Prevalence and Characteristics of Intracranial Microemboli Signals in Patients With Different Types of Prosthetic Cardiac Valves

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Background and Purpose Transcranial Doppler detection of microemboli is widely described, but there is no clear evidence of the clinical significance or nature of the embolic material in vivo. Thromboembolism is a major cause of morbidity in patients with prosthetic cardiac valves. We undertook this study to evaluate the prevalence and the acoustic characteristics of microembolic signals in three groups of patients with different prosthetic valves.

Methods One hundred seventy-nine patients with prosthetic cardiac valves (85 Björk-Shiley, 56 Medtronic-Hall, and 38 Carpentier-Edwards) and 25 normal subjects were examined using transcranial Doppler. Monitoring time was 30 minutes over the right middle cerebral artery.

Results The prevalence and numbers of embolic signals were significantly higher in patients with Björk-Shiley compared with those with Medtronic-Hall and Carpentier-Edwards valves (89% versus 50% and 53%, respectively; P < .001, χ²; 156 [112, 204] versus 2 [1, 4] and 2 [1, 4] signals/h, respectively; median [95% nonparametric confidence interval], both P < .001). No correlation was found between embolic signal numbers and clinical parameters including history of neurological deficit, cardiac rhythm, duration of artificial valve, previous cardiac operations, or intensity of antiaggregation. Embolic signals were not detected in any of the control subjects.

Conclusions Our data showed that the prevalence, quantity, and acoustic characteristics of Doppler embolic signals differ in patients having three different types of prosthetic heart valves. However, no correlation with clinical parameters was identified. (Stroke. 1994;25:587-592.)

Key Words • embolism • heart valve prosthesis • ultrasonics

Since the detection of embolic signals with transcranial Doppler (TCD) was first described, several patient groups with embolic signals have been identified: patients with atrial fibrillation, acute ischemic stroke, prosthetic heart valves, and symptomatic carotid stenosis. Embolic signals have also been detected during cardiac and carotid surgery and cerebral angiography. Experimental studies in bench and animal models have shown similar signals and have indicated some correlation between signal intensity, embolus size, and constituent material.

Thromboembolism is a major complication of prosthetic valve insertion. Embolic signals are readily detectable in this patient group. Quantification of subclinical embolic signals may allow more precise estimation of embolic risk and an objective assessment of treatment effects. However, the clinical relevance and nature of embolic material in vivo remain uncertain. We undertook this study to evaluate the prevalence and acoustic characteristics of embolic signals in patients with prosthetic heart valves. A comparison with results of clinical follow-up studies, in particular the known thromboembolic complication rates, was performed. The relation between quantity of embolic signals and clinical parameters was also examined.

Subjects and Methods

Patients with Björk-Shiley (BS), Medtronic-Hall (MH), or Carpentier-Edwards (CE) valves and healthy volunteers were examined. Patients with dual valve replacements of two different types were excluded. Patients were recruited from anticoagulant clinics and the regional Cardiac Surgical outpatient database (including approximately 4760 patients at the time of this study from the lists of 12 cardiothoracic surgeons; catchment population, 2 million people). No hospitalized patients were examined in this study. Valve replacement was undertaken predominantly for rheumatic disease.

TCD monitoring was performed using an EME TC-2000 (Nicolet) with a 2-MHz transducer. The right middle cerebral artery (MCA) was identified at a depth between 45 to 55 mm according to standard criteria and monitored for 30 minutes per patient. If no satisfactory signal could be obtained from the right MCA, identification of the left MCA was attempted. Patients in whom no MCA signal could be obtained from either MCA were excluded from the study. The transducer was fixed on the head with an elasticized band to maintain a constant angle of insolation. Power was set at 58%, the sample volume at 9 mm, and the sweep speed at 6 seconds; these settings were kept constant throughout the study. Screens with high-intensity signals representing emboli were stored to hard disc for later analysis. Established criteria were used to distinguish between artifact and emboli signals both during the examination (ie, unidirectional signals within the advancing
velocity spectrum; characteristic harmonic sound; short duration [<0.15 seconds for systolic signals; <0.3 seconds for diastolic signals]; intensity at least 3 dB above the background Doppler blood velocity spectrum; random occurrence in the cardiac cycle]

The Doppler waveform (upper part of the Figure) consists of 512 data points on the x-axis and 128 data points on the y-axis. Intensity analysis of a single data point on the x-axis (a column with 128 vertical data points) resulted in an intensity distribution curve (lower part of the Figure). In the absence of abnormal signals this curve shows an even distribution without peaks. Embolic signals caused a unidirectional intensity increase (1 in the Figure) that resulted in a peak in the spectral distribution that was either on the upper or the lower half of the spectrum, depending on the direction of the signal. Artifact signals are bidirectional, and therefore cause a symmetrical intensity increase in both parts of the spectrum (2 and 3 in the Figure).

The total intensity ($I_t$) of an embolic signal (sum of all intensities for both backward and forward flow) was calculated according to the formula

$$I_t = \sum_A A(i)/128$$

where $A(i)$ is the reflected Doppler amplitude and 128 the number of Fourier components. A correction factor for the background intensity was used.

The international normalized ratio (INR) was checked on the day of TCD examination to assess the level of anticoagulation. A history was obtained of neurological events since the day of TCD examination to assess the level of anticoagulation.

**Statistical analysis**

Comparisons with the Bonferroni correction (for normally distributed data); Mann-Whitney or Kruskal-Wallis nonparametric analyses of variance were performed as appropriate for nonparametric data; Kruskal-Wallis or Mann-Whitney tests were used for comparison of frequencies. Significance was declared when probability was less than .05.

**Results**

One hundred seventy-nine patients, 63 men and 116 women, were successfully examined in this study. Eighteen (9.1%) patients in whom no MCA signal could be identified were excluded. In two cases the left MCA was used for monitoring because an adequate signal could not be obtained from the right MCA. Eighty-five patients had a BS valve, 56 an MH, and 38 a CE valve. A single valve (either the aortic or the mitral) was replaced in 152 patients and a dual valve replacement (both aortic and mitral) was performed in the remaining 27 patients. Valve position is shown in Table 1. Patients with BS and MH valves were significantly younger than those with CE valves; there was no significant age difference between patients with BS and MH valves (BS, 59.4±10; MH, 58.5±9; and CE, 67.5±11 years, mean±SD; BS and MH versus CE, both P<.001). There were no significant differences in sex, New York Heart Association class, number of previous open heart procedures, or time since valve insertion (BS, 31±7; MH 31±5; and CE, 61±11 months) among the three patient groups. All patients with BS and MH valves were stabilized on warfarin at the time of the study (Table 2). In the CE group, 32 of 38 patients were taking warfarin (30 because of atrial fibrillation and 2 after a transient ischemic attack). Of the remaining 6, 1 was on aspirin and 5 were taking no antihemostatic drugs. Of the 85 patients with BS valves, 6 had the spherical, 7 the convex-concave, and 76 the monostrut type. Of the patients with CE valves, 25 had the standard and 13 the supra-annular type.

The prevalence and quantity of embolic signals were significantly higher in patients with BS valves compared with patients with MH and CE valves (both P<.001; Table 3). The intensity of embolic signals was significantly higher in patients with BS and MH valves compared with patients with CE valves (both P<.001; Table 3); there were no significant differences in signal intensity between BS and MH patients. In the BS group, patients with a dual valve replacement (aortic and mitral) had a significantly higher number of embolic signals compared with those with sole aortic valve replacement (P<.05; Table 1). No embolic signals were detected in any of the 6 patients with a spherical BS valve. All other differences in signal counts were insignificant. The number of patients with CE valves was too small for a comparison between the different valve positions. There were no significant differences in signal counts between patients with standard and supra-annular CE valves.

Patients with MH and BS valves had a significantly higher embolic signal intensity than patients with CE valves (Table 3). In the BS group patients with mitral valve replacement had significantly lower emboli signal intensity than did BS patients with aortic or dual valve replacement (1770 [1665, 1879] compared with 2808...
Top, Middle cerebral artery Doppler waveform in a patient with prosthetic heart valves. The first signal (1) is unidirectional and arises from an embolus. Signals 2 and 3 are bidirectional, arising from speech (2) and movement artifacts (3). Bottom, Spectral analysis of intensities within the Doppler waveform. Embolus signal (x-axis points 112 through 116), speech artifact (x-axis points 214 through 218), and movement artifact (x-axis points 461 through 465) show characteristic differences in the spectral intensity distribution (see text).

[2664, 2955] and 2875 [2663, 3094] power units, respectively; median [95% confidence interval (CI)]; the intensity difference between aortic and dual valve replacement was insignificant. There were no significant intensity differences among the different valve positions in patients with MH and CE valves.

No significant difference in the number of embolic signals was noted among patients at different intensities of anticoagulation in any of the groups examined. In the CE group patients who were not taking warfarin did not show any difference in embolic signal counts compared with the remaining cases. In 23 patients who were also
taking aspirin (150 or 300 mg/d) the number of embolic signals was not significantly different from the remaining patients (43 [5, 89] versus 40 [22, 45] signals/h, median [95% nonparametric CI]).

The embolic signal count did not vary according to patient age, sex, or duration of valve insertion. The median number of signals in patients with aortic (n=11) or paced (n=3) rhythm and of patients in atrial fibrillation (n=9) were similar (sinus and paced rhythm, 62 [39, 86] and atrial fibrillation, 41 [16, 62] signals/h, median [95% CI]).

Twenty-seven patients had experienced a probable embolic neurological event since their last valve insertion (transient ischemic attack in 14 patients, stroke in 10 patients, and transient monocular blindness in 3 patients). The embolic signal count did not vary according to the type of patients examined in our study is comparable to these

Twenty-five healthy volunteers, 14 women and 11 men, aged 22 through 36 years (median, 25 years) were also examined in this study. No embolic signals were detected in any of these subjects.

Discussion

Our data demonstrated striking differences in the prevalence and quantity of embolic signals among the three valve types. The substantially higher frequency and prevalence of microembolic signals in patients with BS valves has not been previously reported.

No single study has yet compared the long-term clinical performance of BS, MH, and CE valves; studies comparing BS with CE valves21,22 and BS with MH valves23 have shown no significant differences in the incidence of thromboembolic complications. The type of patients examined in our study is comparable to these

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Table 2. Intensity of Oral Anticoagulation and Quantity of Embolic Signals in Patients With Prosthetic Heart Valves

<table>
<thead>
<tr>
<th>Valve Type</th>
<th>INR</th>
<th>No. of Patients</th>
<th>No. of Signals</th>
</tr>
</thead>
<tbody>
<tr>
<td>BS</td>
<td>&lt;2</td>
<td>13</td>
<td>94 (50, 320)</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>30</td>
<td>201 (134, 287)</td>
</tr>
<tr>
<td></td>
<td>3-4.5</td>
<td>34</td>
<td>135 (72, 269)</td>
</tr>
<tr>
<td></td>
<td>&gt;4.5</td>
<td>8</td>
<td>114 (0, 200)</td>
</tr>
<tr>
<td>MH</td>
<td>&lt;2</td>
<td>12</td>
<td>4 (0, 8)</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>21</td>
<td>3 (0, 6)</td>
</tr>
<tr>
<td></td>
<td>3-4.5</td>
<td>20</td>
<td>1 (0, 5)</td>
</tr>
<tr>
<td></td>
<td>&gt;4.5</td>
<td>3</td>
<td>...</td>
</tr>
<tr>
<td>CE</td>
<td>NOW</td>
<td>6</td>
<td>1 (0, 2)</td>
</tr>
<tr>
<td></td>
<td>&lt;2</td>
<td>5</td>
<td>1 (0, 6)</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>18</td>
<td>2 (0, 11)</td>
</tr>
<tr>
<td></td>
<td>3-4.5</td>
<td>9</td>
<td>3 (1, 46)</td>
</tr>
<tr>
<td></td>
<td>&gt;4.5</td>
<td>0</td>
<td>...</td>
</tr>
</tbody>
</table>

INR indicates international normalized ratio; BS, Björk-Shiley; MH, Medtronic-Hall; CE, Carpentier-Edwards; and NOW, not on warfarin. Number of signals is median (95% confidence interval). Ellipses points indicate insufficient data for statistical analysis. Differences among patients with the same valve type were not statistically significant.

Taking aspirin (150 or 300 mg/d) the number of embolic signals was not significantly different from the remaining patients (43 [5, 89] versus 40 [22, 45] signals/h, median [95% nonparametric CI]).

The embolic signal count did not vary according to patient age, sex, or duration of valve insertion. The median number of signals in patients with aortic (n=11) or paced (n=3) rhythm and of patients in atrial fibrillation (n=9) were similar (sinus and paced rhythm, 62 [39, 86] and atrial fibrillation, 41 [16, 62] signals/h, median [95% CI]).

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Table 3. Embolic Signal Results and Proportion of Patients With a History of Neurological Deficit by Prosthetic Valve Type

<table>
<thead>
<tr>
<th>Valve Type</th>
<th>Incidence of Emboli, number/total (%)</th>
<th>No. of Embolic Signals/h (95% CI)</th>
<th>Intensity of Embolic Signal Power Units (95% CI)</th>
<th>Neurological Event, number/total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BS</td>
<td>76/85 (89%)</td>
<td>156 (112, 204)</td>
<td>2435 (2345, 2527)</td>
<td>13/85 (15%)</td>
</tr>
<tr>
<td>MH</td>
<td>28/56 (50%)</td>
<td>*</td>
<td>2 (1, 4)</td>
<td>2120 (1745, 2483)</td>
</tr>
<tr>
<td>CE</td>
<td>20/38 (53%)</td>
<td>*</td>
<td>2 (1, 4)</td>
<td>225 (184, 287)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; BS, Björk-Shiley; MH, Medtronic-Hall; and CE, Carpentier-Edwards. Data are median and nonparametric 95% CI limits.

*P<.001 by χ² test.

†P<.001, nonparametric multiple comparisons with Bonferroni correction.
reports, with some limitations. First, the percentage of patients with CE valves who were on anticoagulation therapy was 49% for mitral and 6% for aortic valves in one study,7,26 not stated in the other,21 and 84% in the present study. Second, patients in the previous studies had convex-concave BS and standard CE valves, whereas the majority of patients with BS valves in our study had the monostrut type, and 34% of patients with a CE valve had the supra-annular type. The prospective clinical follow-up of prosthetic valve patients from our Cardiac Surgery department confirms previous reports of minimal differences in the thromboembolic complication rate among patients with BS, MH, and CE valves.21-23 Thus, there appear to be discrepancies between our TCD embolus detection data and the clinical complication rates in the above studies that raise questions regarding the clinical significance of the Doppler microembolic signals, at least in predicting clinically apparent neurological complications. No correlation between the history of clinical neurological deficit and the number of embolic signals was found in this study.

The significant difference in signal intensity between patients with BS or MH versus CE valves is another important finding of the present study. Differences in signal power have previously been described between patients with metal prosthetic valves and patients with carotid stenosis.24 Assuming that the underlying embolic material is the same in all three patient groups, patients with MH or BS valves would have 3 to 5 times larger emboli than those with CE valves.11,12 In an experimental model an increase in emboli size from 15 to 50 μm resulted in a significant increase in neurological complications.25

We hypothesize that the microembolic signals detected in patients with mechanical prosthetic valves are caused by microbubbles. This hypothesis would explain the observed differences in signal power, as the Doppler effects of gas are more intense than those of solid material.11,12 Embolism of gas would cause less circulatory obstruction than the same volume of solid material.9 Animal models have demonstrated the ability of gas to pass through the pial arterioles into the venous system26; if this also occurs in patients with prosthetic valves it could explain the existence of asymptomatic patients with as many as 1500 embolic signals/h. The lack of influence of the intensity of anticoagulation or the addition of antiplatelet agents on the number of embolic signals in this and other studies26 also supports our assumption. The ability of prosthetic valves to produce microbubbles has been demonstrated in bench circulation models.27 Although cavitation bubbles have been observed to collapse in milliseconds,27 some of them may have a longer lifespan and thereby enter the systemic circulation.

Preliminary reports suggest possible clinical relevance of embolic signals in three patient groups: patients with prosthetic valves,4 patients undergoing cardiac surgery,7,28 and patients with acute stroke.7 The small number of prosthetic valve patients reported in the first study does not allow a meaningful statistical comparison. The other studies used postoperative neuropsychological deficit7,28 or outcome26 as end points. Neuropsychological deterioration might indeed be a more sensitive indicator of deficit in patients with prosthetic heart valves than the concrete neurological events sought in the present study, and we have incorporated neuropsychological testing in our ongoing study of these patients. Longitudinal follow-up and magnetic resonance image scanning may also prove useful in assessing the clinical importance of embolic signals.

We are now examining for activation of the coagulation system in relation to embolic signals, which would provide evidence that embolic material consists of blood clots, and we are formally assessing the effects of antiplatelet therapy, which would inhibit platelet aggregation and therefore reduce the quantity of platelet microemboli. The results of these studies should provide better evidence on the nature of the underlying embolic material in prosthetic valve patients. The results of this study have made clear that such evidence is essential before using the TCD technique as an indicator of clinical complication rates from different valve types.

Acknowledgments

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References


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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/25/3/587