



Original Contribution

The diagnostic efficacy of cardiac CTA combined with D-dimer assay for the detection of left atrial thrombus in patients with atrial fibrillation

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ARTICLE INFO

Article history:

Received 5 June 2018

Received in revised form 6 January 2019

Accepted 11 January 2019

Keywords:

Atrial fibrillation
Left atrial thrombus
Cardiac CTA
D-dimer

ABSTRACT

Purpose: We aimed to evaluate a combination diagnostic method of single-phased, single-contrast injection cardiac computed tomography angiography CTA combined with age-adjusted D-dimer assay for diagnosis of left atrial/left atrial appendage (LA/LAA) thrombus in comparison to transesophageal echocardiography (TEE) in patients with atrial fibrillation. The addition of D-dimer to the CTA is to increase specificity, since CTA is part of the combined method.

Materials and methods: Between October 2016 and December 2017, 113 consecutive patients with non-valvular or valvular AF (male: 72.6%; mean age: 57.9 ± 11.5 y) underwent diagnostic work-up, included TEE, single-phased, single contrast injection cardiac CTA, and age-adjusted D-dimer assay, for the evaluation of LA/LAA thrombus formation.

Results: Cardiac CTA identified 32 patients with filling defects in LA or LAA. Of these patients, 17 had an elevated D-dimer value according to age-adjusted cut-off. TEE detected definitive thrombus formation in 15 patients. Using TEE as the reference standard, the combination diagnostic method had a sensitivity of 100.0%, specificity of 97.9%, positive predictive value (PPV) of 88.2, and negative predictive value of 100.0%. Further, compared to cardiac CTA alone, the combination diagnostic method had significantly better specificity (82.7% vs. 97.9%, respectively; $p < 0.01$) and PPV (46.9% vs. 88.2%, respectively; $p < 0.01$).

Conclusion: The combination diagnostic method comprising single-phase, single-contrast injection cardiac CTA and age-adjusted D-dimer assay had good diagnostic efficacy for the detection of LA/LAA thrombus in patients with AF. The combination diagnostic method had significantly better specificity and PPV than cardiac CTA alone.

The presented diagnostic approach could potentially facilitate rapid diagnosis or exclusion of left atrial thrombus under emergency situation or when TEE is un-available, with good diagnostic efficacy and no TEE related risks.

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1. Introduction

Atrial fibrillation (AF) is a common arrhythmia that increases in prevalence with advancing age [1]. AF is associated with significantly increased risk of thromboembolic events, including ischemic stroke, transient ischemic attack, and systemic emboli [2]. Approximately 47% of thrombi in valvular AF (mostly mitral stenosis) and 91% of those in non-valvular AF are located in the left atrial appendage (LAA) [3].

Transesophageal echocardiography (TEE) is currently considered the gold standard for the detection of thrombus formation in the left atrium (LA) or LAA [4,5]. TEE is a semi-invasive procedure,

that is generally performed safely by experienced operators. However, this technique is time-consuming, not always available during emergencies, and may cause great discomfort, oropharyngeal injury, or even life-threatening complications such as gastrointestinal laceration or perforation [6,7]. Other TEE related risks are 1) conscious sedation and 2) the possibility of hemodynamic instability during TEE especially if the patients have borderline hemodynamics and atrial fibrillation with rapid ventricular response. In addition, TEE is contradicted under several circumstances, such as mental status changes, esophageal pathology, and active gastrointestinal bleeding. Therefore, reliable and non-invasive diagnostic methods are still requested in clinical practice.

Cardiac computed tomography angiography (CTA) has been proposed for the detection of thrombus formation in the LA/LAA. Multi-detector CTA, with or without electrocardiographic gating,

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showed satisfactory sensitivity and negative predictive value (NPV), but specificity and positive predictive value (PPV) remained low and varied among studies [8–13]. Different modalities of cardiac CTA, such as two-phase scan cardiac CTA and dual-enhanced cardiac CTA, had better diagnostic performance; however, these methods require more radiation exposure and contrast agent usage [14–16].

D-dimer, a product from the degradation of cross-linked fibrin, is universally considered the gold standard among the various biomarkers that reflect activation of coagulation, fibrinolysis, or both [17]. D-dimer levels are significantly increased in the presence of an atrial thrombus [18–21]; therefore, D-dimer may be a potential valuable marker for diagnosing left atrial thrombus. However, published data showed that D-dimer levels had only moderate sensitivity and specificity for diagnosing left atrial thrombus in conditions leading to left atrial stasis, such as AF and mitral stenosis [22].

The aim of the present study was to assess the diagnostic performance of a method combining single-phase, single-contrast injection cardiac CTA and blood D-dimer assay to detect LA/LAA thrombi in patients with AF, using TEE as the reference standard.

2. Materials and methods

2.1. Patient selection

This study was approved by the ethics committee from our institution, and patients provided informed consent. These studies were ordered for patients with valvular or non-valvular atrial fibrillation as part of their clinical work-up before contemplated pulmonary vein isolation or heart valve surgery. From October 2015 to December 2016, we consecutively enrolled 113 patients who were admitted to our hospital with a diagnosis of valvular AF or non-valvular AF. Exclusion criteria were as follows: patients with other circumstances that led to elevation of blood D-dimer level (acute coronary syndrome, peripheral artery diseases, pulmonary embolism, tumor, infectious diseases, hemorrhagic diseases, and diffuse intravascular clotting), ongoing anticoagulation therapy, contradictions in contrast CT examination (contrast agent allergy and renal insufficiency), and contradictions of TEE examination (perforated viscous, esophageal pathology, active upper GI bleeding, recent upper GI surgery, esophagostomy, esophagogastrotomy, and conscious disturbance).

2.2. Cardiac CTA examination

Patients fasted for 4 h before cardiac CTA examination, to avoid aspiration in case of contrast agent allergy. A General Electric (GE) Discovery PET/CT 64-slice CT was used (GE Healthcare, Chicago, IL, USA). Patients with a contraindication to contrast CT examinations, such as known allergic reaction to iodinated contrast media, renal insufficiency (serum creatinine >1.5 mg/dL), hyperthyroidism, or advanced heart failure (New York Heart Association grades III–IV), were excluded. For the cardiac CTA, 80 mL of iopromide (iopromide 370, 370 mg/mL; Bayer Healthcare) at a rate of 5 mL/s, followed by 50 mL of intravenous saline injection via a 21-gauge catheter, were administered. Bolus tracking technique was used to appropriately trigger image acquisition when attenuation in the left atrium reached a preset threshold of 100 HU. Image acquisition was performed as follows: 0.625 mm slice thickness, z-axis coverage of 40 mm, heart rate-adapted pitch of 0.18–0.26, gantry rotation time of 350 ms, tube voltage of 120 kV, effective tube current adapted to body mass index (280–750 mA), and ECG-adapted tube modulation. CT datasets were retrospectively reconstructed from mid-diastolic to end-diastolic, as well as additional phases if needed for optimal left atrial visualization.

Filling defects were defined as areas of low attenuation in LA or LAA that were not caused by motion artifacts or cardiac structures like the atrial trabeculae. Hounsfield Units (HU) of low attenuation areas were measured for the assessment of filling defects, based on the homogeneity, HU-value, and the border aspect. Filling defects with low HU-values (<100 HU) [23] and well-defined borders were identified as thrombi.

Blood D-dimer test.

Five mL of venous blood were extracted from the patients and plasma was isolated by centrifugation. All blood sample assays were performed in the laboratory at our institute, and investigators and laboratory personnel were blinded to the patient's clinical status. For the quantitative determination of D-dimers in plasma, plasma D-dimer levels were measured by immunoturbidimetric assay (STA[®]-Liatest D-Di kit; Diagnostica Stago SAS, Asnières-sur-Seine, France). Processing and analysis were performed within 90 min of collection.

The present study used an age-adjusted D-dimer cutoff value (age multiplied by 10 in patients 50 years or older), since age-adjusted D-dimer cutoff had a superior diagnosis yield than a fixed D-dimer cutoff of 500 µg/L for thrombotic disease [24,25].

2.3. TEE examination

TEE was performed using a Philips iE ELITE echocardiography system (Philips, Amsterdam, Netherlands) and 5-MHz multiplane probe positioned in the esophagus. Multiple tomographic planes were obtained to determine the presence of LA or LAA thrombus.

2.4. Statistical analysis

Using TEE as the reference standard, the diagnostic efficacy indexes (sensitivity, specificity, PPV, and NPV) for both cardiac CTA alone and the combination diagnostic method of cardiac CTA and age-adjusted D-dimer assay were calculated. A patient was identified as having a positive LA/LAA thrombus when both cardiac CTA and age-adjusted D-dimer assay had positive results.

The specificity of cardiac CTA and the combination diagnostic method were compared using McNemar's test or Fisher's exact tests, when appropriate. PPVs were compared using Leisenring's test [26]. A p value <0.05 was considered statistically significant.

3. Results

The patients were aged between 27 and 77 y. The demographic characteristics of all 113 patients are summarized in Table 1.

Table 1
Demographic characteristics of the patients, presented as mean ± standard deviation or frequency (%)

	Patients (n = 113)
Sex, male	82 (72.6)
Age, years	57.9 ± 11.5
Persistent AF	46 (40.7)
Paroxysmal AF	67 (59.3)
Valvular AF	4 (3.5)
LVEF	60.9 ± 5.5
LA size	38.9 ± 8.1
CHA2DS2-VASc	
Score distribution (non-valvular AF)	
0	22
1	23
2	24
≥ 3	40

AF, atrial fibrillation; LVEF, left ventricular ejection fraction; LA, left atrium; CHA2DS2-VASc, atrial fibrillation stroke risk score.

Table 2a
Diagnostic efficacy of cardiac CTA, using TEE as a standard reference

Cardiac CTA	TEE		Total
	Thrombus	No thrombus	
Thrombus	15	17	32
No thrombus	0	81	81
Total	15	98	113

CT, computed tomography; TEE, transesophageal echocardiography.

Table 2b
Diagnostic efficacy of age-adjusted D-dimer, using TEE as a standard reference

Age-adjusted D-dimer	TEE		Total
	Thrombus	No thrombus	
Thrombus	15	14	29
No thrombus	0	84	84
Total	15	98	113

TEE, transesophageal echocardiography.

Table 3
Diagnostic efficacy of cardiac CTA combined with blood D-dimer assay, using TEE as a standard reference

Cardiac CTA & D-dimer	TEE		Total
	Thrombus	No thrombus	
Thrombus	15	3	18
No thrombus	0	95	95
Total	15	98	113

CT, computed tomography; TEE, transesophageal echocardiography.

Table 4
Specificity and PPV of cardiac CTA and the combination diagnostic method

	Cardiac CTA	Cardiac CTA & D-dimer	p value
Specificity	82.7%	97.9%	<0.01
PPV	46.9%	88.2%	<0.01

PPV, positive predictive value; CTA, computed tomography angiograph. Specificity and PPV were compared using McNemar's test (or Fisher's exact test, if appropriate) and Leisenring's test [25], respectively.

TEE and cardiac CTA examinations were performed safely without adverse events. Cardiac CTA identified 32 patients with filling defects identified as thrombus in the LA or LAA, 17 of which had an elevated D-dimer value according to age-adjusted cutoff. TEE detected definitive thrombus formation in 15 patients, and spontaneous echo contrast in 11 patients.

Using TEE as the reference standard, cardiac CTA had a sensitivity of 100.0%, specificity of 82.7%, PPV of 46.9%, and NPV of 100.0%. The diagnostic efficacy of cardiac CTA is shown in Table 2a.

Using TEE as the reference standard, age-adjusted D-dimer had a sensitivity of 100.0%, specificity of 86.7%, PPV of 51.7%, and NPV of 100.0%. The diagnostic efficacy of age-adjusted D-dimer is shown in Table 2b.

Moreover, with reference to TEE, the combination diagnostic method of cardiac CTA and D-dimer assay had a sensitivity of

100.0%, specificity of 97.9%, PPV of 88.2%, and NPV of 100.0% (Table 3). In comparing the combination method and cardiac CTA alone, the combination diagnosis method had significantly better specificity and PPV than cardiac CTA (Table 4). The diagnostic accuracy measures of cardiac CTA, D-dimer and the combined method were shown in Table 5.

Two of the true positive cases are shown in Fig. 1, while two of the false positive cases are shown in Fig. 2.

4. Discussion

This study aimed to test the diagnostic efficacy of a combination diagnostic method combining single-phase, single-contrast injection cardiac CTA and age-adjusted blood D-dimer assay in clinical practice to detect LA/LAA thrombi in AF patients. The main finding of this study was that the presented combination diagnostic method had good diagnostic efficacy, evidenced by strong sensitivity, specificity, PPV, and NPV. Furthermore, the combination diagnostic method had significantly better specificity and PPV compared to cardiac CTA alone.

The diagnosis or exclusion of thrombus in LA/LAA is pivotal in the management of AF, including cardioversion and pulmonary vein ablation. TEE is known as an effective and reproducible method for detecting LA/LAA thrombus, and therefore, it remains the gold standard for assessing LA/LAA thrombus formation [2]. Contrast-enhanced cardiac CTA is usually performed prior to pulmonary vein ablation to define the anatomy and dimensions of the LA and the insertions of the pulmonary veins. The same scan can also detect LA/LAA thrombus formation [17,18]. Various scanning protocols for the detection of LA/LAA thrombus have been described and discussed over the past decade [9,10,16,17]. Low specificity and PPV of about 30% are the major limitations of cardiac CTA for LA thrombus detection [17,18,24]. Modified protocols of cardiac CTA, such as two-phase scan cardiac CTA and dual-enhanced cardiac CTA, were developed to improve diagnostic performance. A two-phase scan cardiac CTA protocol included both early-phase scan to evaluate the intracardiac thrombus and late-phase scan to differentiate thrombus from circulatory stasis. This protocol showed promising diagnostic performance by greatly improving diagnostic specificity (98%), while both sensitivity and NPV remained excellent [14,15]. However, the large increase in radiation exposure remains a matter of concern. An alternative dual-enhanced protocol, which involves one scan and two separate boluses of contrast agent injections. The scan was performed only 1 time on a delayed phase, 180 s, after giving the first contrast bolus. The second contrast injection was given to discriminate between thrombus and circulatory stasis with more certainty because a thrombus and circulatory stasis would have a different attenuation density on delayed phase scanning due to the contrast enhancement of the first contrast bolus. Dual-enhanced protocol reported stronger diagnostic performance [15,16]. Although radiation exposure is acceptable with this technique, the significantly larger contrast agent dosage, which is almost double that of the common protocol, remains a matter of concern, especially for patients with impaired renal function and risk of contrast-

Table 5
The diagnostic accuracy measures of cardiac CTA, D-dimer and the combined method.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Cardiac CTA	100.0	82.7	46.9	100.0
Age-adjusted D-dimer	100.0	86.7	51.7	100.0
The combined method	100.0	97.9	88.2	100.0

PPV, positive predictive value; CTA, computed tomography angiograph.

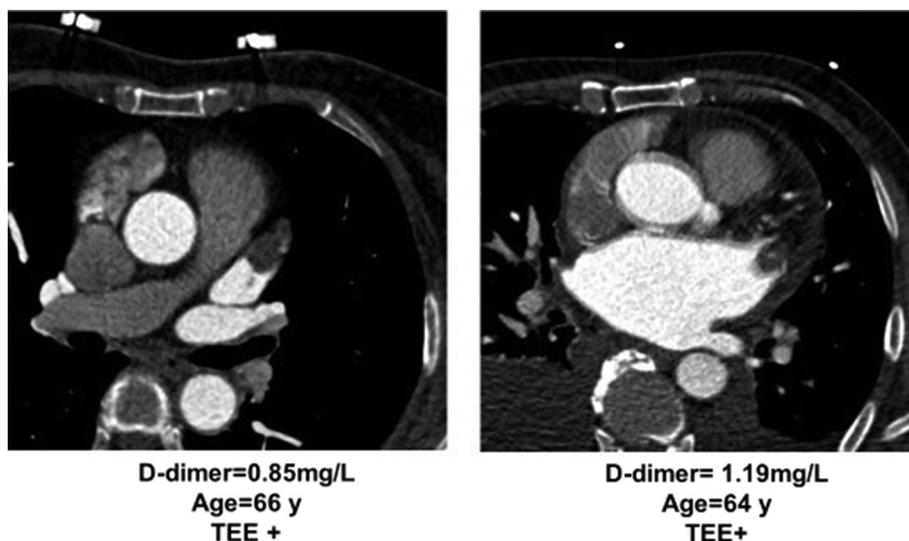


Fig. 1. Two true positive cases with elevated D-dimer (according to age adjusted cut-off) and filling defects on cardiac CTA and TEE.

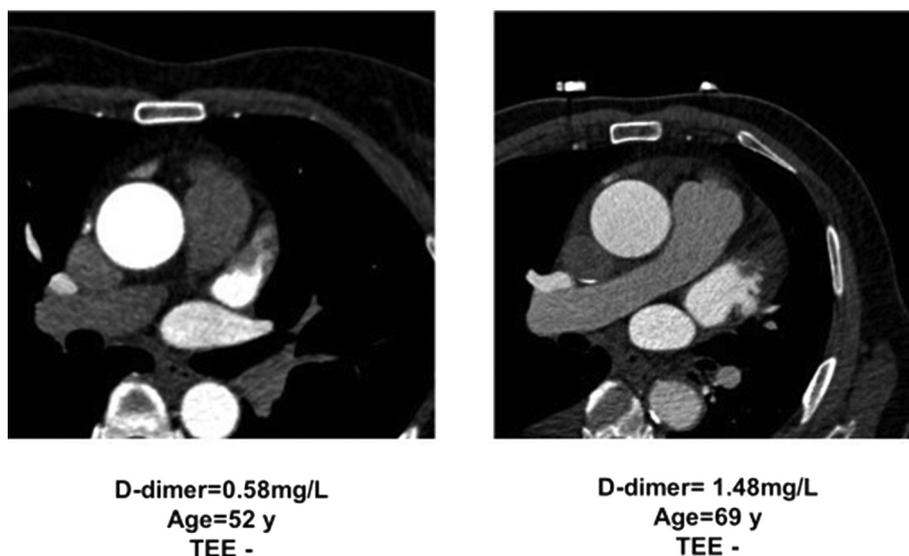


Fig. 2. Two false positive cases with elevated D-dimer (according to age adjusted cut-off) and filling defects on cardiac CTA, but LA thrombus were ruled out by TEE.

induced nephropathy. In addition, the reproducibility of the dual-enhanced protocol requires further validation.

The cardiac CTA protocol we applied involved no extra scan and contrast agent injection. D-dimer assays were implemented as part of the combined diagnosis work to improve diagnostic efficacy. D-dimer levels are higher in AF patients or in those with known risk factors for embolism (i.e., history of embolism or transient ischemic attack, congestive heart failure, hypertension, renal failure, surgery, liver impairment, acute or chronic infection, neoplastic disease, and diabetes mellitus), and it is potentially useful for identification of patients at higher risk of thromboembolic complications [27–29]. Age-adjusted diagnostic cutoffs of D-dimer are demonstrated to be more advisable for risk stratification of patients with suspected thrombotic diseases [30–34]. In the present study, using TEE as the reference standard, age-adjusted D-dimer had a sensitivity of 100.0%, specificity of 86.7%, PPV of 51.7%, and NPV of 100.0%. Previous studies and showed that a D-dimer has moderate to high sensitivity to diagnosis left atrium thrombus. A systematic review indicated that specificity of D-dimer

was 0.81 [95% CI: 0.59,0.93] and, sensitivity was 0.75 [95% CI: 0.65,0.83] by pooling 17 studies and 1756 AF patients, in most of them thrombotic diseases were excluded [22]. Therefore, a negative D-dimer value may be helpful to identify low-risk patients for the presence of left atrium thrombus and to reduce unnecessary image screening for them. However, cut-off values were quite different between previous studies. More importantly, a large portion of studied population had elevated D-dimer level in previous studies [22,35] and our report (30 of 113 patients according to fixed D-dimer cut-off value of 0.5 $\mu\text{g}/\text{ml}$). Therefore, a positive D-dimer occasionally leads to ambiguous diagnosis, and further cardiac imaging examinations may still be warranted.

In the present study, the combined diagnostic method had significantly better diagnostic efficacy than single-phase, single-contrast injection cardiac CTA alone. The diagnostic efficacy of the combined diagnostic method was similar to that of TEE. Therefore, with convenience and rapid diagnosis (or exclusion) of left atrial thrombus, as well as reduced costs for hospitalization and needs for TEE guided cardioversion, the presented combination

diagnostic method could potentially benefit AF patients. For AF patients with both negative results of cardiac CTA and D-dimer, cardioversion or pulmonary vein isolation could be warranted without undergoing TEE. For AF patients with both positive results of cardiac CTA and D-dimer, left atrium thrombus could be a highly probable diagnosis, and anti-coagulation therapy is necessary before invasive treatment. The presented diagnostic method could also make it a follow-up tool for AF patients instead of repeated TTE examination.

4.1. Limitations

The present study had some limitations. First, patients with other conditions that led to elevation of blood D-dimer level (acute coronary syndrome, peripheral artery diseases, pulmonary embolism, tumor, infectious diseases, hemorrhagic diseases, and diffuse intravascular clotting) and ongoing anticoagulation therapy were excluded from this study, limiting the clinical application of the combination diagnostic method in homologous circumstances. Furthermore, the enrolled patients were not scheduled for cardiac CTA with multiple scans or contrast injections due to ethical considerations, as extra radiation exposure and contrast agent usage could be hazardous. Thus, we were unable to compare the diagnostic efficacy of the presented method to that of the cardiac CTA using multiple scans or contrast injections. Further investigation is needed to compare these various cardiac CTA methods in clinical practice.

5. Conclusion

The presented combination diagnostic method comprising a combination of single-phase, single-contrast injection cardiac CTA and age-adjusted D-dimer assay had good diagnostic efficacy for the detection of LA/LAA thrombus in AF patients. The combination diagnostic method also had significantly better specificity and PPV than cardiac CTA alone. Further investigation is needed to compare the presented method to cardiac CTA with multiple scans or contrast injections.

Acknowledgements and interest statement

None declared.

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