Neuropsychological Deficits after Mechanical Aortic Valve Replacement

Jennifer Uekermann[1], Boris Suchan[1], Irene Daum[1], Samer Kseibi[2], Mathias Perthel[2], Joachim Laas[2]

[1]*Institute of Cognitive Neuroscience, Ruhr-University of Bochum,* [2]*Department of Cardio-Thoracic Surgery, Herz-Kreislauf-Klinik Bevensen, Bad Bevensen, Germany*

Background and aim of the study: **Studies using transcranial Doppler monitoring have identified high-intensity transient signals (HITS) after mechanical valve replacement. Although cognitive dysfunction in relation to HITS was reported in some studies, the current data basis is inconsistent. The study aim was to investigate the long-term effects of HITS on cognitive function.**

Methods: **Forty patients who had undergone mechanical valve replacement (mean 5.3 years previously) participated in the study. HITS-measurements were performed on the day of neuropsychological assessment. Patients were allocated to HITS-high and HITS-low groups on the basis of the median HITS-rate. Both patient groups completed a neuropsychological test battery and were compared to healthy controls.**

Results: **Both patient groups showed verbal and visual memory deficits in comparison with controls. The HITS-high group scored lower on verbal memory compared to the HITS-low group. In addition, the HITS-high group showed executive deficits when compared to the HITS-low group and controls. The significant effects with respect to verbal memory and executive functions remained after extracorporeal circulation time differences were controlled for.**

Conclusion: **The study results imply that heart valve replacement with mechanical prostheses may be associated with mild cognitive impairment. The differential impairment pattern of the high- and low-HITS groups further suggests that the number of HITS may be of critical importance. The observed memory impairments were consistent with the view that cognitive dysfunction after valve replacement may be due to temporal lobe dysfunction. However, future studies are required to investigate the association of number of HITS, cerebral changes and cognitive function in further detail.**

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Investigations using transcranial Doppler monitoring have identified so-called high-intensity transient signals (HITS) in connection with mechanical valve replacement (1-3). HITS have been named after their physical characteristics (sound, intensity and duration) (4). It has been shown recently that the number of HITS after mechanical valve replacement depends on the design, type and orientation of the mechanical heart valve implanted (3,5,6).

Although the exact nature of HITS produced by mechanical heart valves is still under debate, recent investigations have focused on their functional and clinical significance. The first study of neuropsychological deficits in patients with mechanical valve substitutes was conducted by Deklunder et al. (7). The authors reported significant working memory impairments associated with the presence of microemboli. This result has been interpreted in terms of a frontotemporal mediation of working memory and a selective vulnerability of hippocampal neurons to transient hypoxia (8). However, further published data regarding the clinical relevance of HITS are controversial. Jacobs et al. (9) observed alterations of neuropsychological functions between eight and 12 days postoperatively, with a recovery within three months; there was no relation to HITS frequency. Nadareishvili et al. (10) also did not observe correlations between HITS rate and cognitive performance, and concluded that HITS represent harmless epiphenomena.

An important issue concerns the time since surgery and the time of assessment of HITS. The mean time from implantation in the study by Deklunder et al. (11) was 32 and 39 months, respectively. In the investiga-

Address for correspondence:
Jennifer Uekermann, Faculty of Psychology, Institute of Cognitive Neuroscience, GAFO 05/607, Ruhr-University of Bochum, 44780 Bochum, Germany
e-mail: Jennifer.Uekermann@ruhr-uni-bochum.de

tion by Jacobs et al. (9), patients were tested after eight days, 12 days and 3 months. Since it is possible that the extent of brain dysfunction related to HITS is accumulative, the time since surgery might be of critical relevance. The investigation of long-term effects after cardiac surgery is particularly relevant in the light of investigations which have shown that cognitive dysfunction is present in up to 42% of patients at five years after coronary artery bypass surgery (12,13).

Assessment of HITS was performed during surgery by Jacobs et al. (9), and at the time of testing by Deklunder et al. (11). Thus, the non-significant associations of HITS and cognitive changes in the former study (9) could be due to the fact that HITS were related to the intraoperative cardiac status rather than to long-term status. This assumption is consistent with the finding by Kofidis et al. (14), who observed a significant correlation between HITS-rate and postoperative time.

In the present study, the association of HITS following mechanical valve replacement with cognitive deficits was investigated by using a comprehensive neuropsychological test battery which included intellectual functioning, affective variables, attention and psychomotor speed, working and long-term memory and executive functions. As the study focused on long-term changes, patients were tested several years after surgery, at a time when the acute effects of surgery had disappeared. The analysis included a comparison of patients with a high number of HITS (HITS-high) and low number of HITS (HITS-low). HITS were measured on the day of cognitive assessment.

Clinical material and methods

Patients

Forty patients (30 males, 10 females; mean age 62.4 years; range: 47 to 77 years) were selected randomly from the Valve Register of the Herz-Kreislauf-Klinik, Bad Bevensen, Germany. The patients had undergone mechanical aortic valve replacement at an average of 5.3 years (range: 2.7 to 7.7) years before testing. Among the patients, 33 had bileaflet valves (28 St. Jude Medical, five CarboMedics), and seven had tilting disk valves (Medtronic-Hall). The mean extracorporeal circulation (ECC) time was 63.03 min (range: 37 to 124 min).

Pre-selection was performed according to the following inclusion criteria. All patients had undergone an isolated aortic valve replacement in optimum orientation, without any concomitant procedures. In addition, all patients were in sinus rhythm and had received effective oral anticoagulation (International Normalized Ratio (INR) >2.0).

All patients suffered from acquired aortic valve disease, there being no congenital lesions. The ratio of aortic stenosis:aortic regurgitation:combined aortic valve lesion was 20:8:12.

All patients underwent assessment with respect to their history of cardiac disease and past medical history. Echocardiography, performed on the day of neuropsychological assessment, was conducted to assess the implanted prosthesis and left ventricular function.

Since carotid and coronary artery disease, as well as atrial fibrillation, are associated with HITS, patients were excluded if they suffered from these disorders, as proven by duplex examination of the external cerebral arteries, by preoperative coronary angiography and actual stress electrocardiography. Further exclusion criteria included a history of stroke, hypertension, psychiatric illness, alcoholism, diabetes, renal disease (defined as a creatinine level >1.0 mg/dl) and active liver disease (defined by abnormal GOT, SGPT, γ-GT). The INR was in the therapeutic range (>2.5).

HITS measurements

HITS measurements were performed on the day of neuropsychological assessment by two independent investigators who were blinded to the valve design used.

A Pioneer TC 4040 (Pioneer, Medilab, Würzburg, Germany) transcranial ultrasound device fitted with 2-MHz probes (Nicolet, Estenfeld, Germany) was used for bilateral HITS detection in the middle cerebral artery (MCA). Initially, online recording was performed using the FS1-algorithm, while data confirmation was obtained by a following offline run of the recorded visual and acoustic signals through a second independent investigator (15).

For the detection of HITS, the MCA was monitored bilaterally for 30 min with 2-MHz probes through the temporal bone window. The probes were connected with a Doppler sonography device (Pioneer TC 4040), allowing online recording.

Only unidirectional signals within the Doppler velocity spectrum with an intensity of 3 dB HTL higher than the background flow signal, lasting less than 300 ms were counted as HITS (15).

Recording and evaluation were performed online, and confirmed by visual and acoustic controls. The performance of this algorithm has been shown to be comparable to that of individual human experts, and only slightly below the mean performance of such a panel (16). All signals were saved onto a hard disc.

Subsequently, on the basis of the median HITS-rate, patients were allocated to either a HITS-high group (n = 21; range: 42 to 531 HITS/h) or a HITS-low group (n = 19; range: 0 to 30 HITS/h). The mean ECC time during surgery was 56.0 ± 12.9 min for the HITS-high group, and 69.4 ± 21.2 min for HITS-low group (p = NS).

Neuropsychological assessment

Neuropsychological investigations were performed by independent neuropsychologists who were blinded to the valve design and HITS frequency.

The control group comprised 17 healthy subjects who were recruited by advertisement and excluded from the study if they had any history of head trauma, substance abuse, psychiatric or neurological illness, or were taking medication with central nervous side effects. The demographic variables and general intellectual abilities of the three groups are listed in Table I.

The patients were comparable to healthy controls with respect to age, education and an estimate of general intellectual ability (see below).

After having provided their consent to participate in cognitive assessment, patients and healthy controls completed the following neuropsychological test battery.

General intellectual abilities and mood

All subjects completed a short version of the Wechsler Adult Intelligence Scale (WIP) (17), including the subtests 'general knowledge', 'similarities', 'picture completion' and 'block design'. Depression was assessed by means of the Beck Depression Inventory (18).

Attention and psychomotor speed

To assess attention, psychomotor speed and cognitive flexibility, the Trail Making Test (19) was administered. This test includes two conditions. In the first condition (A), a sheet of paper including numbers is placed in front of the subject, who is asked to connect digits in ascending order by straight lines. In the second condition (B), number and letters are presented on the paper. The subject is asked to alternately connect numbers and letters (1 to A, 2 to B, and so on) in ascending order. Analysis includes the total time in the first (A) and second (B) condition.

Short-term and working memory

To assess short-term memory, the digit span subtest of the Wechsler Adult Intelligence Scales-Revised (20) was used. In the forward condition, sequences of numbers read out by the experimenter must be repeated. In the backward task, digit sequences must be reproduced in reverse order. Two performance scores are calculated reflecting the number of correctly reproduced sequences for the forward, as well as the backward, condition.

Verbal memory

Verbal memory was assessed using a German version of the California Verbal Learning Test (21). A list of 16 words is read aloud by the experimenter, and the subject is instructed to remember as many words as possible. The list is then re-read for four further trials, and the subject is instructed to repeat as many words as possible after each trial. The overall number of remembered items across the five trials is assessed.

In addition, the subtest Logical Memory (LM) from a German version of the Wechsler Memory Scale (22) was administered to assess verbal memory. A story is read aloud by the experimenter, and the subject is instructed to reproduce it from memory immediately after presentation, and also after a 30-min delay. The sum of correctly repeated items is determined for the immediate (LMi), as well as the delayed (LMd), condition.

Visual memory

Visual memory was assessed by means of the Rey Osterrieth Figure (23), a geometrical figure. The subject is instructed to copy the figure and to reproduce it from memory after a 40-min delay. The number of correctly reproduced details was assessed.

Executive function

Verbal fluency: Three verbal fluency subtests were administered (24). The first part requires the production of a maximum number of country names within a time limit of 1 min (semantic condition). In the second condition, as many nouns as possible beginning with the letter 'b' must be produced (phonemic condition) within 1 min. In the third subtest, subjects are instructed to alternately produce male first names and vegetables (alternate condition) within 1 min. The number of correct exemplars across the three tasks is analyzed.

Data analysis

Data relating to the HITS-high, HITS-low and control subjects were compared by ANOVAs, followed by Tukey tests. As both groups differed significantly with respect to ECC time, covariance analyses with ECC time as covariate were also calculated.

Results

General intellectual functioning and affect

The results of general intellectual functioning are listed in Table I. No significant inter-group differences were found with respect to age, education, depression scores and general intellectual functioning.

Attention and psychomotor speed

The results of the Trail Making Test are listed in Table I. The analysis did not reveal any significant inter-group differences for test scores A and B (both p = NS).

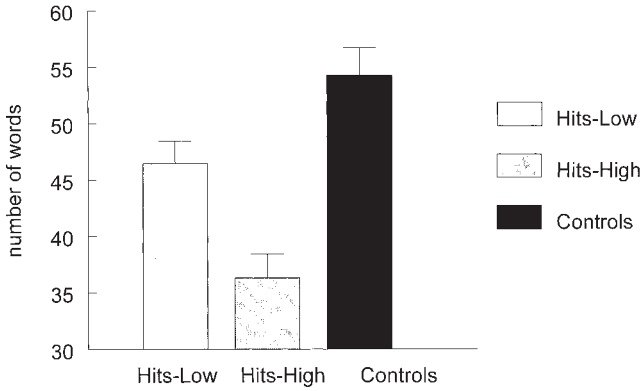

Figure 1: Results of word list recall (values are mean ± SEM).

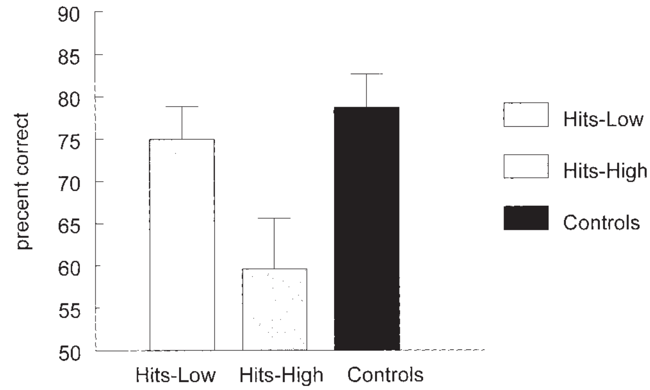

Figure 2: Results of story retention (values are mean ± SEM).

Short-term and working memory

The results for the forward and backward conditions of the digit spans are listed in Table I. Analysis of the digit spans revealed significant inter-group differences for the forward ($F(2,54) = 3.11$; $p = 0.05$) as well as the backward condition ($F(2,54) = 4.60$; $p = 0.02$). Subsequent paired comparisons showed that both patient groups reproduced significant shorter spans in the backward condition compared to controls (both $p < 0.03$), while the HITS-high group showed a tendency for lower scores in the forward condition ($p < 0.06$) compared to controls.

Verbal memory

The results of the overall recall of word lists across the five trials are shown in Figure 1. Group comparisons revealed significant inter-group differences for the overall score across the five trials ($F(2,54) = 20.69$; $p < 0.001$), which were due to lower scores of both patient groups in comparison with controls (both $p = 0.02$). In addition, HITS-high group reproduced fewer words than the HITS-low group ($p < 0.001$).

The results for retention (percent correctly reproduced items) for story recall are illustrated in Figure 2. Group comparisons showed significant differences ($F(2,54) = 4.44$; $p = 0.02$), which were due to impaired performance of the HITS-high group compared to controls ($p = 0.02$).

Visual memory

The results for the recall condition of the Rey Osterrieth Figure are shown in Table I. Post hoc group comparisons yielded significant inter-group differences ($F(2,54) = 6.48$; $p = 0.003$), which were due to significantly lower scores of both patient groups compared to controls (both $p < 0.05$)

Executive function

The results for verbal fluency are shown in Figure 3. Analysis yielded significant inter-group differences

Table I: Demographic data, clinical variables and results of cognitive tests in the three groups.

Parameter	Controls	HITS-low	HITS-high	p-value
No. of patients	17	19	21	
Age (years)*	62.8 ± 6.8	63.1 ± 7.7	61.8 ± 7.3	0.85
Education*	9.6 ± 2.0	9.3 ± 1.9	8.9 ± 1.3	0.42
IQ*	114.7 ± 11.9	113.0 ± 12.9	106.3 ± 14.2	0.12
Depression*	5.8 ± 5.0	7.5 ± 6.0	8.0 ± 6.3	0.51
HITS+	-	9.9 (0-30)	146.1 (42-531)	<0.0001
Trail Making Test A*	42.65 ± 23.35	42.84 ± 15.32	53.92 ± 20.88	0.14
Trail Making Test B*	106.12 ± 36.57	117.13 ± 52.91	107.52 ± 56.64	0.76
Digit spans forward*	8.29 ± 1.65	7.00 ± 1.97	6.81 ± 2.13	0.05
Digit spans backward*	6.65 ± 1.87	5.26 ± 1.41	5.29 ± 1.42	0.02
Rey Osterrieth Figure*	20.2 ± 4.3	12.8 ± 5.9	15.1 ± 7.9	0.003

*Values are mean ± SD.
+Values are mean (range).

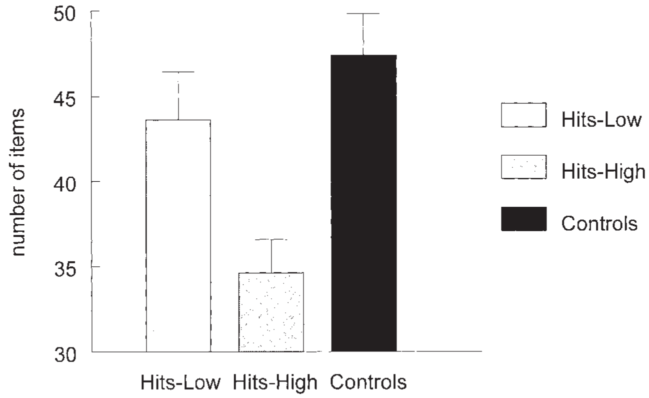

Figure 3: Results of verbal fluency (values are mean ± SEM).

(F(2,54) = 7.68; p = 0.001), which were due to significantly lower scores of the HITS-high group compared to controls (p = 0.001) and to the HITS-low group (p = 0.023).

Influence of ECC time

Covariance analyses with ECC time as covariate yielded significant group effects for word list recall (p = 0.01) and executive function (p = 0.04). In addition, a tendency for story retention was observed (p = 0.08).

Discussion

The results of the present investigation suggest that HITS following mechanical heart valve replacement may be associated with cognitive dysfunction relative to healthy controls. Patients with high and low HITS counts showed working and visual memory problems, but those with a high HITS rate had additional verbal memory and executive impairments.

The finding of impairments in both clinical groups compared to controls suggests that heart valve replacement with mechanical valves may lead to mild cognitive dysfunction. However, in the presence of a high number of HITS (>30 per hour), patients suffered from both quantitatively and qualitatively stronger impairments than those with a low number of HITS. The differential impairment pattern thus suggests that the number of HITS might be of importance. These results are at variance with those investigations which have reported a lack of association between HITS and clinical status or neuropsychological impairments (9,10,14), though in the latter studies neurological standard assessments or dementia rating scales were used, or healthy control subjects were not included. The rating scales in question may have been too insensitive for the detection of more subtle cognitive deficits, which may be relevant for functioning in everyday life. In addition, in the present study HITS measurement was conducted on the same day as the neuropsychological assessment. Cognitive testing was performed on average 5.3 years after surgery, at a time when the acute effects of surgery played no role.

Both patient groups also differed with respect to ECC time. A decline in cognitive function has been associated with ECC (11), and consequently the observed deficits may have been due to group differences in ECC time. However, covariance analyses showed that the significant effects with respect to verbal memory and executive functions were still found when ECC time differences were controlled for.

The results of the present study were consistent with previous findings of an association between the number of HITS and neuropsychological deficits after coronary bypass operation and valve replacement (7,11). In the present investigation, patients showed visual and verbal memory deficits and were impaired with respect to verbal fluency, which requires rule-based retrieval from semantic memory. Memory functions depend on the integrity of medial temporal structures. HITS may be associated with cerebral changes of medial temporal structures. This assumption is consistent with animal and cell culture studies, which imply a selective vulnerability of hippocampal neurons to transient hypoxia (8). In addition, Herrmann et al. (25) reported the release of neuron-specific enolase, a neurobiochemical marker of neuronal damage in patients after valve replacement. This suggests that cognitive dysfunction after mechanical valve replacement may be due to temporal lobe dysfunction.

In future, brain imaging studies which focus on the association of HITS and cognitive function after valve replacement are desirable. Jacobs et al. (9) investigated HITS and cognitive function in patients after coronary artery bypass grafting (CABG). In that study, the number of HITS did not correlate with cognitive alterations, but rather with regional changes of cerebral metabolic rate of glucose. However, the individual regions maximally affected differed between patients. These authors concluded that cognitive change depended more on the location of HITS-related brain damage than on the number of HITS per se (9). However, due to the lack of a healthy control group, the implications of these data assessed in CABG patients for the question of HITS and cognitive change after valve replacement are limited.

In conclusion, the results of the present study showed that mechanical valve replacement is associated with mild cognitive changes, which tends to be exacerbated by a higher number of HITS. Future imaging and neuropsychological studies are, however, desirable to investigate the association of valve type, the number of

HITS, cerebral changes and cognitive function in further detail.

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