Risk factors for systemic thromboembolism after left chamber cardiac thrombi — A retrospective multi-center study

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Research article

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Abstract

Background : We aimed to characterize the independent predictors of systemic thromboembolism (ST) after left chamber thrombi. Methods: A retrospective analysis on the medical records of 175 patients diagnosed with left chamber thrombi by transthoracic echocardiography (TTE) at three centers were carried out. Multivariate logistic regression was performed to determine the relationship of each characteristic with ST. Multivariate Cox proportional survival analysis was conducted, with covariate adjustments, to identify predictors of all-cause mortality. Results: During a median 42 months of follow-up (25th–75th percentile: 20–62 months), 24 (13.7%) patients had ST, and 62 (35.4%) died. History of diabetes and thrombus mobility were independent predictors of ST (P = 0.003, P = 0.02, respectively). There was a significant association between abnormal ejection fraction (EF) and all-cause mortality (P = 0.003). Conclusions: The morbidity associated with ST and the increased risk for mortality associated with left chamber cardiac thrombi relates to medical history, thrombus state, and diminished heart function.

Background

Left chamber cardiac thrombi is a potentially life-threatening condition that may represent a source of systemic thromboembolism (ST), i.e., emboli in the arterial circulation [1]. Most (80%) of ST arise from intracardiac mural thrombi; two-thirds are associated with left ventricular wall infarcts; one-quarter are associated with dilation of the left atria, i.e., secondary to mitral valve disease. ST leads to coronary and cerebral thromboembolic events. Markers used to predict the prognosis of ST include age, gender, abnormal blood glucose or lipid, hypertension, cardiac dysfunction and hypercoagulability of blood. However, the core risk factors determining the morbidity and mortality of the situation are still unclear, which we would elucidate in the present study. Transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), cardiac-enhanced CT (CCT), and cardiovascular magnetic resonance (CMR) are mostly used to evaluate suspected cardiac thrombi. Among them, TTE, as a noninvasive, relatively inexpensive, easy technique, remains the initial tool for the diagnosis and risk stratification of patients predisposed to developing cardiac thrombi. In this study, TTE has been selected as the standard diagnostic approach.

Methods

This retrospective study included 175 patients hospitalized at Changzhou No. 2 People's Hospital (n = 60, 34.3%) Yixing People's Hospital (n = 66, 37.7%) and Changzhou No. 1 People's Hospital (n = 49, 28%), during the period from 2008 to 2018.

All the patients underwent conventional 2D Doppler echocardiography (Vivid E9, GE Healthcare or EPIQ7C, PHILIPS). Thrombus was defined as the presence of a well-defined echogenic intracavity mass with an echo-texture different from that of the underlying endocardium, identifiable in at least two different views. Considering the false-positive value of TTE, we excluded data obtained with spontaneous echo contrast, which can indicate the presence of a local hypercoagulable or even pre-thrombotic state. All echocardiograms were confirmed by two independent echocardiologists. All patients were diagnosed as having left ventricular or left atrial thrombi by TTE.

This study was designed and conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Board of Changzhou No. 2 People's Hospital, Yixing People's Hospital, and Changzhou No. 1 People's Hospital.

Data for normally distributed continuous variables were expressed as mean ± SD, while those with a skewed distribution were expressed as median (IQR). Continuous variables were analyzed using the unpaired t-test. Categorical variables were shown as percentages and the differences between groups were analyzed with the chi-squared test. Logistic regression analysis was used to evaluate correlations between ST and age, gender, history of diabetes, history of hypertension, thrombus characteristics (location, mobility, diameter, and density), left ventricle diameter at the end stages of diastole and systole, diameter of the interventricular septum, diameter of the left atrium, ejection fraction (EF) as calculated by Simpson's method with TTE, regional wall disability, and anticoagulation regimen. Variables with a P-value < 0.1 in univariate analysis were entered into the multivariate model. Age and gender were also added to the model. Cox proportional hazards regression models were established to identify variables contributing to ST-related mortality. A P value of < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software (version 20, IBM, Armonk, NY, USA).

Results

In this multi-center, retrospective, case-control study, 175 patients with the age of 18 years or above [mean age 65.2 ± 13.3 years; 115 male patients (65.7 %)] were recruited, 88 (50.3%) of whom had left ventricular thrombi. During a median follow-up of 42 months (25th–75th percentile: 20-62 months), 24 (13.7%) patients had ST, 4 (2.3%) had a major bleeding, and 62 (35.4%) died.

The baseline characteristics of patients included in the study are listed in Table 1. Only thrombus mobility (p = 0.006) and regional wall disability (p = 0.005) were significant predictors of the development of ST. Univariate logistic regression analysis showed that gender, history of diabetes, hypertension, thrombus mobility, regional wall disability, and previous anticoagulation treatment were significantly correlated with ST (Table 2). However, the results of multivariate logistic regression analysis identified only history of diabetes (OR, 1.692–13.827; P = 0.003), and thrombus mobility (OR, 0.035-0.746; P = 0.02) as significant predictors of ST occurrence.

For categorical variables, the results of univariate Cox proportional hazards regression models analysis revealed the significant correlation of four variables with all-cause mortality: age, impaired EF, history of

diabetes, and hypertension. However, only abnormal EF was sufficient for building a multivariate Cox model (p = 0.003) (Tab. 3). There was a trend toward an association between ST and all-cause mortality, but the statistical significance was not achieved (HR: 0.314–1.266, P = 0.195) (Table. 3).

Discussion

The results obtained in this retrospective case-control study showed that history of diabetes and thrombus mobility were associated with the incidence of ST in patients suffering from left chamber cardiac thrombi. Only impaired EF was significantly associated with all-cause mortality. There was a trend toward a significant correlation between ST and all-cause mortality, but this trend did not achieve statistical significance.

Various factors are involved in the development of ST in patients with left chamber thrombi. Because of the low prevalence of cardiac thrombi, we reviewed data collected at three centers during the 8 years, in order to identify factors significantly associated with the development of ST. We reviewed variables related to individual characteristics (e.g., history of hypertension, diabetes, age, gender), thrombus morphology (location, diameter, density, mobility), and therapeutic treatments (anticoagulation regimen). Eventually, we concluded that history of diabetes and thrombus mobility were the main factors associated with the occurrence of ST. This result was consistent with those presented in Adam's real-world observational study, which identified history of diabetes as the only determinant of thrombus persistence through multivariate analysis [2]. This finding may reflect the fact that coagulation disorders induced by hyperglycemia and insulin resistance increase thrombotic risk.

The relevance of thrombus mobility to ST is understandable. Low cardiac output, aberrant flow, and diminished cardiac contractility promote thrombus formation and instability, which predispose the patient to ST. It is commonly accepted that mobile, protruding, pedunculated, and fresh thrombi are more likely to embolize vessels [3]. However, in our research, we identified only mobility, but not other thrombus features, as a factor correlated with embolism. This discrepancy may due to the limits of TTE; a fresh thrombus is less echogenic, potentially leading to a false-negative echocardiographic result. It is therefore recommended that multiple measurements [e.g., TEE, cardiac-enhanced CT (CCT)], and cardiovascular magnetic resonance (CMR)) and frequent monitoring should be implemented in the management of patients with high risk for ST.

Although previous studies have investigated the use of anticoagulation treatment in reducing the risk for stroke, we did not find any such association. This finding may stem from the fact that the diagnosis of thrombus was often concomitant with the onset of ST. In some patients who first diagnosed with ST, the cardiac thrombus was found simultaneously. Alternatively, the absence of an association between anticoagulation treatment and risk for stroke may reflect a lack of optimized warfarin monitoring (international normalized ratio: 2–3) or the fact that patients included in our study did not use new oral anticoagulation (NOAC) agents. The use of vitamin K anticoagulation is limited by bleeding complications, interactions with various foods and drugs, and a narrow therapeutic window. So although

few studies have investigated NOAC treatment for the prophylaxis and resolution of intracardiac thrombi [2, 4-7], considering the low rate of thromboembolic or hemorrhagic complications, NOAC may be a safe and effective therapeutic alternative for intracardiac thrombi [5, 8].

Because of the small sample size included in this study and the biased nature of disease diagnosis, we did not sub-analyze intracardiac thrombi according to etiology (i.e., stress-induced cardiomyopathy, isolated left chamber noncompaction, peripartum cardiomyopathy, inflammatory bowel disease, Behcet Disease, leukemia) [9-11]. Moreover, as there was no significant correlation between thrombus location and ST, thrombi in the left atrium were not distinguished from those in the left ventricle. Abnormal hemostasis may increase thromboembolic risk, but additional studies will be necessary to confirm the association, so we did not detect it in this work.

Limitations

One limitation of this study is its retrospective nature. Although we have made efforts to ensure accuracy in data recording and follow-up, the possibility of bias could not be completely avoided.

Conclusions

Among patients with left chamber thrombi, history of diabetes and thrombus mobility was significantly associated with the onset of ST, and impaired EF was associated with all-cause mortality. Therefore, when encountering complex cases with high risk for ST, physicians should closely consider the patient's medical history, status of the thrombus, and any changes in cardiac function.

Abbreviations

ST: systemic thromboembolism

TTE: transthoracic echocardiography

EF: ejection fraction

TEE: transesophageal echocardiography

CCT: cardiac-enhanced CT

CMR: cardiovascular magnetic resonance

NOAC: new oral anticoagulation

Declarations

Ethics approval and consent to participate:

This study was designed and conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Board of Changzhou No. 2 People's Hospital, Yixing People's Hospital, and Changzhou No. 1 People's Hospital. We are very glad to provide specific information if necessary.

Consent for publication:

Informed consent to participate in the study was obtained from participants or their legal guardian in the case of unconscious patients. We are also very glad to provide specific information if necessary.

Availability of data and material:

All data generated during this study are included in this supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions:

Shenglan Huang designed, analyzed and substantially revised the work; Weizhou and Shun-yi Shi wrote and interpreted data; Yuan Ji, Xin Chen, Song Yang, Jian-hui Sun collected data. Jun Huang re-evaluated the TTE image.

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Tables

Table 1 Basic characteristics of patients with vs. without ST

	Total (n = 175)	ST (n = 24)	Non-ST (n = 151)	P-value
Gender(male)	115□65.7%□	14	101	0.488
Age	65.22±13.28	64.58±12.57	65.32±13.42	0.802
Diabetes	38(21.7%)	6	32	0.777
Hypertension	76(43.4%)	15	61	0.071
Location(left atrium)	87(49.7%)	10	78	0.363
mobility	9(5.1%)	4	5	0.006*
Diameter	2.44±1.27	2.25±1.30	2.47±1.27	0.477
Density□low□	114(65.1%)	17	96	0.873
IVS	9.34±1.64	9.40±1.51	9.33±1.66	0.845
LVD	54.07±8.96	53.09±10.91	54.21±8.66	0.585
LVS	41.15±10.05	39.64±11.93	41.39±9.75	0.450
LA	47.02±11.33	47.27±9.78	46.99±11.58	0.912
EF	47.77±12.09	51.06±11.54	47.26±12.13	0.161
Regional disability	123(70.3%)	11	112	0.005*
Anticoagulation	94(53.7%)	12	82	0.694

ST: systemic thromboembolism; IVS: diameter of interventricular septum; LVD: end-diastolic left-ventricular volume; LVS: left ventricle diameter at the systolic end-stage; LA: diameter of the left atrium; EF = ejection fraction.

Table 2 Univariate and multivariate logistic regression analysis on the relevance of basic characteristics to ST

	Univariable OR	P	Multivariable OR	P
gender (male)	(0.599,3.477)	0.000*		
Age	0.964,1.028	0.148		
Diabetes	0.317,2.361	0.000*	1.692 13.827	0.003*
Hypertension	0.183,1.087	0.000*		
mobility	(0.043,0.696)	0.014*	0.035,0.746	0.019*
Diameter	0.570,1.300	0.476		
Density low	0.294,1.933	0.556		
IVS	0.780,1.356	0.844		
LVD	(0.936,1.038)	0.583		
LVS	0.936,1.030	0.448		
LA	(0.964,1.042)	0.912		
EF	(0.989,1.067)	0.163		
Regional disability	(1.405,8.197)	0.000*		
anticoagulation	(0.119,0.840)	0.021*		
location	(0.280,1.599)	0.365		

Table 3 Cox proportional regression analysis on the prediction of all-cause mortality among patients with left chamber thrombi.

	K-M/Cox	P-value	Multivariable OR	P-value
gender (male)		0.622		
Age	(1.013,1.054)	0.001*	(0.494,1.461)	0.556
Diabetes		0.008*	(0.546,1.874)	0.970
Hypertension		0.026*		
mobility		0.601		
Density low		0.625		
EF	(0.954,0.995)	0.013*	(0.946,0.988)	0.003*
Regional disability		0.723		
anticoagulation		0.414		
location		0.961		
stroke		0.490	(0.314,1.266)	0.195

Supplementary Files

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