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ORIGINAL ARTICLE

# APICAL LONGITUDINAL STRAIN CAN HELP Predict the Development of Left Ventricular Thrombus After Anterior Myocardial Infarction

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#### ABSTRACT

**Background:** Left ventricular (LV) thrombus formation is a common complication of anterior myocardial infarction (ANT-MI). The aim of this study was to investigate the relationship between apical longitudinal strain (ALS) and LV apical thrombus after ANT-MI. **Methods:** The cross-sectional study included a total of 235 patients who were followed up after primary percutaneous coronary intervention performed for ANT-MI and had a reduced LV ejection fraction (LVEF) ( $\leq$ 40%). Of these patients, 24 were excluded from the study, and the remaining 211 patients were included in the analysis. Patients were divided into two groups based on the presence (n = 42) or absence (n = 169) of LV thrombus detected by echocardiography. ALS was measured using speckle-tracking echocardiography. **Results:** Thrombus was detected in 42 of 211 patients. There was no significant difference between the groups regarding age or gender. Apical strain (AS), global longitudinal strain (GLS), apical wall thickness (AWT), and EF were significantly lower in patients with LV apical thrombus when compared to those without LV apical thrombus (AS,  $-5.00 \pm 2.30\%$  vs.  $-8.54 \pm 2.48\%$ , p < 0.001; GLS,  $-10.6 \pm 3.54\%$  vs.  $-12.1 \pm 2.84\%$ , p = 0.013; AWT, 4.71  $\pm$  1.11 vs. 6.33  $\pm$  1.78 mm, p < 0.001; EF, 31.40  $\pm$  4.10% vs. 37.75  $\pm$  3.17%, p < 0.001). On univariate and multivariate analyses, aneurysm (AA), AS, and AWT were found to be independent predictors of LV apical thrombus (AA, odds ratio [OR] 4.649, p = 0.010; AS, OR 1.749, p < 0.001; AWT, OR 0.729, p = 0.042). **Conclusion:** ALS is highly sensitive and specific for predicting LV thrombus after ANT-MI. An early and accurate evaluation of LV thrombus may prevent embolic complications, particularly cerebrovascular events. (REV INVEST CLIN. 2020;72(6):353-62)

Key words: Apical longitudinal strain. Left ventricular thrombus. Anterior myocardial infarction.

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#### INTRODUCTION

Left ventricular (LV) thrombus formation is a potentially catastrophic complication following myocardial infarction (MI), causing systemic embolism and increased morbidity and mortality<sup>1,2</sup>. However, the reported incidence of LV thrombus after ST-elevation MI (STEMI) is inconsistent, ranging from 2.9% to 15%<sup>3</sup>. It is known that impaired LV wall motion with apical segment involvement, particularly after anterior MI (ANT-MI), is strongly associated with apical thrombus formation<sup>3-5</sup>. Two-dimensional echocardiography (2DE) is a noninvasive and relatively simple technique and represents one of the first diagnostic tools in the assessment and follow-up of LV thrombus<sup>6,7</sup>.

The diagnosis of LV thrombus has advanced remarkably in recent years. 2D speckle-tracking echocardiography (STE) has recently emerged as a popular method in the assessment of LV systolic and diastolic function due to its objectivity and reproducibility<sup>8,9</sup>. Direct strain measurement from 2D grayscale images makes STE a better tool for the evaluation of cardiac mechanics. Furthermore, STE is a more advantageous method for the evaluation of global and regional myocardial deformations when compared to tissue Doppler imaging since it is accurate, highly reproducible, angle-independent and does not require a fixed angle of insonation. Strain echocardiography is better than visual assessment/wall motion in detecting wall motion abnormalities. It is considered that the risk of thrombus formation is increased by the presence of Virchow's triad in regions with the lower strain values, and thus these strain measurements could help predict thrombus formation. To the best of our knowledge, there has been only one study analyzing the relationship between global longitudinal strain (GLS) and LV thrombus formation<sup>10</sup>, and there have been no studies investigating the relationship between apical longitudinal strain (ALS) and LV apical thrombus. In this study, we investigated the relationship between ALS and LV apical thrombus in patients after ANT-MI.

#### **METHODS**

#### Study group

The study included a total of 235 patients who were followed up after primary percutaneous coronary

intervention (PPCI) for anterior STEMI in our clinic between March 2015 and June 2018. The echocardiographic features of patients were evaluated 6 weeks after ANT-MI. A diagnosis of ANT-MI was made based on the presence of ST-segment elevation of at least 2.5 mm in men aged <40 years or 2 mm in men aged ≥40 years, and at least 1.5 mm in women at leads V2–V3 and/or >1 mm observed at two other adjacent chest leads<sup>11</sup>. Patients were eligible for enrolment if they had reduced LV ejection fraction (LVEF) ( $\leq$ 40%). 2DE images were obtained in all patients. Exclusion criteria were end-stage renal or hepatic disease, thrombotic hematological disorders, anticoagulant use, and poor echogenicity (Fig. 1). Based on these criteria, 24 patients were excluded from the study and thus a total of 211 patients were included for the analysis.

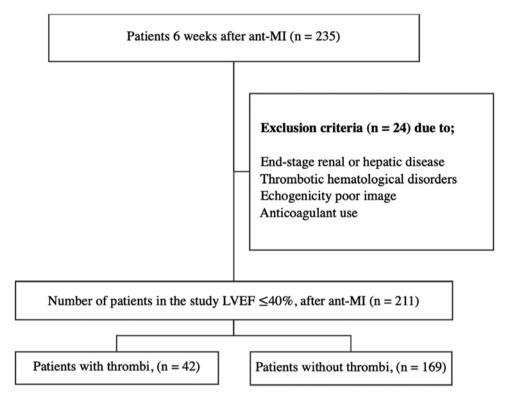
Detailed data on demographic and clinical characteristics and outcomes of the patients were prospectively documented. The study was designed as a cross-sectional study and was approved by the institutional review board. Each participant provided a written informed consent.

#### Definition of thrombus

LV thrombus on echocardiography is defined as a discrete echo-dense mass, laminated or pedunculated, lack of infiltration into the ventricular wall, and alteration in regional wall motion in the LV with defined margins that are distinct from the endocardium and seen throughout systole and diastole.

### Transthoracic 2DE

Transthoracic 2DE was performed in each patient to assess the mechanical myocardial properties of the patients. All the 2DE images were evaluated in the same echocardiographic windows by two independent echocardiographers. An echocardiography was obtained from each patient during clinical visits and was analyzed by two independent experienced cardiologists who were blinded to the study design and patients' clinical data. Conventional echocardiography was performed using EPIQ 7 ultrasound system (Philips QLAB chamber motion quantification [CMQ], version 10.5, Philips, Amsterdam, Netherlands) to evaluate the parasternal and apical angles (2D, M-mode, Figure 1. Flow-chart of the study.



Doppler echocardiography), with the patient placed in the left lateral position after a minimum of 15-min rest. Echocardiographic images were obtained in all four standard views (long-axis parasternal, shortaxis parasternal, two-chamber apical, and four-chamber apical) using the techniques recommended by the American Society of Echocardiography<sup>12</sup>. LVEF was calculated from apical 4- and 2-chamber views by manually tracing end-diastolic and end-systolic endocardial borders, using Simpson's method. The LV apical segment, which is the farthest point from the mitral valve, was analyzed from different angles by adjusting the depth, brightness, and proximity. Apical wall thickness (AWT) was measured at end-diastole from 2D images in the apical 4-chamber view, with the transducer angulated to optimize the visualization of the endocardium and papillary muscles. Measurements were obtained from the apical endocardium to the visceral pericardial surface at the point of maximal thickness. All the images were recorded digitally and re-evaluated for the assessment of apical strain (AS). Myocardial function was assessed through myocardial deformation analyses of 2D STE. End-diastole was defined as the first frame after mitral valve

closure or the frame with the largest LV dimensions/ volume. Endocardial borders were detected at 2D end-systole. When a correction was needed due to false auto-tracking, manual adjustments were made to ensure correct tracking or the width of 2D speckletracking was arranged for full coverage of the LV wall. In all patients, 2D STE was performed to determine the GLSs of the apicoanterior, apicoseptum, apicoinferior, apicolateral, and apical regions<sup>13</sup>. The 2D AS was measured from the apical 4-, 2-, and 3-chamber views. Measurements were obtained for each segment in a modified 17-segment model. The software automatically generated a region of interest (ROI) over the myocardium where speckles were tracked to calculate strain. The width of the ROI was adjusted to include the entire endocardium and exclude the pericardium. A quantitative measurement tool allowed numerical calculation of the median time to the peak velocity within a 15 × 6 mm ROI. The average sum of these series was used for the assessment. Philips EPIQ 7 QLAB-CMQ software was used for the analysis of these data. The peak systolic strain was automatically calculated for each segment. Untraceable segments were excluded from the analysis.

Variables	Thrombus (+) (n = 42)	Thrombus (–) (n = 169)	р	
Age, years	59.24 ± 11.70 55.74 ± 14.18		0.141	
Male Gender, n (%)	36 (85)	131 (77)	0.242	
HT, n (%)	16 (38)	76 (45)	0.421	
DM, n (%)	10 (23)	52 (30)	0.376	
HL, n (%)	21 (50)	82 (48)	0.864	
Smoking, n (%)	27 (64)	89 (52)	0.175	
NT-proBNP (pg/ml)	5427 (3232-9674)	3785 (1993-5283)	0.001	
Creatinine (mg/dl)	$0.83 \pm 0.13$	$0.85 \pm 0.12$	0.481	
Hemoglobin (g/dl)	$12.49 \pm 1.84$	12.76 ± 1.59	0.342	
Hematocrit (%)	39.07 ± 5.65	39.41 ± 4.73	0.690	
Treatment				
Antiplatelet, n (%)	42 (100)	169 (100)	*	
ACEI/ARB, n (%)	36 (85)	129 (76)	0.275	
Spironolactone, n (%)	24 (58)	84 (49)	0.169	
Beta-blocker, n (%)	35 (83)	129 (76)	0.329	
Statins, n (%)	32 (76)	125 (73)	0.802	
Loop diuretics, n (%)	11 (26)	39 (23)	0.782	

Table 1. Demographic and clinical characteristics of patients

HT: hypertension; DM: diabetes mellitus; HL: hyperlipidemia; NT-proBNP: n-terminal pro-brain natriuretic peptide; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

#### Statistical analysis

All statistical analyses were conducted using SPSS 19.0 for Windows (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.). Normal distribution of data was analyzed using Kolmogorov–Smirnov test. Continuous data were expressed as mean ± standard deviation and categorical data were expressed as percentages (%). The differences in categorical variables between groups were determined using Chi-square test. Relationships among parameters were assessed using Pearson's or Spearman's correlation coefficients according to the normality of the data. Student's t-test or Mann-Whitney U-test were used for comparing unpaired samples as needed. Univariate and multivariate logistic regression analyses were used for identifying independent variables of LV apical thrombus. Independent variables in the univariate analysis included N-terminal pro-brain natriuretic peptide (NTproBNP), EF, apical aneurysm (AA), AS, GLS, AWT, end-systolic volume (ESV), end-diastolic volume

(EDV), LV end-diastolic diameter (LVEDD), LV endsystolic diameter (LVESD), and mitral regurgitation (MR). After performing univariate analysis, significant variables were selected into a multivariate logistic regression analysis with the stepwise method. The results of univariate and multivariate regression analyses were presented as the odds ratio (OR) with the 95% confidence interval (CI). The cutoff value for AS with the greatest total sensitivity and specificity in predicting LV apical thrombus was determined using receiver operating characteristic (ROC) curve. Significance was assumed at a two-sided p <0.05.

## RESULTS

Thrombus was detected in 42 out of 211 patients, and their clinical and demographic characteristics are presented in Table 1. There were no differences between the groups regarding age or gender. The 42 patients detected with thrombus included 36 (85%) men, and the 169 patients without thrombus

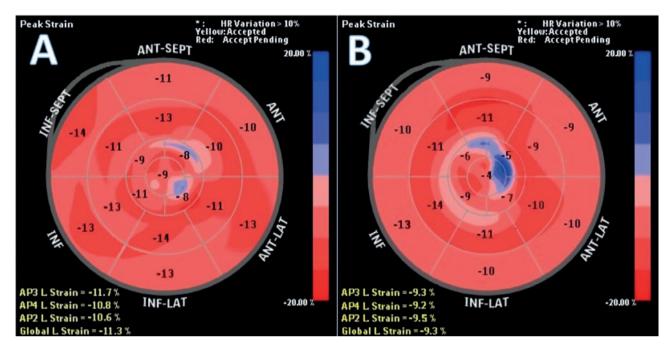


Figure 2. Examples of cases with and without left ventricular thrombus; strain assessment of thrombus (A) and non-thrombus (B) groups presented as bull's eye plots.

included 131 (77%) men. Mean age was 59.24  $\pm$  11.70 years in the thrombus group in contrast to 55.74  $\pm$  14.18 years in the non-thrombus group. No significant difference was found between the groups regarding hypertension, diabetes mellitus, hyperlipidemia, smoking status, and medications (antiplatelet, ACEI/ARB, spironolactone, beta-blocker, statins, and loop diuretics). Although the creatinine, hemoglobin and hematocrit levels were similar between the groups, the NT-proBNP levels were significantly higher in the thrombus group compared to the non-thrombus group (NT-proBNP, 5427 [range, 3232-9674] vs. 3785 [range, 1993-5283], p = 0.001; Table 1 and Fig. 2).

#### **Echocardiographic characteristics**

EF (31.40 ± 4.10% vs. 37.75 ± 3.17%, p <0.001), AA (n = 9 [21%] vs. n = 14 [8%], p = 0.014)], AS (-5.00 ± 2.30% vs.  $-8.54 \pm 2.48\%$ , p < 0.001), GLS (-10.6 ± 3.54% vs.  $-12.1 \pm 2.84\%$ , p = 0.013), and AWT (4.71 ± 1.11 vs. 6.33 ± 1.78 mm, p <0.001) were significantly lower in the thrombus group compared to the non-thrombus group. In contrast, ESV (107.50

 $\pm$  35.16 vs. 81.24  $\pm$  23.07 ml, p < 0.001), EDV (153.38  $\pm$  41.94 vs. 132.89  $\pm$  39.23 ml, p = 0.009), LVEDD (6.07  $\pm$  0.96 vs. 5.66  $\pm$  1.03 cm, p = 0.004), LVESD (5.03  $\pm$  1.01 vs. 4.47  $\pm$  1.19 cm, p = 0.006), and MR (1.81  $\pm$  0.74 vs. 1.51  $\pm$  0.69, p = 0.014) were significantly higher in the thrombus group compared to the non-thrombus group (Table 2).

Pearson's correlation coefficient revealed that AWT significantly decreased as the AS value approached zero, thereby indicating a significant negative correlation between the two variables (r = -0.546, p < 0.001; Fig. 3).

Parameters that significantly differed between the groups in the logistic regression analysis were further evaluated with univariate and multivariate analyses. Initially, NT-proBNP, EF, AA, AS, GLS, AWT, ESV, EDV, LVEDD, LVESD, and MR were assessed by univariate analysis and the parameters that were found to be statistically significant were subsequently evaluated by multivariate analysis. In the multivariate analysis, AA, AS, and AWT were found to be statistically significant for predicting thrombus formation (AA, OR 4.649, p = 0.010; AS, OR 1.749, p < 0.001; AWT, OR 0.729, p = 0.042; Table 3).

Variables	Thrombus (+) (n = 42)	Thrombus (–) (n = 169)	р
 EF (%)	31.40 ± 4.10	37.75 ± 3.17	<0.001
AS (%)	$-5.00 \pm 2.30$	-8.54 ± 2.48	<0.001
GLS (%)	$-10.6 \pm 3.54$	-12.1 ± 2.84	0.013
AWT (mm)	$4.71 \pm 1.11$	6.33 ± 1.78	<0.001
AA, n (%)	9 (21)	14 (8)	0.014
ESV (ml)	107.50 ± 35.16	81.24 ± 23.07	<0.001
EDV (ml)	153.38 ± 41.94	132.89 ± 39.23	0.009
LVEDD (cm)	6.07 ± 0.96	5.66 ± 1.03	0.004
LVESD (cm)	$5.03 \pm 1.01$	4.47 ± 1.19	0.006
MR (degree)	$1.81 \pm 0.74$	1.51 ± 0.69	0.014

#### Table 2. Echocardiographic features

EF: ejection fraction; ESV: end-systolic volume; EDV: end-diastolic volume; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; MR: mitral regurgitation. AS: apical strain; GLS: global longitudinal strain; AWT: apical wall thickness; AA: apical aneurysm.

Table 3. Univariate and multivariate regression analyses of predictors of LV apical thrombus

Variable .	Univariate		Multivariate			
	OR	95% CI	р	OR	95% Cl	р
NT-proBNP	1.000	1.000-1.000	0.516			
EF	0.987	0.930-1.048	0.677			
AS	1.638	1.283-2.092	< 0.001	1.749	1.407-2174	<0.001
GLS	1.124	1.024-1.345	0.033	1.025	0.974-1.077	0.342
AWT	0.695	0.487-0.992	0.045	0.729	0.631-0.902	0.042
AA	3.019	1.206-7.560	0.018	4.649	1.441-14.998	0.010
ESV	1.004	0.987-1.021	0.643			
EDV	0.995	0.983-1.008	0.468			
LVEDD	1.895	0.610-5.887	0.269			
LVESD	0.737	0.260-2.092	0.566			
MR	1.708	0.834-3.501	0.144			

NT-proBNP: n-terminal pro-brain natriuretic peptide; EF: ejection fraction; AS: apical strain; GLS: global longitudinal strain; AWT: apical wall thickness; ESV: end-systolic volume; EDV: end-diastolic volume; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; MR: mitral regurgitation. CI: confidence interval, OR: odds ratio.

In the ROC curve analysis, the predictive value of AS in estimating LV apical thrombus formation at a cutoff value of -6.5 showed a sensitivity and specificity of 83% and 73%, respectively, and the area under the ROC curve was calculated as 0.75 (range, 0.66-0.84) (Fig. 4). Accordingly, patients with a strain value of -6.5 and higher had a 12.7-fold increased thrombus risk.

#### Reproducibility

A total of 20 patients were randomly selected to assess intra- and inter-observer variability expressed as the intraclass correlation coefficient (ICC) for ALS and AWT. The ICCs for intra- and inter-observer variability were found to be 0.85 (95% Cl: 0.76-0.94) and 0.91 (95% Cl: 0.85-0.96) for AWT and 0.87 (95%

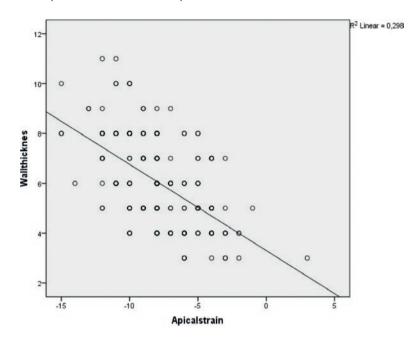
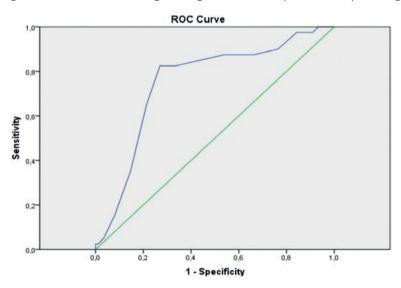


Figure 3. Correlation between apical wall thickness and apical strain value.

Figure 4. Receiver operating characteristic curve showing the diagnostic value of apical strain in predicting thrombus development.



Cl: 0.77-0.96) and 0.92 (95% Cl, range, 0.89-0.95) for ALS, respectively.

#### DISCUSSION

In this study, we investigated the prognostic value of ALS in patients with LV apical thrombus after anterior STEMI. There were three principal findings of our study. First, AS, AWT, and EF were significantly lower in patients with LV apical thrombus compared to those without LV apical thrombus. Second, univariate and multivariate analyses revealed that AA, AS, and AWT were independent predictors of LV apical thrombus. Finally, non-parametric ROC analysis revealed a cutoff value of –6.5 for AS, which was found to be a predictor of LV apical thrombus with a sensitivity of 83% and a specificity of 73% (Fig. 4). According to this cutoff value, patients with a strain value of -6.5 and higher had a 12.7-fold increase in thrombus risk.

Anterior MI (ANT-MI) with apical dysfunction is associated with an increased risk of LV thrombus formation and systemic embolism<sup>1,2</sup>. The incidence of LV thrombus has recently decreased due to the use of PPCI, earlier reperfusion, shorter door-to-balloon times, and intensive antiplatelet and antithrombin therapy. However, thrombus remains a serious risk, particularly in patients with MI affecting high-risk regions like the LV apex.

Although the structure and function of LV are commonly assessed by echocardiography in post-MI patients, the poor image quality and advanced LV remodeling can limit its power in detecting LV thrombus<sup>14,15</sup>. In addition to standard views for a thorough and careful examination, the use of apical views with angulation and the use of transducers with a short focus and higher frequency are required for better near-field resolution. STE is an objective and reproducible method used for quantifying myocardial deformation globally and regionally, regardless of the insonation angle or cardiac translational movements<sup>8,9,15</sup>. Direct strain measurement from 2D grayscale images makes STE a better tool for the evaluation of cardiac mechanics. Furthermore, STE is a more useful method for evaluating global and regional myocardial deformations when compared to tissue Doppler imaging since it is accurate, highly reproducible, and angle-independent and does not require a fixed angle of insonation<sup>16-18</sup>. The strain value reflects myocardial deformation related to wall thickening and poor movement, with low strain values being associated with weak wall movements and facilitating thrombus formation<sup>19,20</sup>. In the present study, we evaluated strain values using the speckle-tracking method and the myocardial thickness of the LV apical segment and found that both parameters were affected by thrombus formation.

In our study, we found a significant correlation between thrombus with low EF and increased LV diastolic and systolic diameters, which was consistent with the studies by Pöss et al. and Sharma et al.<sup>21,22</sup> Moreover, the probability of LVT formation was increased since the blood flow had slowed in the areas with contraction defects, implicating that the thrombus risk increases as the LVEF as a prothrombotic risk factor decreases. The Virchow triad indicated that the reduced flow and deterioration of the endocardial surface predispose individuals to thrombus formation<sup>23</sup>. Recent studies have shown that LV dysfunction, anterior MI, AA, and D-dimer are predictors of LVT<sup>1,2,24-26</sup>. Similarly, heart rate, heart failure severity, reduced EF, anterior apex wall involvement, left anterior descending disease, and non-white race have been reported to be independently associated with LVT formation<sup>1,2,27</sup>. In our study, we found that AS and AWT were independent predictors of LV apical thrombus.

It is well known that wall thinning is associated with the loss of viable myocardial tissue and fibrosis<sup>28,29</sup>. In this study, we found that ALS levels were strongly correlated with AWT. In addition, the risk of such formation was significantly higher in patients with a strain value of less than -6.5 and an AWT  $\leq$ 7 mm, thus entailing a detailed assessment of the apical region in such patients. On the other hand, patients with a strain value of -6.5 and higher had an increased thrombus risk by 12.7-fold.

To the best of our knowledge, there are no comprehensive studies in the literature investigating the association between AS and LV apical thrombus formation after ANT-MI. Kim et al. evaluated 74 patients and reported that echo-quantified longitudinal strain improved stratification for post-MI LV thrombus beyond conventional indices<sup>10</sup>. The present study included 211 patients and found a significant relationship between AS and LV apical thrombus. Moreover, AS and AWT were found to be independently associated with LV apical thrombus in multivariate analysis.

LV thrombosis is a major life-threatening condition<sup>7,30</sup>. Therefore, a detailed echocardiography evaluation of the patient is highly important for early diagnosis and treatment. To date, numerous methods have been described for diagnosing LVT, including contrast-enhanced echocardiography, LV contrast angiography, radionuclide ventriculography, and cardiac magnetic resonance (CMR), which are all expensive, impractical, and hard-to-access methods. Contrast echocardiography highlights the endocardial border and fills the LV cavity, thus facilitating the recognition of the LV mass and thrombus while also improving the diagnostic value of 2DE and reducing the use of additional imaging tests<sup>31</sup>. However, its cost, side effects, absence in many echocardiography laboratories and its irregular administration are among its limitations. CMR offers better specificity and sensitivity compared to 2DE since it is more costly, not portable, not affected by undesirable side effects (radiation and gadolinium-induced nephropathy), and requires long-term shooting<sup>32</sup>. Measurement of strain by 2D STE, particularly ALS, might represent a non-invasive method for predicting LV apical thrombus formation after ANT-MI.

Our study was limited in several ways. First, the data were derived from a single center, and the sample size was relatively small. Second, we did not use contrast material for distinguishing thrombus from trabeculation on 2DE examination. Third, we only evaluated longitudinal strain and did not evaluate radial and circumferential strains. Fourth, patients with an EF >0.40 after ANT-MI were not included in the study and thus the results may not be applicable to this population. Fifth, our cutoff value for AS was assuming the best-case scenario and therefore a validation study in a different population is needed. Sixth, cardiac MRI was not performed in our study for the diagnosis of LV apical thrombus due to its limitations, including high cost, limited availability, and the level of expertise required for its administration. Future large-scale trials are required to substantiate our findings.

In conclusion, transthoracic 2DE is the method of choice in the diagnosis of LV thrombus since other imaging modalities are costly and may not be readily available. ALS is an independent risk factor for LV apical thrombus formation after ANT-MI. An early accurate thrombus evaluation may prevent embolic complications, particularly cerebrovascular events. Assessment of ALS by 2D STE is likely to become a mainstay procedure in clinical practice; however, further comprehensive studies are required.

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