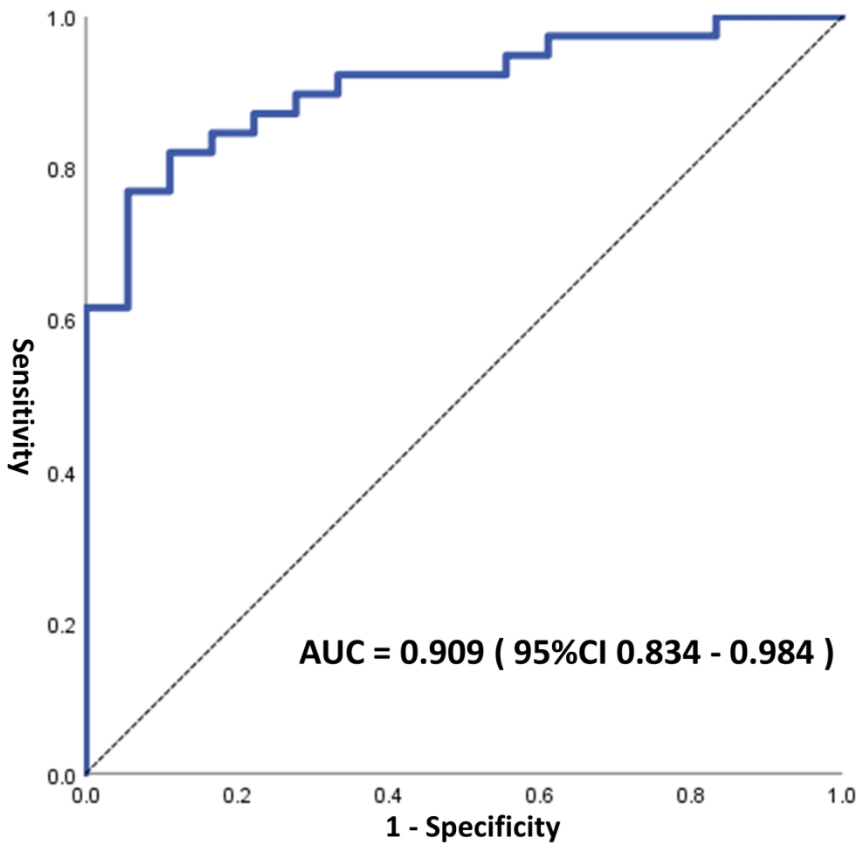
The LAAMFV was calculated by halving the sum of the LAA emptying and filling velocity.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, previous stroke/transient ischemic attack/thromboembolism (doubled), vascular disease, age 65–74 years and sex category (female); LAA = left atrial appendage; LAAMFV = left atrial appendage mean flow velocity; LAAPD= left atrial anterior-posterior diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; TEE = transesophageal echocardiography; TIA = transient ischemic attack.

Table S3 Multivariate analysis of the predictors for false-negative CCT results.

Characteristics	*OR* (95% CI)	*P* value
Thrombus maximum diameter, per 1 mm decrease	0.635 (0.459 ~ 0.879)	0.006
LAA-ostium thrombus	10.981 (1.702 ~ 70.831)	0.012
LAAMFV, per 1 m/s increase	47.926 (0.382 ~ 6014.699)	0.117

Abbreviations: CCT = cardiac computer tomography; CI = confidence interval; LAA = left atrial appendage; LAAMFV = left atrial appendage mean flow velocity; OR = odd ratio.



133x124mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract		From May 2017 to December 2022, 726 patients (male: 60.2%, age: 61±11 years) who had both TEE and CCT before catheter ablation of AF were retrospectively included.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found		Our study aims to evaluate the accuracy of CCT for detecting LAA thrombus in patients undergoing catheter ablation of atrial fibrillation (AF), using transesophageal echocardiography (TEE) as the reference standard.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5	Transesophageal echocardiology (TEE) is currently the gold standard for the assessment of left atrial appendage (LAA) thrombi in patients undergoing catheter ablation of atrial fibrillation (AF)…
Objectives	3	State specific objectives, including any prespecified hypotheses	5	We aimed to evaluate the sensitivity of CCT in detecting LAA thrombus and to analyze the risk factors of false-negative

				results.
Methods				
Study design	4	Present key elements of study design early in the paper		All the patient characteristics and images were acquired from the clinical database. The CHA2DS2-VASc score was calculated following the 2020 ESC guideline.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		From May 2017 to December 2022, patients were routinely scheduled for TEE and CCT before catheter ablation of AF in Guizhou Provincial People's Hospital. Those who had both examinations within a 12-hour interval on the same day were retrospectively included.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants		In the current study, we retrospectively included 726 patients who had both TEE and CCT before catheter ablation for AF.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7	Thrombus was defined as a persistent filling defect in the 30s-delayed scans. The LAA morphology was classified into

			simple or complex according to their main and branching structures on the 3D reconstructions…
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	All patients were examined with a third-generation dual-source CT. The imaging protocol included a standard angiographic-phase acquisition to assess the anatomy of the left atrium and one delayed-phase acquisition at 30 s after contrast injection to detect thrombi…
Bias	9	Describe any efforts to address potential sources of bias	Two independent radiologists with more than eight years of cardiovascular imaging, blinded to all patients' data... Two independent cardiologists with more than five years of experience in echocardiology evaluated the presence of LAA thrombus and measured the flow velocity...
Study size	10	Explain how the study size was arrived at	In the current study, we retrospectively included 726 patients who had both TEE and CCT before catheter ablation for AF.

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8	Using TEE as the reference standard, the diagnostic performance of CCT for LAA thrombi was calculated.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7	Continuous variables were expressed as mean ± SD deviation…
		(*b*) Describe any methods used to examine subgroups and interactions	N/A	
		(*c*) Explain how missing data were addressed	N/A	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7	Using TEE as the reference standard, the diagnostic performance of CCT for LAA thrombi was calculated.
		(*e*) Describe any sensitivity analyses	N/A	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study…
		(b) Give reasons for non-participation at each stage	N/A	
		(c) Consider use of a flow diagram	8	A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study (Fig. 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8	A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study (Fig. 1)…

		(b) Indicate number of participants with missing data for each variable of interest		A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study (Fig. 1).
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		Twenty-nine (50.9%) of the thrombi were located at the LAA ostium and 28(49.1%) were in the LAA. Compared with the CCT true-positive thrombi, the false-negative ones more frequently located at the LAA ostium (83.3% vs. 35.9%, p = 0.001) …
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A	
		(*b*) Report category boundaries when continuous variables were categorized		Given that high sensitivity is essential to exclude LAA thrombus, the CCT results of the LAA thrombi underwent further analysis. By scattering the CCT results on the 2-D plane, the thrombi at the LAA ostium…
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9	The CCT had an overall sensitivity of 68.4% and a specificity of 99.4%... Given that high sensitivity is essential to exclude LAA thrombus, the CCT results of the LAA thrombi underwent further analysis…
Discussion				
Key results	18	Summarise key results with reference to study objectives		We reevaluated the accuracy of CCT for detecting LAA thrombus in the 726 patients undergoing catheter ablation for AF.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		Firstly, this retrospective single-center study included only patients undergoing catheter ablation for AF…
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,11	Thus, the low sensitivity of CCT in our study could be presumed to: (1) inadequate temporal resolution…
Generalisability	21	Discuss the generalisability (external validity) of the study results	12	This retrospective single-center study included only patients undergoing catheter ablation for AF. The study's findings may not be generalizable to other patients with AF…
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13	This study has received funding from the Science and Technology Support plan of Guizhou Province…

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Impact of left atrial appendage thrombus location on diagnostic accuracy of cardiac computer tomography: a case-control study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-079876.R2
Article Type:	Original research
Date Submitted by the Author:	21-Dec-2023
Complete List of Authors:	Guo, Chuxian; Guizhou Provincial People's Hospital, Cardiology Department; Guizhou Medical University Jiang, Zhi; Guizhou Provincial People's Hospital, Cardiology Department He, Jionghong; Guizhou Provincial People's Hospital, Cardiology Department; Guizhou Provincial People's Hospital, Echocardiography Department Ma, Haiyan; Guizhou Provincial People's Hospital, Radiology Department Wang, Yuquan; Guizhou Provincial People's Hospital, Radiology Department Tan, Jing; Guizhou Provincial People's Hospital, Cardiology Department; Guizhou Provincial People's Hospital, Echocardiography Department Ou, Qiaoqiao; Guizhou Provincial People's Hospital, Cardiology Department; Guizhou Medical University Tian, Ye; Guizhou Provincial People's Hospital, Cardiology Department Tian, Longhai; Guizhou Provincial People's Hospital, Cardiology Department Liu, Qifang; Guizhou Provincial People's Hospital, Cardiology Department Huang, Jing; Guizhou Provincial People's Hospital, Cardiology Department Yang, Long; Guizhou Provincial People's Hospital, Cardiology Department
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine, Radiology and imaging
Keywords:	Stroke < NEUROLOGY, Ultrasound < RADIOLOGY & IMAGING, Computed tomography < RADIOLOGY & IMAGING, Thromboembolism < CARDIOLOGY

Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.

Supplementary material_Video S1.mp4

SCHOLARONE™
Manuscripts

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Article Title: Impact of left atrial appendage thrombus location on diagnostic accuracy of cardiac computer tomography: a case-control study

Running Head: Detection of Left Atrial Appendage Thrombus Using Cardiac CT

Authors: Chuxian Guo [ad]*; Zhi Jiang [a]*; Jionghong He [ab]; Haiyan Ma [c]; Yuquan Wang [c]; Jing Tan [ab]; Qiaoqiao Ou [ad]; Ye Tian [a]; Longhai Tian [a]; Qifang Liu [a]; Jing Huang [a]; Long Yang [a]

Affiliations: From [a] Cardiology Department, Guizhou Provincial People's Hospital, Guiyang, China; [b] Echocardiography Department, Guizhou Provincial People's Hospital, Guiyang, China; [c] Radiology Department of Guizhou Provincial People's Hospital, Guiyang City, China; [d] Guizhou Medical University, Guiyang, China.

* Chuxian Guo and Zhi Jiang contributed equally to the study.

Corresponding author: Long Yang, Department of Cardiology, Guizhou Provincial People's Hospital, NO. 83 East Zhongshan Road, Guizhou Province, Guiyang City, 550002, China. E-mail: yanglong1001@outlook.com. Telephone: +86-18198169283. Fax: +86 0851- 85924943

Word count of the main part of the manuscript: 2243

Abstract

Objective Cardiac computed tomography (CCT) is an emerging non-invasive modality for assessing left atrial appendage (LAA) thrombus, but the results were conflicting. Our study aims to evaluate the accuracy of CCT for detecting LAA thrombus in patients undergoing catheter ablation of atrial fibrillation, using transesophageal echocardiography (TEE) as the reference standard.

Design Case-control study.

Setting Patient data were collected from a tertiary hospital in China between 2017 and 2022.

Participants The study enrolled 726 patients (male: 60.2%, age: 61±11 years) who had both TEE and CCT before catheter ablation of atrial fibrillation.

Measures The CCT protocol consisted of one angiographic phase and one delayed scan 30 seconds later. LAA thrombi were defined as solid masses on TEE or persistent defects on CCT. The thrombus dimension and location, the LAA filling and emptying flow velocity were assessed by TEE.

Results Of the 57(7.9%) patients with LAA thrombi identified by TEE, 29(50.9%) were located at the LAA ostium, and 28(49.1%) were in the LAA. The former showed higher motility following blood flow and heartbeats than the latter. The CCT detected 14(48.3%) of the LAA-ostium thrombi but 25(89.3%) of those in the LAA ($p = 0.001$). The LAA-ostium thrombi with the LAA mean flow velocity higher than 0.35m/s and maximum diameters shorter than 10mm were more prone to have CCT false-negative results.

Conclusion For patients undergoing catheter ablation for atrial fibrillation, CCT with a 30s delay scan is less sensitive to LAA thrombi than TEE, especially for LAA-ostium thrombi with smaller sizes and higher LAA flow velocity.

Keywords stroke; embolism; thrombosis; pulmonary vein isolation; cardiac imaging techniques; ultrasound.

Strengths and limitations of this study

1. A major strength of our study is based on a large cohort with high incidence of left atrial appendage thrombi.

2. We first report the impact of thrombus location on the sensitivity of CCT, using TEE as reference standard.

3. A limitation of this study is that it is a single-center and retrospective study.

4. The CCT protocol contained only one delayed-phase scan. Whether multiple delayed-phase scans reduce false-negative CCT results is unclear.

Title: Impact of left atrial appendage thrombus location on diagnostic accuracy of cardiac computer tomography: a case-control study

Introduction

Transesophageal echocardiology (TEE) is currently the gold standard for the assessment of left atrial appendage (LAA) thrombi in patients undergoing catheter ablation of atrial fibrillation (AF)[1]. In the past decades, cardiac computed tomography (CCT) has been widely studied for detecting LAA thrombus[2-5]. Recently, the delayed contrast-enhanced CCT at 6 minutes was reported to reach 100% sensitivity and negative predictive value in detecting LAA thrombus[6]. For patients who are not tolerant of the discomfort associated with TEE, CCT is proposed as a reliable alternative[7]. However, the accuracy of CCT varied between studies[2-5, 8], raising the safety concern and limiting the routine use of CCT.

The left atrial thrombi were classified into a movable ball, fixed ball, and mountain according to their morphology[9]. Around 1/3 of the thrombi in the left atrium were movable. Although CCT is of high spatial resolution, its temporal resolution is 4~17Hz, and it takes 60ms ~ 250ms to acquire one slice[8, 10-12]. Compared to TEE, which allows live display with a high spatiotemporal resolution (<1mm, 20~30Hz)[13], CCT is theoretically inferior for identifying moving objects in the left atrium. In addition, the circulatory stasis and the fibrillation of the atrial wall during AF also increase the difficulty of detecting movable thrombi[14]. In previous studies, the presence of LAA thrombus was 2(0.24%) ~16(19.04%)[2-5, 15]. The high sensitivity and negative predictive value of CCT could be attributed to the low incidence of movable thrombus. Therefore, it is essential to investigate

the diagnostic accuracy of CCT in a larger cohort with a higher incidence of LAA thrombus.

In the current study, we retrospectively included 726 patients who had both TEE and CCT before catheter ablation for AF. 57(7.9%) patients were diagnosed with LAA thrombi using TEE. We aimed to evaluate the sensitivity of CCT in detecting LAA thrombus and to analyze the risk factors of false-negative results.

Methods

Study population

From May 2017 to December 2022, patients were routinely scheduled for TEE and CCT before catheter ablation of AF in Guizhou Provincial People's Hospital. Those who had both examinations within a 12-hour interval on the same day were retrospectively included. All the patient characteristics and images were acquired from the clinical database. The CHA_2DS_2-VASc score was calculated following the 2020 ESC guideline[1]. The study was approved by the institutional ethics committee of Guizhou Provincial People's Hospital. The informed consent was waived due to the retrospective nature, and no identified information was collected.

CCT protocol

All patients were examined with a third-generation dual-source CT (SOMATOM Force, Siemens Healthineers, Forchheim, Germany). The imaging protocol included a standard

angiographic-phase acquisition to assess the anatomy of the left atrium and one delayed-phase acquisition at 30 s after contrast injection to detect thrombi. No electrocardiography gating was used. The tube voltage and current were automatically adjusted using the CARE kV or CARE DOSE 4D with the reference of 100kv and 250mA. The gantry rotation time was 250ms, and the detector collimator was 192×0.6 mm. The scanning image covers the range from the aortic arch to the cardiac base. The monitoring site was localized within the left atrium. The contrast material containing 350 mg/ml of iodine was administrated intravenously at 4-5 ml/s with a total dose of 35 ml by a double-barrel syringe, followed by the same amount of 0.9% saline. For the angiographic phase, the scanning was triggered when the monitoring site reached 90 HU. Then the delayed phase was acquired 30 s later. All images were reconstructed using the ADMIRE algorithm grade 3 with a layer thickness of 1 mm and interlayer spacing of 0.7 mm. The 3D left atrium and pulmonary veins were reconstructed using the Syngo.via software (Siemens Healthcare, Forchheim, Germany).

CCT image analysis

Images were transferred to an external workstation (Syngo VPCT body, Siemens Healthcare, Forchheim, Germany). Two independent radiologists with more than eight years of cardiovascular imaging, blinded to all patients' data, retrospectively evaluated the presence of LAA thrombus and LAA morphology. Thrombus was defined as a persistent filling defect in the 30s-delayed scans. The LAA morphology was classified into simple or complex according to their main and branching structures on the 3D reconstructions[16]. In case of disagreement, a final joint reading was performed to achieve consensus.

Transesophageal echocardiology

A PhilipsiEPIQ7C color Doppler ultrasound diagnostic instrument (Philips, Amsterdam, the Netherlands) and an X7-2t probe were used. The left atrium and LAA were scanned using a complete 2D, colored, pulsed, and continuous-wave Doppler echocardiogram according to the EACVI recommendations[17]. Thrombi were defined as circumscribed echogenic or echolucent masses distinct from the atrial wall. LAA ostium was defined as within the 5mm range of the junction between the smooth atrial wall and trabeculated LAA. The dimensions and locations of thrombi were assessed if present. The LAA filling and emptying velocity was averaged by ten consecutive measurements of the backward and forward flow rates using the pulsed wave Doppler. LAA mean flow velocity (LAAMFV) was calculated by halving the sum of the LAA filling and emptying velocity. Two independent cardiologists with more than five years of experience in echocardiology evaluated the presence of LAA thrombus and measured the flow velocity. Disagreements were resolved by consensus.

Statistical analysis

Continuous variables were expressed as mean ± SD deviation. The Student's t-test was used for comparison if normally distributed; otherwise, the Mann-Whitney U test was used. Categorical variables were expressed as frequency (percentage). The Chi-square test was used for comparison if the expected frequency is more than 5; otherwise, Fisher's exact test was used. A two-tailed *p* value of less than 0.05 was considered statistically significant. Using TEE as the reference standard, the diagnostic performance of CCT for LAA thrombi was

calculated. Multivariate logistic regression model was conducted to determine the predictors of CCT false-negative results. The receiver operating characteristics (ROC) curve with the area under the curve (AUC) was calculated to evaluate the performance of the predictive model. All statistical analysis was performed using SPSS 26.0.

Results

Patient characteristics

A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study (Figure 1). The patients with LAA thrombus had a higher incidence of previous stroke/transient ischemic attack (TIA) and congestive heart failure, larger left atrial size, worse left ventricular function, and a higher rate of complex LAA morphology than those without LAA thrombus ($p < 0.05$) (Table 1).

Twenty-nine (50.9%) of the thrombi were located at the LAA ostium and 28(49.1%) were in the LAA. The clinical characteristics and maximum thrombus diameter were similar between the patients. The thrombi at the LAA ostium were accompanied by higher LAA filling and emptying velocities than those in the LAA (Supplementary material online, Table S1). The former also showed significantly higher mobility following the blood flow and cardiac motion than the latter (Supplementary material online, Video S1).

Diagnostic accuracy of CCT

The CCT had an overall sensitivity of 68.4% and a specificity of 99.4% to the LAA thrombi (Table 1). However, the CCT was less sensitive to the thrombi at LAA ostium than those in the LAA (48.3% vs. 89.3%, $p = 0.001$) (Supplementary material online, Table S1). Representative images are shown in Figure 2.

Given that a high sensitivity is essential to exclude LAA thrombus, the CCT results of the LAA thrombi underwent further analysis. Compared with the CCT true-positive thrombi, the false-negative ones more frequently located at the LAA ostium (83.3% vs. 35.9%, $p = 0.001$), were shorter in the maximum diameters (8±2mm vs. 14±9mm, $p < 0.001$), and were accompanied by higher LAA filling and emptying velocities (0.53±0.15 m/s vs. 0.38±0.19 m/s, $p = 0.001$; 0.55±0.21 m/s vs. 0.37±0.14 m/s, $p < 0.001$) (Table 2). The result was also concordant in the LAA-ostium thrombi subgroup (Supplementary material online, Table S2). By scattering the CCT results on the 2-D plane that consisted of LAAMFV and thrombus maximum diameter, the thrombi at the LAA ostium with the LAAMFVs higher than 0.35m/s and maximum diameters shorter than 10mm were more prone to have CCT false-negative results (Figure 3A). For the thrombi in the LAA, the maximum diameter or LAAMFV did not impact the CCT results (Figure 3B). In the logistic regression model, the thrombus maximum diameter, location, and LAA mean flow velocity (LAAMFV) were independently associated with the CCT false-negative results (Supplementary material online, Table S3). The ROC curve (AUC: 0.909, 95%CI: 0.834 ~ 0.984) is shown in Figure S1.

Discussion

Major findings

We reevaluated the accuracy of CCT for detecting LAA thrombus in the 726 patients undergoing catheter ablation for AF. TEE identified 57(7.9%) patients with LAA thrombi, of which 29(50.9%) were at the LAA ostium and 28(49.1%) in the LAA. The CCT was less sensitive in detecting LAA-ostium thrombi with smaller maximum diameters and higher LAAMFV.

Concordance

LAA thrombus is thought to form initially inside the LAA, where circulatory stasis is the greatest, and then extends towards the ostium. However, we found over half of the thrombi located at the LAA ostium. The result was concordant with a previous study in which 46.3% of the thrombi were at the entrance section of LAA[9]. The presence of pits and troughs adjacent to the LAA orifice was reported in 57.7% of the human heart specimens[18]. It could be the anatomic basis for thrombosis. Another study using TEE discovered small recesses proximal to the entry of LAA in a significant number of patients, but no thrombus related to these structures was detected following LAA occlusion[19]. The discrepancy could be due to patient selection bias. Nonetheless, our findings raised concerns about the role of LAA-ostium recesses in thrombosis.

Although the third-generation 64-slice dual-source CT was employed in the current study, its sensitivity to LAA thrombi was not improved. The sensitivity of 89.3% to the thrombi in the LAA was comparable to the previous studies[2, 10, 11, 20-22]. However, the sensitivity significantly decreased for the LAA-ostium thrombi, which showed higher motility following blood flow and heartbeats than those in the LAA (Supplementary material online, Video S1). We further identified that the LAA-ostium thrombi with smaller sizes and higher LAA flow velocity were more prone to be missed using the CCT. As a higher temporal resolution is essential to detect movable objects[23], our findings suggested the impact of thrombus motility on CCT imaging. By calculating the gantry rotation time of 250ms, the CCT had a temporal resolution of 4Hz, significantly less than that of the TEE (20~40Hz). Thus, the low sensitivity of CCT in our study could be presumed to: (1) inadequate temporal resolution, (2) the high proportion of movable LAA-ostium thrombi, (3) the lack of ECG gating, (4) only one 30s delayed scan was used. The 4 CCT false-positive results in our study could be the misdiagnosis of thrombus due to circulatory stasis during AF[6, 24].

Discordance

Several studies reported that the CCT had 100% sensitivity in detecting LAA thrombi using ECG gating, single-segment reconstruction algorithm[25, 26], or multiple delayed-phase scans[3, 14, 27]. However, these studies have the following limitations: (1) Although the single-segment reconstruction algorithm increased the CCT's temporal resolution to 12Hz, the low incidence of LAA thrombus [2(0.24%) ~16(19.04%)] and the less variation of thrombus location could have overestimated the sensitivity of CCT for detecting LAA thrombi in a broader range of patients. (2) The multiple delayed-phase scans distinguished the thrombi from filling defects due to circulatory stasis. Still, the technique could not necessarily increase the sensitivity to smaller and movable thrombi at the LAA ostium.

We suggest that the CCT approach to detect LAA thrombi could differ according to their location and motility. Persistent filling defects in multiple delayed-phase scans have been well established for static thrombi in LAA. However, LAA-ostium thrombi could be highly motile due to blood flow and myocardial contraction. In our study, the LAA flow velocity indirectly reflected the thrombus motility. The filling defects that indicate the presence of thrombi could still be enhanced as the thrombi swayed much faster than the duration required for scanning. Furthermore, the filling defect size also depended on the thrombi size. Therefore, smaller LAA-ostium thrombi with higher LAA flow velocity could be prone to be missed by CCT. A temporal resolution comparable to TEE (20~40Hz) could be necessary.

Clinical implication

Our study found that the CCT with a 30s delayed scan did not reliably exclude LAA thrombus, especially those located at the LAA ostium. We did not find any clinical characteristics associated with the thrombus location. TEE is the only recommendation for stroke risk management for patients undergoing catheter ablation of AF in the 2020 ESC guideline[1]. For those who do not tolerate TEE, intracardiac echocardiography could be considered[28].

Limitations

Firstly, this retrospective single-center study included only patients undergoing catheter ablation for AF. The study's findings may not be generalizable to other patients with AF. Secondly, the CCT protocol contained only one delayed-phase scan. Whether multiple delayed-phase scans reduce false-negative CCT results is unclear. Thirdly, other factors unaccounted for in this analysis – heart rhythm, atrial/ventricular rate, and blood pressure during the TEE and CCT – could affect the conclusions. Fourthly, although the interval between the TEE and CCT was less than 12 hours, it is theoretically possible for thrombi to form or disappear within this timeframe. Lastly, the incidence of LAA thrombus was higher than that in previous studies (partially due to less adherence to anticoagulation treatment), which could have affected the thrombus location and motility.

Conclusions

In patients undergoing catheter ablation of AF, CCT with a 30s delay scan is less sensitive than TEE in detecting LAA thrombi, especially those located at LAA ostium with smaller sizes and higher LAA flow velocity.

Acknowledgments

We thank Nicholas Tan and Jason Tri from the Mayo Clinic for their dedicated help in preparing the manuscript.

Data sharing statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

This study has received funding from the Science and Technology Support plan of Guizhou Province [NO. (2017)2885 and (2018)2794] to L.Y. and Y.T., the Clinical Special Projects in Guizhou Province [NO. (2019)4430] to Q.L., and the Clinical Research Center Project of the Department of science and technology of Guizhou Province [NO. (2017)5405] to L.Y.

Ethical approval

This study received approval from the institutional ethics committee of Guizhou Provincial People's Hospital.

Contributors

Chuxian Guo and Zhi Jiang: Conceptualization, Methodology, Formal analysis, Writing-original draft, Writing – review & editing. Jionghong He, Haiyan Ma, and Yuquan Wang: Conceptualization, Methodology, Formal analysis, Visualization, Writing – review & editing. Jing Tan: Conceptualization, Methodology, Investigation, Writing – review & editing. Qiaoqiao Ou: Conceptualization, Investigation, Writing – review & editing. Ye Tian and Qifang Liu: Conceptualization, Writing – review & editing, Funding acquisition. Longhai Tian and Jing Huang: Conceptualization, Investigation, Writing – review & editing. Long Yang: Conceptualization, Methodology, Formal analysis, Writing – review & editing, Supervision, Funding acquisition. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Supplementary Materials

Video S1 Representative TEE video of the thrombi at LAA ostium (A-C) and those in the LAA (D-F).

Table S1 Patient characteristics between thrombus locations.

Table S2 Patient characteristics between true-positive and false-negative CCT results.

Table S3 Multivariate analysis of the predictors for false-negative CCT results.

Figure S1 The ROC curve of the logistic regression model for predicting false-negative CCT results.

Abbreviation: AUC= area under the curve; CCT = cardiac computer tomography; CI = confidence interval; ROC= receiver operating characteristics.

References

1. Hindricks G, Potpara T, Dagres N*, et al.* 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021 **42**:373-498.
2. Dorenkamp M, Sohns C, Vollmann D*, et al.* Detection of left atrial thrombus during routine diagnostic work-up prior to pulmonary vein isolation for atrial fibrillation: role of transesophageal echocardiography and multidetector computed tomography. *Int J Cardiol*. 2013 **163**:26-33.
3. Zhai Z, Tang M, Zhang S*, et al.* Transoesophageal echocardiography prior to catheter ablation could be avoided in atrial fibrillation patients with a low risk of stroke and without filling defects in the late-phase MDCT scan: A retrospective analysis of 783 patients. *Eur Radiol*. 2018 **28**:1835-1843.
4. Li W, Yu F, Zhu W, Zhang W, Jiang T. Detection of left atrial appendage thrombi by third-generation dual-source dual-energy CT: Iodine concentration versus conventional enhancement measurements. *Int J Cardiol*. 2019 **292**:265-270.
5. Guha A, Dunleavy MP, Hayes S*, et al.* Accuracy of contrast-enhanced computed tomography for thrombus detection prior to atrial fibrillation ablation and role of novel Left Atrial Appendage Enhancement Index in appendage flow assessment. *Int J Cardiol*. 2020 **318**:147-152.

6. Spagnolo P, Giglio M, Di Marco D*, et al.* Diagnosis of left atrial appendage thrombus in patients with atrial fibrillation: delayed contrast-enhanced cardiac CT. *Eur Radiol*. 2021 **31**:1236-1244.

7. Yu S, Zhang H, Li H. Cardiac Computed Tomography Versus Transesophageal Echocardiography for the Detection of Left Atrial Appendage Thrombus: A Systemic Review and Meta-Analysis. *J Am Heart Assoc*. 2021 **10**:e022505.

8. Kottmaier M, Jilek C, Berglar S*, et al.* Exclusion of left atrial thrombus by dual-source cardiac computed tomography prior to catheter ablation for atrial fibrillation. *Clin Res Cardiol*. 2019 **108**:150-156.

9. Abe Y, Asakura T, Gotou J*, et al.* Prediction of embolism in atrial fibrillation: classification of left atrial thrombi by transesophageal echocardiography. *Jpn Circ J*. 2000 **64**:411-5.

10. Kim YY, Klein AL, Halliburton SS*, et al.* Left atrial appendage filling defects identified by multidetector computed tomography in patients undergoing radiofrequency pulmonary vein antral isolation: a comparison with transesophageal echocardiography. *Am Heart J*. 2007 **154**:1199-205.

11. Tang RB, Dong JZ, Zhang ZQ*, et al.* Comparison of contrast enhanced 64-slice computed tomography and transesophageal echocardiography in detection of left atrial thrombus in patients with atrial fibrillation. *J Interv Card Electrophysiol*. 2008 **22**:199-203.

12. Martinez MW, Kirsch J, Williamson EE*, et al.* Utility of nongated multidetector computed tomography for detection of left atrial thrombus in patients undergoing

catheter ablation of atrial fibrillation. *JACC Cardiovasc Imaging*. 2009 **2**:69-76.

13. Vegas A. Three-dimensional transesophageal echocardiography: Principles and clinical applications. *Ann Card Anaesth*. 2016 **19**:S35-S43.

14. Maltagliati A, Pontone G, Annoni A*, et al.* Multidetector computed tomography vs multiplane transesophageal echocardiography in detecting atrial thrombi in patients candidate to radiofrequency ablation of atrial fibrillation. *Int J Cardiol*. 2011 **152**:251-4.

15. Budoff MJ, Shittu A, Hacioglu Y*, et al.* Comparison of transesophageal echocardiography versus computed tomography for detection of left atrial appendage filling defect (thrombus). *Am J Cardiol*. 2014 **113**:173-7.

16. He J, Fu Z, Yang L*, et al.* The predictive value of a concise classification of left atrial appendage morphology to thrombosis in non-valvular atrial fibrillation patients. *Clin Cardiol*. 2020 **43**:789-795.

17. Flachskampf FA, Decoodt P, Fraser AG, Daniel WG, Roelandt JR. Guidelines from the Working Group. Recommendations for performing transesophageal echocardiography. *Eur J Echocardiogr*. 2001 **2**:8-21.

18. Su P, McCarthy KP, Ho SY. Occluding the left atrial appendage: anatomical considerations. *Heart*. 2008 **94**:1166-70.

19. Meincke F, Schmidt-Salzmann M, Kreidel F, Kuck KH, Bergmann MW. New technical and anticoagulation aspects for left atrial appendage closure using the WATCHMAN® device in patients not taking warfarin. *EuroIntervention*. 2013 **9**:463-8.

20. Homsi R, Nath B, Luetkens JA, Schwab JO, Schild HH, Naehle CP. Can Contrast-Enhanced Multi-Detector Computed Tomography Replace Transesophageal Echocardiography for the Detection of Thrombogenic Milieu and Thrombi in the Left Atrial Appendage: A Prospective Study with 124 Patients. *Rofo*. 2016 **188**:45-52.

21. Shapiro MD, Neilan TG, Jassal DS*, et al.* Multidetector computed tomography for the detection of left atrial appendage thrombus: a comparative study with transesophageal echocardiography. *J Comput Assist Tomogr*. 2007 **31**:905-9.

22. Hur J, Kim YJ, Lee HJ*, et al.* Dual-enhanced cardiac CT for detection of left atrial appendage thrombus in patients with stroke: a prospective comparison study with transesophageal echocardiography. *Stroke*. 2011 **42**:2471-7.

23. Jung B, Föll D, Böttler P, Petersen S, Hennig J, Markl M. Detailed analysis of myocardial motion in volunteers and patients using high-temporal-resolution MR tissue phase mapping. *J Magn Reson Imaging*. 2006 **24**:1033-9.

24. Fukushima K, Fukushima N, Kato K*, et al.* Correlation between left atrial appendage morphology and flow velocity in patients with paroxysmal atrial fibrillation. *Eur Heart J Cardiovasc Imaging*. 2016 **17**:59-66.

25. Kapa S, Martinez MW, Williamson EE*, et al.* ECG-gated dual-source CT for detection of left atrial appendage thrombus in patients undergoing catheter ablation for atrial fibrillation. *J Interv Card Electrophysiol*. 2010 **29**:75-81.

26. Kuronuma K, Matsumoto N, Suzuki Y*, et al.* Usefulness of Dual-Phase Snapshot 320-Detector Computed Tomography for the Detection of a Left Atrial Appendage Thrombus. *Int Heart J*. 2019 **60**:849-853.

27. Wang L, Kadiyala M, Koss E*, et al.* CTA Detection of Left Atrial Stasis and Thrombus in Patients with Atrial Fibrillation. *Pacing Clin Electrophysiol*. 2016 **39**:1388-1393.

28. He G, Liu H, Huang X*, et al.* Intracardiac versus transesophageal echocardiography for diagnosis of left atrial appendage thrombosis in atrial fibrillation: A meta-analysis. *Clin Cardiol*. 2021 **44**:1416-1421.

Figure legends

Figure 1 Patient flowchart.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; LAA = left atrial appendage; TEE = transesophageal echocardiography.

Figure 2 Representative CCT and TEE images of the LAA thrombi.

The left and middle images are from the CCT angiographic and delayed phase. The right images are from the TEE. A-C. Representative false-negative CCT result of the thrombus in the LAA. D-F. Representative false-negative CCT result of the LAA-ostium thrombus. G-I. Representative true-positive CCT result of the thrombus in the LAA. J-L. Representative true-positive CCT result of the LAA-ostium thrombus. White arrows denote the thrombi.

Abbreviation: CCT = cardiac computer tomography; LAA = left atrial appendage.

Figure 3 Scatter plots of CCT results.

Red dots denote the CCT false-negative thrombi. Green dots denote the CCT true-positive thrombi. The LAAMFV was calculated by halving the sum of the LAA emptying and filling velocity. A. For the LAA-ostium thrombi, the CCT false-negative results had the LAAMFV higher than 0.35 m/s and maximum diameters less than 10 mm. B. For the thrombi in the LAA, the maximum diameter or LAAMFV did not significantly impact CCT results.

Abbreviations: CCT = cardiac computed tomography; LAA = left atrial appendage; LAAMFV = left atrial appendage mean flow velocity.

Table 1 Patient characteristics.

Characteristics	Overall (n=726)	LAA thrombus * Positive (n=57)	Negative (n=669)	*P* value
Age, year	61±11	64±10	61±11	0.129
Male	437(60.2)	36(63.2)	401(59.9)	0.634
Paroxysmal AF	436(60.1)	30(52.6)	406(60.7)	0.233
AF course, month	42±83	39±45	43±85	0.540
CHA_2DS_2-VASc score	2±2	3±2	2±2	0.089
Congestive heart failure	116(16.0)	18(31.6)	98(14.6)	0.001
Hypertension	346(47.7)	25(43.9)	321(48.0)	0.550
Diabetes mellitus	107(14.7)	10(17.5)	97(14.5)	0.534
Previous Stroke/TIA	91(12.5)	14(24.6)	77(11.5)	0.004
Vascular disease	292(40.2)	22(38.6)	270(40.4)	0.795
LAAPD, mm	36±7	41±9	36±7	<0.001
LVEDD, mm	46±5	49±7	46±5	0.006
LVEF, %	60±8	56±11	60±7	0.005
Complex LAA morphology	289(39.8)	35(61.4)	254(38.0)	0.001
CCT results				
Filling defects	43(5.9)	39(68.4)	4(0.6)	<0.001
No filling defects	683(94.1)	18(31.6)	665(99.4)	

Values are mean ± SD or n (%).

* The thrombi were detected using the TEE.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, previous stroke/transient ischemic attack/thromboembolism (doubled), vascular disease, age 65–74 years and sex category (female); LAA = left atrial appendage; LAAPD = left atrial anterior-posterior diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; TEE = transesophageal echocardiography; TIA = transient ischemic attack.

Table 2 Patient characteristics between CCT true-positive and false-negative results.

Characteristics	LAA thrombus *		*P* value
	CCT false-negative result (n=18)	CCT true-positive result (n=39)	
Age, years	64±9	64±10	0.810
Male	11(61.1)	25(64.1)	0.828
Paroxysmal AF	12(66.7)	18(46.2)	0.149
AF course, month	42±54	38±40	0.952
CHA_2DS_2-VASc score	3±2	3±2	0.450
Congestive heart failure	5(27.8)	13(33.3)	0.675
Hypertension	10(55.6)	15(38.5)	0.227
Diabetes mellitus	5(27.8)	5(12.8)	0.168
Previous Stroke/TIA	5(27.8)	9(23.1)	0.702
Vascular disease	7(38.9)	15(38.5)	0.975
LAAPD, mm	41±9	41±9	0.770
LVEDD, mm	49±6	49±7	0.336
LVEF, %	59±9	55±12	0.331
Complex LAA	9(50.0)	26(66.7)	0.230
LAA filling velocity, m/s	0.53±0.15	0.38±0.19	0.002
LAA emptying velocity, m/s	0.55±0.21	0.37±0.14	0.001
Thrombi maximum diameter, mm	8±2	14±9	<0.001
Thrombus location			
LAA ostium	15(83.3)	14(35.9)	0.001
In LAA	3(16.7)	25(64.1)	

Values are mean ± SD or n (%).

* The thrombi were detected using the TEE.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, previous stroke/transient ischemic attack/thromboembolism (doubled), vascular disease, age 65–74 years and sex category (female); LAA = left atrial appendage; LAAPD = left atrial anterior-posterior diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; TEE = transesophageal echocardiography; TIA = transient ischemic attack.

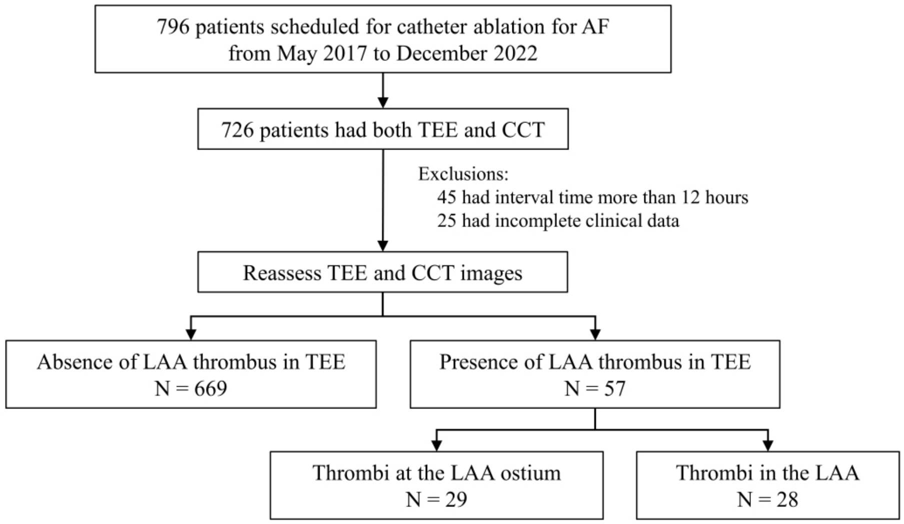


Figure 1 Patient flowchart.
Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; LAA = left atrial appendage; TEE = transesophageal echocardiography.

190x104mm (600 x 600 DPI)

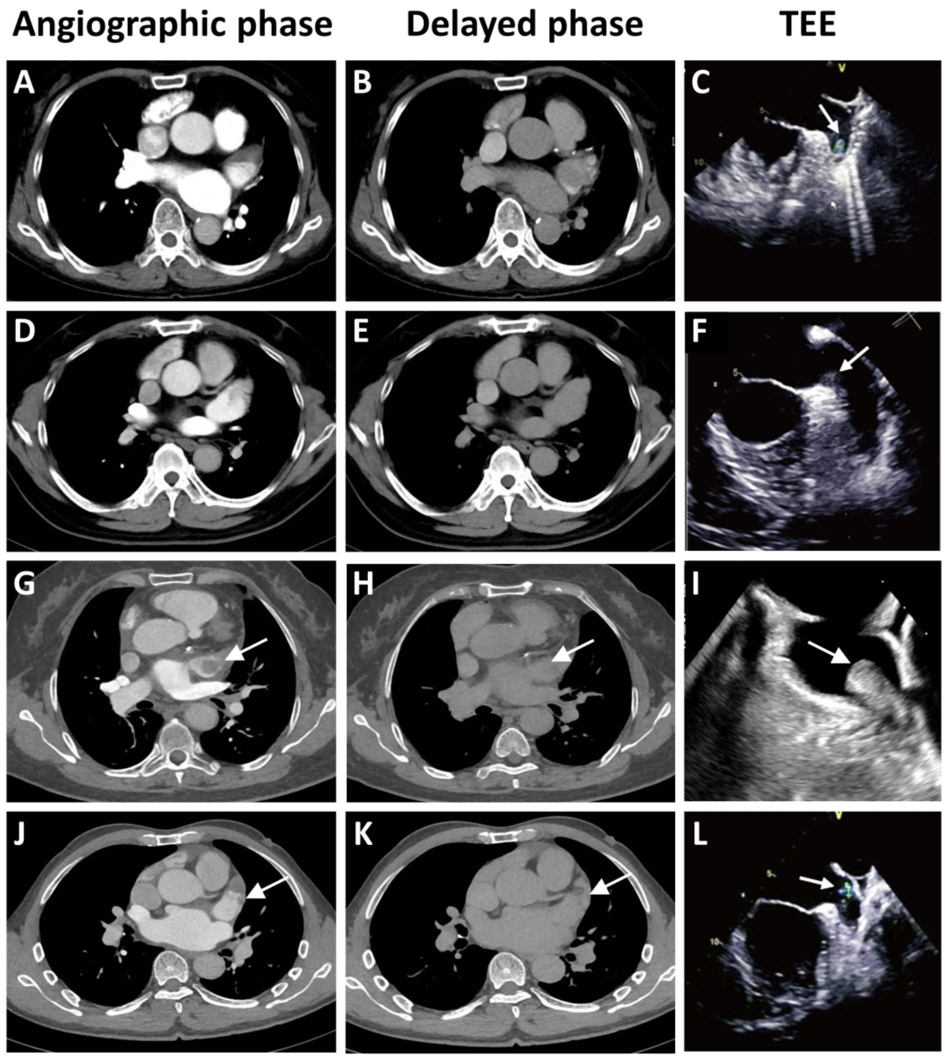


Figure 2 Representative CCT and TEE images of the LAA thrombi.
The left and middle images are from the CCT angiographic and delayed phase. The right images are from the TEE. A-C. Representative false-negative CCT result of the thrombus in the LAA. D-F. Representative false-negative CCT result of the LAA-ostium thrombus. G-I. Representative true-positive CCT result of the thrombus in the LAA. J-L. Representative true-positive CCT result of the LAA-ostium thrombus. White arrows denote the thrombi.
Abbreviation: CCT = cardiac computer tomography; LAA = left atrial appendage.

116x128mm (600 x 600 DPI)

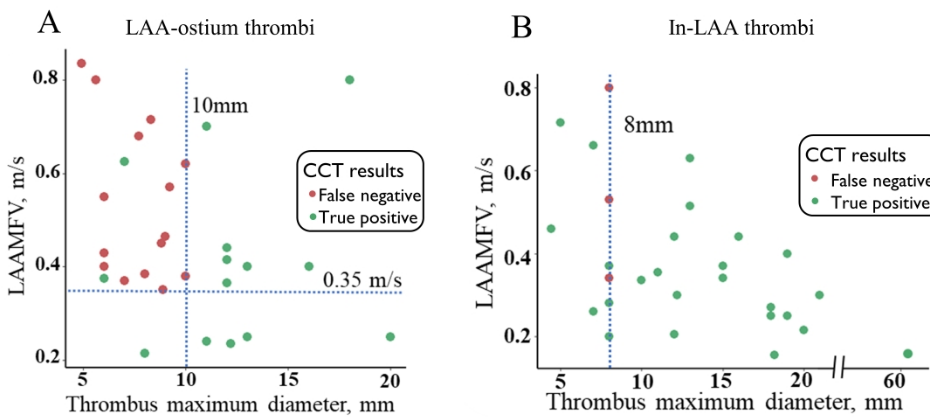


Figure 3 Scatter plots of CCT results.

Red dots denote the CCT false-negative thrombi. Green dots denote the CCT true-positive thrombi. The LAAMFV was calculated by halving the sum of the LAA emptying and filling velocity. A. For the LAA-ostium thrombi, the CCT false-negative results had the LAAMFV higher than 0.35 m/s and maximum diameters less than 10 mm. B. For the thrombi in the LAA, the maximum diameter or LAAMFV did not significantly impact CCT results.

Abbreviations: CCT = cardiac computed tomography; LAA = left atrial appendage; LAAMFV = left atrial appendage mean flow velocity.

190x89mm (600 x 600 DPI)

Table S1 Patient characteristics between thrombus locations.

Characteristics	Thrombus locations *		*P* value
	LAA ostium (n=29)	In LAA (n=28)	
Age, years	63±10	64±10	0.886
Male	20(69.0)	16(57.1)	0.355
Paroxysmal AF	18(62.1)	12(42.9)	0.146
AF course, month	40±52	39±35	0.648
CHA_2DS_2-VASc score	2±2	3±2	0.220
Congestive heart failure	9(31.0)	9(32.1)	0.928
Hypertension	10(34.5)	15(53.6)	0.147
Diabetes mellitus	5(17.2)	5(17.9)	1.000
Previous Stroke/TIA	7(24.1)	7(25.0)	0.940
Vascular disease	9(31.0)	13(46.4)	0.233
LAAPD, mm	41±10	40±8	0.873
LVEDD, mm	49±6	49±8	0.492
LVEF, %	57±11	55±11	0.424
Complex LAA	17(58.6)	18(64.3)	0.661
LAA filling velocity, m/s	0.48±0.19	0.37±0.19	0.021
LAA emptying velocity, m/s	0.47±0.20	0.38±0.16	0.050
LAAMFV, m/s	0.47±0.18	0.37±0.17	0.029
Thrombus maximum diameter, mm	10±4	14±10	0.045
CCT results			
Filling defects	14(48.3)	25(89.3)	0.001
No filling defects	15(51.7)	3(10.7)	

Values are mean ± SD or n (%).

* The thrombus locations were determined using the TEE.

The LAAMFV was calculated by halving the sum of the LAA emptying and filling velocity.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, previous stroke/transient ischemic attack/thromboembolism (doubled), vascular disease, age 65–74 years and sex category (female); LAA = left atrial appendage; LAAMFV = left atrial appendage mean flow velocity; LAAPD= left atrial anterior-posterior diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; TEE = transesophageal echocardiography; TIA = transient ischemic attack.

Table S2 Patient characteristics between true-positive and false-negative CCT results.

Characteristics	LAA-ostium thrombi*		*P* value
	CCT false-negative result (n=15)	CCT true-positive result (n=14)	
Age, years	63±10	64±10	0.726
Male	10(66.7)	10(71.4)	1.000
Paroxysmal AF	10(66.7)	8(57.1)	0.597
AF course, month	44±58	36±45	0.677
CHA_2DS_2-VASc score	3±2	2±2	0.288
Congestive heart failure	4(26.7)	5(35.7)	0.700
Hypertension	8(53.3)	2(14.3)	0.050
Diabetes mellitus	4(26.7)	1(7.1)	0.330
Previous Stroke/TIA	4(26.7)	3(21.4)	1.000
Vascular disease	6(40.0)	3(21.4)	0.427
LAAPD, mm	39±9	44±11	0.221
LVEDD, mm	49±6	48±5	0.370
LVEF, %	59±8	55±13	0.444
Complex LAA	7(46.7)	10(71.4)	0.264
LAA filling velocity, m/s	0.52±0.15	0.43±0.21	0.110
LAA emptying velocity, m/s	0.55±0.21	0.38±0.15	0.027
LAAMFV, m/s	0.53±0.16	0.41±0.18	0.047
Thrombus maximum diameter, mm	8±2	12±4	0.001

Values are mean ± SD or n (%).

* The LAA-ostium thrombi were determined using the TEE.

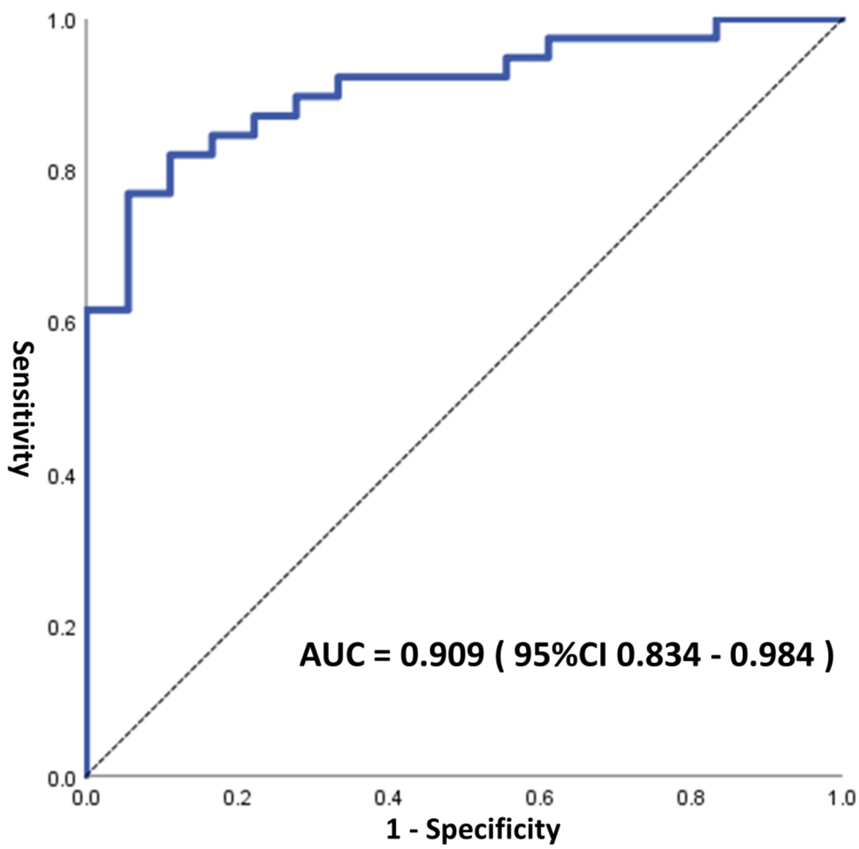
The LAAMFV was calculated by halving the sum of the LAA emptying and filling velocity.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, previous stroke/transient ischemic attack/thromboembolism (doubled), vascular disease, age 65–74 years and sex category (female); LAA = left atrial appendage; LAAMFV = left atrial appendage mean flow velocity; LAAPD= left atrial anterior-posterior diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; TEE = transesophageal echocardiography; TIA = transient ischemic attack.

Table S3 Multivariate analysis of the predictors for false-negative CCT results.

Characteristics	*OR* (95% CI)	*P* value
Thrombus maximum diameter, per 1 mm decrease	0.635 (0.459 ~ 0.879)	0.006
LAA-ostium thrombus	10.981 (1.702 ~ 70.831)	0.012
LAAMFV, per 1 m/s increase	47.926 (0.382 ~ 6014.699)	0.117

Abbreviations: CCT = cardiac computer tomography; CI = confidence interval; LAA = left atrial appendage; LAAMFV = left atrial appendage mean flow velocity; OR = odd ratio.



133x124mm (600 x 600 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract		From May 2017 to December 2022, 726 patients (male: 60.2%, age: 61±11 years) who had both TEE and CCT before catheter ablation of AF were retrospectively included.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found		Our study aims to evaluate the accuracy of CCT for detecting LAA thrombus in patients undergoing catheter ablation of atrial fibrillation (AF), using transesophageal echocardiography (TEE) as the reference standard.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5	Transesophageal echocardiology (TEE) is currently the gold standard for the assessment of left atrial appendage (LAA) thrombi in patients undergoing catheter ablation of atrial fibrillation (AF)…
Objectives	3	State specific objectives, including any prespecified hypotheses	5	We aimed to evaluate the sensitivity of CCT in detecting LAA thrombus and to analyze the risk factors of false-negative

				results.
Methods				
Study design	4	Present key elements of study design early in the paper	5	All the patient characteristics and images were acquired from the clinical database. The CHA2DS2-VASc score was calculated following the 2020 ESC guideline.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	From May 2017 to December 2022, patients were routinely scheduled for TEE and CCT before catheter ablation of AF in Guizhou Provincial People's Hospital. Those who had both examinations within a 12-hour interval on the same day were retrospectively included.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5	In the current study, we retrospectively included 726 patients who had both TEE and CCT before catheter ablation for AF.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7	Thrombus was defined as a persistent filling defect in the 30s-delayed scans. The LAA morphology was classified into

			simple or complex according to their main and branching structures on the 3D reconstructions…
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	All patients were examined with a third-generation dual-source CT. The imaging protocol included a standard angiographic-phase acquisition to assess the anatomy of the left atrium and one delayed-phase acquisition at 30 s after contrast injection to detect thrombi…
Bias	9	Describe any efforts to address potential sources of bias	Two independent radiologists with more than eight years of cardiovascular imaging, blinded to all patients' data... Two independent cardiologists with more than five years of experience in echocardiology evaluated the presence of LAA thrombus and measured the flow velocity...
Study size	10	Explain how the study size was arrived at	In the current study, we retrospectively included 726 patients who had both TEE and CCT before catheter ablation for AF.

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8	Using TEE as the reference standard, the diagnostic performance of CCT for LAA thrombi was calculated.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7	Continuous variables were expressed as mean ± SD deviation…
		(*b*) Describe any methods used to examine subgroups and interactions	N/A	
		(*c*) Explain how missing data were addressed	N/A	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7	Using TEE as the reference standard, the diagnostic performance of CCT for LAA thrombi was calculated.
		(*e*) Describe any sensitivity analyses	N/A	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study…
		(b) Give reasons for non-participation at each stage	N/A	
		(c) Consider use of a flow diagram	8	A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study (Fig. 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8	A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study (Fig. 1)…

		(b) Indicate number of participants with missing data for each variable of interest		A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study (Fig. 1).
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		Twenty-nine (50.9%) of the thrombi were located at the LAA ostium and 28(49.1%) were in the LAA. Compared with the CCT true-positive thrombi, the false-negative ones more frequently located at the LAA ostium (83.3% vs. 35.9%, p = 0.001) …
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A	
		(*b*) Report category boundaries when continuous variables were categorized		Given that high sensitivity is essential to exclude LAA thrombus, the CCT results of the LAA thrombi underwent further analysis. By scattering the CCT results on the 2-D plane, the thrombi at the LAA ostium…
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9	The CCT had an overall sensitivity of 68.4% and a specificity of 99.4%... Given that high sensitivity is essential to exclude LAA thrombus, the CCT results of the LAA thrombi underwent further analysis…
Discussion				
Key results	18	Summarise key results with reference to study objectives	9	We reevaluated the accuracy of CCT for detecting LAA thrombus in the 726 patients undergoing catheter ablation for AF.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12	Firstly, this retrospective single-center study included only patients undergoing catheter ablation for AF…
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,11	Thus, the low sensitivity of CCT in our study could be presumed to: (1) inadequate temporal resolution…
Generalisability	21	Discuss the generalisability (external validity) of the study results	12	This retrospective single-center study included only patients undergoing catheter ablation for AF. The study's findings may not be generalizable to other patients with AF…
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13	This study has received funding from the Science and Technology Support plan of Guizhou Province…

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Impact of left atrial appendage thrombus location on diagnostic accuracy of cardiac computer tomography: a single-center case-control study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-079876.R3
Article Type:	Original research
Date Submitted by the Author:	15-Jan-2024
Complete List of Authors:	Guo, Chuxian; Guizhou Provincial People's Hospital, Cardiology Department; Guizhou Medical University Jiang, Zhi; Guizhou Provincial People's Hospital, Cardiology Department He, Jionghong; Guizhou Provincial People's Hospital, Cardiology Department; Guizhou Provincial People's Hospital, Echocardiography Department Ma, Haiyan; Guizhou Provincial People's Hospital, Radiology Department Wang, Yuquan; Guizhou Provincial People's Hospital, Radiology Department Tan, Jing; Guizhou Provincial People's Hospital, Cardiology Department; Guizhou Provincial People's Hospital, Echocardiography Department Ou, Qiaoqiao; Guizhou Provincial People's Hospital, Cardiology Department; Guizhou Medical University Tian, Ye; Guizhou Provincial People's Hospital, Cardiology Department Tian, Longhai; Guizhou Provincial People's Hospital, Cardiology Department Liu, Qifang; Guizhou Provincial People's Hospital, Cardiology Department Huang, Jing; Guizhou Provincial People's Hospital, Cardiology Department Yang, Long; Guizhou Provincial People's Hospital, Cardiology Department
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine, Radiology and imaging
Keywords:	Stroke < NEUROLOGY, Ultrasound < RADIOLOGY & IMAGING, Computed tomography < RADIOLOGY & IMAGING, Thromboembolism < CARDIOLOGY

Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.

Supplementary material_Video S1.mp4

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Article Title: Impact of left atrial appendage thrombus location on diagnostic accuracy of cardiac computer tomography: a single-center case-control study

Running Head: Detection of Left Atrial Appendage Thrombus Using Cardiac CT

Authors: Chuxian Guo [ad]*; Zhi Jiang [a]*; Jionghong He [ab]; Haiyan Ma [c]; Yuquan Wang [c]; Jing Tan [ab]; Qiaoqiao Ou [ad]; Ye Tian [a]; Longhai Tian [a]; Qifang Liu [a]; Jing Huang [a]; Long Yang [a]

Affiliations: From [a] Cardiology Department, Guizhou Provincial People's Hospital, Guiyang, China; [b] Echocardiography Department, Guizhou Provincial People's Hospital, Guiyang, China; [c] Radiology Department of Guizhou Provincial People's Hospital, Guiyang City, China; [d] Guizhou Medical University, Guiyang, China.

* Chuxian Guo and Zhi Jiang contributed equally to the study.

Corresponding author: Long Yang, Department of Cardiology, Guizhou Provincial People's Hospital, NO. 83 East Zhongshan Road, Guizhou Province, Guiyang City, 550002, China. E-mail: yanglong1001@outlook.com. Telephone: +86-18198169283. Fax: +86 0851- 85924943

Word count of the main part of the manuscript: 2243

Abstract

Objective Cardiac computed tomography (CCT) is an emerging non-invasive modality for assessing left atrial appendage (LAA) thrombus, but the results were conflicting. Our study aims to evaluate the accuracy of CCT for detecting LAA thrombus in patients undergoing catheter ablation of atrial fibrillation, using transesophageal echocardiography (TEE) as the reference standard.

Design Case-control study.

Setting Patient data were collected from a tertiary hospital in China between 2017 and 2022.

Participants The study enrolled 726 patients (male: 60.2%, age: 61±11 years) who had both TEE and CCT before catheter ablation of atrial fibrillation.

Measures The CCT protocol consisted of one angiographic phase and one delayed scan 30 seconds later. LAA thrombi were defined as solid masses on TEE or persistent defects on CCT. The thrombus dimension and location, the LAA filling and emptying flow velocity were assessed by TEE.

Results Of the 57(7.9%) patients with LAA thrombi identified by TEE, 29(50.9%) were located at the LAA ostium, and 28(49.1%) were in the LAA. The former showed higher motility following blood flow and heartbeats than the latter. The CCT detected 14(48.3%) of the LAA-ostium thrombi but 25(89.3%) of those in the LAA ($p = 0.001$). The LAA-ostium thrombi with the LAA mean flow velocity higher than 0.35m/s and maximum diameters shorter than 10mm were more prone to have CCT false-negative results.

Conclusion For patients undergoing catheter ablation for atrial fibrillation, CCT with a 30s delay scan is less sensitive to LAA thrombi than TEE, especially for LAA-ostium thrombi with smaller sizes and higher LAA flow velocity.

Keywords stroke; embolism; thrombosis; pulmonary vein isolation; cardiac imaging techniques; ultrasound.

Strengths and limitations of this study

1. A major strength of our study is based on a large cohort with high incidence of left atrial appendage thrombi.

2. We first report the impact of thrombus location on the sensitivity of CCT, using TEE as reference standard.

3. A limitation of this study is that it is a single-center and retrospective study.

4. The CCT protocol contained only one delayed-phase scan. Whether multiple delayed-phase scans reduce false-negative CCT results is unclear.

Title: Impact of left atrial appendage thrombus location on diagnostic accuracy of cardiac computer tomography: a single-center case-control study

Introduction

Transesophageal echocardiology (TEE) is currently the gold standard for the assessment of left atrial appendage (LAA) thrombi in patients undergoing catheter ablation of atrial fibrillation (AF)[1]. In the past decades, cardiac computed tomography (CCT) has been widely studied for detecting LAA thrombus[2-5]. Recently, the delayed contrast-enhanced CCT at 6 minutes was reported to reach 100% sensitivity and negative predictive value in detecting LAA thrombus[6]. For patients who are not tolerant of the discomfort associated with TEE, CCT is proposed as a reliable alternative[7]. However, the accuracy of CCT varied between studies[2-5, 8], raising the safety concern and limiting the routine use of CCT.

The left atrial thrombi were classified into a movable ball, fixed ball, and mountain according to their morphology[9]. Around 1/3 of the thrombi in the left atrium were movable. Although CCT is of high spatial resolution, its temporal resolution is 4~17Hz, and it takes 60ms ~ 250ms to acquire one slice[8, 10-12]. Compared to TEE, which allows live display with a high spatiotemporal resolution (<1mm, 20~30Hz)[13], CCT is theoretically inferior for identifying moving objects in the left atrium. In addition, the circulatory stasis and the fibrillation of the atrial wall during AF also increase the difficulty of detecting movable thrombi[14]. In previous studies, the presence of LAA thrombus was 2(0.24%) ~16(19.04%)[2-5, 15]. The high sensitivity and negative predictive value of CCT could be attributed to the low incidence of movable thrombus. Therefore, it is essential to investigate

the diagnostic accuracy of CCT in a larger cohort with a higher incidence of LAA thrombus.

In the current study, we retrospectively included 726 patients who had both TEE and CCT before catheter ablation for AF. 57(7.9%) patients were diagnosed with LAA thrombi using TEE. We aimed to evaluate the sensitivity of CCT in detecting LAA thrombus and to analyze the risk factors of false-negative results.

Methods

Study population

From May 2017 to December 2022, patients were routinely scheduled for TEE and CCT before catheter ablation of AF in Guizhou Provincial People's Hospital. Those who had both examinations within a 12-hour interval on the same day were retrospectively included. All the patient characteristics and images were acquired from the clinical database. The CHA_2DS_2-VASc score was calculated following the 2020 ESC guideline[1]. The study was approved by the institutional ethics committee of Guizhou Provincial People's Hospital. The informed consent was waived due to the retrospective nature, and no identified information was collected.

CCT protocol

All patients were examined with a third-generation dual-source CT (SOMATOM Force, Siemens Healthineers, Forchheim, Germany). The imaging protocol included a standard

angiographic-phase acquisition to assess the anatomy of the left atrium and one delayed-phase acquisition at 30 s after contrast injection to detect thrombi. No electrocardiography gating was used. The tube voltage and current were automatically adjusted using the CARE kV or CARE DOSE 4D with the reference of 100kv and 250mA. The gantry rotation time was 250ms, and the detector collimator was 192×0.6 mm. The scanning image covers the range from the aortic arch to the cardiac base. The monitoring site was localized within the left atrium. The contrast material containing 350 mg/ml of iodine was administrated intravenously at 4-5 ml/s with a total dose of 35 ml by a double-barrel syringe, followed by the same amount of 0.9% saline. For the angiographic phase, the scanning was triggered when the monitoring site reached 90 HU. Then the delayed phase was acquired 30 s later. All images were reconstructed using the ADMIRE algorithm grade 3 with a layer thickness of 1 mm and interlayer spacing of 0.7 mm. The 3D left atrium and pulmonary veins were reconstructed using the Syngo.via software (Siemens Healthcare, Forchheim, Germany).

CCT image analysis

Images were transferred to an external workstation (Syngo VPCT body, Siemens Healthcare, Forchheim, Germany). Two independent radiologists with more than eight years of cardiovascular imaging, blinded to all patients' data, retrospectively evaluated the presence of LAA thrombus and LAA morphology. Thrombus was defined as a persistent filling defect in the 30s-delayed scans. The LAA morphology was classified into simple or complex according to their main and branching structures on the 3D reconstructions[16]. In case of disagreement, a final joint reading was performed to achieve consensus.

Transesophageal echocardiology

A PhilipsiEPIQ7C color Doppler ultrasound diagnostic instrument (Philips, Amsterdam, the Netherlands) and an X7-2t probe were used. The left atrium and LAA were scanned using a complete 2D, colored, pulsed, and continuous-wave Doppler echocardiogram according to the EACVI recommendations[17]. Thrombi were defined as circumscribed echogenic or echolucent masses distinct from the atrial wall. LAA ostium was defined as within the 5mm range of the junction between the smooth atrial wall and trabeculated LAA. The dimensions and locations of thrombi were assessed if present. The LAA filling and emptying velocity was averaged by ten consecutive measurements of the backward and forward flow rates using the pulsed wave Doppler. LAA mean flow velocity (LAAMFV) was calculated by halving the sum of the LAA filling and emptying velocity. Two independent cardiologists with more than five years of experience in echocardiology evaluated the presence of LAA thrombus and measured the flow velocity. Disagreements were resolved by consensus.

Statistical analysis

Continuous variables were expressed as mean ± SD deviation. The Student's t-test was used for comparison if normally distributed; otherwise, the Mann-Whitney U test was used. Categorical variables were expressed as frequency (percentage). The Chi-square test was used for comparison if the expected frequency is more than 5; otherwise, Fisher's exact test was used. A two-tailed *p* value of less than 0.05 was considered statistically significant. Using TEE as the reference standard, the diagnostic performance of CCT for LAA thrombi was

calculated. Multivariate logistic regression model was conducted to determine the predictors of CCT false-negative results. The receiver operating characteristics (ROC) curve with the area under the curve (AUC) was calculated to evaluate the performance of the predictive model. All statistical analysis was performed using SPSS 26.0.

Results

Patient characteristics

A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study (Figure 1). The patients with LAA thrombus had a higher incidence of previous stroke/transient ischemic attack (TIA) and congestive heart failure, larger left atrial size, worse left ventricular function, and a higher rate of complex LAA morphology than those without LAA thrombus ($p < 0.05$) (Table 1).

Twenty-nine (50.9%) of the thrombi were located at the LAA ostium and 28(49.1%) were in the LAA. The clinical characteristics and maximum thrombus diameter were similar between the patients. The thrombi at the LAA ostium were accompanied by higher LAA filling and emptying velocities than those in the LAA (Supplementary material online, Table S1). The former also showed significantly higher mobility following the blood flow and cardiac motion than the latter (Supplementary material online, Video S1).

Diagnostic accuracy of CCT

The CCT had an overall sensitivity of 68.4% and a specificity of 99.4% to the LAA thrombi (Table 1). However, the CCT was less sensitive to the thrombi at LAA ostium than those in the LAA (48.3% vs. 89.3%, $p = 0.001$) (Supplementary material online, Table S1). Representative images are shown in Figure 2.

Given that a high sensitivity is essential to exclude LAA thrombus, the CCT results of the LAA thrombi underwent further analysis. Compared with the CCT true-positive thrombi, the false-negative ones more frequently located at the LAA ostium (83.3% vs. 35.9%, $p = 0.001$), were shorter in the maximum diameters (8±2mm vs. 14±9mm, $p < 0.001$), and were accompanied by higher LAA filling and emptying velocities (0.53±0.15 m/s vs. 0.38±0.19 m/s, $p = 0.001$; 0.55±0.21 m/s vs. 0.37±0.14 m/s, $p < 0.001$) (Table 2). The result was also concordant in the LAA-ostium thrombi subgroup (Supplementary material online, Table S2). By scattering the CCT results on the 2-D plane that consisted of LAAMFV and thrombus maximum diameter, the thrombi at the LAA ostium with the LAAMFVs higher than 0.35m/s and maximum diameters shorter than 10mm were more prone to have CCT false-negative results (Figure 3A). For the thrombi in the LAA, the maximum diameter or LAAMFV did not impact the CCT results (Figure 3B). In the logistic regression model, the thrombus maximum diameter, location, and LAA mean flow velocity (LAAMFV) were independently associated with the CCT false-negative results (Supplementary material online, Table S3). The ROC curve (AUC: 0.909, 95%CI: 0.834 ~ 0.984) is shown in Figure S1.

Discussion

Major findings

We reevaluated the accuracy of CCT for detecting LAA thrombus in the 726 patients undergoing catheter ablation for AF. TEE identified 57(7.9%) patients with LAA thrombi, of which 29(50.9%) were at the LAA ostium and 28(49.1%) in the LAA. The CCT was less sensitive in detecting LAA-ostium thrombi with smaller maximum diameters and higher LAAMFV.

Concordance

LAA thrombus is thought to form initially inside the LAA, where circulatory stasis is the greatest, and then extends towards the ostium. However, we found over half of the thrombi located at the LAA ostium. The result was concordant with a previous study in which 46.3% of the thrombi were at the entrance section of LAA[9]. The presence of pits and troughs adjacent to the LAA orifice was reported in 57.7% of the human heart specimens[18]. It could be the anatomic basis for thrombosis. Another study using TEE discovered small recesses proximal to the entry of LAA in a significant number of patients, but no thrombus related to these structures was detected following LAA occlusion[19]. The discrepancy could be due to patient selection bias. Nonetheless, our findings raised concerns about the role of LAA-ostium recesses in thrombosis.

Although the third-generation 64-slice dual-source CT was employed in the current study, its sensitivity to LAA thrombi was not improved. The sensitivity of 89.3% to the thrombi in the LAA was comparable to the previous studies[2, 10, 11, 20-22]. However, the sensitivity significantly decreased for the LAA-ostium thrombi, which showed higher motility following blood flow and heartbeats than those in the LAA (Supplementary material online, Video S1). We further identified that the LAA-ostium thrombi with smaller sizes and higher LAA flow velocity were more prone to be missed using the CCT. As a higher temporal resolution is essential to detect movable objects[23], our findings suggested the impact of thrombus motility on CCT imaging. By calculating the gantry rotation time of 250ms, the CCT had a temporal resolution of 4Hz, significantly less than that of the TEE (20~40Hz). Thus, the low sensitivity of CCT in our study could be presumed to: (1) inadequate temporal resolution, (2) the high proportion of movable LAA-ostium thrombi, (3) the lack of ECG gating, (4) only one 30s delayed scan was used. The 4 CCT false-positive results in our study could be the misdiagnosis of thrombus due to circulatory stasis during AF[6, 24].

Discordance

Several studies reported that the CCT had 100% sensitivity in detecting LAA thrombi using ECG gating, single-segment reconstruction algorithm[25, 26], or multiple delayed-phase scans[3, 14, 27]. However, these studies have the following limitations: (1) Although the single-segment reconstruction algorithm increased the CCT's temporal resolution to 12Hz, the low incidence of LAA thrombus [2(0.24%) ~16(19.04%)] and the less variation of thrombus location could have overestimated the sensitivity of CCT for detecting LAA thrombi in a broader range of patients. (2) The multiple delayed-phase scans distinguished the thrombi from filling defects due to circulatory stasis. Still, the technique could not necessarily increase the sensitivity to smaller and movable thrombi at the LAA ostium.

We suggest that the CCT approach to detect LAA thrombi could differ according to their location and motility. Persistent filling defects in multiple delayed-phase scans have been well established for static thrombi in LAA. However, LAA-ostium thrombi could be highly motile due to blood flow and myocardial contraction. In our study, the LAA flow velocity indirectly reflected the thrombus motility. The filling defects that indicate the presence of thrombi could still be enhanced as the thrombi swayed much faster than the duration required for scanning. Furthermore, the filling defect size also depended on the thrombi size. Therefore, smaller LAA-ostium thrombi with higher LAA flow velocity could be prone to be missed by CCT. A temporal resolution comparable to TEE (20~40Hz) could be necessary.

Clinical implication

Our study found that the CCT with a 30s delayed scan did not reliably exclude LAA thrombus, especially those located at the LAA ostium. We did not find any clinical characteristics associated with the thrombus location. TEE is the only recommendation for stroke risk management for patients undergoing catheter ablation of AF in the 2020 ESC guideline[1]. For those who do not tolerate TEE, intracardiac echocardiography could be considered[28].

Limitations

Firstly, this retrospective single-center study included only patients undergoing catheter ablation for AF. The study's findings may not be generalizable to other patients with AF. Secondly, the CCT protocol contained only one delayed-phase scan. Whether multiple delayed-phase scans reduce false-negative CCT results is unclear. Thirdly, other factors unaccounted for in this analysis – heart rhythm, atrial/ventricular rate, and blood pressure during the TEE and CCT – could affect the conclusions. Fourthly, although the interval between the TEE and CCT was less than 12 hours, it is theoretically possible for thrombi to form or disappear within this timeframe. Lastly, the incidence of LAA thrombus was higher than that in previous studies (partially due to less adherence to anticoagulation treatment), which could have affected the thrombus location and motility.

Conclusions

In patients undergoing catheter ablation of AF, CCT with a 30s delay scan is less sensitive than TEE in detecting LAA thrombi, especially those located at LAA ostium with smaller sizes and higher LAA flow velocity.

Data sharing statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments

We thank Nicholas Tan and Jason Tri from the Mayo Clinic for their dedicated help in preparing the manuscript.

Contributors

Chuxian Guo and Zhi Jiang: Conceptualization, Methodology, Formal analysis, Writing-original draft, Writing – review & editing. Jionghong He, Haiyan Ma, and Yuquan Wang: Conceptualization, Methodology, Formal analysis, Visualization, Writing – review & editing. Jing Tan: Conceptualization, Methodology, Investigation, Writing – review & editing. Qiaoqiao Ou: Conceptualization, Investigation, Writing – review & editing. Ye Tian and Qifang Liu: Conceptualization, Writing – review & editing, Funding acquisition. Longhai Tian and Jing Huang: Conceptualization, Investigation, Writing – review & editing. Long Yang: Conceptualization, Methodology, Formal analysis, Writing – review & editing, Supervision, Funding acquisition. All authors read and approved the final manuscript.

Funding

This study has received funding from the Science and Technology Support plan of Guizhou Province [NO. (2017)2885 and (2018)2794] to L.Y. and Y.T., the Clinical Special Projects in Guizhou Province [NO. (2019)4430] to Q.L., and the Clinical Research Center Project of the Department of science and technology of Guizhou Province [NO. (2017)5405] to L.Y.

Ethical approval

This study received approval from the institutional ethics committee of Guizhou Provincial People's Hospital.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Supplementary Materials

Video S1 Representative TEE video of the thrombi at LAA ostium (A-C) and those in the LAA (D-F).

Table S1 Patient characteristics between thrombus locations.

Table S2 Patient characteristics between true-positive and false-negative CCT results.

Table S3 Multivariate analysis of the predictors for false-negative CCT results.

Figure S1 The ROC curve of the logistic regression model for predicting false-negative CCT results.

Abbreviation: AUC= area under the curve; CCT = cardiac computer tomography; CI = confidence interval; ROC= receiver operating characteristics.

References

1. Hindricks G, Potpara T, Dagres N*, et al.* 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021 **42**:373-498.

2. Dorenkamp M, Sohns C, Vollmann D*, et al.* Detection of left atrial thrombus during routine diagnostic work-up prior to pulmonary vein isolation for atrial fibrillation: role of transesophageal echocardiography and multidetector computed tomography. *Int J Cardiol*. 2013 **163**:26-33.

3. Zhai Z, Tang M, Zhang S*, et al.* Transoesophageal echocardiography prior to catheter ablation could be avoided in atrial fibrillation patients with a low risk of stroke and without filling defects in the late-phase MDCT scan: A retrospective analysis of 783 patients. *Eur Radiol*. 2018 **28**:1835-1843.

4. Li W, Yu F, Zhu W, Zhang W, Jiang T. Detection of left atrial appendage thrombi by third-generation dual-source dual-energy CT: Iodine concentration versus conventional enhancement measurements. *Int J Cardiol*. 2019 **292**:265-270.

5. Guha A, Dunleavy MP, Hayes S*, et al.* Accuracy of contrast-enhanced computed tomography for thrombus detection prior to atrial fibrillation ablation and role of novel Left Atrial Appendage Enhancement Index in appendage flow assessment. *Int J Cardiol*. 2020 **318**:147-152.

6. Spagnolo P, Giglio M, Di Marco D*, et al.* Diagnosis of left atrial appendage thrombus in patients with atrial fibrillation: delayed contrast-enhanced cardiac CT. *Eur Radiol*. 2021 **31**:1236-1244.

7. Yu S, Zhang H, Li H. Cardiac Computed Tomography Versus Transesophageal Echocardiography for the Detection of Left Atrial Appendage Thrombus: A Systemic Review and Meta-Analysis. *J Am Heart Assoc*. 2021 **10**:e022505.

8. Kottmaier M, Jilek C, Berglar S*, et al.* Exclusion of left atrial thrombus by dual-source cardiac computed tomography prior to catheter ablation for atrial fibrillation. *Clin Res Cardiol*. 2019 **108**:150-156.

9. Abe Y, Asakura T, Gotou J*, et al.* Prediction of embolism in atrial fibrillation: classification of left atrial thrombi by transesophageal echocardiography. *Jpn Circ J*. 2000 **64**:411-5.

10. Kim YY, Klein AL, Halliburton SS*, et al.* Left atrial appendage filling defects identified by multidetector computed tomography in patients undergoing radiofrequency pulmonary vein antral isolation: a comparison with transesophageal echocardiography. *Am Heart J*. 2007 **154**:1199-205.

11. Tang RB, Dong JZ, Zhang ZQ*, et al.* Comparison of contrast enhanced 64-slice computed tomography and transesophageal echocardiography in detection of left atrial thrombus in patients with atrial fibrillation. *J Interv Card Electrophysiol*. 2008 **22**:199-203.

12. Martinez MW, Kirsch J, Williamson EE*, et al.* Utility of nongated multidetector computed tomography for detection of left atrial thrombus in patients undergoing

catheter ablation of atrial fibrillation. *JACC Cardiovasc Imaging*. 2009 **2**:69-76.

13. Vegas A. Three-dimensional transesophageal echocardiography: Principles and clinical applications. *Ann Card Anaesth*. 2016 **19**:S35-S43.

14. Maltagliati A, Pontone G, Annoni A*, et al.* Multidetector computed tomography vs multiplane transesophageal echocardiography in detecting atrial thrombi in patients candidate to radiofrequency ablation of atrial fibrillation. *Int J Cardiol*. 2011 **152**:251-4.

15. Budoff MJ, Shittu A, Hacioglu Y*, et al.* Comparison of transesophageal echocardiography versus computed tomography for detection of left atrial appendage filling defect (thrombus). *Am J Cardiol*. 2014 **113**:173-7.

16. He J, Fu Z, Yang L*, et al.* The predictive value of a concise classification of left atrial appendage morphology to thrombosis in non-valvular atrial fibrillation patients. *Clin Cardiol*. 2020 **43**:789-795.

17. Flachskampf FA, Decoodt P, Fraser AG, Daniel WG, Roelandt JR. Guidelines from the Working Group. Recommendations for performing transesophageal echocardiography. *Eur J Echocardiogr*. 2001 **2**:8-21.

18. Su P, McCarthy KP, Ho SY. Occluding the left atrial appendage: anatomical considerations. *Heart*. 2008 **94**:1166-70.

19. Meincke F, Schmidt-Salzmann M, Kreidel F, Kuck KH, Bergmann MW. New technical and anticoagulation aspects for left atrial appendage closure using the WATCHMAN® device in patients not taking warfarin. *EuroIntervention*. 2013 **9**:463-8.

20. Homsi R, Nath B, Luetkens JA, Schwab JO, Schild HH, Naehle CP. Can Contrast-Enhanced Multi-Detector Computed Tomography Replace Transesophageal Echocardiography for the Detection of Thrombogenic Milieu and Thrombi in the Left Atrial Appendage: A Prospective Study with 124 Patients. *Rofo*. 2016 **188**:45-52.

21. Shapiro MD, Neilan TG, Jassal DS*, et al.* Multidetector computed tomography for the detection of left atrial appendage thrombus: a comparative study with transesophageal echocardiography. *J Comput Assist Tomogr*. 2007 **31**:905-9.

22. Hur J, Kim YJ, Lee HJ*, et al.* Dual-enhanced cardiac CT for detection of left atrial appendage thrombus in patients with stroke: a prospective comparison study with transesophageal echocardiography. *Stroke*. 2011 **42**:2471-7.

23. Jung B, Föll D, Böttler P, Petersen S, Hennig J, Markl M. Detailed analysis of myocardial motion in volunteers and patients using high-temporal-resolution MR tissue phase mapping. *J Magn Reson Imaging*. 2006 **24**:1033-9.

24. Fukushima K, Fukushima N, Kato K*, et al.* Correlation between left atrial appendage morphology and flow velocity in patients with paroxysmal atrial fibrillation. *Eur Heart J Cardiovasc Imaging*. 2016 **17**:59-66.

25. Kapa S, Martinez MW, Williamson EE*, et al.* ECG-gated dual-source CT for detection of left atrial appendage thrombus in patients undergoing catheter ablation for atrial fibrillation. *J Interv Card Electrophysiol*. 2010 **29**:75-81.

26. Kuronuma K, Matsumoto N, Suzuki Y*, et al.* Usefulness of Dual-Phase Snapshot 320-Detector Computed Tomography for the Detection of a Left Atrial Appendage Thrombus. *Int Heart J*. 2019 **60**:849-853.

27. Wang L, Kadiyala M, Koss E*, et al.* CTA Detection of Left Atrial Stasis and Thrombus in Patients with Atrial Fibrillation. *Pacing Clin Electrophysiol*. 2016 **39**:1388-1393.

28. He G, Liu H, Huang X*, et al.* Intracardiac versus transesophageal echocardiography for diagnosis of left atrial appendage thrombosis in atrial fibrillation: A meta-analysis. *Clin Cardiol*. 2021 **44**:1416-1421.

Figure legends

Figure 1 Patient flowchart.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; LAA = left atrial appendage; TEE = transesophageal echocardiography.

Figure 2 Representative CCT and TEE images of the LAA thrombi.

The left and middle images are from the CCT angiographic and delayed phase. The right images are from the TEE. A-C. Representative false-negative CCT result of the thrombus in the LAA. D-F. Representative false-negative CCT result of the LAA-ostium thrombus. G-I. Representative true-positive CCT result of the thrombus in the LAA. J-L. Representative true-positive CCT result of the LAA-ostium thrombus. White arrows denote the thrombi.

Abbreviation: CCT = cardiac computer tomography; LAA = left atrial appendage.

Figure 3 Scatter plots of CCT results.

Red dots denote the CCT false-negative thrombi. Green dots denote the CCT true-positive thrombi. The LAAMFV was calculated by halving the sum of the LAA emptying and filling velocity. A. For the LAA-ostium thrombi, the CCT false-negative results had the LAAMFV higher than 0.35 m/s and maximum diameters less than 10 mm. B. For the thrombi in the LAA, the maximum diameter or LAAMFV did not significantly impact CCT results.

Abbreviations: CCT = cardiac computed tomography; LAA = left atrial appendage; LAAMFV = left atrial appendage mean flow velocity.

Table 1 Patient characteristics.

Characteristics	Overall (n=726)	LAA thrombus *		*P* value
		Positive (n=57)	Negative (n=669)	
Age, year	61±11	64±10	61±11	0.129
Male	437(60.2)	36(63.2)	401(59.9)	0.634
Paroxysmal AF	436(60.1)	30(52.6)	406(60.7)	0.233
AF course, month	42±83	39±45	43±85	0.540
CHA_2DS_2-VASc score	2±2	3±2	2±2	0.089
Congestive heart failure	116(16.0)	18(31.6)	98(14.6)	0.001
Hypertension	346(47.7)	25(43.9)	321(48.0)	0.550
Diabetes mellitus	107(14.7)	10(17.5)	97(14.5)	0.534
Previous Stroke/TIA	91(12.5)	14(24.6)	77(11.5)	0.004
Vascular disease	292(40.2)	22(38.6)	270(40.4)	0.795
LAAPD, mm	36±7	41±9	36±7	<0.001
LVEDD, mm	46±5	49±7	46±5	0.006
LVEF, %	60±8	56±11	60±7	0.005
Complex LAA morphology	289(39.8)	35(61.4)	254(38.0)	0.001
CCT results				
Filling defects	43(5.9)	39(68.4)	4(0.6)	<0.001
No filling defects	683(94.1)	18(31.6)	665(99.4)	

Values are mean ± SD or n (%).

* The thrombi were detected using the TEE.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, previous stroke/transient ischemic attack/thromboembolism (doubled), vascular disease, age 65–74 years and sex category (female); LAA = left atrial appendage; LAAPD = left atrial anterior-posterior diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; TEE = transesophageal echocardiography; TIA = transient ischemic attack.

Table 2 Patient characteristics between CCT true-positive and false-negative results.

Characteristics	LAA thrombus *		*P* value
	CCT false-negative result (n=18)	CCT true-positive result (n=39)	
Age, years	64±9	64±10	0.810
Male	11(61.1)	25(64.1)	0.828
Paroxysmal AF	12(66.7)	18(46.2)	0.149
AF course, month	42±54	38±40	0.952
CHA_2DS_2-VASc score	3±2	3±2	0.450
Congestive heart failure	5(27.8)	13(33.3)	0.675
Hypertension	10(55.6)	15(38.5)	0.227
Diabetes mellitus	5(27.8)	5(12.8)	0.168
Previous Stroke/TIA	5(27.8)	9(23.1)	0.702
Vascular disease	7(38.9)	15(38.5)	0.975
LAAPD, mm	41±9	41±9	0.770
LVEDD, mm	49±6	49±7	0.336
LVEF, %	59±9	55±12	0.331
Complex LAA	9(50.0)	26(66.7)	0.230
LAA filling velocity, m/s	0.53±0.15	0.38±0.19	0.002
LAA emptying velocity, m/s	0.55±0.21	0.37±0.14	0.001
Thrombi maximum diameter, mm	8±2	14±9	<0.001
Thrombus location			
LAA ostium	15(83.3)	14(35.9)	0.001
In LAA	3(16.7)	25(64.1)	

Values are mean ± SD or n (%).

* The thrombi were detected using the TEE.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, previous stroke/transient ischemic attack/thromboembolism (doubled), vascular disease, age 65–74 years and sex category (female); LAA = left atrial appendage; LAAPD = left atrial anterior-posterior diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; TEE = transesophageal echocardiography; TIA = transient ischemic attack.

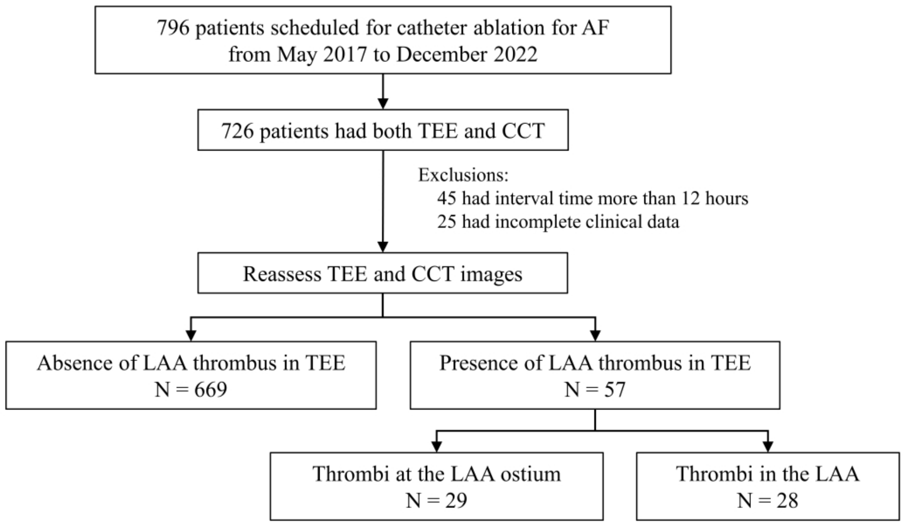


Figure 1 Patient flowchart.
Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; LAA = left atrial appendage; TEE = transesophageal echocardiography.

190x104mm (600 x 600 DPI)

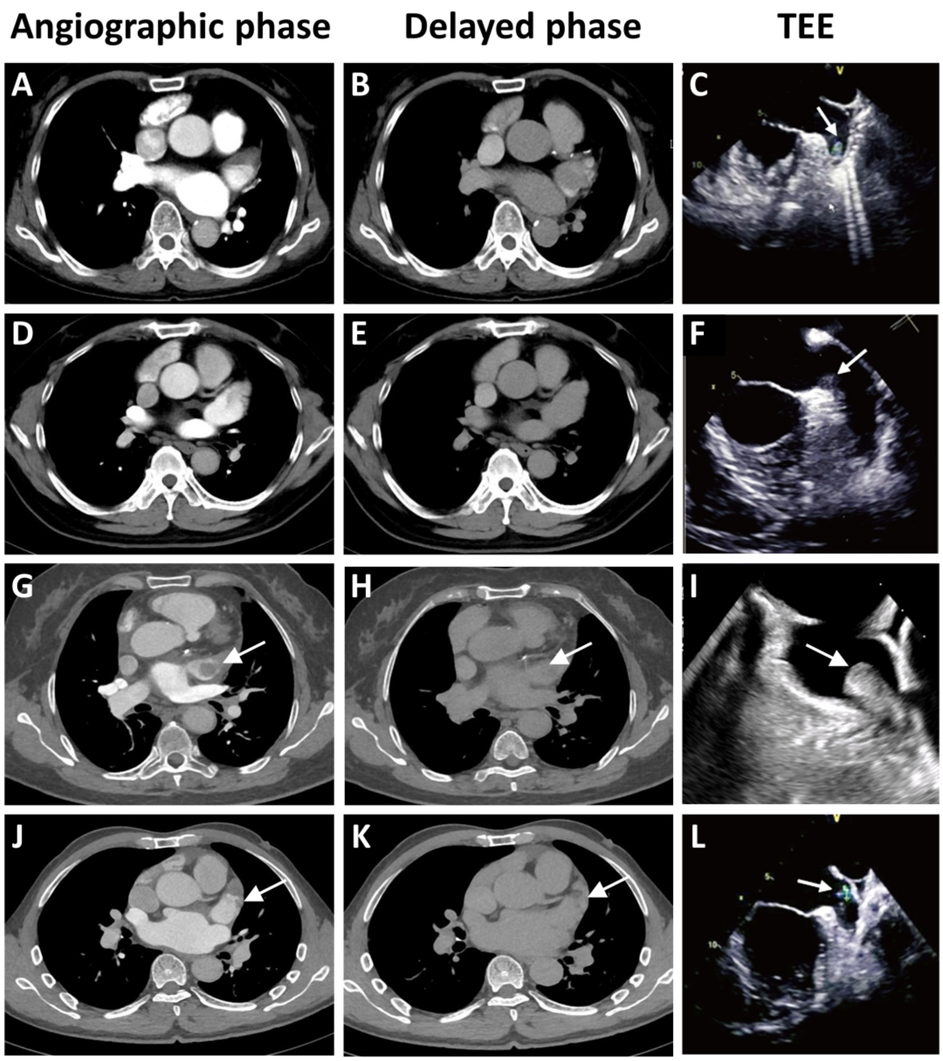


Figure 2 Representative CCT and TEE images of the LAA thrombi.
The left and middle images are from the CCT angiographic and delayed phase. The right images are from the TEE. A-C. Representative false-negative CCT result of the thrombus in the LAA. D-F. Representative false-negative CCT result of the LAA-ostium thrombus. G-I. Representative true-positive CCT result of the thrombus in the LAA. J-L. Representative true-positive CCT result of the LAA-ostium thrombus. White arrows denote the thrombi.
Abbreviation: CCT = cardiac computer tomography; LAA = left atrial appendage.

116x128mm (600 x 600 DPI)

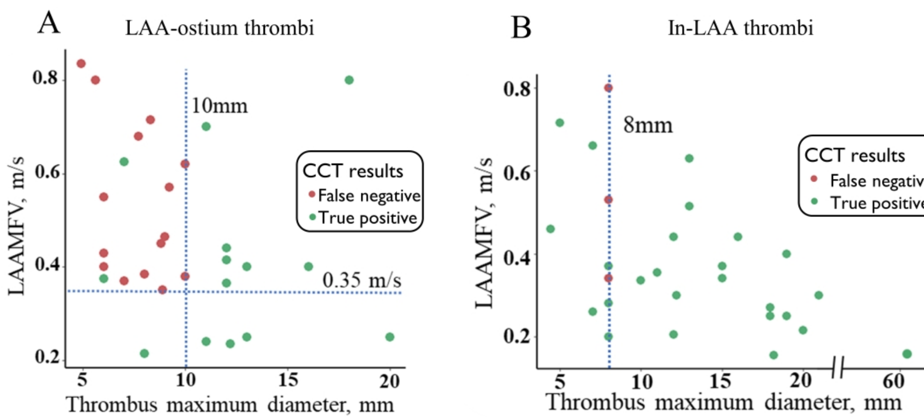


Figure 3 Scatter plots of CCT results.
Red dots denote the CCT false-negative thrombi. Green dots denote the CCT true-positive thrombi. The LAAMFV was calculated by halving the sum of the LAA emptying and filling velocity. A. For the LAA-ostium thrombi, the CCT false-negative results had the LAAMFV higher than 0.35 m/s and maximum diameters less than 10 mm. B. For the thrombi in the LAA, the maximum diameter or LAAMFV did not significantly impact CCT results.
Abbreviations: CCT = cardiac computed tomography; LAA = left atrial appendage; LAAMFV = left atrial appendage mean flow velocity.

190x89mm (600 x 600 DPI)

Table S1 Patient characteristics between thrombus locations.

Characteristics	Thrombus locations *		P value
	LAA ostium (n=29)	In LAA (n=28)	
Age, years	63±10	64±10	0.886
Male	20(69.0)	16(57.1)	0.355
Paroxysmal AF	18(62.1)	12(42.9)	0.146
AF course, month	40±52	39±35	0.648
CHA_2DS_2-VASc score	2±2	3±2	0.220
Congestive heart failure	9(31.0)	9(32.1)	0.928
Hypertension	10(34.5)	15(53.6)	0.147
Diabetes mellitus	5(17.2)	5(17.9)	1.000
Previous Stroke/TIA	7(24.1)	7(25.0)	0.940
Vascular disease	9(31.0)	13(46.4)	0.233
LAAPD, mm	41±10	40±8	0.873
LVEDD, mm	49±6	49±8	0.492
LVEF, %	57±11	55±11	0.424
Complex LAA	17(58.6)	18(64.3)	0.661
LAA filling velocity, m/s	0.48±0.19	0.37±0.19	0.021
LAA emptying velocity, m/s	0.47±0.20	0.38±0.16	0.050
LAAMFV, m/s	0.47±0.18	0.37±0.17	0.029
Thrombus maximum diameter, mm	10±4	14±10	0.045
CCT results			
Filling defects	14(48.3)	25(89.3)	0.001
No filling defects	15(51.7)	3(10.7)	

Values are mean ± SD or n (%).

* The thrombus locations were determined using the TEE.

The LAAMFV was calculated by halving the sum of the LAA emptying and filling velocity.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, previous stroke/transient ischemic attack/thromboembolism (doubled), vascular disease, age 65–74 years and sex category (female); LAA = left atrial appendage; LAAMFV = left atrial appendage mean flow velocity; LAAPD= left atrial anterior-posterior diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; TEE = transesophageal echocardiography; TIA = transient ischemic attack.

Table S2 Patient characteristics between true-positive and false-negative CCT results.

Characteristics	LAA-ostium thrombi*		*P* value
	CCT false-negative result (n=15)	CCT true-positive result (n=14)	
Age, years	63±10	64±10	0.726
Male	10(66.7)	10(71.4)	1.000
Paroxysmal AF	10(66.7)	8(57.1)	0.597
AF course, month	44±58	36±45	0.677
CHA_2DS_2-VASc score	3±2	2±2	0.288
Congestive heart failure	4(26.7)	5(35.7)	0.700
Hypertension	8(53.3)	2(14.3)	0.050
Diabetes mellitus	4(26.7)	1(7.1)	0.330
Previous Stroke/TIA	4(26.7)	3(21.4)	1.000
Vascular disease	6(40.0)	3(21.4)	0.427
LAAPD, mm	39±9	44±11	0.221
LVEDD, mm	49±6	48±5	0.370
LVEF, %	59±8	55±13	0.444
Complex LAA	7(46.7)	10(71.4)	0.264
LAA filling velocity, m/s	0.52±0.15	0.43±0.21	0.110
LAA emptying velocity, m/s	0.55±0.21	0.38±0.15	0.027
LAAMFV, m/s	0.53±0.16	0.41±0.18	0.047
Thrombus maximum diameter, mm	8±2	12±4	0.001

Values are mean ± SD or n (%).

* The LAA-ostium thrombi were determined using the TEE.

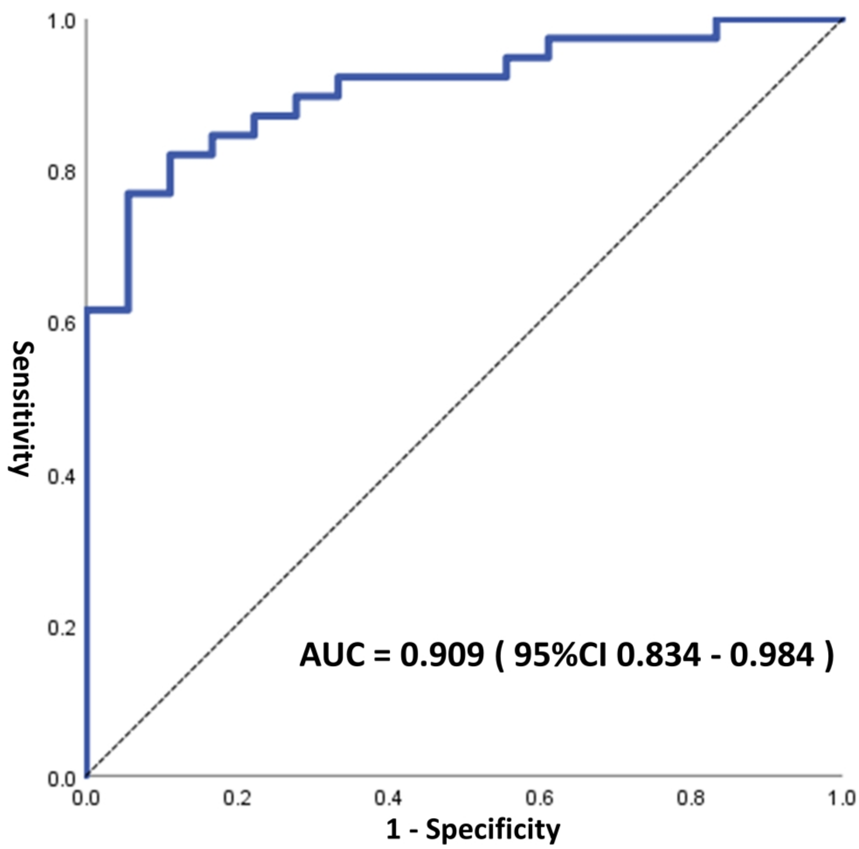
The LAAMFV was calculated by halving the sum of the LAA emptying and filling velocity.

Abbreviations: AF = atrial fibrillation; CCT = cardiac computed tomography; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, previous stroke/transient ischemic attack/thromboembolism (doubled), vascular disease, age 65–74 years and sex category (female); LAA = left atrial appendage; LAAMFV = left atrial appendage mean flow velocity; LAAPD= left atrial anterior-posterior diameter; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; TEE = transesophageal echocardiography; TIA = transient ischemic attack.

Table S3 Multivariate analysis of the predictors for false-negative CCT results.

Characteristics	*OR* (95% CI)	*P* value
Thrombus maximum diameter, per 1 mm decrease	0.635 (0.459 ~ 0.879)	0.006
LAA-ostium thrombus	10.981 (1.702 ~ 70.831)	0.012
LAAMFV, per 1 m/s increase	47.926 (0.382 ~ 6014.699)	0.117

Abbreviations: CCT = cardiac computer tomography; CI = confidence interval; LAA = left atrial appendage; LAAMFV = left atrial appendage mean flow velocity; OR = odd ratio.



133x124mm (600 x 600 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	Impact of left atrial appendage thrombus location on diagnostic accuracy of cardiac computer tomography: a single-center case-control study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Abstract Objective Cardiac computed tomography (CCT) is an emerging non-invasive modality for assessing left atrial appendage (LAA) thrombus…
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	Transesophageal echocardiology (TEE) is currently the gold standard for the assessment of left atrial appendage (LAA) thrombi in patients undergoing catheter ablation of atrial fibrillation (AF)…
Objectives	3	State specific objectives, including any prespecified hypotheses	5	We aimed to evaluate the sensitivity of CCT in detecting LAA thrombus and to analyze the risk factors of false-negative results…
Methods				

Study design	4	Present key elements of study design early in the paper	5	Those who had both examinations within a 12-hour interval on the same day were retrospectively included…
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	From May 2017 to December 2022, patients were routinely scheduled for TEE and CCT before catheter ablation of AF in Guizhou Provincial People's Hospital…
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5	From May 2017 to December 2022, patients were routinely scheduled for TEE and CCT before catheter ablation of AF in Guizhou Provincial People's Hospital…
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5	Those who had both examinations within a 12-hour interval on the same day were retrospectively included.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7	Thrombus was defined as a persistent filling defect in the 30s-delayed scans.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-7*	*All patients were examined with a third-generation dual-source CT (SOMATOM Force, Siemens Healthineers, Forchheim, Germany)…*
Bias	9	Describe any efforts to address potential sources of bias	6,7	In case of disagreement, a final joint reading was performed to achieve consensus.

				Two independent cardiologists with more than five years of experience in echocardiology evaluated the presence of LAA thrombus and measured the flow velocity. Disagreements were resolved by consensus.
Study size	10	Explain how the study size was arrived at	5	All the patient characteristics and images were acquired from the clinical database.

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5	All the patient characteristics and images were acquired from the clinical database.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7	Continuous variables were expressed as mean ± SD deviation…
		(*b*) Describe any methods used to examine subgroups and interactions	7	Continuous variables were expressed as mean ± SD deviation…
		(*c*) Explain how missing data were addressed	N/A	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A	
		(*e*) Describe any sensitivity analyses	7-8	Using TEE as the reference standard, the diagnostic performance of CCT for LAA thrombi was calculated.
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study…
		(b) Give reasons for non-participation at each stage	8	A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study…
		(c) Consider use of a flow diagram	8	A total of 726 patients (age: 61±11 years; male gender: 60.2%) with

				57(7.9%) LAA thrombi diagnosed by TEE were included in the study…
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8	A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study…
		(b) Indicate number of participants with missing data for each variable of interest	8	A total of 726 patients (age: 61±11 years; male gender: 60.2%) with 57(7.9%) LAA thrombi diagnosed by TEE were included in the study…
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	8	Twenty-nine (50.9%) of the thrombi were located at the LAA ostium and 28(49.1%) were in the LAA. The clinical characteristics and maximum thrombus diameter were similar between the patients.
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A	
		(*b*) Report category boundaries when continuous variables were categorized	9	By scattering the CCT results on the 2-D plane that consisted of LAAMFV and thrombus maximum diameter…
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9	The CCT had an overall sensitivity of 68.4% and a specificity of 99.4% to the LAA thrombi (Table 1)… Given that a high sensitivity is essential to exclude LAA thrombus, the CCT results of the LAA thrombi underwent further analysis…
Discussion				
Key results	18	Summarise key results with reference to study objectives	10	We reevaluated the accuracy of CCT for detecting LAA thrombus in the 726 patients undergoing catheter ablation for AF. TEE identified 57(7.9%) patients with LAA thrombi, of which 29(50.9%) were at the LAA ostium and 28(49.1%) in the LAA…
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13	Firstly, this retrospective single-center study included only patients undergoing catheter ablation for AF…
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12	Thus, the low sensitivity of CCT in our study could be presumed to…
Generalisability	21	Discuss the generalisability (external validity) of the study results	12	Our study found that the CCT with a 30s delayed scan did not reliably exclude LAA thrombus, especially those located at the LAA ostium. We did not find any clinical characteristics associated with the thrombus location.
Other information				

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14	This study has received funding from the Science and Technology Support plan of Guizhou Province…

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.