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# Cognitive function after sevoflurane- *vs* propofol-based anaesthesia for on-pump cardiac surgery: a randomized controlled trial

J. Schoen*, L. Husemann, C. Tiemeyer, A. Lueloh, B. Sedemund-Adib, K.-U. Berger, M. Hueppe and M. Heringlake

Department of Anesthesiology, University of Luebeck, Ratzeburger Allee 160, D-23538 Luebeck, Germany

* Corresponding author. E-mail: julika.schoen@uk-sh.de

## Editor's key points

- Cognitive dysfunction after cardiac surgery might be associated with decreases in cerebral oxygen saturation.
- Patients developing intraoperative cerebral desaturation showed worse early postoperative cognitive test results than patients without cerebral desaturation.
- Hypnotic drug selection might be one of the factors attenuating the effects of cerebral desaturation on cognitive outcome after on-pump cardiac surgery.

**Background.** Cognitive dysfunction is a frequent complication after cardiac surgery and has been found to be associated with decreases in cerebral oxygen saturation ($Sc_{O_2}$) measured with near-infrared spectroscopy. Sevoflurane has neuroprotective properties *in vitro* and in animal models. This study was designed to determine cognitive and clinical outcomes after sevoflurane- compared with propofol-based anaesthesia for on-pump cardiac surgery and the impact of decreases in $Sc_{O_2}$ under different anaesthesia regimens.

**Methods.** One hundred and twenty-eight patients were randomly assigned to either i.v. anaesthesia with propofol- (PROP) or sevoflurane-based anaesthesia (SEVO). An intraoperative $Sc_{O_2} < 50\%$ was defined as desaturation. The Abbreviated Mental Test, Stroop Test, Trail-Making Test, Word Lists, and mood-assessment tests were performed before, 2, 4, and 6 days after cardiac surgery. Markers of general outcome were obtained.

**Results.** The analysis groups had differences in baseline cognitive performance. Analysis of variance for repeated measures (incorporating covariance of baseline scores) showed that in three of four cognitive tests, patients with cerebral desaturation showed worse results than patients without desaturation. Patients assigned to sevoflurane-based anaesthesia showed better results in all cognitive tests than patients after propofol. Interactions between the anaesthetic regimen and desaturation were found in all four cognitive tests. There were no differences in markers of organ dysfunction or general clinical outcome.

**Conclusions.** Patients with impaired cognitive performance before operation may be at particular risk for intraoperative cerebral insult. A sevoflurane-based anaesthesia was associated with better short-term postoperative cognitive performance than propofol.

**Keywords:** anaesthetics volatile, sevoflurane; brain, injury; clinical trials; surgery, cardiovascular

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Cognitive alterations after cardiac surgery are of growing importance in an ageing population. After coronary artery bypass grafting (CABG),[1 2] 35–63% of patients show cognitive dysfunction on discharge with one-third still suffering from cognitive decline 5 months after surgery.[3 4] Even though some data suggest that long-term effects of surgery and anaesthesia on cognitive function might be superimposed by effects of normal ageing,[5] a reduction in the incidence of postoperative cognitive dysfunction is of primary importance.

Several attempts have been made to reduce cerebral damage during cardiac surgery, focusing on either the reduction in macro- and microembolism[3] or the optimization of the cerebral oxygen delivery/demand ratio. A non-invasive method for estimation of the cerebral oxygenation is the measurement of the regional cerebral oxygen saturation $Sc_{O_2}$ by near-infrared spectroscopy.[6] Deterioration of the $Sc_{O_2}$ during cardiac or non-cardiac surgery has been shown to be associated with postoperative cognitive dysfunction, focal cerebral deficits,[7 8] longer hospital stay, and increased postoperative morbidity.[9–11] Maintaining $Sc_{O_2}$ above a critical value by structured interventions has led to a lower postoperative morbidity and shorter hospital stay in cardiac[9] and non-cardiac patients.[12]

A possibility of attenuating cerebral injury after cardiopulmonary bypass (CPB) could be anaesthetic pre- and postconditioning. The application of inhalation anaesthetics before and immediately after an ischaemic period has been shown to attenuate the ischaemia–reperfusion injury of several organs. Neuronal anaesthetic preconditioning has been shown *in vitro* and in several animal studies,[13 14] but clinical data are scarce.[15]

The present study was designed to determine whether patients after sevoflurane-based anaesthesia differ from patients after propofol-based anaesthesia in postoperative cognitive test results and the incidence of major organ dysfunction after on-pump cardiac surgery. To control for intraoperative changes in cerebral perfusion, the second objective was the impact of intraoperative cerebral desaturation on postoperative cognitive and major organ function. The third objective was whether the impact of cerebral desaturation on postoperative function was dependent on the anaesthesia regimen used. The question whether patients are able to complete cognitive testing at all as early as 2 days after cardiac surgery was another secondary objective.

## Methods

### Patients and study design

The study is registered in the European Clinical Trials Database no. 2005-004928-39 and the ISRCTN Register (ISRCTN44821042).

After approval of the local ethical committee and written informed consent, 128 patients undergoing elective cardiac surgery with CPB were enrolled in this prospective randomized study. Exclusion criteria were age below 18 yr, overt neurological diseases or dementia, significant stenosis of the carotid arteries, pregnancy, contraindications for sevoflurane, insufficient knowledge of the German language, and emergency indication.

The randomization was performed after written informed consent was obtained. Multiple randomization lists stratified by age ($<$65 and $\geq$65 yr) and type of operative procedure (CABG, valve, or combined procedures) were used to provide equal groups.

### Justification of sample size

The size and direction of a possible difference in cognitive function between different anaesthesia regimens cannot be determined on the basis of empirical data. According to Cohen,[16] an effect size of $d$=0.50 is a low-to-median effect and should be clinically relevant. Assuming an $\alpha$ error of 5% and a $\beta$ error of 20%, a sample size of $N$=126 with $n$=63 in each group is considered sufficient to identify relevant group differences.

### Intervention

Oral premedication followed a standardized institutional protocol. All patients were equipped with a radial artery catheter, central venous catheter, and pulmonary artery catheter. Additionally, all patients were equipped with bi-hemispherical near-infrared spectroscopy sensors (INVOS Cerebral Oximeter 5100, Somanetics, Troy, MI, USA) (see below) and a bispectral index (BIS) probe on the forehead.

Before CPB, all patients received 400 IU kg$^{-1}$ heparin, achieving an activated clotting time above 500 s. Surgery was performed in moderate hypothermia using antegrade blood cardioplegia according to Buckberg and $\alpha$-stat pH management. After weaning from CPB, protamine was applied as appropriate.

#### Anaesthesia protocol for the volatile group (SEVO)

Anaesthesia was induced with etomidate 0.2–0.3 mg kg$^{-1}$ and sufentanil 1 $\mu$g kg$^{-1}$ and maintained with remifentanil 0.2–0.25 $\mu$g kg$^{-1}$ min$^{-1}$ and sevoflurane 0.6–1 mean alveolar concentration aiming at a BIS of 40–50. Pancuronium bromide 0.07–0.1 mg kg$^{-1}$ was used for relaxation.

During the study period, there was no approval of the technical inspection authority to apply sevoflurane during CPB. During CPB, propofol 3–5 mg kg$^{-1}$ h$^{-1}$ was applied according to BIS (aim 40–50). After the release of the aortic cross-clamp, sevoflurane was continued and the propofol infusion stopped. During sternal closure, 1 g of metamizol and piritramid 15 mg were given i.v. For transport to the intensive care unit (ICU), the remifentanil infusion was stopped, and propofol 2 mg kg$^{-1}$ h$^{-1}$ was started and maintained until normothermia, haemodynamic stability, and sufficient spontaneous breathing were achieved. Piritramide and pethidin were applied for analgesia as required. An overview of the two different protocols is given in Table 1.

#### Anaesthesia protocol for the i.v. group (PROP)

Induction of anaesthesia and postoperative treatment in the i.v. group was identical to the volatile anaesthesia group, but anaesthesia was maintained with remifentanil 0.2–0.25 $\mu$g kg$^{-1}$ min$^{-1}$ and propofol 3–5 mg kg$^{-1}$ h$^{-1}$ as required to achieve a BIS of 40–50.

### Neurocognitive and psychometric tests

All patients performed a set of psychometric and neurocognitive tests on the day before surgery and 2, 4, and 6 days after surgery. For all cognitive tests, parallel versions were used at random at the different measurements. The tests were selected on the basis of the Statement of Consensus on Assessment of Neurobehavioral Outcomes After Cardiac Surgery[17] and adapted to a preceding study of our group.[18] Most of the tests are taken from the 'Nuremberg Geriatric

**Table 1** Anaesthesia protocol in the study groups. CPB, cardiopulmonary bypass; MAC, mean alveolar concentration; BIS, bispectral index

| | I.V. group (PROP) | Volatile group (SEVO) |
|---|---|---|
| Induction of anaesthesia | Etomidate 0.2–0.3 mg kg$^{-1}$, sufentanil 1 $\mu$g kg$^{-1}$, pancuronium 0.07–0.1 mg kg$^{-1}$ | |
| Maintenance of anaesthesia before and after CPB | Remifentanil 0.2–0.25 $\mu$g kg$^{-1}$ min$^{-1}$, propofol 3–5 mg kg$^{-1}$ h$^{-1}$ achieving a BIS of 40–50 | Remifentanil 0.2–0.25 $\mu$g kg$^{-1}$ min$^{-1}$, sevoflurane 0.6–1 MAC (age-adapted) achieving a BIS of 40–50 |
| During CPB | Propofol 3–5 mg kg$^{-1}$ h$^{-1}$ according to BIS (aim 40–50) | |