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Right Ventricular Dysfunction contributes to Left Ventricular Thrombus Formation in Patients post Anterior Myocardial Infarction

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Die Promovendin ist Ärztin

Dedicated to my family and my dearest grandmother

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1. Introduction

1.1. Background

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

However, the incidence of ischemic heart disease overall is still constantly increasing worldwide and several serious, potentially fatal complications of AMI remain challenging in clinical practice.[2, 3] Among the spectrum of life-threatening complications following AMI are thromboembolic events such as stroke due to left ventricular thrombus (LVT) formation.

1.2. Relevance

Both in the thrombolysis and pPCI era, LVT has been found to be an independent predictor of systemic embolism.[4, 5] The incidence of systemic embolism in patients with AMI complicated by LVT was reported to be approximately 16% in the pPCI era, while the historic risk of embolization in the thrombolysis era has been reported to be up to 20%.[4-6] However, the data on the exact frequency of embolization in the PCI era is still lacking. LVT with its related embolic complications persists as an important part of the management of AMI even successfully treated with pPCI and intensive dual antiplatelet therapy especially among anterior infarcts. Moreover, the benefit of combing anticoagulation with dual antiplatelet therapy (acetylsalicylic acid [ASA] and a P2Y12

inhibitor) remains a matter of debate considering of increased bleeding risk in the setting of triple antithrombotic therapy.[7-10] Nonetheless, a recent study comprising of 1850 AMI patients suggested that the appropriate treatment with vitamin K antagonists may decrease the incidence of systemic embolism in patients with first AMI complicated by LVT without increasing the bleeding risks.[4]

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 in order to provide evidence for decision making on the prevention and optimal management of LVT post AMI.

1.3. Current recommendation from American College of Cardiology Foundation / American Heart Association (ACCF/AHA)

In the 2013 ACCF/AHA guidelines for the management of ST-elevation myocardial infarction (STEMI), anticoagulant therapy with a vitamin K antagonist is recommended for patients with AMI and evidence of asymptomatic LV mural thrombi (Class II a, Level of Evidence: C).[11]

Prophylactic anticoagulation may be reasonable for the patients with STEMI and anterior apical akinesia or dyskinesis but without evidence of LVT (Class II b, Level of Evidence: C). In consideration of the increased bleeding risk under triple antithrombotic therapy, the guidelines suggest that target INR should be limited to a lower range (e.g. from 2.0 to 2.5) in patients with STEMI who are receiving dual antiplatelet therapy.[11]

1.4. Incidence of LVT in the pPCI era

The advent of PCI and widespread use of dual antiplatelet therapy have led to a remarkable decrease in incidence of LVT in the setting of AMI by reducing the extent of myocardial damage and salvaging the myocardium at risk.[12-14] In the pPCI era, the incidence of LVT has been reported to range from 2.5 to 15%, while early data from the pre-thrombolytic and thrombolytic eras showed that LVT was present in 7-46% of patients with AMI.[13-17] The variations in the reported incidence could relate to the differences in patient selection, diagnostic modalities and timing of examination. So far, it is known that the risk of LVT formation is highest during the first 2-3 months after AMI.[15] Even so, there is still no consensus about the timing of examination for the detection of LVT in the setting of AMI.

1.5. Pathogenesis of LVT formation

Virchow's triad [disturbance of flow (stasis or turbulence), hypercoagulability, and endothelial injury/dysfunction] serves as the pathological basis for LVT formation (**Figure 1**).[15]

The loss of contractility in the weak ischemic segment of ventricle leads to LV dysfunction and severe LV wall motion abnormalities (akinesia, dyskinesia or aneurysm), thus resulting in blood stagnation or abnormal blood flow. To the matter worse, ischemia induces endocardial damage with inflammatory changes could greatly favour LVT formation. In addition, MI causes a hypercoagulable and proinflammatory state through unclear pathological mechanisms. Elevated levels of Fibrinogen, C-reactive protein (CRP), tissue factor (TF), D-dimer and anticardiolipin antibodies (IgM and IgG) have been found to be associated with increased risk for the development of LVT, indicating

that hypercoagulability may pay a key role in the genesis of LVT.[18-20] Eventually, these three components of Virchow triad contribute to LVT formation in patients with AMI.

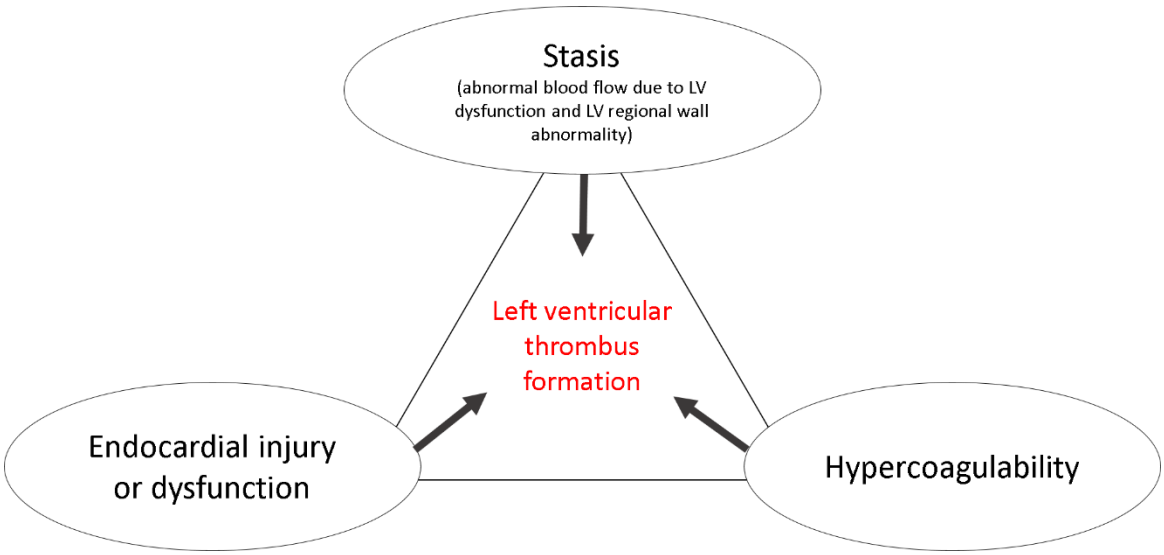

Figure 1 Virchow's triad in left ventricular thrombus formation

1.6. The known risk factors of LVT formation

Based on limited data, currently well-recognized 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 (i.e. dyskinesia, akinesia, aneurysms).[13, 17, 21]

Reduced LVEF and anterior site of MI have been identified to be strong independent predictors of LVT formation.[14] The largest observation study consisting of a total of 8326 AMI patients observed the highest rate of occurrence of LV thrombosis among patients with anterior AMI and an ejection fraction <40%, which are repeatedly confirmed in the latter studies.[14, 22] With the exclusion of high-risk patients with severe LV dysfunction, this study population is at low to medium risk for the development of LVT.[21, 22] This study identified the association between the extent of myocardial injury, the impairment of LV function and LVT formation, implying blood stagnation in dysfunctional segment of ventricle plays a crucial role in LVT formation. The deterioration of LV systolic function reflected by reduced LVEF could potentially lead to stagnant or abnormal blood flow pattern, which could greatly favour the appearance of LVT.[15] Furthermore, larger infarct size especially in the setting of anterior wall infarction has identified to be associated with more extensive myocardial injury and thus more severe wall motion abnormalities including LV aneurysm and apical akinesia and is thereby at higher risk of developing LVT.[16, 23] This same correlation between anatomic extent of transmural myocardial damage and LVT formation was also observed in the pathological studies.[24] Another important risk factor to predict the development of LVT is the presence of LV aneurysm.[21, 25]

1.7. The statement of the purpose

It remains unexplored whether there are additional clinical parameters capable of predicting LVT formation. The purpose of this study was therefore to define additional determinants of LVT formation following anterior AMI besides the known risk factors through comparing clinical and echocardiographic characteristics between patients with and without LVT formation during the first 3 months after anterior AMI.

2. Methods

2.1. Study design and patient selection

Present study was a retrospective, single-center, matched case-control study. All enrolled subjects were selected from the REDEAL-HF trial database (Clinical trial registration NCT03966729; n=2354). The REDEAL-HF trial included all patients with symptoms of heart failure and at least 2 echocardiographic examinations in the Department of Cardiology of the University Hospital Würzburg between 2009 and 2017. Finally, 55 patients with LVT identified within 3 months following AMI and 55 patients without LVT after AMI were included for final analysis.

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.

2.2. Enrollment criteria

Enrollment criteria in both groups included:

i) acute or subacute ST segment elevation or non-ST segment elevation myocardial infarction (STEMI or NSTEMI);

ii) anterior or apical AMI with severe regional wall motion abnormalities (i.e. akinesia, dyskinesia, or aneurysm).

2.3. Study flowchart

The controls were matched with anterior AMI patients without LVT by age, sex, LVEF, as well as prevalence of first MI, and multi-vessel coronary artery disease (**Figure 2**). The presence and absence of LVT was identified by transthoracic echocardiography (TTE), contrast echocardiography (n=3), and/or cardiac magnetic resonance imaging (cMRI, n=61).

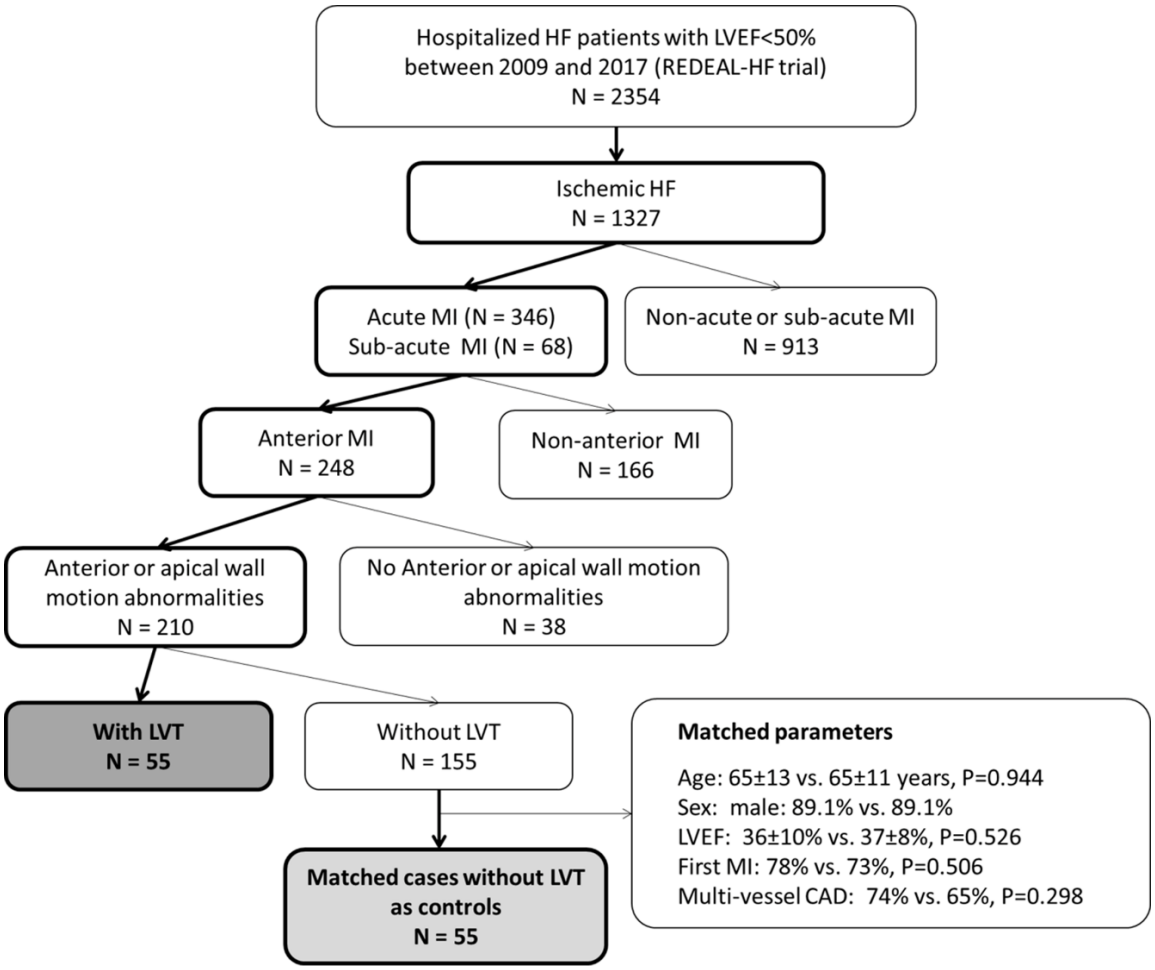

Figure 2 Study flowchart. HF: heart failure; LVEF: left ventricular ejection fraction; MI: myocardial infarction; LVT: left ventricular thrombus; CAD: coronary artery disease.

2.4. Identification of LVT

In all cases where LVT was suspected in echocardiography examinations, images were reviewed by a senior imaging physician, and monitored by serial two-dimensional transthoracic echocardiography (TTE) with the use of contrast agent if necessary. LVT was evaluated by apical 4-, 2-, and 3-chamber views, which was visible throughout systole and diastole and identifiable in at least two views. A thrombus was defined as an echo-dense mass within the left ventricular cavity with distinct margin attached to the LV wall accompanied by asynergic wall motion abnormality (hypokinetic or akinetic), but distinct from the underlying myocardium.[26, 27] On contrast images, thrombus appeared as a dark linear or protruding structure, adjacent to akinetic myocardium, surrounded by blood in the left ventricular cavity. **Figure 3** displays an example of LVT detected by TTE in a 73 years old male patient affected by AMI.

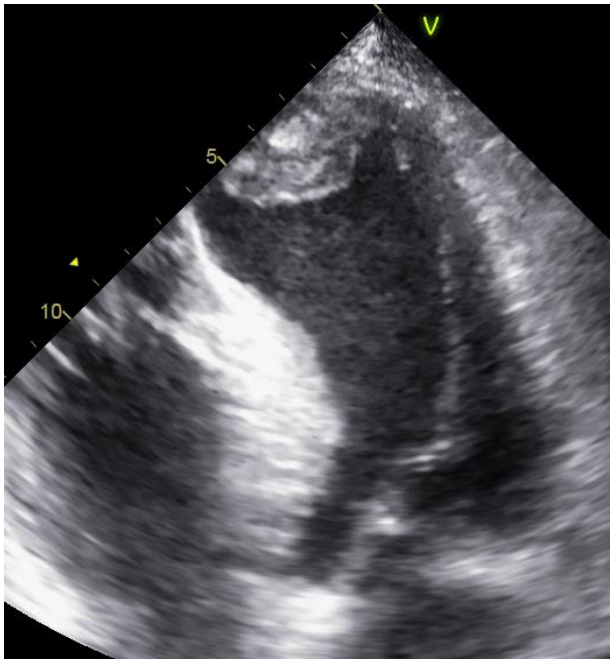

Figure 3 An example of LVT detected by two-dimensional transthoracic echocardiography (TTE) in a 73 years old male patient presenting with AMI.

2.5. Echocardiography

Two-dimensional transthoracic echocardiography (TTE) has been long established as a reliable method for the detection of the LV thrombus.[15] As the most widely used diagnostic technique for primary screening of LVT, TTE could be beneficial to provide accurate information about the natural history and features of LVT, identify the echocardiographic determinants for LVT formation in patients after AMI and estimate the risk of embolization in patients after AMI complicated by LVT.

A routine transthoracic echocardiography examination was performed at baseline (GE, Vingmed Vivid 7 or IE9, GE Vingmed Ultrasound, Horten, Norway). Standard echocardiographic measurements for the assessment of cardiac geometry and systolic and diastolic function were performed according to the American Society of Echocardiography (ASE) guidelines using dedicated software (EchoPAC^{TM}, version 202, General Electric Co., Norway).[28, 29]

Special attention was taken to recognize technical artefact or distinguish LVT from other cardiac structures such as papillary muscles, muscle trabeculae, chordal structure and tangential left ventricular muscle by optimal gain settings to minimize false positive results.[17]

2.5.1. Structural and functional measurements of left-side heart

Images were obtained in parasternal left ventricular (LV) long axis views utilizing standard M-mode to assess left atrial and ventricular dimensions, including LV end-diastolic (LVEDD), end-systolic dimensions (LVESD), end-diastolic thickness of the posterior wall (LVPWd) and the septum (IVSd).[28]

LV mass, indexed to body surface area (LVMI) was estimated by LV cavity dimension and wall thickness at end diastole[30] : LV mass (g) = 0.8 x [1.04 x (LVEDD + LVPWd + IVSd)^3 – LVEDD^3)] + 0.6. LA volume was also measured in both the apical 4- and 2-chamber views using the biplane disk summation technique method of disks. Left atrial maximum volume index (LAVi) was calculated by dividing LA volume by body surface area of subjects.

Left ventricular ejection fraction (LVEF) was calculated with the use of the modified Simpson's biplane method in apical 4- and 2- chamber views. LVEF was calculated using the following formula: LVEF = (LVEDD - LVESD / LVEDD) x 100. Mitral annular plane systolic excursion (MAPSE) at lateral and septal sites of mitral ring was assessed in the 4-chamber view utilizing the standard M-mode technique. The long-axis excursion of the mitral annulus was measured by determining the distance between the nadirs of the annulus motion profile corresponding to the maximal backward displacement of the mitral annulus from the apex, which is defined as point of peak upward excursion towards LV apex during systole.[31, 32] Caution was paid to not include the post-systolic motion towards the apex during the isovolumetric relaxation period in the measurement of MAPSE, which are often related to ischaemia, fibrosis or pressure overload, as previously described.[31, 33]

2.5.2. Diastolic dysfunction

Pulsed-wave Doppler was performed in the apical 4-chamber view to obtain mitral inflow velocities for assessment of LV diastolic function. We measured peak velocity of early (E) and atrial (A) diastolic filling and deceleration time of E wave (DT) and calculated the E/A ratio. Tissue-Doppler derived E´ was acquired at the septal and lateral annular site, as well as E/E´ was calculated.

Besides the above mentioned pulsed-wave Doppler parameters for the evaluation of diastolic filling pattern, diastolic function was assessed through consideration of three additional variables including septal E/E´ ratio, peak velocity of tricuspid regurgitation jet (TRVmax) and left atrial maximum volume index (LAVi).

In this cohort, mild DD were defined as if: E/A ratio ≤0.8 and peak E velocity ≤50 cm/s, or none or one above mentioned variables (LAVi >34 ml/m², septal E/E´ ratio>14, and TRVmax >2.8 m/s) met the cut-off value in case of E/A ratio ≤0.8 and peak E velocity >50, or E/A ratio = 0.8 - 2.0; moderate DD was defined as if: a) E/A ratio ≤0.8 and peak E velocity >50, or E/A ratio = 0.8 - 2.0 and two or all of three variables (LAVi >34 ml/m², septal E/E´ ratio>14, and TRVmax >2.8 m/s) met the cut-off values; severe DD was defined as if E/A ratio >2, and two or all of three variables (LAVi >34 ml/m², septal E/E´ ratio >14, and TRVmax >2.8 m/s) met the cut-off values (**Figure 4**).

For patients with atrial fibrillation or pacemaker rhythm, in which E/A ratio was not available, mild DD was defined as if one of the three variables (LAVi >34 ml/m², septal E/E´ ratio >14, and TRVmax >2.8 m/s) met the cut-off values.

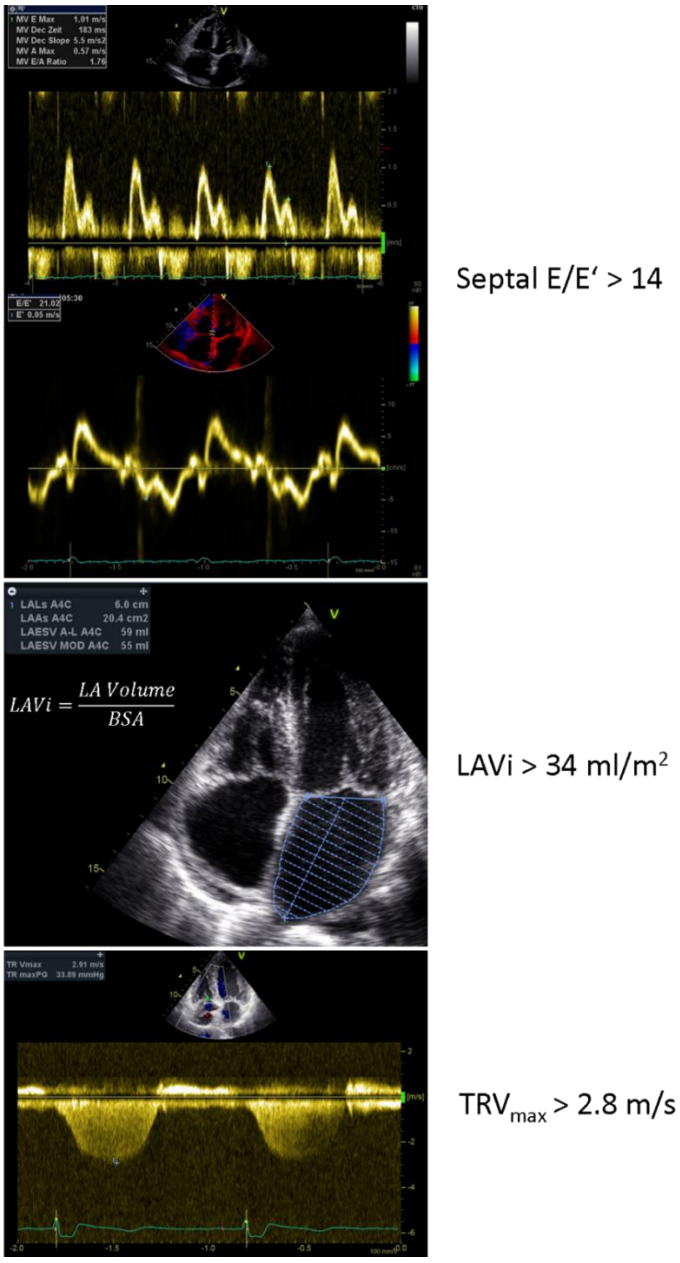

Figure 4 Diastolic function related echocardiographic parameters: septal E/E´ ratio, left atrial maximum volume index (LAVi), and peak velocity of tricuspid regurgitation jet (TRVmax). In combination with pulsed-wave Doppler parameters for the evaluation of diastolic filling pattern, diastolic dysfunction was comprehensively identified through these 3 additional parameters abnormalities (septal E/E´ >14, TRVmax >2.8 m/s, and LAVi >34 ml/m²).

2.5.3. The measurement of right ventricle

The relevant right ventricular (RV) measurements as guided by the ASE guideline have been previously described.[34, 35]

Right ventricular and atrial dimension

In brief, right atrial and ventricular dimensions, including end-diastolic RV basal and middle diameters (basal and mid RVD), end-systolic RA area (RAA) were measured from a RV focused apical 4-chamber view (**Figure 5**).

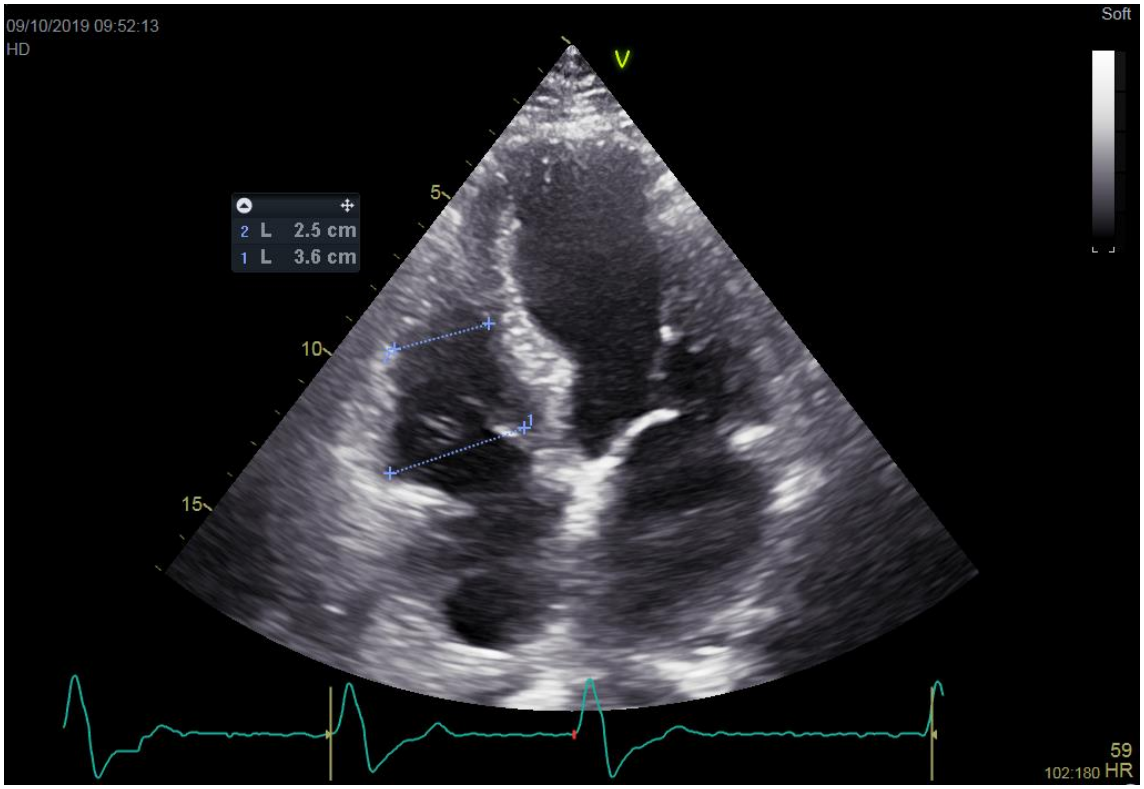

Figure 5 Echocardiographic image from apical 4-chamber view showing the right ventricular (RV) end-diastolic basal (L1) and mid (L2) diameters. The transducer is adjusted to focus on the RV chamber, with the goal of maximizing RV chamber size.

TAPSE

Tricuspid annular plane systolic excursion (TAPSE) was assessed from a standard apical 4-chamber window 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 from end-diastole toward the apex at end-systole (**Figure 6**).

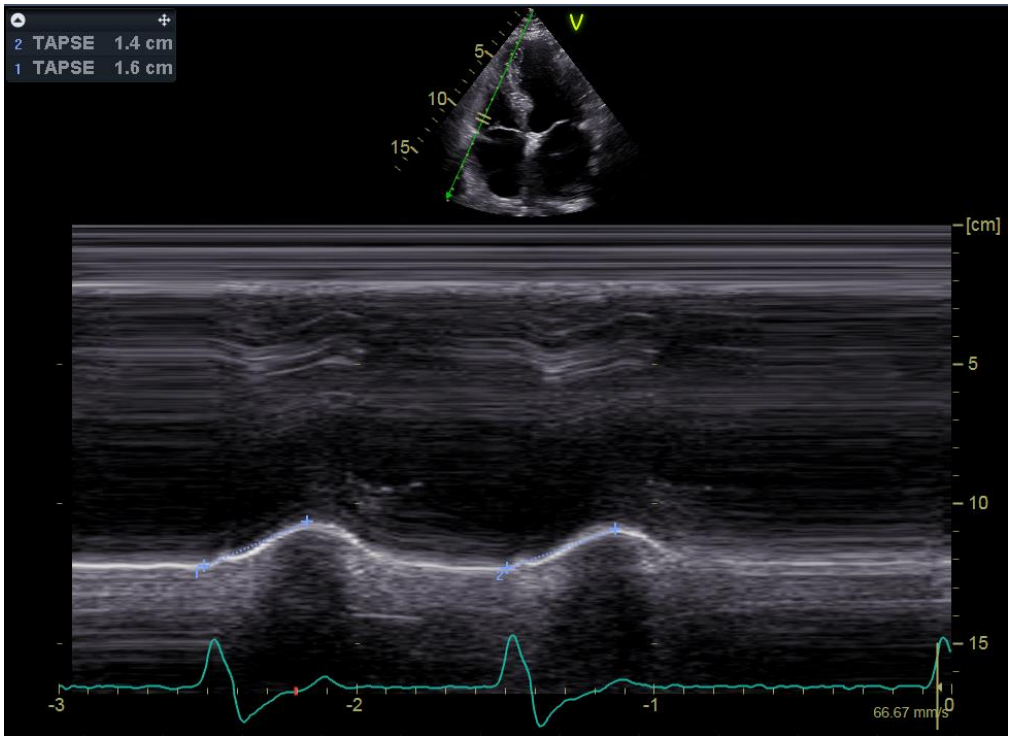

Figure 6 Echocardiographic measurement of tricuspid annular plane systolic excursion (TAPSE) using M-mode at the junction of the tricuspid valve plane with the free wall of the right ventricle.

FAC

The RV fractional area change (FAC) is obtained in apical 4-chamber views by tracing the RV endocardial border from the tricuspid annulus, along the free wall to the apex, and then back to the annulus, along the interventricular septum both at end-diastole and end-systole. Care was taken to trace the free wall beneath the trabeculations tricuspid leaflets, and chords. FAC was calculated as: FAC = (RV end-diastolic area – RV end-systolic area) / RV end-diastolic area (**Figure 7**).

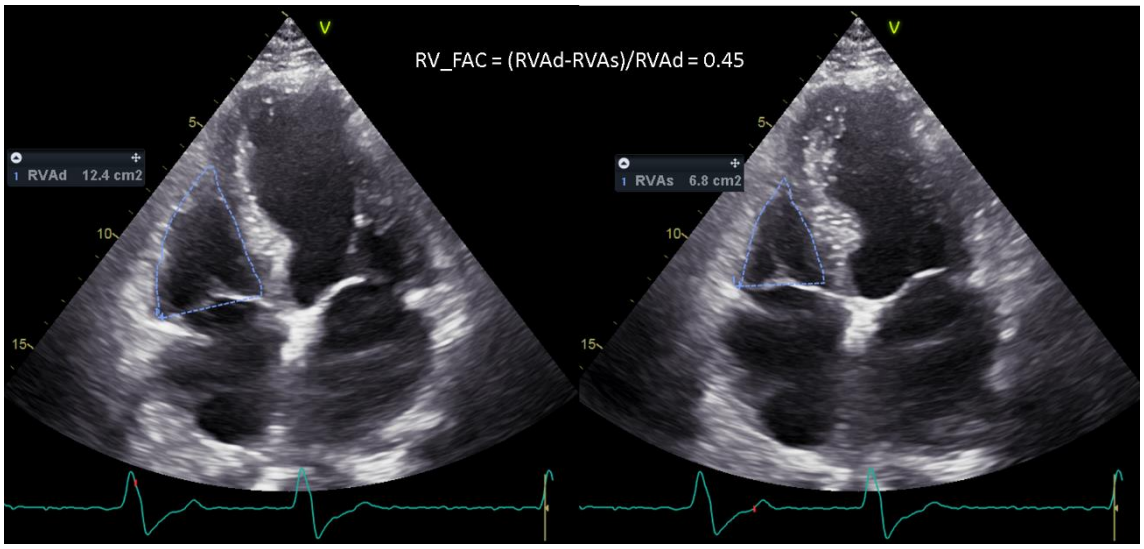

Figure 7 Echocardiographic measurement of fractional area change (FAC). Right ventricular end-diastolic (RVAd) and end-systolic areas (RVAs) are measured from an apical 4-chamber view. FAC is calculated as: (RVAd – RVAs)/RVAd.

sPAP

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 $(TRVmax)^2$ + RAP, where TRVmax indicates the peak TR jet velocity (**Figure 8**). RAP denoted right atrial pressure, estimated from inferior vena cava diameter and respiratory changes. IVC diameter and inspiratory collapsibility were detected from the subcostal view. Normal RAP of 5 mmHg was defined as IVC diameter ≤2.1 cm and inspiratory collapsibility >50%; 10 mmHg was defined as IVC diameter ≤2.1 cm and inspiratory collapsibility <50%; high RAP of 15 mmHg was defined as IVC diameter >2.1 cm and inspiratory collapsibility <50%.[35]

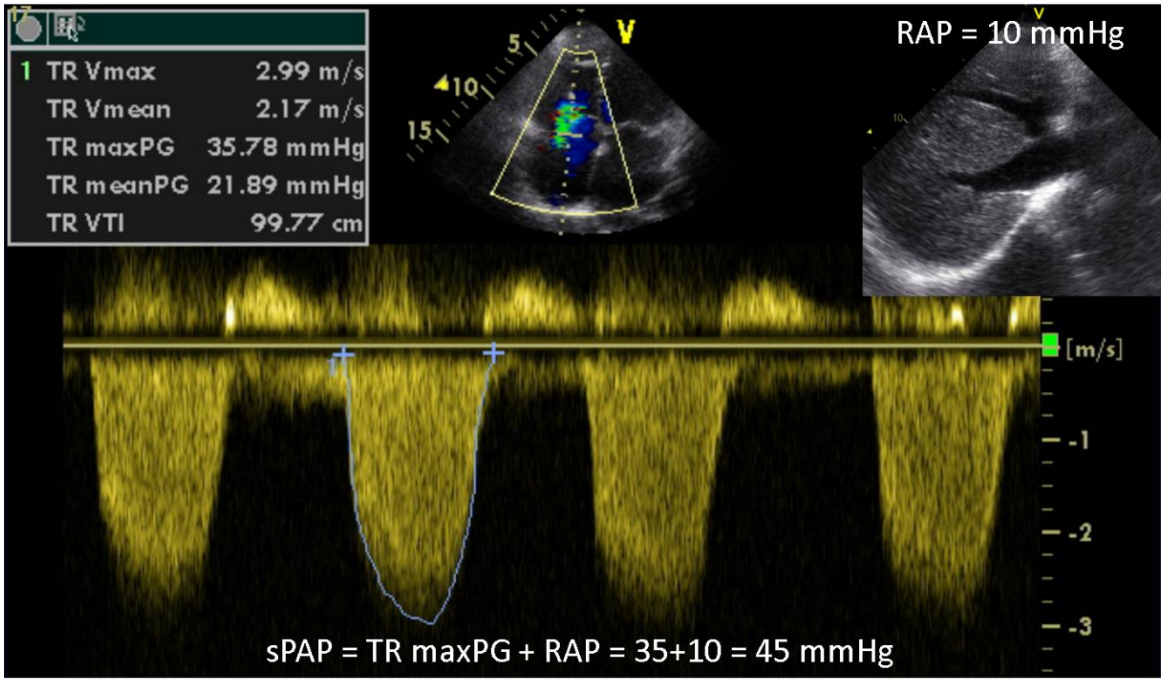

Figure 8 Echocardiographic measurement of systolic pulmonary artery pressure (sPAP), which is calculated as sPAP = 4 $(TRVmax)^2$ + RAP, where TRVmax indicates the peak TR jet velocity and RAP right atrial pressure.

2.5.4. Definition of LV aneurysm

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.[36, 37]

2.6. cMRI

Cardiac magnetic resonance imaging (cMRI) is nowadays considered as the gold standard for the detection of LVT in patients with systolic dysfunction. [38] Its highly accurate ability of identifying the presence of LVT is based on tissue characteristics rather than anatomical appearance. [38] The fact that thrombus has essentially no gadolinium uptake in contrary to myocardium facilitates the distinction of thrombus from other certain cardiac structures through cMRI irrespective of the morphology or location of LVT.[38] However, cMRI is not widely applied in comparison to echocardiography in the current clinical practice because it is costly, time consuming and not generally available.

In our cohorts, the presence of LVT was confirmed by cMRI in all cases where diagnosis was uncertain. **Figure 9** displays an example of LVT detected by cMRI in a patient with AMI**.**

cMRI was performed using a 1.5 Tesla full body MRI scanner (Magnetom Symphony Quantum/Avanto, Siemens Medical Systems, Erlangen, Germany). Late gadolinium enhancement (LGE) images were acquired 15 minutes after intravenous injection of 0.2 mmol/kg gadopentetate dimeglumine, using T1-weighted inversion recovery imaging sequences (field of view 240×320 mm^2, matrix size 165×256, slice thickness 8 mm, echo time 3.4 ms, repetition time 7.5 ms). The areas with signal intensity above the average of the normal myocardium plus 2 standard deviations were defined as LGE positive. The severity of LGE for individual patients was defined according to blinded evaluation of all clinical data by at least two specialized radiologists as described before.[39]

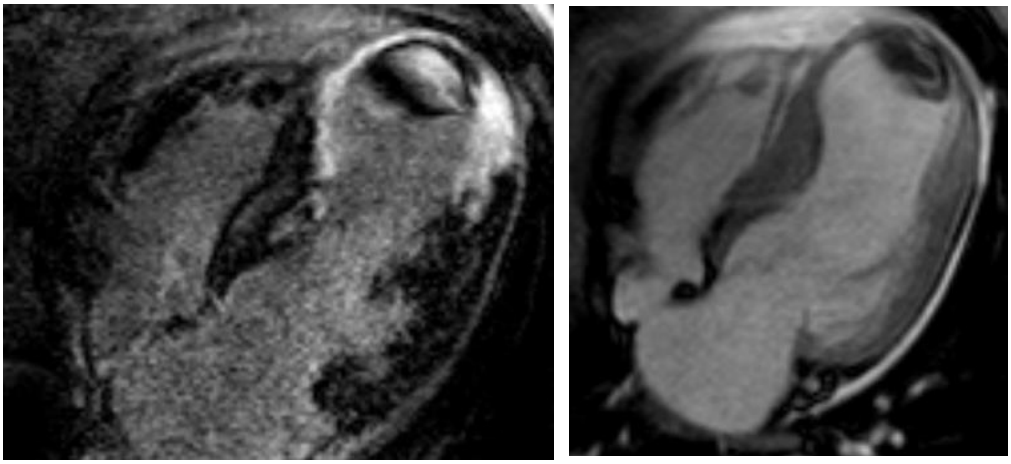

Figure 9 Detection of left ventricular thrombus by cardiac magnetic resonance imaging (cMRI). Left: cMRI without contrast agent; Right: cMRI with late gadolinium enhancement (MRI-LGE).

2.7. 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 percent, and the differences between groups were compared using Chi-square test or Fischer's exact test, as indicated. 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.

3. Results

3.1. Clinical characteristics

According to the study protocol, patients with LVT and without LVT (as controls) were matched for age (mean age 65±13 vs. 65±11 years, P=0.944), sex (male 89.1% vs. 89.1%), LVEF (35.8±9.9% vs. 36.9±8.4%, P=0.526), the prevalence of prior MI (78.2% vs. 72.7%, P=0.506), and the presence of multi-vessel coronary artery disease (74.5% vs. 65.4%, P=0.298) (**Table 1**). Prevalence of hypertension and anemia were significantly lower in the LVT group than in the control group (P=0.002 and 0.004).

After gathering information about clinical characteristics from electronic medical records at the time of hospitalization and comparing these data between the groups with and without LVT, the proportions of other cardiac risk factors and comorbidities, including atrial fibrillation, obesity, diabetes, dyslipidaemia, smoking, TIA/ stroke, and chronic kidney disease were similar between the two groups, besides hypertension and anaemia. The presence of hypertension and anaemia appear to be associated with reduced risk of LVT formation in anterior AMI patients.

Table 1 Clinical characteristics

	Control N=55	LVT N=55	P value
Age (years)	65±11	65±13	0.944
Male [n (%)]	49 (89.1)	49 (89.1)	-
BMI (kg/m²)	29±4	27±4	0.061
NYHA class III-IV [n (%)]	20 (36.4)	19 (34.5)	0.842
Risk factors and co-morbidities [n, %]			
Atrial fibrillation	7 (12.7)	13 (23.6)	0.092
Obesity	19 (34.5)	12 (21.8)	0.138
Hypertension	45 (81.8)	33 (60.0)	0.012
Diabetes mellitus	11 (20.0)	17 (30.9)	0.189
Dyslipidemia	33 (60.0)	25 (45.5)	0.127
Smoking	30 (54.5)	23 (41.8)	0.182
Anemia	24 (43.6)	10 (18.2)	0.004
TIA or Stroke	4 (7.3)	6 (10.9)	0.507
Chronic kidney disease >II	18 (32.7)	16 (29.1)	0.680
MI characteristics [n (%)]			
First MI	40 (72.7)	43 (78.2)	0.506
Recurrent MI	15 (27.3)	12 (21.8)	
Involved coronary arteries			0.519
1	14 (25.5)	19 (34.5)	
2	17 (30.9)	13 (23.6)	
3	24 (43.6)	23 (41.8)	

LVT, left ventricular thrombus; BMI, body mass index; NYHA, New York Heart Association; MI, myocardial infarction; LVEF, left ventricular ejection fraction.

3.2. Echocardiographic characteristics

Echocardiographic characteristics are listed in **Table 2**. The proportion of patients with apical aneurysm was significantly higher in patients with LVT as compared to those without LVT (32.7% vs. 12.7%, P=0.012, OR 3.34, 95% CI 1.26-8.82). 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±2.5mm, P=0.001, OR=0.74, 95% CI 0.62-0.89). The proportion of moderate or severe diastolic dysfunction was significantly higher in the LVT group than in the control group (70.9% vs. 49.1%, P=0.020, OR=2.53, 95% CI 1.15-5.55).

RV functional parameters assessed included TAPSE, RV_FAC, and RVDs. Basal RV diameter (37.0±5.8 vs. 34.3±7.5mm, P=0.038, OR=1.06, 95% CI 1.00-1.13) and mid-ventricular RV diameter (29.5±5.3 vs. 26.5±7.1mm, P=0.012, OR=1.08, 95% CI 1.01-1.15) were significantly higher in the LVT group than in the control group. TAPSE was significantly lower in the LVT group as compared to the control group (15.4±4.7 vs. 18.7±5.8mm, P=0.001, OR=0.88, 95% CI 0.82-0.96). 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, OR=2.86, 95% CI 1.12-7.30, P=0.021).

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	0.132
IVSd (mm)	9.9±1.6	9.8±1.4	0.926
LVPWd (mm)	9.4±1.9	10.0±1.6	0.099
LVMi (g/m²)	103.0±25.2	104.2±30.1	0.813
LVEF (%)	36.9± 8.4	35.8± 9.9	0.526
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	0.075
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	0.112
RV_FAC <0.35 [n (%)]	8 (14.5)	18 (32.7)	0.025
RAA (cm²)	16±4	16±4	0.310
LAVi (ml/m²)	33±11	36±12	0.192
E wave (cm/s)	79±25	79±21	0.867
DT (ms)	174±56	173±61	0.973
E/A ratio	1.33±0.78	1.40±0.82	0.636
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	0.313
Moderate to severe DD [n (%)]	27 (49.1)	39 (70.9)	0.020

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

3.3. Risk factors associated with LVT formation after anterior AMI

Multivariable binary logistic regression analysis demonstrated that independent determinants associated with LVT formation included apical aneurysm (OR=5.06, 95% CI 1.65-15.48), reduced septal MAPSE (<7mm, OR=4.70, 95% CI 1.84-11.95), advanced (i.e. moderate or severe) diastolic dysfunction (OR=2.71, 95% CI 1.11-6.57), reduced TAPSE (<17mm, OR=5.48, 95% CI 2.12-14.13), reduced RV_FAC (<0.35, OR=3.32, 95% CI 1.20-9.18), and increased RVDs (per 5mm increase, OR=1.51-1.62) after adjusted for body mass index, hypertension and anemia (**Table 3, Figure 10**).

Table 3 Clinical and echocardiographic factors associated with LVT formation

	Crude odds ratio (95% CI)	P value	*Clinical covariates adjusted odds ratio (95% CI)	P value
Clinical variables				
Age (years)	0.999 (0.969-1.030)	0.944		
BMI (kg/m²)	0.915 (0.832-1.006)	0.065		
Atrial fibrillation	2.122 (0.775-5.815)	0.143		
Hypertension	0.333 (0.139-0.797)	0.014		
Anemia	0.287 (0.120-0.684)	0.005		
Echocardiographic variables				
Apical aneurysm	3.336 (1.261-8.823)	0.015	5.059 (1.653-15.485)	0.005
LVEF (%)	0.987 (0.947-1.028)	0.522		
Septal MAPSE	0.741 (0.617-0.890)	0.001		
<7mm vs. ≥7mm	3.740 (1.644-8.510)	0.002	4.695 (1.844-11.954)	0.001
Lateral MAPSE	0.871 (0.747-1.015)	0.078		
Moderate to severe DD	2.528 (1.152-5.548)	0.021	2.708 (1.115-6.574)	0.028
TAPSE	0.884 (0.816-0.958)	0.003		
<17mm vs. ≥17mm	3.391 (1.538-7.480)	0.002	5.478 (2.124-14.132)	<0.001
RV_FAC <0.35 vs. ≥0.35	2.858 (1.119-7.299)	0.028	3.321 (1.202-9.178)	0.021
RVD_basal	1.063 (1.002-1.127)	0.042	1.089 (1.016-1.168)	0.016
per 5mm increase	1.326 (0.994-1.769)	0.055	1.515 (1.071-2.142)	0.019
RVD_mid	1.083 (1.015-1.155)	0.016	1.102 (1.024-1.186)	0.010
per 5mm increase	1.489 (1.077-2.059)	0.016	1.623 (1.125-2.342)	0.010

*adjusted for clinical covariates including BMI, hypertension, and anemia.

For abbreviations, see Tables 1 and 2.

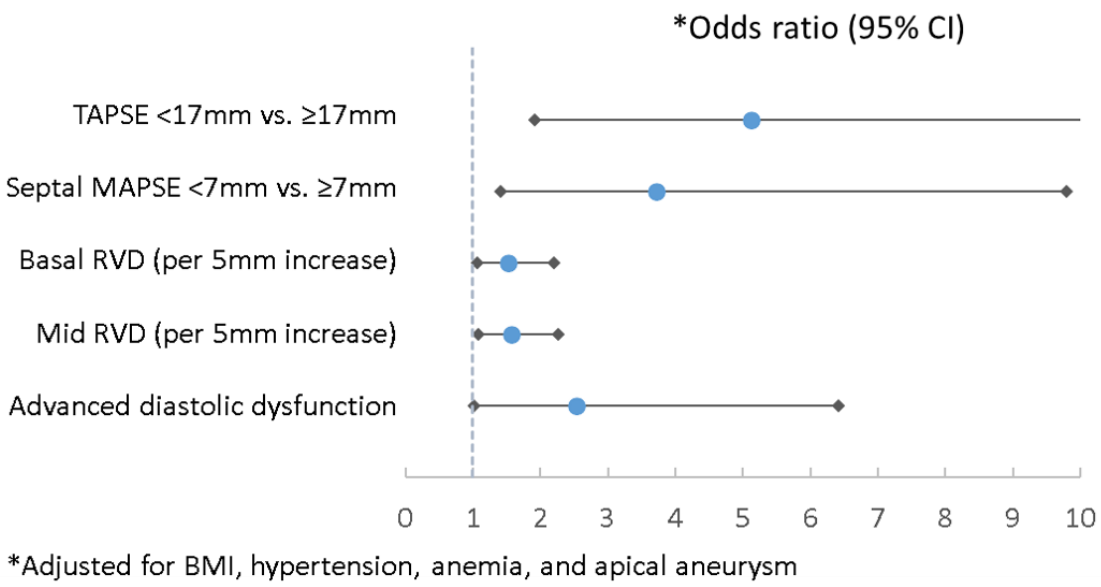

Figure 10 Forest plot of odds ratios (big blue dots) and 95% confidence intervals (bars) for the risk of development of left ventricular thrombus after anterior acute myocardial infarct adjusted for BMI, hypertension, anemia, and apical aneurysm.

TAPSE: tricuspid annular plane systolic excursion; MAPSE: mitral annular plane systolic excursion; RVD: right ventricular diameter; BMI: body mass index.

3.4. Right ventricular dysfunction associated with LVT formation post anterior AMI

For further identifying the relationship between RV dysfunction and LVT formation in this cohort, apical aneurysm, MAPSE, and advanced diastolic dysfunction were added into logistic regression models as additional confounders (**Table 4A**).

Overall, 85% of anterior AMI patients who presented with TAPSE <17mm and RV_FAC <0.35 were found to have LVT in this cohort. The results suggest that especially reduced TAPSE together with reduced RV_FAC were strongly associated with an increased risk of LVT formation in post infarction patients independent of BMI, hypertension, anemia, apical aneurysm, MAPSE, and advanced diastolic dysfunction (OR=7.11, 95% CI 1.60-31.62, P=0.010).

As expected, the prevalence of LVT in AMI patients with apical aneurysm was significantly higher than in patients without aneurysm (72.0% vs. 43.5%, P=0.012). When focusing on the subgroup of AMI patients presented without apical aneurysm (i.e., apical akinesia without protruding beyond the outline of the LV chamber, n=85), RV dysfunction (i.e., TAPSE <17mm and/or RV_FAC <0.35) was significantly associated with increased prevalence of LVT (LVT prevalence: 57.9% in RV dysfunction group vs. 31.9% in non-RV dysfunction group, P=0.016). While in the subgroup of AMI patients with apical aneurysm (n=25), RV dysfunction was not associated with an increased risk of LVT (LVT prevalence: 68.8% in RV dysfunction group vs. 77.8% in non-RV dysfunction group). The prevalence of LVT was 61.1% (33/54) in AMI patients with apical akinesia or aneurysm complicating with RV dysfunction defined by echocardiography (i.e., TAPSE <17mm and/or RV_FAC <0.35), while the prevalence of LVT was 39.3% (22/56) in patients with apical akinesia or aneurysm without RV dysfunction (P=0.022).

As shown in **Table 4B**, after adjusted for potential clinical covariates (BMI, hypertension, and anemia), TAPSE<17mm (OR=7.04, 95% CI 2.28-21.77, P=0.001) and RV_FAC<0.35 (OR=3.779, 95% CI 1.151-12.413, P=0.028) were associated with increased risk of LVT formation in the subgroup of patients without apical aneurysm. Of note, when MAPSE and advanced DD were entered into multivariable logistic regression models, only TAPSE remained an independent determinant of LVT formation (OR=5.119, 95% CI 1.449-18.077, P=0.011) while RV_FAC was not an independent determinant of LVT anymore (OR=1.579, 95% CI 0.415-6.005, P=0.502).

Table 4A Right ventricular dysfunction associated with LVT formation post anterior AMI

	Percent of LVT	*Adjusted odds ratio (95% CI)	P value
TAPSE <17 mm	66.7% (32/48)	3.845 (1.374-10.754)	0.010
RV_FAC <0.35	69.2% (18/26)	2.125 (0.711-6.349)	0.177
TAPSE <17mm + RV_FAC <0.35	85.0% (17/20)	7.114 (1.601-31.618)	0.010

*adjusted for BMI, hypertension, anemia, apical aneurysm, MAPSE, and advanced DD. For abbreviations, see Tables 1 and 2.

Table 4B Predictive performance of TAPSE and RV_FAC in patients without and with apical aneurysm

	*Clinical covariates adjusted odds ratio (95% CI)	P value	**Clinical and echo covariates adjusted odds ratio (95% CI)	P value
Without apical aneurysm (n=85, events=37, 43.5%)				
TAPSE <17mm	7.044 (2.279-21.774)	0.001	5.119 (1.449-18.077)	0.011
RV_FAC <0.35	3.779 (1.151-12.413)	0.028	1.579 (0.415-6.005)	0.502
With apical aneurysm (n=25, events=18, 72.0%)				
TAPSE <17mm	0.893 (0.111-7.194)	0.916		
RV_FAC <0.35	2.500 (0.194-32.194)	0.428		

*adjusted for BMI, hypertension, and anemia.

**adjusted for BMI, hypertension, anemia, MAPSE, and advanced DD.

For abbreviations, see Tables 1 and 2.

4. Discussion

4.1. The main finding of this study

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 reflects severe impairment of RV longitudinal and radial function, showed particularly strong association with an increased risk of LVT formation in patients post anterior AMI, independent of confounders including apical aneurysm, MAPSE, and advanced diastolic dysfunction. To our knowledge, this is the first report describing the role of RV dysfunction on LVT formation post anterior AMI.

Previous studies have defined numerous risk factors of LVT formation post anterior AMI, including large infarct size, apical aneurysm/akinesia, reduced left ventricular longitudinal systolic function (MAPSE), and advanced diastolic dysfunction.[15, 40, 41] Notably, blood stasis in larger dysfunctional ischemic areas serves as key factors of LVT formation in line with Virchow's triad.[15] Advanced diastolic dysfunction, 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.[41] 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 AMI patients.

In line with the findings of previous studies, the current study confirmed again that apical aneurysm serves as a strong predictor of LVT formation in AMI patients. However, we found that in the presence of RV dysfunction the risk of LVT formation was significantly higher even in the absence of apical aneurysm. Furthermore, TAPSE and RV_FAC was

identified to be independent predictor of LVT formation among patients without apical aneurysm irrespective of clinical and echocardiographic confounders. It could be speculated 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. Thus, RV dysfunction might result from septal dysfunction after AMI. On the other hand, one may speculate on a link between RV dysfunction and diastolic dysfunction; since both disease entities lead to impaired hemodynamics in pulmonary circulation and LV filling, there might be a close link in pathophysiology of thrombus formation such as fluid stasis in the lungs.

4.2. Hypertension and anemia as protective factors against LVT formation

In our present study, the presence of hypertension was revealed as a protective factor against LVT formation among anterior AMI patients. This result is consistent with the finding of a previous report showing less ventricular thrombus post AMI among patients with or without history of hypertension (0.5% vs. 1.5%, $P<0.03$) in a large AMI patient cohort (n=4994).[42] It might be speculated that greater severity of coronary atherosclerosis induced by hypertension may result in more extensive development of collateral circulation with a consequently less severe extension of the infarction area, which could account for the better left ventricular systolic function in the presence of hypertension in patients affected by AMI.[42] Obviously, further mechanistic prospective studies are warranted to validate the observed results to see if hypertension really serves as protective factor for LVT formation post anterior AMI.

Interestingly, we found that anemia might be another protective factor against the development of LVT in patients after anterior AMI. Theoretically, anemia reduces the oxygen carrying capacity of blood and may theoretically exacerbate ischemia, increasing myocardial injury.[43] Previous reports indicated that iron-deficiency anemia is linked with increased risk of venous thromboembolism[44] and cerebral venous thrombosis.[45] In a review article, Franchini and colleagues concluded that both iron deficiency and overload have been associated with an increased thrombotic risk in experimental and clinical studies.[46] The reason why less prevalence of LVT was observed in anterior AMI patients complicating with anemia is, therefore, unclear and deserves further prospective experimental and clinical studies.

4.3. Clinical implications

Our study implies that special attention is needed to check for LVT in patients with anterior AMI complicated by RV dysfunction, especially if apical akinesia/aneurysm or additional risk factors such as a reduced MAPSE or diastolic dysfunction 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 importance to evaluate the efficacy of thrombus prevention by oral anticoagulants in future studies.

4.4. Limitations

Several limitations in this study must be acknowledged.

Firstly, this was a retrospective study from a single centre and thus has all limitations of this kind of study. The exclusion of patients without anterior AMI introduces a selection bias in this study design. With this exclusion, the study population was therefore at higher risk of developing LVT. However, this study aimed to focus on the LVT high-risk group which is prone to developing LVT to find out other potential determinants of LVT formation among these patients.

Secondly, echocardiography is the most commonly used diagnostic regimen of identifying the presence of LVT in the current clinical practice, but it may overlook the presence of LVT compared with other diagnostic modalities such as contrast-enhanced echocardiography or cMRI. cMRI as the gold standard for the detection of LVT, was not performed in all study patients. Given that cMRI is superior to echocardiography in terms of sensitivity and specificity, multimodality regimen for the detection of LVT is needed to be established.

Finally, sample size of LVT in our study was small. Further large-scale prospective studies are thereby warranted to confirm the impact of right ventricular dysfunction on LVT formation in patients after AMI complicated by LVT.

5. 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 left ventricular abnormalities, RV dysfunction likewise contributes LVT formation in patients with acute anterior MI.

6. References

1. Shepard D, VanderZanden A, Moran A, Naghavi M, Murray C, Roth G. Ischemic heart disease worldwide, 1990 to 2013: Estimates from the global burden of disease study 2013. *Circulation. Cardiovascular quality and outcomes*. 2015;8:455-456.

2. Bajaj A, Sethi A, Rathor P, Suppogu N. Acute complications of myocardial infarction in the current era: Diagnosis and management. *Journal of Investigative Medicine*. 2015;63:844-855.

3. Luscher TF. Myocardial infarction: Mechanisms, diagnosis, and complications. *European Heart Journal*. 2015;36:947-949.

4. Maniwa N, Fujino M, Nakai M, Nishimura K, Miyamoto Y, Kataoka Y, Asaumi Y, Tahara Y, Nakanishi M, Anzai T, Kusano K, Akasaka T, Goto Y, Noguchi T, Yasuda S. Anticoagulation combined with antiplatelet therapy in patients with left ventricular thrombus after first acute myocardial infarction. *European Heart Journal*. 2018;39:201-208.

5. Vaitkus PT, Barnathan ES. Embolic potential, prevention and management of mural thrombus complicating anterior myocardial infarction: A meta-analysis. *Journal of the American College of Cardiology*. 1993;22:1004-1009.

6. Bastiany A, Grenier ME, Matteau A, Mansour S, Daneault B, Potter BJ. Prevention of left ventricular thrombus formation and systemic embolism after anterior myocardial infarction: A systematic literature review. *Canadian Journal of Cardiology*. 2017;33:1229-1236.

7. Nikolsky E, Mehran R, Dangas GD, Yu J, Parise H, Xu K, Pocock SJ, Stone GW. Outcomes of patients treated with triple antithrombotic therapy after primary percutaneous coronary intervention for st-elevation myocardial infarction (from the harmonizing outcomes with revascularization and stents in acute myocardial infarction [horizons-ami] trial). *American Journal of Cardiology*. 2012;109:831-838.

8. Sorensen R, Hansen ML, Abildstrom SZ, Hvelplund A, Andersson C, Jorgensen C, Madsen JK, Hansen PR, Kober L, Torp-Pedersen C, Gislason GH. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin k antagonists in denmark: A retrospective analysis of nationwide registry data. *Lancet*. 2009;374:1967-1974.

9. Karjalainen PP, Porela P, Ylitalo A, Vikman S, Nyman K, Vaittinen MA, Airaksinen TJ, Niemela M, Vahlberg T, Airaksinen KE. Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. *European Heart Journal*. 2007;28:726-732.

10. Mattichak SJ, Reed PS, Gallagher MJ, Boura JA, O'Neill WW, Kahn JK. Evaluation of safety of warfarin in combination with antiplatelet therapy for patients treated with coronary stents for acute myocardial infarction. *Journal of Interventional Cardiology*. 2005;18:163-166.

11. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX. 2013 accf/aha guideline for the management of st-elevation myocardial infarction: A report of the american college of cardiology foundation/american heart association task

force on practice guidelines. *Journal of the American College of Cardiology*. 2013;61:e78-e140.

12. Khoury S, Carmon S, Margolis G, Keren G, Shacham Y. Incidence and outcomes of early left ventricular thrombus following st-elevation myocardial infarction treated with primary percutaneous coronary intervention. *Clinical Research in Cardiology: official journal of the German Cardiac Society*. 2017;106:695-701.

13. Zielinska M, Kaczmarek K, Tylkowski M. Predictors of left ventricular thrombus formation in acute myocardial infarction treated with successful primary angioplasty with stenting. *American Journal of the Medical Sciences*. 2008;335:171-176.

14. Gianstefani S, Douiri A, Delithanasis I, Rogers T, Sen A, Kalra S, Charangwa L, Reiken J, Monaghan M, MacCarthy P. Incidence and predictors of early left ventricular thrombus after st-elevation myocardial infarction in the contemporary era of primary percutaneous coronary intervention. *American Journal of Cardiology*. 2014;113:1111-1116.

15. Delewi R, Zijlstra F, Piek JJ. Left ventricular thrombus formation after acute myocardial infarction. *Heart*. 2012;98:1743-1749.

16. Solheim S, Seljeflot I, Lunde K, Bjornerheim R, Aakhus S, Forfang K, Arnesen H. Frequency of left ventricular thrombus in patients with anterior wall acute myocardial infarction treated with percutaneous coronary intervention and dual antiplatelet therapy. *American Journal of Cardiology*. 2010;106:1197-1200.

17. Asinger RW, Mikell FL, Elsperger J, Hodges M. Incidence of left-ventricular thrombosis after acute transmural myocardial infarction. Serial evaluation by two-

dimensional echocardiography. *New England Journal of Medicine*. 1981;305:297-302.

18. Solheim S, Seljeflot I, Lunde K, Bratseth V, Aakhus S, Forfang K, Arnesen H. Prothrombotic markers in patients with acute myocardial infarction and left ventricular thrombus formation treated with pci and dual antiplatelet therapy. *Thrombosis Journal*. 2013;11:1.

19. Okuyan E, Okcun B, Dinckal MH, Mutlu H. Risk factors for development of left ventricular thrombus after first acute anterior myocardial infarction-association with anticardiolipin antibodies. *Thrombosis Journal*. 2010;8:15.

20. Shacham Y, Leshem-Rubinow E, Ben Assa E, Rogowski O, Topilsky Y, Roth A, Steinvil A. Comparison of c-reactive protein and fibrinogen levels in patients having anterior wall st-segment elevation myocardial infarction with versus without left ventricular thrombus (from a primary percutaneous coronary intervention cohort). *American Journal of Cardiology*. 2013;112:57-60.

21. Jiang YX, Jing LD, Jia YH. Clinical characteristics and risk factors of left ventricular thrombus after acute myocardial infarction: A matched case-control study. *Chinese Medical Journal (Engl.)*. 2015;128:2415-2419.

22. Chiarella F, Santoro E, Domenicucci S, Maggioni A, Vecchio C. Predischarge two-dimensional echocardiographic evaluation of left ventricular thrombosis after acute myocardial infarction in the gissi-3 study. *American Journal of Cardiology*. 1998;81:822-827.

23. Johannessen KA, Nordrehaug JE, von der Lippe G. Left ventricular thrombosis and cerebrovascular accident in acute myocardial infarction. *British Heart Journal*. 1984;51:553-556.

24. Pirolo JS, Hutchins GM, Moore GW. Infarct expansion: Pathologic analysis of 204 patients with a single myocardial infarct. *Journal of the American College of Cardiology*. 1986;7:349-354.

25. Cabin HS, Roberts WC. Left ventricular aneurysm, intraaneurysmal thrombus and systemic embolus in coronary heart disease. *Chest*. 1980;77:586-590.

26. Meltzer RS, Guthaner D, Rakowski H, Popp RL, Martin RP. Diagnosis of left ventricular thrombi by two-dimensional echocardiography. *British Heart Journal*. 1979;42:261-265.

27. Asinger RW, Mikell FL, Sharma B, Hodges M. Observations on detecting left ventricular thrombus with two dimensional echocardiography: Emphasis on avoidance of false positive diagnoses. *American Journal of Cardiology*. 1981;47:145-156.

28. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the american society of echocardiography and the european association of cardiovascular imaging. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2015;28:1-39 e14.

29. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the american

society of echocardiography and the european association of cardiovascular imaging. *European Heart Journal Cardiovascular Imaging*. 2016;17:1321-1360.

30. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: A report from the american society of echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the european association of echocardiography, a branch of the european society of cardiology. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2005;18:1440-1463.

31. Hu K, Liu D, Herrmann S, Niemann M, Gaudron PD, Voelker W, Ertl G, Bijnens B, Weidemann F. Clinical implication of mitral annular plane systolic excursion for patients with cardiovascular disease. *European Heart Journal Cardiovascular Imaging*. 2013;14:205-212.

32. Willenheimer R, Cline C, Erhardt L, Israelsson B. Left ventricular atrioventricular plane displacement: An echocardiographic technique for rapid assessment of prognosis in heart failure. *Heart*. 1997;78:230-236.

33. Claus P, Weidemann F, Dommke C, Bito V, Heinzel FR, D'Hooge J, Sipido KR, Sutherland GR, Bijnens B. Mechanisms of postsystolic thickening in ischemic myocardium: Mathematical modelling and comparison with experimental ischemic substrates. *Ultrasound in Medicine and Biology*. 2007;33:1963-1970.

34. Hu K, Liu D, Stork S, Herrmann S, Oder D, Ertl G, Voelker W, Weidemann F, Nordbeck P. Echocardiographic determinants of one-year all-cause mortality in

patients with chronic heart failure complicated by significant functional tricuspid regurgitation. *Journal of Cardiac Failure*. 2017;23:434-443.

35. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the american society of echocardiography endorsed by the european association of echocardiography, a registered branch of the european society of cardiology, and the canadian society of echocardiography. *Journal of the American Society of Echocardiography*. 2010;23:685-713; quiz 786-688.

36. Faxon DP, Ryan TJ, Davis KB, McCabe CH, Myers W, Lesperance J, Shaw R, Tong TG. Prognostic significance of angiographically documented left ventricular aneurysm from the coronary artery surgery study (cass). *American Journal of Cardiology*. 1982;50:157-164.

37. Friedman BM, Dunn MI. Postinfarction ventricular aneurysms. *Clinical Cardiology*. 1995;18:505-511.

38. Weinsaft JW, Kim HW, Shah DJ, Klem I, Crowley AL, Brosnan R, James OG, Patel MR, Heitner J, Parker M, Velazquez EJ, Steenbergen C, Judd RM, Kim RJ. Detection of left ventricular thrombus by delayed-enhancement cardiovascular magnetic resonance prevalence and markers in patients with systolic dysfunction. *Journal of the American College of Cardiology*. 2008;52:148-157.

39. Kramer J, Niemann M, Liu D, Hu K, Machann W, Beer M, Wanner C, Ertl G, Weidemann F. Two-dimensional speckle tracking as a non-invasive tool for identification of myocardial fibrosis in fabry disease. *European Heart Journal*. 2013;34:1587-1596.

40. You J, Wang X, Wu J, Gao L, Du P, Liu H, Li J, Wang Y, Liang Y, Guo W, Zhang Q. Predictors and prognosis of left ventricular thrombus in post-myocardial infarction patients with left ventricular dysfunction after percutaneous coronary intervention. *Journal of Thoracic Disease*. 2018;10:4912-4922.

41. Choi UL, Park JH, Sun BJ, Oh JK, Seong SW, Lee JH, Choi SW, Jeong JO, Kwon IS, Seong IW. Impaired left ventricular diastolic function is related to the formation of left ventricular apical thrombus in patients with acute anterior myocardial infarction. *Heart and Vessels*. 2018;33:447-452.

42. Abrignani MG, Dominguez LJ, Biondo G, Di Girolamo A, Novo G, Barbagallo M, Braschi A, Braschi G, Novo S. In-hospital complications of acute myocardial infarction in hypertensive subjects. *American Journal of Hypertension*. 2005;18:165-170.

43. Xenocostas A, Hu H, Lu X, Chin-Yee I, Feng Q. Effect of anemia and red blood cell transfusion in acute myocardial infarction. *Blood*. 2007;110:454-454.

44. Hung SH, Lin HC, Chung SD. Association between venous thromboembolism and iron-deficiency anemia: A population-based study. *Blood Coagulation and Fibrinolysis*. 2015;26:368-372.

45. Stolz E, Valdueza JM, Grebe M, Schlachetzki F, Schmitt E, Madlener K, Rahimi A, Kempkes-Matthes B, Blaes F, Gerriets T, Kaps M. Anemia as a risk factor for cerebral venous thrombosis? An old hypothesis revisited. *Journal of Neurology*. 2007;254:729-734.

46. Franchini M, Targher G, Montagnana M, Lippi G. Iron and thrombosis. *Annals of Hematology*. 2008;87:167-173.

List of figures

Announcement:

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8. Curriculum Vitae

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Schulbildung

1997 – 2003	Besuch der Grundschule „Erligou“ in Peking
2003 – 2006	Besuch der Mittelschule „National Day School“ in Peking
2006 – 2009	Besuch der Oberschule „National Day School“ in Peking

Ausbildung und Studium

2009 – 2011	Studium der Krankenpflege in der medizinischen Universität von der Hauptstadt in China, Peking
09.2011 – 09.2012	Besuch des Studienkollegs Sachsen, Leipzig
10.2012 – 09.2019	Studium der Humanmedizin an der Universität Würzburg
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Famulaturen

01.03.16 – 31.03.16	Famulatur am Uniklinikum Würzburg (Pneumologie)
01.08.16 – 31.08.16	Famulatur in der Anästhesiepraxis Würzburg
04.09.16 – 05.10.16	Famulatur in dem Pekinger Krankenhaus des Chaoyang Bezirks, China (Karidologie)
10.02.17 – 13.03.17	Famulatur in der Hausarztpraxis, Berlin

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21.05.18 – 09.09.18	1. Tertial am Uniklinikum Würzburg (Chirurgie)

10.09.18 – 30.12.18	2. Tertial am Charité – Universitätsmedizin Berlin Campus Benjamin Franklin (Innere Medizin)
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Sonstige Qualifikationen

Sprachkenntnisse:	Deutsch fließend
	Englisch gute Kenntnisse
	Chinesisch Muttersprache
Sonstiges:	EDV- Kenntnisse, hier MS WORD, EXCEL; POWERPOINT
Hobby:	Ausdauersport (Marathon, Schwimmen), Musik