Diffusion-Weighted Magnetic Resonance Imaging and Neurobiochemical Markers After Aortic Valve Replacement
Implications for Future Neuroprotective Trials?

Erwin Stolz, MD; Tibo Gerriets, MD; Alexander Kluge, MD; Wolf-Peter Klövekorn, MD; Manfred Kaps, MD; Georg Bachmann, MD

Background and Purpose—Cardiac surgery carries a high risk of neurological complications; therefore, these patients would be an appropriate target population for neuroprotective strategies. In this study, we evaluated postoperative diffusion-weighted imaging (DWI) as a potential surrogate marker for brain embolism and its relationship to neurobiochemical markers of brain injury.

Methods—Of a total of 45 consecutive patients undergoing aortic valve replacement, 37 completed preoperative and postoperative MRI. At the time of the MRI studies, serum S100β and neuron-specific enolase concentrations were determined. Preexisting T2 and postoperative DWI lesion volumes were quantified. All patients had a blinded neurological examination before and after operation.

Results—New perioperative DWI lesions were present in 14 patients (38%), of whom only 3 developed focal neurological deficits. Eighteen small lesions were found in the white matter or vascular border zones in all but 2 patients with territorial stroke. The appearance of new DWI lesions correlated with age, pre-existing T2 lesion volume, and postoperative S100β concentrations on days 2 to 4 after surgery. In a forward stepwise canonical discrimination model, only T2 lesion volume was selected as a relevant variable.

Conclusions—The incidence of postoperative DWI lesions in aortic valve replacement is high, and a suitable marker for neuroprotective trials would be a reduction in the number of such lesions. The volume of preexisting T2 lesions is related to the development of perioperative DWI lesions. (Stroke. 2004;35:888-892.)

Key Words: embolism ■ magnetic resonance imaging ■ neuron-specific enolase ■ stroke ■ S100 proteins

Perioperative stroke is a devastating complication of heart surgery. The reported frequencies range between 1% and 4% in patients undergoing coronary artery bypass grafting (CABG), with the risk nearly doubled in older age.1-5 Similar rates were found for patients receiving heart valve replacement.6,7 Cognitive deficits after heart surgery have been observed in 33% to 83% of patients during the first weeks after surgery.8 Both stroke and cognitive disturbance are thought to be related to macroembolism and microembolism during surgery.9

Patients undergoing heart surgery could be a suitable target population for neuroprotective trials including preemptive neuropharmacological approaches. However, to examine large patient cohorts, easy-to-use and reliable surrogate markers for brain embolism are needed. Neuropsychological tests are time consuming, show a considerable variability in results depending on the number and type of test systems used, and are confounded by several variables such as the frequent development of postoperative delirium.8 The release of biochemical markers of neuronal injury such as S100β or neuron-specific enolase (NSE) has been found to be associated with postoperative cognitive deficits after both heart surgery10,11 and embolic stroke.12,13 The measurement of these markers is fairly easy, but their relationships to symptomatic embolic stroke and subclinical embolism are not yet clear. Diffusion-weighted MRI (DWI) is an emerging surrogate marker for clinical and subclinical brain embolism.

In this study, we analyzed clinical and subclinical brain embolism by DWI and the release of neuronal destruction markers in serum in a cohort of patients undergoing aortic valve replacement (AVR).

Patients and Methods

Patients
Between January 2001 and July 2002, 45 consecutive patients underwent elective AVR and were enrolled prospectively in this study after giving written informed consent. Patients with combined procedures, history of previous stroke, and carotid artery stenosis of
Demographic, Clinical, and Imaging Data of the Patient Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Cohort (n=37)</th>
<th>Post-OP DWI Neg (n=23)</th>
<th>Post-OP DWI Pos (n=14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n (%)</td>
<td>15 (41)</td>
<td>8 (35)</td>
<td>7 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>22 (59)</td>
<td>15 (65)</td>
<td>7 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>66±10</td>
<td>64±10</td>
<td>71±9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (59%)</td>
<td>14 (61%)</td>
<td>8 (57%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (14%)</td>
<td>3 (13%)</td>
<td>2 (14%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>22 (59%)</td>
<td>13 (57%)</td>
<td>9 (64%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>5 (14%)</td>
<td>5 (22%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-OP T2 lesion volume</td>
<td>5.8±10.3</td>
<td>2.2±2.6</td>
<td>11.3±14.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(median, range), cm³</td>
<td>(1.6, 0.1–49.7)</td>
<td>(1.3, 0.1–8.9)</td>
<td>(4.9, 0.5–49.7)</td>
<td></td>
</tr>
<tr>
<td>Operative values</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operation time, min</td>
<td>175±61</td>
<td>167±62</td>
<td>187±54</td>
<td>NS</td>
</tr>
<tr>
<td>Extracorporeal circulation time, min</td>
<td>92±38</td>
<td>90±35</td>
<td>97±39</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic cross-clamp time, min</td>
<td>68±28</td>
<td>67±27</td>
<td>70±29</td>
<td>NS</td>
</tr>
<tr>
<td>Deepest intra-OP temperature, °C</td>
<td>30±3</td>
<td>29±4</td>
<td>30±2</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-OP Hb, g/L</td>
<td>14.0±1.2</td>
<td>14.1±1.1</td>
<td>13.9±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Lowest intra-OP Hb, g/L</td>
<td>7.6±1.3</td>
<td>7.7±1.0</td>
<td>7.5±1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Post-OP Hb, g/L</td>
<td>10.7±1.2</td>
<td>11.0±1.2</td>
<td>10.4±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Post-OP S100β days 2 to 4, μg/L</td>
<td>0.25±0.2</td>
<td>0.15±0.1</td>
<td>0.39±0.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Post-OP NSE days 2 to 4, μg/L</td>
<td>14.4±8.7</td>
<td>10.2±3.9</td>
<td>12.6±6.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

OP indicates operation; Neg, negative; and Pos, positive.
*Comparing the groups with and without new DWI lesions.

≥70% on duplex ultrasound examination were excluded. The Table summarizes the basic characteristics of the patient cohort.

Anesthesia and Surgery
All patients were operated on with standardized anesthetic and surgical procedures. Twenty-four patients received an artificial valve (Carbomedics, Medtronic, or St Jude Medical), and 12 received biological valves (Baxter Perimount Bio, Mitroflow Bio, or Lapcor Bio). A 20-μm filter was used in the heart-lung machine reservoir, and an air bubble trap was used in the venous circulation. Twenty-eight patients received Bretschneider and 20 received Bruckberg cardioplegia. Variables related to the operation are summarized in the Table.

Clinical Evaluation
A comprehensive clinical examination, including a detailed neurological examination, was performed by a neurologist before and on day 2 or 3 after operation in a blinded fashion.

MRI Scans
All MRI scans were acquired on a 1.5-T unit using a head coil (Vision, Siemens). Baseline MRI studies of the brain were obtained 1 to 2 days before surgery. Follow-up MRI was scheduled for the first or second postoperative day. This was achieved in only 18 patients (49%); 16 patients (43%) received the postoperative MRI on day 3 or 4 and 3 patients (8%) had MRI on day 5 or 6 because of hemodynamic compromise or external cardiac pacing. Three patients of the original cohort did not complete the postoperative, and 5 patients did not have the postoperative MRI and were excluded.

The preoperative and postoperative imaging protocol included (1) a proton- and T2-weighted turbo spin-echo sequence (repetition time [TR], 4657 ms; echo time [TE], 15/135 ms; turbo factor, 8; slices, 20; acquisition, 1; acquisition time, 2.01 minutes), (2) a T1-weighted turbo spin-echo sequence (TR, 600 ms; TE, 20 ms; slices, 20; acquisitions, 2), and (3) a diffusion-weighted spin-echo-planar imaging sequence (TR, 4657; TE, 118 ms; matrix, 128×128; gradients of b values; 0, 500, 1000 s/mm²). The apparent diffusion coefficients were calculated for each pixel and composed on an apparent diffusion coefficient map.

MRI scans were evaluated by 2 blinded independent observers, a neuroradiologist and a neurologist as the second observer. The preoperative lesion load was determined by planimetry of the area of the T2-hyperintense lesions and multiplying the measured area by slice by the respective slice distance (T2LV). There was no interslice gap. Likewise, postoperative new lesions were quantified on the DWI images with maximum contrast between lesion and normal brain regions. For image analysis, the software of the MRI unit was used.

Biochemical Markers
Preoperative and postoperative S100β and NSE were determined from venous blood collected on the day of the respective MRI study. Samples were immediately centrifuged for 20 minutes at 5000 min⁻¹ and stored at −20°C for later analysis.

S100β concentrations were determined with a monoclonal 2-sided immunoradiometric assay (Byk Sangtec 100 IRMA). NSE was measured with an enzyme immunoassay based on the sandwich technique with the solid-phase monoclonal antibody raised against the γ-subunit of NSE (Cobas Core II, Roche Diagnostics).

Statistical Analysis
Frequencies were compared with a χ² or, when appropriate, Fisher’s exact test. The agreement of observers on the T2LV and postoperative DWI lesion volumes was analyzed by use of the Bland-Altman method⁴ resulting in 2-SD confidence intervals (2SD-CI). With an intraclass correlation coefficient, the agreement on the presence of DWI lesions was tested. Nonparametric data were compared with a Mann-Whitney U test. An association between the presence of DWI lesions and continuous variables was examined by use of Spearman’s rank correlation. For correlation of continuous variables, a linear
regression analysis was used. We used a stepwise canonical discrimination function based on the unexplained variance to separate patients with or without new DWI lesions by entering the variables significantly related to new DWI lesions on univariate or bivariate analysis into the model. A value of $P<0.05$ was considered significant.

**Results**

**MRI Scans**

Twenty-six patients (70%) already showed pre-existing T2 lesions (the Table). Interobserver agreement on the T2LV was acceptable with a 2SD-CI of $\pm 4.3$ cm³. Preexisting lesions were found mostly in the white matter of the hemispheres predominantly in the frontal lobe representing microcirculation damage, ie, leukoaraiosis and lacunar infarcts, and were significantly associated with older age ($P<0.05$). Statistical power was not sufficient to show an association with cardiovascular risk factors. No DWI lesions were found preoperatively.

Postoperative DWI lesions were present in 14 patients (38%) (the Table). Two patients developed territorial infarcts in the left cerebellar hemisphere and left posterior lobe, respectively (Figure 1); the remaining 12 patients had 18 total small globular lesions in the white matter or cortical border zones with diameters of 5 to 12 mm (Figure 1). Only 3 patients displayed a single lesion. Ten DWI lesions were located in the vertebrobasilar and 8 in the anterior circulation. The agreement of 2 blinded observers on the presence of new DWI lesions was perfect (intraclass correlation coefficient, $\kappa = 1.0$). DWI lesion volume ranged from 0.1 to 24.8 cm³ (median, 0.5 cm³; mean, $3.8\pm 8.4$ cm³) with a 2SD-CI of $\pm 0.92$ cm³.

The appearance of DWI lesions correlated with the preoperative T2LV ($r=0.33$, $P<0.05$) and age ($r=0.36$, $P<0.05$). No correlation was found for DWI lesions and the operative variables, as well as the lowest intraoperative hemoglobin (Hb) concentration.

We found no significant correlation between the frequency of DWI lesions and the latency between surgery and MRI examination.

**Neurological Evaluation**

Postoperatively, only 3 patients had focal neurological deficits. New large territorial lesions were found in 2 patients, and a small white matter lesion was seen in 1 patient. Neurological examination revealed no clinically apparent deficits in the remaining 11 patients with postoperative DWI lesions.

**Biochemical Markers**

Both S100β and NSE increased significantly after AVR (Figure 2) but independently from operative variables. However, concentrations significantly decreased with the interval from AVR to measurement ($r=0.57$, $P<0.01$). We used the difference in the postoperative and lowest intraoperative Hb concentrations as a crude measure of the intraoperative volume loss or transfusion volume, respectively. With increasing transfusion volume, S100β concentrations showed a clear trend to decrease ($r = -0.29$, $P=0.08$), and NSE showed a weak trend to increase ($r=0.27$, $P=0.11$) (Figure 3).

**Relationship Between Biochemical Markers and Imaging Results**

The highest correlation between postoperative S100β concentrations ($r=0.54$, $P<0.01$) and the preoperative to postoperative difference ($\Delta S100\beta$; $r=0.45$, $P<0.01$) and the presence and volume (post-OP S100β, $r=0.64$, $P<0.01$; $\Delta S100\beta$, $r=0.59$, $P<0.01$) of new DWI lesions was found for the measurements on days 2 to 4. Measurements on the first or after the fourth postoperative day did not correlate...
with the presence of new DWI lesions. Neither postoperative NSE concentrations nor ∆NSE showed any association with new DWI lesions. Canonical discrimination function (canonical correlation, 0.40; eigenwert, 0.2; Wilk’s λ, 0.84; $P<0.05$) included only the T2LV (Fisher’s discrimination coefficient, 0.15) as the relevant variable. This model correctly identified 65% of cases.

**Discussion**

The high incidence of neurological problems would make cardiac surgery a suitable field for neuroprotective strategies. Clinical risk factors for perioperative stroke in CABG procedures were found to be atherosclerotic disease of the aorta and the carotid arteries, including their surrogate markers advanced age, peripheral vasculopathy, and atherosclerotic risk factors, together with recent myocardial infarction and postoperative atrial fibrillation, supporting the hypothesis of an embolic origin.15 Further support for an embolic nature of brain injury is provided by postmortem studies,9,16 with numerous emboli logged in the microcirculation.

However, neuroprotective trials need robust and objective markers for brain injury. Problems associated with neuropsychological testing were outlined in the introduction. S100β and NSE concentrations have been found to correlate closely with the volume of territorial ischemic stroke.12,17 However, timing of measurements is crucial. Best correlations with infarct volume were found for the 2-to-4-day interval after stroke.12,17 In this time interval, we found an association between S100β concentrations and the presence and volume of postoperative DWI lesion. However, on the level of single measurements (Figure 4), we doubt the clinical usefulness of this parameter for identifying patients with perioperative embolic brain lesions because the lesion volume in these patients is generally small and the power of S100β to separate groups with or without postoperative DWI lesions is weak. Corresponding to clinical observations of others,18 our results showed no relationship between NSE concentrations and perioperative DWI lesions. The measurement of neurobiochemical markers is influenced by several confounding factors such as hemodilution or hemolysis, as demonstrated in this study and by others,18 release from ganglionic cells in the operation field or other extracerebral sources, suction autotransfusion, or renal failure.19–21 In the case of NSE, Johnsson and coworkers18 observed a close association between hemolysis during extracorporeal perfusion and NSE because NSE is not strictly neuron specific but can be set free from hemolized erythrocytes. During operation, erythrocyte concentrates that show a certain amount of hemolysis usually are given. This may explain our observed trend of increasing NSE levels with increasing intraoperative to postoperative Hb difference. However, this sheds considerable doubt on the usefulness of these markers for neuroprotective trials.

Several studies used postoperative MRI to identify embolic brain lesions.22 Most of them applied conventional spin-echo sequences, flair techniques, or contrast-enhanced studies that proved not to be appropriate for detecting acute postoperative lesions.

DWI is a new development with a high sensitivity for acute ischemic brain lesions combined with a high spatial resolution. The advantage of choosing an AVR cohort is that the operative procedure is fairly standardized. We found new perioperative DWI lesions in 38% of the patients, 3 of whom had focal neurological deficits. This rate complies with the few studies using postoperative DWI after CABG.23–26 Most of these lesions were small and located in the border zones of brain circulation or within regions affected by leukoaraiosis. Except for the 2 patients with territorial stroke, the DWI lesion volume was small, so reducing the number of DWI lesions would be a suitable surrogate marker for neuroprotective trials.
Despite the low frequency of neurologically symptomatic patients, asymptomatic DWI lesions are likely to originate from the same sources as macroemboli, so DWI lesions might represent mostly the lower end of brain embolism in terms of size. This may be of importance, for example, for evaluating new surgical techniques. We cannot comment on a relationship between small DWI lesions and cognitive deficits; this topic requires further study.

In agreement with others, we found an association between new DWI lesions and the preexisting T2LV caused by microcirculation damage. So far, the only studies evaluating postoperative brain perfusion by MRI were not able to show any focal perfusion lesions, so, considering the location of most of the asymptomatic DWI lesions, a decreased microcirculation washout as proposed by Caplan and Hennerici caused by preexisting microcirculation damage may play a role. The implication is that, in neuroprotective trials, the reduction of the rate of embolism should be considered, for example, for evaluating new surgical techniques. We cannot comment on a relationship between new DWI lesions and the preexisting T2LV caused by microcirculation damage. MRI is the most useful technique.

References

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