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The Telltale of Left Atrial Thrombus Formation in Mitral Stenosis: Revisiting the Virchow's Triad

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ORIGINAL ARTICLE

The Telltale of Left Atrial Thrombus Formation in Mitral Stenosis: Revisiting the Virchow's Triad

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Abstract

Aims: **This study was conducted to assess the relationship of simple hematological parameters with the incidence of left atrial thrombus in rheumatic mitral stenosis in addition to conventional contributing factors.**

Methods: **A cross-sectional study was conducted in patients with significant rheumatic stenosis from 1 January 2018 to 31 July 2021. The presence of thrombus was evaluated by transthoracic or transesophageal echocardiography. Laboratory tests were performed within 10 days prior to the echocardiographic evaluation. Subjects with significant mitral regurgitation were excluded.**

Results: **Of the 318 subjects with significant rheumatic mitral stenosis included in the study, 102 patients (32%) had a thrombus in the left atrium. Of all the patients, 63.8% were in atrial fibrillation and 36.2% were in sinus rhythm. Atrial fibrillation (OR 2.39; 95% CI 1.10−5.20, p = 0.028), left ventricular ejection fraction <56.68% (OR 0.42; 95% CI 0.23−0.77, p = 0.005), TAPSE <18.10 mm (OR 0.44; 95% CI 0.230−0.83, p = 0.011), and hematocrit ≥45.15% (OR 2.98; 95% CI 1.27−6.98, p = 0.012) were associated with left atrial thrombus.**

Conclusion: **Increased hematocrit was significantly associated with left atrial thrombus in patients with rheumatic mitral stenosis, which may have contributed to the hypercoagulable state component of the Virchow's triad.**

Keywords: Simple hematology analysis, Left atrial thrombus, Rheumatic mitral stenosis

Introduction

Over a century ago, the concept of Virchow's triad was introduced as an important component for the development of thrombosis; hypercoagulability, stasis, and endothelial damage [1]. In rheumatic mitral stenosis; Virchow's triad can be present as follows: (1) endothelial damage can result from turbulence in the chamber or in the blood vessel as a result of impaired blood flow [2]; (2) The component "stasis" in Virchow's triad is confined to the left atrial region as a result of impaired blood flow from the left atrium to the left ventricle and atrial fibrillation that often accompanies mitral stenosis [3]; and (3) "Hypercoaguability" has also been shown to occur in patients with mitral stenosis. Hypercoagulable state is localized in the left atrium and in the systemic circulation in patients with mitral stenosis [4].

Several hematological parameters such as red cell distribution width (RDW) and platelet counts have been shown to be associated with thrombus formation in various diseases [5−8]. But to date, only few studies have investigated the relationship between hematological parameters and left atrial thrombus in patients with rheumatic mitral stenosis.

Thrombus formation is classified into venous and arterial types with difference in composition. A thrombus that forms in an artery is rich in platelets and forms on the side or area of the ruptured

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atherosclerotic plaque. Because of these components, the arterial thrombus is often referred to as white thrombus. In contrast, venous thrombus, which forms even though the endothelial wall appears intact, is rich in fibrin and red blood cells. Due to the dominance of red blood cells, this type of thrombus is known as red thrombus [9]. On the other hand, arterial thrombus occurs in areas of high blood flow, whereas venous thrombosis occurs in areas of low blood flow [10]. However, the mechanism of thrombus formation remains controversial. A study by Yapan Y et al. and Yasushi et al. [11,12] revealed that red thrombus might also be found in the coronary artery based on the analysis of thrombus aspiration in patients with ST-segment elevation myocardial infarct (STEMI). Moreover, red thrombus was present in two-thirds of STEMI cases. Thus, fibrinolytic is only used in STEMI cases and not in non-ST elevation acute coronary syndrome [13].

Left atrial thrombus formation in rheumatic mitral stenosis was rarely studied. Therefore, this study aims to shed light on the mechanism of left atrial thrombus formation in patients with rheumatic mitral stenosis with the use of hematological analysis.

Method

Study design and setting

In this cross-sectional study, we collected data from the Department of Cardiology and Vascular Medicine, National Cardiovascular Center Harapan Kita (NCCHK), Indonesia, from May 2021 to October 2021. Subjects included in the study consist of patients 18 years old and above with moderate to severe rheumatic mitral stenosis. The patients who had undergone transthoracic and/or transesophageal echocardiography examination to explore the presence of a thrombus in the period from 1 January 2018 to 31 July 2021 were included in the study. Data of the subjects were retrieved from electronic medical records, along with a recorded video of transesophageal echocardiography. Patients with acute infection, hematological disease, autoimmune disease, and moderate to severe mitral regurgitation were excluded from the study.

Echocardiography examination

Echocardiography was performed by cardiologists using General Electric (GE) Vivid E95, Vivid E9 and Philips Epiq 7 echo machines. Severity of mitral stenosis was evaluated with 3D planimetry. Examination protocol and calculation was performed according to ASE/EACVI recommendation [14]. If no visible thrombus was seen from transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) was performed to assess for the presence of thrombus. Anticoagulant was withheld for 3–5 days before examination.

Laboratory examination

Hematology examination (hematocrit, platelet count, red cell distribution width corpuscular volume) and INR examination was done using the Sysmex Automated hematology Analyzer with flow cytometry method. The accuracy of examination was ±3% for hematocrit, ±5% for platelet count, and ±2% for red cell distribution width corpuscular volume (RDW-CV). Blood was taken from the brachial vein within 10 days before the echocardiography procedure.

Data analysis

Data analysis was done using SPSS version 24 for MacBook. This study is a correlation study to see the relationship between simple laboratory tests such as RDW-CV, hematocrit, and platelet count with the incidence of thrombus in the left atrium.

Categorical data are presented in the form of frequency and proportion. If the data distribution is normal, numerical data is presented as mean value with standard deviation (mean ±SD). If the data distribution is not normal, then numerical data is presented as median value with minimum and maximum values (median, minimum–maximum). Numerical data with abnormal distribution will be further explored with graphs, kurtosis, and skewness.

Collinearity was evaluated between independent variables. Evaluation will be carried out using a correlation test. The cut-off point was performed on independent variables (hematocrit, RDW, and platelet count) and dependent variables (left ventricular ejection fraction, left atrial volume index (LAVI), and tricuspid annular plane systolic excursion (TAPSE)) using receiver operating characteristic curves.

Logistic regression analysis was done to evaluate the relationship between each variable (RDW, hematocrit, and platelet count) and the presence of a thrombus.

Ethical approval

This study has been reviewed and approved by the Ethics Committee of NCCHK. The data used will be kept confidential.

Table 1. Baseline characteristics of patients.

	All patients (n = 318)	Left Atrial Thrombus		p value
		No (n = 216)	Yes (n = 102)	
Basic data of the patients				
Gender (number, N (%))				
Man	94 (29.60%)	55 (25.50%)	39 (38.20%)	0.021
Woman	224 (70.40%)	161 (74.50%)	63 (61.80%)	
Age (year; mean (SD))	44.15 ± 10.49	43.44 ± 10.21	45.67 ± 10.94	0.078
Weight (kg; median (min–max))	54.0 [29.0–95.0]	54.0 [29.0–95.00]	54.0 [33.0–82.0]	0.825
Height (cm; median (min–max))	156.0 [140.0–181.0]	155.0 [140.0–181.0]	156.5 [142.0–173.0]	0.438
BSA (m2; median (min–max))	1.53 [1.14–2.15]	1.54 [1.15–2.15]	1.53 [1.14–1.89]	0.677
Comorbidities (N (%))				
Atrial fibrillation	203 (63.80%)	116 (53.70%)	87 (85.30%)	<0.001
Hypertension	9 (2.80%)	5 (2.30%)	4 (3.90%)	0.425
Diabetes	11 (3.50%)	5 (2.30%)	6 (5.90%)	0.117
History of stroke	26 (8.20%)	14 (6.50%)	12 (11.80%)	0.113
History of BMV	22 (6.90%)	17 (7.90%)	5 (5.00%)	0.345

SD: Standard deviation; BSA: Body surface area; BMV: Balloon mitral valvuloplasty.

Results

A total of 342 patients with mitral stenosis who underwent TTE or TEE were included. A total of 24 patients were excluded due to moderate to severe mitral regurgitation, so the final analysis involved 318 subjects.

Of 318 patients with moderate-severe mitral stenosis, 102 patients (32%) had thrombus in the left atrium. A total of 17 (16.67%) patients with thrombus in the left atrium, did not undergo further TEE because thrombus was found in the left atrium from TTE. A total of 85 subjects (83.33%) had thrombus in the left atrial appendage shown by TEE. Baseline characteristics are depicted in Tables 1–3.

Based on the results of echocardiography (Table 3), patients with thrombus in the left atrium tended to have a larger LAVI (106.00 [50.0–789.0] mL/m^2 vs 90.00 [25.60–602.00] mL/m^2) but with worse left ventricular ejection fraction(58.375 [23.00–81.00]% vs. 61.50 [20.50–81.00] %) and TAPSE (15.98 ± 4.60 vs 19.85 ± 5.803), along with smaller MVA planimetry size (0.65 ± 0.24 cm vs. 0.71 ± 0.23 cm). Pulmonary hypertension was also found to be more severe in patients with thrombus in the left atrium compared to those without; this is illustrated by a higher tricuspid regurgitation velocity maximum (TR V-Max) (3.76 [1.10–5.81] m/sec vs. 3.43 [1.40–35.00]m/sec) and lower pulmonary valve acceleration time (PVACCT) (78.00 [37.00–158.00] ms vs. 92.30 [37.00–217.00] ms). The most common variation of valve involvement was significant (moderate-severe) tricuspid regurgitation with a prevalence of 41.5%, followed by significant aortic regurgitation (7.9%) and finally significant aortic stenosis (4.7%).

In laboratory tests (Table 4) higher values of hemoglobin, hematocrit, MCV, MCHC, RDW-CV, 3-

Table 2. Baseline characteristics of patients (continued; therapies used).

	All patients (n = 318)	Left Atrial thrombus		P value
		No (n = 216)	Yes (n = 102)	
Therapy (N (%))				
ACE-i	51 (16.0%)	30 (13.9%)	21 (20.6%)	0.131
ARB	19 (6.0%)	16 (7.4%)	3 (2.9%)	0.13
Beta blocker	267 (84.0%)	185 (85.6%)	82 (80.4%)	0.193
Digoxin	82 (25.8%)	45 (20.8%)	37 (36.3%)	0.004
Warfarin	251 (78.9%)	160 (74.1%)	91 (89.2%)	0.003
Furosemide	281 (88.4%)	187 (86.6%)	94 (92.2%)	0.152
Spironolactone	271 (85.2%)	187 (86.6%)	84 (82.4%)	0.324
phenoxymethylpenicillin/ Erythromycin	158 (49.7%)	107 (49.5%)	51 (50.0%)	0.939

ACE-i: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

Table 3. Baseline patient characteristics (continued; echocardiographic data).

	All patients (n = 318)	Left Atrial Thrombus		P value
		No (n = 216)	Yes (n = 102)	
Echocardiographic data				
LAVI (mL/m2; Median (Min-Max))	93.0 [25.60−789.0]	90.00 [25.60−602.00]	106.00 [50.0−789.0]	0.015
LVEF (%; Median (Min-Max))	60.85 [20.50−81.00]	61.50 [20.50−81.00]	58.375 [23.00−81.00]	0.002
TAPSE (mm; Mean (SD))	18.61 ± 5.73	19.85 ± 5.803	15.98 ± 4.604	<0.001
Mean MVG (mmHg; Median (Min-Max))	12.0 [3.0−35.0]	12.0 [3.0−35.0]	12.0 [3.2−33.0]	0.052
MVA planimetry (cm; Mean (SD))	0.69 ± 0.24	0.71 ± 0.23	0.65 ± 0.24	0.041
TR V-Max (m/sec; Median (Min - Max))	3.50 [1.10−35.00]	3.43 [1.40−35.00]	3.76 [1.10−5.81]	0.583
PVACCT (millisecond; Median (Min - Max))	88.00 [37.0−217.0]	92.30 [37.00−217.00]	78.00 [37.00−158.00]	<0.001
Aortic Regurgitation (N (%))				0.65
Non-significant	293 (92.10%)	198 (91.70%)	95 (93.10%)	
Significant	25 (7.90%)	18 (8.30%)	7 (6.90%)	
Aortic Stenosis (N (%))				0.915
Non-significant	303 (95.30%)	206 (95.40%)	97 (95.10%)	
Significant	15 (4.70%)	10 (4.60%)	5 (4.90%)	
Tricuspid regurgitation (N (%))				<0.001
Non-significant	186 (58.50%)	145 (67.10%)	41 (40.20%)	
Significant	132 (41.5%)	71 (32.90%)	61 (59.80%)	

LAVI: left atrial volume index; TAPSE: tricuspid annular plane systolic excursion; Mean MVG: mean mitral valve gradient; MVA planimetry: mean valve area planimetry; TR V-max: tricuspid regurgitation maximal velocity; PVACCT: Pulmonary valve acceleration time.

Table 4. Baseline characteristics of patients (continued; laboratory data).

	All patients (n = 318)	Trombus Atrium Kiri		P value
		No (n = 216)	Yes (n = 102)	
Laboratory data				
HGB (g/dL, Mean (SD))	13.31 ± 1.70	13.20 ± 1.69	13.53 ± 1.70	0.111
HCT(%, Mean (SD))	39.69 ± 4.56	39.35 ± 4.40	40.43 ± 4.84	0.054
RBC (million/μL, mean (SD))	4.69 ± 0.56	4.68 ± 0.53	4.73 ± 0.63	0.466
MCV (fL, Median (Min-Max))	86.20 [54.50−99.50]	85.40 [60.60−99.00]	87.80 [54.50−99.50]	0.023
MCH (pg, Median (Min-Max))	28.90 [15.90−33.70]	28.80 [17.20−33.70]	29.50 [15.90−33.10]	0.232
MCHC (%, Median (Min-Max))	33.50 [26.40−37.80	33.60 [28.30−37.80]	33.30 [26.40−37.70]	0.887
RDW CV (%, Median (min−max))	13.30 [11.50−26.90]	13.30 [11.50−26.90]	13.50 [11.60−23.40]	0.095
WBC (10^9/L, Median (Min-Max))	7.90 [3.40−18.20]	7.80 [4.0−15.37]	8.12 [3.40−18.20]	0.096
Total platelet (thousand/μL, median (min−max))	246.0 [122.0−530.0]	247.0 [122.0−530.0]	241.5 [141.0−441.0]	0.158
Mean INR 3 months (Median (Min-Max))	1.25 [0.64−4.71]	1.18 [0.64−3.88]	1.50 [1.00−4.71]	0.002

SD: Standard deviation; HGB: Hemoglobin; HCT: Hematocrit; RBC: red blood cell; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW-CV: red cell distribution width corpuscular volume; INR: international normalized ratio.

month INR, and leukocytes were observed in patients with left atrial thrombus. However, the platelet counts tend to be lower in subjects with left atrial thrombus.

There was no significant correlation among the variables, namely hematocrit, RDW, platelet count, mean platelet volume, left ventricular ejection fraction, LAVI, TAPSE, age, and mean INR at three months.

Prediction of left atrial thrombus

Based on receiver operating characteristic (ROC) curve analysis, optimal prediction cut-offs of several variables were obtained for thrombus in the left atrium. The best cut-offs were as follows: Hematocrit ("45.15%"), RDW-CV("14.75%"), Platelets ("222.50 103/μL"), left ventricular ejection fraction (LVEF) ("56.68%"), TAPSE ("18.10 mm"), LAVI ("76.62 mL/m2"), and age ("35.5 years").

Univariate and multivariate analysis

Based on univariate analysis (Table 5), all variables can be included in the multivariate analysis (Table 6). It was found that independent predictors for left atrial thrombus were atrial fibrillation (OR 2.39; 95% CI 1.10–5.20, p = 0.028) and hematocrit >45.15% (OR 2.98; 95% CI 1.27–6.98, p = 0.012). In contrast, TAPSE> 18.10 mm (OR 0.44; 95% CI 0.230–0.83, p = 0.011) and LVEF> 56.68% (OR 0.42; 95% CI 0.23–0.77, p = 0.005) are independent predictors for absence of left atrial thrombus.

Discussion

Our study showed that hematocrit was the only hematologic parameter associated with LA thrombus. Although platelets are involved in the process of thrombus formation, the hematocrit, which is directly related to red blood cells, is the main component of thrombus that occurs in the venous system with low-velocity blood flow (including thrombus in the left atrium). So far, there have been no studies that directly link hematocrit to thrombus formation in the left atrium. However, a study performed in 1993 by Black et al. found that hematocrit was associated with the formation of left atrial spontaneous echo contrast, which is the forerunner of thrombus formation in the left atrium [15]. A study on the hematocrit as a risk factor of venous thromboembolism, the Tromsø study, found that an increase in the gradient of the hematocrit was associated with the occurrence of venous thromboembolism, especially in the hematocrit level in the top 20th percentile when compared with the bottom 40th percentile with an OR of 2.4 (95% CI 1.36–4.15) [16]. The underlying pathophysiological mechanism of this condition relates to the role of the hematocrit

Table 5. Univariate analysis for left atrial thrombus.

		Total patients (n = 318)	Left atrial thrombus		P value	OR	CI 95%	
			None (n = 216)	Present (n = 102)			Minimal	Maximum
Heart rhythm	Sinus rhythm	115 (36.2%)	100 (46.3%)	15 (14.7%)	<0.001	5	2.73	9.2
	Atrial Fibrillation	203 (63.8%)	116 (53.7%)	87 (85.3%)				
LAVI	<76.62 mL/m2	105 (33.3%)	86 (40.0%)	19 (19.0%)	<0.001	2.84	1.62	5.02
	≥76.62 mL/m2	210 (66.7%)	129 (60.0%)	81 (81.0%)				
LVEF	<56.68%	83 (26.1%)	40 (18.5%)	43 (42.2%)	<0.001	0.31	0.19	0.53
	≥56.68%	235 (73.9%)	176 (81.5%)	59 (57.8%)				
TAPSE	<18.10 mm	167 (52.7%)	90 (41.9%)	77 (75.5%)	0.001	0.24	0.14	0.4
	≥18.10 mm	150 (47.3%)	125 (58.1%)	25 (24.5%)				
Hematocrit	<45.15%	276 (88.7%)	198 (93.0%)	78 (79.6%)	0.001	3.39	1.649	6.95
	≥45.15%	35 (11.3%)	15 (7.0%)	20 (20.4%)				
RDW-CV	<14.75%	240 (77.2%)	174 (81.7%)	66 (67.3%)	0.006	2.16	1.25	3.74
	≥14.75%	71 (22.8%)	39 (18.3%)	32 (32.7%)				
Platelets	<222.50 thousand/μl	111 (35.7%)	67 (31.5%)	44 (44.9%)	0.022	0.56	0.34	0.92
	≥222.50 thousand/μL	200 (64.3%)	146 (68.5%)	54 (55.1%)				
Average INR	INR 3 months < 1.5	206 (64.8%)	151 (69.9%)	55 (53.9%)	0.006	1.99	1.22	3.23
	INR 3 months ≥ 1.5	112 (35.2%)	65 (30.1%)	47 (46.1%)				
Gender	Male	94 (29.60%)	55 (25.50%)	39 (38.20%)	0.021	0.55	0.33	0.91
	Female	224 (70.40%)	161 (74.50%)	63 (61.80%)				
Age	<35.50 years	63 (19.80%)	51 (23.60%)	12 (11.80%)	0.015	2.32	1.18	4.57
	≥35.50 years	255 (80.20%)	165 (76.40%)	90 (88.20%)				

AF: Atrial fibrillation; CI 95%: 95% confidence interval; LAVI: Left Atrial Volume Index; TAPSE: Tricuspid Annular Plane Systolic Excursion; LVEF: Left ventricular ejection fraction; RDW-CV: Red Cell Distribution Width Corpuscular Volume; INR: International Normalized Ratio.

Table 6. Multivariate analysis for left atrial thrombus.

	Adjusted OR	CI 95%		P value
		Minimum	Maximum	
Age ≥35.5 years	1.81	0.79	4.12	0.16
Female gender	1.06	0.54	2.07	0.871
AF	**2.39**	**1.10**	**5.20**	**0.028**
LAVI ≥76.62 mL/m2	1.37	0.70	2.68	0.356
LVEF ≥ 56.68%	**0.42**	**0.23**	**0.77**	**0.005**
TAPSE ≥ 18.10 mm	**0.44**	**0.23**	**0.83**	**0.011**
Hematocrit ≥ 45.15%	**2.98**	**1.27**	**6.98**	**0.012**
RDW ≥14.75%	1.51	0.78	2.94	0.223
Number of platelets ≥222.50 10^3/μL	0.62	0.34	1.13	0.12
Average INR 3 Months ≥ 1.5	1.26	0.71	2.24	0.435

AF: atrial fibrillation; CI 95%: 95% confidence interval; LAVI: left atrial volume index; TAPSE: tricuspid annular plane systolic excursion; LVEF: Left ventricular ejection fraction; RDW-CV: red cell distribution width corpuscular volume; INR: international normalized ratio.

to hemostasis and thrombosis. Hematocrit is the primary determinant of blood viscosity [17]. Thus, the hematocrit has a vital role in the occurrence of thrombosis in low-pressure system, like the veins and left atrium.

We have shown in our study that increased hematocrit, atrial fibrillation and decreased left ventricular function were significantly associated with left atrial thrombus formation. These are related to the "stasis" and "hypercoagulable" components of the Virchow's triad.

Limitation

Other laboratory parameters for inflammation, d-dimer, fibrinogen, and uric acid were not done in this study. In the future, incorporating inflammation parameters in similar studies might give additional information on the role of inflammation in causing left atrial thrombus in patients with rheumatic mitral stenosis.

Conclusion

Increased hematocrit was significantly associated with left atrial thrombus. Other factors, such as atrial fibrillation, low left ventricular ejection fraction, and low TAPSE, were also significantly associated with left atrial thrombus in rheumatic mitral stenosis.

Conflict of interest

The authors declare that they have no conflicts of interest relevant to this study.

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Ethical information

This study has been approved by the Ethics Committee of NCCHK.

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