

Hemolysis, High-Intensity Transient Signals (HITS) and Hemodynamic Results after Aortic Valve Replacement with the Medtronic Hall Easy-Fit™ Heart Valve Prosthesis

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Background and aim of the study: Previous studies have shown a correlation between type, orientation and valve size of mechanical heart valve prostheses and the incidence of high-intensity transient signals (HITS). The study aim was to investigate the presence of HITS and hemolysis and the impact of valve size and hemodynamic parameters following aortic valve replacement (AVR) using the new Medtronic Hall Easy-Fit™ prosthesis.

Methods: A total of 150 patients (120 males, 30 females; mean age 62 ± 8 years; range: 32-78 years) underwent AVR (n = 94; 63% concomitant procedures) with the Easy-Fit valve in its optimal orientation. Patients were investigated at between three and 36 months after AVR using transcranial Doppler examination of the right and left middle cerebral artery, and the incidence of HITS was determined. For evaluation of hemolysis, serum lactate dehydrogenase (LDH), hemoglobin and bilirubin were measured. These parameters were related to valve size.

The Medtronic Hall™ heart valve prosthesis, which has been in clinical use since 1977, is a tilting-disc valve that uses a single pyrolytic carbon disc occluder pivoting within a titanium housing. The housing is machined into its final configuration from a single piece of solid titanium. The occluder pivots about a central guide member of the valve housing, and a rotatable, fabric sewing ring is affixed to the valve.

The design features of the prosthesis have been shown to introduce very low susceptibility to valve thrombosis by eliminating areas of low-velocity flow. Previous 20-year long-term follow up data have

Transthoracic echocardiography was performed in all patients.

Results: Among the patients, 112 (75%) showed no or low HITS (34% none, 41% <30/h), while only 38 (25%) had elevated HITS (range 31-100/h, 14%; range >100/h, 11%). Statistical analysis showed a linear association between the HITS count and valve size. A positive correlation between valve size and LDH was observed; hemoglobin and bilirubin showed normal values.

Conclusion: The valve size-dependent increase in LDH after AVR corresponds with the observation that the presence of HITS increases with valve size. In light of these findings, the surgical approach to implant the largest size Easy-Fit valve possible should be discussed, given the excellent hemodynamic results provided by the valve, even in smaller sizes.

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shown excellent clinical and hemodynamic outcome (1-3).

Experimental and clinical studies have demonstrated the importance of the orientation of mechanical aortic valve prostheses (4), and this applies particularly to tilting-disc valves.

The left ventricle to left ventricular outflow tract axes have been shown to form an angle between 140 and 150°, causing a deviation of the bloodstream line towards the convexity of the ascending aorta, with the majority of blood flow across the non-coronary cusp (5). Using an in-vivo rotation device in animal studies, the optimal orientation of aortic valve prostheses was determined showing near-physiological turbulence in the Medtronic Hall prosthesis, when the great orifice is placed toward the non-coronary cusp (6). In contrast, the St. Jude Medical bileaflet valve showed significant downstream turbulences when placed in any orientation (10-12). Clinical investigations with the Medtronic Hall aortic valve prosthesis in optimal orientation

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showed excellent hemodynamic results, with lower mean gradients, lower supra-annular turbulences and faster left ventricular mass regression compared to bileaflet valves being demonstrated (7). These advantages of the tilting-disc mechanism were even more pronounced in the smaller-sized valves.

Introduced in 2001, the Medtronic Hall Easy-Fit™ heart valve prosthesis has a new sewing cuff design which facilitates implantation and provides an improved tissue-to-inner diameter ratio.

Previous studies have shown a correlation between type, size and orientation of mechanical heart valve substitutes following aortic valve replacement (AVR) and the incidence of high-intensity transient signals (HITS) detected by transcranial Doppler examination (8-22). Although platelet microparticles have been associated with microembolic signals (23), strong evidence exists that, in patients with prosthetic cardiac valves, these HITS are gaseous and not solid (24-26). The deterioration of working memory in neuropsychological examinations has been related to the presence of cerebral microemboli in patients following the implantation of mechanical heart valves (27,28).

In patients with normally functioning valve substitutes, subclinical hemolysis with elevated levels of serum lactate dehydrogenase (LDH) is a frequent finding (29-34).

The aim of the present study was to investigate the presence of HITS and hemolysis after implantation of the Easy-Fit prosthesis, and their relationship to valve size. Furthermore, possible correlations between LDH and HITS with effective orifice area (EOA), effective orifice area indexed to body surface area (EOAI) and peak, as well as mean, transvalvular gradients were evaluated.

Clinical material and methods

Patients

A total of 150 patients (120 males, 30 females; mean age 62 ± 8 years; range: 32 to 78 years) (Fig. 1) was investigated at between three and 36 months' follow up after AVR with the Easy-Fit prosthesis in its optimal orientation (intra-annular, $n = 129$ (86%); supra-annular, $n = 7$ (5%); epi-annular, $n = 14$ (9%)). The distribution of valve sizes is detailed in Table I. Additional procedures were conducted in 94 patients (63%); these included coronary artery bypass grafting (CABG) in 71 (47.3%), aortic surgery in 11 (7.4%), CABG + aortic surgery in six (4%), and other procedures in six (4%). Reoperations were performed in two patients (1.3%). Preoperatively, 130 patients (86.6%) were in NYHA classes III or IV (75.3% in class III, 11.3% in class IV). Twenty-two patients (14.7%) had aortic stenosis and 22 (14.7%) had aortic insufficiency, while 106 patients

(70.6%) showed combined aortic lesions.

The study was approved by the local Ethical Committee of Lower Saxony, Germany; written informed consent was obtained from each of the participating patients.

Clinical investigations

Patients were investigated clinically, by transthoracic echocardiography and transcranial Doppler examination. The presence of hemolysis was assessed on the basis of serum LDH, hemoglobin and bilirubin, all patients showing values within the normal range preoperatively. Transthoracic echocardiography was performed using an Acuson 128 XP device (Acuson, Mountain View, CA, USA); M-mode echocardiography as well as continuous-wave and pulsed-wave Doppler examinations were conducted in all patients. The Bernoulli equation was used to calculate pressure gradients, and the continuity equation to calculate the EOA. Valve-related complications were registered at the follow up examination. Doppler examination of the right and left middle cerebral artery for detection of HITS was conducted in all patients using 2-MHz probes (Nicolet, Estenfeld, Germany) fixed in a head-frame and connected to a Doppler sonography device (Pioneer TC 4040; Medilab, Würzburg, Germany). The registration of signals followed the guidelines of microembolus detection by transcranial Doppler (35).

Data and statistical analysis

Data were analyzed statistically using a SPSS 12.0 software package (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean \pm SD, median and range. Variables with positive skewed dis-

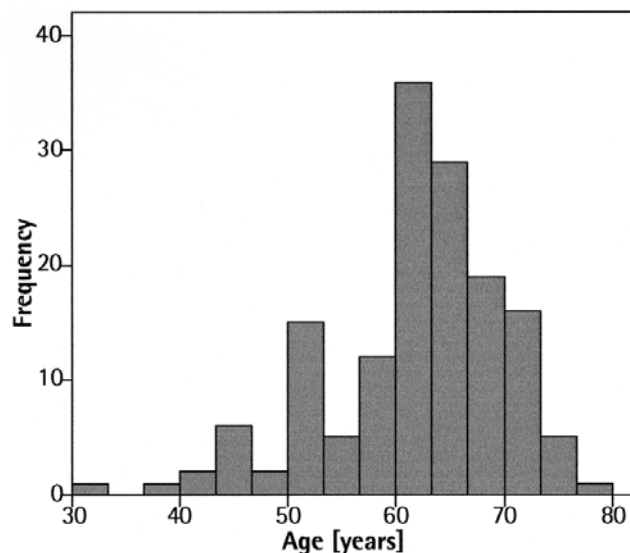


Figure 1: Age distribution of the patient population ($n = 150$ patients).

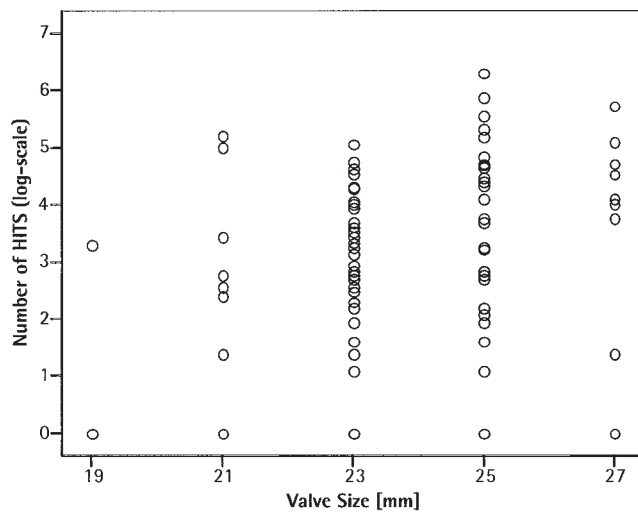


Figure 2: Valve size-dependent frequency of HITS/h (log-scale).

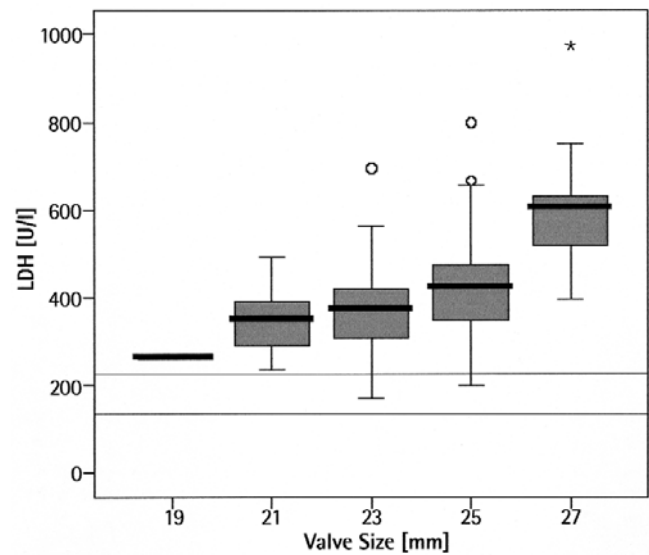


Figure 3: Valve size-dependent level of lactate dehydrogenase (LDH) (the normal range is marked between 135-225 U/l).

tribution were log-transformed before applying parametric tests. The correlation between valve size, LDH, HITS and hemodynamic parameters was determined by the method of Pearson. Differences between groups for baseline variables were tested using the unpaired *t*-test, chi-squared or Fisher's Exact test, as appropriate. All tests were performed two-sided at a significance level of $\alpha = 0.05$.

Results

Among the patients, 112 (75%) showed no or a low incidence of HITS (none in 51 cases (34%); one to 30 HITS/h in 61 cases (41%)), while 38 patients (25%) had elevated HITS counts (31-100 HITS/h in 21 (14%) and >100 HITS/h in 17 (11%)). A linear association between valve size and HITS count was demonstrated.

Furthermore, a positive correlation between valve size and LDH with LDH levels above the normal range (135-225 U/l) was observed in the majority of patients, while hemoglobin and bilirubin showed normal values without any significant differences between valve sizes. Clinical outcome assessed by NYHA classification showed 147 patients (98%) to be in NYHA classes I or II (68% in class I, 30% in class II) and three patients (2%) in NYHA class III. The HITS counts and LDH values related to valve size as well as the hemodynamic data are listed in Table I. No cases of structural valve deterioration, impingement, valve thrombosis or prosthetic valve endocarditis were found at the follow up examinations. Further evaluation of postoperative complications revealed two episodes of major bleeding (gastrointestinal), no history of stroke, and eight transient neuroembolic events, which showed no signifi-

Table I: HITS, LDH, transvalvular gradients, effective orifice area (EOA) and effective orifice area indexed to body surface area (EOAI) related to valve size.

Parameter	Valve size (mm)				
	19 (n = 2)	21 (n = 20)	23 (n = 60)	25 (n = 55)	27 (n = 13)
HITS/h					
0-30	2 (100)	18 (90)	47 (78)	39 (71)	6 (46)
>30	0 (0)	2 (10)	13 (22)	16 (29)	7 (54)
LDH (U/l)	260 ± 0	350 ± 71	372 ± 92	427 ± 113	601 ± 147
Mean gradient (mmHg)	8.5 ± 2.1	10.9 ± 4.8	9.8 ± 2.1	8.5 ± 2.4	8.2 ± 1.6
Peak gradient (mmHg)	16.9 ± 1.5	21.5 ± 7.8	20.0 ± 6.2	17.0 ± 4.4	15.5 ± 2.5
EOA (cm ²)	1.41 ± 0	1.69 ± 0.36	2.15 ± 0.44	2.40 ± 0.41	2.78 ± 0.30
EOAI (cm ² /m ²)	0.88 ± 0.04	0.95 ± 0.1	1.08 ± 0.23	1.22 ± 0.23	1.35 ± 0.17

cant correlation to either valve size or HITS count.

Statistical analysis showed a significant correlation between valve size and HITS count ($\alpha = 0.05$; Fig. 2), and between valve size and LDH ($\alpha = 0.01$; Fig. 3). Evaluation of the hemodynamic data showed significant correlation between valve size and transvalvular peak and mean gradients, EOA and EOA indexed to body surface area (EOAI) ($\alpha = 0.01$). Further statistical analysis showed significant correlation between LDH and EOA/EOAI ($\alpha = 0.01$), as well as between HITS and EOA ($\alpha = 0.05$) and EOA ($\alpha = 0.01$). Furthermore, no correlation of LDH and HITS with transvalvular peak and mean gradients was observed. No relationship was found between the technique of implantation (supra-, intra- or epi-annular) and hemodynamic data, HITS counts and LDH values.

Discussion

The presence of HITS has been shown to be a frequent observation after implantation of mechanical heart valve substitutes, though contradictory reports of this phenomenon have been made. Sliwka and Georgiadis (9) found a relationship between HITS and valve type and in certain valve types, the position of the implant, but no correlation between HITS count and valve size as well as the time since valve insertion. The study of Brækken et al. (8), however, showed a significant increase in cerebral embolic signals with longer duration since valve implantation and a positive correlation between the frequency of these signals and valve size.

The activation of platelets following the exposure of blood to artificial surfaces, as well as a reduced cavitation threshold, have been discussed as possible explanations for these findings. Furthermore, Brækken et al. described a valve size-dependent increase in LDH levels, showing also a correlation between the frequency of HITS and LDH.

Previous studies have emphasized the importance of the optimal orientation of mechanical aortic valve substitutes and the impact on cerebral microembolization. In optimal orientation, which has been described above (4-7), the Medtronic Hall prosthesis showed a low incidence of HITS, even when compared with biological prostheses, while bileaflet valves demonstrated significant HITS counts in any orientation (10-13). The hypothesis, that microembolic signals in recipients of mechanical aortic valve substitutes appear to be a major prognostic factor for an impending cardioembolic stroke, is supported only by few data. In neuropsychological investigations, a deterioration of working memory was attributed to the presence of HITS, confirming a long-term effect of the chronic exposure to microemboli (27,28).

Since subclinical hemolysis, as assessed by serum LDH levels, is a frequent observation after mechanical valve replacement, decompensated hemolytic anemia is rare and usually attributed to paraprosthetic leakage (29). The hypothesis of valve type-dependent regurgitant flow phenomena is discussed in this context.

In the present study, valve orientation was not a variable, as all aortic valve substitutes were implanted in the optimum position. A linear association between valve size and HITS count, as well as a significant correlation between valve size and LDH levels, was detectable. This supported the hypothesis that cavitation and adhesion phenomena are a frequent observation in larger-size Easy-Fit heart valve substitutes in the aortic position. The significant correlations between HITS and EOA/EOAI and between LDH and EOA/EOAI reflected the importance of this hemodynamic parameter in clinical investigations compared to in-vivo transvalvular gradients, and were consequences of the valve size dependency of the above-mentioned phenomena. This dependency is pronounced by the fact that the Easy-Fit prosthesis has an improved tissue-to-inner diameter ratio due to a new sewing cuff design.

In light of the above-mentioned neuropsychological data, which showed a relationship between an increase in HITS count and a long-term negative impact on cognitive abilities, a follow up study to evaluate possible neuropsychological changes in the present patient group appears necessary. In case of a positive correlation between the presence of HITS and a deterioration of working memory in this population, and of a valve size-dependent incidence of these changes, a surgical approach to implant the largest Easy-Fit valve possible in the aortic position must be reconsidered. This applies in particular to the 27-mm prosthesis, given the excellent hemodynamic and clinical data of the Easy-Fit prosthesis provided even in smaller sizes in the present study

Study limitations

Among study limitations, it should be noted that no carotid ultrasonography was performed at the time of investigation. However, retrospective analysis of hospital records showed either no significant stenosis of the carotid arteries preoperatively or in four cases of endarterectomy because of significant stenosis at post-operative control ultrasonography. Neither was any evaluation of neurocognitive function performed, though this is the aim of further investigations in the present patient group. The small number of patients (two females, with small body surface area) who received a 19-mm Easy-Fit prosthesis, and showed low transvalvular gradients, did not permit any statistical consideration, but these data were reported for com-

pletteness. Furthermore, it must be emphasized that the Easy-Fit prosthesis provides an improved tissue-to-inner diameter ratio compared to the conventional Medtronic Hall prosthesis, which might explain the low gradients in this small subgroup.

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