Microemboli in Cerebral Circulation and Alteration of Cognitive Abilities in Patients With Mechanical Prosthetic Heart Valves

Ghislaine Deklunder, MD, PhD; Martine Roussel, MSc; Jean-Louis Lecroart, PhD; Alain Prat, MD; Corinne Gautier, MD

Background and Purpose—It has been shown previously that cerebral microemboli may occur frequently in patients with a normal mechanical heart valve (MHV) without prior history of stroke. Some arguments strongly suggest that these microemboli have a gaseous origin. In other circumstances such as extracorporeal circulation or decompression in divers, it has been demonstrated that cerebral microbubbles could lead to some deterioration in cognitive functions. Therefore, we have studied attention and memory, which are among the most impaired cognitive functions as demonstrated in previous studies, in patients with an MHV.

Methods—Three groups of 12 volunteers each were composed of patients with an MHV and embolic signals in the cerebral circulation (group 1), patients with biological prostheses (group 2), and healthy subjects (group 3). Groups were carefully matched for age and verbal intellectual abilities. For each group, a transcranial Doppler examination was performed and a set of cognitive tests assessing sustained and selective attention and episodic and working memory was administered.

Results—The mean embolic rate was 29 per hour in patients with an MHV. No embolus was detected in the other 2 groups. Episodic memory was significantly modified in both groups 1 and 2 compared with the control group for tasks that required high-processing resources. Working memory performance was significantly decreased in MHV patients. No between-groups differences were observed for the other parameters.

Conclusions—Alteration of episodic memory can be attributed to a long-term effect of the surgical procedure. Deterioration of working memory can be related to the presence of cerebral microemboli in MHV patients. (Stroke. 1998;29:1821-1826.)

Key Words: heart-valve prosthesis ■ HITS ■ cognitive abilities ■ transcranial Doppler

Most patients who have a mechanical heart valve (MHV) prosthesis implanted exhibit high-intensity transient signals (HITS) in the cerebral circulation that are usually detected by a transcranial Doppler examination of the middle cerebral artery (MCA).1 The prevalence of HITS is high, from 50% to 100% according to some studies, 2–5 and thus it has an important clinical and economic effect considering the high number of MHVs implanted in patients each year worldwide. In view of this population, the rate of HITS widely varies according to the prosthesis type, size, and status. However, the presence of HITS is also observed in patients with normally functioning MHVs and without other embolic source. In any case, the HITS rate can reach several hundreds per hour.

The nature of HITS in patients with a normal MHV is still being debated, but there are strong arguments in favor of a gaseous origin: microbubbles can be produced at the level of the valve leaflets where local high-pressure gradients are present during the cardiac cycle, especially at valve closure. These pressure gradients could lead to the appearance of a cavitation-like phenomenon that can release part of the dissolved blood gas under the form of microscopic bubbles into the circulation.6–8

Circulating microbubbles have been reported in other circumstances, eg, during coronary artery bypass grafting.9,10 A decline in cognitive performances of these patients has been reported, and its amplitude has been correlated to the amount of gas emboli delivered during the extracorporeal circulation (ECC). The consensus is increasing that diffuse microembolization, secondary to ECC, is the primary cause of cerebral damage in any uncomplicated open heart surgery.11–13 In divers, central nervous system damage has been reported using magnetic resonance imaging.14 Moreover, a direct deleterious effect of gaseous microembolization has been demonstrated on the cerebral microvasculature.15,16

These observations were made during situations of acute embolization. Although most of the chronic emboli in patients with an MHV are clinically silent, it is reasonable to
assume that such repeated events could have subtle cumulative effects on the cerebral microcirculation and thus on some cerebral functions.

The presence of memory and attention disorders is frequently reported in patients with brain damage and particularly after open heart surgery. As in previous studies conducted on patients after cardiac surgery, the present study was designed to assess attention and memory of patients with MHV-associated HITS. Neuropsychological procedures were selected on the basis of their use in previous studies.

Sustained attention and selective attention were the 2 types of attention explored in this study. The assessment of short-term memory was investigated with regard to the working memory model of Baddeley. This model refers to a limited capacity system that is responsible for the temporary storage and processing of information while cognitive tasks are being performed. Long-term memory performance was assessed by testing the episodic memory, which concerns facts of personal experience.

A specifically designed battery of neuropsychological tests has been used to explore the sustained and selective attention and the working and episodic memory. This battery of tests was applied to (1) a group of patients with an MHV and repeatedly occurring HITS, (2) a group of patients having undergone a similar cardiac surgery procedure with implantation of a biological valve, and (3) a group of healthy subjects. These last 2 groups did not present any HITS.

### Subjects and Methods

#### Subjects

Patients were randomly selected from those regularly attending Lille University Hospital who also met the inclusion criteria. Control subjects were recruited by announcement, and the data obtained from this group were used as reference values for the neuropsychological tests. All subjects were informed about the study protocol and gave consent to enter the study.

Eligible subjects were tested for inclusion criteria and group matching on entry in the study. Thirty-six subjects met the inclusion criteria used for the HITS detection were those originally proposed by Spencer's characteristic chirping sound, initially unidirectional signal in the Doppler spectrum, random appearance within the cardiac cycle, and intensity increase ≥10 dB above the background spectrum. The embolic rate was determined by counting the number of HITS during the recording period (20 minutes). Results were reported as the number of events per hour.

#### Cognitive Tests

##### Attention

Sustained-attention abilities were evaluated by a simple visual reaction time test with 100 stimuli. The visual stimulus was a red spotlight presented until the subject responded by depressing a button with his or her index finger. The subjects were told to respond as quickly as possible. At the beginning of the procedure, practice trials were administered to familiarize the subjects with the test. Reaction time was measured after each response. At the end of the task, the mean reaction time was computed.

Selective-attention abilities were assessed by a sign-crossing task. A sheet with 500 meaningless, randomized, mixed-up signs was presented to each subject. Three signs placed at the top of the sheet were designed as targets. The subject was asked to scan the sheet as quickly as possible. For each sign, the subject was asked to cross it if possible, as quickly as possible. The time required to cross all the signs was recorded.
quickly as possible, keeping errors to a minimum, and to cross the target signs each time he or she found one of them. The time used to complete the task was measured as well as the number of correct responses (targets crossed) and false alarms (nontargets crossed).

Focused attention and inhibition abilities were assessed using an adaptation of the Stroop color task. In this task, a list of words printed in colored ink was presented to each subject. First, he or she was asked to read the list of words as quickly and accurately as possible. The time to read the list and the number of reading errors were counted. Afterward, each subject was asked to name the color of ink in which the word was presented. The time to name the colors and the number of naming errors were counted. Interference was evidenced by the time ratio of the 2 parts of the task: time to name the colors/time to read the words.

**Memory**
Episodic memory was assessed by asking the subject to learn and recall a 12-word list. The words were read to the subject at a rate of 1 word every 2 seconds. Immediately after this reading, the subject was asked to recall the words. The number of correct recalls and intrusions was counted. Ten minutes after the free recall, a recognition task was performed. A list of 36 words containing the 12 target words among 24 distractors was presented to each subject; for each word, he or she was asked to say whether or not the word was learned earlier. The number of correct and false recognitions was counted.

Episodic memory was also tested by using an adaptation of the paradigm of Smith and Milner. The subject named and evaluated the price of 16 miniature articles representing real-life objects (eg, chair, chest, bottle of milk); the subject was instructed that a recall of the articles would be asked later. Afterward, the subject was asked to recall most of the previously presented articles. A recognition stage was performed in which the subject was presented a list of 48 words, including the name of the 16 learned articles among 32 distractors. Each word was read to the subject who had to indicate whether or not the article was in the ones presented. Performance was assessed by the number of items correctly recalled during the recall task and the number of correct and false recognitions during the recognition task.

The visuospatial working memory task was assessed using a modified version of the task developed by Peterson and Peterson. The subject was presented with 3 visual meaningless signs that had to be recognized after a delay (7 seconds), during which he or she was distracted by a subsidiary task. The subsidiary task consisted of counting backward by sevens during 7 seconds from a random number given orally by the examiner. At the beginning of the procedure, practice trials were administered to familiarize the subject with the task. The subject was tested on 12 trials. The dependent variables were the number of correct recalls and the number of false recognitions.

### Data Analysis
Data were analyzed using a 1-way ANOVA with a post hoc Student t test to compare the cognitive abilities of the 3 groups. A P value <0.05 was considered statistically significant. Values are reported as mean±SD.

### Results
The mean HITS rate of patients in group 1 was 29 per hour (range 12–60 per hour). There was no significant difference in HITS rate between the left or right MCA (mean paired difference =1.3±1.8). No HITS were observed in groups 2 and 3.

Intellectual level assessed by the WAIS-R with the vocabulary and digital symbol subtests did not significantly differ among the 3 groups: (F(2,33)=0.04, P=NS), (F(2,33)=0.66, P=NS), and (F(2,33)=0.42, P=NS), respectively (Table 1). The results of the cognitive tests are presented in Table 2 for each group.

### Table 2. Scores for Reaction Time, Sign-Crossing Test, Stroop Color Test, and Episodic Memory and Working Memory Tasks

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 MHV</th>
<th>Group 2 Biological Valve</th>
<th>Group 3 Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple reaction time test, sec</td>
<td>0.247±0.63</td>
<td>0.237±0.77</td>
<td>0.243±0.39</td>
</tr>
<tr>
<td>Sign-crossing task</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR (rt)</td>
<td>4.92±1.88</td>
<td>5.25±0.96</td>
<td>5.92±1.24</td>
</tr>
<tr>
<td>FA (rt)</td>
<td>10.0±1.8</td>
<td>9.08±2.02</td>
<td>10.5±1.09</td>
</tr>
<tr>
<td>Time, min</td>
<td>2.0±1.54</td>
<td>1.92±2.06</td>
<td>1.67±1.50</td>
</tr>
<tr>
<td>Stroop color test (1935), time ratio</td>
<td>3.35±1.1</td>
<td>3.28±1.01</td>
<td>3.36±1.8</td>
</tr>
<tr>
<td>Episodic memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-word list</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR (fr)</td>
<td>10.67±1.77*</td>
<td>10.67±1.61</td>
<td>13.58±0.51</td>
</tr>
<tr>
<td>CR (rt)</td>
<td>15.08±0.67</td>
<td>15.75±0.45</td>
<td>15.75±0.62</td>
</tr>
<tr>
<td>FA (rt)</td>
<td>1.0±1.48</td>
<td>0.42±1.16</td>
<td>0.0±0</td>
</tr>
<tr>
<td>16-word list</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR (fr)</td>
<td>3.83±1.58*</td>
<td>5.25±1.48</td>
<td>5.58±1.67</td>
</tr>
<tr>
<td>CR (rt)</td>
<td>5.5±2.43</td>
<td>5.05±1.86</td>
<td>4.5±1.38</td>
</tr>
<tr>
<td>FA (rt)</td>
<td>0.45±1.01</td>
<td>1.48±0.42</td>
<td>1.16±0.58</td>
</tr>
<tr>
<td>FA (fr)</td>
<td>1.0±1.48</td>
<td>0.42±1.16</td>
<td>0.0±0</td>
</tr>
</tbody>
</table>
| CR indicates number of correct responses; FA, number of false alarms; fr, free recall; and rt, recognition tasks. Values are mean±SD. *Values significantly different from controls (P<0.05).
Attention Evaluation
There was no significant difference between the 3 groups concerning the simple reaction time ($F_{2,33}=0.071, P=NS$). The number of correct responses and false alarms was not significantly different across groups for the sign-crossing task ($F_{2,33}=0.35, P=NS; F_{2,33}=0.72, P=NS$). The time required for the task completion did not significantly differ across groups ($F_{2,33}=0.19, P=NS$), and no significant difference was found for the Stroop$^{35}$ interference task ($F_{2,33}=0.07, P=NS$).

Memory Evaluation
Episodic Memory
There was no significant difference between groups for the free recall of the 12-word list ($F_{2,33}=1.55, P=NS$), the number of correct recalls ($F_{2,33}=2.17, P=NS$), or the number of false alarms in the recognition task ($F_{2,33}=2.43, P=NS$). However, there was a significant difference between groups for correct recalls ($F_{2,33}=16.95, P<0.05$), with a lower performance in groups 1 and 2 compared with the control group, as assessed by the paradigm of Smith and Milner.$^{26}$ Post hoc analysis showed significant differences between groups 1 and 3 ($t_{22}=5.47, P<0.01$) and between groups 2 and 3 ($t_{22}=5.96, P<0.05$) but no differences between groups 1 and 2. The recognition task did not differ across groups in the number of correct responses ($F_{2,33}=1.36, P=NS$) or false alarms ($F_{2,33}=2.57, P=NS$).

Working Memory
There was a significant difference between groups in the number of correct responses for the working memory task ($F_{2,33}=4.13, P<0.05$), with a lower performance in group 1 (Table 2). Post hoc analysis showed that the performance in group 1 was lower compared with group 2 ($t_{22}=2.26, P<0.05$) and the control group ($t_{22}=2.63, P<0.05$).

Discussion
Doppler ultrasonography has been used for years to investigate gas bubbles in blood vessels under various circumstances.$^{28-31}$ and more recently to detect formed element emboli.$^{32,33}$ In experimental studies, it has been demonstrated that various embolic materials, including fat, gas, and thrombus and platelet aggregates, can be detected with ultrasonography.$^{34}$ The power of backscattered ultrasound and thrombus and platelet aggregates, can be detected with a sharp MHV motion, creating a local, transient, high-pressure gradient that may cause a cavitation-like phenomenon, especially during closure, as demonstrated in vitro.$^{6}$ Microbubbles can survive in the vessels, as demonstrated by decompression follow-up$^{29}$ or detection of echo contrast agents far from the injection site, and therefore can be detected in the arteries, downstream to the prosthesis.

From the literature, it seems that some cognitive abilities are impaired in up to two thirds of patients in the early stages after coronary artery bypass grafting compared with the preoperative status.$^{18}$ The origin of the cerebral injury after cardiac surgery is probably multifactorial and is still being debated,$^{43}$ because the neuropsychological impairment observed in open heart patients can be caused by both the severe preexisting cardiac disease and the cardiac surgical procedure itself. However, the cause seems mainly related to prolonged or severe hypoperfusion and to gaseous emboli from the bypass circuit.$^{11,12}$ The cognitive impairments are reversible in some patients but not in others, in whom impairment still can be observed 2 months$^{17}$ or 6 months$^{44}$ later. The cognitive impairment severity seems to be causally related to the bypass duration and the number of microemboli delivered during surgery.$^{16}$ Because gaseous microemboli delivered during the course of a few hours (duration of surgery) are able to induce some transient or even persisting neuropsychological alterations, it may be hypothesized that the chronic microembolization occurring in patients with an MHV can induce comparable effects. These neurological effects are possibly related to the memory complaints reported by the patients with an MHV.

The present study was designed with 2 control groups. A true control group was composed of healthy subjects to obtain reference values; this is mandatory when nonstandard neuropsychological tests are used and when normative data are not available. The second control group was composed of patients with a biological valve prosthesis implanted. These subjects underwent a similar surgical procedure compared with the subjects who had an MHV implanted. Moreover, the preoperative medical history and disease were similar for the patients of these 2 groups. The formation of the second control group was necessary because it is difficult to have a group of patients with an MHV and free of HITS, whereas most patients with normal biological prostheses do not have a normal heart valve. Therefore, a group of patients with only an MHV and not with a biological valve prosthesis was necessary.

There was a significant difference between groups in the number of correct responses ($F_{2,33}=22.89, P<0.05$) but no differences between groups 1 and 2. The recognition task did not differ across groups in the number of correct recalls ($F_{2,33}=2.17, P=NS$) or false alarms ($F_{2,33}=2.57, P=NS$).

Embolic Sources
The embolic sources are likely to be due to large solid emboli or gaseous bubbles that have a high-ultrasound reflectivity. Several arguments have been made in favor of a gaseous origin of HITS associated with MHV and have been previously discussed.$^{4}$ Among these arguments, the lack of relationship between the degree of anticoagulation, antithrombotic, or antiplatelet therapy and the HITS rate must be highlighted.$^{37-39}$ Moreover, microembolic signals are not observed in normally functioning biological valves.$^{40}$ A low HITS rate has however been reported in patients with biological prostheses. It must be stressed that in these reports there was no valve nor carotid control, and the microemboli observed could be of a solid nature.$^{41}$

It can be assumed that microbubbles are generated by the sharp MHV motion, creating a local, transient, high-pressure gradient that may cause a cavitation-like phenomenon, especially during closure, as demonstrated in vitro.$^{6}$ Microbubbles can survive in the vessels, as demonstrated by decompression follow-up$^{29}$ or detection of echo contrast agents far from the injection site, and therefore can be detected in the arteries, downstream to the prosthesis.
Milner.26 In this paradigm, the subjects must name the 
but only as assessed with the procedure of Smith and 
produced by an MHV is of a different nature.

The brain aggression provoked by the acute microembo-
ment in attentional performance was not found in the present 
study nor was there a slowing of patient responses in the 
reaction time test. It must be emphasized that the reaction 
time test used in the present study involved only simple 
stimuli and simple motor responses whereas other investiga-
tors have used reaction time tests involving more complex 
cognitive processes.17 The discrepancy between the results 
then can be attributed to different memory loads or different 
general difficulty levels of the tasks. Nevertheless, because 
the time of the postoperative testing interval is longer than in 
the previous studies (32 months), the observed normal atten-
tional performance could be due to a progressive reversibility 
of the impaired process. Otherwise, this reversibility implies 
that the brain aggression provoked by the acute microembo-
larization during ECC and the chronic microembolization 
produced by an MHV is of a different nature.

For episodic memory, a lower performance was observed in the 
2 groups of patients with prosthetic valves implanted 
but only as assessed with the procedure of Smith and 
Milner.26 In this paradigm, the subjects must name the 
presented objects and evaluate the price. Thus, the encoding 
process is double (visual and verbal) and deeper compared 
with the 12-word list test. In healthy control subjects, this 
encoding process resulted in a higher percentage of recalled 
items in the paradigm of Smith and Milner compared with the 
12-word list test. On the contrary, patients with prosthetic 
valves implanted performed worse and did not seem to 
benefit from the deeper encoding process. The difference 
between the results in controls and patients could be inter-
preted as a difference in encoding strategy. Therefore, the 
long-term memory impairment observed in the 2 groups of 
patients with prosthetic valves could be attributed to a 
common surgical event that is probably an ECC effect.

The task of Peterson and Peterson57 used in the present 
study has been shown to be highly sensitive to the effects of 
brain injury.48 The results obtained with this task point out a 
short-term memory deficit in the patients with an MHV 
whereas patients with biological valves and controls present 
comparable performance. Because of time constraints for the 
subjects, the design of the neuropsychological test battery did 
not address all the subsystems of the short-term memory 
declared in the model of Baddeley.19 Consequently, it is not 
possible to adequately identify the specific components of the 
model that may be affected by the presence of an MHV 
prosthesis. Whatever the exact mechanism, this impairment 
hits an important clinical implication because it could be 
related to the presence of repeated microemboli in patients 
with an MHV. It must be stressed that microemboli produc-
tion is causally related to the mechanical properties of the 
prosthesis and that its prevalence is high in any type of 
commercially available mechanical valve.

Nevertheless, the small size of the groups in the present 
study does not allow for definite conclusions and does not 
yield the possibility of determining a relationship between the 
HITS rate and the degree of cognitive impairment. A serial 
study that is based on this experiment and that uses a refined 
battery of tests is currently being conducted to analyze the 
cumulative effects of microemboli on brain morphology and 
cognitive functions and to specify the components of the 
Baddeley9 memory model that are affected.

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