Clinical relevance of intracranial high intensity transient signals in patients following prosthetic aortic valve replacement

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Abstract

Objectives: There has been frequent report on transcranially detected microembolic signals (HITS) following cardiac surgery using extracorporeal bypass support. The clinical relevance of HITS, however, has yet to be clarified. The incidence of thromboembolic events is increased following mechanical heart valve replacement. The purpose of this study was to quantify postoperative HITS after implantation of two types of prosthetic aortic valves and to compare both types of mechanical valves with respect to the generation of HITS. In addition, HITS rates were correlated with clinical, echocardiographical and laboratory findings.

Methods: Forty-two patients following implantation of either a Sorin Biomedica mechanical valve (n = 22, group A) or a Tekna Duromedics mechanical valve (n = 20, group B) were examined. A group of ten healthy volunteers served as control. Clinical, echocardiographic, carotid artery duplex and laboratory examinations were performed in all patients. A 60 min bilateral transcranial doppler monitoring of the medial cerebral artery (MCA) was also carried out in order to evaluate cerebral blood flow.

Results: In group A 14 of 22 patients were positive for HITS (53%), with an average of 16.4 ± 19 HITS/pt.h. In group B 15 of 20 patients were HITS positive (75%) with an average amount of 14.4 ± 24 HITS/pt.h. The incidence of HITS was not significantly different between the two groups. No correlation was seen between the HITS-rate/h and neurological findings, duplex sonographic results, mechanical valve size and anticoagulation regimen (P > 0.05). However, a negative correlation was observed between patient age and HITS-rate (P = 0.02) as well as between the NYHA degree and HITS-rate (P = 0.018). The HITS-rate also correlated with postoperative time (P = 0.04). No HITS were detected in the control group.

Conclusions: HITS do not correlate with the individual clinical status and, thus, cannot predict the occurrence of neurological deficits in patients following mechanical aortic valve implantation.

Keywords: High intensity transient signals; Thromboembolism; Aortic valve replacement; Mechanical valves

1. Introduction

The number of thromboembolic complications following mechanical aortic valve replacement is low [1,2]. Currently, the clinical relevance of the detection of microembolic signals after mechanical heart valve implantation is intensively discussed [3,4].

Transcranial doppler monitoring has frequently been employed to detect microemboli in patients with atrial fibrillation, symptomatic carotid artery stenosis, acute stroke, acute myocardial infarction, ventricular aneurysm and rheumatic heart disease [5–10]. Such in vivo investigations have revealed so called high intensity transient signals (HITS); named after their physical characteristics, which are sound, intensity and duration [11–15]. It is not clear whether HITS are induced by solid elements such as thrombotic aggregates or gas bubbles. The latter are generated under hemodynamic stress due to turbulent blood flow at the valvular level [16]. These turbulences are caused by cavitation at areas of high shier stress and high pressure gradients [17–20].

The aims of this study were, first, to quantify the amount of HITS generated following aortic mechanical valve replacement comparing two commonly implanted bileaflet prosthetic valves—the Sorin Biomedica and the Tekna Duromedics mechanical valve. Secondly, we correlated the quantity of HITS with clinical, echocardiographic and laboratory parameters. Third, factors that support the generation of HITS are determined.
2. Materials and methods

Data from 42 consecutive patients were recorded prospectively. Prior to their inclusion into the study, informed consent was obtained from all patients. Three study groups were formed. Group A consists of 22 patients that received a Sorin Biomedica® (Sorin Biomedica Cardio, Saluggia, Italy) bileaflet prosthesis in aortic position. In group B, a Tekna Duromedics® (Edwards Lifesciences Corp, Irvine, CA) prosthesis was implanted into 20 patients in aortic position. All prostheses were implanted in a 200–270° position as recommended by the manufacturers. The control group (group C) included ten healthy volunteers. The demographic data are depicted in Table 1. All groups were comparable regarding age; groups A and B were comparable regarding age, underlying disease, postoperative course, medication and accompanying diseases. In all study patients cardiological and neurological examinations were performed. Carotid artery duplex examination was performed using the Hewlett Packard 77025A equipment (Hewlett Packard, Dallas, TX). All patients were in sinus rhythm at the time of operation and none did carry a pacemaker. The New York Heart Association classification (NYHA) was used to score the degree of heart failure. A bilateral transcranial doppler monitoring of the medial cerebral artery (Medasonics® CDS, Newark, NJ) was performed in all patients. For this purpose the patient was placed in supine position and two 2-MHz ultrasound transducers were attached bitemporally over the preauricular transcranial ‘window’. The insonation depth was adjusted to the best possible doppler signal. The power was set at 30%, the range of sensitivity was individually adjusted depending on the doppler signal. Acoustic signals were recorded for offline analysis. In order to achieve most accurate results, all HITS measurements have been performed by two neurologists, who were blinded to the study groups and who were familiar with the off-line detection of HITS. HITS were identified as typical visual and acustic signals (Fig. 1), which usually appear as linear, high intensity, unidirectional ‘clicks’, ‘chirps’ or ‘moans’ of short duration and variable amplitude, mostly located in the systolic peak flow curve of the median cerebral artery. Artefacts may be caused by speaking, cauphing, swallowing, and manipulation of the transducer. Artificial signals are very often biphasic, wide (of longer duration) and of various acustic quality.

Coagulation and hemolysis parameters were analyzed in venous blood. Hemolysis was defined as an increase in two of the following measures: LDH (normal range: 20–240 U/l), reticulocytes (normal range: six to 25/1000 for males, eight to 41/1000 for females), free serum hemoglobin P (normal range: <1 mg/dl) and A-2-haptoglobin S (normal range: 0.77–3.00 g/l). Echocardiographic examination (Siemens® SI 1200, Munich, Germany) was performed to validate the ejection fraction, valvular pressure gradient and global pump function.

2.1. Statistical analyses

A chi-square test was used to compare clustered variables of both treatment groups. Bivariate analysis (Student’s t-test) for independent samples was used for comparison of normally distributed numerical variables. P < 0.05 was considered as statistically significant.

3. Results

Fourteen out of 22 patients (63%) in group A were positive for HITS. The mean number of HITS/h was 16.4 ± 19
(range: one to 64 HITS/h). In group B, 15 out of 20 pts (75%) were positive for HITS with a minimum of 1 and a maximum of 90 HITS/h and an average of 14.4 ± 24 (P = 0.14). No HITS were detected in the control group. Mild to moderate hemolysis was found in seven out of 22 (32%) patients in group A and in 11 out of 20 (55%) patients in group B. The occurrence of neurological complications in study groups is summarized in Table 4.

There were no statistical differences in the left ventricular ejection fraction (EF) between study groups as shown in Table 2. The mean EF in group A was 62.6 ± 13% and in group B 62.5 ± 8%. The mean EF in the control group was 72.1 ± 14%. The valvular pressure gradient (DP) in group A was 17.8 ± 8 and 27.8 ± 9 mmHg in group B (P < 0.001). The DP in the control group was 3.9 ± 2 mmHg, which was significantly lower compared to the treatment groups (P < 0.001). Carotid duplex sonography revealed clinically irrelevant stenoses of the internal carotid artery in three patients only (n = 2 between 20 and 50% and one of more than 50%), various plaques of either bulbus or the internal (ICA) or external (ECA) carotid artery in six patients, wall thickening without plaque or stenosis in nine patients and one vascular ‘kinking’ in a patient in group A. In the Duromedics group, one patient showed an ICA stenosis of more than 50%, two patients had an ICA stenosis and one patient had an ECA stenosis between 20 and 50%, seven patients showed various plaques, nine patients had wall thickening without stenosis and one patient had a kinking of the ICA. Free serum hemoglobin was found to be higher in the group B with 2.9 ± 2 mg/dl compared to 1.5 ± 1 mg/dl in group A (P = 0.014), as shown in Table 2. Other hemolysis indicators did not differ from each other in the mechanical valve groups (Table 5).

There is only a trend observable towards higher HITS rates in the Duromedics® group (group B) compared to the Sorin group (group A). However this was not significant. No statistical differences between the two valve types were found regarding neurologic findings, NYHA degree of heart failure, EF and coagulation status. Furthermore, no significant correlation between HITS and carotid artery duplex findings, neurologic results, coagulation status, hemolysis and valve size was found (Table 3). In contrast, the time after valve implantation correlated with the HITS rate (P = 0.042). In addition, there was a negative correlation between HITS and age as well as between HITS and NYHA degree of heart failure. Finally, a correlation between hemolysis and neurological findings was calculated (P = 0.03).

### 4. Discussion

Here we demonstrate that HITS occur in the postoperative period in patients following mechanical aortic valve replacement. In this study two different types of mechanical aortic valves were implanted. The numbers of HITS in both groups, however, was not significantly different from each other. The detected acoustic events of high intensity are well distinguishable from various artefacts. At present it is not clear, whether they originate from microthromboembolic or gaseous events [21].

Interestingly, the activity of the coagulation system, as measured by the international normal ratio (INR), and the quantity of HITS did not correlate with each other. In patients with decreased INR, HITS were not increased compared to patients with INR in therapeutic range after prosthetic heart valve replacement [22]. Non-solid, probably gaseous elements, which have been shown to evolve out of high pressure areas at the valvular level, may help to

### Table 2
Comparison of the two protheses groups\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sorin Biomedica (group A)</th>
<th>Tekna Duromedics (group B)</th>
<th>Statistical significance (P &lt; 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (%)</td>
<td>62.6 ± 13</td>
<td>62.5 ± 8</td>
<td>P = 0.15</td>
</tr>
<tr>
<td>DP (mmHg)</td>
<td>17.8 ± 14</td>
<td>27.8 ± 9</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>Pts with HITS</td>
<td>13/22</td>
<td>15/20</td>
<td>P = 0.337</td>
</tr>
<tr>
<td>HITS/pt</td>
<td>16.4 ± 19</td>
<td>14.4 ± 24</td>
<td>P = 0.81</td>
</tr>
<tr>
<td>Free Hb (mg/dl)</td>
<td>1.5 ± 1</td>
<td>2.8 ± 2</td>
<td>P = 0.014</td>
</tr>
<tr>
<td>Thrombocyte count (× 1000/μl)</td>
<td>217 ± 35</td>
<td>223 ± 58</td>
<td>P = 0.63</td>
</tr>
</tbody>
</table>

\(^a\) Statistical significance is highlighted by bold letters.

### Table 3
Correlations between different variables and the incidence of HITS\(^a\)

<table>
<thead>
<tr>
<th>Variable or clinical condition</th>
<th>Presence of HITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological status</td>
<td>P = 0.147</td>
</tr>
<tr>
<td>DP (pressure gradient)</td>
<td>P = 0.747</td>
</tr>
<tr>
<td>EF (ejection fraction)</td>
<td>P = 0.377</td>
</tr>
<tr>
<td>INR</td>
<td>P = 0.898</td>
</tr>
<tr>
<td>Free Hb</td>
<td>P = 0.346</td>
</tr>
<tr>
<td>Age</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>NYHA class</td>
<td>P = 0.018</td>
</tr>
<tr>
<td>Valve diameter</td>
<td>P = 0.382</td>
</tr>
<tr>
<td>Postoperative time</td>
<td>P = 0.042</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>P = 0.174</td>
</tr>
<tr>
<td>Gender</td>
<td>P = 0.420</td>
</tr>
</tbody>
</table>

\(^a\) Statistical significance is highlighted by bold letters.
Table 4
Occurrence of neurological events after mechanical aortic valve replacement*

<table>
<thead>
<tr>
<th>Group</th>
<th>Free of neurological events (n)</th>
<th>Postoperative TIA/PRIND (n)</th>
<th>Postoperative stroke (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n = 22)</td>
<td>17</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>B (n = 20)</td>
<td>12</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Total (n = 42)</td>
<td>29</td>
<td>12</td>
<td>1</td>
</tr>
</tbody>
</table>

* TIA: transient ischemic attack; and PRIND: prolonged reversible ischemic neurologic deficit.

explain the frequent transcranial findings of HITS [23]. Bubbles may be transported from their area of origin to the brain via the blood stream and, consequently, cause HITS [24,25]. This hypothesis and, moreover, the lack of correlation between the HITS rate and the occurrence of neurologic complications has caused a change in terminology that microemboli are now called HITS. The above considerations raise the question of which quantity of HITS is clinically relevant? Similar to what Rambod et al. have reported previously [16], our results support the theory that non-particulate elements cause transcranially detected HITS [17,23]. It has been shown that cavitation-induced gas bubbles normally disintegrate within milliseconds and only a small fraction enters the cerebral microcirculation [12,16]. Animal studies have revealed that a considerable fraction of such bubbles are able to pass the pia arterioles and reach the cerebral venous drainage system. Thus, the extend of obstructive events, caused by these phenomena, still remains difficult to objectify — especially in patients with HITS rates lower than 40 per h.

The incidence of HITS correlated negatively with patients age in our study. Young and active individuals, which frequently perform physical exercising, generated more HITS/h than elderly patients. This interesting observation which suggests that higher hemodynamic stresses to the mechanical valve function are probably involved in the generation of HITS [1,26]. This assumption is reinforced by the additional correlation between HITS rates and length of postoperative time. This observation suggests that corrosion phenomena on the leaflet surface which occur over time may lead to the hemodynamic events that cause HITS. This theory is further supported by the fact that HITS correlated negatively with the NYHA degree of heart failure. On the other hand, no correlation between prevalence of HITS and other hand, no correlation between prevalence of HITS and the left ventricular ejection fraction or between HITS and other hand, no correlation between prevalence of HITS and the NYHA degree of heart failure. On the other hand, no correlation between prevalence of HITS and other hand, no correlation between prevalence of HITS and the NYHA degree of heart failure. On the other hand, no correlation between prevalence of HITS and other hand, no correlation between prevalence of HITS and the NYHA degree of heart failure. On the other hand, no correlation between prevalence of HITS and the occurrence of HITS and abnormally high DPs (>20 mmHg), as assessed by echocardiography.

Despite of similar construction, the Tekna Duromedics® valve seems to build up a higher pressure gradient across the valve and higher levels of free hemoglobin representing hemolysis compared to the Sorin Biomedica® valve. Based on this study further progress in mechanical heart valve engineering will be essential for future improvement of the outcome following mechanical heart valve replacement.

In summary, HITS frequently occur in the postoperative period following mechanical valve implantation. The underlying mechanisms of the generation of HITS, however, are not clear. Due to the lack of correlation between HITS and coagulation status or occurrence of neurologic events, no clinical relevance of HITS can be assumed at the present time. Future studies on the clinical relevance of HITS in patients following mechanical heart valve replacement will have to focus on new physiological and neurofunctional endpoints to bring additional light into the dark field of high intensity transient signals.

References


