Coagulation Activity and Emboli Counts in Patients With Prosthetic Cardiac Valves

Dimitrios Georgiadis, MD; Annette Mallinson, MBChB; Donald G. Grosset, MD; Kennedy R. Lees, MD

Background and Purpose The underlying embolic material detected by transcranial Doppler ultrasound in patients with prosthetic heart valves remains unknown. We undertook this study to evaluate the relation between the number of Doppler emboli signals and the activity of the coagulation system.

Methods Patients with various types of prosthetic valves (n=120) and patients in atrial fibrillation (n=20) were monitored for 30 minutes using transcranial Doppler with a 2-MHz probe. The plasma concentrations of cross-linked d-dimer, antithrombin-III, and thrombin-antithrombin III complex were measured.

Results No correlation between the levels of any of the hematologic parameters and the number of emboli was demonstrated in the studied groups. The d-dimer levels were significantly higher in patients with mechanical prosthetic valves with an international normalized ratio under 2.0 compared with those with an international normalized ratio between 2 and 3.5 or above 3.5, and in patients with Medtronic-Hall versus Björk-Shiley or Carpentier-Edwards valve prostheses.

Conclusions The lack of correlation between the activity of the coagulation system and the number of Doppler emboli in patients with prosthetic valves suggests that the underlying embolic material in these patients is not thrombotic. Our results also suggest that an increase of the anticoagulation intensity to an international normalized ratio above 3.5 does not result in a further decrease of the activity of the unstimulated coagulation system in patients with mechanical prosthetic valves.

Key Words • coagulation • embolism • heart valve prosthesis • ultrasonics

Although the detection of microemboli signals in patients with prosthetic heart valves using transcranial Doppler ultrasound has been widely described since 1990, no conclusive evidence exists concerning the size or constitution of the underlying embolic material. Three pathogenetic mechanisms should be considered: (1) local activation of the coagulation system in the area of the prosthetic valve, resulting in the generation of thrombus; (2) local increase of platelet aggregation, and (3) generation of microbubbles. Mechanical heart valves have been demonstrated to generate short-lived cavitation bubbles, their capacity to generate longer-lived systemic microbubbles remains to be evaluated.

Warfarin anticoagulation is routinely used to decrease the thromboembolic risk of patients with prosthetic mechanical valves and patients with bioprosthetic valves who are in atrial fibrillation or have a history of neurological events. The ideal intensity of oral anticoagulation in these patients is still not established. The current guidelines of the British Society for Haematology suggest an international normalized ratio (INR) of 2 to 3 for patients with bioprosthetic heart valves and patients in atrial fibrillation and 3 to 4.5 for patients with mechanical prosthetic valves. Various long-term clinical studies have compared the efficacy of different anticoagulation regimens in preventing thromboembolic complications. Some of them have argued for less intensive anticoagulant regimens both for patients with mechanical and for patients with biological heart valves.

An alternative way of evaluating the thromboembolic risk is by measuring the activity of the coagulation system. Plasma concentrations of cross-linked D-dimer (Dd), thrombin–antithrombin III (TAT) complex, and antithrombin III (AT-III) activity have been reported to be sensitive markers of hypercoagulability in patients with various thrombotic disorders.

We undertook this study to evaluate the relation of the emboli count to the intensity of oral anticoagulation and the activity of the coagulation system in patients with prosthetic heart valves (both mechanical and biological) and patients in atrial fibrillation. A correlation between emboli counts and coagulation activity would support the hypothesis that the underlying embolic material in these patients is of thrombotic nature. Significant differences in the coagulation activity among patients with various intensities of oral anticoagulation would allow some assumptions regarding the efficacy of anticoagulation regimens.

Subjects and Methods

One hundred patients with mechanical prosthetic valves (44 Björk-Shiley [BS], 45 Medtronic-Hall [MH], 11 other types [OT]), 20 patients with bioprosthetic valves (Carpentier-Edwards [CE]) plus atrial fibrillation (AF), and 20 patients in AF were examined. Patients with mechanical prosthetic valves were significantly younger compared with patients with bioprosthetic valves or patients in AF (mechanical valves, 60±1
years; AF, 65±2 years; bioprosthetic valves, 66±2 years; mean±SE, mechanical prosthetic valves versus bioprosthetic valves P<.01, mechanical valves versus AF P<.03). There were no significant age differences between patients with BS and MH valves (BS, 60±1 years; MH, 59±1 years; mean±SE, P>.05). All patients were recruited from the anticoagulant clinic, where they had already been stabilized on warfarin, and were not receiving any additional antplatelet agents at the time of examination. Each patient underwent a single transcranial Doppler examination and hematologic study.

Transcranial Doppler was performed using a pulsed Doppler ultrasound machine (EME TC-2000, Nicolet) with a 2-MHz probe, which was fixed on the skull with an elasticized band to allow prolonged monitoring. Examination time was 30 minutes over the right middle cerebral artery (MCA). Standard criteria were used to differentiate emboli from artifact signals. Details of the technique of embolus detection have been described elsewhere.3,12 In short, emboli were distinguished from artifacts both by their acoustic qualities and the caused intensity increase on-line and by their characteristic spectral distribution on off-line analysis. Emboli signals were stored on the hard disk for later evaluation.

Venous blood samples (20 mL per patient) were obtained immediately after transcranial Doppler examination with a 21-gauge needle and a plastic syringe, with the use of a tourniquet. Samples were collected into sodium citrate (final concentration, 10%). A 5-mL blood sample was used to determine the INR, and the remaining blood was centrifuged for 15 minutes at 3000 rpm and 4°C. The plasma was frozen in plastic tubes at −70°C until batch analysis was performed. At the time of the assay the plasma samples were placed in a water bath (37°C) for 15 minutes and subsequently handled at room temperature. The following parameters were determined: Dd, AT-III, and TAT levels. An enzyme immunoassay was used to determine TAT levels (Enzygnost-TAT).13 The lower limit of detection with this method is 0.5 μg/L, and the coefficient of variation is 2% to 6% for concentrations in the range 5 to 40 μg/L. AT-III level was evaluated using a kinetic method with chromogenic substrate (Imunochrom AT III, Immuno AG). Dd levels were measured using an enzyme immunoassay (EIA dimer micro).14 The sensitivity of this test is 0.5 μg/L, and the coefficient of variation is 2% to 4% within the range 10 to 600 μg/L.

Twenty healthy blood donors, aged 31±5 years, were used as normal control subjects for the hematologic parameters. These subjects were significantly younger than the patients studied (P<.001). Transcranial Doppler examination was not performed in normal control subjects.

Statistical ANOVA was performed using a two-sample t test for age of the patients and nonparametric multiple comparisons with Bonferroni correction, all other differences among groups insignificant. All data are median and 95% nonparametric confidence interval.

### Results

The incidence of emboli signals was 70% in patients with mechanical valves (BS, 91%; MH, 48%; OT, 75%), 50% in patients with bioprosthetic valves, and 40% in patients in atrial fibrillation. The number of emboli signals per hour was significantly higher in patients with mechanical prosthetic valves compared with patients with bioprosthetic valves and patients in atrial fibrillation (84 [24 to 120] in the mechanical, 1 [0 to 3] in the porcine, and 0.5 [0 to 1] in the AF group, median [95% nonparametric confidence interval], each P<.001, Mann-Whitney versus mechanical valves). In the group with mechanical cardiac valves, the emboli number was significantly higher in the BS group compared with the MH group (BS, 212 [150 to 304]; MH, 1 [1 to 4] emboli per hour; median [95% nonparametric confidence interval], P<.001, Mann-Whitney).

The levels of Dd, AT-III, and TAT and the emboli counts according to the intensity of oral anticoagulation are listed in Table 1. In the group of patients with mechanical valves, the subjects with an INR <2.0 had significantly higher Dd levels compared with the other subgroups. Those were the only subjects whose Dd levels were not significantly lower compared with the

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**TABLE 1. Coagulation Parameters, Intensity of Oral Anticoagulation, and Emboli Numbers in Patients With Prosthetic Valves, Patients in Atrial Fibrillation, and Normal Control Subjects**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>INR</th>
<th>Patient No.</th>
<th>Emboli per Hour</th>
<th>Dd, μg/L</th>
<th>TAT, μg/L</th>
<th>AT-III, % of Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV &lt;2.0</td>
<td>18</td>
<td>84 [2-246]</td>
<td>39 [26-96]</td>
<td>3.3 [1.5-5.8]</td>
<td>113 [102-124]</td>
<td></td>
</tr>
<tr>
<td>&gt;3.5</td>
<td>27</td>
<td>54 [34-94]</td>
<td>23 [18-34]</td>
<td>2 [1.3-8.3]</td>
<td>96 [87-108]</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>100</td>
<td>84 [24-120]</td>
<td>24 [21-29]*</td>
<td>3.5 [2.5-4.8]</td>
<td>100 [95-105]</td>
<td></td>
</tr>
<tr>
<td>PV &lt;2.0</td>
<td>3</td>
<td>1 [0-2]</td>
<td>33 [18-47]†</td>
<td>1.5 [1-2]</td>
<td>112 [99-127]</td>
<td></td>
</tr>
<tr>
<td>2.3-5</td>
<td>15</td>
<td>1 [0-2]</td>
<td>38 [28-51]†</td>
<td>2 [1.2-4.5]</td>
<td>112 [103-121]</td>
<td></td>
</tr>
<tr>
<td>&gt;3.5</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>20</td>
<td>1 [0-3]</td>
<td>30 [17-140]†</td>
<td>1 [1-1.5]†</td>
<td>94 [14-140]</td>
<td></td>
</tr>
<tr>
<td>2.3-5</td>
<td>3</td>
<td>1.6 [0-4]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3.5</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>20</td>
<td>1 [0-2]</td>
<td>23 [18-39]†</td>
<td>1.3 [1-1.8]</td>
<td>99 [77-119]</td>
<td></td>
</tr>
<tr>
<td>NC</td>
<td>NA</td>
<td>20</td>
<td>98 [43-165]</td>
<td>1.8 [1.5-2.3]</td>
<td>96 [93-106]</td>
<td></td>
</tr>
</tbody>
</table>

INR indicates international normalized ratio; Dd, d-dimer; TAT, thrombin-antithrombin III complex; AT-III, antithrombin III; MV, mechanical prosthetic valves; PV, porcine prosthetic valves; AF, atrial fibrillation; and NC, normal control subjects.

*P<.001; †P<.01, compared to the NC; ‡P<.001, MV INR <2 vs MV INR >3.5; ††P<.05, MV INR <2 vs NC INR >4.5; | Mean±SE for statistical analysis; NA, not applicable; multiple comparisons with Bonferroni correction, all other differences among groups insignificant. All data are median and 95% nonparametric confidence interval.
normal control subjects. There was no relation between the number of emboli signals and the hematologic parameters in any of the examined groups (Table 1). Clinical parameters (patient age, duration of valve insertion, position of prosthetic valve, prevalence of neurological deficit) did not influence the coagulation system activity.

The concentrations of Dd, TAT, and AT-III and the emboli counts in patients with BS, MH, and CE valves are listed in Table 2. Dd levels in patients with BS valves were significantly lower compared with those with MH or CE valves; AT-III levels were significantly lower in BS compared with CE patients. The INR levels of patients with BS, MH, and CE valves were not significantly different. (In BS, MH, and CE valve patients, the INR was <2 in 7, 10, and 3 cases; 2 to 3.5 in 25, 22, and 15 cases; and >3.5 in 12, 13, and 2 cases, respectively.)

**Discussion**

The lack of correlation between the numbers of emboli signals and the hematologic parameters in patients with mechanical prosthetic valves suggests that the underlying embolic material in this patient group is not thrombotic. The number of emboli signals detected in patients with porcine valves and patients with atrial fibrillation was too small to interpret further. The fact that all patients with porcine valves examined in this study were also in atrial fibrillation impairs interpretation of the results in these patients.

The significantly lower Dd levels in patients with BS valves compared with patients with MH or CE valves, despite the higher number of emboli in this group, are striking. Dd levels are known to be age related,15,16 which could explain the difference between patients with BS and CE valves. However, the observed differences between BS and MH valves are not explained on this basis. Repeat measurements of Dd at different time points might provide additional information on this aspect.

A limitation of this study was the age difference between patients and normal control subjects. Despite the younger age of the control subjects, their Dd levels were significantly higher than those of all studied patients, with the exception of patients with mechanical prosthetic valves and an INR <2. This result suggests that while low-intensity (INR <2) anticoagulation may lead to a sufficient reduction of the coagulation activity in patients in AF, it is not effective in patients with mechanical prosthetic valves. This assumption is also supported by the differences in Dd levels depending on the level of oral anticoagulation in patients with mechanical valves. Patients with an INR between 2.0 and 3.5 had significantly lower Dd levels compared with those with an INR <2.0, while a further INR increase did not result in lower Dd levels. A similar result was obtained in a study assessing the coagulation markers in patients with prosthetic heart valves at different intensities of oral anticoagulation, although the measured levels of Dd were higher than those in our study.17 Our results support previous clinical studies which suggested that the rate of thromboembolic complications in patients with prosthetic valves is not reduced further by more aggressive anticoagulant therapy.6,7 However, long-term clinical trials are required to assess the optimum degree of anticoagulation.

Having excluded thrombi as an underlying embolic material in patients with prosthetic valves, the possibilities of platelet aggregates and gaseous material remain to be investigated. The additional effect of antiplatelet treatment on the number of emboli signals should be examined to assess the possibility of signals being due to platelet aggregates. Definitive evidence on the nature of the underlying material of the Doppler emboli signals would be of particular clinical relevance, since pharmacological approaches would be ineffective if such material is gaseous.

**Acknowledgments**

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**References**


8. Turpie AGG, Gustensen J, Hirsh J, Nelson H, Gent M. Randomised comparison of two intensities of oral anticoagulant

**Table 2. Coagulation Parameters and Emboli Counts in Patients With Different Types of Prosthetic Valves**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Patient No.</th>
<th>Emboli per Hour</th>
<th>Dd, μg/L</th>
<th>TAT, μg/L</th>
<th>AT-III, % of Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>BS</td>
<td>44</td>
<td>212 [150-304]</td>
<td>20 [17-23]*</td>
<td>2.5 [1.8-4.3]</td>
<td>94 [58-102]*</td>
</tr>
<tr>
<td>CE</td>
<td>20</td>
<td>1 [0-3]</td>
<td>38 [28-51]*</td>
<td>2 [1.3-4.5]</td>
<td>112 [103-121]*</td>
</tr>
</tbody>
</table>

Dd indicates D-dimer; TAT, thrombin-antithrombin III complex; AT-III, antithrombin III; MH, patients with Medtronic-Hall valve; BS, patients with Bjork-Shiley valve; and CE, patients with Carpentier-Edwards valve. Eleven patients with various other types of mechanical prosthetic valves were not included in this table. All data are median and [95% nonparametric confidence interval].

*Difference significant at P<.001; †difference significant at P<.01, nonparametric multiple comparisons with Bonferroni correction.


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