Clinical Correlations of Doppler Microembolic Signals in Patients With Prosthetic Cardiac Valves
Analysis of 580 Cases

Ulrich Sliwka, MD; Dimitrios Georgiadis, MD

Background—The clinical relevance of Doppler microembolic signals (MES) in patients with prosthetic cardiac valves was evaluated by merging and statistically reanalyzing patient data from four research institutions (Departments of Neurology, Universities of Aachen, Halle, and Münster, Germany; Department of Medicine and Therapeutics, University of Glasgow, Scotland, and Department of Cardiothoracic Surgery, Western Infirmary, Glasgow, Scotland).

Methods—Transcranial Doppler monitoring for MES was performed over the middle cerebral arteries for 30 to 60 minutes per patient. Prevalence of neurological complications was evaluated with a standard neurological questionnaire in patients carrying the valve implant longer than 3 months (n=369).

Results—Significant differences in MES prevalence and counts were noted among the 580 patients depending on valve type (presented with medians and [95% confidence intervals]): St Jude Medical, n=200, 72%, 4 [3 to 6]; Björk-Shiley Monostrut, n=99, 92%, 133 [93 to 181]; Medtronic Hall, n=80, 47%, 1 [2 to 5]; ATS, n=61, 52%, 3 [2 to 5]; Tecna, n=38, 71%, 2 [1 to 4]; Carbomedics, n=37, 81%, 8 [5 to 13]; Carpentier-Edwards supraannular, n=54, 39%, 1 [0 to 3]; Sorin biological, n=11, 9%, 0 [0 to 0]. No relation between MES counts and valve size, international normalized ratio, patients’ age, cardiac rhythm, or valve type was noted. No significant differences in MES counts or prevalence (22 [3 to 68] versus 5 [3 to 6] and 63% versus 69%, both P>.05), in valve duration, valve position, valve type, patients’ age, sex, cardiac rhythm, or international normalized ratio were evident between neurologically symptomatic (n=42) and asymptomatic patients.

Conclusions—MES in patients with prosthetic cardiac valves depend on the type and, in certain valve types, the position of the valve implant and possess no direct clinical significance. (Stroke. 1998;29:140-143.)

Key Words: embolism ■ heart valve prosthesis ■ ultrasonics

Six years after the first description of Doppler MES in patients with prosthetic cardiac valves,1 no conclusive evidence has been produced concerning their clinical relevance. Results of recently published articles were contradictory.2–4 In an attempt to clarify this intriguing issue, databases from four research institutions (Departments of Neurology, Universities of Aachen, Halle, and Münster, Germany; Department of Medicine and Therapeutics, University of Glasgow, Scotland, and Department of Cardiothoracic Surgery, Western Infirmary, Glasgow, Scotland) were merged and the results statistically reanalyzed.

Methods
Ultrasound devices used were Trans-Scan, EME (Aachen); Multi-Dop X-4, DWL (Halle); TC-2000, EME (Glasgow); and Pioneer 4040, EME (Münster). Bilateral monitoring was performed for 1 hour in patients monitored in Halle, but results of the right MCA were used for further analysis. Unilateral TCD monitoring (30 minute duration) was performed in all other patients. MES counts were expressed as counts per hour.

MES were recognized according to standard criteria: characteristic sound, random appearance in the cardiac cycle, intensity increase at least 3 dB above background, and unidirectional woven within the Doppler spectrum.5

The following data were collected from all patients: age, duration, type and size of valve implant, cardiac rhythm, antihemostatic treatment, and occurrence of neurological complications. This assessment was based on a standard neurological questionnaire evaluating the occurrence of limb weakness and speech or visual deficit. Patients monitored within 3 months of valve insertion were included in the study but not in the evaluation of the influence of MES on neurological symptoms.

Two-sample t test was used for comparison of normally distributed data and the Mann-Whitney U test for nonnormally distributed data. Correlation of nonparametric data were evaluated with the Spearman-Rank test. The $\chi^2$ test was used for comparison of frequencies. Significance was declared at P<.05 level.

Results
Valve Type
MES counts and their prevalence were significantly higher in patients with mechanical valves compared with those with porcine valves (6 [5 to 7.5] versus 0 [0 to 1] and 26.2% versus 70.3%, respectively; both P<.01, Mann-Whitney U test and $\chi^2$ test, Table 1). Additionally, MES counts were significantly
higher in patients with BSM valves compared with other valve types (all P<.01; Mann-Whitney U test; Table 1) and in patients with Carbomedics compared with those with SJM, MH, Tecna, and ATS valves (all P<.05; Mann-Whitney U test).

Valve Position

Overall, MES counts were significantly higher in patients with dual valve replacement compared with those with sole aortic or sole mitral valve replacement (P<.002 and P<.04, respectively; Table 2). The same was true for patients with SJM and BSM valves (all P<.01; Mann-Whitney U test; Table 2). Additionally, in patients with ATS valves, significantly higher MES counts were noted when comparing aortic with mitral position (P<.001; Mann-Whitney U test; Table 2).

Valve Size

There was no correlation between MES counts and valve size on evaluation of all patients or when separately evaluating aortic and mitral positions in patients with BSM, MH, and SJM valves (BSM, mitral position r = −0.18, aortic position r = 0.03; SJM, aortic position r = 0.1, mitral position r = 0.03; MH, aortic position r = −0.3, mitral position r = −0.02).

Cardiac Rhythm

Cardiac rhythm was sinus in 426 patients and atrial fibrillation in 146 patients, whereas 8 patients carried a pacemaker. No relation between MES counts and cardiac rhythm was found in the examined patients or in any subgroups (overall MES counts in patients in sinus rhythm and atrial fibrillation 5 [4 to 6.5] and 5.5 [3.4 to 10], respectively).

Neurological Complications

Two hundred eleven patients were examined within the first 3 months after cardiac surgery and thus excluded from further analysis as far as neurological deficit was concerned. Forty-two of the remaining patients (11.4%) had experienced a neurological event 3±0.5 months (mean±SE, minimum 1 week, maximum 11 months) before examination (transient ischemic attack, n = 17; amaurosis fugax, n = 3; ischemic stroke, n = 22; Table 3). Mean time between occurrence of neurological symptoms and valve insertion was 37±5 months.

Prevalence of neurological complications was significantly higher in patients with mechanical valves compared with those with porcine valves (12.3% versus 4.4%; P<.05, χ² test). The same was true for patients with BSM, MH, and Tecna, compared with remaining mechanical valve implants. No differences in MES counts or prevalence were evident between neurologically symptomatic and asymptomatic patients (all P>.05, Mann-Whitney U test and χ² test, Table 3). Type and site of neurological events in relation to each valve are listed in Table 3.

Clinical Parameters

No relation between patient’s age, sex, and duration of valve implant to the number or prevalence of MES was found in the examined patients or in any subgroups.

Discussion

The present study represents the largest collection of patients with prosthetic cardiac valves monitored with transcranial Doppler, regarding both number of examined patients and different valve types. It must be stressed that because a limited number of valve types is used in each cardiothoracic department, recruitment of patients from different institutions was essential. The resulting use of various Doppler equipment and evaluation of MES counts by more than one observer constitute a weakness of the present study. However, as the interobserver variability in MES counts in patients with prosthetic valves is low, particularly through the high MES intensity in these patients, this limitation is not likely to have greatly influenced our results. The performance of unilateral

Table 1. Clinical Details and Results of TCD Monitoring in 580 Patients With Prosthetic Heart Valves

<table>
<thead>
<tr>
<th>Type</th>
<th>n</th>
<th>Age, y (mean±SE)</th>
<th>Female</th>
<th>Duration, m* (mean±SE)</th>
<th>INR, median (95% CI)</th>
<th>MES %</th>
<th>MES Counts, median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSM†</td>
<td>99</td>
<td>63±3</td>
<td>58</td>
<td>31±3</td>
<td>3 (2.8-3.2)</td>
<td>92</td>
<td>133 (93-181)</td>
</tr>
<tr>
<td>MH‡</td>
<td>80</td>
<td>60±1</td>
<td>51</td>
<td>22±3</td>
<td>2.8 (2.6-3)</td>
<td>47</td>
<td>1 (1-2.5)</td>
</tr>
<tr>
<td>AT5†</td>
<td>61</td>
<td>64±1</td>
<td>35</td>
<td>5±1</td>
<td>3 (2.8-3.4)</td>
<td>52</td>
<td>3 (2-5)</td>
</tr>
<tr>
<td>SJM†</td>
<td>200</td>
<td>62±1</td>
<td>77</td>
<td>6±0</td>
<td>2.8 (2.7-3)</td>
<td>72</td>
<td>4 (3-6)</td>
</tr>
<tr>
<td>TEC†</td>
<td>38</td>
<td>62±2</td>
<td>20</td>
<td>12±3</td>
<td>2.7 (2.4-3)</td>
<td>71</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td>CM†</td>
<td>37</td>
<td>59±1</td>
<td>20</td>
<td>1±1</td>
<td>2.8 (2.5-3.1)</td>
<td>81</td>
<td>8 (5-13)</td>
</tr>
<tr>
<td>CESA‡</td>
<td>54</td>
<td>68±2</td>
<td>26</td>
<td>18±3</td>
<td>2.8 (2.4-3.1)</td>
<td>39</td>
<td>1 (0-3)</td>
</tr>
<tr>
<td>SOBi‡</td>
<td>11</td>
<td>50±5</td>
<td>6</td>
<td>3±4</td>
<td>3 (2.2-3.4)</td>
<td>9</td>
<td>...</td>
</tr>
<tr>
<td>Total</td>
<td>580</td>
<td>62±0</td>
<td>293</td>
<td>15±1</td>
<td>2.9 (2.8-3)</td>
<td>65</td>
<td>4.5 (4-6)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; BSM, Björk-Shiley monostrut; MH, Medtronic-Hall; SJM, St Jude Medical; TEC, Tecna; CM, Carbomedics; CESA, Carpentier-Edwards supraannular; SOBi, Sorin biological; and MES %, prevalence of MES. Ellipses indicate insufficient data for analysis.

*Months since valve insertion; †mechanical prosthetic valves; ‡porcine prosthetic valves.
monitoring in 79% of cases, and the fact that neurologically symptomatic patients were not routinely monitored over the cerebral vessel supplying the affected territory or immediately after onset of neurological symptoms, constitute further methodological weaknesses. The insignificant differences between right and left MCA demonstrated in the present study, which are in agreement with the report of Grosset et al3 in prosthetic valve patients and Georgiadis et al4 in patients with potential cardioembolic source, suggest that whereas bilateral monitoring provides more accurate results, it would hardly improve our findings. Obviously, monitoring prosthetic valve carriers immediately after symptom onset would be preferable. Still, the report of Georgiadis et al,5 who found insignificant differences in MES counts in 50 patients examined on three different occasions within one year, suggests that the MES-generating mechanism is stable, and thus the methodology of the present study acceptable.

To date, three studies with patient numbers adequate for statistical analysis were published concerning the clinical relevance of MES (Sliwka et al5 [n = 179], Braekken et al5 [n = 92], and Georgiadis et al5 [n = 257]). Patients were examined within the first week after surgery and 10 to 13 months after valve implantation by Sliwka et al; 1 week, 1 year, and 5 years after valve implantation by Braekken et al; and between 3 days and 10 years after implantation by Georgiadis et al. The study of Braekken et al evaluated patient numbers that were too small (total of 14 symptomatic patients) and acquired marginally significant differences between symptomatic and asymptomatic patients6; their results therefore could be coincidental. Sliwka et al also described significantly higher MES counts in symptomatic patients, but this was true only for the subgroup based on 7 symptomatic patients.5 No significant differences in

### TABLE 2. Dependence of MES on Valve Position

<table>
<thead>
<tr>
<th>Valve Type</th>
<th>Aortic MES Counts, median (95% CI)</th>
<th>Mitral MES Counts, median (95% CI)</th>
<th>Aortic+Mitral MES Counts, median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MES %</td>
<td>n</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>BSM*</td>
<td>103 (67-152)</td>
<td>53</td>
<td>87</td>
</tr>
<tr>
<td>MH*</td>
<td>1 (0-4)</td>
<td>28</td>
<td>43</td>
</tr>
<tr>
<td>ATS*</td>
<td>1 (0-2)</td>
<td>44</td>
<td>41</td>
</tr>
<tr>
<td>SJM*</td>
<td>4 (3-6)</td>
<td>133</td>
<td>70</td>
</tr>
<tr>
<td>TEC*</td>
<td>2 (1-4)</td>
<td>18</td>
<td>61</td>
</tr>
<tr>
<td>CM*</td>
<td>4 (1-8)</td>
<td>28</td>
<td>75</td>
</tr>
<tr>
<td>CESAt</td>
<td>1 (0-2)</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>SOBi†</td>
<td>...</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>338</td>
<td>4 (3-5.5)</td>
<td>68</td>
</tr>
</tbody>
</table>

CI indicates confidence interval, BSM, Björk-Shiley monostent; MH, Medtronic-Hall; SJM, St Jude Medical; TEC, Tecna; CM, Carbomedics; CESAl, Carpentier-Edwards supraannular; SOBi, Sorin biological; and MES %, prevalence of MES. Ellipses indicate insufficient data for analysis.

*Mechanical prosthetic valves; †porcine prosthetic valves.

### TABLE 3. MES Prevalence and Counts in Neurologically Asymptomatic Symptomatic Patients

| Valve Type | Neurol | No. of Asymp- | MES, % | Aortic MES Counts/h, median (95% CI) | No. of Sym- | Mitral MES Counts/h, median (95% CI) | No. of Sym- | Mitral MES Counts/h, median (95% CI) | Valve, M/A/ MA* | Aortic + Mitral Deficit, TIA/AF/ IST† | Aortic + Mitral Hemisph, R/L | Ant/Post Circulation‡ | OP§, m | TCD¶, m |
|------------|--------|---------------|-------|-------------------------------------|------------|-------------------------------------|------------|-------------------------------------|----------------|-------------------------------------|------------------|------------------------|-------------|---------|--------|
| BSM¶       | 17.6%  | 56            | 93    | 152 (88-245)                        | 12         | 100                                 | 165 (101-228) | 5/6/1                               | 6/0/6         | 1/3/0                               | 1/1/2             | 35±10                  | 2±0.5        |         |
| MH¶        | 24.5%  | 37            | 43    | 2 (0-6)                             | 12         | 50                                  | 1 (0-2)     | 6/3/3                               | 6/1/5         | 1/0/0                               | 1/0/0             | 49±10                  | 3±1         |         |
| ATS¶       | 4.3%   | 44            | 37    | 1 (0-2)                             | 2          | 50                                  | ...         | 0/1/1                               | 0/0/2         | 0/2                                 | 2/0               | 32±12                  | 4±1         |         |
| SJM¶       | 7.6%   | 109           | 67    | 6 (4-8)                             | 9          | 75                                  | 5 (0-22)   | 1/5/3                               | 3/0/6         | 4/5                                 | 9/0               | 24±10                  | 7±1         |         |
| TEC¶       | 17.4%  | 19            | 79    | 2 (1-3)                             | 4          | 50                                  | ...         | 1/3/0                               | 1/1/2         | 2/2                                 | 4/0               | 32±12                  | 4±1         |         |
| CM¶        | 5%     | 19            | 79    | 3 (1-10)                            | 1          | 100                                 | ...         | 0/1/0                               | 0/0/1         | 1/0                                 | 0/1               | ...                    | ...         |         |
| CESAl      | 5.9%   | 32            | 31    | 1 (0-2)                             | 2          | 50                                  | ...         | 1/1/0                               | 1/1/0         | 1/1                                 | 2/0               | ...                    | ...         |         |
| SOBi#      | 0%     | 11            | 9     | 0 (0-0)                             | 0          | ...                                 | ...         | 0/0/0                               | 0/0/0         | 0/0                                 | 0/0               | ...                    | ...         |         |
| Total      | 11.4%  | 327           | 63    | 5 (3-6)                             | 42         | 69                                  | 22 (3-68)  | 14/20/8                             | 17/3/22       | 17/25                               | 38/4              | 37±5                   | 3±0.5       |         |

BSM indicates Björk-Shiley monostent; MH, Medtronic-Hall; SJM, St Jude Medical; TEC, Tecna; CM, Carbomedics; CESAl, Carpentier-Edwards supraannular; SOBi, Sorin biological; Neurol, prevalence of neurological complications; and MES %, prevalence of MES. Ellipses indicate insufficient data for statistical analysis.

*Position of prosthetic valve in symptomatic patients: M, mitral; A, aortic; MA, dual.
†Type of symptoms: TIA, transient ischemic attack; AF, amaurosis fugax; IST, ischemic stroke.
‡Site of lesion: Ant, anterior circulation (all MCA territory); Post, posterior circulation (posterior cerebral artery territory, n=3; basilar artery territory, n=1.
§Time period between operation and occurrence of neurological deficit.
¶Time period between occurrence of neurological symptoms and TCD monitoring.

 AsyncStorage; IS: Ichthyotic stroke.

* Mechanical prosthetic valves; †porcine prosthetic valves.
MES counts were demonstrated in the study of Georgiadis et al., which is in agreement with our current results.

The demonstrated lack of clinical correlations lends further support to the hypothesis that the underlying embolic material in patients with prosthetic cardiac valves is gaseous. Several previous observations also argue for gaseous embolic material:(1) the lack of influence of the intensity and mode of anticoagulation on MES counts,2,3,10,11 (2) the lack of relation of MES counts to D-dimer, thrombin-antithrombin, and antithrombin III serum levels,12 (3) the generation of MES in a hydrodynamic function tester with mechanical valves and degassed saline as circulating medium,13 (4) the significant changes in MES counts in valve patients after decompression14 or oxygen inhalation,15 and (4) the evidence on changes of the reflecting frequency of MES in valve patients under multifrequency insolation.16 Whereas the generation of cavitation bubbles by artificial heart valves is a generally accepted phenomenon widely described in circulatory mock-loops,17,18 these are supposed to implode within milliseconds and therefore not enter the systemic circulation. However, it is possible that interactions between cavitation bubbles and blood components prolong their life span. Additionally, a portion of these bubbles has been described to be bigger, and thus energetically more stable, so that their detection in the MCA appears feasible.

MES in patients with porcine valves could not be caused by cavitation, because the energy thresholds are not reached by native valves. We assume that MES in these patients are instead caused by formed material associated with interactions between blood elements and the biological valve. As these patients were older compared with those with mechanical valves, MES could also arise from coexisting cardiac or aortic embolic sources.

Our failure to provide evidence for a relation between MES counts and prevalence of neurological complications does not necessarily suggest that these have no impact on brain function, because the continuous embolization could be causing more subtle deficit that might only become evident by the application of neuropsychological testing. Unfortunately, only preliminary results19 are available in this intriguing issue.

In conclusion, our results strongly argue against any clinical significance of MES in patients with prosthetic cardiac valves and suggest that routine TCD monitoring for emboli is not warranted in these patients.

Acknowledgments

Mr A. Faichney, Department of Cardiothoracic Surgery, Western Infirmary, Glasgow, Scotland; Professor H.R. Zerkowski, Department of Cardiothoracic Surgery, University of Halle; Dr F. Schönрубe, Department of Cardiothoracic Surgery, University of Aachen; and Professor H.H. Scheld, Department of Cardiac and Vascular Surgery, University of Münster, provided valuable help in patient recruitment. Dr K.R. Lees and Dr D.G. Grosset, Acute Stroke Unit, University Department of Medicine and Therapeutics, and Dr A. Mallinson, Department of Hematology, Western Infirmary, Glasgow, Scotland; Professor J. Noth, Department of Neurology, University of Aachen; and Professor Zierz and Dr Lindner, Department of Neurology, University of Halle, actively supported parts of this project. We are also indebted to Professor D.J. Wheatley and Dr T.G. Mackay, Department of Cardiac Surgery, University of Glasgow, Scotland; Professor M. Kaps, Department of Neurology, University of Lübeck; and Professor H. Reul, Helmholtz Institute for Biomedical Engineering, Aachen, for their constructive comments concerning microembolic signals in valve patients. Finally, we would like to thank a number of medical students who were actively involved in parts of this research project: B. Meyer and F. Schönрубe in Aachen; S. Stirling and P. Coburn in Glasgow; A. Lührmann and A. Wenzel in Halle; and T. Mumme, M. Hill, and M. König in Münster.

References

Clinical Correlations of Doppler Microembolic Signals in Patients With Prosthetic Cardiac Valves: Analysis of 580 Cases
Ulrich Sliwka and Dimitrios Georgiadis

Stroke. 1998;29:140-143
doi: 10.1161/01.STR.29.1.140

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/29/1/140