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Relationship between endothelial dysfunction and prosthetic heart valve thrombosis: a preliminary investigation

H. KAYA, M. ÖZKAN*, M. YILDIZ*

Department of Cardiology, Dicle University School of Medicine, Diyarbakir, Turkey
*Department of Cardiology, Kosuyolu Kartal Heart Training and Research Hospital, Istanbul, Turkey

Abstract. – AIM: The etiopathogenesis of prosthetic heart valve thrombosis (PHVT) is multifactorial. Since the relationship between PHVT and endothelial function is never studied, we aimed to analyze the role of endothelial function in patients with PHVT.

PATIENTS AND METHODS: Twenty-two patients with PHVT (14 female, 31.8% with atrial fibrillation, mean age 46.0±12.2) and 22 controls with prosthetic heart valves (17 female, 36.4% with atrial fibrillation, mean age 45.7±11.5) were prospectively evaluated. Two groups had similar demographic and echocardiographic characteristics. Endothelial function was evaluated in all patients by the non-invasive measurement of flow mediated dilatation (FMD) of brachial artery. High-resolution ultrasound was used to measure brachial artery diameter at rest, during reactive hyperemia (endothelium-dependent, FMD), and following sublingual administration of nitroglycerin (endothelium-independent, nitroglycerin-mediated vasodilatation, NMD).

RESULTS: Functional capacity at presentation determined as mean NYHA functional capacity class was worse in patients with PHVT than in control group (2.1±0.6 vs. 1.3±0.6; $p < 0.0001$). FMD was significantly reduced in patients with PHVT compared with control group (4.01±1.52 vs. 8.48±3.37; $p < 0.0001$). NMD did not differ between two groups (11.77±2.30 vs. 13.38±3.50; $p = 0.08$). FMD level of < 5.65 predicted prosthetic valve thrombosis with an 82% sensitivity and 77% specificity (area under the curve = 0.888, $p < 0.0001$).

CONCLUSIONS: This study demonstrated the endothelial dysfunction in patients with PHVT compared with well-matched control group. In this study, we found that patients with PHVT have endothelial dysfunction which might contribute to the development of thrombosis.

Key Words:
Endothelial function, Prosthetic heart valve, Thrombosis.

Introduction

For many patients with valvular heart disease, prosthetic valve replacement is the only effective therapy[1]. The development of thrombosis represents one of the most important causes of morbidity and mortality in patients with prosthetic valves[1]. Inadequate anticoagulant therapy is the main cause of these complications, but surgical technique is an inevitable contributing factor due to endocardial fibrosis and the exposure of foreign surfaces such an prosthetic and suture materials to blood stream[2].

The endothelium plays an integral role in the regulation of vascular tone, platelet activity, leukocyte adhesion, and is intimately involved in the development of thrombosis[3]. Since endothelial function of patients with prosthetic heart valves is not evaluated, hence the role of endothelial dysfunction in prosthetic heart valve thrombosis (PHVT) is not known.

In this study we aimed to examine endothelial function in patients with PHVT, compared with a well-matched group of patients with mechanical heart valves who never developed this complication.

Patients and Methods

Patients

Consecutive patients admitted to our Echocardiography Unit for PHVT between January 2009 and December 2009 were eligible for recruitment. Patients with left ventricular systolic dysfunction (ejection fraction < 40%), acute cardiovascular and cerebrovascular incident in the past 3 months, malignancy, connective tissue disease, active/chronic infection or inflammation, diabetes mellitus, hypertension, chronic liver failure, chronic renal failure, hypercholesterolemia or lipid-lowering therapy and smoking were excluded. The control group consisted of patients with mechanical valves who had never experienced PHVT. Control group of patients were completely free of signs and symptoms of pros-

Corresponding Author: Hasan Kaya, MD; e-mail: dr_hasankaya@yahoo.com

thetic valve obstruction, anamnesis and retrospective analysis of these patients did not reveal a history of PHVT. Informed consent was obtained and the study was approved by the local Ethics Committee.

Echocardiography

Complete transthoracic and transesophageal echocardiographic studies were performed in all patients, by use of transthoracic echocardiography, two-dimensional transesophageal echocardiography, and real-time three-dimensional transesophageal echocardiography (Philips iE33, Philips Medical System, Andover, MA, USA) for the diagnosis of thrombus.

Prosthetic valve thrombus was recognized as soft and homogeneous, mobile or fixed echo densities located at the valve occluder and/or valve struts. Obstructive valve thrombosis was diagnosed when the Doppler mitral valve area was < 1.5 cm^2 and the mitral valve mean gradient was > 10 mmHg, or when the aortic mean gradient was > 40 mmHg[4]. Transesophageal echocardiographic examinations of control patients revealed normally functioning prosthetic valves.

Endothelial Function Study

All patients were studied at least 12 h after their last meal, according to a standard protocol previously described[5]. Briefly, the patients were instructed to lie quietly in a supine position for 10 min before the study. All studies were performed in a temperature-controlled room (20 to 25°C). Brachial artery was imaged with a VingMed Vivid System 5 (General Electric, Horten, Norvey) ultrasound system and 10 MHz linear-array transducer. Arterial flow was interrupted for 5 min by cuff placed on the proximal forearm at whichever occlusion pressure would be higher 200 mmHg or 50 mmHg + systolic blood pressure. The brachial artery was scanned in longitudinal section, the focus zone was set to optimize images of the lumen-arterial wall interface, and machine operating parameters were not changed during the rest of the study. Measurements were taken from the anterior to posterior "m" line at end diastole, incident with the R-wave on the ECG. Three cardiac cycles (in patients with atrial fibrillation seven cardiac cycles) were analyzed for each scan, and measurements were averaged. Arterial diameter was measured 60 sec after cuff deflation. After 10 minutes of vessel recovery, rest scan repeated. Sublingual nitrate (0.3 mg glyceryl trinitrate) was then administrated to evaluate endothelium independent vasodilation. The last scan was performed 3 min after nitrate intake. Endothelium-dependent, post ischemic flow mediated vasodilation (FMD) was determined by the maximal brachial artery diameter after exactly 60 sec of reactive hyperemia, compared with baseline vessel diameter, and was expressed as percent of FMD. Endothelium-independent, nitrate mediated vasodilation (NMD) was expressed as the percent change in baseline vessel diameter 3 min after sublingual nitrate administration.

FMD study of patients with obstruction was made before thrombolytic or surgery treatment.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation. Comparison of continuous variables between two groups was performed using Student's *t* test or Mann-Whitney U test, where appropriate. Categorical variables were compared using chi-square tests. To predict PHVT, receiver operator characteristics (ROC) analysis was used in order to determine cut-off values for FMD. Analysis were performed using Statistical Package for Social Sciences, version 15.0, statistical software (SPSS Inc., Chicago, IL, USA), and statistical significance was set at $p < 0.05$.

Results

The study group consisted of 22 patients with PHVT (14 women, mean age 46.0±12.2) who satisfied our inclusion and exclusion criteria. Of the 22 patients, 14 (63.6%) had mechanical valve at the mitral position, 1 (4.5%) at the aortic position, 5 (22.7%) at both aortic and mitral position and 2 (9.1%) at aortic, mitral and tricuspid position. The control group consisted of 22 matched patients with mechanical valves (17 women, mean age 45.7±11.5) who had not experienced an episode of prosthetic valve thrombosis. Of the 22 control patients, 16 (72.7%) had mechanical valve at the mitral position, 2 (9.1%) at the aortic position and 4 (18.2%) at both aortic and mitral position. The clinical and demographical characteristics of the two groups are presented in Table I.

In PHVT group 5 obstructive (3 mitral, 2 tricuspid) and 17 non-obstructive (11 mitral, 1 aortic, 5 both aortic and mitral) thrombus were diagnosed with transesophageal echocardiography. All patients with obstructive thrombosis present-

ed with dyspnea. Five patients with non-obstructive thrombosis presented with dyspnea, 8 patients with ineffective INR values, 5 patients with cerebrovascular accident or transient ischemic attack, 3 patients with previous history of non-obstructive thrombosis and one patient with non-obstructive thrombosis presented with inferior myocardial infarction.

8 patients (4 obstructive thrombosis) undergone successful thrombolytic treatment with tissue plasminogen activator (t-PA), one patient presented with non-obstructive thrombosis and cerebrovascular accident and one patient with obstructive thrombosis undergone surgery treatment.

In PHVT group 7 (31.8%) patients and in control group 8 (36.4%) patients were in atrial fibrillation ($p = 0.50$).

Functional capacity at presentation determined as mean New York Heart Association (NYHA) functional capacity class was worse in patients with PHVT than in control group (2.1±0.6 vs. 1.3±0.6; $p < 0.0001$).

The mean International Normalized Ratio (INR) levels were lower in patients with PHVT than in control group (1.9±0.9 vs. 2.5±0.8; $p = 0.047$).

According to echocardiographic studies, left ventricular ejection fractions, left atrial diameters and left ventricular systolic and diastolic diameters did not differ between two groups.

FMD was significantly reduced in patients with PHVT compared with control group (4.01±1.52 vs. 8.48±3.37; $p < 0.0001$). NMD did not differ between two groups (11.77±2.30 vs. 13.38±3.50; $p = 0.08$) (Figure 1).

For entire group of patients FMD was similar between patients with sinus rhythm and atrial fibrillation (5.45±3.07 vs. 6.66±3.59; $p = 0.27$). Mean age and postoperative time of patients with atrial fibrillation was higher than in pa-

Table I. Comparisons of clinical characteristics between patients with prosthetic heart valve thrombosis and control group.

Clinical parameters	PHVT (n=22)	Control (n=22)	*p* value
Age (year)	46.0 ± 12.2	45.7 ± 11.5	0.95
Gender (Male/Female)	8/14	5/17	0.51
Body mass index (kg/m^2)	26.6 ± 4.7	28.0 ± 4.9	0.34
Post-operative time (month)	87.1 ± 7	75.6 ± 46.1	0.54
Prosthetic valve position			
Mitral (%)	14 (63.6)	16 (72.7)	
Aortic (%)	1 (4.5)	2 (9.1)	
Mitral+aortic (%)	5 (22.7)	4 (18.2)	
Mitral+aortic+tricuspid (%)	2 (9.1)	0	
Ryhthm			0.50
Sinus ryhthm (%)	15 (68.2)	14 (63.6)	
Atrial fibrillation (%)	7 (31.8)	8 (36.3)	
NYHA class	2.14 ± 0.56	1.27 ± 0.55	< 0.0001
INR level	1.94 ± 0.92	2.47 ± 0.79	0.047
Echocardiographic parameters			
LA (cm)	4.27 ± 0.56	4.67 ± 0.78	0.16
LVEDD (cm)	5.00 ± 0.46	5.16 ± 0.68	0.51
LVESD (cm)	3.38 ± 0.59	3.49 ± 0.81	0.70
LVEF (%)	61.18 ± 6.59	61.2 ± 7.38	0.99
Medications			
Warfarin (%)	22 (100)	22 (100)	1.00
Aspirin (%)	3 (13.6)	7 (31.8)	0.28
ACEI/ARB (%)	7 (31.8)	7 (31.8)	1.00
Beta blocker (%)	3 (13.6)	7 (31.8)	0.28
CCB (%)	1 (4.5)	3 (13.6)	0.61
Digoxin (%)	2 (9.1)	2 (9.1)	1.00
FMD (%)	4.01 ± 1.52	8.48 ± 3.37	< 0.0001
NMD (%)	11.77 ± 2.30	13.38 ± 3.50	0.08

PHVT: Prosthetic heart valve thrombosis, NYHA: New York Heart Association, INR: International Normalized Ratio, LA: Left atrium, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, LVEF: Left ventricular ejection fraction, ACEI: Angiotensin converting enzyme inhibitors, ARB: Anjiotensin receptor blockers, CCB: Calcium channel blockers, FMD: Flow mediated vasodilation, NMD: Nitrate mediated vasodilation.

tients with sinus rhythm (51.6±10.4 vs. 42.9±11.4 years; p = 0.017 and 110.9±66.0 vs. 66.0±52.3 months; p = 0.019, consecutively).

Among patients with PHVT, FMD was not statistically different between patients with sinus rhythm and atrial fibrillation (4.05±1.73 vs. 3.91±1.06; p = 0.83). FMD was not different between obstructive and non-obstructive PHVT group (3.93±0.98 vs. 4.03±1.67; p = 0.90).

FMD level of < 5.65 predicted prosthetic valve thrombosis with an 82% sensitivity and 77% specificity (area under the curve = 0.888, p < 0.0001).

Discussion

This study is the first to examine endothelial function in patients with PHVT compared with well-matched control group. Endothelial function was assessed by brachial artery FMD, which serves as a measure of endothelial vasodilator function in humans[5]. In the present study, we have demonstrated that patients with PHVT have significantly lower levels of FMD than control group of patients without PHVT.

Thrombosis is a serious complication of prosthetic heart valves and is associated with substantial morbidity and mortality[6]. It should be suspected in patients with worsening functional class, embolic phenomena and inadequate anticoagulation[7].

The prerequisite conditions for PHVT can be presented in the context of Virchow's triad – abnormalities of vascular endothelial surface, stasis of blood flow and abnormalities within circulating blood – with modifications for the introduction of a fourth component, an artificial surface[8].

The process of thrombus formation on a prosthetic heart valve appears to involve two concurrent mechanisms. The first mechanism involves disruption of the vascular endothelial surface and exposure of underlying prothrombotic substrate or introduction of prothrombotic materials into the circulation. The second mechanism is mediated by triggering of thrombosis in areas of stasis via activation of coagulation pathways[8]. Artificial surfaces can promote platelet activation, which is dependent on the surface properties, including physical characteristics, electrical charge, surface chemistry, and on the shear rate of blood flow[8,9].

Inadequate anticoagulant therapy is the main cause of the prosthetic valve thrombosis, but surgical technique is an inevitable contributing factor due to endocardial fibrosis and the exposure of foreign surfaces such as prosthetic and suture materials to bloodstream[2].

The endothelium plays an integral role in the regulation of vascular tone, platelet activity, leukocyte adhesion, and in the development of thrombosis[3]. Risk factors of smoking, aging, hypercholesterolemia, hypertension, hyperglycemia, and a family history of premature atherosclerotic disease are all associated with an attenuation/loss of endothelium dependent vasodilation. Studies have shown that the severity of endothelial dysfunction relates to the risk for an initial or recurrent cardiovascular events[10]. A noninvasive method have been developed to evaluate flow mediated dilation, an endothelium dependent function, in the brachial artery. This stimulus provokes the endothelium to release nitric oxide with subsequent vasodilation that can be imaged and quantitated as an index of vasomotor function[5].

It was reported that patients with mitral valve disease have increased plasma von Willebrand factor (vWf) levels (index of endothelial damage or dysfunction) when compared with healthy con-

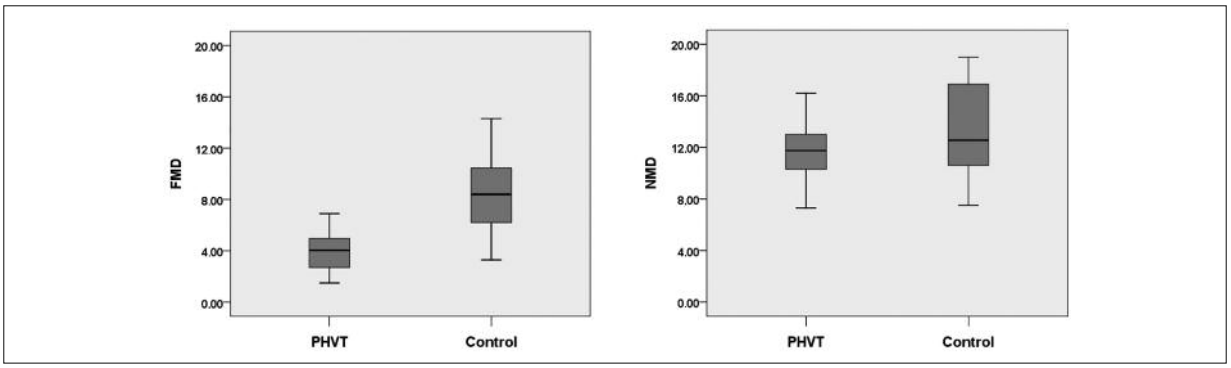

Figure 1. Flow mediated vasodilation (FMD) and nitrate mediated vasodilation (NMD) values in prosthetic heart valve thrombosis (PHVT) and control groups.

trols, with a further increase after mitral valve replacement[11]. Conversely, patients undergoing mitral valve repair did not demonstrate any significant change in indices of endothelial dysfunction.

It is known that inadequate anticoagulant therapy is the main cause of PHVT[2]. Deviri[12] et al showed that 70% of patients with PHVT have inadequate anticoagulant therapy. In our study INR levels were lower in patients with PHVT than in control group.

In this investigation, we have demonstrated that patients with PHVT have significantly lower levels of FMD, as compared to age and sex matched control group of patients without PHVT. Patients did not differ from controls with respect to the traditional risk factors for atherosclerosis and medications. Endothelial dysfunction measured by FMD is predominantly the consequence of the presence of PHVT itself. However, the nature of the study does not answer whether endothelial dysfunction is cause or effect.

Studies have showed that patients with atrial fibrillation have impaired FMD and this impairment is reversible by restoration of sinus rythym[13]. In our study, FMD did not reached statistical difference between patients with sinus and atrial fibrillation rhythm, thought to be small size of samples.

Because of the nature of this study, the effects of medications on endothelial functions were not evaluated.

Conclusions

This study demonstrates the endothelial dysfunction in patients with PHVT compared with well-matched control group. In this preliminary study, we found that patients with PHVT have endothelial dysfunction which might contribute to the development of thrombosis.

Conflict of Interest

None to declare.

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