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Detection of left atrial appendage thrombi by third-generation dual-source dual-energy CT: Iodine concentration versus conventional enhancement measurements

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ABSTRACT

Background: Dual-energy computed tomography (DECT) can differentiate iodine from other materials through the material decomposition technique. The purpose of this study was to compare the diagnostic performance of DECT-derived iodine concentration (mg/ml) with conventional enhancement measurements (HU), in detecting left atrial appendage (LAA) thrombi and differentiating thrombi from circulatory stasis in atrial fibrillation (AF) patients referred for catheter ablation.

Methods: Consecutive patients were prospectively recruited and scanned using a third-generation dual-source CT system in dual-energy mode. Regions of interest were placed inside the filling defect in the LAA and ascending aorta (AA) of the same sections, to determine iodine concentration and the LAA/AA HU ratio. The diagnostic performance of iodine concentration and LAA/AA HU ratios were compared using transesophageal echocardiography (TEE) as the reference standard.

Results: Among 302 patients, 10 thrombi and 27 cases with spontaneous echo contrast (SEC) were detected by TEE. Diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of iodine concentration were superior to those of LAA/AA HU ratios (iodine concentration: 99.7%, 100%, 99.7%, 90.9%, and 100% vs. LAA/AA HU ratios: 96.0%, 100%, 95.9%, 45.5%, and 100%) in detecting LAA thrombi. The area under the receiver operating characteristic curve of iodine concentration (0.996; 0.898–1.000) was significantly larger than that of the LAA/AA HU ratio (0.881; 0.733–0.964) in differentiating thrombi from circulatory stasis ($p < 0.05$).

Conclusions: DECT-derived iodine concentration was associated with improved diagnostic accuracy compared with conventional enhancement measurements in detecting LAA thrombi and differentiating thrombi from circulatory stasis in AF patients.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia. Patients with AF are at risk of developing thromboembolism, and the condition is associated with considerable morbidity and increased rates of mortality [1–3]. Catheter ablation (CA) is commonly used to isolate pulmonary veins as therapy for AF [4,5]. The presence of a thrombus in the left atrium (LA) or left atrial appendage (LAA) is considered an absolute contraindication to CA, because the navigation of catheters inside the LA may dislodge the thrombus, resulting in thromboembolic complications [6,7].

In current clinical practice, transesophageal echocardiography (TEE) is considered the gold standard imaging modality used prior to CA, to exclude the presence of thrombi in the LA or LAA [5]. However, this modality is semi-invasive, time-consuming, and causes physical discomfort for patients [8]. This technique also has absolute (esophageal pathology and active gastrointestinal bleeding) and relative (coagulopathy and recent upper gastrointestinal bleeding) contraindications [9]. Additionally, TEE may not allow for complete visualization and assessment of all pulmonary veins or their precise relationships with other thoracic structures.

Abbreviations: CT, computed tomography; DECT, dual-energy CT; DSCT, dual-source CT; AF, atrial fibrillation; LA, left atrial; LAA, left atrial appendage; TEE, transesophageal echocardiography; HU, Hounsfield units; SEC, spontaneous echocardiographic contrast; CA, catheter ablation; AA, ascending aorta; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; AUC, area under the ROC curve.

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Computed tomography (CT) is routinely used prior to CA to provide exact anatomic details of the LA dimensions, as well as the number and anatomy of pulmonary veins [8,10,11]. Few data have been published regarding the precision of CT at identifying thrombi in the LA or LAA, with limitations including old CT technology. Using recently introduced dual-source dual-energy CT (DECT) scanner with two tube-detector systems, it is possible to differentiate iodine from other materials through the material decomposition method. We hypothesized that this technique is valuable for differentiating iodine-containing phenomena, such as intracardiac blood pools with circulatory stasis or normality from nonenhancing thrombi.

The purpose of this study was to compare the diagnostic performance of iodine concentration (in mg/ml) derived from dual-source DECT with conventional enhancement measurements (in Hounsfield units [HU]), in detecting thrombi in the LAA, and differentiating thrombi from circulatory stasis in patients with symptomatic AF referred for CA.

2. Methods

2.1. Study population

This study was approved by the local institutional review board and written informed consent was obtained from all patients who met the inclusion criteria. From January 2017 to October 2018, we prospectively enrolled consecutive patients with AF referred for CA. These patients underwent cardiac CT for anatomic evaluation of the LA, LAA, and pulmonary veins, and TEE for exclusion of LAA thrombi before undergoing CA (Fig. 1).

2.2. CT data acquisition

All patients were scanned using a third-generation dual-source CT (DSCT) (SOMATOM Force; Siemens Healthineers, Forchheim, Germany) in dual-energy mode, using prospective ECG-gating. The scanning parameters for DECT were as follows: 2 × 64 × 0.6 mm acquisition collimation with the z-flying focal spot technique. Automated tube current modulation (Care Dose 4D, Siemens Healthcare) was used in all examinations. One tube of the DSCT system was operated with 444 reference mAs per rotation at 70 kV, and the second tube was automatically operated with 127 reference mAs per rotation at 150 kV. All scans were performed in the cranio-caudal direction with patients in the supine position during midinspiratory breath-hold.

Contrast agent was injected with a dual-syringe injector (Stellant D, Medrad, Indianola, USA) using an 18-gauge intravenous needle inserted in the right antecubital vein. A triphasic injection protocol was used. First, 40 ml of contrast media (Iopromide, Ultravist 370, 370 mg/ml, Bayer-Schering Pharma, Berlin, Germany) was administered. Following this injection, there was a 15-s delay before administration of a second bolus of contrast agent (40 ml). Finally, 30 ml of saline was administered. The injection rate for all phases was 4 ml/s. Contrast agent application was controlled using a bolus tracking technique. After the second bolus injection, there was a 5-s delay before the monitoring scan. A region of interest was placed in the LA, and image acquisition was automatically started 7 s after the attenuation reached the predefined threshold of 100 HU.

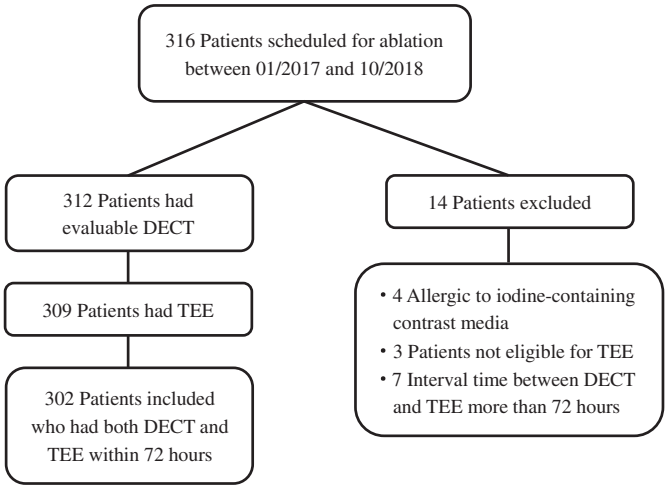

Fig. 1. Flowchart of patient enrollment. DECT = dual-energy CT; TEE = transesophageal echocardiography.

2.3. TEE examination

TEE was performed using commercially available echocardiograms (Toshiba Nemio, Tokyo, Japan) with a 5.0-MHz multiplane transducer. A thrombus was defined as an echo-dense mass that was distinct from adjacent normal tissue without signs of vascularization on color Doppler and without any detectable Doppler flow velocity in the LAA. Spontaneous echocardiographic contrast (SEC) was defined as hyperechogenic sparkling that could not be eliminated by adjusting the gain settings in the presence of residual flow velocity in the LAA. SEC was classified according to intensity and distribution range: grade 0, no SEC was observed (normal group); grade 1 (mild) SEC showed sparse blood flow echo signals lasting only for a moment and was detected by echocardiography at a high gain; grade 2 (mild-to-moderate) SEC was defined by sparse vortex-like blood flow echo signals that were slightly stronger than those associated with grade 1 SEC and were detected without any increase of gain; grade 3 (moderate) SEC was defined by dense vortex-like blood flow echo signals that were present throughout the entire cardiac cycle; and grade 4 (severe) SEC was defined by dense, smoke-like echo signals that were detected in both the conventional state and in a low gain state [8].

2.4. Image analysis

All DECT images were transferred to an external workstation (Syngo Via, VB10, Siemens Healthcare), and patient information was removed. All DECT images were assessed by two experienced radiologists (W.-H.L. and F.-F.Y., with 9 and 10 years of experience with cardiac CT, respectively) who were blinded to all clinical and echocardiographic data. Disagreements between radiologists were settled by consensus. Upon DECT imaging, if the entire LAA was not fully opacified with contrast media by visual assessment, a filling defect was deemed to be present. We then proceeded to quantitative assessment by placing a region of interest inside the filling defect in the LAA and ascending aorta (AA) in the same axial plane, to determine the iodine concentration and LAA/AA HU ratio.

Receiver operating characteristic (ROC) curves were constructed using the iodine concentration and LAA/AA HU ratio. The optimal cutoff value for the differentiation between thrombi and SEC using TEE as the reference standard was determined. Retrospective analysis demonstrated that the optimal cutoff values for differentiating thrombi from circulatory stasis were −1.3 mg/ml for iodine concentration and 0.304 for the LAA/AA HU ratio.

2.5. Statistical analysis

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) or MedCac version 11.4.1 (Medcalc Software, Mariakerke, Belgium). Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as frequencies or percentages. A Student's *t*-test and the Wilcoxon test were performed for normally and non-normally distributed variables, respectively. Using TEE as the reference standard, the sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and diagnostic accuracy were calculated, including the 95% confidence interval based on binomial distribution. Diagnostic performance was compared with ROC analysis using the DeLong method. A two-tailed p-value <0.05 was considered statistically significant. Intraclass correlation coefficients were used to assess intra- and interobserver agreement in iodine concentration measurements in 10 randomly selected patients.

3. Results

A total of 302 consecutive patients were analyzed (162males and 140 females, with mean age of 63.72 ± 7.10 years) (Fig. 1). Of the 302 patients, 172 (57%) patients had paroxysmal AF, 118 (39%) patients had persistent AF, and 12 (4%) patients had long-standing persistent AF. Mean CHA2DS2-VASc score was 1.46 ± 1.3 points. In all cases, the time between DECT and TEE was <72 h, and within 24 h in 78% of cases. Image quality for all DECT and TEE examinations was considered acceptable for evaluation. The mean effective radiation dose was 2.45 ± 0.54 mSv (dose-length product × 0.014 mSv/mGy·cm).

Among the study population, TEE revealed a thrombus in 10 (3%) patients, SEC in 27 (9%) patients and no abnormality in 265 (88%) patients. All thrombi were located in the LAA. According to DECT, the LAA iodine concentration was −2.6 ± 1.5 mg/ml in the thrombus group, 1.5 ± 1.7 mg/ml in the circulatory stasis group, and 11.1 ± 4.4 mg/ml in the normal group, and there were significant differences among the three groups (all $p < 0.001$). Regarding conventional enhancement measurements, the LAA/AA HU ratio was 0.2 ± 0.1 in the thrombus group, 0.4 ± 0.1 in the circulatory stasis group, and 0.9 ± 0.2 in the normal group, and there were significant differences among the three groups (all $p < 0.001$). According to TEE, SEC was categorized as severe in three patients, moderate in three patients, mild-to-moderate in eight patients, and mild in 13 patients. According to

DECT, the iodine concentration did not vary significantly among SEC grades as determined using TEE (−0.7 ± 0.1 mg/ml for severe SEC, 0.7 ± 0.5 mg/ml for moderate SEC, 1.2 ± 1.3 mg/ml for mild-to-moderate, and 2.4 ± 1.8 mg/ml for mild SEC) ($p > 0.05$) except for the iodine concentration between severe SEC and mild SEC ($p < 0.001$). The LAA/AA HU ratio did not vary significantly among SEC grades determined using TEE (0.3 ± 0.1 for severe SEC, 0.4 ± 0.0 for moderate SEC, 0.3 ± 0.1 for mild-to-moderate SEC, and 0.4 ± 0.1 for mild SEC) (all $p > 0.05$).

Sensitivity, specificity, PPV, NPV, and accuracy for the detection of LAA thrombi are presented in Table 1. According to ROC analysis, the area under the ROC (AUC) of iodine concentration (AUC, 0.996; 95% CI, 0.898–1.000) was significantly larger than that of the LAA/AA HU ratio (0.881; 0.733–0.964) in differentiating thrombi from circulatory stasis ($p < 0.05$) (Fig. 2). The optimal cutoff values were −1.3 mg/ml for iodine concentration and 0.304 for the LAA/AA HU ratio. Intraobserver and interobserver agreements for the measurement of iodine concentration (ICC = 0.894, ICC = 0.871) were all excellent.

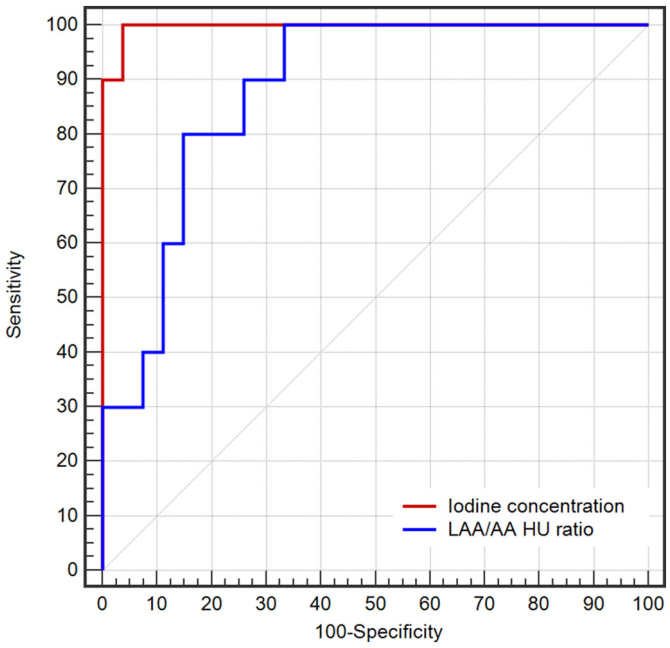

Fig. 2. ROC analysis in differentiating thrombi from circulatory stasis using TEE as the reference standard. The area under the ROC of iodine concentration (0.996; 0.898–1.000) was significantly larger than that of the LAA/AA HU ratio (0.881; 0.733–0.964) ($p < 0.05$). The optimal cutoff values were −1.3 mg/ml for iodine concentration and 0.304 for the LAA/AA HU ratio.

4. Discussion

In the present study, we analyzed symptomatic AF patients who were referred for CA. We found that a novel method that employs DECT technology to determine iodine concentration demonstrated improved diagnostic accuracy compared with conventional enhancement measurements, in detecting thrombi in the LAA and differentiating thrombi from circulatory stasis, under the same contrast injection protocol using TEE as the reference standard.

A convenient alternative to TEE for the exclusion of LA or LAA thrombi would be of substantial clinical value. Emerging data suggest there are potential risks associated with the regular use of TEE before ablation, in particular the risks for esophageal lesions in patients exposed to high levels of anticoagulation required during AF ablation [12–14].

Previous studies using CT demonstrated excellent sensitivity and NPV, but poor specificity and PPV for the detection of LAA thrombi, owing to the limited capacity of CT to differentiate thrombi from SEC in the presence of an LAA filling defect [8,15,16]. Kim et al. [17] reported that the sensitivity, specificity, PPV, and NPV for the detection of severe SEC and thrombi using cardiac CT were 93%, 85%, 31%, and 99%, respectively. A recent meta-analysis, which included 19 relevant studies (n = 2955) showed a mean weighted PPV of 33% for LAA thrombus detection [18].

To improve the specificity and PPV of CT, a two-phase scan protocol or dual-enhanced single-phase CT protocol were proposed [19–22]. For the two-phase scan protocol, a second set of images is acquired following a short delay after the initial scan. Using surgical findings as the reference standard, Choi et al. [23] reported that sensitivity, specificity, PPV, and NPV of early phase CT were 100%, 53%, 100%, and 60%, while those for two-phase CT with quantitative assessment were 100%, 96%, 90%, and 100%, respectively, for the detection of thrombi on a patient basis. However, a two-phase scan protocol increases the patient's radiation exposure. Instead of a second delayed-phase CT, a dual-enhanced single-phase CT scan (as used in our patients) can be performed by administering contrast twice with a delay between the first and second contrast boluses.

Hur et al. [24] compared double-contrast single phase CT with TEE in patients with ischemic stroke. In their results, the sensitivity, specificity, PPV, and NPV were 85%, 94%, 73%, and 97%, respectively. A subsequent study from the same group reported that the overall sensitivity, specificity, PPV, and NPV of CT for the detection of thrombi in the LAA were 89%, 100%, 100%, and 99%, respectively, using TEE as the reference standard [25]. Compared with the conventional contrast injection protocol, their specificity and NPV were significantly improved. Some of the disparities between the results from this group using the same CT scan protocol may be attributed to differences between the two groups of patients studied. One study analyzed patients with ischemic stroke, while the other analyzed those with symptomatic AF. Another possibility is that conventional enhancement measurements in HU may be affected by confounding factors characterized by both unenhanced CT attenuation densitometry and contrast material-enhanced densitometry. To improve the accuracy of CT in thrombus detection, many studies quantified HU attenuation in the LAA relative to the AA to derive the LAA/AA HU ratio.

Emerging evidence indicates that iodine concentration in DECT allows for a reliable distinction between enhancing and nonenhancing

Table 1
Statistical results for the detection of LAA thrombus (N = 302).

Image series	Accuracy	Sensitivity	Specificity	PPV	NPV
Iodine concentration	99.7	100.0	99.7	90.9	100.0
	(301/302)	(10/10)	(291/292)	(10/11)	(291/291)
	[98.2–99.9]	[69.2–100]	[98.1–99.9]	[58.7–99.8]	[98.7–100]
LAA/AA HU ratio	96.0	100.0	95.9	45.5	100.0
	(290/302)	(10/10)	(280/292)	(10/22)	(280/280)
	[93.2–97.9]	[69.2–100.0]	[92.9–97.9]	[24.4–67.8]	[98.7–100]

Values are % (raw data) [95% confidence interval].
PPV = positive predictive value; NPV = negative predictive value.

phenomena, with higher accuracy compared with conventional enhancement measurements. Because the iodine concentration is unaffected by unenhanced CT attenuation densitometry, it has the potential to capture even subtle variances in iodine concentration, providing a more accurate metric of differences between nonenhancing thrombi and intracardiac blood pools with circulatory stasis or normality. In our study, iodine concentration showed the same sensitivity (100%) as the LAA/AA HU ratio of conventional enhancement measurements. However, the PPV of the iodine concentration ratio was significantly higher than that of the LAA/AA HU ratio in detecting LAA thrombi (90.91% vs. 45.45%). In distinguishing thrombi from circulatory stasis, iodine concentration demonstrated a significantly improved diagnostic performance over the LAA/AA HU ratio (AUC: 0.996 vs. 0.881, $p < 0.05$) (Figs. 2 and 3), which was mostly consistent with a previous study performed by single-source fast-kilovoltage-switching dual-energy CT (1.000 vs. 0.797, $p < 0.05$) [26]. Compared with this previous study, the AUC of the LAA/AA HU ratio was higher in ours (0.881 vs. 0.797). This may represent a result of the third-generation DSCT systems used herein which offer improved hardware- and software-based reduction of scatter radiation. More importantly, additional tin filter (Sn) has been introduced for the high kilovoltage peak tube, reducing beam-hardening artifacts. In contrast, the previous study used earlier generation scanners with relatively lower spatial and temporal resolution. Furthermore, their optimal cutoff values for iodine concentration (1.74 mg/ml) and the LAA/AA HU ratio (0.19) were different from ours (−1.3 mg/ml and 0.304, respectively). This discrepancy in cutoff values may have been caused by the different types of dual-energy CT hardware platforms used. This is consistent with a recent study that compared the measured and true iodine concentrations, and showed that iodine concentration was underestimated by DSCT systems compared with fast kilovolt peak-switching systems in DECT-based iodine concentration measurements [27].

In the present study, to achieve a sufficient attenuation difference between iodine-enhancing and nonenhancing phenomena, a dual-enhanced protocol involving two injections of iodinated contrast media was used. Given that the lack of atrial contractions in AF patients causes slow atrial filling, contrast opacification in the LAA may take longer. Accordingly, in this study, a delay time was used between administering the first and second contrast boluses.

A concern regarding the use of DECT for the evaluation of the LAA is radiation exposure. Indeed, the tube currents can be tailored in DSCT

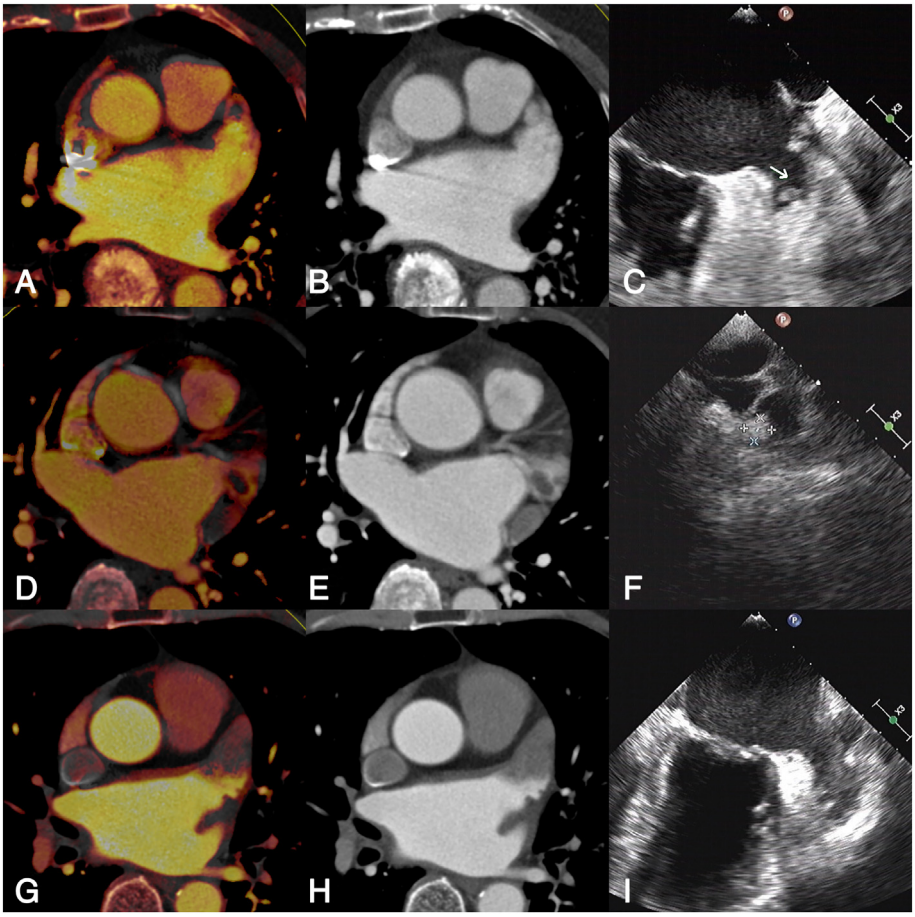

Fig. 3. Panels A–C: Representative images from an 80-year-old male patient with AF. Iodine map (panel A) shows a filling defect in the LAA (iodine concentration = −5.8 mg/ml) (true positive finding). Conventional enhancement CT (panel B) shows no definite filling defect in the LAA (LAA/AA HU ratio = 0.332) (false negative finding). TEE image (panel C) shows a thrombus (arrow) with SEC. Panels D–F: Representative images from a 69-year-old female patient with AF. Iodine map (panel D) shows a filling defect in the LAA (iodine concentration = −2.1 mg/ml) (true positive finding). Conventional enhancement CT (panel E) shows a filling defect in the LAA (LAA/AA HU ratio = 0.096) (true positive finding). TEE image (panel F) shows a thrombus. Panels G–I: Representative images from a 62-year-old female patient with AF. Iodine map (panel G) shows partial filling defect in the LAA (iodine concentration = 1.9 mg/ml) (true negative finding). Conventional enhancement CT (panel H) shows a filling defect in the LAA (LAA/AA HU ratio = 0.232) (false positive finding). TEE image (panel I) shows severe SEC without a thrombus. For quantitative assessment, an iodine concentration of −1.3 mg/ml or less was considered positive for thrombi. An LAA/AA HU ratio of 0.304 or less was considered positive for thrombi. Conventional enhancement CT images (combined 70-kV and 150-kV images) which approximate the image quality of a conventional 120-kV and iodine maps were automatically generated from DECT scans.

systems, so that the dose from both tubes matches that of the routine single-source CT scan protocol [28]. Moreover, third-generation DSCT systems are equipped with Stellar detectors, which are more sensitive to electron influx and are therefore dose-efficient. Our data regarding radiation doses (2.45 ± 0.54 mSv) in DECT using a third-generation DSCT system are well below the recently reported dose (7.5 mSv) that results in DNA damage [29].

It is well known that the lack of synchronization with cardiac movements may hinder visualization of small structures inside the LAA and create imaging artifacts. The gating technique used in our study not only improved the diagnostic accuracy of CT in detecting thrombi, but enables the evaluation of coronary artery disease.

5. Limitations

Our study had several limitations. First, TEE without ultrasound contrast agents is considered the gold standard, and the presence or absence of an LAA thrombus was not confirmed by direct visual inspection of anatomic or surgical specimens. Furthermore, this is a preliminary study using dual-source CT system with no validation group for the optimal cutoff value. Future studies with validation group using different DECT systems are needed to confirm our preliminary findings. Also, although the majority of intervals between DECT and TEE were within 24 h, and the risk of "new" thrombus formation was low, we could not entirely eliminate the possibility that this occurred between studies, thereby altering our findings. Finally, this was a single-center analysis with a relatively small number of positive cases. Although small, the results are encouraging but require further validation in larger cohorts.

6. Conclusions

In conclusion, DECT-derived iodine concentration was associated with improved diagnostic accuracy compared with conventional enhancement measurements in detecting LAA thrombi and differentiating thrombi from circulatory stasis in patients with AF. Therefore, we believe that dual-energy cardiac CT may be clinically useful for detecting and ruling out intracardiac thrombi in AF patients. It may also serve as an alternative diagnostic tool to TEE.

Disclosures

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.04.079.

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