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Detection of Left Ventricular Thrombus by Delayed-Enhancement Cardiovascular Magnetic Resonance

Prevalence and Markers in Patients With Systolic Dysfunction

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Objectives This study sought to assess the prevalence and markers of left ventricular (LV) thrombus among patients with systolic dysfunction.

Background Prior studies have yielded discordant findings regarding prevalence and markers of LV thrombus. Delayed-enhancement cardiovascular magnetic resonance (DE-CMR) identifies thrombus on the basis of tissue characteristics rather than just anatomical appearance and is potentially highly accurate.

Methods Prevalence of thrombus by DE-CMR was determined in 784 consecutive patients with systolic dysfunction (left ventricular ejection fraction [LVEF] <50%) imaged between July 2002 and July 2004. Patients were recruited from 2 separate institutions: a tertiary-care referral center and an outpatient clinic. Comparison to cine-cardiovascular magnetic resonance (CMR) was performed. Follow-up was undertaken for thrombus verification via pathology evaluation or documented embolic event within 6 months after CMR. Clinical and imaging parameters were assessed to determine risk factors for thrombus.

Results Among this at-risk population (age 60 ± 14 years; LVEF 32 ± 11%), DE-CMR detected thrombus in 7% (55 patients) and cine-CMR in 4.7% (37 patients, $p < 0.005$). Follow-up was consistent with DE-CMR as a better reference standard than cine-CMR, including 100% detection among 5 patients with thrombus verified by pathology (cine-CMR, 40% detection), and logistic regression analysis testing the contributions of DE-CMR and cine-CMR simultaneously, which showed that only the presence of thrombus by DE-CMR was associated with follow-up end points ($p < 0.005$). Cine-CMR generally missed small intracavitary and small or large mural thrombus. In addition to traditional indices such as low LVEF and ischemic cardiomyopathy, multivariable analysis showed that increased myocardial scarring, an additional parameter available from DE-CMR, was an independent risk factor for thrombus.

Conclusions In a broad cross section of patients with systolic dysfunction, thrombus prevalence was 7% by DE-CMR and included small intracavitary and small or large mural thrombus missed by cine-CMR. Prevalence increased with worse LVEF, ischemic etiology, and increased myocardial scarring. (J Am Coll Cardiol 2008;52:148–57)

Patients with heart failure are at increased risk for thromboembolic events that may result in major clinical sequelae. Left ventricular (LV) thrombus provides a substrate for events and a rationale for anticoagulation (1). However, prior echocardiography studies have yielded discordant results regarding thrombus prevalence. Among populations with similar degrees of systolic dysfunction, studies have reported over a 20-fold difference in prevalence, ranging from 2.1% to 50% (2–4). Moreover, when thrombus is identified, discordant findings have been reported concerning the risk of future embolic events (4–7). One potential reason for these disparate findings may relate to limitations of echocardiography, which has been the predominant modality used to identify LV thrombus. Prior echocardiography studies have reported significant interobserver variability in diagnosing LV thrombus (8). Others have shown

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that up to 46% of echocardiograms may be diagnostically inconclusive for thrombus (9). As the benefits of anticoagulation for treatment of thrombus are counterbalanced by hemorrhagic risk, patient management and outcome may be improved by a better understanding of the prevalence and risk factors for LV thrombus.

Cardiovascular magnetic resonance (CMR) provides high-resolution images of anatomy with improved reproducibility as compared with echocardiography (10). However, a simple anatomical approach may be relatively insensitive for thrombus because thrombus may be indistinguishable from surrounding myocardium (11). Delayed-enhancement cardiovascular magnetic resonance (DE-CMR) using gadolinium contrast has been well validated as a means of characterizing viable and infarcted myocardium on the basis of contrast uptake patterns (12). More recently, this technique has also shown promise as a sensitive method for detecting LV thrombus (13,14); DE-CMR differentiates thrombus from surrounding myocardium as thrombus is avascular and thus characterized by an absence of contrast uptake (13,14). In studies of selected groups, DE-CMR identified thrombus not detected by anatomical imaging using either cine-CMR or echocardiography (13,14). At present, however, DE-CMR has not been used to study thrombus in a general, unselected population at risk for thrombus, such as patients with systolic dysfunction. The aims of the current study were 3-fold: first, to assess the prevalence of thrombus using DE-CMR among a broad cross section of patients with systolic dysfunction; second, to compare DE-CMR to anatomical imaging using cine-CMR; and third, to determine predisposing risk factors for LV thrombus formation by evaluating numerous clinical and imaging parameters.

Methods

Population. The study population consisted of consecutive patients with systolic dysfunction who underwent cine- and DE-CMR during a single imaging session between July 2002 and July 2004. Patients were recruited from the Duke Cardiovascular Magnetic Resonance Center (Durham, North Carolina), a tertiary-care referral center, or the Nashville Cardiovascular Magnetic Resonance Institute (Brentwood, Tennessee), a clinical outpatient facility. Systolic dysfunction was defined as a left ventricular ejection fraction (LVEF) below 50% measured quantitatively on cine-CMR. Patients were referred to CMR most commonly for evaluation of myocardial viability, assessment of myocardial infarction, or evaluation of scar patterns in cases of suspected cardiomyopathy. Institutional review board approval was obtained at both participating sites; all patients provided written informed consent.

On the day of the CMR procedure, a complete medical history including cardiac risk factors, medication regimen, and information regarding prior coronary revascularization, myocardial infarction, and thromboembolic events, was obtained to assess potential predictors of thrombus. Additionally, clinical records were reviewed including prior X-ray coronary angiography results, and established criteria were used to classify the etiology of systolic dysfunction as ischemic or nonischemic: patients were considered to have ischemic cardiomyopathy if there was angiographically significant disease (≥70% stenosis of a major epicardial artery or ≥50% of the left main artery [15]), history of biomarker proven myocardial infarction, or evidence of ischemia on clinical stress testing (16). All other patients were classified as having nonischemic cardiomyopathy. The majority of patients (86%) had previously undergone coronary angiography.

Abbreviations and Acronyms

CMR = cardiovascular magnetic resonance
CVA = cerebrovascular accident
DE-CMR = delayed-enhancement cardiovascular magnetic resonance
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
TI = inversion time
TIA = transient ischemic attack

Clinical follow-up and validation of imaging. Follow-up was performed prospectively in all patients to provide data regarding the choice of a truth standard for the diagnosis of LV thrombus. Specifically, all records were carefully reviewed in patients who had direct inspection and pathology evaluation of the left ventricle (i.e., patients who underwent heart transplantation, LV aneurysmectomy, or post-mortem necropsy) within 6 months after CMR without intervening events. Additionally, all specimens were re-examined thoroughly by a cardiovascular pathologist (C.S.). Follow-up was also performed for identification of clinical embolic events that were highly suggestive of the presence of LV thrombus. These events consisted of a documented cerebrovascular accident (CVA) or transient ischemic attack (TIA) that prompted the initial clinical workup or occurred within 6 months after CMR. A relatively short follow-up time of 6 months was chosen to increase the likelihood that clinical events were related to findings at the time of imaging. Clinical information was obtained via: 1) telephone interview with the patient, or, if deceased, with family members; 2) contact with the patient's physician; and 3) hospital records. Death was not considered evidence of LV thrombus unless directly linked to a cerebrovascular embolic event.

Image acquisition. MAGNETIC RESONANCE IMAGING. 1.5-T clinical scanners (Siemens Sonata, Siemens, Malvern, Pennsylvania) with phased-array coil systems were used. In all patients, CMR consisted of 2 components as previously described (17). Briefly, cine-CMR was performed for anatomical and functional assessment using a steady-state free-precession sequence (repetition time, 3.0 ms; echo time, 1.5 ms; in-plane spatial resolution, 1.7 × 1.4 mm; temporal resolution, 35 to 40 ms), and DE-CMR was performed for tissue characterization using a segmented inversion-recovery sequence (18) (in-plane spatial resolution, 1.8 × 1.3 mm; temporal resolution, 160 to 200 ms) 10 min after contrast administration (gadoverset-

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amide, 0.15 mmol/kg). Cine- and DE-CMR images were obtained in matching short- and long-axis planes (slice thickness, 6 mm). Short-axis images were acquired every 1 cm (gap, 4 mm) throughout the entire LV. Long-axis images were obtained in standard 2-, 3-, and 4-chamber orientations.

For DE-CMR, inversion times were adjusted in the standard fashion to null viable myocardium (17). Additionally, for images with filling defects that were suspicious for thrombus, serial imaging was performed at 10-min intervals for at least 30 min post-contrast to verify absence of contrast uptake (19).

DE-CMR thrombus identification and "long-inversion time (TI)" imaging. Thrombus was diagnosed on DE-CMR as an LV mass with post-contrast inversion-recovery characteristics consistent with avascular tissue (14,19). Typically, this meant that thrombus was easily identified as a low signal-intensity mass surrounded by high signal-intensity structures such as cavity blood and/or hyperenhanced myocardial scar (14). However, prior experience at our center has shown that occasionally the diagnosis may be less straightforward. With conventional DE-CMR, both viable myocardium and thrombus will appear relatively dark and may be difficult to distinguish from one another. Although contrast uptake is low in viable as compared with infarcted myocardium, it is not zero, as is the case with avascular tissue such as thrombus. Thus, using standard DE-CMR with an inversion time tailored to null viable myocardium, thrombus may not appear homogeneously black but instead have an "etched" appearance (19) with a black border and a central gray zone, which may complicate the diagnosis (Fig. 1) (standard DE-CMR). The difference in contrast uptake between viable myocardium and thrombus, however, can be used to improve the conspicuity of thrombus. For the purposes of this study, a modified DE-CMR sequence was designed in which the inversion time was increased from that needed to null viable myocardium (approximately 350 ms) to a fixed time of 600 ms, which nulls avascular tissue such as thrombus (19). With this "long inversion time" (long-TI) sequence, regions with contrast uptake such as viable myocardium increase in image intensity (i.e., appear gray rather than black), thrombus appears homogeneously black, and there is improved thrombus delineation (Fig. 1). Because standard DE-CMR was necessary for the assessment of myocardial viability and long-TI imaging required additional breath-holds, scanner operators were instructed to perform long-TI DE-CMR judiciously (31% of patients), when additional imaging would clarify the presence or absence of thrombus.

Data analysis. THROMBUS ASSESSMENT. All images were interpreted by consensus of 2 experienced readers (both level-3 trained in CMR) who were blinded to subject identifiers and clinical history. A pre-designated third reader was consulted in cases of interpretive discordance (cine-CMR 1%, DE-CMR 3%). Studies were read in random order. Cine- and DE-CMR were interpreted independently of each other.

For DE-CMR, thrombus morphology was classified as either mural (if borders were contiguous with adjacent endocardial contours) or intracavitary (borders were distinct from endocardial contours with protrusion into LV cavity) (6). Thrombus volume was measured quantitatively via planimetry. Thrombus location was scored based on adjacent myocardial segments using a standard American Heart Association 17-segment LV model. Previously established criteria (13,19) were used to distinguish thrombus from an area of acute myocardial infarction with microvascular obstruction (20), which may also appear as a filling defect. In brief, differentiating features included: 1) surrounding structures (no-reflow zones should be completely encompassed in 3-dimensional space by hyperenhanced myocardium or LV cavity, this is not an absolute finding for thrombus); 2) appearance (no-reflow occurs within the myocardium, thrombus can occur in the LV cavity, and features such as protruding structures and abrupt transitions suggest thrombus); and 3) stability of size on consecutive DE-CMR acquisitions (no-reflow size shrinks from contrast fill-in at the periphery, thrombus size is stable).

For cine-CMR, LV thrombus was diagnosed using established anatomical criteria (21). Thrombus was defined as a mass within the LV cavity with margins distinct from ventricular endocardium and distinguishable from papillary muscles, chordae, trabeculations, or technical artifact. Thrombus was excluded based on inspection of both short- and long-axis views.

Imaging markers of thrombus. CMR indices of LV function, geometry, and scarring were measured to determine whether these parameters were related to the presence of thrombus. The LVEF and LV volumes were quantitatively measured on the basis of end-diastolic and -systolic endocardial contours from the stack of short-axis cine images. Regional wall motion and scarring were assessed on a standard 17-segment model using previously described methods (17). Regional function on cine-CMR was graded on a 5-point scale as follows: 0 = normal contraction; 1 = mild-to-moderate hypokinesia; 2 = severe hypokinesia; 3 = akinesia; 4 = dyskinesia. Cine-CMR was also scored for the presence of LV aneurysm, defined as a discrete akinetic or dyskinetic bulge interrupting the normal LV contour in diastole and systole (22). Regional scarring based on area of hyperenhanced (bright) myocardium on DE-CMR was graded on a 5-point scale as follows: 0 = no hyperenhancement; 1 = 1% to 25%; 2 = 26% to 50%; 3 = 51% to 75%; 4 = 76% to 100%. Global scar size as a percentage of LV myocardium was calculated by summing the segmental scores (each weighted by the midpoint of the range of hyperenhancement) and dividing by the total number of regions (23).

Statistical methods. Normally distributed continuous data were expressed as mean ± SD and between-group comparisons were performed using 2-sample *t* tests. Comparisons of non-normally distributed continuous data such as thrombus volumes were also made using 2-sample *t* tests after

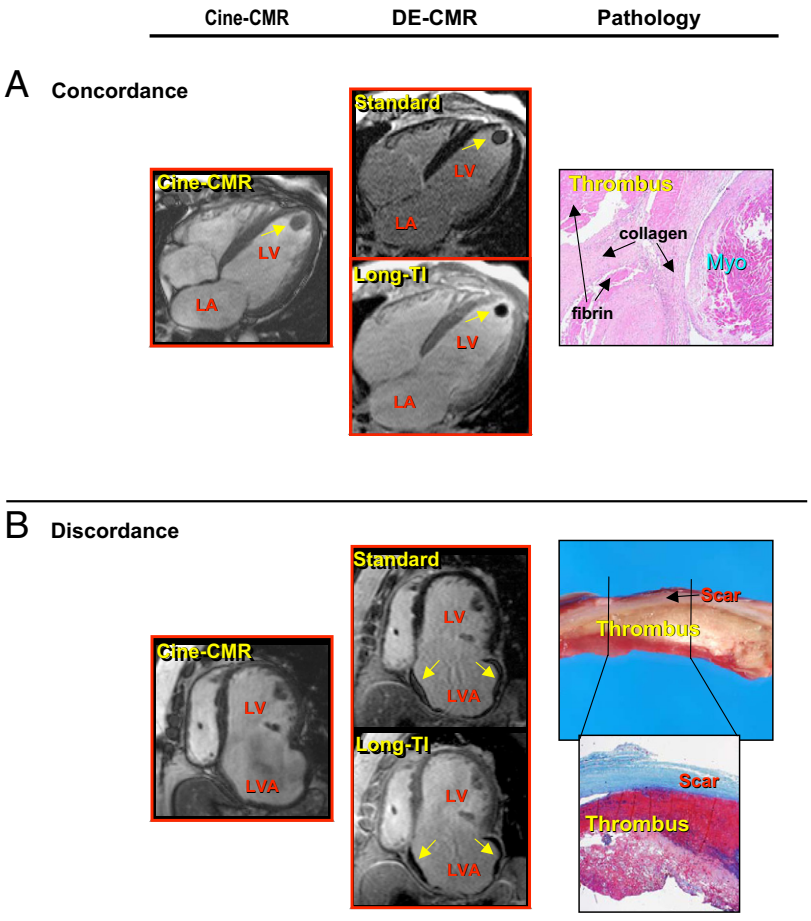

Figure 1 DE-CMR Compared With Cine-CMR for Identification of Pathology-Verified Thrombus

(A) Typical images from a patient with concordant findings by DE-CMR and cine-CMR. Both techniques show an intracavitary thrombus within the LV apex (4-chamber views). Pathology (hematoxylin and eosin stain, low power) confirmed the presence of thrombus with organizing features, including prominent collagen and fibrin content. **(B)** Typical images from a patient with discordant findings by DE-CMR and cine-CMR. DE-CMR demonstrates a large mural thrombus adherent to a left ventricular inferior wall aneurysm, whereas cine-CMR shows no evidence of thrombus (midventricular short-axis views). Thrombus was verified by pathology (gross examination **[overlay]** and histopathology [**inset**, Masson trichrome stain]). Both patient examples show that thrombus may have an etched appearance with a black border and a central gray zone on standard inversion time (TI) DE-CMR, whereas it appears homogeneously black on long-TI imaging. See text for details. Thrombus denoted by **yellow arrows**. CMR = cardiac magnetic resonance; DE-CMR = delayed-enhancement cardiovascular magnetic resonance; LA = left atrium; LV = left ventricle; LVA = left ventricular aneurysm; Myo = myocardium.

initial logarithmic transformation; results are expressed as the antilog of the mean and 95% confidence intervals. Chi-square tests were used to compare discrete data between groups; in those cases in which the expected cell count was <5, the Fisher exact test was used. The McNemar test was used to compare the prevalence of thrombus by DE- and cine-CMR. To test the validity of the imaging techniques for the presence of LV thrombus, the relationship between follow-up end points and the detection of thrombus by DE- and cine-CMR, separately and then together, were evaluated using logistic regression analysis.

Two separate multivariable approaches were used to analyze the value of clinical variables for predicting the presence of thrombus by DE-CMR. In the first approach, the best clinical model was identified using stepwise logistic regression analysis in which all clinical variables in Table 1 were considered. Then, the incremental value of adding LVEF by cine-CMR and myocardial scarring by DE-CMR were assessed using likelihood ratio tests. In the second approach, we identified the best overall model in which all clinical and CMR variables were simultaneously considered. All statistical tests were 2-tailed; values of $p < 0.05$ were regarded as significant.

Results

Population characteristics. The study population was composed of 784 consecutive patients. Clinical and imaging char-

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Table 1 Baseline Patient Characteristics

	Overall (n = 784)	DE-CMR Thrombus Present (n = 55)	DE-CMR Thrombus Absent (n = 729)	p Value
Clinical parameters				
Age (yrs)	60.4 ± 14.1	58.7 ± 10.4	60.4 ± 14.4	0.20
Male gender	552 (70%)	39 (71%)	513 (70%)	0.93
Atherosclerosis risk factors				
Diabetes mellitus	228 (29%)	17 (31%)	211 (29%)	0.76
Hypertension	469 (60%)	30 (55%)	439 (60%)	0.41
Tobacco use	214 (27%)	20 (36%)	194 (27%)	0.12
Hypercholesterolemia	400 (51%)	30 (55%)	370 (51%)	0.59
Prior myocardial infarction				
Within 1 month of CMR	133 (17%)	16 (29%)	117 (16%)	**0.01**
Within 6 months of CMR	147 (19%)	17 (31%)	130 (18%)	**0.02**
Any history before CMR	377 (48%)	44 (80%)	333 (46%)	**<0.0001**
Coronary revascularization	335 (43%)	30 (55%)	302 (41%)	0.06
Percutaneous intervention	208 (27%)	18 (33%)	190 (26%)	0.28
Coronary artery bypass grafting	189 (24%)	19 (35%)	170 (23%)	0.06
Ischemic cardiomyopathy	555 (71%)	51 (93%)	504 (69%)	**0.0002**
Atrial fibrillation or atrial flutter	119 (15%)	6 (11%)	113 (15%)	0.36
Lifetime history of prior cerebrovascular event				
CVA	59 (8%)	5 (9%)	54 (7%)	0.65
TIA	38 (5%)	2 (4%)	36 (5%)	0.66
CVA or TIA	92 (12%)	7 (13%)	85 (12%)	0.81
Chronic anticoagulation				
Aspirin	511 (65%)	37 (67%)	474 (65%)	0.74
Warfarin	136 (17%)	14 (25%)	122 (17%)	0.10
Thienopyridines	112 (14%)	8 (15%)	104 (14%)	0.95
Heart failure medications				
Beta-blocker	511 (65%)	35 (64%)	476 (65%)	0.80
ACE inhibitor	454 (58%)	33 (60%)	421 (58%)	0.74
Angiotensin receptor blocker	85 (11%)	6 (11%)	79 (11%)	0.99
Loop diuretic	320 (41%)	25 (45%)	295 (40%)	0.47
Spironolactone	122 (16%)	9 (16%)	113 (16%)	0.86
Digoxin	189 (24%)	13 (24%)	176 (24%)	0.93
Nitroglycerin	194 (25%)	18 (33%)	176 (24%)	0.15
CMR				
LV function and morphology				
Ejection fraction (%)	31.8 ± 10.8	26.1 ± 11.0	32.2 ± 10.7	**<0.0001**
Percent LV with akinesia or dyskinesia	24.4 ± 19.2	34.8 ± 18.4	23.6 ± 19.2	**<0.0001**
End-diastolic volume (ml)	207.1 ± 85.9	242.6 ± 120.1	204.5 ± 82.3	**0.02**
End-systolic volume (ml)	146.0 ± 80.2	185.6 ± 115.8	143.0 ± 76.2	**0.01**
Aneurysm present	101 (13%)	15 (27%)	86 (12%)	**0.001**
LV scarring				
Scar size (% LV)	15.6 ± 14.3	24.1 ± 13.7	15.0 ± 14.1	**<0.0001**
Percent LV with >50% transmural scar	14.2 ± 15.9	24.5 ± 15.3	13.4 ± 15.6	**<0.0001**

Numbers in **bold** indicate p values <0.05.

ACE = angiotensin-converting enzyme; CVA = cerebrovascular accident; CMR = cardiovascular magnetic resonance; DE-CMR = delayed-enhancement cardiovascular magnetic resonance; LV = left ventricular; TIA = transient ischemic attack.

acteristics of the overall population at the time of CMR are shown in Table 1. Nearly one-half had a history of a prior myocardial infarction, and 71% had ischemic cardiomyopathy. Few patients had a history of a prior cerebrovascular event. Seventeen percent of patients were on chronic warfarin therapy at the time of CMR; the most common indication was for atrial fibrillation, which included 43% of patients on warfarin. In 2%, warfarin was used for treatment of suspected LV thrombus.

Cine-CMR showed evidence of advanced systolic dysfunction. The mean LVEF was 31.8 ± 10.8%. Left ventricular aneurysms were present in 13%. Myocardial scarring was shown by DE-CMR in 73%; mean scar size was 15.6 ± 14.3% of total LV myocardium.

Comparison of DE-CMR with cine-CMR for thrombus detection. PREVALENCE. Thrombus was identified by DE-CMR in 55 patients, resulting in an overall prevalence of 7.0%. The prevalence at Duke Medical Center was similar

to that at Nashville (7.6% vs. 5.3%, p = 0.3). A total of 44 of the 55 patients (80%) had thrombus located solely (n = 37) or partially (n = 7) in the LV apex.

In comparison, cine-CMR detected thrombus in 37 patients, yielding a prevalence of 4.7%, which was lower than by DE-CMR (p < 0.005) (Table 2). Prevalence of thrombus by cine-CMR was similar at Duke and Nashville (5.0% vs. 3.8%, p = 0.5).

Validation of DE-CMR. Eight patients had direct inspection and pathology evaluation of the LV either at the time of cardiothoracic surgery or at necroscopy (aneurysmectomy = 5, transplantation = 2, necropsy = 1). Five had thrombus verified by pathology, and DE-CMR detected all 5. Conversely, cine-CMR detected only 2 of 5 thrombi (40%). Among the 3 patients who had thrombus excluded by pathology, neither DE- nor cine-CMR detected thrombus. Representative images showing concordance and discordance of findings between imaging techniques with pathological verification are shown in Figure 1.

For the pre-defined window of 6 months after CMR, 709 patients (90.4%) had complete follow-up for the entire interval. Patients with complete follow-up were not different from those without follow-up in LVEF or prevalence of thrombus by DE- or cine-CMR (all, p = NS). Figure 2 stratifies patients according to imaging findings and follow-up end points. Patients with thrombus identified by DE-CMR had over a 7-fold higher rate of end points (CVA, TIA, or pathology verification of thrombus) than patients without thrombus (15.1% vs. 2.1%, p < 0.0001), despite a markedly higher proportion of patients on warfarin during the follow-up window (64% vs. 18%, p < 0.0001). In comparison, there was only a 3.0-fold higher rate of end points in patients with thrombus identified by cine-CMR (8.6% vs. 2.8%, p = 0.06) even though warfarin utilization (cine-CMR thrombus present vs. absent: 60% vs. 19% warfarin use) was similar to that of patients grouped by DE-CMR thrombus.

Figure 2 also shows that imaging by cine-CMR did not add to the information provided by DE-CMR. After stratification by DE-CMR, the subgroup in whom cine-CMR was positive for thrombus had a similar rate of end points to those in whom imaging was negative (p = 0.29 in DE-CMR positive group, p = 0.72 in DE-CMR negative group). Additionally, a bivariate logistic model testing the contributions of cine- and DE-CMR simultaneously showed that only DE-CMR had a significant relationship between the presence of thrombus by imaging and follow-up end points (p < 0.0001).

Table 2 Detection of Thrombus by CMR

	DE-CMR Thrombus		
Cine-CMR Thrombus	Present	Absent	Total
Present	31	6	37*
Absent	24	723	747
Total	55*	729	784

*DE-CMR prevalence: 7.0% (55 of 784) versus cine-CMR prevalence: 4.7% (37 of 784); p < 0.005.
Abbreviations as in Table 1.

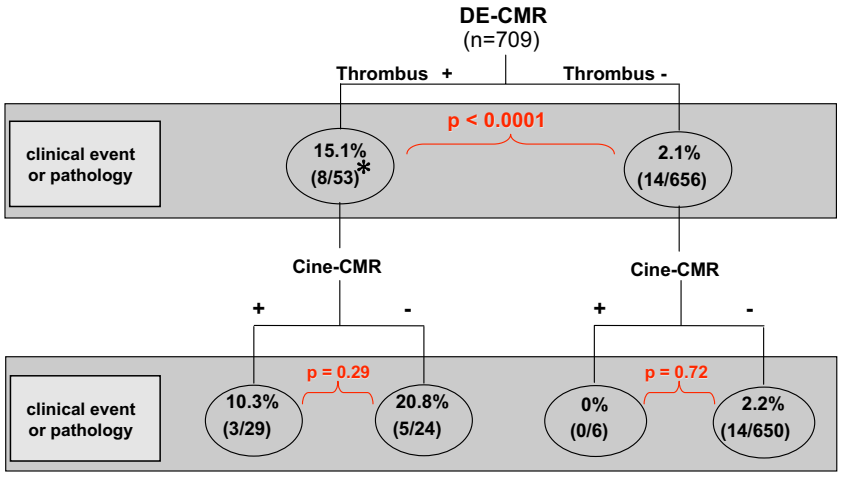
Thrombus morphology. Table 3 shows that the detection of thrombus by cine-CMR varied as a function of size and type. Overall, thrombi that were detected by cine-CMR were larger in volume (4.1 cm^3 vs. 1.8 cm^3). However, cine-CMR detected only 42% (8 of 19) of mural as compared with 64% (23 of 36) of intracavitary thrombi identified by DE-CMR, despite the nearly 2-fold greater size on average of mural thrombus (4.2 cm^3 vs. 2.3 cm^3). After stratifying by type, only intracavitary thrombus showed a relationship between detection and size (p = 0.003).

Clinical and structural markers of the presence of thrombus. UNIVARIABLE MARKERS. Patients with LV thrombus by DE-CMR did not differ from those without thrombus on the basis of coronary disease risk factors, atrial arrhythmias, antecedent thromboembolic events, or baseline medication regimen including anticoagulation therapy (Table 1). Patients with thrombus, however, were more likely to have had a prior myocardial infarction, have more advanced systolic dysfunction and adverse cardiac remodeling by cine-CMR, and more myocardial scarring by DE-CMR.

The prevalence of thrombus varied according to the etiology of cardiomyopathy. Figure 3 shows over a 5-fold higher prevalence of thrombus among patients with ischemic compared to those with nonischemic cardiomyopathy (9.2% vs. 1.7%, p = 0.0002), despite similar mean LVEF (31.8 ± 10.5% vs. 31.7 ± 11.6%, p = 0.88) and anticoagulation rate (p = 0.72). Figure 3 also shows that although thrombus prevalence increased as LVEF decreased for both ischemic and nonischemic patients, the prevalence was higher in patients with ischemic disease for every LVEF group. Interestingly, the prevalence of myocardial scarring was 2-fold higher (86% vs. 43%, p < 0.0001) and mean scar size was 3-fold higher (19.4% vs. 6.4% LV, p < 0.0001) in patients with ischemic disease, paralleling the increased prevalence of thrombus.

MULTIVARIABLE MODELS. When considering only traditional clinical variables, the best model predicting the presence of thrombus included age, prior myocardial infarction, and ischemic etiology of cardiomyopathy (Fig. 4A). The addition of LVEF by cine-CMR resulted in an improved model (chi-square increased from 34.99 to 56.43, p < 0.0001) (Fig. 4B). The addition of myocardial scarring by DE-CMR, specifically the percentage of LV more than 50% transmurally scarred, improved the model further (chi-square from 56.43 to 60.95, p < 0.03). Interestingly, our second multivariable approach by considering all clinical and CMR variables simultaneously resulted in the same final model for thrombus (chi-square = 60.95). Younger age, prior MI, ischemic cardiomyopathy, LVEF, and percent LV with >50% transmural scar were all independent markers for thrombus.

Concerning the novel index of myocardial scarring, our findings suggest that every 10-point increase in percent LV with transmural scarring would result in a 22% increase in likelihood of thrombus. The independent value of myocardial scarring is also illustrated in Figure



* Patients with DE-CMR thrombus and supportive pathology or clinical event

Patient	Clinical or Pathology Endpoint	DE-CMR		Ejection Fraction (%)	Cardiomyopathy	Cine CMR
		Thrombus Size (cm^3)	Thrombus Type			
1	surgical thrombectomy	35.4	mural	17	ischemic	**thrombus absent**
2	surgical thrombectomy	36.9	mural	17	ischemic	**thrombus absent**
3	surgical thrombectomy	7.2	intracavitary	18	ischemic	thrombus present
4	surgical thrombectomy	5.4	intracavitary	14	ischemic	thrombus present
5	surgical thrombectomy	1.5	mural	26	ischemic	**thrombus absent**
6	transient Ischemic attack	3.5	intracavitary	28	ischemic	thrombus present
7	cerebrovascular accident	1.2	intracavitary	9	non-ischemic	**thrombus absent**
8	cerebrovascular accident	0.8	mural	23	ischemic	**thrombus absent**

Figure 2 **Validation of DE-CMR During Clinical Follow-Up**

Stratification of patients with 6-month follow-up according to presence or absence of thrombus by DE-CMR yielded over a 7-fold difference in study end points (TIA, CVA, or pathology-verified thrombus) between groups (15.1% vs. 2.1%). Further stratification based on cine-CMR did not improve differentiation of patients. Details regarding the 8 patients who were DE-CMR–positive for thrombus and had clinical event or pathology confirmation are shown in the corresponding table **(bottom)**. CVA = cerebrovascular accident; TIA = transient ischemic attack; other abbreviations as in Figure 1.

4C, which shows the synergistic nature of considering both myocardial contraction and scarring as markers for thrombus.

Discussion

This is the first investigation to evaluate the prevalence of thrombus using CMR. There were 3 main findings: 1) among a broad population of patients with systolic dysfunction, 7% had thrombus identified by DE-CMR; 2) prevalence of thrombus was lower by cine- than DE-CMR ($p < 0.005$); and 3) myocardial scarring, also detected by DE-CMR, was identified as a novel risk factor for thrombus.

Identification of thrombus and associated risk factors has important implications for management of heart failure, a

Table 3 **Thrombus Morphology**

	Thrombus Identified by DE-CMR (n = 55)			
	Overall	Cine-CMR + (n = 31)	Cine-CMR − (n = 24)	p Value
Volume (cm^3)	2.9 (0.2–35.3)	4.1 (0.4–42.1)	1.8 (0.2–21.5)	0.01
Type				
Intracavitary	36 (65%)	23	13	0.12
Mural	19 (35%)	8	11	
Volume according to type				
Intracavitary (cm^3)	2.3 (0.2–26.7)	3.6 (0.3–39.4)	1.1 (0.2–57.0)	0.003
Mural (cm^3)	4.2 (0.3–53.0)	5.9 (0.7–49.0)	3.3 (0.2–53.6)	0.34

Indices reported as absolute number (percentage) or antilog of mean (95% confidence intervals) of log transformed data. Abbreviations as in Table 1.

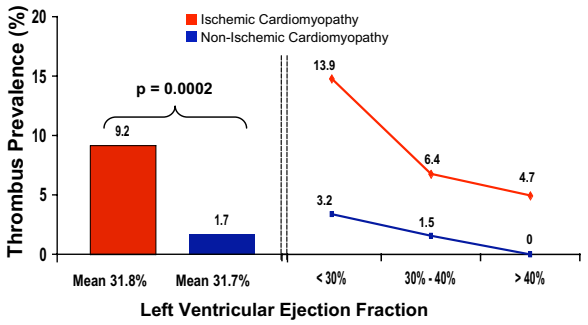


Figure 3 **Thrombus Prevalence According to Etiology and Severity of Myopathic Dysfunction**

Thrombus prevalence (bar graph, **left**) was over 5-fold higher among patients with ischemic cardiomyopathy as compared with those with nonischemic cardiomyopathy (9.2% vs. 1.7%) despite nearly identical left ventricular ejection fraction. When each group was stratified according to ejection fraction (line graph, **right**), prevalence was higher in patients with ischemic disease for every ejection fraction group.

growing global epidemic (24). Although large-scale studies have found that, overall, patients with systolic dysfunction have an increased risk of stroke (25), initiation of anticoagulation based solely on clinical characteristics such as LVEF or post-MI status may decrease thromboembolic events in some, at the cost of major bleeding episodes in others (26). As LV thrombus provides a substrate for thromboembolic events and a rationale for anticoagulation, thrombus detection using DE-CMR holds the potential to improve therapeutic decision-making and clinical care of patients with systolic dysfunction.

Among the 55 patients with LV thrombus identified by DE-CMR in the current study, 44% (24 of 55) had cine-CMR examinations that were negative for thrombus. This finding is consistent with prior studies that have compared DE-CMR with anatomical imaging using either cine-CMR or echocardiography. Mollet et al. (13) reported that among 12 patients with thrombus detected by DE-CMR, 50% (6 of 12) were not detected by cine-CMR and

A

Clinical Model for Thrombus ($\chi^2 = 34.99$; $p < 0.001$)

Variable	Odds Ratio	95% Confidence Interval	P
Age	0.97	0.95 – 0.99	0.02
Prior Myocardial Infarction	3.13	1.49 – 6.56	0.03
Ischemic Cardiomyopathy	4.02	1.28 – 12.69	0.02

Clinical + LV Function Model for Thrombus ($\chi^2 = 56.43$; $p < 0.0001$)

Variable	Odds Ratio	95% Confidence Interval	P
Age	0.97	0.95 – 0.99	0.0006
Prior Myocardial Infarction	3.85	1.78 – 8.31	0.0006
Ischemic Cardiomyopathy	4.18	1.24 – 14.05	0.02
Left Ventricular Ejection Fraction	0.94	0.91 – 0.97	< 0.0001

Clinical + LV Function + LV Scar Model for Thrombus ($\chi^2 = 60.95$; $p < 0.0001$)

Variable	Odds Ratio	95% Confidence Interval	P
Age	0.97	0.95 – 0.99	0.01
Prior Myocardial Infarction	3.13	1.42 – 6.89	0.005
Ischemic Cardiomyopathy	3.42	1.003 – 11. 68	< 0.05
Left Ventricular Ejection Fraction	0.94	0.92 – 0.97	< 0.00001
% LV with >50% Transmural Scar	1.02	1.002 – 1.04	0.03

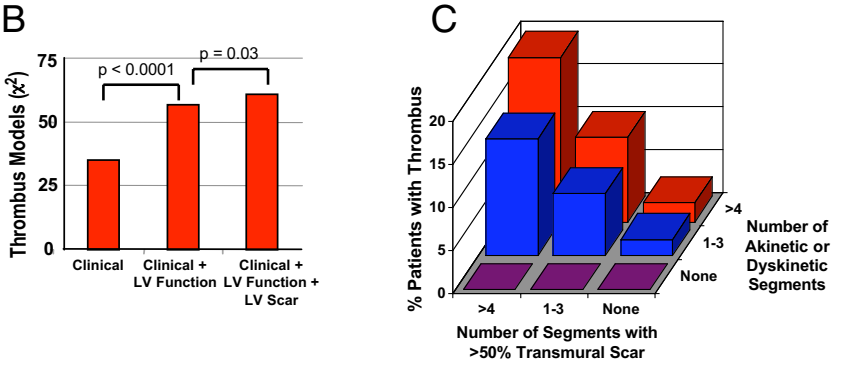


Figure 4 **Utility of Clinical, Functional, and Scar Markers for Thrombus**

(A) Components of clinical, LV ejection fraction, and LV scar inclusive multivariable models for thrombus presence. **(B)** Adding LV ejection fraction and then LV scar results in an improved model. **(C)** The synergistic nature of considering both myocardial contraction and scarring as markers for thrombus presence. See text for details. LV = left ventricular.

58% (7 of 12) were not detected by echocardiography. A more recent study by Srichai et al. (14) compared CMR with echocardiography in a cohort of patients undergoing LV reconstruction surgery in whom surgical and/or pathology verification of thrombus was uniformly performed. This study reported that the sensitivity of transthoracic echocardiography was 23% and transesophageal echocardiography was 40%, compared with 88% for CMR. However, because DE-CMR was interpreted in conjunction with cine-CMR, this investigation did not permit conclusions to be made regarding the utility of DE-CMR alone for thrombus detection.

In the current study, validation of DE-CMR as an appropriate imaging standard for LV thrombus was obtained via two means. First, all records were reviewed to identify patients who had direct inspection of the LV, and pathology specimens were carefully re-examined by a cardiovascular pathologist blinded to imaging findings. With this assessment, DE-CMR detected thrombus correctly among all 5 patients with pathology verified thrombus, whereas cine-CMR detected thrombus in only 2. Second, to obtain additional evidence supporting the diagnosis of thrombus among the overall study population, prospective follow-up was performed on all patients for clinical embolic events highly suggestive of thrombus within a pre-specified 6-month window after CMR. These results also supported DE-CMR as a more appropriate reference standard than cine-CMR. Patients with thrombus identified by DE-CMR had over a 7-fold higher rate of pathology and clinical end points than those without thrombus; cine-CMR provided lower discrimination between end points and no additional stratification once patients were grouped according to presence or absence of thrombus by DE-CMR (Fig. 2).

On the other hand, the occurrence of CVA/TIA does not prove the presence of LV thrombus because other sources such as carotid atherosclerosis could potentially explain cerebrovascular events. However, given that LV thrombus was present on imaging, attributing CVA/TIA to this rather than to other sources seems reasonable. Additionally, our follow-up was intentionally kept short to enhance the temporal link between the presence of thrombus at the time of imaging and clinical events. Although our follow-up protocol was tailored to relate clinical end points to imaging findings, absolute verification of the imaging diagnosis of thrombus would require uniform pathology evaluation. However, we note that a population in which all patients could undergo pathology verification would be a highly selected cohort that would not have allowed us to evaluate thrombus prevalence and markers in a broad cross section of patients with LV dysfunction, which was the primary aim of this study.

The ability of DE-CMR to identify thrombus based on tissue characteristics rather than anatomical appearance alone may explain why it provided improved thrombus imaging compared with cine-CMR. Because of its avascularity, thrombus has essentially no gadolinium uptake, and this fact can be used to discern thrombus from myocardium irrespective of its morphology or location. Although one prior CMR study (27) reported that chronic organized thrombus can show inhomogeneous gadolinium enhancement, this study included only 5 patients with LV thrombus and used an older pulse sequence with poor temporal and spatial resolution and limited T1-weighting compared with DE-CMR. In our study, thrombus showed a uniform lack of gadolinium enhancement. Likewise, Kirkpatrick et al. (11) using contrast perfusion echocardiography showed absence of contrast enhancement in cardiac thrombi, and this consistent feature was found to greatly facilitate the diagnosis of cardiac masses by differentiating thrombus from neoplasm. Moreover, because the primary distinguishing characteristic is the presence or absence of contrast uptake, cine-CMR after gadolinium infusion is likely superior to nonenhanced cine-CMR for thrombus identification.

A particular advantage of DE-CMR is that it can distinguish mural thrombus from immediately adjacent myocardium. Our results show that although intracavitary thrombi were typically detected by cine-CMR when large and generally missed when small, both small and large mural thrombi often were undetected. For instance, cine-CMR had lower sensitivity for mural than intracavitary thrombus despite a nearly 2-fold larger average size of mural thrombus. Identification of mural thrombus is potentially of clinical importance. In prior studies, up to 40% of embolic events have occurred in patients with nonprotuberant or immobile thrombus (28).

One of the main aims of the present study was to examine clinical and imaging markers for the presence of LV thrombus. As expected, a strong inverse relationship between LVEF and thrombus prevalence was found. Interestingly, multivariable analysis showed that increased myocardial scarring, an additional parameter available from DE-CMR, was an independent risk factor for thrombus. Although prior studies of patients with myocardial infarction have observed that patients with larger infarcts have greater likelihood for thrombus formation (29,30), the mechanism has always been assumed to be more extensive systolic dysfunction and/or remodeling, and not necessarily the presence of scarring per se. Our results, however, show that *both* the amount of myocardial scarring and the extent of systolic dysfunction are independent markers for thrombus presence, with the 2 parameters providing additive predictive value (Fig. 4C). For example, thrombus prevalence was often higher among patients with less extensive contractile dysfunction but with widespread myocardial scarring than those with extensive dysfunction but without scarring. The independent value of myocardial scarring may in part explain the marked difference in thrombus prevalence according to cardiomyopathic etiology. For example, patients with ischemic cardiomyopathy had over a 5-fold higher prevalence of thrombus than patients with nonischemic cardiomyopathy despite a nearly identical LVEF (Fig.

3). The increase in prevalence was paralleled by an increase in scar burden, with scar size more than 3-fold higher among ischemic patients.

Conclusions

In summary, this study shows that DE-CMR is a clinically useful tool for the detection of LV thrombus. Anatomical assessment using cine-CMR was especially limited in patients with mural-type thrombus, among whom even large thrombus was often missed. Additionally, myocardial scar as identified by DE-CMR was found to be a novel independent risk factor for thrombus. Further investigation is needed to ascertain whether DE-CMR findings can be used to guide anticoagulant therapy and improve clinical outcomes among the growing population of patients with heart failure at risk for LV thrombus and related complications.

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