Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction

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Background. Postoperative delirium in elderly patients is a frequent complication and associated with poor outcome. The aim of this parallel group study was to determine whether monitoring depth of anaesthesia influences the incidence of postoperative delirium.

Methods. Patients who were planned for surgery in general anaesthesia expected to last at least 60 min and who were older than 60 yr were included between March 2009 and May 2010. A total of 1277 patients of a consecutive sample were randomized (n=638 open, n=639 blinded) and the data of 1155 patients were analysed (n=575 open, n=580 blinded). In one group, the anaesthesiologists were allowed to use the bispectral index (BIS) data to guide anaesthesia, while in the other group, BIS monitoring was blinded. Cognitive function was evaluated at baseline, 1 week, and 3 months after operation.

Results. Delirium incidence was lower in patients guided with BIS. Postoperative delirium was detected in 95 patients (16.7%) in the intervention group compared with 124 patients (21.4%) in the control group (P=0.036). In a multivariate analysis, the percentage of episodes of deep anaesthesia (BIS values <20) were independently predictive for postoperative delirium (P=0.006; odds ratio 1.027). BIS monitoring did not alter the incidence of postoperative cognitive dysfunction (7th day P=0.062; 90th day P=0.372).

Conclusions. Intraoperative neuromonitoring is associated with a lower incidence of delirium, possibly by reducing extreme low BIS values. Therefore, in high-risk surgical patients, this may give the anaesthesiologist a possibility to influence one precipitating factor in the complex genesis of delirium.


Keywords: consciousness monitors; delirium; mild cognitive impairment

Accepted for publication: 20 December 2012
Depth of anaesthesia and cognitive outcome

presents the depth of anaesthesia as a single value. BIS values range from 0 to 100 and correlate with sedation and hypnosis. The BIS is used clinically to titrate anaesthetic drugs. BIS levels from 40 to 60 are deemed adequate for surgery. BIS was one of the earlier EEG index, and became one of the most widely used tools for EEG analysis. The BIS may help to provide patients with an anaesthesia that is neither too deep nor too light. BIS-guided anaesthesia may influence postoperative cognitive dysfunction and mortality, however, this still remains controversial. Crosby stated in a recent editorial, that current monitoring devices may be useful as a generic, all-purpose index of the brain’s response to anaesthetics, by changing ways of managing anaesthesia.

An influence of depth of sedation on delirium has been suggested; however, the influence on postoperative delirium remains unclear. We, therefore, designed a prospective, randomized clinical trial to assess whether BIS-guided anaesthesia vs routine care reduces the incidence of postoperative delirium in elderly patients.

Methods
Study design
This parallel group randomized controlled trial was conducted at the Charité-Universitätsmedizin Berlin, Germany, Department of Anaesthesiology and Surgical Intensive Care Medicine, at Campus Charité Mitte (CCM), and at Campus Virchow-Klinikum (CVK) between March 2009 and May 2010, and the follow-up was until August 2010. The institutional review board (IRB) approved the study (ref.: EA1/242/08) and all patients gave written informed consent. Local data privacy and security regulations were followed and the study was registered under ISRCTN 36437985.

The study was designed, the data were collected and analysed, and the manuscript was prepared exclusively by the study investigators. All authors ensured the accuracy and completeness of the data and the analysis.

Patients were eligible for the study if ≥ 60 yr undergoing elective surgery expected to last at least 60 min. The surgical procedures included interventions in general, abdominal, thoracic, vascular, orthopaedic, otorhinolaryngological, oral and maxillofacial, gynaecological, and urologic surgery. Patients who had cognitive impairment characterized by Mini-Mental State Examination (MMSE) of ≤ 24, or patients who had a history of neurologic deficits (e.g. stroke, history of seizures, etc.) were excluded. Other exclusion criteria were participation in a pharmaceutical study or patients not planned for general anaesthesia. Because a verbal response was needed for all tests, patients who did not speak the local language or who were unable to provide written informed consent were excluded.

The patients were consecutively recruited and after stratification according to American Society of Anesthesiologists’ physical status (ASA PS; I or II vs III or IV) and electronically randomized into two study groups. In one group, anaesthesia was provided with blinded BIS monitoring, while in the other group, BIS data were allowed to be included into the management of anaesthesia. After patients were enrolled and randomized, the OR schedule was checked. In case the already planned anaesthetist of the respective group was assigned, nothing changed. Otherwise, the OR schedule was adapted by the operating theatre coordinator. He selected the anaesthetists of the respective adjacent operating theatre, till an appropriate match was found, and was not involved in any other aspect of the study. Anaesthetists providing care for patients in the BIS-open group were instructed on BIS monitoring beforehand. Anaesthesiologists taking care of patients in the blinded group remained in this group for the duration of the study. Therefore, one group of anaesthetists always used BIS while the other group of anaesthetists never used BIS in this trial. This was introduced in order to avoid ‘learning contamination bias’. They suggested that using any new monitoring on a regular base might increase the awareness for changes caused by anaesthetics, especially in vulnerable patients, and therefore change the way of managing anaesthesia. Both teams were, however, regarding qualifications broadly comparable in order to avoid a possible ‘investigator bias’. A switch between the teams was excluded. Unblinding of monitoring was allowed if it was deemed necessary for the patient’s benefit.

Anaesthesia
All patients received pre-, peri- and postoperative treatment, as specified in the standard operating procedures (SOPs) of the Charité-Universitätsmedizin Berlin. Characteristics of the patients—including patient characteristic data—were recorded. According to our SOPs, premedication was ordered as described by Radtke and colleagues. Anaesthesia was performed and analgesia was provided as described by Mei and colleagues. According to our SOPs in case a sedative premedication is needed midazolam is prescribed in a dosage of 0.1 mg kg⁻¹ midazolam adjusted to the patient’s condition. Anaesthesia was induced using thiopental, propofol, or etomidate (depending on the indications), in combination with fentanyl or remifentanil, followed by neuromuscular block to facilitate tracheal intubation. Anaesthesia was maintained by total i.v. anaesthesia with propofol or volatile anaesthetics (desflurane, isoflurane, or sevoflurane). Patients received nitrous oxide at the discretion of the individual anaesthesiologist in charge. The anaesthesiologist was free to use standard regimens of opioid analgesics and neuromuscular blocking agents as required. Typically, for general anaesthesia without a combination with regional anaesthesia, intraoperative non-opioid (paracetamol 1 g/100 ml, metamizole 1–2 g/100 ml, or both) was routinely given 30 min before the end of surgery for postoperative pain management. For major operations such as gastrectomy, partial hepectectomy and thoracotomy, etc., opioid (piromid or morphine, 0.05–0.1 mg kg⁻¹) was given in combination with non-opioid 30 min before emergence. In the recovery
room, opioid and non-opioid pain medication was administered by nursing staff if numeric rating scale (NRS) >4; in case of NRS=3 or 4 pain medication was optional and given according to the patient’s desire.

**Measurements**

**Intraoperative monitoring**

Before induction of anaesthesia, bilateral BIS electrodes (Covidien, Boulder, CO, USA) were applied to the patient’s forehead as recommended by the manufacturer.

In the blinded group, the BIS monitor value was concealed, so that only the signal quality indicator was visible. During anaesthesia (including induction and emergence), data were recorded at minimum intervals of 1 min. Data were transferred directly from the monitor via Rugloop (http://www.demed.be/rugloop.htm). Manual records of anaesthesia and data from the internal memory of the BIS monitor were used as alternative sources in case of incomplete computer data.

**Assessment of delirium**

Delirium screening was performed by trained medical personnel, instructed and supervised by a psychiatrist and delirium experts. The observers were unaware of the treatment group. The group allocating patients and taking care of the equipment in the operating theatre were independent of the group that monitored patients after operation. In order to avoid bias research assistants rotated between both groups. Delirium was assessed twice daily (morning and night) on the ward or in the intensive care unit from the first to the seventh postoperative day. Postoperative delirium was assessed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM IV).

**Assessment of postoperative cognitive dysfunction**

The neuropsychological test battery consisted of tests provided by CANTAB® (Cantab Cognition, Cambridge, UK) which included a Motor Screening Test, two tests of visual memory (pattern recognition memory and spatial recognition memory) and a test of attention (choice reaction time). In addition, we used the visual verbal learning test and the Stroop Color Word interference test in three parallel versions that were applied in random order.

The first test session was administered the evening before surgery, as well as 7 days and 3 months after surgery or as soon as possible thereafter. The postoperative test was administered at the same time of day to avoid changes in cognitive function caused by time of day. The tests were carried out in quiet rooms and only the patient and investigator were present.

For definition of POCD the reliable change index (RCI) was used. A control group of 93 test persons older than 60 yr not undergoing surgery was used for calculation of the RCI according to the recommendations of Rasmussen and colleagues.25 The age- and MMSE-matched control group was recruited in nursing homes and senior citizens’ clubs.

POCD was defined in an individual when the RCI score was \(< -1.96\) on \(\geq 2\) tests, the combined \(Z\) score was \(< -1.96\), or both.

**Mortality**

Mortality was recorded for 3 months after operation. A multiple logistic regression analysis between known risk factors (BIS open vs blinded, age, MMSE values, duration of surgery, ASA physical status, delirium, and % BIS<20) and mortality was conducted.

**Statistical analysis**

**Sample size calculation**

The expected delirium incidence was assumed to be 15% and anaesthesia with additional BIS monitoring was expected to reduce the incidence of early delirium to 10% (33%) and considered clinically relevant. Thus, it follows for the patients number with Fisher’s exact test and two groups of equal proportions. Odds ratio (OR)=1, 2 sided test with a power of 80%, test significance level, \(\alpha =0.050\).

Group 1 proportion, \(\pi_1=0.150\),

Group 2 proportion, \(\pi_2=0.100\), and

\(n\) per group=725.

With a dropout rate of ~5% overall 1522 patients (761 per group) were to be included into the study. They were to be recruited consecutively.

Results were expressed as arithmetic mean standard deviation (sd) or frequencies with percentages, respectively, as described by Radtke and colleagues.25 ORs and regression coefficients with 95% confidence intervals (CIs) were determined in the logistic regression analysis. A two-tailed \(P\)-value of \(< 0.05\) was considered statistically significant. In order to avoid overfitting of the logistic regression we applied a 10-fold cross-validation procedure with the following characteristics: we selected those features in the repeated backward feature selections, which arose at least eight times and had a correlation which each other of \(\leq 0.6\) in the validations. With the obtained features we constructed a new (validated) regression model. With respect to the primary endpoint POD the following features resulted: BIS open vs blinded, age, MMSE values, duration of surgery, ASA physical status, and % BIS<20. Concato and Feinstein26 stated when the ratio of events to the number of covariates in logistic regression is \(<10\rightarrow 20\), the algebraic model leads to imprecise or spurious results.

Referring to the primary endpoint POD with altogether 111 events, we included these fix factors into the logistic regression, leading to a ratio of \(111/6=18.5\) that fulfils Concato’s condition.

For reasons of comparability we chose the same features in the calculation of mortality.

All numerical calculations were performed with SPSS, Version 19. Forest plots were created with Microsoft Excel.
2003 and forest plots in Excel software (data sheet) from Clark and Djulbegovic (available at www.evidencias.com).

Results
An estimated 13,605 patients were screened for eligibility (7,200 at Campus Charité Mitte and 6,405 at Campus Virchow-Klinikum). Of these, 1,277 were enrolled over the course of a 15-month period, from March 2009 through May 2010. The trial was stopped early because of limited funding. A total of 11,155 patients (n=575 open, n=580 blinded) remained for outcome in an intention to treat analysis (Fig. 1) Patient characteristics were similar in both groups (BIS guided and blinded; Table 1). Years of training of the anaesthesiologists were also similar (4.03 yr vs 4.14 yr, P=0.427).

Two surgical specialties and duration of surgery showed a significant difference between the two groups.

The number of average BIS values <20 showed a significant difference and absolute and relative numbers of BIS suppression ratio.

Postoperative delirium
Postoperative delirium was detected in 191 patients (18.8%). Of these, 95 patients (16.7%, 95% CI: 13.9–20.0) belonged to the open group while 124 patients (21.4%; 95% CI: 18.3–24.9%) were in the blinded group (P=0.036).

Patients with postoperative delirium showed BIS values <20 in absolute numbers and also in relation to surgical duration (%) significantly more often (Table 2). This was confirmed in multivariate analysis (Fig. 2). In addition, age, duration of surgery, and MMSE were significantly different in univariate (Table 2) and multivariate analysis (Fig. 2). BIS-guided anaesthesia vs BIS-blinded anaesthesia differed significantly in univariate analysis (Table 2), but not in multivariate analysis.

Delirium was associated with an increased length of hospital stay, higher incidence of POCD at 7 days and at 3 months after operation and increased mortality (P=0.015; OR; 2.05; CI=1.15–3.65).

After adjusting for relevant known covariates duration of surgery, ASA PS, and delirium were independent predictors for mortality (Fig. 3).
Postoperative cognitive dysfunction

POCD on the seventh postoperative day was increased in tendency in the BIS-blinded group [90 (23.9%) vs 70 (18.1%) P = 0.062; Table 2]. There was no correlation for POCD on the 19th postoperative day with BIS monitoring [28 (10.3%) vs 21 (8.0%), P = 0.372; see Table 2].

Patients who were unblinded for different durations during the procedure, remained in the BIS-blinded group as randomized. In addition to this intention to treat analysis we also performed a per protocol analysis. Therefore, we included patients of the BIS-blinded group, into the BIS-open group, which led to non-significant association between BIS-open/blinded patients and postoperative delirium (P = 0.053; 4.7%, 95% CI, 0–9.5%).

Discussion

The main finding of this study was that BIS-guided anaesthesia vs routine care reduces the incidence of delirium in elderly patients. This may be caused by reducing extreme low BIS values. BIS values <20 significantly correlated with the

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**Table 1** Patient characteristics. ASA PS, American Society of Anesthesiologists physical status; MMSE, mini–mental state examination. Data were expressed as mean (so) except for categorical data as number and percentage; P-values with respect to χ² test or Mann–Whitney U-test, respectively, for independent variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>BIS guided (n = 575)</th>
<th>BIS blinded (n = 580)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean in yr)</td>
<td>69.7 (6.3)</td>
<td>70.1 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>257 (44.7%)</td>
<td>276 (47.6%)</td>
<td></td>
</tr>
<tr>
<td>ASA PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I and II</td>
<td>305 (53.0%)</td>
<td>300 (51.7%)</td>
<td></td>
</tr>
<tr>
<td>III and IV</td>
<td>270 (47.0%)</td>
<td>280 (48.3%)</td>
<td></td>
</tr>
<tr>
<td>Surgical specialty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General surgery</td>
<td>275 (47.8%)</td>
<td>284 (49.0%)</td>
<td></td>
</tr>
<tr>
<td>Orthopaedics</td>
<td>182 (31.7%)</td>
<td>153 (26.4%)</td>
<td></td>
</tr>
<tr>
<td>Urology</td>
<td>40 (7.0%)</td>
<td>63 (10.9%)</td>
<td></td>
</tr>
<tr>
<td>Gynaecology</td>
<td>64 (11.1%)</td>
<td>61 (10.5%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>14 (2.4%)</td>
<td>19 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>MMSE (mean)</td>
<td>28.8 (1.5)</td>
<td>28.9 (1.5)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2** Comparison of BIS guided in contrast to BIS-blinded anaesthesia. LOS, length of stay; N Avg BIS, number of average BIS values; % Avg BIS, percentage of BIS values in relation to total BIS values; SR, suppression ratio. Data were expressed as mean (so) except for categorical data as number and percentage; P-values with respect to χ² test or Mann–Whitney U-test, respectively, for independent variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>BIS guided (n = 575)</th>
<th>BIS blinded (n = 580)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaesthetic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol (TIVA)</td>
<td>178 (31.0%)</td>
<td>149 (25.7%)</td>
<td>0.050</td>
</tr>
<tr>
<td>Volatile anaesthesia</td>
<td>397 (69.0%)</td>
<td>431 (74.3%)</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>409 (71.1%)</td>
<td>391 (67.4%)</td>
<td>0.181</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>166 (28.9%)</td>
<td>189 (32.6%)</td>
<td></td>
</tr>
<tr>
<td>Postoperative delirium (DSM-IV)</td>
<td>95 (16.7%; 95% CI: 13.87–19.96%)</td>
<td>124 (21.4%; 95% CI: 18.24–24.90%)</td>
<td>0.036</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>164 (98)</td>
<td>175 (105)</td>
<td>0.055</td>
</tr>
<tr>
<td>POCD 7th postoperative day</td>
<td>70 (18.1%)</td>
<td>90 (23.9%)</td>
<td>0.062</td>
</tr>
<tr>
<td>POCD 9th postoperative day</td>
<td>21 (8.0%)</td>
<td>28 (10.3%)</td>
<td>0.372</td>
</tr>
<tr>
<td>Death</td>
<td>31 (5.4%; 95% CI: 3.82–7.55%)</td>
<td>31 (5.3%; 95% CI: 3.79–7.49%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Postoperative LOS</td>
<td>15.7 (16.9)</td>
<td>15.9 (14.6)</td>
<td>0.818</td>
</tr>
<tr>
<td>N BIS values</td>
<td>163.2 (99.2)</td>
<td>169.7 (104.9)</td>
<td>0.307</td>
</tr>
<tr>
<td>Mean Avg BIS</td>
<td>39.0 (7.2)</td>
<td>38.7 (7.4)</td>
<td>0.472</td>
</tr>
<tr>
<td>N Avg BIS &gt;60</td>
<td>4.9 (12.0)</td>
<td>4.6 (11.3)</td>
<td>0.601</td>
</tr>
<tr>
<td>N Avg BIS &lt;40</td>
<td>81.5 (74.5)</td>
<td>85.2 (82.3)</td>
<td>0.431</td>
</tr>
<tr>
<td>N Avg BIS &lt;30</td>
<td>24.7 (41.0)</td>
<td>27.5 (47.8)</td>
<td>0.295</td>
</tr>
<tr>
<td>N Avg BIS &lt;20</td>
<td>3.7 (10.8)</td>
<td>5.6 (19.5)</td>
<td>0.040</td>
</tr>
<tr>
<td>Mean Avg SR</td>
<td>7.1 (12.9)</td>
<td>8.8 (16.3)</td>
<td>0.059</td>
</tr>
<tr>
<td>% Avg BIS &gt;60</td>
<td>2.3 (5.4)</td>
<td>2.4 (7.5)</td>
<td>0.963</td>
</tr>
<tr>
<td>% Avg BIS 60–45</td>
<td>21.4 (24.7)</td>
<td>23.6 (27.9)</td>
<td>0.183</td>
</tr>
<tr>
<td>% Avg BIS 40–45</td>
<td>26.0 (22.4)</td>
<td>25.4 (22.4)</td>
<td>0.675</td>
</tr>
<tr>
<td>% Avg BIS &lt;40</td>
<td>50.4 (34.2)</td>
<td>49.6 (34.9)</td>
<td>0.709</td>
</tr>
<tr>
<td>% Avg BIS &lt;30</td>
<td>16.4 (23.9)</td>
<td>17.2 (26.6)</td>
<td>0.596</td>
</tr>
<tr>
<td>% Avg BIS &lt;20</td>
<td>2.4 (6.7)</td>
<td>3.4 (9.9)</td>
<td>0.065</td>
</tr>
<tr>
<td>% Avg SR</td>
<td>5.1 (9.3)</td>
<td>7.5 (14.5)</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Fig 2 Comparison of patients with and without postoperative delirium (multivariate analysis). MMSE, Mini–Mental State Examination. Multiple logistic regression with delirium as response was conducted in order to confirm the results multivariately with BIS open vs blinded, age, MMSE values, duration of surgery, ASA physical status, and % BIS < 20 as variables.

Fig 3 Multivariate analysis of mortality after 3 months. ASA PS, American Society of Anesthesiologists physical status. Multiple logistic regression with mortality at 3 months as response was conducted with BIS open vs blinded, age, MMSE values, duration of surgery, ASA physical status, delirium, and % BIS < 20 as variables.
incidence of postoperative delirium. However, as BIS<20 was a post hoc analysis, this is merely a hypothesis-generating observation. In addition, the average burst suppression ratio and BIS values <20 in absolute and relative numbers were increased in the routine care (blinded) group. The suppression ratio quantifies the percentage of suppression during burst suppression pattern. According to Bruhn and colleagues, BIS values <30 are linearly correlated with the burst suppression ratio. This suggests that BIS monitoring helped to avoid extreme low values. Interestingly, the mean BIS values in both groups did not differ. In neither group did the mean BIS value decrease in the suggested range of 40–60. This may indicate that the anaesthetists either did not aim to follow the recommended BIS range despite repeated training, or were not capable of attaining the suggested range in clinical routine. Instead they incorporated the additional information mainly to avoid extreme low values.

Patients responding with low BIS values to anaesthetics might indicate a higher vulnerability. A different pharmacodynamic caused by an increased comorbidity may be the reason leading to higher mortality in these patients. According to Fedorow and Grocott using the BIS to titrate anaesthetic agents may avoid unnecessary increases in anaesthesia levels and possible neurotoxic effects in especially vulnerable patients.

Neuromonitoring may lead to a less ‘roller-coaster’-like anaesthesia. Rundshagen and colleagues suggest that guidance of anaesthesia with neuromonitoring leads to fewer deviations from a defined target than clinical assessment of anaesthetic depth only.

Other known risk factors for an increased incidence of delirium such as duration of surgery, prolonged fluid fasting, low Mini Mental Score, higher age and ASA physical status, and surgical specialty did not differ between both study groups.

To further evaluate BIS monitoring and depth of anaesthesia as independent predictors for delirium, we performed a multivariate analysis adjusted with relevant covariates.

In multivariate analysis, we confirmed the influence of extremely low BIS values for delirium. Additional factors such as duration of surgery, MMSE, and age were also confirmed. Although delirium was an independent predictor for mortality, monitoring depth of anaesthesia showed no significant difference between both study groups with regards to mortality after 3 months (Fig. 3).

Limitation of the study
Of the BIS-blinded group 141 patients were unblinded during the procedure at some point of time. Some of these patients remained open for the remainder of the procedure, while others were just unblinded for one or more phases during the procedure. We analysed these patients in an intention to treat approach attributable to the fact most of these patients still received predominantly BIS-blinded anaesthesia. The delirium incidence in these 141 patients, was 19.9% (28/141), being in between both groups (16.7 and 21.4%). However, if these 141 patients were included in the BIS-open group, the association between blinded/open BIS and postoperative delirium would no longer be significant (P=0.053).

In conclusion, intraoperative neuromonitoring may change anaesthetic management and is correlated with a lower incidence of delirium, possibly by reducing extreme low BIS values. Therefore, in high-risk surgical patients this may give the anaesthesiologist at hand a possibility to influence one precipitating factor in the complex genesis of delirium.

Acknowledgements
Anja Harbeck-Seu, MD, Department of Anaesthesiology and Surgical Intensive Care Medicine, Campus Charité Mitte and Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, data collection, received no compensation. Edith Weiss-Gerlach, Doctor of Health Sciences Psychologist, Department of Anaesthesiology and Surgical Intensive Care Medicine, Campus Charité Mitte and Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, data collection, received no compensation. Bruno Neuner, MD, Psychiatrist, Department of Anaesthesiology and Surgical Intensive Care Medicine, Campus Charité Mitte and Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, data collection, received no compensation.

Declaration of interest
None declared.

Funding
This work was supported by Charité-Universitätsmedizin Berlin with additional funding provided by Aspect Medical Systems, now Covidien.

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Handling editor: A. R. Absalom