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Original Article

Risk Factors Associated with Heart Valve Thrombosis in Patients with Prosthetic Heart Valve Dysfunction

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Abstract

Background: Thrombotic and thromboembolic events are important causes of mortality and morbidity in patients with prosthetic heart valve. The aim of this study is to evaluate the factors that may contribute to prosthetic heart valve thrombosis.

Methods: This was a cross-sectional study in Rajaie Heart Center on patients with prosthetic heart valve malfunction, within a year. According to the echocardiographic and fluoroscopic findings, the patients were divided into two groups (thrombosis and non-thrombosis groups). The patients' demographic, clinical and laboratory data were recorded and analyzed with SPSS software.

Results: A total of 142 patients participated in this study. Ninety-four patients (66.2%) were diagnosed with thrombosis. There was a significant relationship between thrombosis and inadequate anti-coagulation (international normalized rati [INR] <2.5) (odds ratio [OR]: 4.15, 95% CI: 1.98-9.87, P = 0.003), history of infection (OR: 12.81, 95% CI: 3.52-19.02, P<0.001), prothrombin time (PT) check interval (OR: 2.38, 95% CI: 1.63-8.47, P = 0.019), atrial fibrillation (AF) rhythm (OR: 3.96, 95% CI: 1.75-8.09, P = 0.019), and plasma fibrinogen level (OR: 6.90, 95% CI: 2.58-14.69).

Conclusion: Based on this study, inadequate anti-coagulation, AF rhythm, recent infection and plasma fibrinogen level were the factors most contributing to prosthetic valve thrombosis. As there were many cases of thrombosis in patients with history of infection, this factor can be considered for risk assessment in prosthetic valve.

Keywords: Heart valve prosthesis, Risk factors, Thrombosis

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Introduction

An average of 350 000 heart valves are replaced worldwide every year.[1] The main objective of valve replacement is to expand life expectancy and improve life quality in patients who have significant symptoms.[2] One of the important steps in treatment of these patients is sufficient administration of anticoagulants to prevent thrombus formation on the valve.[3] The incidence of prosthetic heart valve thrombosis depends on the type of the prosthetic valve. In mechanical valves, the risk of thrombosis is higher compared to biological valves. There is an incidence rate of thrombosis of approximately 0.1% to 5.7% in mechanical heart valves and 0.03% in biological heart valves, reported every year. Also, it is reported that thrombosis occurs by a rate between 0.1 to 6.0% for each year of patient's age, in the mitral and the aortic valves and up to 20% in the tricuspid valve.[4] Diagnostic techniques including echocardiography, fluoroscopy, and therapeutic measures involving re-surgery, thrombolytic therapy, or anti-coagulant treatments impose significant costs on individuals and the whole community.[5,6] Prosthetic Valve Thrombosis (PVT) results in valve malfunction, thromboembolic events, the clot serving as a nest for viral or bacterial growth, etc.[7] This study aims to assess the risk factors and incidence of prosthetic valve thrombosis in patients with prosthetic valve malfunction.

Materials and Methods

Study Design and Participants

This was a cross-sectional study in Rajaie Heart Centre on patients with prosthetic heart valve malfunction. Depending on the purpose and type (census) of the study, all patients (referred from other hospitals, emergency admittance and routine visits) with valve malfunction (symptomatic or asymptomatic changes in the prosthetic valve's hemodynamic status on echocardiographic assessment, including stenosis and regurgitation) from April 2015 to April 2016 were included in the study. The criteria for excluding patients were: 1) missing data obtained by laboratory tests or interview, and 2) the patient not consenting to the study.

In case of clinical suspicion for prosthetic valve thrombosis, transthoracic echocardiography was performed in advance. Based on the leaflet mobility and gradient, hemodynamic status, and identification of thrombus, the trans-esophageal echocardiography was performed in

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the absence of contraindications. The considered signs of thrombosis on echocardiography were restriction of leaflet mobility or observing echogenic thrombotic mass on the leaflet or valve ring. If thrombosis was diagnosed, fluoroscopy was performed to confirm the restriction of the related leaflet movement.[8]

Variables

The patients' demographic data, in addition to medical and drug history, were obtained through interviews. The interviewer was blinded to the other data of the patients. Then, a blood sample was collected aseptically by antecubital puncture, followed by a urine test. Laboratory measurements included the international normalized ratio (INR), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), plasma fibrinogen level and proteinuria. Researchers who collected either the interview or laboratory data were blinded to the other data.

Statistical Analysis

The collected data were analyzed using the IBM SPSS Statistics software (version 16.0, SPSS, Chicago, Illinois). Chi-square test was used to compare qualitative variables. Quantitative variables were compared using Student's *t* test. Significance differences were shown with odds ratio (95% CI) computed using chi-square test. Logistic regression was used to assess the relationship between the variables and PVT and determining the confounder effects. *P* values < 0.05 were considered significant.

Results

Demographic Data and Medical History

A total of 154 eligible patients participated in the study. Twelve patients were excluded due to lack of co-operation or missing data. Finally, data from 142 patients were analyzed. Ninety-four patients (66.2%) were diagnosed with thrombosis and 48 (33.8%) were without thrombosis (infective endocarditis, para-valvular leakage, valve deterioration). One hundred and two patients (71.8%) had dyspnea at the time of presentation which was the most prevalent symptom. Thirteen patients (9.2%) had palpitation, 13 (9.2%) had CVA (cerebrovascular accidents) and TIA (transient ischemic attack) and 1 (0.7%) experienced syncope. None of the patients were addicted to drugs or alcohol but 19 (13.4%) used to smoke cigarettes. Ninety-four patients (66.2%) were females and 48 (33.8%) were males with an average (mean ± SD) age of 49.8 ± 13.13 years. Seventy-five patients (52.8%) had a history of an infectious disease other than endocarditis in the month preceding admission [69 (92%) in the thrombosis versus 6 (8%) in the non-thrombosis group]: among them, 54 (72%) had upper respiratory infection (OR: 19.320, 95% CI: 7.323–50.969). According to the history of prothrombin time (PT) check intervals, 57 patients (60.7%) with thrombosis versus 3 (6.2%) without thrombosis had erratic PT check. In other words, the non-thrombosis group had considerably regular PT check intervals (P<0.001) (Table 1). Logistic regression showed that history of recent infection and PT check interval were

Table 1. Patients' Demographic Characteristics and Medical History

Variables	Thrombosis (n = 94), No. (%)	Non-Thrombosis (n = 48), No. (%)	*P* Value	OR	CI (95%)	
					Lower	Upper
Gender						
Female	65 (69.1)	29 (60.4)	0.298	1.468	0.711	3.033
Male	29 (30.9)	19 (39.6)				
PT check interval						
<1-month	2 (2.1)	6 (12.5)	<0.001	1.09	0.95	1.25
Monthly	35 (37.2)	39 (81.3)		Base	—	—
Erratic	57 (60.7)	3 (6.2)		8.67	2.88	26.11
Recent infection						
Yes	69 (73.4)	6 (12.5)	<0.001	19.320	7.323	50.969
No	25 (26.6)	42 (87.5)				
Aspirin(80) + warfarin						
Yes	36 (38.3)	34 (70.8)	<0.001	0.256	0.121	0.540
No	58 (61.7)	14 (29.2)				
Season						
Spring	19 (20.2)	14 (29.2)				
Summer	17 (18.1)	13 (27.1)	0.811	—	—	—
Fall	23 (24.5)	8 (16.6)				
Winter	35 (37.2)	13 (27.1)				
Replaced valve number						
1	57 (60.6)	39 (81.3)	0.004	—	—	—
2	36 (38.3)	9 (18.7)				
3	1 (1.1)	0 (0.0)				

PT, prothrombin time; OR, odds ratio; CI, confidence interval.

the risk factors most contributing to thrombosis (OR: 12.81, 95% CI: 3.52–19.02, *P*<0.001 and OR: 2.38, 95% CI: 1.63-8.47, *P* = 0.019, respectively) (Table 2).

Clinical Findings

One hundred and twenty patients (84.5%) had normal metallic sound and 22 (15.5%) had reduced metallic sound. All of the reduced sounds pertained to the thrombosis group and the difference was significant (OR: 1.66, 95% CI: 1.44–1.92, *P*<0.001). Among patients with atrial fibrillation (AF), 52 (77.61%) were in the thrombosis group and 15 (22.39%) were in the non-thrombosis group, indicating a significant difference (*P* = 0.008) (Table 3).

Also, a significant relationship was observed between AF rhythm and thrombosis (OR: 3.96, 95% CI: 1.75–8.09, *P* = 0.018). Additional information regarding the effects of these factors is illustrated in Table 2.

Laboratory Measurements

According to Table 4, the mean INR level was 1.8 in the first group and 2.3 in the second group. Thrombotic events were observed with significantly higher frequency in the patients with INR ≤ 2.5 (*P*<0.001). Analysis showed a direct relationship between the INR level of less than 2.5 and thrombotic events (OR: 4.15, 95% CI: 1.98–9.87, *P* = 0.003). The CRP level increased in 66 patients (46.5%), 55 of whom (83.33%) were in the thrombosis group. There was a significant difference between the two groups based on the CRP level (OR: 2.55, 95% CI: 1.47–4.40, *P*<0.001). In the urine analysis, 37 patients (39.4%) had 1+ proteinuria and 7 patients (7.4%) had 2+ proteinuria in the thrombosis group. In the non-thrombosis group, no patient had 2+ proteinuria. There was a significant difference between the two groups based on the proteinuria level (*P*<0.001) (Table 4). According to Table 2, the effects of CRP and proteinuria were not significant in logistic regression. Although there was a significant difference between the two groups, they were considered as confounder factors (Table 2).

Discussion

Valvular heart disease is prevalent in developing countries. Surgical replacement is an advanced therapy for this disease, with optimal long-term results. One of the most important complications of valve replacement surgery

Table 2. Relationship Between Risk Factors and Thrombosis in Logistic Regression Analysis

Risk Factors	*P* value	OR	CI (95%)	
			Lower	Upper
PT Check Interval	0.019	2.38	1.63	8.47
Recent infection	<0.001	12.81	3.52	19.02
Concurrent use of aspirin and warfarin	0.138	0.211	0.027	1.65
Replaced valve number	0.282	2.47	0.292	5.51
CRP	0.100	2.11	0.656	4.56
Proteinuria	0.180	0.16	0.011	2.32
Plasma fibrinogen	0.006	6.90	2.58	14.69
Fluoroscopy	0.264	2.05	0.295	3.54
AF rhythm	0.018	3.96	1.75	8.09
INR level	0.003	4.15	1.98	9.87

PT, prothrombin time; CRP, C-reactive protein; AF, atrial fibrillation; INR, international normalized ratio; OR, odds ratio; CI, confidence interval.

Table 3. Patients' Clinical and Imaging Findings

Variables	Thrombosis (n = 94), No. (%)	Non-Thrombosis (n = 48), No. (%)	*P* Value	OR	CI (95%)	
					Lower	Upper
Metallic sound						
Decreased	22 (23.4)	0 (0.0)	<0.001	1.66	1.44	1.92
Normal	72 (76.6)	48 (100)				
Rhythm						
Sinus	42 (44.7)	33 (68.7)	0.008	1.77	1.12	2.79
AF	52 (55.3)	15 (31.3)				
Fluoroscopy						
Limited	49 (52.1)	6 (12.5)	<0.001	4.17	1.92	9.03
Normal	45 (47.9)	42 (87.5)				
LVEF						
<35%	15 (15.9)	5 (10.4)		1.44	0.68	3.02
36%-50%	69 (73.4)	36 (75)	0.44	1.04	0.89	1.22
>50%	10 (10.6)	7 (14.6)		Base	—	—

AF, atrial fibrillation; LVEF, left ventricular ejection fraction; OR, odds ratio; CI, confidence interval.

Table 4. Laboratory Measurements

Variables	Thrombosis (n = 94), No. (%)	Non-Thrombosis (n = 48), No. (%)	*P* Value	OR	CI (95%)	
					Lower	Upper
INR						
<1.5	34 (36.2%)	5 (10.4%)		3.32	1.51	7.31
1.5-2.5	49 (52.1%)	26 (54.2%)	<0.001	2.91	1.19	7.12
>2.5	11 (11.7%)	17 (35.4%)		Base	—	—
Mean	1.8	2.35		—	—	—
CRP						
Normal	39 (41.5%)	37 (77.1%)	< 0.001	2.55	1.47	4.40
Increased	55 (58.5%)	11 (22.9%)				
ESR						
Normal	80 (85.1%)	42 (87.5%)	0.698	1.19	0.49	2.90
Increased	14 (14.9%)	6 (12.5%)				
Proteinuria						
Normal	50 (53.2%)	41 (85.4%)		Base	—	—
+1	37 (39.4%)	7 (14.6%)	< 0.001	2.91	1.41	6.03
+2	7 (7.4%)	0 (0.0%)		1.54	1.15	3.14
Plasma fibrinogen						
Normal	46 (48.9%)	47 (97.9%)	< 0.001	24.51	3.48	172.19
Increased	48 (51.1%)	1 (2.1%)				

INR, international normalized ratio; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; OR, odds ratio; CI, confidence interval.

is dysfunction due to valve thrombosis which can lead to thromboembolic events and fatal stroke.[4] According to Table 4, inadequate anti-coagulation at the time of admission had a strong relationship with thrombosis. Similarly, as mentioned in other studies, the cause of thrombosis in prosthetic valves is often due to insufficient anticoagulation, which is directly related to the patients' culture and their awareness regarding correct use of anticoagulant drugs.[4,9] The most common symptom at the time of admission was dyspnea, and later with other findings such as palpitation, CVA, TIA, decreased prosthetic valve sounds and syncope. These findings are consistent with another study conducted by Bonou et al.[10] In this study, the highest rate of thrombosis observed was in winter in the months of January and February (Table 1). Pham et al[11] reported that PVT has a higher prevalence during winter compared to other seasons. It seems that this caused by the change in plasma fibrinogen levels in different seasons. In winter, plasma fibrinogen levels increase. Also, the increase in plasma viscosity in this season may be the cause for an increase in thrombosis. Our study also found a significant relationship between plasma fibrinogen levels and thrombosis which increased the incidence of thrombosis in those with higher plasma fibrinogen levels. This also confirms all above.[12] In this study, AF rhythm on ECG had a direct and significant relationship with valve thrombosis. Dürrleman et al.[13] reported that AF rhythm was observed in 45% of patients with PVT. Furthermore, Cáceres-Lóriga et al[14] reported that this rhythm was present in 56% of patients with PVT and there was a significant relation between AF and thrombosis, which is consistent with our study. The results show a significant relationship between history of infection, particularly upper respiratory infection in the month preceding admission, and PVT. Since none of the patients with previous infections, especially upper respiratory tract infection, were diagnosed with endocarditis, it can be argued that the presence of upper respiratory tract infections without direct involvement of cardiac tissue, could be an independent factor in development of thrombotic events in prosthetic valves. We did not find any study addressing this issue in the databases. In this study, the CRP level was considered as a confounder factor for PVT, but Gürsoy et al[15] reported that the increased CRP level contributed to the prosthetic mitral valve thrombosis. A possible reason why this factor was considered a confounding factor in this study is that CRP is an acute phase reactant and can change quickly in conditions other than valve dysfunction. We also found proteinuria level as a confounding factor.

One of the limitations of our study was the presence of infection before the patients' admission as a subjective item. We were not able to confirm the presence of infection with para-clinical tests, and we could not differentiate the bacterial or the viral nature of the infection. Another limitation was that our study was conducted in a single clinical heart center. Consequently, the results may not have enough power or validity to be generalized. Also, in this study, we did not evaluate the effect of the time lapse between valve surgery and the dysfunction which could be an important factor; this needs to be considered in future studies.

In conclusion, based on the results of our study, it may be

concluded that inadequate anti-coagulation, AF rhythm, recent infection and plasma fibrinogen level are the factors most contributing to prosthetic valve thrombosis. Due to the high rates of thrombosis in patients with history of recent infection, this factor can be considered as a factor in prosthetic valve risk assessment, requiring further investigations in larger populations.

Authors' Contribution

FNB: made total concept, designing the study and manuscript review. HAB: definition of intellectual content and design the study. SG: searching the literatures, manuscript preparation, definition of intellectual content and data curation. HA: designing the study, performing clinical section, data acquisition and manuscript editing. TR: data statictical analysis.

Conflict of Interest Disclosures

Hereby the authors declare no conflict of interest.

Ethical Statement

The study was conducted in accordance with the principles of the declaration of Helsinki and approved by the ethic committee of Iran University of Medical Sciences. All patients provided their written informed consent.

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None.

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