Solid Cerebral Microemboli and Cerebrovascular Symptoms in Patients With Prosthetic Heart Valves

Mona Skjelland, MD; Annika Michelsen, PhD; Frank Brosstad, MD, PhD; Jan L. Svennevig, MD, PhD; Rainer Brucher, PhD; David Russell, FRCPE

Background and Purpose—Although cerebral microemboli are often detected by transcranial Doppler ultrasonography in mechanical heart valve patients, the clinical significance of such microemboli is unclear. The aim of this study was to determine the frequency and composition of cerebral microemboli in a prosthetic heart valve population and to correlate these findings to cerebrovascular symptoms, blood inflammation, and coagulation parameters.

Methods—Seventy-six consecutive patients with a total of 81 prosthetic (54 mechanical, 27 biologic) heart valves were monitored for cerebral microemboli by multifrequency transcranial Doppler ultrasonography 1 year after valve replacement. Cerebrovascular events in the first year were recorded by a neurologist. Inflammation and coagulation markers were measured by immunoassays.

Results—Microemboli were detected in mechanical heart valve patients only (28 patients, 56%). Twelve percent were solid, occurring in 17 (34%) of the mechanical heart valve population. The presence of solid cerebral microemboli was the only variable that was associated with cerebrovascular symptoms after a final regression analysis (P=0.026). The plasma monocyte chemotactic protein-1 level was raised in patients with solid microemboli (P=0.014).

Conclusions—Solid cerebral microemboli were detected by multifrequency transcranial Doppler ultrasonography in 35% of a mechanical heart valve population, and the frequency was higher in patients who experienced cerebrovascular events during the first year after valve replacement. The results suggest that the detection of solid cerebral microemboli may be helpful in predicting the risk of ischemic stroke in mechanical heart valve patients. (Stroke. 2008;39:1159-1164.)

Key Words: cerebral microemboli ■ embolic stroke ■ prosthetic heart valve ■ transcranial Doppler ultrasonography

The frequency of thromboembolic complications in mechanical heart valve (MHV) patients is 1% to 4% per patient-year despite optimal anticoagulation.1,2 The majority of these thromboembolic events involve the cerebral circulation, resulting in an increased frequency of transient ischemic attacks (TIAs) and ischemic strokes.3 This risk is continuous and cumulative over time. Cerebral microembolic signals (MESs) have been detected by transcranial Doppler ultrasonography (TCD) in 35% to 97% of the MHV population.4–7 The large variability in the incidence and frequency of detected cerebral MESs in previous studies is most likely due to differences with regard to detection criteria, unilateral versus bilateral monitoring, and different monitoring durations. The clinical significance of MESs in prosthetic heart valve patients remains unclear. Some authors have found evidence that suggests an increased risk of ischemic injury to the brain,4,8,9 whereas others have not.7,10–12 The first aim of this study was to determine the incidence, frequency, and composition of cerebral microemboli in a prosthetic heart valve population by multifrequency TCD. The second aim was to determine whether the number or type of microemboli is correlated to cerebrovascular symptoms or to platelet activation, coagulation, and inflammatory status of the patients.

Subjects and Methods

Patients

The study prospectively included 75 consecutive patients with a total of 79 prosthetic heart valves. Two patients with an internal carotid artery stenosis (>50%) detected by precerebral color duplex examinations and 1 patient with both a mechanical and a biologic valve were excluded. The mean age of the patients was 67 years (range, 17 to 87 years); 56 (75%) patients were male; and 19 (25%) were female. Sixty-two (79%) of the 79 valves were in the aortic position and 17 (22%) in the mitral position. Four patients had double valve replacement. Patients were divided into 2 groups: those with MHVs (n=53) and those with biologic heart valves (BHV, n=26). The MHV valve types were CarboMedics (CarboMedics Inc, Austin, Tex; 18 valves), Advantage (Medtronic Advantage Medical Carbon Research Institute, Austin, Tex; 11 valves), and On-X (On-X...
Medical Carbon Research Institute, LLC, Austin, Tex; 24 valves). The BHV group included Perimount (15 valves), Hancock (7 valves), and Freestyle (4 valves). Seventeen (23%) of the 75 patients had atrial fibrillation. Patients in the MHV and BHV groups were comparable with regard to baseline variables except for a higher mean age in the BHV group (77 versus 62 years) and differences with regard to anticoagulation and antiplatelet treatment (Table 1).

All MHV patients were treated with anticoagulation therapy with a mean international normalized ratio (INR) of 2.6 (SD = 0.7; range, 1.1 to 4.5). Thirty-one (62%) patients were within the target INR level of 2.5 to 4.0. Five (10%) patients with an MHV were also receiving antiplatelet therapy (acylsalicylic acid) due to cerebrovascular symptoms or ischemic coronary heart disease.

Cerebrovascular events in the first year after valve replacement were recorded by a neurologist who also performed a clinical neurologic examination of all patients. A cerebral computed tomography or magnetic resonance imaging examination was carried out in patients who had experienced cerebrovascular symptoms. All patients gave informed consent before the study, which was approved by the regional ethics committee.

**Table 1. Baseline Variables in the MHV and BHV Patient Groups (N=75)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>MHV n=53</th>
<th>BHV n=26</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age, y</td>
<td>62 (14.7)</td>
<td>77 (5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex*</td>
<td>38 (76)</td>
<td>18 (72)</td>
<td>0.435</td>
</tr>
<tr>
<td>Valve position, aortic*</td>
<td>39 (74)</td>
<td>23 (89)</td>
<td>0.131</td>
</tr>
<tr>
<td>Double valve replacement*</td>
<td>3 (6)</td>
<td>1 (4)</td>
<td>0.615</td>
</tr>
<tr>
<td>Valve size, mm</td>
<td>25 (3.6)</td>
<td>24 (2.5)</td>
<td>0.198</td>
</tr>
<tr>
<td>Atrial fibrillation*</td>
<td>9 (18)</td>
<td>5 (20)</td>
<td>0.811</td>
</tr>
<tr>
<td>Anticoagulation therapy*</td>
<td>50 (100)</td>
<td>7 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antiplatelet therapy*</td>
<td>5 (10)</td>
<td>14 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>INR</td>
<td>2.6 (0.7)</td>
<td>1.6 (0.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Numbers are unadjusted means (SD) or *numbers (percentages).

**Measurement of Platelet-Derived Microparticles**

After being thawed, 1 aliquot of CTAD-plasma was filtered through 0.1-μm pores (Millipore, Billerica, Mass). Both unfiltered plasma and filtrate (1 volume) were mixed with 1 volume of Delfia assay buffer (Perkin-Elmer Life Science, Boston, Mass) containing 1% of the nonionic detergent Igepal CA-630 (Sigma, St. Louis, Mo) before analysis. The total amount of platelet-derived microparticles (PMPs) was measured in unfiltered plasma (total PMPs), whereas measurements in filtrate were considered to reflect the amount of small PMPs (<0.1 μm). Large PMPs were calculated as the difference between the total amount of PMPs and the amount of small PMPs. This immunometric method has been described in detail previously.

**Statistical Methods**

The numbers of MEs during the 30-minute monitoring period are shown as median and range (nonnormal distribution). Statistical analyses included descriptive statistics with mean (±SD) and median (range) for continuous variables and number (percentage) for categorical variables. We used Student’s t test for comparison of normally distributed data and nonparametric tests for data with a nonnormal distribution. Pearson’s χ² test was used to assess associations between categorical variables. Multiple logistic-regression analysis was carried out to measure the odds ratio for cerebrovascular events. The explanatory variables were solid microemboli, gaseous microemboli, age, sex, valve type (mechanical or biologic), number of valves, valve position, antiplatelets, and anticoagulation. A probability value <0.05 was considered statistically significant. All statistics were 2-sided. All calculations were carried out with SPSS for Windows statistical software (version 13.0; SPSS Inc, Chicago, Ill).

**Results**

**Cerebrovascular Symptoms**

Patients with MHVs experienced more cerebrovascular symptoms in the first year after valve replacement compared with patients with BHVs (P = 0.045, Table 2). Twelve patients (21%) with MHVs experienced a cerebrovascular event: 1 ischemic hemispheric stroke, 9 hemispheric TIs, and 2 cases of amaurosis fugax. One (4%) of the 27 patients with a BHV had a hemispheric TIA.

**Cerebral Microemboli**

Cerebral microemboli were detected in 28 (56%) of the 50 patients with MHVs. Fifty-six (12%) of these microemboli were classified as solid and 481 (88%) as gaseous. Seventeen (34%) of the 50 patients with MHVs had solid microemboli. No emboli were detected in the BHV patients. In the MHV population, the median number of solid emboli was 0 (range, 0 to 15) and 3 gaseous (range, 0 to 79). All patients with solid emboli also had gaseous emboli, and the number of gaseous...
Emboli was higher in these patients (median, 18; range, 2 to 79) compared with patients without solid emboli (median, 0; range, 0 to 12; \( P<0.001 \)). Patients who had experienced stroke, TIA, or amaurosis fugax had a higher total number \( (P<0.001) \), a higher number of solid \( (P<0.001) \), and a higher number of gaseous \( (P<0.001) \) emboli compared with patients without cerebrovascular symptoms (Table 2). Solid microemboli were, however, the only predictor for cerebrovascular events (odds ratio \( =18.6; \text{95\% CI, 1.4 to 245.5, } P=0.026 \)) when a stepwise logistic-regression model was performed with cerebrovascular events during the first year after heart valve replacement as the dependent variable.

The mean age of MHV patients with emboli, for both solid and gaseous emboli, was lower (58 years) compared with patients without emboli (68 years, \( P=0.022 \)). The position or size of the valve, the number of implanted valves (only 3 patients with a mechanical double valve replacement), or the frequency of atrial fibrillation did not influence the presence, frequency, or type of emboli.

Platelet Function, Coagulation, and Inflammatory Parameters

Patients with MHVs who had solid emboli had higher MCP-1 values compared with patients without solid emboli \( (P=0.014, \) Table 3). There was no correlation between MCP-1 values and the frequency of gaseous emboli or cerebrovascular events. (MCP-1 measurements were performed only in 5 patients with cerebrovascular events.) Patients with gaseous emboli had decreased \( \text{F1+2} \) \( (P=0.014) \) values compared with patients without gaseous emboli, but there were no differences with regard to fibrinogen levels (Table 4). There was no correlation between \( \text{F1+2} \) or D-dimer levels and the frequency of solid emboli. Patients with solid emboli had nonsignificantly higher levels of total PMPs and small PMPs (Table 3). There was no significant association between the frequency of solid or gaseous emboli and other tests for inflammation (C-reactive protein, leukocyte count), coagulation (INR), or platelet activity (soluble CD62P, platelet count; Tables 3 and 4).

| Table 2. Univariate Statistics Between Patients With Cerebrovascular Events and Patients Without Cerebrovascular Events in the First Year After Valve Implantation (\( N=75 \)) |
|-------------------------------------------------|---------------------------------|-----------------|
| Cerebrovascular Events \( (n=12) \) | No Cerebrovascular Events \( (n=63) \) | \( P \) |
| Solid MESs* | 3 (0–15) | 0 (0–4) | \(<0.001\) |
| Gaseous MESs* | 8 (0–79) | 0 (0–51) | \(<0.001\) |
| Mechanical valve | 11 (92) | 39 (62) | 0.045 |
| Small PMPs \( (n=42) \)* | 171.5 (118–298) \( (n=5) \) | 326.5 (103–582) \( (n=37) \) | 0.183 |
| Large PMPs \( (n=42) \)* | 79 (48–704) \( (n=5) \) | 115 (34–265) \( (n=37) \) | 0.636 |
| \( \text{F1+2} \) \( (n=42) \)* | 49 (34–55) \( (n=5) \) | 88 (18–471) \( (n=37) \) | 0.023 |
| MCP-1 \( (n=41) \)* | 92.5 (32–124) \( (n=5) \) | 88.5 (0–228) \( (n=36) \) | 0.499 |
| Male sex | 11 (91.7) | 48 (69.6) | 0.140 |
| Patient age † | 58.4 (13.2) | 68.4 (13.8) | 0.003 |
| Antiplatelet therapy | 4 (33.3) | 15 (21.7) | 0.487 |
| Anticoagulation | 12 (100) | 50 (72.5) | 0.028 |

* Numbers are *median (range), †unadjusted means (SD), or numbers (percentages). |

| Table 3. Differences in Blood Parameters in MHV Patients With Solid Emboli Compared With Patients Without Solid Emboli \( (N=54 \) Valves) |
|-----------------------------------------------|-----------------|-----------------|
| Solid Microemboli \( (n=41) \)* | No Solid Microemboli | \( P \) |
| MCP-1, pg/mL \( (n=41) \)* | 127.09 (45.9) | 79.6 (45.3) | 0.014 |
| Leukocyte count, \( 10^9/L \)* | 7.4 (2.9) | 7.3 (1.9) | 0.893 |
| C-reactive protein* | 6.8 (4.5) | 5.7 (1.4) | 0.355 |
| Platelet count, \( 10^9/L \)* | 241.6 (60.5) | 266 (153.2) | 0.511 |
| Total PMPs, \( \mu g/L \) \( (n=42) \) | 461 (185–982) | 333 (137–752) | 0.446 |
| Large PMPs, \( \mu g/L \) \( (n=42) \) | 101 (48–704) | 115 (34–265) | 0.811 |
| Small PMPs, \( \mu g/L \) \( (n=42) \) | 294 (118–582) | 221 (103–487) | 0.349 |
| Soluble CD62P, ng/mL \( (n=42) \)* | 43.3 (12.6) | 44.6 (14.3) | 0.820 |
| \( \text{F1+2} \), pmol/L \( (n=42) \) | 53 (27–92) | 79 (18–241) | 0.349 |
| Fibrinogen, g/L* | 3.6 (0.66) | 3.8 (0.8) | 0.624 |
| D-dimer, mg/L* | 2.7 (0.11) | 0.3 (0.36) | 0.156 |
| INR | 2.7 (1.4–4.5) | 2.5 (1.1–3.8) | 0.238 |

* Numbers are unadjusted *means (SD) or median (range).
MHV Types
The numbers of both solid and gaseous emboli were higher in patients with CarboMedics valves (2 solid; range, 0 to 15; and 8 gaseous; range, 0 to 79) compared with patients with On-x valves (0 solid; range, 0 to 4; \( P < 0.001 \); and 0 gaseous; range, 0 to 11, \( P = 0.006 \)) or Advantage valves (0 solid; range, 0 to 3, \( P = 0.006 \); and 0 gaseous; range, 0 to 20, \( P = 0.042 \)). There were also more cerebrovascular events in patients with CarboMedics valves (8 patients, 44%) compared with On-x (3 patient, 12%, \( P = 0.017 \)) and Advantage (0 patients, \( P = 0.011 \)) valves but no difference between patients who had On-x compared with Advantage valves.

Discussion
In this study, we found evidence that suggests that the detection of solid cerebral microemboli may be helpful in predicting the risk for ischemic stroke in MHV patients. Fifty-seven percent of MHV patients had cerebral microemboli, and 12% of these were solid. Patients who had experienced cerebrovascular symptoms had significantly higher numbers of both solid and gaseous emboli compared with those without symptoms, but the presence of solid emboli only was significantly associated with cerebrovascular events after a final stepwise regression analysis was carried out. No emboli were detected in BHV patients.

This is the first study wherein an attempt was made to differentiate cerebral microemboli in a prosthetic heart valve population. We used multifrequency TCD,\(^{13,14}\) which is a relatively new method for embolus differentiation. This method has 3 potential limitations; ie, sensitivity when detecting small, solid emboli (<80 \( \mu \)m, corresponding to an EBR of <7 dB), correctly differentiating small, gaseous emboli (<3 \( \mu \)m, corresponding to an EBR of <7 dB), and counting all of the emboli when several enter the sample volume at the same time.\(^{15}\) It is important to stress, however, that the criteria for automatic embolus detection and differentiation by multifrequency TCD were clearly defined before the study and therefore were exactly the same for all patients. The aforementioned limitations were therefore similar for all patients. This differs from previous studies, wherein embolus detection alone without differentiation was based on the opinion of observers, which may yield considerable variations in the number of emboli counted due to environmental changes and the obvious individual limits of the human auditory system.\(^{17,18}\)

Solid microemboli due to MHVs may consist of platelet aggregates or whole blood. Mechanical valve implants may induce platelet activation by increasing shear stress conditions.\(^{19}\) In our study, the mean values of PMPs analyzed by an immunofluorometric method\(^{16}\) were nonsignificantly increased in MHV patients with solid cerebral MESs compared with patients without solid MESs. There was, however, no association between PMP values and cerebrovascular events. This contrasts with the findings of others.\(^{20}\) In our study, other coagulation and platelets parameters such as F1 +2, soluble CD62P values, and platelet counts were not associated with solid emboli. A nonsignificant increase in PMPs without a soluble CD62P or F1 +2 increase cannot exclude platelet activation in patients with solid emboli, but our results suggest that if present, this activation did not reach the secondary irreversible phase of platelet aggregation.

The present study showed that an increased MCP-1 value was associated with solid emboli in MHV patients, which suggests that monocyte activation and inflammation may contribute to the production of solid emboli. MCP-1 values did not influence the frequency of gaseous emboli. The lack of correlation between MCP-1 and cerebrovascular events may be explained by the small number of patients with cerebrovascular events and MCP-1 measurements. MCP-1 was measured in 41 patients, but only 5 of these had experienced a cerebrovascular event. Previous studies have shown that activated platelets may induce dysregulation of platelet/endothelium interactions, which contribute to vascular inflammation and atherosclerosis.\(^{21}\) Activated platelets induce the secretion of MCP-1, which belongs to a group of cytokines known as chemokines.\(^{22}\) MCP-1 induction enhances monocyte attraction and local inflammation, which in turn leads to an imbalance between the procoagulant and anticoagulant properties of the endothelium. This can cause local stimulation of the coagulation cascade. However, the
lack of a correlation between activity of the coagulation system or INR values and the frequency of solid MESs in MHV patients in this study argues against whole-blood clots as the basis for solid emboli. A high D-dimer level in 1 study was the only parameter that predicted the occurrence of thromboembolic events in patients with MHV, whereas this and other studies showed no association with embolization. Although we excluded patients with severe carotid atherosclerosis, it is impossible to exclude the possibility that some of the solid emboli may have been due to atherosclerosis. We did not, however, detect any MESs in the older BHV patients, who may be expected to have a greater atherosclerotic risk.

The majority of previous studies have indirectly suggested that most cerebral MESs in MHV patients are gaseous. This study confirms these findings, wherein 88% of the MESs were gaseous. Gaseous emboli are probably cavitation bubbles produced by local high-pressure gradients during valve closure, causing “cavitation,” with the release of dissolved blood gases. In vitro studies have shown, however, that cavitation gas emboli usually collapse in <1 ms. Interaction between cavitation bubbles and blood components, eg, activated platelets, may, however, lead to their stabilization, and they might then last long enough to reach the cerebral circulation. As cavitation bubbles and platelet injury are probably caused by local high-pressure gradients during valve closure, hemodynamic characteristics of the different valves may influence the frequency of embolization. In vitro studies have shown that valves with different orientations and designs vary with regard to their valve outlet configuration, downstream turbulence, and rate of embolization. It is therefore reasonable to suppose that the design of MHV is important for both the degree of cavitation and platelet activation. MHV with a high local shear stress may lead to both the stabilization of gas bubbles and the promotion of inflammation, which may contribute to the formation of solid embol. This is a possible explanation as to why all patients who had solid emboli also had gaseous emboli and why there were increased numbers of gaseous emboli in patients with solid emboli compared with patients without solid emboli.

Some previous studies have shown that cerebral embolization depends on valve type, whereas other could not confirm this difference. Our study showed more cerebral microemboli and cerebrovascular events in the mechanical Carbomedics valves compared with Advantage or On-x valves. However, these results should be interpreted with caution due to the very small numbers of patients in the different valve groups.

We found that both gaseous and solid emboli were more frequent in younger patients. Other studies that analyzed the total number of emboli also found an inverse correlation between the total number of emboli and patient age. Animal models have shown that myocardial contractility affects microembolus frequency. Younger patients have better myocardial contractility and a higher left ventricular ejection fraction compared with older MHV patients. An increased frequency of gaseous emboli in younger patients may therefore be due to greater pressure gradients and subsequent cavitation at the site of the valve. The position or size of the valve or the presence of atrial fibrillation did not influence the frequency of MESs, which supports findings from previous studies.

Conclusions
In conclusion, this study has shown that solid cerebral emboli may be detected by multifrequency TCD in 34% of an MHV population. It also provides the first preliminary evidence that suggests that the presence of solid cerebral microemboli may be helpful in predicting the risk for ischemic stroke in MHV patients. Confirmation of these findings will require larger prospective multicenter studies.

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Disclosures
None.

References


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