Diagnostic Value of D-Dimer and Antithrombin-III Levels in Predicting Prosthetic Heart Valve Thrombosis

The aim of this prospective study was to investigate the diagnostic value of plasma D-dimer levels and antithrombin-III activity in predicting prosthetic valve thrombus. The study group comprised 97 consecutive patients with prosthetic heart valves (59 with mitral, 21 with aortic, and 17 with both mitral and aortic prostheses) and 35 healthy control subjects. Six patients presented with symptoms of obstruction; the remaining 91 were asymptomatic. Patients were evaluated by both transthoracic and transesophageal echocardiography. Asymptomatic nonobstructive thrombus was detected in 13 patients (13%), whereas obstructive thrombus was demonstrated in all symptomatic patients. Plasma antithrombin-III levels of patients with prosthetic valve thrombi were slightly lower than those of patients without thrombus and of the control group, but the difference was not statistically significant. However, significantly higher plasma D-dimer levels were observed in patients with prosthetic valve thrombi, compared with patients without thrombus and the control group (735 ± 633 µg/L, 372 ± 342 µg/L, and 228 ± 219 µg/L, respectively). Valve thrombus, the prosthetic heart valve itself, and INR levels were identified as major determinants of plasma D-dimer levels. A plasma D-dimer level of >445 µg/L predicted the presence of a prosthetic valve thrombus with 57.8% sensitivity and 83.3% specificity (positive predictive value, 47.8%; negative predictive value, 87.8%).

Current data suggest that increased plasma D-dimer levels can be clinically helpful in predicting the presence of prosthetic valve thrombus. Plasma antithrombin-III activity does not seem to have a diagnostic value in predicting prosthetic valve thrombosis. (Tex Heart Inst J 2003;30:268-79)

Prosthetic valve thrombosis is a rare but potentially serious complication of heart valve replacement. A quick and easily applicable diagnostic method is needed for identifying patients with prosthetic valve thrombosis. The diagnosis of prosthetic valve thrombosis is relatively easy in patients who present with clinical symptoms of prosthetic valve obstruction or with an arterial embolic event. Transthoracic echocardiography (TTE) and cinefluoroscopy, singly or in combination, are usually sufficient for diagnosis in patients with clinical signs and symptoms of prosthetic valve thrombosis.1 On the other hand, these methods may not be sensitive enough to reveal nonobstructive thrombi in asymptomatic patients and in some patients with clinical signs and symptoms of prosthetic valve thrombosis. Transesophageal echocardiography (TEE) is currently recognized as the most accurate method of detecting both obstructive and nonobstructive prosthetic valve thrombi.1, 12 However, TEE may not be available in certain centers or may still be insufficient in differentiating thrombi, particularly from panni or vegetations. Therefore, clinicians are still in need of quick, relatively noninvasive, and easily applicable diagnostic methods for identifying prosthetic valve thrombi. The purpose of this study was to prospectively define the diagnostic role of D-dimer and antithrombin-III (AT-III) levels in identifying prosthetic valve thrombosis.

Patients and Methods

Patients
The study group comprised 97 consecutive patients (60 women and 37 men; mean age, 48 ± 12 years) with prosthetic heart valves who were referred to our echocardi-
Transthoracic studies were performed with a 2.5-MHz transducer from the standard echocardiographic laboratory from January 2000 to April 2001. At the time of echocardiographic study, 1 to 276 months (mean time interval, 35 ± 46 months) had elapsed since surgery. Fifty-nine patients had a mitral valve prosthesis, 21 patients had an aortic prosthesis, and 17 patients had both mitral and aortic prostheses. The prosthetic valves implanted in the mitral position were as follows: Sorin Bicarbon (n=40), St Jude (n=17), Carbomedics (n=3), Medtronic (n=2), Duromedics (n=1), Björk-Shiley (n=1), and Starr-Edwards (n=1). Those in the aortic position were: Sorin Bicarbon (n=20), St Jude (n=12), Duromedics (n=1), Carbomedics (n=1), and Medtronic (n=1). The manufacturers of the remaining 11 mitral and 3 aortic bileaflet prosthetic valves were unknown and could not be determined from the hospital records, because those patients had undergone surgery in another center.

Ninety-one of the 97 patients were referred to the echocardiography laboratory for recruitment in the study after they were seen in the outpatient clinic for routine clinical follow-up. These patients were completely free of signs and symptoms of either prosthetic valve obstruction or arterial embolism. There was no clinical suspicion of a prosthetic-valve-related complication. Anamnesis and retrospective analysis of the hospital records of these patients also did not reveal a history of prosthetic valve thrombosis or arterial embolism. On the other hand, the remaining 6 patients presented with clinical signs and symptoms of prosthetic valve obstruction, such as shortness of breath, fatigue, orthopnea, acute pulmonary edema, and disappearance of the prosthetic valve sound. Of the 97 patients, 52 patients (53.6%) presented with sinus rhythm and 45 patients (46.4%) with atrial fibrillation (AF). Atrial fibrillation was present in 33 of the 59 patients (55.9%) with mitral valve replacement (MVR), in 10 of the 17 patients (58.8%) with both mitral and aortic valve replacement (MVR-AVR), and in only 2 of the 21 patients (9.5%) with aortic valve replacement (AVR). All patients were receiving oral anticoagulant therapy with warfarin at the time of echocardiographic examination.

Thirty-five healthy subjects (mean age, 48 ± 11 years; 21 women and 14 men; all in sinus rhythm) with no drug treatment constituted the control group. A written informed consent was obtained from each patient and healthy subject before entry into the study.

Echocardiographic Study
All patients were initially examined by means of 2-dimensional echocardiography and Doppler TTE, using a VingMed® System 5 echocardiographic imaging system (General Electric; Horten, Norway). Transthoracic studies were performed with a 2.5-MHz transducer from the standard echocardiographic views. The continuous Doppler technique was used to evaluate the flow across the prosthetic valves by performing an optimal alignment between the Doppler cursor and the prosthetic flow jet demonstrated by color Doppler guidance. Peak pressure gradients were calculated from peak velocities according to the modified Bernoulli equation. Mean pressure gradients were measured by the planimetry of the continuous Doppler tracings with the software package of the ultrasound unit. In patients with a mitral prosthesis, the effective orifice area was calculated by the pressure half-time method. In patients with an aortic prosthesis, the effective orifice area was calculated by the continuity equation method. The effective orifice area index (effective orifice area/body surface area) and the performance index (effective orifice area/geometric orifice area provided by the manufacturer’s manual) were also calculated for each aortic and mitral prosthetic valve. Doppler measurements included an average of 3 cardiac cycles in patients who were in sinus rhythm, and an average of 5 cardiac cycles in those with atrial fibrillation.

After undergoing transthoracic echocardiography, all patients were examined by use of TEE, with a 5-MHz multiplane transducer connected to the same system. All patients received oropharyngeal anesthesia (with lidocaine in aerosol form) and conscious sedation (with intravenous midazolam, 1–2 mg) before TEE. The prosthetic valves, left atrium, left atrial appendage, left ventricle, and other cardiac structures were carefully examined for the presence of thrombus from multiple transesophageal echocardiographic views. The function of the prosthetic valves was also assessed by evaluation of the mobility of the leaflets. Prosthetic valve thrombus was defined as a soft, homogeneous, mobile or fixed echodense structure attached to the valve occluder, the valve struts, or both. A fixed, bright, echodense structure, with or without focal calcific deposits, along the valve ring with extension into the valve orifice, was recognized as pannus formation and was not regarded as thrombus. Fibrin strands, also not considered thrombus, were defined as thin, mobile, linear, echogenic densities structurally attached to prosthetic valves. A diagnosis of “obstructive prosthetic valve thrombus” was made when thrombus was associated with increased gradients (mean gradient ≥10 mmHg for the mitral prosthesis, and ≥40 mmHg for the aortic prosthesis) and decreased prosthetic valve area (≤1.5 cm² for the mitral prosthesis), with or without or restricted mobility of the leaflets in a symptomatic patient. Prosthetic valve thrombus in an asymptomatic patient with normal prosthetic valve gradients, normal valve area, and unlimited motion of the leaflets was defined as “nonobstructive thrombus.”
Laboratory Studies

Venous blood samples were drawn from each patient just before the echocardiographic examination. Antithrombin-III levels were determined by the STACHROM®-AT III chromogenic assay (Diagnostica Stago; Asnières, France), and D-dimer levels were determined by STA®-LIATEST® D-Di quantitative D-dimer, micro-latex immunoassay (Diagnostica Stago). Normal values for our protocol were 50–192 µg/L for D-dimer levels and 75%–125% for AT-III levels. Venous blood samples were also analyzed for prothrombin time, international normalized ratio (INR), and fibrinogen levels.

Statistical Analysis

All data are expressed as mean ± standard deviation. Differences between the different groups for discrete variables were analyzed by the χ² test or Fisher’s exact test. For continuous variables, groups were compared with the unpaired Student’s t-test or Mann-Whitney U test, where appropriate. Correlation between different variables was analyzed with Pearson linear regression analysis or Spearman rank correlation. Kruskal-Wallis analysis of variance was used for making comparisons between multiple groups. A multiple logistic regression analysis was performed for identifying independent factors for nonobstructive thrombus formation in patients with prosthetic valves. Multiple regression analyses were performed for identifying factors that determine the D-dimer and AT-III levels. A P value of <0.05 was accepted as significant in all analyses. All statistical analyses were performed by using SPSS 10.0 statistical program (SPSS Inc.; Chicago, Ill).

Results

Transthoracic Echocardiography

In asymptomatic patients with prosthetic valves (91 patients: 55 with MVR, 20 with AVR, and 16 with AVR + MVR), TTE revealed that the mean and maximum transprosthetic gradients and valve areas were in the normal range (Table I). The mean effective orifice area, geometric orifice area, effective orifice area index, and performance index values were as follows: 1.79 ± 0.62 cm², 2.39 ± 0.58 cm², 1.01 ± 0.33 cm²/m², and 72.48% ± 9.8%, respectively, for the aortic prostheses; and 3.2 ± 0.5 cm², 3.92 ± 0.65 cm², 1.90 ± 0.35 cm²/m², and 82.56% ± 11.2%, respectively, for the mitral prostheses.

Transthoracic echocardiography revealed an abnormal echo-density (>1 mm in width) consistent with a thrombus attached to the ventricular side of the prosthetic valve in 2 patients with AVR and in 3 patients with MVR (all of these patients had normal leaflet motion and normal transprosthetic gradients) (Fig. 1). Six patients with signs and symptoms of prosthetic valve obstruction also had increased transprosthetic gradients and diminished prosthetic valve areas that were evident on transthoracic echocardiographic examination (Table II). Restricted motion of the prosthetic valve leaflets and an abnormal echo-density consistent with a thrombus attached to the prosthetic valve was observed in 2 patients with MVR, 1 patient with AVR, and 1 patient with AVR + MVR (Fig. 2). The other 2 patients with mitral prosthetic valves demonstrated restricted motion of valve leaflets only on 2-dimensional TTE.

Transeophageal Echocardiography

Transeophageal echocardiography revealed a mild-to-moderate degree of paravalvular regurgitation in 2 asymptomatic patients with mitral valve prostheses and in 1 asymptomatic patient with an aortic valve prosthesis during color Doppler examination. All of the remaining 88 asymptomatic patients had normally functioning prosthetic valves (71 mitral prostheses, 36 aortic prostheses), with no restriction of the valve leaflets.

Transeophageal echocardiography demonstrated the presence of a distinct mobile echo interpreted as a local thrombus on the atrial surface of the mitral pros-

<table>
<thead>
<tr>
<th>TABLE I. Doppler Echocardiographic Findings in 91 Asymptomatic Patients with Prosthetic Valves in Transthoracic Echocardiography</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MVR (n=55)</strong></td>
</tr>
<tr>
<td>Mitral mean gradient (mmHg)</td>
</tr>
<tr>
<td>Mitral maximum gradient (mmHg)</td>
</tr>
<tr>
<td>Prosthetic mitral valve area (cm²)</td>
</tr>
<tr>
<td>Aortic mean gradient (mmHg)</td>
</tr>
<tr>
<td>Aortic maximum gradient (mmHg)</td>
</tr>
</tbody>
</table>

AVR = aortic valve replacement; MVR = mitral valve replacement
**Fig. 1** Transthoracic echocardiographic appearance of nonobstructive thrombus A) in a patient with a mitral prosthesis and B) in a patient with an aortic prosthesis.

AO = aortic valve; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Group</th>
<th>Symptoms and Signs</th>
<th>Mitral Mean Gradient (mmHg)</th>
<th>Mitral Maximum Gradient (mmHg)</th>
<th>Prosthetic MV Area (cm²)</th>
<th>Aortic Mean Gradient (mmHg)</th>
<th>Aortic Maximum Gradient (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MVR</td>
<td>Pulmonary edema, absence of mechanical valve sound</td>
<td>29</td>
<td>45</td>
<td>1.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>MVR</td>
<td>Shortness of breath, orthopnea</td>
<td>27</td>
<td>45</td>
<td>0.9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>MVR</td>
<td>Pulmonary edema</td>
<td>16.6</td>
<td>34.2</td>
<td>1.1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>MVR</td>
<td>Pulmonary edema, hemoptysis</td>
<td>14</td>
<td>38</td>
<td>1.23</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>AVR</td>
<td>Fatigue, shortness of breath, diminished valve sound</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>57</td>
<td>104</td>
</tr>
<tr>
<td>6</td>
<td>AVR + MVR</td>
<td>Fatigue, exertional dyspnea</td>
<td>5</td>
<td>19.5</td>
<td>2.74</td>
<td>42</td>
<td>69</td>
</tr>
</tbody>
</table>

AVR = aortic valve replacement; MV = mitral valve; MVR = mitral valve replacement
patients: 4.65 ± 0.95 mmHg for the mean mitral prosthetic gradient, 14.9 ± 5.37 mmHg for the maximal mitral gradient, 3.08 ± 0.51 cm² for the mitral prosthetic valve area, 15.26 ± 7.43 mmHg for the mean aortic prosthetic gradient, and 32.7 ± 2 mmHg for the maximal aortic prosthetic gradient.

Transesophageal echocardiography also confirmed the presence of an obstructive thrombus in all 6 symptomatic patients. An obstructive thrombus extending from the prosthetic valve into the left atrium could be demonstrated in 2 patients with mitral prostheses, in whom TTE had revealed restricted mobility of the valve leaflets but not the thrombi. Transesophageal echocardiography also showed an additional nonobstructive thrombus on the mitral prosthesis in a patient with AVR + MVR, in whom an obstructive thrombus was also present on the aortic prosthesis. A definitive pannus formation was not present in any of the patients with obstructive symptoms.

A fibrinous strand was demonstrated in 18 patients with MVR (2 of these patients had also nonobstructive thrombus on the prosthetic valve), 4 patients with

Fig. 2 Increased transprosthetic gradients (bottom images, left to right) and decreased prosthetic valve area (top images, left to right) in a patient with a huge obstructive thrombus on the mitral prosthesis.

(LA = left atrium; LV = left ventricle; PV = prosthetic valve)
AVR + MVR (all of the strands were located on the mitral prosthetic valve; 1 of these patients also had nonobstructive thrombus on the mitral valve), and 1 patient with AVR. Transesophageal echocardiography also showed an organized thrombus in the left atrial appendix in 6 patients with MVR (none of these patients had a thrombus on the prosthetic valve). Spontaneous echo contrast was detected in the left atrium, the left atrial appendix, or both in 23 asymptomatic patients with MVR (3 of these patients also had nonobstructive thrombus on the mitral prosthesis) and in 7 patients with AVR + MVR (3 of these patients also had nonobstructive thrombus on the mitral prosthesis).

**Laboratory Findings**

Prothrombin time (PT), INR, and fibrinogen levels of the patients with and without prosthetic valve thrombus are presented in Table IV. The PT and INR levels were significantly lower in patients with prosthetic valve thrombus, compared with the patients without thrombus ($P = 0.03$ and $P = 0.0039$; respectively) (Fig. 4). Fibrinogen levels were not significantly different between the patients with and without mechanical valve thrombus. Fibrinogen levels appeared to be lower in patients with obstructive thrombus, but the patient group was too small to reach a definitive statistical decision (Table IV).

Both univariate regression analysis and multiple logistic regression analysis were used to assess the effects upon nonobstructive thrombus formation of age, sex, postoperative duration, atrial fibrillation, left ventricular systolic and diastolic dimensions, left ventricular ejection fraction, left atrial dimension, effective orifice area of the prosthetic valve, geometric orifice area, effective orifice area index, prosthetic valve performance index, transprosthetic mean and maximal gradients, PT, INR, and fibrinogen levels. Multiple logistic regression analysis identified INR levels as the only significant independent factor for nonobstructive thrombus formation ($r = -0.28$, $P = 0.049$). Although PT levels significantly correlated with nonobstructive thrombus formation in univariate analysis ($r = -0.25$, $P = 0.01$), this relation did not reach statistical significance in multiple logistic regression ($P = 0.052$). No other factor was significantly related to thrombus formation, either in univariate or multivariate analyses.

**TABLE III. Location of the Nonobstructive Thrombi in Asymptomatic Patients with Prosthetic Heart Valves**

<table>
<thead>
<tr>
<th>Nonobstructive thrombus</th>
<th>Mitral prosthesis (n=16)</th>
<th>Aortic prosthesis (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic patients with prosthetic valves (n=91)</td>
<td>13 (14.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Patients with MVR (n=55)</td>
<td>5 (9%)</td>
<td></td>
</tr>
<tr>
<td>Patients with AVR (n=20)</td>
<td>3 (15%)</td>
<td></td>
</tr>
<tr>
<td>Patients with AVR + MVR (n=16)</td>
<td>5 (31%)</td>
<td></td>
</tr>
</tbody>
</table>

AVR = aortic valve replacement; MVR = mitral valve replacement

Fig. 3 Transesophageal echocardiographic appearance of a mobile, nonobstructive thrombus located on the left atrial side of a mitral prosthesis.

LA = left atrium; LV = left ventricle
levels than did the control group and the patients without prosthetic valve thrombus, the difference was not statistically different ($P = 0.10$ and $P = 0.26$, respectively). There was an important amount of overlap between the AT-III levels of the 3 groups (Fig. 5).

D-dimer levels of the patients with prosthetic valve thrombus was significantly higher than levels in the patients without prosthetic valve thrombus and the control group ($P = 0.02$ and $P = 0.001$, respectively) (Fig. 5). Patients without prosthetic valve thrombus also had significantly higher D-dimer levels, when compared with the control group ($P = 0.024$); however, there was substantial overlap of D-dimer levels between the 2 groups (Fig. 5). A cutoff D-dimer value of 445 µg/L was determined for discriminating between the patients with and without prosthetic valve thrombus. In patients with prosthetic valve thrombus, 11 out of 19 (57.8%) patients had D-dimer levels of >445 µg/L. On the other hand, of the patients with no prosthetic valve thrombus, only 16.6% (13 out of 78 patients) had D-dimer levels of >445 µg/L. D-dimer levels of >445 µg/L predicted prosthetic valve thrombus with a 57.8% sensitivity and 83.3% specificity (positive predictive value, 47.8%; negative predictive value, 87.8%).

The whole study group (control group and all patients with prosthetic valves) was also evaluated with multiple regression analysis to identify major independent factors affecting AT-III and D-dimer levels. None of the factors, including the presence of a prosthetic valve, was identified as a significant independent predictor of AT-III levels. Age, sex, and atrial fibrillation were not significantly related to AT-III levels ($P = 0.10$, $P = 0.44$, $P = 0.13$, respectively). Neither the presence of a prosthetic valve thrombus nor that of a left atrial appendix thrombus was identified as a significant independent predictor of AT-III levels ($P = 0.23$ and $P = 0.68$, respectively). On the other hand, when control subjects were excluded, the geometric orifice area of the prosthetic valve was identified as the only independent determinant factor for AT-III activity in the subgroup of all patients with prosthetic valves (that is, patients with and without thrombus) ($P = 0.036$, $r = -0.23$). Prosthetic valve

<table>
<thead>
<tr>
<th>TABLE IV. Prothrombin Times (PT), International Normalized Ratios (INR), and Fibrinogen Levels in Patients with and without Prosthetic Valve Thrombus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prosthetic Valve without Thrombus (n=78)</strong></td>
</tr>
<tr>
<td><strong>Nonobstructive (n=13)</strong></td>
</tr>
<tr>
<td>PT (sec)</td>
</tr>
<tr>
<td>INR</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
</tr>
</tbody>
</table>

Fig. 4 Comparison of the prothrombin times (PT) and international normalized ratios (INR) of the patients with and without prosthetic valve thrombus.

The mean ± SD and median AT-III and D-dimer levels of the control group and patients with and without prosthetic valve thrombus are presented in Table V. Analysis of variance did not reveal a significant difference between the AT-III levels of the 3 groups of patients ($P = 0.29$). Although patients with prosthetic valve thrombus seemed to have relatively lower AT-III levels than did the control group and the patients without prosthetic valve thrombus, the difference was not statistically different ($P = 0.10$ and $P = 0.26$, respectively). There was an important amount of overlap between the AT-III levels of the 3 groups (Fig. 5).
thrombosis was again not identified as a determinant of AT-III levels in this subgroup analysis.

The presence of a prosthetic thrombus was identified as the most significant independent factor affecting the D-dimer levels in multiple regression analysis ($P = 0.002$, $r = 0.35$). Having a prosthetic valve and low INR levels were also identified as significant independent determinants of D-dimer levels ($P = 0.035$, $r = 0.23$; and $P = 0.04$, $r = -0.21$, respectively). Age, sex, and AF were not significantly related to D-dimer levels ($P = 0.083$, $P = 0.46$, and $P = 0.30$, respectively). Having a prosthetic valve fibrinous strand or thrombus in the left atrial appendage also did not affect D-dimer levels significantly ($P = 0.45$ and $P = 0.16$, respectively).

**Therapeutic Consequences and Follow-Up**

All patients with obstructive thrombus were hospitalized to receive thrombolytic therapy. A slow infusion of streptokinase (100,000 U/hour for 24 hours) was administered as described in the literature. When the persistence of thrombus was documented by a follow-up TEE, a second 24-hour infusion of streptokinase was administered. Thrombolytic therapy was successful in 4 out of 6 patients (2 of them needed a 2nd session of thrombolytic infusion), which was demonstrated by the normalized transprosthetic gradients and complete disappearance of the thrombus on follow-up TEE. These patients were also symptom free at the end of thrombolytic therapy. However, 1 patient had only minimal reduction in thrombus size and transprosthetic gradients, together with worsening of the pulmonary edema. Thrombolytic therapy was considered ineffective, and the patient was referred to surgery. Surgical exploration revealed a huge thrombus lodged within the prosthetic valve, and the prosthesis was replaced with a new one. Another patient developed left-sided hemiplegia 4 hours after the onset of thrombolytic infusion and died of respiratory insufficiency.

All patients with asymptomatic prosthetic valve thrombus were also hospitalized and received a slow infusion of streptokinase. A TEE after thrombolytic therapy revealed complete disappearance of the non-obstructive thrombus in 10 of 13 patients, without any complication of the thrombolytic therapy. One patient experienced transient, central facial paralysis 1 hour after the cessation of thrombolytic infusion. However, TEE also demonstrated complete lysis of the thrombus in this patient. Another patient had a transient ischemic attack with right-sided hemiparesis 6 hours after the onset of thrombolytic infusion, which was terminated after the neurologic event.

**TABLE V.** Antithrombin-III (AT-III) and D-Dimer Levels of the Control Group and Patients with and without Prosthetic Valve Thrombus

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n=35)</th>
<th>Prosthetic Valve without Thrombus (n=78)</th>
<th>Prosthetic Valve with Thrombus (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT-III (%) (M)</td>
<td>106.5 ± 11.5 (109)</td>
<td>101.7 ± 19.67 (104)</td>
<td>97.6 ± 20.6 (97)</td>
</tr>
<tr>
<td>D-dimer (µg/L) (M)</td>
<td>228.8 ± 219 (184)</td>
<td>372.8 ± 342 (230)</td>
<td>735.3 ± 633 (445)</td>
</tr>
</tbody>
</table>

(M) = median values

![Graph showing comparison of antithrombin-III (AT-III) and D-dimer levels of the control group and of patients with and without prosthetic valve thrombus.](image)

**Fig. 5** Comparison of antithrombin-III (AT-III) and D-dimer levels of the control group and of patients with and without prosthetic valve thrombus.
follow-up TEE demonstrated partial lysis of the nonobstructive thrombus in this patient. Neither of these patients had specific findings in cranial computed tomography performed 48 hours after the neurologic event, nor was there a permanent neurologic deficit. In another patient with nonobstructive thrombus, follow-up TEE revealed partial lysis of the thrombus with only slight reduction in size despite 2 sessions of full-dose infusion of thrombolytic therapy. The overall success rate of the slow-dose thrombolytic therapy was 84.6% (11 of 13 patients) in patients with asymptomatic nonobstructive prosthetic valve thrombus.

All of these patients also received increased doses of oral warfarin until an INR value of >3.0 was obtained. All patients were discharged on oral warfarin treatment and were monitored at the outpatient clinic with weekly follow-up TTE and TEE for the 1st month and with monthly visits thereafter. Oral warfarin doses were adjusted to maintain INR values of 3.0–4.0 during the follow-up period. During 13 ± 5 months of follow-up, none of the surviving patients (including the patient who underwent surgical thrombectomy) experienced a new neurologic or vascular thromboembolic event.

**Discussion**

Thrombosis is a serious complication of prosthetic heart valve replacement. In a large series of 13,088 patients with prosthetic heart valves, the incidence of valve thrombosis was approximately 0.2 per 100 patient-years. The incidence of major embolism was approximately 1.0, and that of total embolism was 1.8 per 100 patient-years. The incidence of aortic valve thrombosis was 0.1 per 100 patient-years, and this rate was 5-fold greater in patients with a mitral prosthesis. The incidences of major embolic events and of major and minor embolic events combined were also higher in patients with mitral prosthesis.

Acute thrombosis with an obstructive thrombus or, in certain instances, partially obstructing thrombi can be easily diagnosed with TTE, cinefluoroscopy, or both. On the other hand, a small nonobstructive thrombus cannot be detected with TTE or cinefluoroscopy in most cases, particularly when it is located on the left atrial side of the prosthetic valve. Therefore, TEE is usually necessary to detect a nonobstructive thrombus. There are still very limited data about the exact incidence of nonobstructive thrombus in the population of asymptomatic patients with prosthetic heart valves. Previous studies for detecting nonobstructive prosthetic valve thrombus were all performed in a mixed group of patients, including both asymptomatic patients and patients with histories of embolic events. Gueret and colleagues have screened nonobstructive thrombus in 114 patients with mitral prosthetic valves, in whom TEE was performed for recent systemic emboli, fever of unknown origin, routine early postoperative examination, hemolytic anemia, unexplained congestive heart failure, and fatigue. The incidence of nonobstructive thrombus was 17.5% in this relatively high-risk group of patients. In a larger series of 338 patients with mitral or aortic prosthesis, including patients with a history of an embolic event, nonobstructive prosthetic valve thrombus was detected in 18% of patients (21% of patients with mitral prosthesis and 12% of those with aortic prosthesis). In the current study, transesophageal echocardiographic screening of asymptomatic patients (without a history of an embolic event) revealed a 14.2% incidence of nonobstructive thrombus. The incidence of nonobstructive thrombus formation on the mitral prosthetic valves was also higher than that on the aortic valves (14% vs 8.3%, respectively). These findings indicate that asymptomatic patients without a history of a systemic embolic event may have quite high rates of nonobstructive thrombus. Previous studies have revealed that these patients also carry an increased risk of systemic embolization.

Therefore, such patients should be properly identified and treated before a thromboembolic event occurs.

Transesophageal echocardiography is currently recognized as the most accurate method of detecting both obstructive and nonobstructive prosthetic valve thrombi. However, TEE may not be available in certain centers or may not be rapidly performed in all asymptomatic patients when such patients are screened in outpatient clinic settings. In addition, TEE may not be tolerated by all patients with obstructive symptoms, and TTE may sometimes be insufficient in differentiating thrombus, particularly from pannus, vegetations, or other causes of prosthetic valve dysfunction. Therefore, clinicians still need rapid, relatively noninvasive, and easily applicable diagnostic methods for identifying prosthetic valve thrombus.

The laboratory measurement of D-dimer detects cross-linked fibrin degradation products and has been demonstrated to be a useful marker of endogenous coagulation activation. The plasma D-dimer level also reflects fibrin turnover, as well as the efficacy of fibrinolysis, without being affected by fibrinogen or noncross-linked fibrin. High plasma D-dimer levels have been detected in patients with acute ischemic stroke and peripheral vascular disease, and have proved to be useful in the diagnosis of deep vein thrombosis.

Plasma D-dimer levels have also been found to be predictive of left atrial thrombi in patients with mitral stenosis who are undergoing mitral valve surgery. D-dimer levels were significantly higher in patients with left atrial thrombi than in those without thrombi or in normal subjects. D-dimer levels were also signifi-
cantly correlated with the weights of the left atrial thrombi. Increased postoperative plasma D-dimer levels were found in patients who underwent prosthetic valve replacement, compared with the preoperative levels. In another study, high plasma D-dimer levels were identified as a predictive marker of thromboembolic events during the long-term follow-up of patients with prosthetic valves. However, the predictive value of plasma D-dimer levels as a marker of prosthetic valve thrombosis has not been investigated until this present study.

This current study also demonstrates increased plasma D-dimer levels in patients with prosthetic valves, when compared with normal subjects. This probably is a consequence of increased fibrin turnover and continuous fibrinolysis in association with prosthetic valves. The increase in plasma D-dimer levels was observed to be most prominent in patients with prosthetic valve thrombus, who probably experience markedly increased fibrin turnover, fibrinolysis, and production of fibrin degradation products. This finding may be clinically useful and may have a predictive value in identifying those patients with prosthetic valve thrombus. High levels of plasma D-dimer (>445 μg/L) predicted the presence of a prosthetic valve thrombus with a high specificity and moderate sensitivity. The reason for the relatively lower sensitivity may be that D-dimer levels were influenced by the presence of the prosthetic valve itself, as well as by the level of coagulation activity. It has been shown that INR levels in patients with prosthetic valves are an important predictor of D-dimer levels and are the most important predictor of thrombus formation on the prosthetic valves. Previous studies have demonstrated a negative correlation between the plasma D-dimer levels and the intensity of oral anticoagulation in patients with prosthetic heart valves. Georgiadis and colleagues have shown that the D-dimer levels were significantly higher in patients with mechanical valves who had an INR of less than 2.0, compared with those who had an INR of more than 2.0. Giansante and associates have demonstrated that D-dimer levels also correlated with the duration of time spent below the adequate level of INR in patients with prosthetic valves.

Some of the previous studies have shown that AF is associated with increased levels of plasma D-dimer levels. These data would appear to conflict with our findings, except that the patient groups of these studies did not have prosthetic heart valves and only some portion of patients in the study groups were receiving anticoagulant therapy. On the other hand, Giansante and associates have demonstrated that the presence of AF did not influence plasma D-dimer levels in patients with prosthetic valves. They have suggested that the presence of a prosthetic valve and the efficacy of anticoagulant therapy may be 2 important determining factors of plasma D-dimer levels that can mask the differences between patients with AF and patients in normal sinus rhythm. Our results also support this hypothesis, since we identified both of these factors as independent determinants of plasma D-dimer levels in patients with prosthetic valves.

The current data concerning the relationship between plasma AT-III levels and prosthetic valve thrombosis are much more limited. Some previous studies have reported increased levels of thrombin-antithrombin-III complexes and depleted AT-III levels in patients with prosthetic heart valves. In a very small group of patients, Bedeleanu and colleagues reported lower levels of plasma AT-III activity in patients with mitral prosthetic valves than in those who underwent mitral commissurotomy. Antithrombin-III activity was even more depressed in patients who developed thromboembolic complications. In the current study, the geometric orifice area was found to be the major determinant of AT-III levels in patients with prosthetic valves. The implantation of a prosthetic valve places a large foreign surface in contact with the bloodstream. The geometric orifice area of a prosthetic valve is the main surface of the foreign material (for example, valve occluders) that comes into contact with the bloodstream and thereby activates coagulation. Therefore, decreased AT-III activity can be considered as a marker of ongoing in vivo activation of coagulation in patients with prosthetic cardiac valves. However, our results have shown that the degree of such activation of coagulation is so slight that plasma AT-III levels of patients with mechanical valves were not significantly lower than those of the control group.

Although the plasma AT-III activity of patients with prosthetic valve thrombus was significantly lower than it was in both the control subjects and the patients without prosthetic valve thrombus, the presence of a prosthetic valve thrombus was not identified as an independent determinant of plasma AT-III levels. In addition, there was a substantial overlap between the AT-III levels of the 3 groups, which makes it difficult to use AT-III levels as a differentiating parameter. Therefore, these results suggest that AT-III levels cannot be used as a clinical marker for identifying patients with prosthetic valve thrombus.

The main limitation of the current study is the relatively small number of patients with prosthetic valve thrombus. Future studies with larger groups of patients should confirm these data and may help to identify better cutoff values for plasma D-dimer levels, in order to discem patients with thrombus. Before applying this assay to clinical practice, each laboratory should determine its own standard cutoff values.
Although we have used well-defined criteria for the diagnosis of prosthetic valve thrombosis, thrombi are sometimes mixed with vegetations or pannus formations; or the echocardiographic images can be false, merely simulating thrombi. However, the subsequent echocardiographic documentation of complete or partial lysis of the thrombi and the thromboembolic events that followed thrombolytic infusion (apparently in association with lysis) suggest that the diagnosis of prosthetic valve thrombus was correct in these patients.

The best therapeutic approach for asymptomatic, nonobstructive prosthetic valve thrombus is still unclear. Very few randomized studies compare thrombolytic therapy with conservative treatment in this group of patients. In our study, the overall success of fibrinolytic therapy was about 84% in patients with nonobstructive thrombus. Transient neurologic events were observed in 15% (2 out of 13) of our patients with nonobstructive thrombus. On the other hand, Lengyel and colleagues have reported complete success with thrombolytic therapy, and no cerebrovascular complications. Although the study group was small, Lengyel was able to reach a tentative conclusion that fibrinolytic therapy was both more effective and safer than conservative treatment with anticoagulant therapy. Further randomized studies with larger groups of patients are needed to determine the optimum treatment for these patients with asymptomatic, nonobstructive thrombus.

It should be noted that hematologic assays for D-dimer levels differ in both assay methodology and sensitivity. Therefore, these data cannot be broadly extrapolated to all D-dimer assays; similar studies will need to be performed in accordance with those other methods.

The interpretation of D-dimer levels may be difficult in patients with prosthetic heart valves who present with dyspnea. In such patients, pulmonary embolism should also be considered as an underlying cause for elevated D-dimer levels. In our study, a definitive obstructive thrombus and increased transprosthetic gradients were echocardiographically demonstrated in all patients who presented with dyspnea; therefore, the most probable reason for increased D-dimer levels was prosthetic valve thrombosis, rather than pulmonary embolism.

This study has demonstrated that plasma D-dimer levels were also increased in patients with no prosthetic valve thrombus, when they were compared with the normal subjects. Therefore, it should be noted that even in the absence of a prosthetic thrombus the increased fibrin turnover caused by the mechanical valve itself might interfere with the diagnostic value of D-dimer levels as a screening tool for pulmonary embolism and deep venous thrombosis in these patients.

In conclusion, the current data suggest that plasma D-dimer levels may be used as a marker of prosthetic valve thrombosis with a moderate sensitivity and relatively high specificity. Increased plasma D-dimer levels are not by themselves diagnostic of prosthetic valve thrombus but may alert the clinician to refer the patient for more detailed examination, preferably by TEE. Normal plasma D-dimer levels highly predict the absence of a prosthetic valve thrombus, especially if the TTE examination is normal. Current data also suggest that plasma AT-III levels are not of diagnostic value in predicting prosthetic valve thrombus.

References


