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ORIGINAL ARTICLE

Echocardiographic risk factors of left ventricular thrombus in patients with acute anterior myocardial infarction

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Abstract

Aims This study aimed to identify echocardiographic determinants of left ventricular thrombus (LVT) formation after acute anterior myocardial infarction (MI).

Methods and results This case–control study comprised 55 acute anterior MI patients with LVT as cases and 55 acute anterior MI patients without LVT as controls, who were selected from a cohort of consecutive patients with ischemic heart failure in our hospital. The cases and controls were matched for age, sex, and left ventricular ejection fraction. LVT was detected by routine/contrast echocardiography or cardiac magnetic resonance imaging during the first 3 months following MI. Formation of apical aneurysm after MI was independently associated with LVT formation [72.0% vs. 43.5%, odds ratio (OR) = 5.06, 95% confidence interval (CI) 1.65–15.48, $P = 0.005$]. Echocardiographic risk factors associated with LVT formation included reduced mitral annular plane systolic excursion (<7 mm, OR = 4.69, 95% CI 1.84–11.95, $P = 0.001$), moderate–severe diastolic dysfunction (OR = 2.71, 95% CI 1.11–6.57, $P = 0.028$), and right ventricular (RV) dysfunction [reduced tricuspid annular plane systolic excursion < 17 mm (OR = 5.48, 95% CI 2.12–14.13, $P < 0.001$), reduced RV fractional area change < 0.35 (OR = 3.32, 95% CI 1.20–9.18, $P = 0.021$), and enlarged RV mid diameter (per 5 mm increase OR = 1.62, 95% CI 1.12–2.34, $P = 0.010$)]. Reduced tricuspid annular plane systolic excursion (<17 mm) significantly associated with increased risk of LVT in anterior MI patients (OR = 3.84, 95% CI 1.37–10.75, $P = 0.010$), especially in those patients without apical aneurysm (OR = 5.12, 95% CI 1.45–18.08, $P = 0.011$), independent of body mass index, hypertension, anaemia, mitral annular plane systolic excursion, and moderate–severe diastolic dysfunction.

Conclusions Right ventricular dysfunction as determined by reduced TAPSE or RV fractional area change is independently associated with LVT formation in acute anterior MI patients, especially in the setting of MI patients without the formation of an apical aneurysm. This study suggests that besides assessment of left ventricular abnormalities, assessment of concomitant RV dysfunction is of importance on risk stratification of LVT formation in patients with acute anterior MI.

Keywords Myocardial infarction; Aneurysm; Left ventricular thrombus; Right ventricular dysfunction; Echocardiography; Cardiovascular magnetic resonance

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Introduction

Over the past decades, there has been marked improvement in mortality following acute myocardial infarction (MI) due to the development and widespread application of reperfusion therapy, primary percutaneous coronary intervention (PCI), optimal antiplatelet and anticoagulant therapy, and secondary prevention strategies.[1]

However, the incidence of ischaemic heart disease overall is still constantly increasing worldwide and several serious,

potentially fatal complications of acute MI remain challenging in clinical practice.[2,3] Among the spectrum of life-threatening complications following acute MI is thromboembolic events such as stroke due to left ventricular thrombus (LVT) formation. It is known that the risk of LVT formation is the highest during the first 3 months after acute MI, ranging about 8–15%.[4,5] LVT is most frequently seen in acute anterior MI, and more than 90% of LVT occurred in the context of a left anterior descending infarct-related artery.[6,7] In patients with anterior ST-segment elevation MI treated by primary PCI, the incidence of LVT is approximately 9% by transthoracic echocardiography (TTE)[8] and approximately 12% by cardiovascular magnetic resonance (CMR).[9]

Three components of Virchow triad contribute to LVT formation in AMI.[4] Abnormal blood flow due to LV dysfunction and LV regional wall abnormality (i.e. akinesia, dyskinesia, or aneurysm) might result in more blood stagnation in the affected LV segment/area. Myocardial endocardial damage post-AMI is followed by enhanced inflammatory responses, both factors might favour LVT formation in anterior AMI patients. In addition, elevated levels of fibrinogen, C-reactive protein, tissue factor, D-dimer, and anti-cardiolipin antibodies (IgM and IgG) have been found to be associated with increased risk for the development of LVT, indicating Virchow's triad plays a central role on the genesis of thrombosis not only in blood vessels but also in the left ventricle.[10–12]

Clinically, there are situations for AMI patients, who complicated with other clinical scenarios, which might favour thrombosis formation (such as hypertension, diabetes, smoking, or cardioembolic stroke related to hypercoagulability and inflammation).[13] For these patients with prone thrombosis features, more intensive screening, prophylaxis and management of LVT is essential. In terms of echocardiographic parameters, based on limited data, known risk factors for the development of LVT include MI location in the anterior and/or apical segments, large infarct size, low left ventricular ejection fraction (LVEF), and severe LV regional wall motion abnormalities.[14] It remains unexplored whether there are additional echocardiographic parameters (such as diastolic function grade, right-side morphology and function) capable of predicting LVT formation. The purpose of this study was to define additional determinants of LVT formation following acute anterior MI besides the known risk factors through comparing clinical and echocardiographic characteristics between patients with and without LVT formation during the first 3 months after acute anterior MI.

Methods

Study population

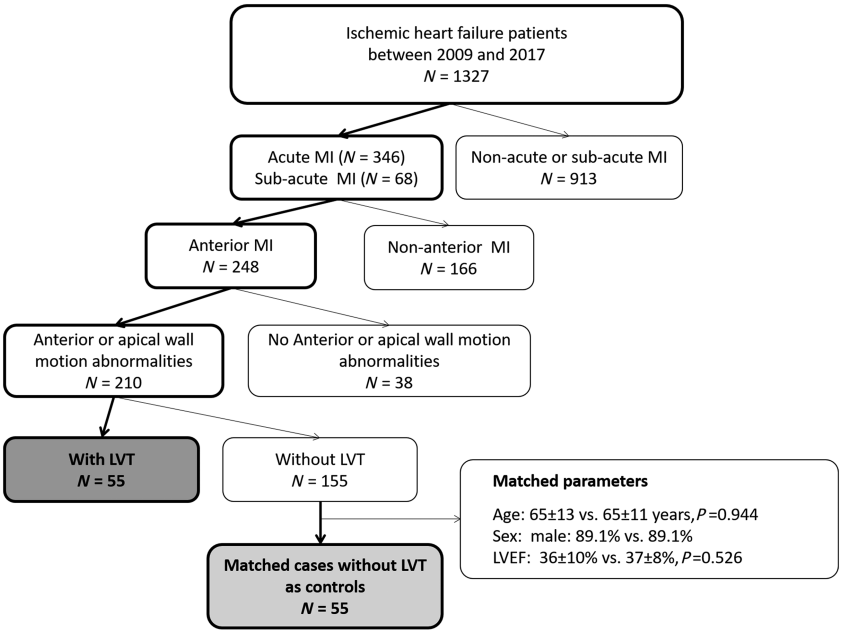
This retrospective case–control study comprised 55 acute anterior MI patients with LVT as cases and 55 acute anterior MI patients without LVT as controls, and patients were selected from a cohort of consecutive patients with ischaemic heart failure (n = 1327) in the department of cardiology of the University Hospital Würzburg between 2009 and 2017 based on the database of the REDEAL-HF trial (Clinical trial registration NCT03966729) described previously.[15] Enrolment criteria in both groups included (i) acute or subacute ST segment elevation (STEMI) or non-ST segment elevation myocardial infarction (NSTEMI); (ii) anterior or apical MI with severe regional wall motion abnormalities (i.e. akinesia, dyskinesia, or aneurysm). The LVT was identified by TTE combined with contrast echocardiography or CMR during the first 3 months following MI. The cases and controls were matched for age, sex, and LVEF (*Figure 1*). Clinical data including the use of anticoagulation therapy following LVT diagnosis were collected through medical reports.

The study was approved by the local Ethics Committee at the University of Würzburg and conducted in accordance to the Declaration of Helsinki. Written informed consent due to applicable provisions was obtained from all patients or their guardians.

Echocardiography

A routine transthoracic echocardiography examination was performed at baseline visit (GE, Vingmed Vivid 7 or IE9). Standard echocardiographic measurements for the assessment of cardiac structure and function were performed according to the American Society of Echocardiography (ASE) guidelines using the dedicated software (EchoPAC™, version 202, General Electric Co., Norway).[16,17] The relevant RV parameters were measured as previously described.[18] In brief, right ventricular (RV) and right atrial (RA) dimensions, including end-diastolic RV basal and middle diameters (RVD_basal and RVD_mid), end-systolic RA area (RAA) were measured from a RV focused apical four-chamber view. Tricuspid annular plane systolic excursion (TAPSE) was assessed by placing an M-mode cursor through the tricuspid annulus at the RV free wall and measuring the amplitude of longitudinal motion of the annulus during systole. The RV fractional area change (FAC) was calculated as: FAC = (RV end-diastolic area − RV end-systolic area) /RV end-diastolic area. Systolic pulmonary artery pressure (sPAP) was derived from peak tricuspid regurgitation (TR) jet velocity using the simplified Bernoulli equation in combination with an estimated RA pressure: $sPAP = 4\ V^2 + RAP$, where V indicates the peak TR jet velocity. Right atrial pressure (RAP) was estimated from inferior vena cava diameter and respiratory changes. In this study, LV aneurysm was defined as a thinning segment of the ventricular wall protruding beyond the normal outline of the LV chamber and displaying either akinesia or dyskinesia during systole.[19,20]

Figure 1 Flow diagram for the enrolment of study participants in this case–control study. LVEF, left ventricular ejection fraction; LVT, left ventricular thrombus; MI, myocardial infarction.



Identification of left ventricular thrombus

Left ventricular thrombus was evaluated in apical 4-chamber, 2-chamber, and 3-chamber views by TTE, which were visible throughout systole and diastole and identifiable in at least two views. A thrombus was defined as an echo-dense mass within the LV cavity with distinct margin attached to the LV wall accompanied by asynergic wall motion abnormality (hypokinetic or akinetic), but distinct from the underlying myocardium.[21,22] In all cases where LVT was suspected by TEE, images were reviewed by a senior imaging physician, and confirmed by serial TTE with the use of contrast agent if necessary. On contrast images, thrombus appeared as a dark linear or protruding structure, adjacent to akinetic myocardium, surrounded by blood in the LV cavity. In all cases where diagnosis was uncertain, presence of LVT was further confirmed by CMR if indicated. In this cohort, LVT was clearly and sufficiently observed in 12 patients by transthoracic echocardiography. Patients with suspected LVT underwent further evaluation by contrast echocardiography or CMR, LVT was confirmed in three patients by contrast echocardiography and in 40 patients by CMR. *Figure 2* displays an example of an acute anterior MI patient with LVT detected by TTE and CMR.

Statistical analysis

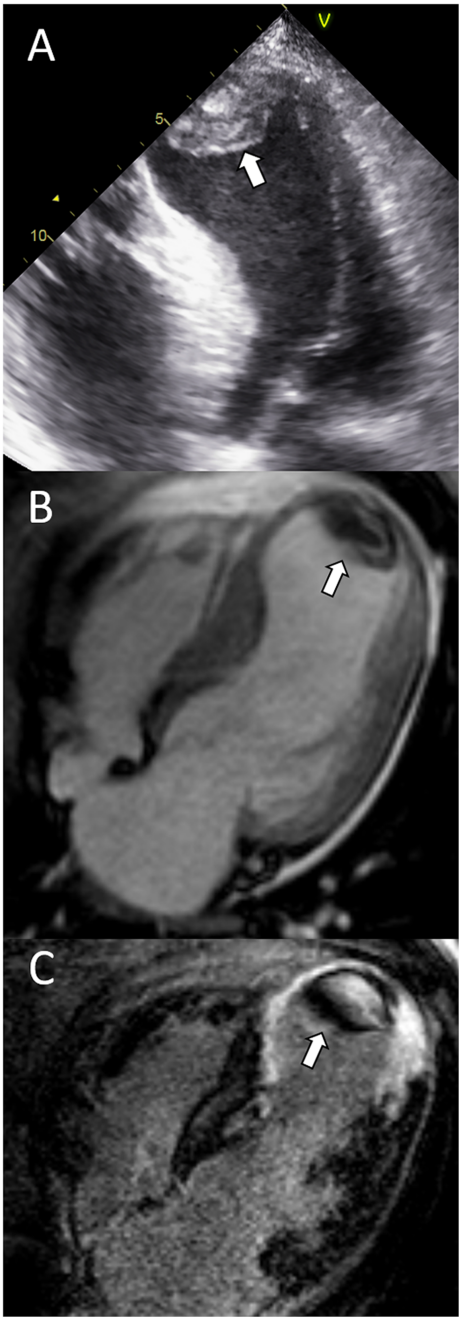
Statistical analyses were conducted using SPSS 25.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range, IQR). Normal distribution of all continuous variables was checked by inspecting Q–Q plots and Shapiro–Wilk test. Differences between groups were compared using unpaired Student *t* test or Mann–Whitney *U* test, as appropriate. Categorical variables were expressed as count and per cent, and the differences between groups were compared using χ^2 test or Fischer's exact test, as indicated. For each pair of columns, the column proportions were compared using a *z* test, and Bonferroni corrections were used to adjust the significance values. A two-tailed probability value of less than 0.05 was considered significant.

Binary logistic regression analysis was conducted to determine the risk factors of LVT formation. Crude and adjusted odds ratio (OR) and 95% confidence interval (CI) for each variable were calculated. Variables with P value <0.10 for initial comparisons were examined in the univariable regression models firstly. Secondly, variables with P value <0.05 were retained in the multivariable models to identify the independent predictive performance.

Results

According to the study protocol, patients with LVT (as cases) and without LVT (as controls) were matched for age (mean age 65 ± 13 vs. 65 ± 11 years, P = 0.94), sex (male 89.1% vs. 89.1%), and LVEF (35.8 ± 9.9% vs. 36.9 ± 8.4%, P = 0.53). The proportion of prior MI (78.2% vs. 72.7%, P = 0.51) and

Figure 2 Left ventricular thrombus formation (arrow) in a patient with acute anterior myocardial infarction detected by transthoracic echocardiography (A), cardiac magnetic resonance imaging (B), and late-gadolinium enhancement imaging (C), respectively.



the proportion of multi-vessel coronary artery disease (74.5% vs. 65.4%, *P* = 0.30) were similar between groups. Prevalence of hypertension (60.0% vs. 81.8%, *P* = 0.002) and anaemia (18.2% vs. 43.6%, *P* = 0.004) were significantly lower in the LVT group than in the control group (*Table 1*).

There were three AMI patients with LVT received anticoagulation therapy before inclusion: 1 with rivaroxaban for atrial fibrillation (AFib), 1 with warfarin for ischaemic stroke and AFib, and 1 with warfarin for deep vein thrombosis in the leg. In the LVT group, 53 (96.4%) patients were treated with anticoagulation plus dual antiplatelet therapy and remaining two patients (3.6%) were treated with antiplatelet therapy alone due to high bleeding risk. Anticoagulation therapy following LVT included low molecular weight heparin, vitamin K antagonist (warfarin), or direct acting oral anticoagulants (*Table 1*).

Echocardiographic characteristics are listed in *Table 2*. The proportion of patients with apical aneurysm was significantly higher in patients with LVT as compared with those without LVT (32.7% vs. 12.7%, *P* = 0.012). Septal mitral annular plane systolic excursion (MAPSE) was significantly lower in the LVT group than in the control group (6.5 ± 2.4 vs. 8.2 ± 2.5 mm, *P* = 0.001). The proportion of moderate–severe diastolic dysfunction (DD) was significantly higher in the LVT group than in the control group (70.9% vs. 49.1%, *P* = 0.020).

Right ventricular functional parameters included TAPSE, RV_FAC, and RVDs. RVD_basal diameter (37.0 ± 5.8 vs. 34.3 ± 7.5 mm, *P* = 0.038) and RVD_mid diameter (29.5 ± 5.3 vs. 26.5 ± 7.1 mm, P = 0.012) were significantly higher in the LVT group than in the control group. TAPSE was significantly lower in the LVT group as compared with the control group (15.4 ± 4.7 vs. 18.7 ± 5.8 mm, *P* = 0.001). The proportion of reduced RV_FAC (<0.35) was significantly higher in the LVT group compared with the control group (32.7% vs. 14.5%, *P* = 0.025).

Significant associations between LVT formation and echocardiographic parameters were also identified with binary stepwise regression analysis (*Table 3*). Apical aneurysm (OR = 3.34, 95% CI 1.26–8.82, *P* = 0.015), reduced septal MAPSE (<7 mm, OR = 3.74, 95% CI 1.64–8.51, *P* = 0.002), moderate–severe DD (OR = 2.53, 95% CI 1.15–5.55, *P* = 0.021), enlarged RV (RVD_mid, per 5 mm increase: OR = 1.49, 95% CI 1.08–2.06, *P* = 0.016), reduced TAPSE (<17 mm, OR = 3.39, 95% CI 1.54–7.48, *P* = 0.002), and reduced RV_FAC (<0.35, OR = 2.86, 95% CI 1.12–7.30, *P* = 0.028) were significantly associated with increased risk of LVT thrombus in this cohort.

We analysed the prevalence of five echocardiography-detected risk factors, including apical aneurysm, reduced MAPSE, moderate–severe DD, reduced TAPSE, and reduced RV_FAC, for LVT formation in this patient cohort. As shown in *Figure 3*, the proportion of patients with ≥3 risk factors was significantly higher in patients with LVT compared with patients without LVT (54.5% vs. 20.0%, *P* < 0.05).

Multivariable binary logistic regression analysis demonstrated that apical aneurysm (OR = 5.06, 95% CI 1.65–15.48, *P* = 0.005), reduced septal MAPSE (<7 mm, OR = 4.69, 95% CI 1.84–11.95, *P* = 0.001), moderate–severe DD (OR = 2.71, 95% CI 1.11–6.57, *P* = 0.028), reduced TAPSE (<17 mm,

Table 1 Clinical characteristics

	Control $N = 55$	LVT $N = 55$	P value
Age (years)	65 ± 11	65 ± 13	0.94
Male [*n* (%)]	49 (89.1)	49 (89.1)	—
BMI (kg/m^2)	29 ± 4	27 ± 4	0.06
NYHA Class III–IV [*n* (%)]	20 (36.4)	19 (34.5)	0.84
Risk factors and co-morbidities [*n*, %]			
Atrial fibrillation	7 (12.7)	13 (23.6)	0.09
Prior	2 (3.6)	4 (7.3)	
New-onset	5 (9.1)	9 (16.4)	
Obesity	19 (34.5)	12 (21.8)	0.14
Hypertension	45 (81.8)	33 (60.0)	0.012
Diabetes mellitus	11 (20.0)	17 (30.9)	0.19
Dyslipidaemia	33 (60.0)	25 (45.5)	0.13
Smoking	30 (54.5)	23 (41.8)	0.18
Anaemia	24 (43.6)	10 (18.2)	0.004
TIA or stroke	4 (7.3)	6 (10.9)	0.51
Chronic kidney disease >II	18 (32.7)	16 (29.1)	0.68
MI characteristics [*n* (%)]			
First MI	40 (72.7)	43 (78.2)	0.51
Recurrent MI	15 (27.3)	12 (21.8)	
Involved coronary arteries			0.52
1	14 (25.5)	19 (34.5)	
2	17 (30.9)	13 (23.6)	
3	24 (43.6)	23 (41.8)	
Previous anticoagulation therapy	0	3 (5.5)	0.24
VKA		2	
DOACs		1	
Antithrombotic strategy following LVT			
Anticoagulation plus dual antiplatelet therapy		53 (96.4)	
Antiplatelet therapy alone		2 (3.6)	
Anticoagulation type following LVT			
VKA alone		9 (17.0)	
DOACs alone		1 (1.9)	
LMWH alone		11 (20.7)	
LMWH with DOACs		31 (58.5)	
LMWH with DOACs		1 (1.9)	

BMI, body mass index; DOACs, direct acting oral anticoagulants; LMWH, low-molecular-weight heparin; LVT, left ventricular thrombus; MI, myocardial infarction; NYHA, New York Heart Association; TIA, transient ischemic attack; VKA, vitamin K antagonist.

OR = 5.48, 95% CI 2.12–14.13, $P < 0.001$), reduced RV_FAC (<0.35, OR = 3.32, 95% CI 1.20–9.18, $P = 0.021$), and increased RVDs (per 5 mm increase, OR = 1.51 and 1.62, $P = 0.019$ and 0.010) were independent determinants associated with LVT formation, after adjusted for body mass index, hypertension and anaemia (*Table 3*).

In this cohort, the prevalence of LVT was 61.1% (33/54) in anterior MI patients with RV dysfunction defined as TAPSE <17 mm and/or RV_FAC < 0.35, while the prevalence of LVT was 39.3% (22/56) in anterior MI patients without RV dysfunction ($P = 0.022$). For further identifying the independent association between RV dysfunction and LVT formation, apical aneurysm, MAPSE, and moderate–severe DD were added into logistic regression models as additional confounders (*Table 4*). Reduced TAPSE independently associated with LVT formation after adjusted for other potential confounders (adjusted OR = 3.84, 95% CI 1.37–10.75, $P = 0.010$) while RV_FAC did not ($P = 0.18$). Moreover, 17 out of 20 (85%) anterior MI patients who presented with TAPSE <17 mm and RV_FAC < 0.35 were found to have LVT. The results suggest that especially reduced TAPSE together with reduced RV_FAC were strongly associated with an increased risk of LVT formation in acute anterior MI patients independent of BMI, hypertension, anaemia, apical aneurysm, MAPSE, and advanced DD (adjusted OR = 7.11, 95% CI 1.60–31.62, $P = 0.010$).

As expected, the prevalence of LVT in anterior MI patients with apical aneurysm was significantly higher than in those patients without aneurysm (72.0% vs. 43.5%, $P = 0.012$). When focusing on the subgroup of anterior MI patients presented without apical aneurysm ($n = 85$), RV dysfunction as determined by TAPSE <17 mm and/or RV_FAC < 0.35, was significantly associated with increased risk of LVT formation (LVT prevalence: 57.9% in RV dysfunction group vs. 31.9% in non-RV dysfunction group, $P = 0.016$). While in the subgroup of anterior MI patients with apical aneurysm ($n = 25$), RV dysfunction was not associated with an increased risk of LVT (prevalence of LVT: 68.8% in RV dysfunction group vs. 77.8% in non-RV dysfunction group, $P > 0.05$). As shown in *Table 5*, after adjusted for potential clinical covariates (BMI, hypertension, and anaemia), TAPSE <17 mm (OR = 7.04, 95% CI 2.28–21.77, $P = 0.001$) and RV_FAC < 0.35 (OR = 3.78, 95% CI

Table 2 Echocardiographic characteristics

	Control $N = 55$	LVT $N = 55$	P value
Apical aneurysm [*n* (%)]	7 (12.7)	18 (32.7)	0.012
LVEDD (mm)	55.3 ± 7.5	53.1 ± 7.2	0.13
IVSd (mm)	9.9 ± 1.6	9.8 ± 1.4	0.93
LVPWd (mm)	9.4 ± 1.9	10.0 ± 1.6	0.10
LVMi (g/m^2)	103.0 ± 25.2	104.2 ± 30.1	0.81
LVEF (%)	36.9 ± 8.4	35.8 ± 9.9	0.53
TAPSE (mm)	18.7 ± 5.8	15.4 ± 4.7	0.001
Septal MAPSE (mm)	8.2 ± 2.5	6.5 ± 2.4	0.001
Lateral MAPSE (mm)	10.3 ± 2.5	9.4 ± 2.7	0.07
RVD_basal (mm)	34.3 ± 7.5	37.0 ± 5.8	0.038
RVD_mid (mm)	26.5 ± 7.1	29.5 ± 5.3	0.012
RV_FAC	0.44 ± 0.10	0.40 ± 0.12	0.11
RV_FAC $<$ 0.35 [*n* (%)]	8 (14.5)	18 (32.7)	0.025
RAA (cm^2)	16 ± 4	16 ± 4	0.31
LAVi (ml/m^2)	33 ± 11	36 ± 12	0.19
E wave (cm/s)	79 ± 25	79 ± 21	0.87
DT (ms)	174 ± 56	173 ± 61	0.97
E/A ratio	1.33 ± 0.78	1.40 ± 0.82	0.64
e′ (cm/s)	5.6 ± 1.6	7.0 ± 2.0	0.002
E/e′ ratio	15.3 ± 6.6	11.9 ± 4.3	0.013
sPAP (mmHg)	32.3 ± 13.9	34.8 ± 12.3	0.31
Moderate or severe DD [*n* (%)]	27 (49.1)	39 (70.9)	0.020

DD, diastolic dysfunction; DT: deceleration time of E wave; E wave: mitral inflow early diastolic filling velocity; E/A ratio: the ratio of mitral inflow early filling velocity to late diastolic filling velocity; E/e′ ratio: the ratio of early diastolic mitral inflow velocity to mitral annular tissue velocity; e′: tissue Doppler derived mitral annular early diastolic velocity; FAC, fractional area change; IVSd, end-diastolic interventricular septal thickness; LAVi: left atrial volume indexed to body surface area; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass indexed to body surface area; LVPWd, end-diastolic posterior wall thickness; LVT, left ventricular thrombus; MAPSE, mitral annular plane systolic excursion; RAA, end-systolic right atrial area; RV, right ventricular; RVD, end-diastolic mid-right ventricular diameter; sPAP: systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

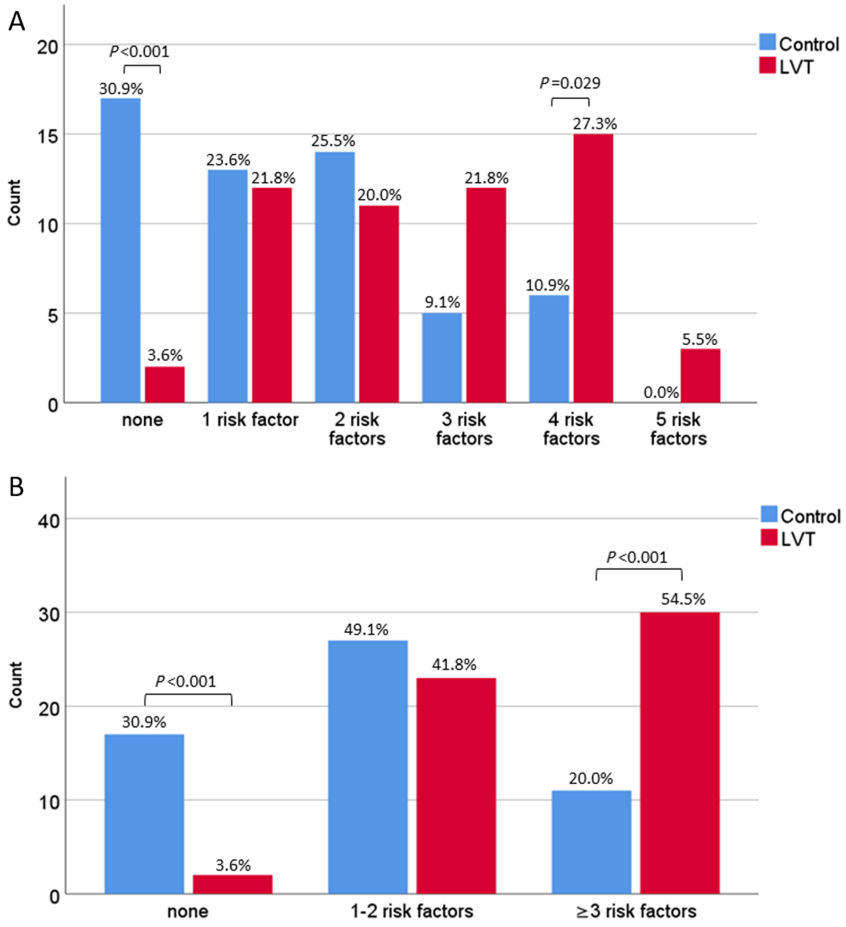
Table 3 Clinical and echocardiographic parameters associated with LVT formation after anterior MI

	Unadjusted odds ratio (95% CI)	P value	Clinical covariates adjusted odds ratio[a] (95% CI)	P value
Clinical variables				
Age (years)	1.00 (0.97–1.03)	0.94		
BMI (kg/m^2)	0.91 (0.83–1.01)	0.06		
Atrial fibrillation	2.12 (0.77–5.81)	0.14		
Hypertension	0.33 (0.14–0.80)	0.014		
Anaemia	0.29 (0.12–0.68)	0.005		
Echocardiographic variables				
Apical aneurysm	3.34 (1.26–8.82)	0.015	5.06 (1.65–15.48)	0.005
LVEF (%)	0.99 (0.95–1.03)	0.52		
Septal MAPSE	0.74 (0.62–0.89)	0.001		
$<$7 mm vs. $\geq$7 mm	3.74 (1.64–8.51)	0.002	4.69 (1.84–11.95)	0.001
Lateral MAPSE	0.87 (0.75–1.01)	0.08		
Moderate or severe DD	2.53 (1.15–5.55)	0.021	2.71 (1.11–6.57)	0.028
TAPSE	0.88 (0.82–0.96)	0.003		
$<$17 mm vs. $\geq$17 mm	3.39 (1.54–7.48)	0.002	5.48 (2.12–14.13)	$<$0.001
RV_FAC $<$ 0.35 vs. $\geq$0.35	2.86 (1.12–7.30)	0.028	3.32 (1.20–9.18)	0.021
RVD_basal	1.06 (1.00–1.13)	0.042	1.09 (1.02–1.17)	0.016
per 5 mm increase	1.33 (0.99–1.77)	0.055	1.51 (1.07–2.14)	0.019
RVD_mid	1.08 (1.01–1.15)	0.016	1.10 (1.02–1.19)	0.010
per 5 mm increase	1.49 (1.08–2.06)	0.016	1.62 (1.12–2.34)	0.010

[a]Adjusted for clinical covariates including BMI, hypertension, and anaemia.
For abbreviations, refer to *Tables 1 and 2*.

1.15–12.41, P = 0.028) were associated with increased risk of LVT in the subgroup of patients without apical aneurysm. Of note, when MAPSE and advanced DD as other echocardiographic confounders were entered into multivariable models, only reduced TAPSE remained an independent determinant of LVT formation (OR = 5.12, 95% CI 1.45–18.08, P = 0.011) while RV_FAC was not an independent determinant of LVT anymore (OR = 1.58, 95% CI 0.41–6.00, P = 0.50).

Figure 3 Comparison of prevalence of risk factors for left ventricular thrombus (LVT) formation between the control and LVT groups (A: none, 1, 2, 3, 4, and 5 risk factors; B: none, 1–2, and ≥3 risk factors). Each pair of column proportions is compared using a *z* test and Bonferroni correction. DD, diastolic dysfunction; MAPSE, mitral annular plane systolic excursion; RV_FAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion.



Echocardiography-detected risk factors for LVT formation

i. Apical aneurysm
ii. Reduced septal MAPSE (<7mm)
iii. Moderate to severe DD
iv. Reduced TAPSE (<17mm)
v. Reduced RV_FAC (<0.35)

Table 4 Right ventricular dysfunction associated with LVT formation after anterior MI

	Control	LVT	*P* value	Adjusted odds ratio[a] (95% CI)	*P* value
TAPSE < 17 mm	16 (29.1)	32 (58.2)	0.002	3.84 (1.37–10.75)	0.010
RV_FAC < 0.35	8 (14.5)	18 (32.7)	0.025	2.12 (0.71–6.35)	0.18
TAPSE <17 mm + RV_FAC < 0.35	3 (5.5)	17 (30.9)	0.001	7.11 (1.60–31.62)	0.010

[a]Adjusted for BMI, hypertension, anaemia, apical aneurysm, MAPSE, and moderate or severe DD.
For abbreviations, refer to *Tables 1 and 2*.

Table 5 Predictive performance of TAPSE and RV_FAC in anterior MI patients without and with apical aneurysm

	Clinical covariates adjusted odds ratio[a] (95% CI)	*P* value	Clinical and other echocardiographic covariates adjusted odds[b] ratio (95% CI)	*P* value
Without apical aneurysm (n = 85, events = 37, 43.5%)				
TAPSE < 17 mm	7.04 (2.28–21.77)	0.001	5.12 (1.45–18.08)	0.011
RV_FAC < 0.35	3.78 (1.15–12.41)	0.028	1.58 (0.41–6.00)	0.50
With apical aneurysm (n = 25, events = 18, 72.0%)				
TAPSE <17 mm	0.89 (0.11–7.19)	0.92		
RV_FAC < 0.35	2.50 (0.19–32.19)	0.43		

[a]Adjusted for BMI, hypertension, and anaemia.
[b]Adjusted for BMI, hypertension, anaemia, MAPSE, and moderate or severe DD.
For abbreviations, refer to*Tables 1 and 2*.

Discussion

The main finding of the present study is that RV dysfunction defined by reduced TAPSE (<17 mm), reduced RV_FAC (<0.35), as well as enlarged RVD, is independently associated with LVT formation after adjustment for potential confounders. A combination of reduced TAPSE together with reduced RV_FAC, which reflect severe impairment of RV longitudinal and radial function, showed particularly strong association with an increased risk of LVT formation in patients after acute anterior MI, independent of confounders including apical aneurysm, MAPSE, and advanced DD. To our knowledge, this is the first report describing the role of RV dysfunction on LVT formation after acute anterior MI.

Previous studies have defined numerous risk factors of LVT formation after acute MI, including large infarct size, apical aneurysm/akinesia, reduced left ventricular longitudinal systolic function (MAPSE), and advanced DD.[4,23,24] Notably, blood stasis in larger dysfunctional ischaemic areas serves as key factors of LVT formation in line with Virchow's triad.[4] Advanced DD, which is related to increased stiffness of the LV, has been shown to increase blood stasis as another risk factor of LVT formation in such patients.[24] Our findings are in line with and extend these previous reports, highlighting that presence of RV dysfunction additionally enhanced the likelihood of LVT formation in anterior MI patients.

In line with the findings of previous studies, the current study confirmed that apical aneurysm serves as a strong predictor of LVT formation in acute anterior MI patients. Moreover, we found that the risk of LVT formation was significantly higher even in the absence of apical aneurysm in the presence of RV dysfunction. One may speculate that RV dysfunction further enhances blood stasis in the LV apical region: since the intraventricular septal wall is shared by left and right ventricle, RV dysfunction might further reduce the movement capacity of the apical segment of the intraventricular septum.[25,26] Thus, RV dysfunction might result from septal dysfunction after MI. On the other hand, one may speculate on an association between RV dysfunction and advanced DD. Because both disease entities could lead to impaired haemodynamics in pulmonary circulation and LV filling[27]; thus, there might be a close link in pathophysiology of thrombus formation between two chambers cardiac dysfunction and fluid stasis in the lungs in patients with LVT post-AMI.

In our present study, the presence of hypertension was revealed as a protective factor for LVT formation among anterior MI patients. This result is in line with a previous report showing less ventricular thrombus after acute MI among patients with or without history of hypertension (0.5% vs. 1.5%, $P < 0.03$) in a large acute MI patient cohort (n = 4994).[28] Obviously, further mechanistic prospective studies are warranted to validate the observed results to see if hypertension really serves as protective factor for LVT formation after anterior MI.

Interestingly, we found that anaemia might be another protective factor against the development of LVT in patients after acute anterior MI. Theoretically, anaemia reduces the oxygen carrying capacity of blood and may theoretically exacerbate ischemia, increasing myocardial injury.[29] Previous reports indicated that iron-deficiency anaemia is linked with increased risk of venous thromboembolism[30] and cerebral venous thrombosis.[31] In a review article, Franchini *et al*. concluded that both iron deficiency and overload have been associated with an increased thrombotic risk in experimental and clinical studies.[32] The reason why less prevalence of LVT was observed in anterior MI patients complicating with anaemia is, therefore, unclear and deserves further prospective experimental and clinical studies.

Management of LVT with related embolic complications is a clinical challenge in AMI patients treated with or without PCI. Although anticoagulant therapy with a vitamin K antagonist is recommended for patients with AMI and evidence of LV mural thrombi according to the recent guideline,[33] the benefit of combining anticoagulation with dual antiplatelet therapy remains a matter of debate considering of increased bleeding risk in the setting of triple antithrombotic therapy.[34–38] Maniwa *et al*. reported that, among AMI patients complicated with LVT and treated with vitamin K antagonists (n = 84), only one embolic event developed in the therapeutic range (TTR) ≥ 50% group and nine embolic events developed in the TTR < 50% group (2.9% vs. 19.0%, P = 0.036). Moreover, there was no difference in major bleeding events between the two groups (TTR ≥ 50% vs. <50%

group: 9.0% vs. 8.0%, $P = 0.89$).[39] These results suggest that the appropriate treatment with vitamin K antagonists may decrease the incidence of systemic embolism in patients with first AMI complicated by LVT and does not increase the bleeding risks in these patients. Data on the use of direct oral anticoagulants (DOACs) and low molecular weight heparin to treat LVT are limited and their efficacy is not yet proved by randomized clinical trials.[40–43] It is thus of great clinical importance to specify the risk factor profiles related to LVT formation and to evaluate the efficacy of applied pharmacological management options on dissolving LV thrombus on the basis of thoroughly assessment of bleeding risk in order to provide evidence for decision making on the prevention and optimal management of MI with LVT.

AFib and LVT serve as the two leading causes of cardiogenic emboli and presenting an indication for oral anticoagulants therapy.[44] In line with this context, proportion of prior (7.3% vs. 3.6%) or new-onset AFib (16.4% vs. 9.1%) tended to be higher in the LVT group than in the control group in our study patients (both $P > 0.05$). Of these, only two patients in the LVT group received anticoagulation therapy before inclusion (one with warfarin and one with rivaroxaban). Our data are insufficient to determine the relationship between AFib and LVT in AMI patients due to limited sample size. Future studies are warranted to explore the contribution of AFib as well as the impact of anticoagulation treatment before admission, in-hospital, post discharge on LVT formation and dissolving in AMI patients.

Clinical implication

Our study implies that special attention is needed to check for LVT in patients with acute anterior MI complicate by RV dysfunction, especially if apical akinesia/aneurysm or additional risk factors such as a reduced MAPSE or DD are present. In patients presenting with these risk factors, it might be indicated to prolong the monitoring time point for LVT (no less than 3 months). In these patients, it might be of particular importance to evaluate the efficacy of thrombus prevention by oral anticoagulants in future studies.

Conclusions

Our current data demonstrate that besides the known risk factors, including apical aneurysm, reduced left ventricular longitudinal systolic function (MAPSE) and advanced diastolic dysfunction, RV dysfunction as determined by reduced TAPSE or RV_FAC is independently associated with LVT formation in acute anterior MI patients, especially in the setting of anterior MI without the formation of an apical aneurysm. This study suggests that besides assessment of left ventricular abnormalities, assessment of concomitant RV dysfunction is of importance on risk stratification of LVT formation in patients with acute anterior MI.

Conflict of interest

None declared.

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