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Predicting Left Atrial Appendage Thrombus from Left Atrial Volume and Confirmation by Computed Tomography with Delayed Enhancement.

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Left Atrial Volume as Predictor of Left Atrial Appendage Thrombus Detected by Cardiac Computed Tomography

(Abstract)

Assessing thromboembolic risk is crucial for proper management of patients with atrial fibrillation. Left atrial volume is a promising predictor of cardioembolism. Therefore, we investigated the association between left atrial volume and the presence of left atrial appendage thrombus in patients with a history of atrial fibrillation.

This prospective study enrolled 73 patients. Left atrial and ventricular volumes were evaluated by cardiac computed tomography with retrospective electrocardiographic gating and then indexed to body surface area. The presence of left atrial appendage thrombus was confirmed or excluded by delayed-enhancement cardiac computed tomography.

Seven patients (9.6%) had left atrial appendage thrombus; 66 (90.4%) did not. Those with thrombus had a significantly higher mean left atrial end-systolic volume index (139 ± 55 mL/m^2 vs 101 ± 35 mL/m^2; P=0.0097) and significantly higher mean left atrial end-diastolic volume index (122 ± 45 mL/m^2 vs 84 ± 34 mL/m^2; P=0.0077). As shown by multivariate logistic regression analysis, the left atrial end-systolic volume index (per 10 mL/m^2 increase) was significantly associated with left atrial appendage thrombus (odds ratio [OR]=1.24; 95% CI, 1.03–1.50; P=0.02); so too was the left atrial end-diastolic volume index (per 10 mL/m^2 increase) (OR=1.29; 95% CI, 1.05–1.60; P=0.02).

These findings suggest that increased left atrial volume, as evaluated by cardiac computed tomography, increases the risk of left atrial appendage

thrombus. Left atrial enlargement therefore warrants careful interpretation as an aid to diagnosis of left atrial appendage thrombus in patients with atrial fibrillation. **(Tex Heart Inst J 2020;47(2):555-555)**

(Introduction)

Atrial fibrillation (AF) increases the risk of life-threatening and severely disabling thromboembolic events.[1] Assessing thromboembolic risk is crucial for proper management of patients with AF. Stroke risk is assessed by calculating a CHA_2DS_2-VASc score based on an established set of clinical parameters, a score of 0 corresponding to lowest and a score of 9 to highest annual risk.[1] The presence of thrombus in the left atrial appendage (LAA) is usually assessed initially by conventional, noninvasive transthoracic echocardiography[2] or by more accurate, but invasive, transesophageal echocardiography (TEE).[3]

Recent technological improvements in cardiac computed tomography (CCT) have made it a viable alternative to TEE for assessing cardiac structures in patients with AF.[3] However, CCT often identifies areas of low-contrast enhancement that may or may not represent LAA thrombus. For patients with AF, this finding can be problematic if it increases the need for additional TEE studies with their attendant risks to rule out an LAA thrombus.[3] This shortcoming of CCT is overcome with delayed-enhancement imaging.[3]

Left atrial enlargement is thought to be a structural precursor of AF.[4] Accurate imaging and detection of this cardiac abnormality would be useful in identifying patients at risk for stroke. The association between presence of LAA thrombus and CCT-derived cardiac measurements such as left atrial (LA) and left ventricular (LV) volume[5] or left ventricular ejection fraction (LVEF)[6] has not yet been fully investigated. Therefore, our aim in this study was to examine the association between LA volume and the presence of LAA thrombus as evaluated by delayed-enhancement CCT in patients with AF.

Patients and Methods

Study Population

For this study, we prospectively enrolled 73 consecutive patients with a history of AF who were treated with warfarin for suspected coronary artery disease at our institution between December 2014 and July 2016 (Table I). Eight patients also had a history of pacemaker implantation; 7, coronary artery revascularization; 4, valvular replacement; and 1, untreated mitral valve stenosis. All 73 patients underwent delayed-enhancement CCT by means of multidetector computed tomography (MCT) with retrospective electrocardiographic gating to analyze cardiac volumes and to confirm or exclude LAA thrombus. This study was approved by an institutional ethics committee and conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent before being enrolled in the study.

Atrial Fibrillation Classification and CHA_2DS_2-VASc Score

Each patient's AF at baseline was classified as persistent or not persistent. Persistent AF was defined as recurrent AF lasting ≥7 days.[7] The CHA_2DS_2-VASc score at baseline was calculated for each patient according to the following point system.[8] Two points were assigned for a history of stroke or transient ischemic attack or age ≥75 years. One point was assigned for age 65–74 years; history of hypertension, diabetes, heart failure, and vascular disease (myocardial infarction, complex aortic plaque, or peripheral artery disease); and female sex.

Multidetector Computed Tomography

Multidetector computed tomography was performed with a 64-slice Lightspeed VCT scanner (GE Healthcare) as described elsewhere.[9] The MCT scanning parameters were as follows: collimation, 64 × 0.625 mm; table pitch adapted to heart rate, 0.18–0.24; rotation time, 350 ms; tube current-time product, 350-780 mA-s; and tube voltage, 100-120 kV. Before scanning, any patient with a persistently high heart rate of >60 beats/min was given β-blockers to achieve a target resting heart rate of <60 beats/min. Immediately before scanning, all patients were given sublingual nitroglycerin or nitroglycerin spray (0.4 mg). A test MCT image acquisition was performed to determine how long to delay scanning after contrast enhancement. This was done at the level of the ascending aorta after administration of 10-15 mL of contrast medium (Omnipaque 350; GE Healthcare) followed by 20 mL of normal saline. The delay (40 s) was calculated by adding 5 s to the time to peak enhancement in the ascending aorta.

Retrospective electrocardiogram (ECG)-gated CCT with dose modulation was performed after intravenous administration of a 4-phase contrast bolus. First, 20-25 mL of contrast medium was administered at a rate of 5.5-5.7 mL/s, followed by 60 mL of contrast medium at 5.4 mL/s, 35-40 mL of contrast medium diluted 50% at 5.5 mL/s, and 35-40 mL of saline as a chaser bolus at 5.0 mL/s. Scanning for the presence of LAA thrombus was delayed 40 s, without additional contrast, after the initial CCT scan. The effective radiation dose in each phase of the CCT study was estimated from the dose-length product.

Volumetric Analysis

All volumetric analysis was done by an experienced cardiologist (KO) blinded to the results of delayed-enhancement CCT. Multidetector computed tomographic images were reconstructed at 5% intervals of the cardiac cycle. In each phase, the LA and LV volumes were delineated according to the atrial and ventricular contours and calculated by using the Simpson method for numerical integration on an Advantage Workstation 4.6 (GE Healthcare).[10] The calculated volumes were then manually corrected for minor errors. The workstation software automatically calculated a time-volume curve. The maximal and minimal peaks on this curve were used to determine the LA and LV end-diastolic and end-systolic volumes, respectively. The workstation software also automatically calculated LV stroke volume and LVEF. The pulmonary vein confluences and LAA were excluded from volumetric analysis. Left atrial and LV volumes were divided by body surface area (calculated according to the DuBois formula[11]) to obtain the LA end-systolic volume index (LAESVI), LA end-diastolic volume index (LAEDVI), LV end-systolic volume index (LVESVI), and LV end-diastolic volume index (LVEDVI).

The reproducibility of LA volume readings was assessed by 2 readers (KO and RN) blinded to the original readings. One reader (KO) read each of 73 CCT studies twice to determine intraobserver variability. The other reader (RN) re-read 45 CCT studies to determine interobserver variability.

Left Atrial Appendage Thrombus Assessment

Images obtained by delayed-enhancement CCT were visually assessed for filling defects suggestive of LAA thombus.[9] Assessments were independently performed by 2 experienced cardiologists (MB and KO). A CCT study was read as *negative* if it showed no filling defects in the LAA; as *positive*, if it showed a definite filling defect suggestive of thrombus.

Statistical Analysis

Continuous variables were expressed as mean ± SD or median and interquartile range. Differences between groups were evaluated using the Student *t* test (for continuous variables) and Pearson χ2 test or Fisher exact test (for categorical variables). Univariate analysis and stepwise multivariate logistic regression analysis were used to calculate the odds ratio (OR) for the relationship between the presence of LAA thrombus and either LAESVI (model 1) or LAEDVI (model 2). Each regression analysis was adjusted for persistent AF, CHA_2DS_2-VASc score, international normalized ratio of prothrombin time (PT-INR) (at the time of CCT), LVEF, and AF duration (years since diagnosis). Intra- and interobserver variability was assessed in terms of Pearson correlation coefficients. *P* values <0.05 (2-sided) were considered statistically significant. All statistical analyses were done with SPSS version 23.0 for Windows (SPSS, an IBM company).

Results

Of the 73 patients enrolled, 7 (9.6%) had LAA thrombus, and 66 (90.4%) did not (Table I). Overall, the mean CHA_2DS_2-VASc score was 2.8 ± 1.6. Overall, 40 patients (55%) showed AF during computed tomographic image acquisition; all 40 had persistent AF at baseline. Thirty-six patients had a heart rate <60 beats/min while receiving a beta-blocker. The mean heart rate during image acquisition was 64 ± 12 beats/min overall and did not differ significantly between patients with and without LAA thrombus (61 ± 10 vs 64 ± 13 beats/min; *P*=0.56). In terms of percentage, significantly more patients with LAA thrombus were ≥75 years of age (43% vs 8%; *P*=0.03). The mean PT-INR was 2.5 ± 0.7 overall and similar in those with and without LAA thrombus (2.3 ± 0.5 vs 2.5 ± 0.7; *P*=0.42). Overall, the mean effective radiation dose and dose-length product for CCT studies were 8.1 ± 2.8 mSv and 579 ± 203 mGy·cm, respectively.

Fig. 1 shows representative delayed-enhancement CCT images of an LAA thrombus in a 75-year-old woman. Compared with patients without LAA thrombus, those with LAA thrombus had a significantly higher mean LAESVI (139 ± 55 mL/m^2 vs 101 ± 35 mL/m^2; P=0.0097) and significantly higher mean LAEDVI (122 ± 45 mL/m^2 vs 84 ± 34 mL/m^2; P=0.0077) (Table II). The 2 patient groups were similar in terms of LVESVI, LVEDVI, and LVEF (Fig. 2). The intra- and interobserver correlation coefficients for LV volume measurements were r=0.93 (P<0.001) and r=0.94 (P<0.001), indicating little variability within and among reader assessments. After adjustment for persistent AF, CHA_2DS_2-VASc score, PT-INR (at the time of CCT), LVEF, and AF duration (years since diagnosis), multivariate logistic regression analysis revealed that LAESVI (per 10 mL/m^2 increase) was significantly associated with the presence of LAA thrombus (OR=1.24; 95% CI, 1.03–1.50; P=0.02) (Table III, model 1). When LAEDVI was substituted for LAESVI in the model, LAEDVI (per 10 mL/m^2 increase) was also significantly associated with the presence of LAA thrombus (OR=1.29; 95% CI; 1.05–1.60; P=0.02) (Table III, model 2).

Discussion

In this study, we found that increased LAESVI and LAEDVI measured by CCT were independently associated with the presence of LAA thrombus detected by delayed-enhancement CCT in patients with a history of AF receiving anticoagulation therapy. This was true even after adjusting for CHA_2DS_2-VASc score, persistent AF, PT-INR, LVEF, and AF duration. In contrast, LV volumes and LVEF were not associate with the presence of LAA thrombus. Although we believe that delayed-enhancement image acquisition should be included in all CCT studies in individuals with AF or a history of AF, the opportunity to do so is sometimes missed in actual clinical settings. A finding of LA enlargement on the initial cardiac computed tomogram could be a predictor of LAA thrombus and provide a chance to perform additional delayed-enhancement imaging.

The clinical utility of CCT in assessing and managing AF is already established. It is used routinely to evaluate the location, size, and number of pulmonary veins before ablation for AF.[12] It can also be used with high diagnostic accuracy to assess the coronary anatomy for coronary artery disease[13] and to exclude LAA thrombus[3] in patients with AF. However, delayed-enhancement imaging could dramatically increase diagnostic accuracy in detecting LAA thrombus even further beyond that of first-pass CCT.[14,15] Ideally, because some individuals with AF will still have LAA thrombus despite effective anticoagulation,[16-18] delayed-enhancement imaging should be included when CCT is performed in a patient with a history of AF.

Several echocardiographic studies have revealed significant relationships between LA dilatation and LAA thrombus.[19,20] Furthermore, LA enlargement is a potential predictor of stroke. In a study by Osranek and colleagues in patients with lone AF, LAESVI >32 mL/m^2 was an independent risk factor for adverse events, and all cerebral infarctions occurred in patients with an LAESVI >32 mL/m^2.[21] Similarly, in a recent population-based prospective cohort study, echocardiographically confirmed LA enlargement (>45 mm) was independently associated with stroke incidence even after adjustment for CHA_2DS_2-VASc score and anticoagulation therapy (hazard ratio = 1.74; 95% CI, 1.25-2.42; *P*<0.01).[22] In the Heinz Nixdorf Recall study, LA size measured by noncontrast computed tomography was associated with major cardiovascular events including stroke.[23] In our present study, the mean LAESVI in individuals with LAA thrombus was 139 mL/m^2, significantly outside the normal range of 31.1–77.7 mL/m^2 established by Lin and colleagues.[24] Left atrial enlargement measured by CCT was also independently associated with the presence of LAA thrombus, an established risk factor for stroke. Together, these findings suggest that patients shown by CCT to have an enlarged left atrium should be considered at high risk for thromboembolism and therefore carefully managed.

Increased $CHADS_2$ and CHA_2DS_2-VASc scores are potential risk factors for LAA thrombus.[25,26] In our study, however, mean CHA_2DS_2-VASc scores did not differ significantly between patients with and without LAA thrombus (2.7 vs. 2.8, *P*=0.95) (Table I). In contrast, age ≥75 years--one component of the CHA_2DS_2-VASc score--was significantly more prevalent in patients with LAA thrombus than in those without. Advanced age itself is an independent risk factor for LA enlargement and cardioembolic stroke,[1] and this may explain why the mean LA volumes recorded in our study differed so much between patients with and without LAA thrombus.

This intriguing finding may be due to our study population being relatively younger than those in other studies (mean, 60 vs 66-69 years) and thus potentially more likely to have lower CHA_2DS_2-VASc scores.[25,26] Moreover, in our study, LAA thrombus was detected in 3 patients (4.1%) who had low CHA_2DS_2-VASc scores of 0-1. In one recent study of AF patients with low CHA_2DS_2-VASc scores, the investigators concluded that LA enlargement might be one of several complementary factors associated with increased thromboembolic risk that are not measured or accounted for in the CHA_2DS_2-VASc score.[27] If supported by future outcomes data, this finding might warrant careful management of patients with AF who have an enlarged left atrium even if they have low CHA_2DS_2-VASc scores.

Study Limitations

Our study had several limitations. First, it was a prospective, single-center study that included only 73 patients with AF and suspected coronary artery disease. Studies in larger populations are warranted. Second, LAA thrombus was diagnosed by delayed-enhancement CCT alone. Several studies that established the accuracy of CCT in detecting LAA thrombus used TEE as a reference standard.[3,9,16] Third, all CCT images were acquired with retrospective ECG gating, which exposes patients to radiation throughout the cardiac cycle. Our current protocol could be improved by using radiation-reducing strategies such as lowering tube voltage, adjusting tube current by weight, electrocardiographically controlling dose modulation, or prospectively acquiring sequential images.[28] Prospectively gated CT image acquisition with systolic triggering may reduce the radiation exposure to patients with AF even when performing standard 64-multidetector row CT.[29] However, the delayed-enhancement step in our current protocol adds only <1 mSv to the total effective radiation dose, requires imaging of only the upper half of the heart, and is done prospectively and at low kilivoltage (typically 100 kVp). In the future, newer generations of dual-energy CT scanners might be used without ECG gating to differentiate between LAA thrombus and slow flow by measuring iodine concentrations in LAA filling defects.[30] However, the clinical experience with dual-energy methods is limited, and additional clinical trials in a larger population are needed.

Conclusion

Increased LAESVI and LAEDVI are each independently associated with the presence of LAA thrombus detected by delayed-enhancement CCT in patients with AF. Left atrial enlargement may provide a clue to the diagnosis of LAA thrombus in this patient population and warrants careful evaluation and interpretation. This may in turn help refine the thromboembolic risk stratification and management of patients with AF.

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(Legends)

Fig. 1. Representative cardiac computed tomograms show a left atrial appendage (LAA) thrombus in a 75-year-old woman with hypertension (CHA_2DS_2-VASc score of 4). This patient had a large LA end-systolic volume of 159.3 mL (LAESVI, 97.9 mL/m^2) and a large LA end-diastolic volume of 146.1 mL (LAEDVI, 89.8 mL/m^2). Shown are **A)** a single axial slice of the cardiac computed tomogram acquired initially and **B)** an image of the LAA thrombus (arrows) acquired after a 40-s delay for contrast enhancement. **[AU: Wording here has been revised to clarify further the timing of the delayed-enhancement scan. Is the revised wording accurate? If yes, please say. If no, please update as needed. Thank you.- YES]** AA = ascending aorta; LA = left atrium; LAESVI = left atrial end-systolic volume index; LAEDVI = left atrial end-diastolic volume index; PA = pulmonary artery; SVC = superior vena cava

Fig. 2. Box plots compare the estimated values for cardiac volumetric parameters derived from cardiac computed tomograms in patients with versus without left atrial appendage (LAA) thrombus: **A)** Left atrial end-systolic volume index (LAESVI); **B)** left atrial end-diastolic volume index (LAEDVI); **C)** left ventricular end-systolic volume index (LVESVI); **D)** Left ventricular end-diastolic volume index (LVEDVI); and **E)** left ventricular

ejection fraction (LVEF). The line inside a box marks the median (50th percentile). The bottom and top of a box mark the interval between the 25th and 75th percentiles. Whiskers indicate the interval between the minimum and maximum values, excluding the 4 outlier values for each. $P<0.05$ (2-sided) was considered statistically significant.

TABLE I Baseline Characteristics of the 73 Patients

Variable	LAA Thrombus		Total	*P* Value
	With (n=7)	**Without** (n=66)	**Total** (N=73)	***P* Value**
Clinical characteristics				
Age (yr)	65 ± 18	59 ± 10	60 ± 11	0.22
Age ≥75 years	3 (43)	5 (8)	8 (11)	0.03
Male	4 (57)	42 (64)	46 (63)	0.74
Body mass index (kg/m^2)	30 ± 9	33 ± 9	33 ± 9	0.39
Hypertension	6 (86)	62 (94)	68 (93)	0.41
Dyslipidemia	5 (71)	50 (76)	55 (75)	0.8
Diabetes mellitus	2 (29)	29 (44)	31 (42)	0.43
Current smoker	0 (0)	5 (8)	5 (7)	0.45
Family history of CAD	2 (29)	25 (38)	27 (37)	0.63
PT-INR	2.3 ± 0.5	2.5 ± 0.7	2.5 ± 0.7	0.42
AF duration (yr)	4.0 [1.5-6.0]	3.0 [1.0-6.0]	3.0 [1.0-6.0]	0.91
History of HF or LVEF <0.40	0 (0)	14 (21)	14 (19)	0.18
History of stroke	1 (14)	8 (12)	9 (12)	0.87
CHA_2DS_2-VASc score	2.7 ± 2.0	2.8 ± 1.5	2.8 ± 1.6	0.95
Persistent AF	5 (71)	35 (53)	40 (55)	0.65
Drugs				
Antihypertensive	6 (86)	59 (89)	65 (89)	0.77
Antidyslipidemic	5 (71)	42 (64)	47 (64)	0.68
Antidiabetic	2 (29)	24 (36)	26 (36)	0.68

AF = atrial fibrillation; CAD = coronary artery disease; HF = heart failure; LAA = left atrial appendage; LVEF = left ventricular ejection fraction; PT-INR = international normalized ratio of prothrombin time

Values are expressed as median and interquartile range (AF duration), as mean ± SD (all other continuous variables), or as number and percentage (categorical variables). $P<0.05$ was considered statistically significant for differences between groups.

[AU: in footnote above, should "*P*<0.05" read "*P*<0.05 (2-sided)"? Either way, please say add 2 sided]

TABLE II Volume Measurements by Cardiac Computed Tomography in the 73 Patients

	LAA Thrombus						
	With (n=7)		**Without** (n=66)		**Total** (N=73)		
Variable	**Mean ± SD**	**95% CI**	**Mean ± SD**	**95% CI**	**Mean ± SD**	**95% CI**	***P* Value**
LAESVI (mL/ m^2)	139 ± 55	88-191	101 ± 35	92-109	104 ± 38	95-113	0.0097
LAEDVI (mL/ m^2)	122 ± 45	81-164	84 ± 34	75-92	88 ± 37	79-96	0.0077
LVESVI (mL/ m^2)	48 ± 18	32-65	46 ± 22	41-52	47 ± 21	42-52	0.81
LVEDVI (mL/ m^2)	100 ± 29	74-127	91 ± 24	85-97	92 ± 25	87-98	0.38
LVEF (%)	52 ± 5	48-57	51 ± 13	48-54	51 ± 12	48-54	0.78

LAA = left atrial appendage; LAEDVI = left atrial end-diastolic volume index; LAESVI = left atrial end-systolic volume index; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index

$P<0.05$ was considered statistically significant for differences between groups.

[AU: in footnote above, should "*P*<0.05" read "*P*<0.05 (2-sided)"? Either way, please say add 2 sided]

TABLE III Univariate and Multivariate Analysis of Predictors of Left Atrial Appendage Thrombus

Variable	Univariate		Multivariate			
			Model 1*		Model 2**	
	Odds Ratio (95% CI)	***P* Value**	**Odds Ratio** (95% CI)	***P* Value**	**Odds Ratio** (95% CI)	***P* Value**
Persistent AF	2.14 (0.39-11.86)	0.38	1.47 (0.24-9.17)	0.68	1.34 (0.20-8.91)	0.76
CHA_2DS_2-VASc score	0.98 (0.59-1.62)	0.94	0.97 (0.55-1.74)	0.93	0.96 (0.54-1.71)	0.88
PT-INR	0.61 (0.18-2.05)	0.42	0.58 (0.16-2.02)	0.39	0.56 (0.17-1.86)	0.34
LVEF	1.01 (0.95-1.08)	0.78	1.02 (0.94-1.10)	0.65	1.02 (0.94-1.11)	0.57
AF duration (yr)	0.99 (0.86-1.14)	0.91	1.02 (0.88-1.18)	0.80	1.02 (0.89-1.18)	0.78
LAESVI (per 10 mL/m^2)	1.24 (1.03-1.49)	0.02	1.24 (1.03-1.50)	0.02		
LAEDVI (per 10 mL/m^2)	1.29 (1.05-1.60)	0.02			1.29 (1.05-1.60)	0.02

AF = atrial fibrillation; LAA = left atrial appendage; LAEDVI = left atrial end-diastolic volume index; LAESVI = left atrial end-systolic volume index; LVEF = left ventricular ejection fraction; OR = odds ratio; PT-INR = international normalized ratio of prothrombin time

* Model 1 was adjusted for persistent AF, CHA_2DS_2-VASc score, PT-INR, LVEF, AF duration (years), and **LAESVI** (per 10 mL/m^2).

** Model 2 was adjusted for persistent AF, CHA_2DS_2-VASc score, PT-INR, LVEF, AF duration (years), and **LAEDVI** (per 10 mL/m^2).

P<0.05 was considered statistically significant.

[AU: in footnote above, should “*P*<0.05” read “*P*<0.05 (2-sided)"? Either way, please say add 2 sided]

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