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

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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
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.7,8 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.19 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,20 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 and pairing criteria and were then assigned to 1 of 3 groups according to their heart valve status: group 1, 12 patients with 1 or 2 MHVs implanted and exhibiting HITS in both the left and right MCA; group 2, 12 patients with a biologic heart valve implanted and presenting no HITS; and group 3, 12 healthy control subjects, with no prostheses.

The noninclusion criteria were defined to eliminate cerebrovascular risk factors and neurological and psychological disorders. Patients with prior history of stroke, multiple sclerosis, vascular disorders with possible cerebral affection, diabetes mellitus, general psychiatric disorders, illiteracy, and pharmacological treatment known to interfere with cognitive performance were excluded on the basis of a neurological examination. Patients were then submitted to clinical and echographic cardiac examinations to exclude patients with arrhythmia, hypertension, cardiac insufficiency, dysfunction of the prosthesis, or presence of any other cardiac embolic source. Duplex carotid examination was performed to exclude subjects with significant carotid atheroma (>70% stenosis or heterogeneous and irregular plaques), which is the most common extradural source of cerebral microemboli.21 Blood tests were performed on MHV patients to ensure the efficiency of anticoagulation therapy. Patients with an international normalized ratio <3 were excluded. Because anxiety may affect neuropsychological performance, the anxiety test of Catell22 was administered to all subjects, and they were excluded if their scores reached the pathological anxiety level.

Patients in group 1 had a St. Jude prosthesis (St. Jude Medical, Inc) implanted in either the mitral (5 subjects) or the aortic position (5 subjects) or in both the mitral and aortic positions (2 patients). Mean time from implantation was 32 months (range 12–76 months). The prosthesis size ranged from 27 to 31 in the mitral position and from 21 to 25 in the aortic position.

Patients of group 2 had a Carpentier-Edwards prosthesis (Baxter Inc) implanted in the mitral position (7 subjects) or a Carpentier-Edwards prosthesis (2 subjects) and a Toronto SPV prosthesis (St. Jude; 3 subjects) implanted in the aortic position. Mean time from implantation was 39 months (range 18–88 months).

Subjects in the 3 groups were matched for age and verbal intellectual abilities obtained by administering the vocabulary subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R).23 This test estimates the global intellectual function that is not expected to change after a cardiac operation. Basic clinical and neuropsychological data are provided in Table 1.

Microemboli Detection

Each subject was submitted to a transcranial sonographic examination of the left and right MCA, with the use of Acuson 128XP equipment (Acuson) and a 2-MHz sector scanning probe. The transcranial Doppler study was performed in the pulsed Doppler mode, with the guidance of color Doppler imaging. The MCA was imaged through the temporal acoustic window. The sample volume of the pulsed Doppler was placed in the first segment of the vessel, at approximately 50 mm deep; its length was 5 mm. Real-time spectrum analysis of the Doppler signal was continuously recorded for 10 minutes on each side. The Doppler spectrum and audio signals were recorded on videotape and analyzed off-line by an independent observer who was blinded to the clinical status of the subjects.

The gain of the spectrum analyzer was set up to a low value to obtain a background Doppler signal within a few color levels. The 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, 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. 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 the subject; for
each word, he or she was asked to say whether or not the word was
presented. The subject was presented with 3 visual meaningless signs that had
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: \( F_{2,33} = 0.04, P = \text{NS}, \) \( F_{2,33} = 0.66, P = \text{NS}, \) and \( F_{2,33} = 0.42, P = \text{NS}, \) respectively (Table 1). The results of the cognitive tests are presented in Table 2 for each group.

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.

| TABLE 2. Scores for Reaction Time, Sign-Crossing Test, Stroop Color Test, and Episodic Memory and Working Memory Tasks |
|-----------------------------------------------|-----------------|-----------------|-----------------|
|                                                | Group 1         | Group 2         | Group 3         |
|                                                | MHV             | Biological Valve| Controls       |
| Simple reaction time test, sec                | 0.247±0.63      | 0.237±0.77      | 0.243±0.39      |
| Sign-crossing task                            |                 |                 |                 |
| CR                                             | 155.33±24.64    | 157.08±23.05    | 161.58±13.01    |
| FA                                             | 0.58±0.9        | 0.92±1.16       | 0.58±0.9        |
| Time, min                                      | 8.57±2.5        | 9.86±3.57       | 9.04±2.49       |
| Stroop color test (1935), time ratio           | 3.35±1.1        | 3.28±1.01       | 3.36±1.8        |
| Episodic memory                               |                 |                 |                 |
| 12-word list                                   |                 |                 |                 |
| CR (fr)                                        | 4.92±1.88       | 5.25±0.96       | 5.92±1.24       |
| CR (rt)                                        | 10.0±1.8        | 9.08±2.02       | 10.5±1.09       |
| FA (fr)                                        | 2.0±1.54        | 1.92±2.06       | 1.67±1.50       |
| 16-word list                                   |                 |                 |                 |
| CR (fr)                                        | 10.67±1.77*     | 10.67±1.61*     | 13.58±0.51      |
| CR (rt)                                        | 15.08±0.67      | 15.75±0.45      | 15.75±0.62      |
| FA (fr)                                        | 1.0±1.48        | 0.42±1.16       | 0.0±0           |
| Working memory                                |                 |                 |                 |
| CR                                             | 3.83±1.58*      | 5.25±1.48       | 5.58±1.67       |
| FR                                             | 5.5±2.43        | 5.05±1.86       | 4.5±1.38        |

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 \( (F_{2,33} = 0.071, P = \text{NS}) \). The number of correct responses and false alarms was not significantly different across groups for the sign-crossing task \( (F_{2,33} = 0.35, P = \text{NS}; F_{2,33} = 0.72, P = \text{NS}) \). The time required for the task completion did not significantly differ across groups \( (F_{2,33} = 0.19, P = \text{NS}) \), and no significant difference was found for the Stroop \( (F_{2,33} = 0.07, P = \text{NS}) \).

Memory Evaluation
Episodic Memory
There was no significant difference between groups for the free recall of the 12-word list \( (F_{2,33} = 1.55, P = \text{NS}) \), the number of correct recalls \( (F_{2,33} = 2.17, P = \text{NS}) \), or the number of false alarms in the recognition task \( (F_{2,33} = 2.43, P = \text{NS}) \). 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. 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 \( (F_{2,33} = 1.36, P = \text{NS}) \) or false alarms \( (F_{2,33} = 2.57, P = \text{NS}) \).

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 depends, to a large extent, on the size and acoustic impedance of particles in the blood. When circulating emboli are either much larger, eg, formed emboli, or of greatly different acoustic impedance, eg, gas microbubbles, than individual blood cells, they result in an increased Doppler signal power that can be easily detected, the so-called HITS. \( 35 \) The embolic events may occur, and HITS may be detected in different vascular regions, depending on the location of the embolic source, and in any vascular bed, if a cardiac source is concerned. However, special attention has been focused on the cerebral circulation because stroke is a major concern.

HITS are commonly reported in the cerebral circulation of patients with MHVs. \( 34 \) The embolic signals recorded from these patients have been described as being more intense than those found in patients with other potential embolic sources \( 2,36 \) and thus 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. \( 37 \) Among these arguments, the lack of relationship between the degree of anticoagulation, antithrombotic, or antiplatelet therapy and the HITS rate must be highlighted. \( 38,39 \) 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. \( 41,42 \)

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. \( 42 \) Microbubbles can survive in the vessels, as demonstrated by decompression follow-up or detection of echo contrast agents far from the injection site, \( 42 \) 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. \( 43 \) The origin of the cerebral injury after cardiac surgery is probably multifactorial and is still being debated, \( 44 \) 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 \( 45 \) 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
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Milner.26 In this paradigm, the subjects must name the but only as assessed with the procedure of Smith and in the 2 groups of patients with prosthetic valves implanted production by an MHV is of a different nature. lization during ECC and the chronic microembolization that the brain aggression provoked by the acute microembolization for 12 to 76 months.

The neuropsychological tests used in this study concern the cognitive abilities that are likely to be affected after cardiac surgery.46,47 eg, psychomotor speed, attention, and new learning abilities. Parts of these tests derived for the present study have been described in the experimental cognitive literature. Contrary to previous postcardiac surgery studies, a decrement 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 used in the present study involved only simple stimuli and simple motor responses whereas other investigators 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 attentional performance could be due to a progressive reversibility of the impaired process. Otherwise, this reversibility implies that the brain aggression provoked by the acute microembolization 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 interpreted 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 Peterson 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 defined 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 prostheses. Whatever the exact mechanism, this impairment has 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 production 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 Baddeley memory model that are affected.

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References
Cognitive Abilities and MHV


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