A Prothrombotic State in Patients With a History of Left Ventricular Thrombus

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Left ventricular thrombus (LVT) is associated with a hypercoagulable state and occurs most frequently after myocardial infarction (MI). Blood prothrombotic alterations might predispose to LVT formation, its recurrence, and subsequent cerebrovascular events. We investigated 58 patients with a history of LVT unrelated to recent MI or LV ejection fraction <25% and 58 well-matched control subjects. We determined plasma clot permeability, fibrinolytic efficiency, thrombin generation, and endothelial markers after 3 to 6 months of anticoagulant treatment. During follow-up we recorded LVT and thromboembolic events. Patients with LVT more often had LV akinesia, congestive heart failure, and prothrombotic state as evidenced by increased endogenous thrombin potential, lower antithrombin, lower clot permeability, and longer clot lysis time associated with lower antiplasmin, higher plasminogen activator inhibitor-1, thrombin activatable fibrinolysis inhibitor, and von Willebrand factor. During follow-up (57.5 ± 8.1 months for LVT patients and 59.6 ± 5.3 months for controls) strokes, transient ischemic attacks, or LVT occurred in 18 (31%) LVT patients and in 6 (10.3%) control subjects (4.1 vs 1.4% per year, p = 0.006). LVT recurred in 10 (2.3%/year) patients, who had higher risk of stroke/transient ischemic attacks (relative risk = 4.73, 95% confidence interval 1.8 to 40.4). The most compact clot formation at baseline, defined as the lowest quartile of clot permeability ($\leq 5.4 \times 10^{-9}$ cm^2) was a predictor of recurrent LVT (relative risk = 4.67, 95% confidence interval 1.32 to 18.37). This study shows that a persistent prothrombotic state involving enhanced thrombin generation, hypofibrinolysis, and formation of more compact fibrin clots characterizes patients who develop LVT not related to MI and those prone to its recurrence. **(Am J Cardiol 2019;123:1358−1363)**

Left ventricular thrombus (LVT) occurs most frequently after acute myocardial infarction (AMI), at low LV ejection fraction (LVEF ≤35%), and LV aneurysm.[1] On transthoracic echocardiography (TTE), the LVT can be observed in 4.3% of patients in 90 days after AMI.[1]

Reports on the relation of thrombophilia with LVT are inconsistent. Factor (F)V Leiden was found to be an independent predictor for LVT in dilated cardiomyopathy.[2,3] Occasionally, LVT has been reported within a structurally normal LV in individuals with protein C and protein S deficiency[4] and in antiphospholipid syndrome (APS).[5] The prothrombotic plasma fibrin clot phenotype, involving formation of densely packed and relatively resistant to lysis fibrin networks, has been shown in patients after MI and ischemic stroke.[6] Heart failure (HF) with both preserved and reduced LVEF have been shown to be associated with a prothrombotic state and faster formation of compact fibrin clots.[7,8] To our knowledge, there have been no reports assessing blood prothrombotic alterations in patients with a history of LVT and their potential association with the risk of recurrent thromboembolic events. In this study we sought to fill this gap in a unique cohort of patients who experienced LVT unrelated to recent MI or LVEF <25%.

Methods

In this prospective study we evaluated 110 consecutive patients with a history of LVT referred to an outpatient clinic (John Paul II Hospital, Krakow, Poland) from October 2006 to December 2014. Patients were eligible if acute coronary syndrome did not occur within the 3 preceding months. The exclusion criteria for both groups were: acute illness, known cancer, end-stage kidney disease, LVEF <25%, prosthetic heart valve, moderate-to-severe mitral or aortic valve stenosis, previous infectious endocarditis, implanted cardioverter defibrillator or pacemaker, recent surgery or trauma, permanent atrial fibrillation (AF), and current anticoagulant treatment. Patients were eligible after documented LVT disappearance at least 1 month since anticoagulation withdrawal. In patients after LVT, 15 subjects were excluded due to LVEF <25%, 17 due to persistent LVT, 10 patients had severe co-morbidities, 2 acute infection, 2 subjects had a history of previous endocarditis, and 6 patients had current anticoagulation. Data regarding demographic characteristics, risk factors, co-morbidities,

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and medications were collected at enrolment. Thrombus was documented by TTE (n = 42) and magnetic resonance imaging (n = 10) or computed tomography (n = 6). Patients received a 3 to 6-month treatment started with low-molecular-weight heparins, mostly enoxaparin, with the subsequent oral anticoagulation with warfarin or acenocoumarol with target international normalized ratio of 2 to 3. Thrombus resolution after anticoagulant therapy was confirmed by magnetic resonance imaging.

Age-, gender-, and body mass index-matched control subjects without documented intracardiac thrombus (based on TTE screening) in the past were enrolled at the same time. Control subjects were also matched for a history of myocardial infarction as a key risk factor for LVT.

Paroxysmal AF was diagnosed when episodes were self-terminating and continuing for up to 7 days, while persistent AF was defined as AF episodes lasting longer than 7 days or requiring termination by cardioversion. Arterial hypertension was diagnosed based on a history of hypertension (blood pressure >140/90 mm Hg) or preadmission antihypertensive treatment. Heart failure was defined as the presence of relevant symptoms and signs and left ventricular ejection fraction ≤45%. The study protocol was approved by the Ethics Committee of the Jagiellonian University. All subjects gave written informed consent.

Fasting blood samples were drawn from an antecubital vein using minimal stasis from 8:00 A.M. to 11:00 A.M. Plasma samples (9:1 of 3.2% sodium citrate) were centrifuged within 20 minutes of collection and stored at −80°C. Lipid profile, glucose, creatinine, blood cell count, D-dimer, and clotting times were assayed by routine laboratory techniques. Fibrinogen was determined with the Clauss method. Antithrombin (AT) was measured using the FXa-based assay (Siemens). FVIII was determined by 1-stage clotting assay using factor-deficient plasma (Siemens). Von Willebrand factor antigen was measured by latex immunoassay on a STAR coagulation instrument (Diagnostica Stago, Asnieres, France). Plasminogen activator inhibitor-1 (PAI-1) and thrombin activatable fibrinolysis inhibitor (TAFI) antigen were measured by enzyme-linked immunoabsorbent assays (both, American Diagnostica, Stamford, Connecticut). Plasma α_2-antiplasmin (α_2AP) and plasminogen were measured by chromogenic assays (Diagnostica Stago).

Calibrated automated thrombography (Thrombinoscope BV, Maastricht, the Netherlands) was used to measure thrombin generation, as previously described.[9] Briefly, platelet poor plasma was mixed with a reagent containing recombinant tissue factor and phospholipids, with the final concentrations of 5 pM and 4 mM, respectively. The fluorescence intensity was recorded by the Fluoroskan Ascent fluorometer (Thermo Fisher Scientific, Vantaa, Finland) using the software (Thrombinoscope BV). The area under the curve of thrombin generation represents endogenous thrombin potential (ETP), a measure of thrombin formation capacity in plasma.

Plasma fibrin clot structure and lysability were determined in duplicate (intra-assay and interassay coefficients of variation, 5%-7%). Fibrin clot permeability, a key measure of clot structure assessed ex vivo, was determined as described.[10] Briefly, 60 μl of citrated plasma were mixed with 60 μl of a reagent mixture at final concentrations of 1 U/ml human thrombin (Calbiochem, Darmstadt, Germany) and 20 mM $CaCl_2$. A permeation coefficient (K_s), which indicates the average size of pores formed in the fiber network, was calculated from the equation: $K_s = Q \times L \times \eta / t \times A \times \Delta p$, where Q is the flow rate in time t, L is the length of a fibrin gel, η is the viscosity of liquid (in poise), t is percolating time, A is the cross-sectional area (in cm^2), and Δp is a differential pressure (in dyne/cm^2). Clot lysis time (CLT) was measured as described previously.[11,12] Briefly, fibrin formation was initiated by 0.6 pM human tissue factor (Innovin, Siemens, Liederbach, Germany) in the presence of 15 mM calcium chloride and 12 μM phospholipid vesicles (Phospholipid-TGT, Rossix, Mölndal, Sweden), together with proteolysis induced by 60 ng/ml recombinant tissue-type plasminogen activator (Boehringer Ingelheim, Ingelheim, Germany). Optical density values were kinetically recorded (450 nm, at 37°C), using a Tecan Sunrise Instrument (Tecan, Groeding, Austria). CLT was determined as the time needed for the 50% reduction of the maximum optical density value.

All patients were screened for thrombophilia, including protein C, protein S or AT deficiency, FV Leiden, and prothrombin mutation G20210A.[13] The diagnosis of APS was established based on the modified classification criteria.[14]

All participants were contacted at least twice a year by telephone or through clinic visits. All recurrent LVT episodes were confirmed using magnetic resonance imaging. The primary composite end point was the occurrence of symptomatic stroke or TIA, systemic embolization and recurrent or first-ever (for controls) LVT. Stroke/TIA was diagnosed based on the AHA/ASA guidelines.[15] TTE was performed in all patients with ischemic cerebrovascular events during follow-up to exclude LAA thrombus. Secondary end points were (1) symptomatic stroke or TIA, (2) MI, (3) systemic embolization, or (4) intracardiac thrombi. MI was defined according to the universal definition proposed by the Joint ESC/ACCF/AHA/WHF Task Force.[16] Follow-up was censored at the time of recurrence of thrombus, thromboembolic event and/or death. TTE was performed at least once a year to confirm the absence of thrombus in all control subjects and those from the LVT group free of the primary composite end point. The final assessment was performed in December 2017.

Continuous variables are shown as median (the first-third quartile) or mean ± standard deviation, while categorical variables as count/percentage. Continuous variables were checked for normal distribution by the Shapiro-Wilk test. The Mann-Whitney *U* or Student *t* tests were used as appropriate. The chi-square test was used to compare the category frequencies. The Pearson or Spearman rank correlation coefficients were calculated to test the association between 2 variables with a normal or non-normal distribution, respectively. The odds of LVT were estimated using logistic regression and presented as an odds ratio with the corresponding 95% confidence interval (CI). Congestive heart failure, diabetes, time of first AF diagnosis, plasma levels of α_2-antiplasmin, AT, fibrinogen, and fibrin clot features were screened as potential factors influencing the odds for the study end points. Identified factors were used as potential predictors in multiple regression analysis with

forward or background stepwise regression, depending on number of factors. Analyses were adjusted for age, gender, body-mass index, fibrinogen, and aspirin if appropriate. Cox regression was used to identify predictors of stroke/TIA, MI, systemic embolization, and first or recurrent LVT. All tests were 2-sided and p values of <0.05 were considered statistically significant. Statistical analyses were performed using JMP, Version 13.1.0. SAS Institute Inc., Cary, North Carolina, 2016. The study was powered to have a 90% chance of detecting a 10% difference in CLT using a p value of 0.05.[17] In order to demonstrate such a difference or greater, 57 patients were required in the group. In turn, to demonstrate such a difference in K_s using a p value of 0.05, at least 50 patients were required in the group.[18]

Results

Fifty eight patients with previous LVT and 58 control subjects were studied (Table 1, Table S1). There was no difference in the prevalence of inherited and acquired thrombophilia between the LVT patients and controls (Table S2). LV with akinetic segments was found more often in patients with LVT (Table S3). In 45 (77.6%) patients, LVT was detected incidentally, in 7 (12.1%) patients after cerebrovascular accidents, and in 6 (10.3%) patients during exacerbation of HF.

ETP was 5.1% higher in LVT patients compared with controls (Table 1). Of note, ETP was similar in LVT patients with previous MI and those without this event (1,680 ± 125 nM/min vs 1,676 ± 127 nM/min, p = 0.99, respectively). We found lower AT activity in the former group, though all patients had the latter variable within the reference range (80% to 120%). ETP was inversely correlated with AT (r = −0.53, p <0.0001). Endothelial injury in patients with previous LVT was evidenced by 13.5% higher vWF compared with controls (Table 1).

Patients with a history of LVT formed more compact plasma fibrin clots resistant to lysis, reflected by 13% lower K_s and 11.7% longer CLT (Table 1). Fibrinolysis inhibitors, PAI-1 and TAFI, were higher in the LVT group by 27.3% and 8.2%, respectively, while α_2AP was 9.4% lower in those patients. No differences in fibrinogen or plasminogen levels were noted. In the LVT group, K_s correlated with CLT (r = −0.31, p = 0.018), PAI-1:Ag (r = −0.46, p = 0.003), and vWF (r = −0.39, p = 0.003), whereas CLT was associated with PAI-1:Ag (r = 0.79, p <0.0001) and ETP (r = 0.43, p = 0.0007).

In univariate logistic regression analysis, reduced K_s and prolonged CLT were associated with previous LV thrombus, also after adjustment for aspirin intake (Table 2). Lower AT was an independent predictor of the primary study end point, while absence of congestive HF, higher AT, and α_2AP activity were found to be independent negative predictors of LVT (Table 3). In the Cox regression analysis, only AT increase by 1% was associated with lower risk of LVT (relative risk [RR] = 0.88, 95% CI 0.78 to 0.98).

During follow-up (57.5 ± 8.1 months for the LVT group and 59.6 ± 5.3 months for controls) the primary end point occurred in 18 (31%) LVT patients and in 6 (10.3%) control subjects (4.1 vs 1.4% per year, p = 0.006). The occurrence of stroke/TIA was higher in the LVT group than in controls (2.3 vs 0.7% per year, p = 0.04), while the frequency of documented AF was similar in LVT patients compared with controls (1.4 vs 0.7% per year, p = 0.30) during follow-up (Table S4). Of note, presence of thrombophilia, defined as inherited thrombophilia, APS or FVIII>150%, was the predictor of stroke during follow-up (RR = 4.73,

Table 1
Patient characteristics

Variable	Left ventricular thrombus group (n = 58)	Control group (n = 58)
Age (years)	59.0 ± 6.6	60.2 ± 5.6
Women	14 (24.1%)	16 (27.6%)
Body-mass index (kg/m^2)	28.4 (25.9-32.1)	27.4 (24.5-29.5)
Current smokers	25 (43.1%)	33 (56.9%)
Clinical characteristics		
Paroxysmal atrial fibrillation	8 (13.8%)	4 (6.9%)
Persistent atrial fibrillation	3 (5.2%)	5 (8.6%)
Congestive heart failure	24 (41.4%)*	9 (15.5%)
Left ventricular ejection fraction 30-40%	9 (15.5%)	12 (20.7%)
Arterial hypertension	47 (81%)	49 (84.5%)
Diabetes mellitus	22 (37.9%)*	5 (8.6%)
Coronary heart disease	30 (51.7%)	21 (36.2%)
Prior myocardial infarction†	29 (50%)	19 (32.8%)
Prior stroke or transient ischemic attack	9 (15.5%)	4 (6.9%)
Prior venous thromboembolism	11 (19%)	4 (6.9%)
Family history of venous thromboembolism	6 (10.3%)	3 (5.2%)
Family history of myocardial infarction	8 (13.8%)	7 (12.1%)
Medications		
Aspirin	10 (17.2%)*	23 (39.7%)
Statin	31 (53.4%)	34 (58.6%)
Angiotensin-converting enzyme inhibitors	33 (56.9%)	35 (60.3%)
Beta blockers	46 (79.3%)*	30 (51.7%)
Metformin	17 (29.3%)*	8 (13.8%)
Laboratory investigations		
Fibrinogen (g/L)	3.67 (3.12-4.04)	3.75 (3.10-4.40)
D-dimer (ng/mL)	328 (245-500)*	243 (212-315)
Antithrombin (%)	93 (88-100)*	100 (94-104)
von Willebrand factor (%)	227 ± 48*	201 ± 54
Plasminogen activator inhibitor 1 antigen (ng/mL)	39.7 (32.3-43.5)*	31.2 (25.4-38.3)
Thrombin activatable fibrinolysis inhibitor antigen (%)	106.0 (97.0-119.0)*	98.0 (87.3-108.3)
Plasminogen (%)	105.0 (96.8-112.3)	107.0 (94.5-126.5)
α_2-antiplasmin (%)	101.5 (91.8-111.3)*	111.0 (101.8-119.5)
Fibrin clot permeability (K_s, 10^{-9}cm^2)	6.05 (5.38-7.00)*	6.95 (6.38-7.50)
Clot lysis time (min)	109.5 (98.5-129.0)*	98.0 (83.5-110.8)
Endogenous thrombin potential (nM•min)	1678 ± 125*	1598 ± 196

* p value <0.05 versus controls.
† Median time from myocardial infarction to blood collection: 26 (14 to 46) months for left ventricular thrombus patients and 27 (13.5 to 44) months for controls. Continuous variables are shown as median (the first-third quartile) or mean ± standard deviation, while categorical variables as count/percentage.

Table 2
Logistic regression models for risk factors associated with left ventricular thrombus formation

Variable, unit	Univariate analysis		Adjusted for aspirin	
	Odds ratio (95% confidence interval)	p	Odds ratio (95% confidence interval)	p
Fibrin clot permeability (K_s, $10^{-9}cm^2$)	0.39 (0.24-0.61)	0.0001	0.40 (0.25-0.64)	<0.0001
Clot lysis time (min)	1.03 (1.01-1.05)	0.0024	1.03 (1.01-1.05)	0.0028
D-dimer (ng/mL)	1.04 (1.01-1.07)*	0.0025	1.04 (1.01-1.07)*	0.006
Plasminogen activator inhibitor 1 antigen (ng/mL)	1.11 (1.05-1.17)	0.0001	1.11 (1.05-1.17)	0.0001
Endogenous thrombin potential (nM•min)	1.08 (1.007-1.15)*	0.013	1.07 (1.002-1.14)*	0.01
von Willebrand factor (%)	1.10 (1.01-1.20)*	0.0082	1.10 (1.01-1.20)*	0.0074
Thrombin activatable fibrinolysis inhibitor antigen (%)	1.04 (1.01-1.07)	0.0037	1.04 (1.01-1.07)	0.0028
Plasminogen (%)	0.98 (0.96-1.00)	0.10	0.98 (0.96-1.01)	0.16
α_2-antiplasmin (%)	0.94 (0.91-0.97)	0.0003	0.94 (0.91-0.97)	<0.0001
Antithrombin (%)	0.91 (0.87-0.96)	0.0004	0.91 (0.87-0.96)	0.0001

* Odds ratio and 95% confidence interval for increase in a given hemostatic variable by 1 unit or by 10 units.

Table 3
Independent predictors of the study end points

Variable	Odds ratio (95% confidence interval)	p
Primary composite end point		
Antithrombin (%)	0.94 (0.88-0.99)	0.042
Left ventricular thrombus		
α_2-antiplasmin (%)	0.86 (0.77-0.94)	<0.0001
Antithrombin (%)	0.83 (0.71-0.95)	0.0034
Absence of congestive heart failure	0.02 (0.001-0.21)	0.0002

Odds ratio for left ventricular thrombus formation for increase in given hemostatic variable by 1 unit. Adjusted for age, gender, body mass index, and fibrinogen.

95% CI 1.45 to 21.13). MI was diagnosed in 10 LVT subjects and in 7 controls during follow-up (2.3 vs 1.6% per year, p = 0.43). Pulmonary embolism occurred in 5 (1.2% per year) LVT patients but not in controls (p = 0.57). LVT recurred in 10 (17.2%) patients (2.3% per year), including 5 (8.6%) individuals who experienced concomitant cerebrovascular events. No LVT was detected in controls during the follow-up.

There were no differences with regard to demographic and clinical parameters, including baseline anticoagulation duration (3 [3 to 4.5] vs 4 [3 to 6] months, p = 0.07, respectively) between patients with recurrent LVT and those without, except a lower proportion of current smokers in the former group (10% vs 50%, p = 0.02). Incidence of stroke/TIA was higher in patients with LVT recurrence compared with the remainder (p = 0.009), while AF during follow-up was diagnosed only in patients without recurrent LVT (p = 0.58; Table S4). Patients with LVT recurrence had at baseline 11% higher fibrinogen (4.0 ± 0.7 vs 3.6 ± 0.7 g/L, p = 0.04), 6% higher ETP (1,760 ± 141 vs 1,661 ± 117 nM•min, p = 0.02), 12.9% lower K_s (5.4 ± 0.8 vs 6.2 ± 0.9•10^{-9} cm^2), 16.4% longer CLT (124.5 [106.3 to 148] vs107 [95.3 to 127.3] min, p = 0.03), and 7.6% lower TAFI antigen levels (99.8 ± 7.2 vs 108 ± 13.6%, p = 0.01) compared with those without recurrence, while other hemostatic variables were comparable. Differences in fibrin clot properties and thrombin generation associated with recurrent LVT remained significant also after adjustment for fibrinogen (all p <0.05). Univariate regression analysis showed that a decrease in K_s by 1 unit, the increase in CLT by 1 minute and in ETP by 10 units was associated with a higher risk of LVT recurrence, respectively (Table S5). Reduced K_s, defined as the lowest quartile in the LVT group (≤5.4•10^{-9} cm^2) in univariate analysis predicted recurrent LVT (RR = 4.67, 95% CI 1.32 to 18.37) alone.

Discussion

The present study presents the largest cohort of unique patients with LVT unrelated to recent MI or severe HF followed for about 5 years after anticoagulation withdrawal. We showed several prothrombotic alterations in patients with previous LVT including higher thrombin generation, denser clot networks combined with impaired fibrinolysis associated with elevated levels of fibrinolysis inhibitors and reduced α_2AP. We have provided evidence that LVT was prone to recur at an annual rate of 2.3% and that prothrombotic markers together with unfavourably modified fibrin clot structure were the predictors of LVT recurrence, similarly to recurrent venous thrombotic episodes, including PE.[19–21] LVT patients were characterized by prolonged fibrinolysis, which is in line with findings in patients with VTE or MI.[20,22] This study increases our knowledge on the thrombotic background of the rare phenomenon, that is LVT of unknown origin, which implicates a significant risk of recurrence with thromboembolic complications during follow-up. From a practical point of view, it might be speculated that patients after LVT of unknown origin should be treated with oral anticoagulants on a long-term basis to prevent thromboembolic episodes. Fibrin clot characteristics

might be helpful parameters in the management of LVT patients at high risk of recurrent episodes.

Our study showed that the compact clot structure seems to be a key fibrin variable in the prediction of LVT unrelated to MI and recurrent LVT. Our data support the hypothesis that formation of more compact fibrin clots predisposes to thrombosis also at unusual locations.[6]

Looking at fibrinolysis determinants, unexpectedly lower α_2AP activity was the independent predictor of LVT, which was most likely overcome by prothrombotic effects associated with decreased AT activity. In contrast, we observed reduced TAFI antigen and slightly higher PAI-1 antigen levels but unchanged α_2AP and plasminogen levels in patients with recurrent LVT, but none of these parameters showed independent association with recurrent thrombotic episodes. Taken together, disturbed fibrinolysis appears of minor significance in the pathophysiology of LVT.

We also identified heightened thrombin formation after LVT in part driven by lower AT, a major thrombin inhibitor in vivo. Thrombin generation parameters, including ETP, were associated with fibrin network properties, including K_s and CLT.[10,23] High thrombin generation has been shown to persist in 6 months' follow-up in patients after AMI.[24] However, previous MI did not explain increased thrombin generation in our cohort. Thus, it is likely that prothrombotic alterations rather than impaired susceptibility to fibrinolysis contribute to LVT formation. Local and systemic hemostatic response to intracardiac thrombus, along with cardiovascular disease might be related to the occurrence of recurrent LVT. This issue requires further investigation.

Aspirin also rendered fibrin clot structure more permeable and more susceptible to lysis in healthy subjects and patients with cardiovascular disease[6] in part due to fibrinogen acetylation with enhanced clot susceptibility to lysis.[25] In our study adjustment for the use of aspirin did not change the predictive values of LVT risk factors, suggesting a weak effect of this agent on a prothrombotic state on our patient cohort. Lower use of aspirin in the LVT group could however contribute to increased risk of LVT recurrence.[26] Although reduced ventricular contractility, local injury of myocardium, and hypercoagulability are known contributors to LVT and its thromboembolic complications, to our knowledge there were no reports describing the risk of such episodes in recurrent LVT. Our study showed that presence of thrombophilia predicted stroke in LVT patients during follow-up. It suggests that thrombophilia screening should be considered in selected LVT patients.

This study has several limitations. First, our cohort comprising individuals with a rare pathology was rather small but sufficiently powered to detect intergroup differences. Second, samples were drawn only once, therefore we cannot exclude changes in the variables tested over time. Finally, silent MI or stroke cannot be excluded in the patients studied.

In conclusion, patients with LVT not related to AMI and low LVEF manifest a prothrombotic state, including enhanced thrombin generation and formation of compact fibrin clot resistant to lysis. The prothrombotic fibrin clot phenotype, particularly increased clot density, is associated with LVT recurrences and the risk of such events is not negligible. How to prevent thromboembolism in patients after LVT of unknown origin remains to be established.

Disclosures

The investigators have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.01.007.

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