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Review

Imaging of left heart intracardiac thrombus: clinical needs, current imaging, and emerging cardiac magnetic resonance techniques

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***Abstract*:** Intracardiac thrombus in the left atrium and atrial appendage (LA/LAA) and left ventricle (LV) increases the risk of systemic thromboembolism and causes potentially devastating diseases such as ischemic stroke and acute ischemia in abdominal organs and lower extremities. Detecting the presence and monitoring the resolution of left heart intracardiac thrombus are of vital importance for stratifying patients and guiding treatment decisions. Currently, echocardiography is the most frequently used method for the above clinical needs, followed by computed tomography. An increasing number of studies have been performed to investigate the value of cardiac magnetic resonance (CMR) as an alternative imaging modality given its several unique strengths. This article provides an overview of the clinical relevance of the LA/LAA and LV thrombus as well as the diagnostic performance of the current imaging modalities and emerging CMR techniques.

Keywords: cardiac magentic resonance, intracardiac thrombus, left heart

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Introduction

Assessment of intracardiac masses is a critical part of cardiac imaging. Intracardiac thrombus is the most common type of cardiac mass. Thrombus in the left ventricle (LV) or left atrium is of particular clinical concern due to significant risk of embolic events in the brain or other organs resulting in significant morbidity and mortality.[1] Left atrium and atrial appendage (LA/LAA) thrombus is prevalent in patients with atrial fibrillation (AF) and also may be associated with valvular disease.[2,3] LV thrombus is associated with severe myocardial dysfunction, which may occur in both ischemic and non-ischemic etiologies.[4] The presence of LA/LAA or LV thrombus typically requires adjustment in clinical management, and therefore detection and assessment of left chamber intracardiac thrombus are highly clinically relevant.[4]

There are multiple modalities currently available for imaging of intracardiac thrombus. Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) are the most frequently used methods.[5,6] TTE is inferior to TEE in visualizing LA/LAA thrombus, and apical thrombus may also be obscured by near-field clutter artifacts.[7,8] However, access to TEE is limited by its moderately invasive nature and is contraindicated in patients with significant esophageal disease.[9]

Contrast-enhanced cardiac computed tomography (CCT) identifies masses with high precision; however, tissue characterization is limited, as the appearance of tumor and thrombus is similar.[10] In addition, the risks of ionizing radiation exposure and contrast-related nephropathy limit broad application. Over the past decade, studies have demonstrated that cardiac magnetic resonance (CMR) has the potential to safely and accurately identify intracardiac thrombus without invasive measurement, radiation, or iodinated contrast exposure.[11,12] The aim of this article is to provide an overview of the clinical relevance of LA/LAA and LV thrombus and review the diagnostic performance of the current imaging modalities and

emerging CMR techniques for the identification of LA/LAA and LV thrombus.

Left atrial thrombus

Pathophysiology of LA/LAA thrombus

AF is one of the most common cardiac arrhythmias in the world.[13] The worldwide prevalence of AF in 2017 was estimated at 37,574 million cases in 2017.[14] Thromboembolic complications, especially stroke, are the main cause of death and disability in patients with AF, at a rate of nearly fivefold the general population.[1,15] Thrombus most frequently forms in the LAA due to poor blood movement during AF. While other left atrial locations are possible in the setting of concurrent pathology (e.g. valvular disease), more than 90% of atrial thrombi in patients with non-valvular AF are located in the LAA.[16,17] Compared with non-AF-related stroke, AF-related stroke showed more severe disability, higher fatality, and recurrence rate.[18,19]

The diagnosis of LA/LAA thrombus impacts clinical care. Anticoagulation is recommended for the treatment of confirmed thrombus in patients with AF, as well as prophylactic therapy in most patients. However, approximately one-third of eligible AF patients do not receive appropriate anticoagulant therapy. Nearly half of the cases were due to the physicians' clinical judgment, which may not always be based on evidence-based risk schemes and guidelines.[20] Even with appropriate medical therapy, 20–40% of AF patients with LAA thrombus have persistent thrombus.[2,21,22] Thus, accurate and non-invasive imaging techniques may be beneficial to monitor treatment response for intensification or alteration of therapy. On the other hand, ruling out the presence of LAA thrombus is of vital importance in patients prior to electrocardioversion, radiofrequency ablation, and LAA occlusion procedures due to risk of intraprocedural thromboembolic events.[23]

Conventional diagnostic modalities for LA/LAA thrombus

TEE is considered the gold standard for the detection of LA/LAA thrombus in patients with AF who are selected for undergoing electrocardioversion or pulmonary vein isolation.[24] A thrombus appears as an echo-dense material acoustically separate from the endocardium (Figure 1). Previous studies have shown that the prevalence of LAA thrombus detected by TEE is around 3.6–8.8% in AF patients under anticoagulation therapy.[25–28] Compared with TTE, TEE provides superior visualization of the LAA, with sensitivity and specificity as high as 100% and 99%, respectively.[29,30] However, TEE requires esophageal intubation which has rare but potentially serious complications like esophageal perforation.[31] Furthermore, the procedure requires experienced echocardiographers and support staff, is time-consuming, may cause patient discomfort, and has significant financial cost.[32] TEE also cannot provide essential information about pulmonary vein anatomy for pulmonary vein isolation studies, which frequently benefit from volumetric views of the pulmonary venous anatomy.[33]

The utility of TTE in the detection of LA/LAA thrombus is limited due to its low sensitivity.[34] However, with continued technological development and the use of harmonic imaging and administration of ultrasound contrast agents, the visualization and delineation of the LAA on TTE have been substantially improved.[35,36] Agoston *et al.*[37] showed that three-dimensional (3D) TTE has a better detection rate for LAA compared with two-dimensional (2D) TTE (68.1% *versus* 45.5%) in 204 consecutive patients. In a subgroup of 37 patients, thrombus was detected in 8 patients using both 3D TTE and TEE (kappa = 1.0). Karakus *et al.*[38] suggested that combined 2D TTE and 3D TTE may have comparable accuracy to TEE in evaluating LAA thrombus; however, this approach has not yet experienced significant clinical uptake, as the clinical consequences of missing intracardiac thrombus are high.

As CCT is often performed prior to AF ablation to assess the number, location, and size of the pulmonary veins, as well as the size and morphology of LA/LAA, many studies had proposed to use CCT as a non-invasive alternative method for screening LA/LAA thrombus.[39–42] With the use of contrast medium, thrombus is detected as a filling defect on initial and delayed image acquisition (Figure 2). Delayed image acquisition is critical, as reduced LAA filling rates can cause false-positive filling defects during first-pass perfusion. A meta-analysis published in 2013 demonstrated that the mean sensitivity and specificity of CCT in assessing LA/LAA thrombus were 96% and 92%, whereas the positive

predictive value and negative predictive value were 41% and 99%, respectively.[43] The diagnostic accuracy significantly improved from 94% to 99% in a sub-analysis of studies in which delayed imaging was performed. A recent study by Spagnolo *et al.*[44] evaluated the optimal delay time for data acquisition in a cohort of consecutive patients with persistent AF referred for radiofrequency ablation to differentiate between thrombus and effects of slow LAA filling. The study reported that 10 (4%) out of 260 patients were diagnosed with LAA thrombi. Among 63 patients with LAA early filling defects on CCT, 15 had a persistent defect at 1 min, 12 at 3 min, and 10 at 6 min after contrast injection. The sensitivity, specificity, and positive and negative predictive values were all 100% at 6-min delayed phase. In comparison with TEE, CCT has high temporal and spatial resolution, yet additional radiation burden and potential nephrotoxicity caused by required iodinated contrast agents cannot be ignored. Furthermore, irregular and fast heart rates in patients with AF can reduce the probability of high-quality image acquisition on CCT.[45]

CMR diagnosis of LA/LAA thrombus

CMR can be used for LA/LAA thrombus detection with or without contrast medium. The utility of non-enhanced turbo spin-echo double- or triple-inversion recovery sequences for the assessment of thrombus in the LAA was explored by Ohyama *et al.*[46] in 50 patients with nonrheumatic continuous AF and a history of cardioembolic stroke. CMR was found to have high intra- and interobserver reproducibility, with a high agreement in detecting LAA thrombus compared with TEE (overall kappa = 0.876, SE = 0.068). The authors also noticed that the thrombus sizes detected on CMR were consistently ≈20% larger than those on TEE. Another early study showed that the diagnostic accuracy of contrast-enhanced CMR in ruling out LAA thrombus was low due to insufficient spatial resolution.[47] Compared with TEE, the sensitivity of 2D saturation-recovery steady-state free precession sequence and 3D turbo fast low-angle shot in detecting LAA thrombus was 47% and 35%, respectively, and the specificity was 50% and 67%, respectively. Both 2D and 3D techniques overestimated the size of the thrombus compared with TEE measurements by 66% and 25%, respectively.

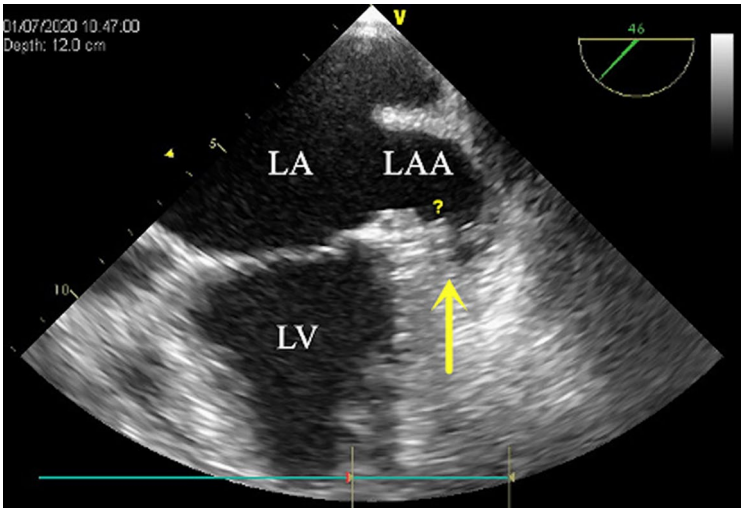

Figure 1. A 65-year-old man with permanent atrial fibrillation. Transesophageal echocardiography shows a thrombus in the left atrial appendage (arrow).

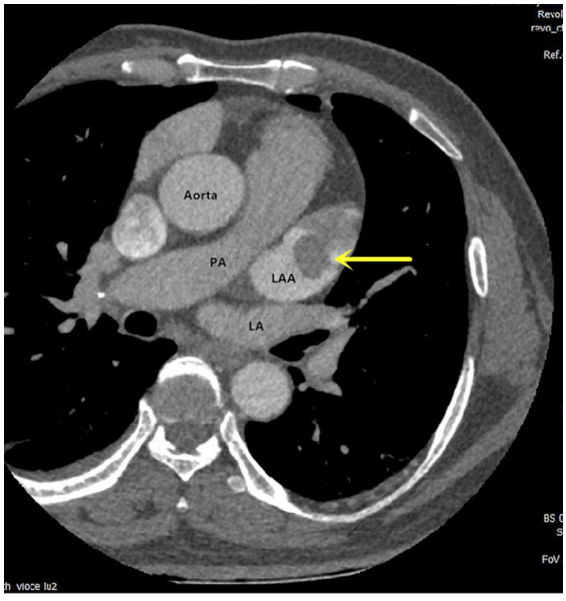

Figure 2. A 73-year-old man with permanent atrial fibrillation.
CT, computed tomography; LA, left atrium; LAA, left atrial appendage; PA, pulmonary artery.
Cardiac CT shows a thrombus in the LAA (arrow).

With recent advances in sequence development combined with the ability of paramagnetic contrast agents, an increasing number of studies have shown the improvement of CMR in diagnostic accuracy. Rathi *et al.*[48] compared the performance of 2D non-contrast cine images, 2D/3D

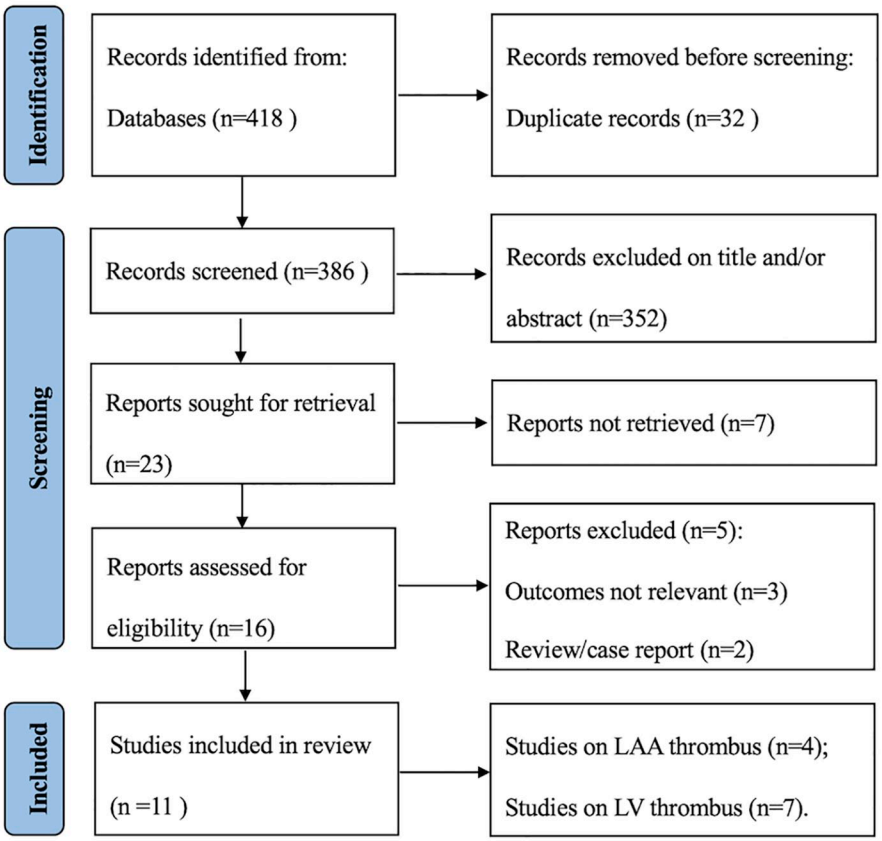

Figure 3. Flow diagram of literature search strategy.

contrast-enhanced CMR sequences, and TEE for the detection of LAA thrombus in 97 patients with AF. Both 2D and 3D contrast-enhanced CMR were positive for thrombus in 2 of the 97 patients with 100% concordance to TEE, whereas 2D cine-CMR was indeterminate in 6 patients. Kitkungvan *et al.*[49] used TEE as a reference standard to study the diagnostic performance of different CMR techniques in the detection of LAA thrombus in 261 patients for pulmonary venous anatomy mapping. Nine patients were diagnosed with LA/LAA thrombus using TEE. Long inversion time delayed enhancement CMR (DE-CMR) had the highest diagnostic accuracy (99.2%), sensitivity (100%), and specificity (99.2%), followed by contrast-enhanced magnetic resonance angiography (MRA) (accuracy, 94.3%; sensitivity, 66.7%; and specificity, 95.2%) and cine-CMR (accuracy, 91.6%; sensitivity, 66.7%; and specificity, 92.5%) with excellent interobserver agreement in all three techniques. The findings suggest that CMR could be an alternative imaging modality to TEE for the assessment of LA/LAA thrombus. The characteristics of the studies are summarized in Table 1. Relevant studies between 1 January 1972 and 1 January 2022 were searched on PubMed, Embase, Cochrane Library, and Medline. The detailed literature search strategy is shown in Figure 3.

A major advantage of CMR over echocardiography and CCT is its ability to characterize tissue, including differentiation of tissue and thrombus and identification of myocardial tissue scarring through delayed enhancement imaging.[50] DE-CMR now has high enough resolution to visualize scar in the LA wall.[51] Several studies have shown the feasibility of using DE-CMR to localize and quantify LA fibrosis that is associated with increased risk of cerebro-cardiovascular diseases and is a helpful indicator of the severity and prognosis of AF.[52–56]

Table 1. Summary of the characteristics of the LAA thrombus study.

Source	n	Study population	Modality	CMR Protocol	Findings
Ohyama *et al.*[46]	50	NVAF or cardioembolic stroke	CMR (1.5 T), TEE	Double- and triple-IR sequence	TEE identified 16 LAA thrombi; CMR identified 19 LAA thrombi
Mohrs *et al.*[47]	25	NVAF	CMR (1.5 T), TEE	2D True-FISP, 3D turbo FLASH	TEE identified 17 LAA thrombi 2D True-FISP: Sn 47%, Sp 50%, PPV: 73%, NPV: 25% 3D turbo FLASH: Sn 35%, Sp 67%, PPV: 75%, NPV: 27% 2D True-FISP + 3D turbo FLASH: Sn 44%, Sp 67%, PPV: 80%, NPV: 29%
Rathi *et al.*[48]	97	NVAF	CMR (1.5 T), TEE	2D non-contrast cine, 2D/3D contrast-enhanced CMR	TEE and CMR identified 2 LAA thrombi; 2D cine-CMR images were indeterminate in 6 patients
Kitkungvan *et al.*[49]	261	NVAF	CMR (1.5 T or 3.0 T), TEE	Cine, CE-MRA, long TI DE-CMR	TEE identified 9 LAA thrombi Cine: Sn 66.7%, Sp 92.5% CE MRA: Sn 66.7%, Sp 95.2% Long TI DE-CMR: Sn 100% and Sp 99.2%

3D turbo FLASH, three-dimensional turbo fast low-angle shot; CE-MRA, contrast-enhanced magnetic resonance angiography; CMR, cardiac magnetic resonance; IR, inversion recovery; LAA, left atrial appendage; long TI DE, long inversion time delayed enhancement; NPV, negative predictive value; NVAF, nonvalvular atrial fibrillation; PPV, positive predictive value; Sn, sensitivity; Sp, specificity; TEE, transesophageal echocardiography; True-FISP, true fast imaging with steady state precession.

LV thrombus

Pathophysiology of LV thrombus

LV thrombus may lead to embolic complications such as stroke, with devastating consequences.[4] The main risk factors for LV thrombus development are the duration of myocardial ischemia, infarct size, and reduced cardiac function.[4] Ventricular cavity dilation, wall akinesia and dyskinesia, and the formation of LV aneurysm all result in stasis of blood within the LV, which leads to LV thrombus formation.[57] The incidence of LV thrombus after myocardial infarction ranges from under 2%[58] to over 34%.[59] In patients with significant LV dysfunction, the incidence of LV thrombus ranges from 7% to 26%,[60,61] and it can reach as high as 57.1% in patients with left ventricular ejection fraction (LVEF) below 20%.[62] LV thrombus has a dynamic nature of development and resolution,[63,64] which requires active monitoring to guide anticoagulation therapy to balance risks of embolization *versus* bleeding.

Conventional diagnostic modalities for LV thrombus

TTE is currently the first choice for assessing the structural consequences of myocardial infarction owing to its wide availability and excellent cost-effectiveness balance.[65] LV thrombus is identified as a discrete echocardiographic mass seen in the LV with well-defined margins that are distinct from the endocardium and seen throughout systole and diastole in an area with corresponding significant LV regional or global wall motion abnormalities (Figure 4).[66] Unfortunately, routine TTE detects LV thrombus only based on anatomic appearance, resulting in low sensitivity.[67,68] Compared with DE-CMR, the sensitivity and specificity of TTE in diagnosing LV thrombus were 33% and 91% in patients with impaired systolic function (LVEF <50%).[60] Intravenous echo contrast is frequently used during TTE to improve the diagnostic assessment of LV thrombus. Studies reported contrast echo sensitivity of 61–64% compared with 33–35% of non-contrast echo.[69,70] Mural thrombus and small thrombus are still sub-optimally visualized by TTE.[70]

TEE has a limited role in the detection of LV thrombus because the apex is farthest from the transducer, and the apex is often foreshortened and not well visualized.[66] In 361 patients with ischemic heart disease who had surgical and pathological confirmation of the presence (106, 29%) or absence of LV thrombus, TEE showed 40 ± 14% sensitivity and 96 ± 3.6% specificity for thrombus detection.[68]

CCT is a straightforward and widely available diagnostic tool with less operator/patient dependency compared with TTE.[10] A quantitative study of 31 patients found that the CT attenuation of the myocardial wall was significantly higher than that of the thrombus.[71] A threshold of 65 HU yielded sensitivity, specificity, and positive and negative predictive values of 94%, 97%, 94%, and 97%, respectively, to differentiate LV thrombus from the myocardial wall. A few case reports showed the use of CCT in detecting LV thrombus that was initially missed by echocardiography.[72,73]

CMR diagnosis of LV thrombus

CMR is considered the reference technique in detecting LV thrombus.[74] With a high spatial resolution for morphological definition of the LV thrombus and high soft-tissue contrast, CMR showed higher sensitivity for detecting LV thrombus when compared with TTE. A meta-analysis recently reported that the incidence of LV thrombus detected by CMR in ST-elevation myocardial infarction (STEMI) and anterior STEMI patients was 6.3% and 12.2%, respectively,[11] which is more than twice the incidence reported by TTE.[75] The study also showed that the sensitivity of TTE to detect LV thrombus was 29% with a specificity of 98%.[11] In a retrospective study of 171 patients with a history of coronary artery disease, contrast-enhanced CMR sequences were compared with TTE for diagnostic accuracy.[76] TTE revealed LV thrombus formation in 35 patients, while 43 were identified by CMR. LV thrombus was missed by TTE in one patient with an LVEF of 30–40% and in seven patients with an LVEF <30%. These results suggest that TTE may be suboptimal for diagnosis, particularly in significantly reduced ejection fraction. Srichai *et al.*[68] found that in 361 patients with surgically and pathologically confirmed presence or absence of LV thrombus, contrast-enhanced CMR provided the highest sensitivity and specificity (88 ± 9% and 99 ± 2%, respectively) compared with TTE and TEE. Among different CMR sequences, contrast-enhanced inversion recovery gradient-echo fast low-angle-shot sequence was found to be superior to dark-blood-prepared half-Fourier acquisition single-shot turbo spin-echo sequence and fast imaging steady-state free precession cine sequence in revealing intracardiac thrombi.[77] A systematic review analyzed seven studies and found that DE-CMR was the most accurate modality in detecting LV thrombus, with a sensitivity of 88% and specificity of 99%, followed by cine-CMR with a sensitivity of 58–79% and specificity of 99%.[78] The result is in line with the study by Surder *et al.*[79] that DE-CMR was superior to cine-CMR in the detection of LV thrombus. The characteristics of the studies are summarized in Table 2. The detailed literature search strategy is shown in Figure 3.

CMR can also be used in evaluating the evolution of LV thrombus. In 194 STEMI patients who had undergone primary percutaneous coronary intervention (PCI) with stent implantation, CMR was performed at 2–7 days and repeated at 4 months after primary PCI.[67] At baseline, 17 (8.8%) patients had LV thrombus. At 4-month follow-up, LV thrombus persisted in only 2 of the original 17 patients but spontaneously occurred in an additional 12 patients. Another study of 392 STEMI patients showed that 5% of the patients displayed LV thrombus at 1 week, three-quarters of which resolved at 6 months.[80] Moreover, LV thrombus was newly detected in 2% of the total patients at 6 months.

The use of CMR in evaluating the age of thrombus has also been explored, which may help assess the risk of embolism. An acute thrombus usually has intermediate signal intensity on both T1- and T2-weighted images, but it is rare to obtain MR images at the very acute phase. In the subacute phase, thrombus is typically T1- and T2-hyperintense. In chronic thrombi, the signal intensity decreases on both T1- and T2-weighted images (Figure 5). It has been shown that T1 mapping may differentiate between recent (<1 week) and old (>1 month) thrombi.[81]

CMR has been investigated for its capability of detecting the cardioembolic sources of ischemic stroke.[82] In a study of 106 patients (85 with ischemic stroke and 21 with transient ischemic attack), TTE detected LV thrombus in two patients, while two

Table 2. Summary of the characteristics of the LV thrombus study.

Source	n	Study population	Modality	CMR Protocol	Findings
Weinsaft *et al.*[60]	243	Impaired systolic function (LVEF <50%)	CMR (1.5 T), TTE	Cine, DE-CMR	DE-CMR identified 24 LV thrombi TTE: Sn 91%, Sp 33%, PPV: 29%, NPV: 93%
Delewi *et al.*[67]	194	Post MI	CMR (1.5 T), TTE	Cine, DE-CMR	DE-CMR identified 17 LV thrombi TTE: Sn 21–24%, Sp 95–98%
Srichai *et al.*[68]	361	Post MI	CMR (1.5 T), TTE, TEE, pathology	Cine, DE-CMR	Pathology identified 106 LV thrombi DE-CMR: Sn 88%, Sp 99% TTE: Sn 23%, Sp 96% TEE: Sn 40%, Sp 96%
Weinsaft *et al.*[69]	201	Post MI	CMR (1.5 T), TTE	Cine, DE-CMR	DE-CMR identified 17 LV thrombi. Noncontrast TTE: Sn 35%, Sp 98% Contrast TTE: Sn 64%, Sp 99%
Weinsaft *et al.*[70]	121	Post MI or heart failure	CMR (1.5 T), TTE	Cine, DE-CMR	DE-CMR identified 24 LV thrombi. Noncontrast TTE: Sn 33%, Sp 82%, PPV: 57%, NPV: 85% Contrast TTE: Sn 61%, Sp 92%, PPV: 93%, NPV: 91% Cine: Sn 79%, Sp 99%, PPV: 95%, NPV: 95%
Staab *et al.*[76]	171	Coronary heart disease	CMR (1.5 T), TTE	Cine, HASTE, SSFP, black-blood T2 TSE, True-FISP	DE-CMR identified 43 LV thrombi TTE identified 35 LV thrombi.
Surder *et al.*[79]	177	Post MI	CMR (1.5 T), TTE ($n = 113$)	Cine, DE-CMR	DE-CMR identified 11 LV thrombi TTE: Sn 80%, Sp 96.1%.

CMR, cardiac magnetic resonance; DE, delayed enhancement; HASTE, half-Fourier acquisition single shot turbo spin echo; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity; SSFP, steady-state free precession; TEE, transesophageal echocardiography; True-FISP, true fast imaging with steady state precession; TSE, turbo-spin-echo; TTE, transthoracic echocardiograph.

additional cases were detected after the use of cine- and DE-CMR. The value of contrast-enhanced CMR in etiology workup was further explored in a cohort of 797 consecutive ischemic stroke patients.[83] Sixty patients who had previous myocardial infarction or LV dysfunction (LVEF <50%) underwent contrast-enhanced CMR, and LV thrombus was seen in 12 patients, whereas only 1 had been detected on TTE. The findings suggest that CMR might be a more sensitive diagnostic method for LV thrombus in the diagnostic workup in patients with potential cardioembolic stroke.

Challenges of CMR in clinical practice

So far, no large prospective study involving multiple centers has compared the diagnostic value of CMR and conventional imaging modalities for intracardiac thrombus detection. There is also no consensus regarding the use of CMR for an

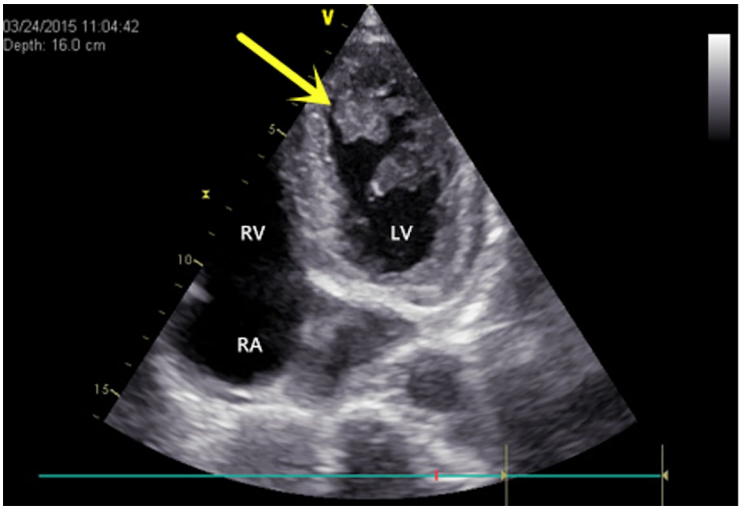

Figure 4. A 54-year-old man with chronic systolic heart failure. Transthoracic echocardiography showed a thrombus in the left ventricle (arrow).

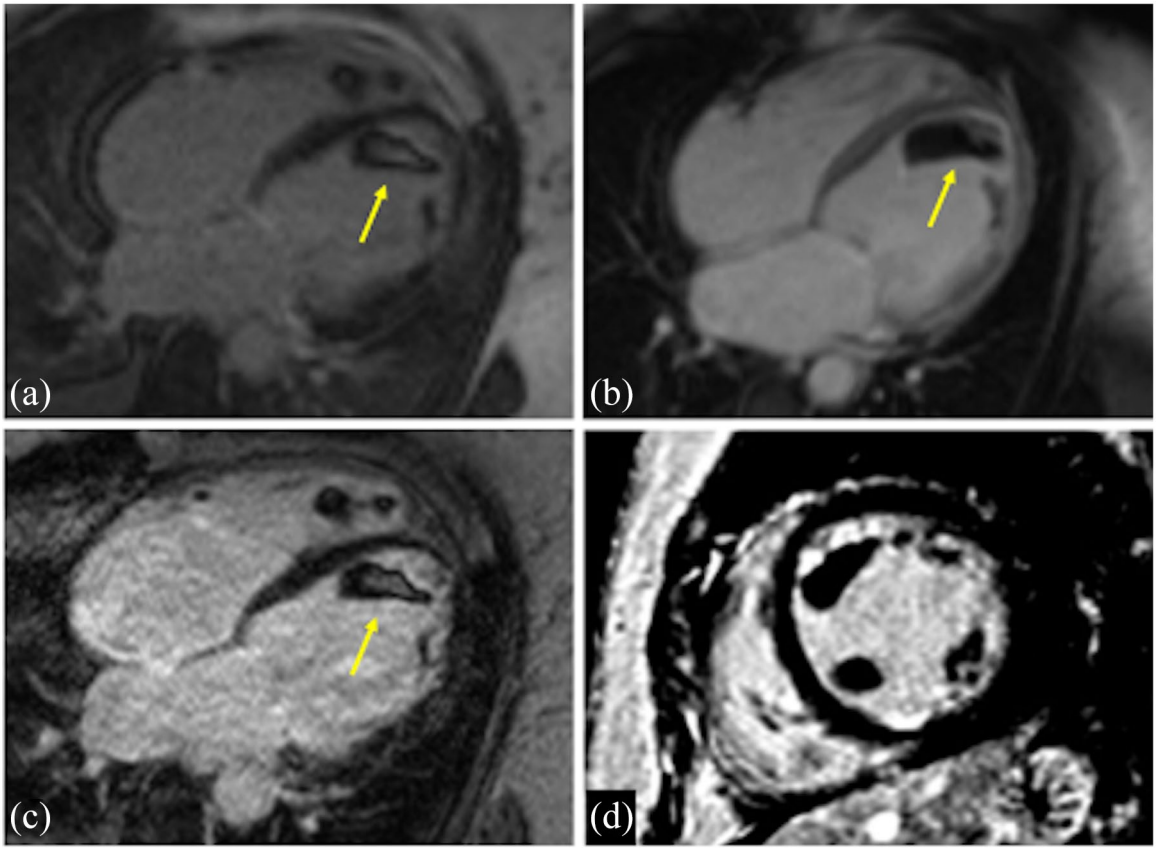

Figure 5. A 54-year-old woman with biventricular non-ischemic cardiomyopathy. Images show left ventricular apical thrombus (yellow arrow). (a) Four-chamber view, steady-state free precession delayed enhancement; (b) four-chamber early gadolinium enhancement with long inversion time, highlighting differential composition of thrombus; (c) four-chamber view, turbo FLASH delayed enhancement; (d) short-axis view, inversion recovery gradient-echo late enhancement with phase-sensitive inversion recovery reconstruction.

efficient and comprehensive assessment of left heart intracardiac thrombus. Despite the high diagnostic accuracy of CMR, current barriers include long acquisition time and breath-holding, which can be difficult for severely ill patients. In addition, cost, availability, renal dysfunction, and technical expertise may also limit its widespread use. However, given these barriers to LA/LAA and LV thrombus detection, improving access and performance of CMR is critical, as well as identifying optimal patients for imaging by CMR.

Conclusion

Detection of intracardiac thrombus has a major impact on clinical care of patients with AF and patients at risk of LV thrombus, with changes in care necessary for protecting against cardioembolic morbidity and mortality. Our literature review suggests that CMR is the most accurate modality for detecting LV thrombus. Although echocardiography is currently the most widely used imaging modality in detecting LA/LAA thrombus, with the development of new techniques, CMR may provide an alternative diagnostic modality without the need for esophageal intubation, thus improving safety and patient comfort.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Peng Chang: Conceptualization; Investigation; Resources; Visualization; Writing – original draft; Writing – review & editing.

Jiayu Xiao: Writing – original draft; Writing – review & editing.

Zhehao Hu: Investigation; Resources; Writing – review & editing.

Alan C. Kwan: Conceptualization; Visualization; Writing – review & editing.

Zhaoyang Fan: Conceptualization; Resources; Supervision; Writing – review & editing.

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Conflict of interest statement

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Availability of data and materials

Not applicable.

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