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Monitoring level of sedation with bispectral EEG analysis: comparison between hypothermic and normothermic cardiopulmonary bypass†

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The level of sedation of 28 patients undergoing elective coronary artery bypass grafting with fentanyl–propofol anaesthesia was monitored with bispectral analysis (BIS), spectral edge frequency, and band power of the electroencephalogram. Fourteen patients underwent hypothermic cardiopulmonary bypass (CPB) (32°C, group H), and 14 normothermic CPB (group N). The level of sedation was measured with Observer's Assessment of Alertness/Sedation Score and with Ramsay Sedation Score. BIS was the only EEG measurement that paralleled the clinical course of the patients' sedation level. Values (median, 95% confidence intervals (CI)) changed significantly over time in both groups ($P<0.0001$). In group H, BIS decreased from 97 (95, 99) the day before surgery to 48 (44, 52) after tracheal intubation, to 46 (41, 52) before going off CPB, to 91 (85, 97) immediately before extubation. In group N, values were 93 (91, 97) the day before surgery, 53 (47, 59) after tracheal intubation, 48 (43, 53) before going off CPB, and 90 (84, 96) before extubation. During CPB, BIS values were significantly different between the two groups. Group H had a median of 41 (95% CI, 39, 42), and group N had a median of 49 (95% CI, 48, 51, $P<0.0001$). Peak values of all other processed EEG parameters during anaesthesia and surgery overlapped with values from the day before, when patients had no sedating medication, and these values did not correlate to the patients' course of sedation during the study. There was no explicit recall of the surgery in either group. During the phases of anaesthesia and surgery without CPB, the progression of BIS levels was comparable with previously published data for non-cardiac surgery. During normothermic CPB, the highest BIS values were close to values representing insufficient depth of sedation. It remains to be elucidated whether the much lower BIS values in the hypothermic group were solely a result of brain cooling or if increased serum propofol concentrations, because of slowed pharmacodynamics during hypothermia, also contributed.

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Anaesthesia during cardiopulmonary bypass (CPB) is unique, and potential awareness remains a particular problem.[1–3] The fact that CPB alters pharmacokinetics and pharmacodynamics of drugs and that virtually all physiological processes of drug absorption, distribution, metabolism, and elimination are affected by abnormal conditions, including haemodilution, hypotension, hypothermia, and nonpulsatile blood flow, may lead to administration of inappropriately high or low doses of hypnotics and anaesthetics. The oxygenator and tubing may bind large amounts of drugs used in cardiac anaesthesia.[4 5] Hypothermia and hypothermic CPB are associated with a decreased level of consciousness and decreased metabolic rate. It is, therefore, hypothesized that the high-risk periods occur when the patient is rewarmed.[1]

Many reports suggest that electroencephalographic (EEG) variables do not predict depth of anaesthesia,[6–9]

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but these studies use the classic definition of anaesthetic depth, which means that they do not separate clinical signs, such as the patient's movements or arterial pressure rise, from awareness. The definition of awareness is a degree of consciousness occurring during the period in which the patient is presumed to be under general anaesthesia.[2] This state of consciousness has been revealed post-operatively by testing explicit memory and relies on the patient's ability to remember, with or without prompting, events that occurred during general anaesthesia.[2]

Several years ago, an EEG processing method based on the interfrequency relationship was introduced to clinical monitoring. This bispectral analysis of the EEG has provided a new variable, the bispectral index (BIS), which has been shown to be of great value in detecting consciousness and predicting movement during anaesthesia of surgical patients.[10 11] The EEG and BIS are known not to be affected by transition to CPB,[11] but at the same time there are no studies that compare the effects of moderately hypothermic CPB with those of normothermic CPB for cardiac surgical patients.

The aim of this study was to compare the effects of hypothermic and normothermic CPB on processed EEG parameters and BIS in patients undergoing elective cardiac surgery with a standard anaesthetic procedure. It was thought that phases of undersedation during rewarming or during any phase of normothermic CPB might be detected. The known correlation (or lack of it) between these parameters and the clinical level of sedation during induction of and emergence from anaesthesia in non-cardiac surgery[10] was expected to be reproducible and not different between the two groups.

Patients and methods

After obtaining approval from the ethics committee and written, informed patient consent, 28 patients scheduled for coronary artery bypass grafting (CABG) surgery were enrolled in the study. Fourteen patients underwent hypothermic CPB (group H) and 14 with normothermic CPB (group N). Exclusion criteria were pre-operative neurological disease, severely impaired renal or hepatic function, and a history of alcohol or drug abuse.

Pre-operative medications were continued until the day of surgery, with the exception of acetylsalicylic acid, diuretics, and angiotensin-converting enzyme inhibitors. During the pre-operative visit, the anaesthetist completed pre-operative risk score forms (Euroscore, Parsonnet Score). All patients were premedicated with oral flunitrazepam 45 min before induction.

Routine monitoring included two-channel electrocardiogram (II and V5), radial artery pressure, pulse oximetry, central venous pressure, transoesophageal echocardiography, blood and rectal temperature, capnography, and continuous monitoring of end-expiratory isoflurane concentration. The data from the routine monitoring were logged by computer at 60-s intervals.

Anaesthesia, provided by an anaesthetist blinded for EEG data, was induced with i.v. flunitrazepam and fentanyl. At loss of consciousness, the patients were paralysed with pancuronium, 0.1 mg kg^{-1}, the trachea was intubated, and the lungs were ventilated with air/oxygen by a Servo 900C ventilator (Siemens Elema AB, Upplands Väsby, Sweden). Central venous and, if indicated, pulmonary artery catheters (Baxter Intellicath or VIP, 7.5 F, Baxter Healthcare Corp., Irvine, CA, USA) were placed via the right internal jugular vein. Anaesthesia before CPB consisted of additional fentanyl and was supplemented, if indicated, with isoflurane. Inadequate anaesthesia was defined as an increase in mean arterial pressure of $\geqslant$15% above the normal arterial pressure for that patient (the mean of three pre-operative measurements) or by other autonomic signs, such as sweating or flushing, or somatic responses such as muscle movement, swallowing, or eye movement; and by a Ramsay Sedation Score of <6, which was assessed every 15 min during anaesthesia.[12] During CPB, sedation was provided by propofol, and analgesia was maintained with additional fentanyl.

After surgery, patients remained sedated with propofol in the intensive care unit (ICU) until they had rewarmed completely and had no significant bleeding. Subsequently, they were weaned from mechanical ventilation.

A post-operative risk assessment using APACHE II and SAPS II scoring systems was performed by the ICU residents who were blinded for all intra-operative EEG and BIS data.

We recorded two bipolar EEG channels (FpZ-F7, FpZ-F8 with an Aspect A 1000 EEG analyzer, Aspect Medical Systems, Natick, MA, USA) as recommended for BIS monitoring by the manufacturer of the monitor. Zipprep electrodes (Aspect Medical Systems) were applied to the scalp after mild abrasion with a cotton sponge, resulting in contact impedance <5 kΩ.

A baseline BIS value was recorded the day before surgery to avoid the effect of premedication. Recordings were made before induction, after induction, immediately before and after laryngoscopy and tracheal intubation, immediately before CPB, at 15-min intervals during CPB, immediately after CPB, at the end of surgery, and in the ICU when patients began to move.

The raw EEG signals were band-pass filtered to 0.5–30 Hz and processed in real time using version 3.12 of the BIS algorithm. Additional quantitative EEG variables, including absolute band powers and 95th-percentile spectral edge frequency, were also calculated online. With the help of the serial port, the quantitative EEG variables were digitally recorded every 5 s for the duration of the study, as were time-synchronized markers describing all clinical assessment events. Data were stored on a personal computer as text file and analysed off line with the help of Microsoft Excel™ (Microsoft Corp., Redmond, WA, USA).

Parameters containing BIS values above 100, parameters showing sudden high values in the electromyogram, as well as electrocautery, were identified as artefacts and were eliminated from further analysis. A band-power determination for the range 70–110 Hz was performed before band-pass filtering. The mean of the two EEG channels was used for statistical analysis. The values of EEG parameters at each event were calculated by averaging the values during 60–360 s of stable recording immediately before and after the selected events.

The level of sedation following premedication and before induction of anaesthesia was assessed by using the Observer's Assessment of Alertness/Sedation Score (OAAS)[13] (1=no response to tactile stimulation, 5=wide awake).

All patients were interviewed at 18 h after extubation by an investigator (P.H.). After an initial introduction, the structured interview began. Each patient was asked the following standard set of questions:

(1) What was the last thing you remember before surgery?

(2) What was the very next thing you remember?

(3) Can you remember anything in between these two periods?

(4) Did you have any dreams during your operation?

Data were analysed with ANOVA for repeated measurements and Greenhous-Geisser correction, with Mann–Whitney *U*-test and Bonferroni correction for differences between specific time points. For differences between groups with respect to pre-operative and intra-operative patient and procedure data, factorial ANOVA and Mann–Whitney *U*-test without Bonferroni correction were performed. *P* values of <0.05 were considered significant. Analyses were performed on an Apple Power Mac G 3 computer (MacOS 8.6) with Statview 4.5 and SuperAnova 1.11 software (Abacus Concepts Inc., Berkeley, CA, USA).

Results

Data as median value and 95% CI. Patient groups did not differ with respect to age, sex, body weight, pre-operative risk scores, or pre-operative medication (beta-blockers, nitrates, angiotensin-converting enzyme inhibitors, and calcium antagonists). There was also no difference in the doses of flunitrazepam, fentanyl, propofol, or isoflurane (Table 1).

The number of CABG anastomoses performed and the duration of the procedure did not differ between groups. However, duration of CPB, aortic cross-clamp time, and CPB temperature were significantly different (Table 2).

At the beginning of surgery, there was a significant increase in mean arterial pressure during tracheal intubation (median 71 (95% CI, 67, 75) before *vs* 77 (71, 83) after intubation) and during sternal split (76 (72, 80) before *vs* 84 (80, 88) after sternal split). Heart rate also significantly increased after sternal split (56 (52, 60) before *vs* 59 (57, 63) after). The two groups did not differ significantly with respect to mean arterial pressure or heart rate during the study period.

BIS values changed significantly over time (Fig. 1); baseline values were as expected for alert patients the day before surgery: median 97 (95% CI 95, 99) (group H) and 93 (91, 97) (group N). BIS values were lower when premedicated patients arrived in the operating theatre: 80 (76, 84) (group H) and 89 (77, 101) (group N). Values decreased further after induction of anaesthesia: 48 (44, 52) (group H) and 53 (47, 59) (group N). After discontinuation of sedation, BIS values gradually increased until they reached pre-operative baseline values before extubation in the ICU: 91 (85, 97) (group H) and 90 (84, 96) (group N). These values were not significantly different between groups (Fig. 1).

During CPB, BIS values were significantly lower in group H than in group N: median 41 (95% CI, 39, 42) (group H) *vs* 49 (48, 51) (group N) ($P=0.0001$). However, when corrected for temperature, BIS values were not significantly different between groups and did not change significantly over time (Fig. 2).

BIS was the only EEG-derived measurement that represented the time course of the patient's sedation, assessed either by OAAS or by clinical judgement (Ramsay Sedation Score, other autonomic signs). No overlapping occurred between values obtained the day before surgery (when patients were without sedating medication) and values obtained during anaesthesia and surgery (Fig. 1).

The time course of the remaining EEG parameters did not reflect sedation: values were either higher than baseline (as expected for A beta following benzodiazepine premedication) when patients arrived in the operating theatre (SEF, A alpha, A beta, A theta) (Fig. 1) or did not significantly change over time (A delta). Overlapping between values obtained the day before surgery and intra-operative values occurred in all these parameters.

With the exception of A theta, which showed no dependence on CPB temperature (median 50 (95% CI, 49, 50) (group H) *vs* 48 (47, 49) (group N)), during CPB, group H had significantly lower EEG parameter values than group N: SEF, 10 (10, 11) (group H) *vs* 13 (13, 14) (group N) ($P=0.0016$, Fig. 1); A alpha, 48 (47, 49) (group H) *vs* 51 (50, 52) (group N) ($P=0.0001$); A beta, 42 (41, 43) (group H) *vs* 44 (43, 45) (group N) ($P=0.0001$); A delta, 48 (47, 49) (group H) *vs* 51 (50, 52) (group N) ($P=0.0001$).

The values for OAAS differed significantly between those obtained the day before surgery (when all patients were fully alert and had a score of 5) and those obtained after premedication as well as those obtained shortly before induction of anaesthesia (Table 2). One of the patients remembered the insertion of catheters under local anaesthesia. The last thing all the other patients remembered was leaving their room on the ward, and no patients had explicit memory of intra-operative events as stated in the post-

Table 1 Patient and anaesthetic characteristics. Values are expressed as median and 95% confidence interval. No significant differences between groups. Abbreviations: CPB=cardiopulmonary bypass; LV=left ventricular; ACE=angiotensin-converting enzyme; Ca=calcium; EEG=electroencephalogram

	Hypothermic CPB 14 patients	**Normothermic CPB 14 patients**
Age (yr) [range]	66 (62, 70) [range 54–78]	68 (64, 72) [range 49–77]
Sex (f/m)	4/10	2/12
Body Mass Index	26.1 (24.5, 27.8)	26.3 (25.1, 27.5)
Pre-op LV ejection fraction (%)	62.5 (55.5, 69.5)	60.0 (63.4, 66.6)
Euroscore	3 (1, 5)	3 (1, 5)
Parsonnet Score	6 (4, 8)	4 (4, 8)
Pre-operative medication	*Number of patients*	*Number of patients*
Beta-blockers	12	10
Nitrates	5	6
ACE inhibitors	5	2
Ca antagonists	5	3
Premedication		
Flunitrazepam (μg kg^{-1})	24 (22, 26)	26 (23, 29)
Intra-operative anaesthetics		
Flunitrazepam (μg kg^{-1})	24 (20, 28)	19 (17, 21)
Fentanyl (μg kg^{-1})	36 (32, 40)	32 (30, 36)
Propofol during CPB (mg kg^{-1} h^{-1})	2.0 (1.6, 2.4)	1.6 (1.2, 2.0)
Propofol during entire anaesthesia (mg kg^{-1} h^{-1})	1.6 (1.2, 2.0)	1.3 (1.1, 1.5)
Isoflurane (vol. %)	0.14 (0.08, 0.2)	0.13 (0.07, 0.19)
Anaesthesia time (h)	7.0 (6.4, 7.6)	7.2 (6.4, 8.0)

Table 2 Sedation, surgical procedures and outcome. *Significantly different from the other two times (day before, entering the OR, or before induction) ($P<0.0001$). **Significantly different between groups ($P=0.002$). ***Significantly different between groups ($P=0.0003$). ****Significantly different between groups ($P<0.0001$). Values are expressed as median and 95% confidence interval. Abbreviations: CPB=cardiopulmonary bypass; OR=operating room; ICU=intensive care unit; ECG=electrocardiogram; RBB=right bundle branch block

	Hypothermic CPB 14 patients	**Normothermic CPB 14 patients**
Observer's Assessment of Alertness/Sedation Score		
Day before surgery	5 (0)	5 (0)
Entering the OR (premedicated)	3.8 (3.4, 4.2)	3.8 (3.6, 4.0)*
Before induction	3.4 (2.8, 4.0)	3.4 (3.0, 3.8)*
Surgical procedures		
Operation time (h)	4.6 (4.2, 5.0)	4.8 (4.2, 5.0)
CPB duration (min)	136 (118, 153)	87 (74, 100) **
Aortic cross-clamp time (min)	76 (64, 88)	45 (37, 53) ***
CPB temperature (°C)	33.5 (29.9, 34.1)	37.7 (37.5, 37.9) ****
Anastomoses performed	5.0 (4.4, 5.6)	5.0 (4.4, 5.6)
Outcome/complications		
APACHE II	12 (10, 13)	13 (12, 14)
SAPS II	25 (23, 27)	24 (21, 27)
Neurological dysfunction (transient post-op delirium)	2	1
Post-operative intubation time (h)	5.2 (2.7, 6.3)	4.2 (3.6, 4.8)
Length of stay in ICU (days)	2.0 (1.2, 2.8)	1.0 (0.4, 1.6)
ECG changes	0	1 (new RBB)
Atrial fibrillation	3	2
Significant enzyme elevation	0	0

operative structured interview. Patients did not wake up before weaning from the ventilator in the ICU.

The two groups did not differ with respect to the measured outcome variables (Table 2).

Discussion

BIS values found during our study were representative of sedation depth in all phases of anaesthesia without CPB and were comparable with previously published data for non-cardiac surgery. During CPB, there was a significant difference between the hypothermic group (group H) and the normothermic group (group N), and there were values in the normothermic group that were close to the level of undersedation, according to previous studies.

It is now well recognized that each anaesthetic produces a unique spectrum of pharmacologic actions, so the concept of a common 'depth of anaesthesia' may need to be revised to reflect the separate components of the ideal anaesthetic state. In general, a monitor of depth of anaesthesia can

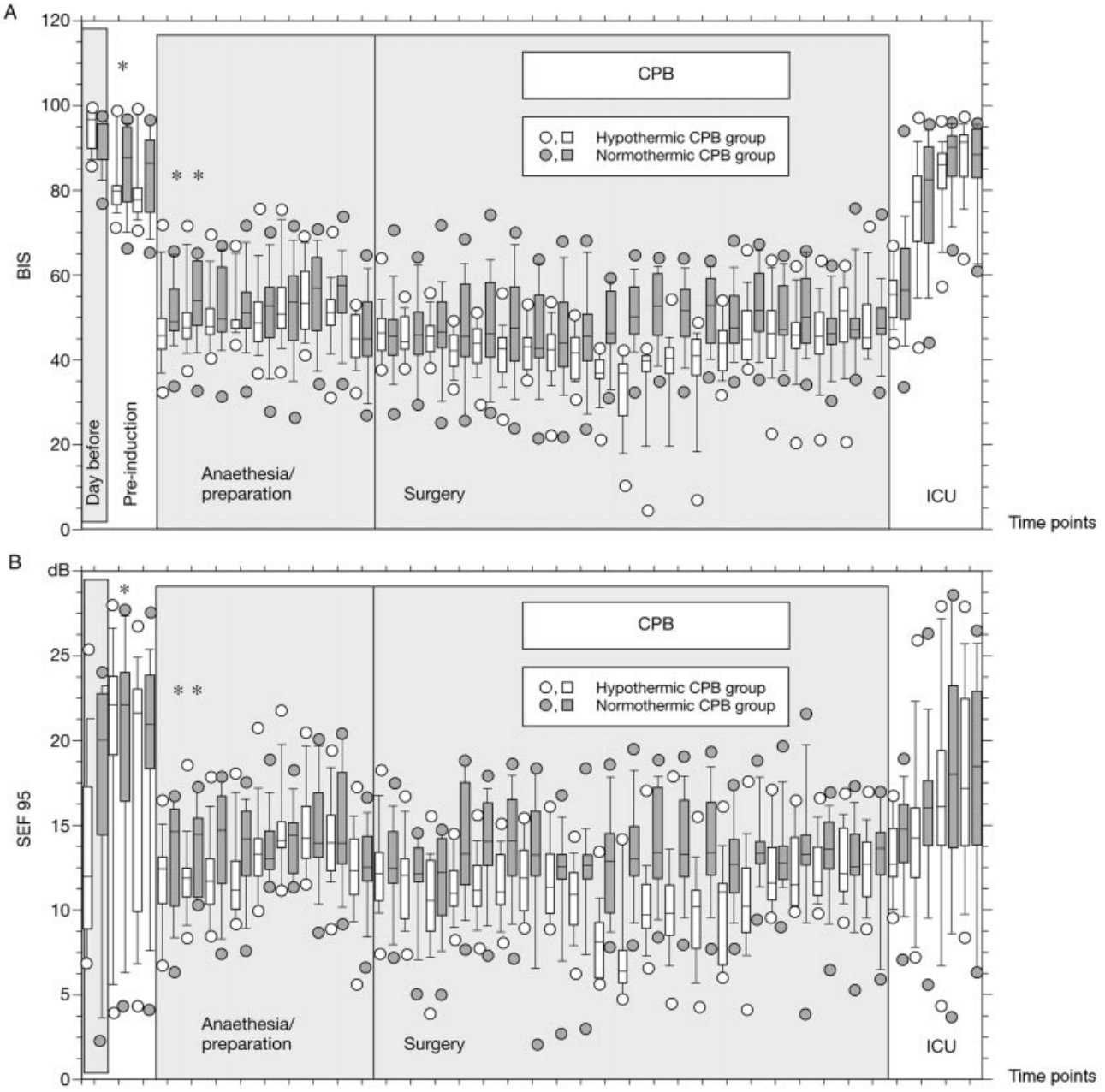

Fig 1 Processed EEG parameters (BIS, SEF 95). Open symbols represent the hypothermic CPB group, hatched symbols the normothermic CPB group. Significant changes over time are indicated by *, **, and ¶, as described below. Values of the box plots are expressed as median, 10th, 25th, 75th, and 90th percentile. Isolated values are depicted as circles. (A) BIS (bispectral analysis). *Day before surgery *vs* before induction of anaesthesia; P=0.0003. **Before induction *vs* after induction of anaesthesia; P<0.0003. ¶End of surgery *vs* clinical awakening; (P<0.0003). (B) SEF 95 (spectral edge frequency at 95% level). *Day before surgery *vs* before induction of anaesthesia; P=0.049. **Before induction *vs* after induction of anaesthesia; P=0.0024. ¶End of surgery *vs* clinical awakening; P=0.0018.

measure only one of these components, such as level of sedation, obtundity of noxious reflexes, or neuromuscular block.[14] Electromyogram signals of the frontotemporal region, however, play a role in the BIS algorithm; BIS values, therefore, may be influenced by temporalis muscle activity. In a study comparing BIS and frontal electromyogram at different propofol concentrations, Struys and colleagues[15] found only a weak correlation between these two parameters, especially during recovery from propofol anaesthesia.[11] Obligatory electrocautery caused interruption of the EEG signal; therefore, some critical phases of the operation were not monitored by that means.

EEG contamination by artefacts may be an issue when patients are at light levels of sedation and when muscle relaxation is no longer present, especially during emergence from anaesthesia in the ICU. Another source of artefacts is

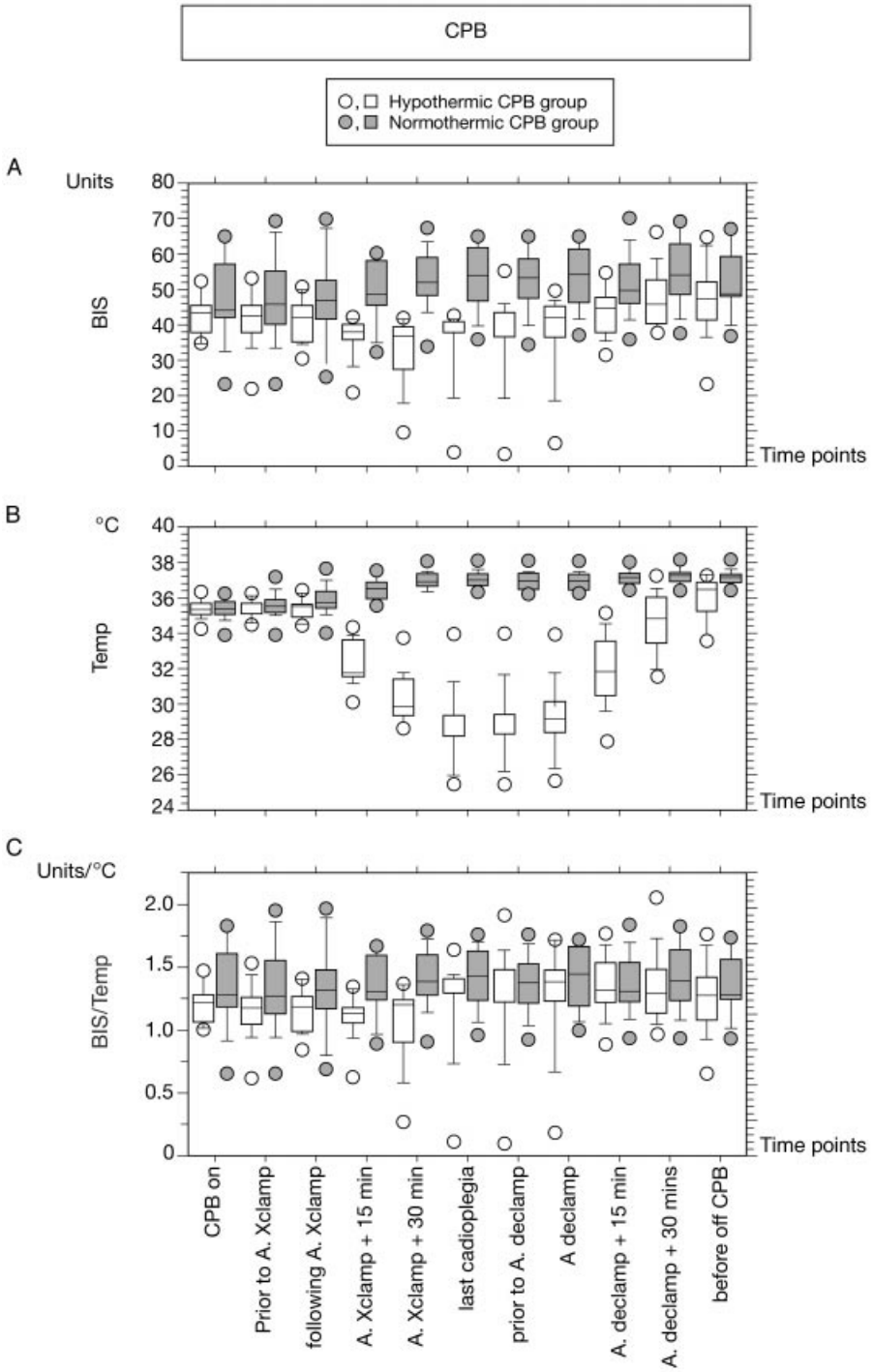

Fig 2 BIS and temperature during CPB. Open symbols represent the hypothermic CPB group, hatched symbols the normothermic CPB group. Values of the box plots are expressed as median, 10th, 25th, 75th, and 90th percentile. Isolated values are depicted as circles. (A) BIS during CPB. Values between groups were significantly different; P=0.001. (B) Blood temperature during CPB. Values between groups were significantly different; P<0.0001. (C) BIS values divided by blood temperature. There was no difference over time and no difference between the hypothermic and normothermic CPB groups.

direct moving of the EEG cables, which frequently happened because of manipulations of the transoesophageal probe or the pulmonary artery catheter. The electromyogram displayed on the BIS monitor made detection of these artefacts easy.

Because implicit memory recall was not assessed, we cannot exclude the possibility that patients perceived information during surgery that they did not explicitly recall. It is known that patients may respond to commands and display consciousness during surgery without post-

operative explicit memory.[16] In addition, flunitrazepam (like other benzodiazepines) produces at least some pharmacologically reversible antegrade amnesia,[17] a fact that may reduce the formation of explicit memory further. Because of its low reported incidence,[1–3] to detect cases of explicit awareness during CPB would require a much larger study population.

Different anaesthesia was used before CPB than during and after the bypass. At our institution, it is neither usual nor feasible to add isoflurane to the CPB circuit. Therefore, propofol was started with aortic cannulation and continued until weaning from the respirator in the ICU. There was no difference between groups, however, in application dose of isoflurane or propofol at any time point.

This study demonstrates that the decrease in OAAS rating (e.g. the decrease in patients' alertness) following flunitrazepam-induced sedation is reflected by BIS (Fig. 1). This finding was described by Liu and co-workers[18] for midazolam. As reported by others,[19 20] we found a benzodiazepine-induced increase in high-frequency beta power with sedation. SEF 95 also increased significantly following premedication, although variation of the values was very large (Fig. 1).

We found two phases of significantly increased mean arterial pressure—after intubation and after sternotomy. BIS levels in the same periods did not increase (Fig. 1). The difference between level of sedation and autonomic reaction to noxious stimuli was evident at these two time points.

BIS is an easily readable monitor of sedation in the phases of anaesthetic induction and emergence from anaesthesia, as demonstrated in non-cardiac surgery.[21 22] Our results for BIS values as well as for the other EEG parameters are in accordance with the findings of those studies.

During emergence from anaesthesia, BIS levels gradually increased until they reached pre-anaesthetic levels immediately before extubation. As has been shown in non-cardiac surgical patients, the increasing BIS values paralleled clinical awakening, individually and in the entire study group. We did not find overlapping BIS values between pre-anaesthetic levels and values during hypothermic CPB, in contrast to Doi and colleagues.[11]

Initiating CPB did not affect BIS levels. The fact that hypothermia significantly decreases BIS levels has been reported previously[11] and is expected because other EEG parameters also decrease when brain temperature decreases. Contrary to Doi's data, we found no variation in BIS values in the hypothermic group (Fig. 1). In his study, however, a different EEG-electrode montage (At1 and At2 with Fpz as reference and Fp1 as ground electrodes), a different propofol drug regimen (target-controlled infusion system) with target values between 3.5 (before CPB) and 2.0 mg ml^{-1} (30 min following CPB) as well as a different opioid (alfentanil) with continuous application technique was used. It remains speculative whether these methodological differences may account for the higher variation of BIS values during hypothermia in Doi's study.

We found no BIS value above 55 during hypothermia. Neither the difference from Doi's data nor the clinical significance of the lower BIS levels during hypothermia can be explained by our findings. We can only speculate that while we used almost identical doses of propofol in both groups during CPB, a relative underdosing of propofol during normothermia, as expressed by relatively high values of BIS, may have resulted. Plasma concentrations with comparable doses of propofol during hypothermic CPB were shown to be within the therapeutic range.[23 24] In the normothermic group, the 90th percentile of BIS during CPB was 64, whereas it was 54 in the hypothermic group. This means that some normothermic CPB patients (Fig. 2) exhibited critically high levels of BIS during extracorporeal circulation. As is known from previous work, BIS95 (the BIS level at which 95% of all patients do not present consciousness or recall) in a combined anaesthesia/sedation with opioids/propofol is about 50 for consciousness and 64 for recall in healthy volunteers.[14 25 26] In patients with midazolam/fentanyl anaesthesia, BIS levels during moderately hypothermic CPB varied considerably, leading to the authors' conclusion that in this type of anaesthesia, BIS does not accurately reflect either serum drug concentrations or the danger of awareness.[27]

The significantly lower BIS values during hypothermic CPB may imply that patients in this group were more sedated than those in the normothermic group, even if there was no measurable difference in sedation level between the groups with our study design. This could be the result of increased propofol blood concentrations due to decreased propofol biotransformation during hypothermia[23] and/or a simple effect of brain cooling and reduced electric activity of the brain. While the median difference of BIS between normothermia and hypothermia was as small as 8 and may seem to be clinically irrelevant, the variation of the values resulted in a considerable number of patients reaching critically high levels in the normothermic group.

It is evident, however, that either a higher dose of propofol for normothermic patients or a lower dose for hypothermic patients is required to achieve the same target BIS values. A controlled infusion of propofol with a target value of BIS must, therefore, be effective independent of temperature, as our data suggest when BIS is normalized for temperature.

To our knowledge, this study is the first to compare sedation by means of processed EEG parameters between patients undergoing hypothermic CPB with those undergoing normothermic CPB for CABG surgery. BIS was the only EEG parameter that correctly paralleled the various states of sedation and anaesthesia, from baseline to sedation and return to consciousness. The remaining EEG parameters measured in our study did not reliably reflect sedation, as reported previously.[15 28]

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