Impact of Bispectral Index Monitoring on Stress Response and Propofol Consumption in Patients Undergoing Coronary Artery Bypass Surgery

Michael Bauer, M.D.,* Wolfram Wilhelm, M.D.,† Thomas Kraemer, Ph.D.,‡ Sascha Kreuer, M.D.,§ Andreas Brandt, M.D.,§ Hans Anton Adams, M.D.,‖ Gudrun Hoff, M.D.,§ Reinhard Larsen, M.D.#

Background: Bispectral Index (BIS)–titrated administration allows a reduction of propofol infusion rates in patients undergoing surgery. Resulting differences in anesthetic depth might affect the stress response to surgery involving neural circuitry not reflected in the electroencephalogram.

Methods: Forty patients scheduled to undergo elective coronary artery bypass grafting receiving a background infusion of remifentanil ($0.3~\mu g \cdot kg^{-1} \cdot min^{-1}$) were anesthetized with intravenous propofol delivered by target-controlled infusion according to the Marsh pharmacokinetic model under BIS monitoring. In a randomized, prospective design, 20 patients received propofol at a target concentration of 3 $\mu g/ml$, whereas in 20 patients propofol was titrated to maintain a BIS value of 40–50. Plasma concentrations of propofol (by means of gas chromatography–mass spectrometry), epinephrine, norepinephrine (by means of high-pressure liquid chromatography), cortisol (by means of radioimmunoassay), and interleukins 6 and 10 (by means of enzyme-linked immunosorbent assay) were measured repeatedly throughout surgery.

Results: BIS monitoring allowed a 30% reduction of propofol infusion rates and a similar decrease in plasma propofol concentrations in the BIS group without affecting the stress response to surgery for the group mean. None of the patients reported awareness during a standardized interview. Interestingly, propofol–remifentanil anesthesia blunted the release of epinephrine and cortisol to bypass surgery completely even when the propofol infusion rate was reduced according to BIS values.

Conclusions: Total intravenous anesthesia using propofol–remifentanil effectively attenuates the neurohumoral stress response to coronary bypass surgery involving cardiopulmonary bypass. Titration of propofol using BIS allows for significant reduction of propofol consumption, with only minor effects on stress response under these conditions.

ELECTROENCEPHALOGRAPHIC monitoring may be used to assess effects of anesthetic drugs on the central nervous system, offering a tool to assess central nervous functional suppression or depth of anesthesia. More specifically, computerized electroencephalogram processing and display technology, such as Bispectral Index (BIS) monitoring, may be a useful tool to (1) titrate the hypnotic component of anesthesia[1–6]; (2) reduce drug consumption, thereby allowing faster recovery from anesthesia; and (3) avoid untoward side effects of anesthetics, such as hemodynamic instability.[7–11] However, there might be a substantial discrepancy regarding chosen pharmacodynamic endpoints and their individual correlation with the degree of electroencephalographic depression. Although the latter correlates well with the magnitude of hemodynamic responses to noxious stimulation resulting, for example, from laryngoscopy[12,13] as well as memory or awareness, the individual correlation with gross unpurposeful movement in response to surgical incision is less well defined.[14,15] There is widespread agreement that these inconsistent results reflect various factors, including the lack of linear changes in electroencephalographic depression with changes in depth of anesthetic plane as well as the fact that the electroencephalogram is a phenomenon of rostral structures, most notably the cerebral cortex, whereas changes in neuronal circuits in the brainstem or spinal cord are poorly reflected.[15]

The potential benefit of individual titration of anesthetic drugs based on electroencephalographic monitoring is particularly obvious in patients who are at risk of adverse effects of inadequate anesthesia, most notably hemodynamic instability. Therefore, the current study was designed to assess the impact of BIS-adjusted infusion of propofol on the stress response in patients undergoing coronary artery bypass surgery. This response to major surgery affects a variety of central nervous structures, such as the mesencephalon and diencephalon, which are influenced by central nervous networks involved in pain reception but which are not responsible *per se* for the generation of the electroencephalographic signal.

Materials and Methods

All chemicals were obtained from Sigma Chemicals (Munich, Germany) if not otherwise specified.

Patients and Study Design

After obtaining approval from the local ethics committee (Ärztekammer des Saarlandes, Saarbrücken, Germany) and written informed consent, 40 consecutive

* Associate Professor, Department of Anesthesiology and Critical Care Medicine, University of Saarland. Current position: Associate Professor, Department of Anesthesiology and Critical Care Medicine, Friedrich-Schiller-University, Jena, Germany. † Assistant Professor, § Resident, # Professor and Chair, Department of Anesthesiology and Critical Care Medicine, ‡ Assistant Professor, Department of Pharmacology and Clinical Toxicology, University of Saarland. ‖ Associate Professor, Department of Anesthesiology II, Hannover Medical School.

Address reprint requests to Dr. Bauer: Klinik für Anaesthesiologie und Intensivtherapie, der Friedrich-Schiller-Universität, Erlanger Allee 101, D-07747 Jena, Germany. Address electronic mail to: michael.bauer@med.uni-jena.de. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

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patients scheduled to undergo elective coronary artery bypass grafting (CABG) were enrolled in a prospective, randomized design. Patients with a history of previous cardiac surgery, concomitant congestive (ejection fraction < 40%; New York Heart Association grades III and IV) or valvular heart disease, myocardial infarction during the last 3 months, or evidence of coexisting malignant or immunologic diseases were excluded, as well as diabetic patients or those with significant renal (creatinine > 1.5 mg%) or hepatic dysfunction (aspartate amino transferase, alanine amino transferase > 50% over normal range). Oral premedication consisted of 1 mg flunitrazepam 1.5 h before induction. In the operating room, intravenous and arterial lines were inserted during local anesthesia, and standard monitors were applied, including an Aspect A-2000 BIS® monitor (Version XP; Aspect Medical Systems B.V., Leiden, The Netherlands); electrodes were placed on the forehead according to the manufacturer's instructions. Baseline readings of hemodynamics and BIS were taken 5–10 min after cannulation had been completed, and samples were obtained simultaneously for measurements of stress hormones and plasma propofol (baseline). Subsequently, patients were allowed to breathe oxygen and a remifentanil infusion was started at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The opioid was supplemented with propofol for hypnosis after 5 min using a commercial target-controlled infusion (TCI, Diprifusor; AstraZeneca, Wedel, Germany) initially adjusted to a target concentration of 3 $\mu g/ml$ according to the model of Marsh et al.[16] After loss of consciousness, oxygen was given by facemask ventilation, and atracurium was used to provide neuromuscular blockade; neuromuscular blockade was controlled by train-of-four monitoring, and additional boluses of atracurium were provided to ensure relaxation throughout surgery. The trachea was intubated 3–5 min later at a BIS values of less than 60, and the lungs were ventilated with oxygen-enriched air (fraction of inspired oxygen = 0.5) to an end-tidal carbon dioxide concentration of 35 mmHg, which was adjusted to maintain normocapnia based on arterial blood gas analysis.

Patients (n = 20/group) were randomly allocated to either standard practice, i.e., continuous infusion of propofol using a TCI target of 3 $\mu g/ml$ (TCI group), or a BIS-controlled adjustment of the propofol infusion to achieve a BIS value of 40–50 during the whole surgical procedure (BIS group). Propofol infusion rates were adjusted in the BIS group in increments or decrements of 10% of the actual infusion rate every 5–10 min, so that actual measurement could be out of the defined range in between adjustments. However, propofol infusion rates were not reduced below a predicted target concentration of 1 $\mu g/ml$.

The remifentanil infusion was adjusted to 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with surgical incision in all patients. All data were analyzed on an intent-to-treat basis with respect to allocation to TCI and BIS groups, irrespective of the achieved BIS values in both groups.

The extracorporal circuit was primed with 1 l lactated Ringer's solution and 0.5 l colloidal gelatin (Gelafundin; Braun, Melsungen, Germany), and cardiopulmonary bypass (CPB) was performed with moderate hypothermia (31°–32°C rectal temperature) and acid–base correction. A perfusion volume of 2.4 $l \cdot min^{-1} \cdot m^{-2}$ was maintained throughout CPB, and myocardial protection was achieved by antegrade application of cooled St. Thomas' solution into the aortic root after cross clamping. Norepinephrine (≤ 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was used to restore systemic vascular resistance, i.e., the constant infusion was adjusted to a target mean arterial pressure of 60 mmHg at a CPB flow rate of 2.4 $l \cdot min^{-1} \cdot m^{-2}$ while no other catecholamines were administered for weaning from CPB. All patients were transferred from the operating room to the surgical intensive care unit, where they were weaned from ventilation on the day of admission according to standard protocols and based on the decision of the attending cardiac surgeon. All measurements were repeated, and samples specified above for baseline were taken again after intubation of the trachea (intubation), after sternotomy (sternotomy), immediately before weaning from CPB (extracorporeal circulation), and after skin closure (end of operation). Patients were followed up with a standardized interview for intraoperative awareness on the first and third postoperative day as described by Dowd et al.[17]

Assessment of Plasma Propofol Concentration

Samples were taken from the arterial line into pyrogen-free serum tubes (Sarstedt Monovette, Nuembrecht, Germany), and serum was stored at −80°C after centrifugation until analysis.

Sample Preparation. Serum samples (200 μl) in 1.5-ml reaction vials were mixed with toluol (200 μl). The reaction vials were sealed and left on a rotary shaker at room temperature for 10 min. Thereafter, the vials were centrifuged (10,000g, 2 min), and 100 μl of the upper phase was transferred to autosampler vials. Aliquots (2 μl) were injected into the gas chromatography–mass spectroscopy system. Aliquots of blank serum (200 μl) were spiked with propofol to obtain calibration samples at concentrations of 0.1, 1.0, 2.5, 5.0, 7.5, and 10.0 $\mu g/ml$. Quality control samples were prepared at concentrations of 2.0 and 8.0 $\mu g/ml$.

Gas Chromatography–Mass Spectrometry. The samples were analyzed using a Hewlett Packard HP 6890 Series GC system (Agilent, Waldbronn, Germany) combined with an HP 5972 Series mass selective detector, an HP 6890 Series injector, and an HP Chem Station G1701AA version A.03.00. The gas chromatography conditions were as follows: splitless injection mode; column, HP capillary (12 m × 0.2 mm ID), cross-linked methylsilicone, 330-nm film thickness; injection port

temperature, 280°C, carrier gas, helium; flow-rate 1 ml/min; column temperature, programmed from 100° to 310°C at 30°/min, initial time 3 min, final time 8 min. Mass spectrometry conditions were as follows: transfer line heater, 280°C; source temperature, 140°C; electron ionization mode; ionization energy, 70 eV; selected-ion monitoring with the ions m/z 163 (target ion), 178, and 117 (qualifiers). The propofol concentrations in the serum samples were calculated *via* daily prepared calibration curves. The method was selective and proved to be linear from 0.1 to 10 μg/ml. Accuracy and precision were within the required limits.

Measurements of Epinephrine, Norepinephrine, and Cortisol

Samples were taken from the arterial line into pyrogen-free EDTA (for assessment of epinephrine and norepinephrine)– or heparin (for assessment of cortisol)–containing tubes (Sarstedt Monovette) and kept on ice until centrifugation. Supernatants were subsequently frozen in liquid nitrogen and stored at −80°C until analysis. Epinephrine, norepinephrine, and cortisol plasma concentrations were measured in the supernatant using commercially available kits and standards (Clin Rep; Recipe, Munich, Germany; Coat-A-Count, Diagnostic Products Corp., Los Angeles, CA) by means of high-performance liquid chromatography (epinephrine, norepinephrine) or radioimmunoassay (cortisol) as we have described in detail previously.[18]

Measurement of Interleukins 6 and 10

Samples were taken from the arterial line into pyrogen-free citrate-anticoagulated tubes (Sarstedt Monovette) and kept on ice until centrifugation. Supernatants were frozen immediately in liquid nitrogen and kept at −80°C until analysis. Interleukin (IL)-6 and IL-10 concentrations were determined in supernatants by means of an enzyme-linked immunosorbent assay (Medgenix/Biosource, Ratingen, Germany). A detailed protocol including intraassay and interassay coefficients of variance for our laboratory has been published previously.[18,19]

Statistical Analysis

All data are presented as mean and SD, median, 25th and 75th percentile and range, or as individual data points for nonlinear regression analysis. Median prediction error (bias, equation 1) and median absolute prediction error (precision, equation 2) of the Diprifusor system were calculated according to the equations

$$\text{Bias} = \text{Median }\{PE_{ij}, i = 1, \ldots, k; j = 1, \ldots, N_i\} \quad (1)$$

$$\text{Precision} = \{|PE_{ij}|i = 1, \ldots, k; j = 1, \ldots, N_i\}, \quad (2)$$

Table 1. Demographic Data and Duration of Surgery, CPB, and AXC

	BIS	TCI
Age, yr	60 (48–65)	61 (46–64)
Height, cm	176 (164–188)	172 (164–183)
Weight, kg	84 (55–102)	79 (63–89)
Body mass index, kg/m^2	28 (19–31)	26 (21–31)
Duration of surgery, min	247 (202–288)	243 (189–303)
Duration of CPB, min	93 (48–124)	84 (43–132)
Duration of AXC, min	67 (33–100)	58 (21–108)

Data for patients receiving standard care (target-controlled infusion [TCI] or Bispectral Index (BIS)–titrated anesthesia. Data are presented as median (range) for n = 20 patients each; no significant differences were observed. AXC = aortic cross clamping; CPB = cardiopulmonary bypass.

where the prediction error of the jth measurement of the ith patient was calculated according to

$$PE_{ij} = (C_{measured} - C_{target})/C_{target} \times 100, \quad (3)$$

where N_i equals number of measurements of the ith patient, and k equals the number of patients.

Differences between the two groups were tested using the Mann–Whitney U test, whereas statistical differences from baseline were determined by Friedman repeated-measures analysis of variance on ranks, followed when significant by the Dunnett *post hoc* test. *A priori* power analysis indicated that a total of 20 patients/group would be sufficient to detect a 20–25% change in the stress hormone release with a power greater than 90% at α = 0.05. To assess for intersubject variability, nonlinear regression analysis for BIS, propofol concentration, and parameters of the stress response with a sigmoidal model were performed for the individual patients during the course of the operation using SigmaPlot 5.0 software (Jandel GmbH, Erkrath, Germany), and the best, worst, and median fits are shown. All other statistical tests were performed using the SigmaStat software package (Jandel GmbH). All P values are two-sided and are considered significant if P is less than 0.05.

Results

Demographic Data, Duration of Surgery, and Evidence of Awareness

Both groups were comparable with respect to age, weight, height, body mass index, duration of surgery, extracorporal circulation, and ischemia. Biometric data and patient characteristics are summarized in table 1. None of the patients reported intraoperative recall during the standardized interview on postoperative days 1 and 3.

Propofol Requirement, Plasma Concentrations, and Resulting BIS Values

A reduction of the infusion rates of propofol was required to maintain BIS values in the range of 40–50 in 16

of 20 patients in the BIS group, whereas 10 of 20 patients in the TCI group displayed BIS values of less than 40. Two patients in the BIS-guided group had BIS values repeatedly less than 40 because the study protocol prevented a further reduction of the infusion rate of propofol to a predicted target concentration of less than 1 μg/ml. The median propofol infusion rate including the induction dose equaled 6.8 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} for TCI, whereas electroencephalographic monitoring allowed for a reduction of the infusion rate to 4.3 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} in the BIS group ($P < 0.05$). Plasma concentrations of propofol displayed a similar reduction of roughly 30% as compared with standard practice when the propofol infusion was adjusted to achieve a BIS value of 40–50 (fig. 1). The higher propofol plasma concentrations in the TCI group were paralleled by lower BIS values reaching statistical significance after weaning from CPB (fig. 1). A significant correlation of TCI-predicted and measured propofol concentrations for the group mean was observed ($r^2 = 0.36$, $P < 0.01$; fig. 2), whereas no correlation between measured propofol concentration and BIS values ($r^2 = 0.003$) was established for individual patients (fig. 3). Bias and precision of the Diprifusor system were calculated as 39.4% and 40%, respectively. Figure 2B shows the results of nonlinear regression analysis for measured and predicted propofol concentrations in individual patients over time, with a median R of 0.73. The line of identity between measured and predicted plasma propofol concentration confirms a predominant underestimation of the measured plasma concentration for this patient group by the Diprifusor system. The individual correlation for measured propofol and BIS is summarized in figures 3B and C, indicating a median of −0.7 to −0.8 for the correlation of plasma propofol and electroencephalographic suppression.

Neurohumoral Stress Response

Total intravenous anesthesia using propofol–remifentanil prevented the substantial induction of a neurohumoral stress response with significant increases in the concentrations of circulating cortisol and catecholamines to CABG reported by us[18] and others,[20] which is likely to be influenced by suppression of nociceptive stimuli.[20] Plasma epinephrine concentrations were largely unaffected by surgery, whereas cortisol concentrations even decreased as compared with respective baseline values without differences between TCI and BIS groups for the group mean. Nonlinear regression analysis also revealed only a moderate or barely any correlation between plasma propofol concentration (fig. 4) or BIS (fig. 5) and the stress hormones epinephrine or cortisol. The significantly increased plasma norepinephrine concentrations at the end of extracorporal circulation and before discharge from the operating room reflect similar requirements of exogenous norepinephrine for weaning from CPB (table 2).
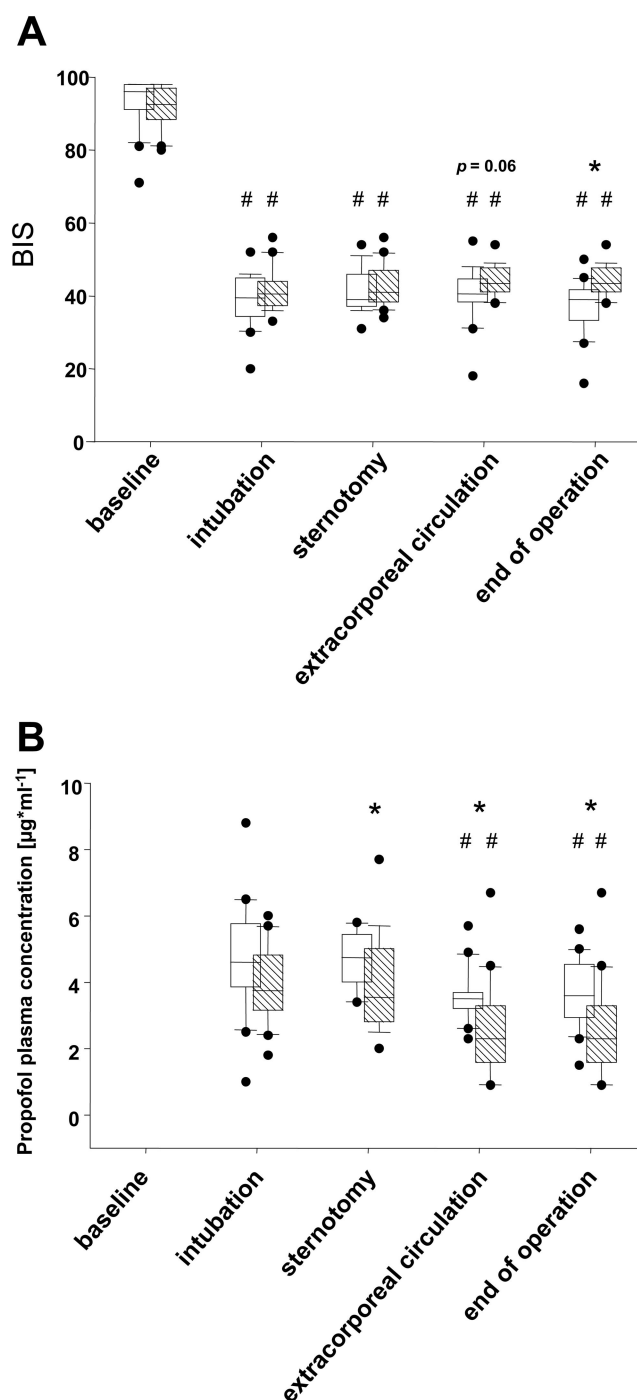

Fig. 1. Bispectral Index (BIS) values (*A*) and corresponding propofol plasma concentrations (*B*) in patients undergoing coronary artery bypass grafting during total intravenous anesthesia with propofol and remifentanil. Patients were randomly allocated to receive propofol either as a "fixed" target-controlled infusion with a target of 3 μg/ml (standard care; *empty bars*) or as a BIS-titrated infusion to maintain a BIS value of 40–50 (*hatched bars*). *Box plots* indicate median and 25th and 75th percentiles. # $P < 0.05$ as compared with respective baseline value for repeated-measures analysis of variance on ranks followed by Dunnett test. * $P < 0.05$ between standard care and BIS-titrated anesthesia.
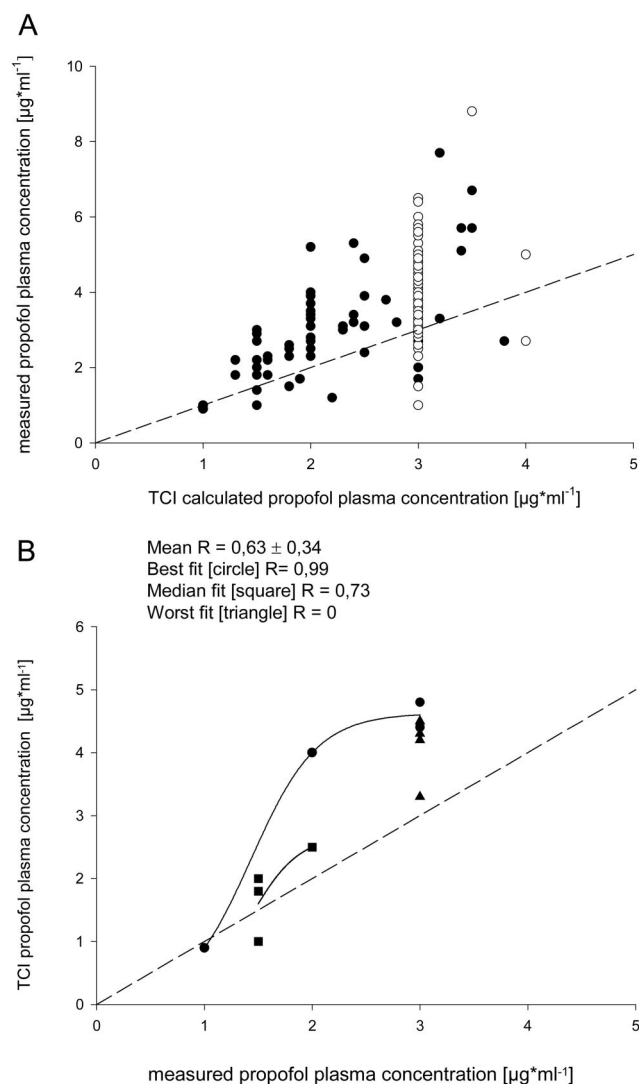
Fig. 2. (A) Pharmacokinetic performance of the target-controlled infusion (TCI) system according to the Marsh model in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. *Empty symbols* indicate measurements in the fixed TCI group. *Filled symbols* indicate correlation of TCI-calculated and measured propofol plasma concentrations in patients who underwent Bispectral Index–titrated adjustment of propofol infusion rates. (B) (Inset) Individual relations between measured and TCI-predicted plasma propofol concentrations for the patient with best (circle), median (square), and worst (triangle) fits. *Dashed lines* indicate line of identity.
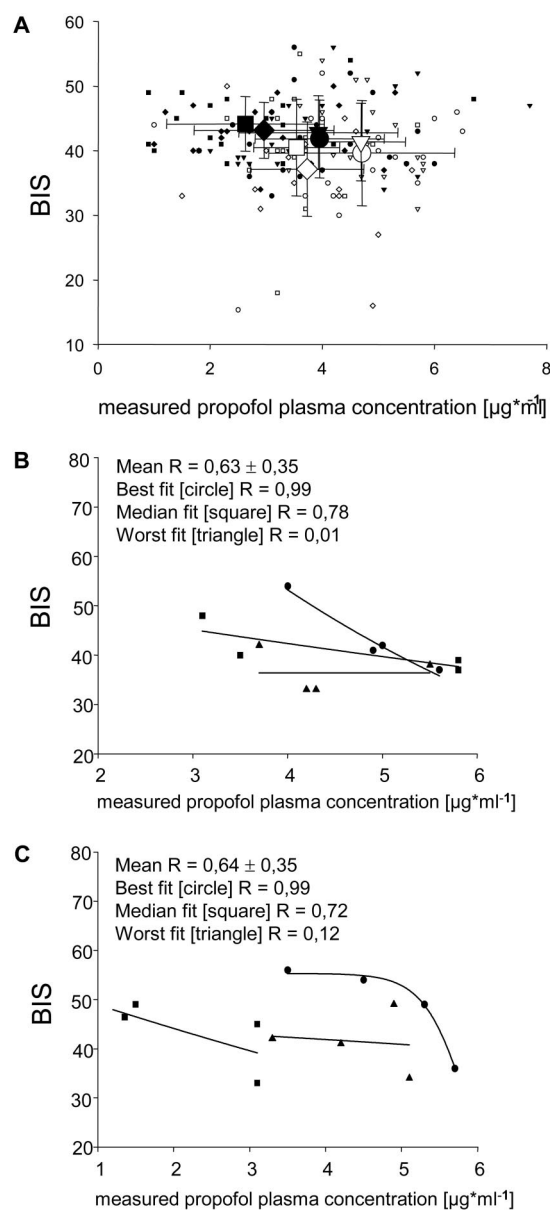
Fig. 3. Correlation of measured plasma propofol concentration and Bispectral Index (BIS) at different time points (*empty symbols* indicate target-controlled infusion/fixed infusion rate; *filled symbols* indicate BIS-titrated adjustment; *circles*, *triangles*, *squares*, and *diamonds* indicate the group mean ± SD for intubation, sternotomy, end of extracorporeal circulation, and end of operation, respectively). Data indicate a leftward (lower propofol) and upward (higher BIS) displacement with BIS-titrated propofol infusion as compared with target-controlled infusion according to the Marsh model (A). To address intersubject variability, individual correlations of measured plasma propofol concentrations *versus* BIS were performed for each patient over time indicating a moderate negative correlation for the group mean in both groups (B: target-controlled infusion; C: BIS). *Circle* indicates patient with best fit, *square* indicates patient with median fit, and *triangle* indicates patient with worst fit.

Hemodynamics and Catecholamine Support

Patients displayed stable macrohemodynamics throughout as reflected by mean arterial pressure and heart rates (table 3), and none of the patients required catecholamines before CPB. Central venous (TCI group, 4.5 [2.7/6.4]; BIS group, 3.3 [1.4/5.2] mmHg) and left atrial (TCI group, 3.2 [2.0/4.4]; BIS group, 3.5 [2.5/4.3] mmHg) filling pressures were similar after weaning from CPB. At this time point, lower BIS values (< 40), which are indicative of an inappropriate depth of anesthesia, were observed more frequently in the TCI group and tended to result in higher norepinephrine require-

ments, although this difference did not reach statistical significance. The body temperature was restored to approximately 36°C before weaning from CPB, and there were no differences regarding body temperature during
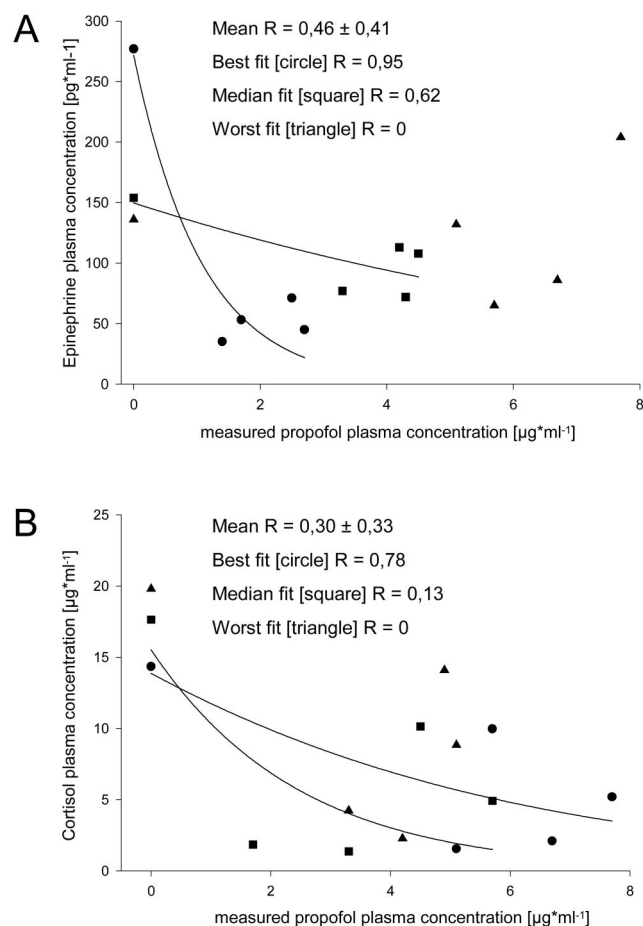
Fig. 4. Nonlinear regression analysis of measured propofol plasma concentration and stress hormones epinephrine (*A*) and cortisol (*B*) in plasma during coronary artery bypass grafting involving cardiopulmonary bypass for each patient over time. Individual relations between measured plasma propofol and the stress hormones are shown for the patient with best (*circle*), median (*square*), and worst fit (*triangle*). *R* = coefficient of correlation.

Fig. 5. Nonlinear regression analysis of Bispectral Index and stress hormones epinephrine (*A*) and cortisol (*B*) in plasma during coronary artery bypass grafting involving cardiopulmonary bypass for each patient over time. Individual relations between measured plasma propofol and the stress hormones are shown for the patient with best (*circle*), median (*square*), and worst fit (*triangle*).

the course of the investigation between the two groups (table 3).

Plasma Cytokine Concentrations

Coronary artery bypass grafting and CPB during propofol–remifentanil anesthetic evoked a significant IL-6 and IL-10 release, which was in a similar order of magnitude as we have described previously under total intravenous anesthesia with midazolam–fentanyl.[18] Similar to what was observed for the neurohumoral stress hormones, this response was not affected by BIS-guided reduction of propofol infusion rates (table 4).

Discussion

In the current study, using propofol–remifentanil anesthesia, we aimed to assess the influence of adjusting propofol infusion rates by means of BIS monitoring on the stress response to CABG, *i.e.*, a response potentially
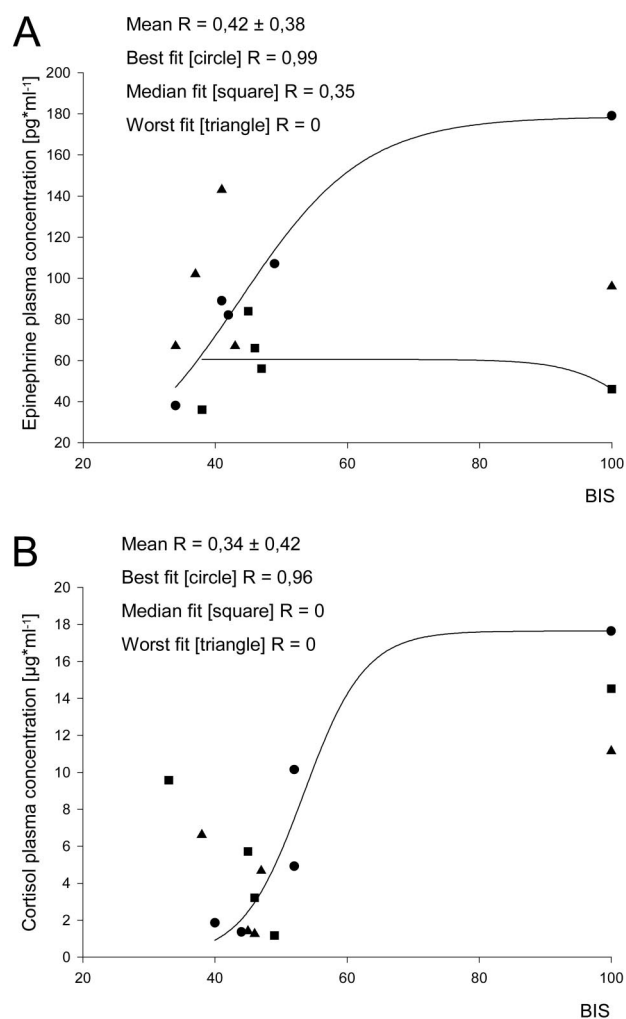
affecting morbidity and outcome in cardiac risk patients.[21] BIS monitoring allowed for a reduction of approximately 30% in propofol infusion rates and plasma concentrations compared with TCI, whereas the stress response as reflected by plasma epinephrine, cortisol, and cytokine concentrations was identical in both groups. Furthermore, the comparable plasma norepinephrine concentrations in both groups reflect similar requirements of norepinephrine support to restore mean arterial pressure irrespective of the allocation to either the BIS or the TCI group. In addition, none of the patients reported awareness in a standardized interview. Plasma concentrations of propofol correlated with the concentrations predicted by the TCI system particularly during and after CPB, with prediction errors similar to previous reports in different patient populations,[22] whereas they correlated only moderately with the phar-

Table 2. Stress Response to CABG and BIS-titrated Reduction of Propofol Infusion Rates

	Baseline	Intubation	Sternotomy	End of ECC	End of Surgery
Epinephrine, pg/ml					
TCI	131 (83/188)	86 (48/133)	100 (76/137)	128 (85/315)	103 (57/158)
BIS	154 (100/219)	108 (68/131)	87 (53/136)	97 (72/174)	83 (60/139)
Norepinephrine, pg/ml					
TCI	286 (212/311)	149 (103/219)	168 (159/189)	1,190 (934/1,753)*	1,347 (733/2,298)*
BIS	274 (212/460)	187 (118/275)	130 (72/206)	1,271 (572/2,834)*	950 (234/2,366)*
Cortisol, μg/ml					
TCI	11.6 (8.95/16.84)	9.2 (6.44/14.10)	5.1 (4.16/7.20)*	2.1 (1.55/3.69)*	2.8 (1.61/4.48)*
BIS	14.4 (12.00/18.71)	10.1 (8.70/14.82)	6.3 (4.79/9.66)*	2.8 (1.64/4.53)*	2.7 (1.81/4.75)*

Patients were randomly allocated to receive standard target-controlled infusion (TCI) of propofol according to the Marsh pharmacokinetic model (target, 3 μg/ml) or Bispectral Index (BIS)–titrated adjustment of the infusion rate (target, 40–50) along with background remifentanil anesthesia (0.3 μg · kg^{-1} · min^{-1}). High plasma concentrations of norepinephrine reflect the use of this catecholamine to restore mean arterial pressure during and after cardiopulmonary bypass.

* $P < 0.05$ compared with respective baseline level for repeated-measures analysis of variance on ranks followed by Dunnett test.

CABG = coronary artery bypass grafting; ECC = extracorporal circulation.

macodynamic effect, *i.e.*, electroencephalographic depression as assessed by BIS when data were analyzed for patients individually over time. This reflects an overall good performance of the TCI system despite a broad spectrum of confounding factors, such as changes in body temperature and cardiac output in this patient population. In particular, the known increase in cardiac output during and after CPB might explain the better performance of the TCI system during and after CPB. Lower BIS values after weaning from CPB in the TCI group tended to be paralleled by higher requirements of catecholamine support, although this effect did not reach statistical significance. Therefore, titration of propofol based on BIS monitoring allowed for a significant reduction of propofol requirements without negatively affecting the stress response to CABG/CPB.

Total intravenous anesthesia using propofol and remifentanil has been proposed as a safe anesthetic procedure for patients undergoing cardiac surgery, even in those with substantially impaired left ventricular function.[23,24] Attenuation of the neuroendocrine stress response, most notably release of catecholamines, to noxious stimulation as it may result from intubation, sternotomy, and initiation of CPB is an important con-

cern in the anesthetic treatment of these patients. Regarding the latter, propofol–remifentanil completely prevented the release of the stress hormones epinephrine and cortisol in response to the above-mentioned stimuli. In contrast, a marked release of stress hormones in response to CABG has been reported for other anesthetics, *e.g.*, midazolam combined with high-dose fentanyl.[18] It has been shown that propofol and remifentanil synergize to decrease BIS.[25] Nevertheless, the lack of effect on the neuroendocrine stress response of reducing the propofol infusion rate according to the BIS values in the current study would suggest that this effect is attributable primarily to fixed remifentanil administration. Consistent with this notion, a recent study demonstrated that remifentanil blunted the catecholamine response to laparoscopic fundoplication in a dose-dependent fashion,[26] and intravenous anesthesia with propofol–remifentanil results in a favorable hemodynamic profile in patients undergoing cardiac surgery,[27] indicative of excellent stress protection. Although blunting the neuroendocrine response to painful or noxious stimuli seems intuitively opportune in the operating room setting, data obtained for sedation using etomidate for several days in intensive care patients[28]—which inhibits

Table 3. Macrohemodynamic Variables and Body Temperature in Patients Undergoing CABG during Propofol–Remifentanil TIVA

	Baseline	Intubation	Sternotomy	End of ECC	End of Surgery
MAP, mmHg					
TCI	95 (84/102)	82 (78/94)	77 (75/88)*	76 (67/83)*	76 (72/88)*
BIS	95 (86/102)	87 (77/98)*	78 (71/87)*	78 (68/89)*	78 (73/92)*
Heart rate, l/min					
TCI	64 (57/71)	71 (63/78)	66 (61/73)	92 (78/98)*	87 (68/93)*
BIS	66 (58/76)	64 (59/74)	65 (57/70)	88 (85/95)*	88 (82/89)*
Body temperature, °C					
TCI	NM	NM	35.8 (35.3/36.8)	36.5 (36/36.8)	36.4 (36/36.7)
BIS	NM	NM	35.9 (35.5/36.1)	36.3 (36/36.9)	35.9 (35.6/36.6)

Patients (n = 20 each) were randomly allocated to standard care target-controlled infusion (TCI) or Bispectral Index (BIS)–titrated propofol infusion.

* $P < 0.05$ *vs.* baseline for repeated-measures analysis of variance on ranks followed by Dunnett test.

No significant differences were observed between the groups.

CABG = coronary artery bypass grafting; ECC = extracorporal circulation; MAP = mean arterial pressure; NM = not measured; TIVA = total intravenous anesthesia.

Table 4. Cytokine Response to CABG/CPB

	Baseline	Intubation	Sternotomy	End of ECC	End of Surgery
IL-6, pg/ml					
TCI	1,13 (0,11/3,00)	0,98 (0,35/1,75)	1,91 (0,77/3,17)	23,89 (14,51/37,73)*	52,75 (23,6/85,35)*
BIS	3,09 (1,44/5,13)	3,27 (1,61/4,41)	3 (2,09/4,73)	36,26 (20,54/48,48)*	67,69 (45,92/107,18)*
IL-10, pg/ml					
TCI	0 (0/0)	0 (0/0)	0 (0/0)	58,93 (40,18/98,57)*	62,84 (40,23/140,21)*
BIS	0 (0/0)	0 (0/0)	0 (0/0)	63,64 (30,94/84,14)*	52,94 (26,45/79,24)*

Coronary artery bypass grafting with cardiopulmonary bypass (CABG/CPB) induced a significant release of interleukin (IL)-6 and IL-10 into plasma. Bispectral Index (BIS)–titrated reduction of propofol infusion rates did not affect this immunologic stress response as compared with standard care (target-controlled infusion [TCI]).

* $P < 0.05$ as compared with respective baseline value for repeated-measures analysis of variance on ranks followed by Dunnett test.

ECC = extracorporal circulation.

11β-hydroxylase activity and thus cortisol biosynthesis—would suggest that the pronounced effects of propofol–remifentanil on the neuroendocrine stress response might be of concern in long-term application in the intensive care unit.

Whereas propofol–remifentanil completely blunted the neuroendocrine response to bypass surgery, a cytokine response as reflected in a significant appearance of IL-6 and IL-10 in plasma paralleled CABG. Moreover, the concentrations of IL-6 and IL-10 were in a similar order of magnitude to those we had observed previously during midazolam–fentanyl anesthesia.[18] Therefore, although the neuroendocrine and immunologic stress responses are known to interfere with each other in this patient population,[18] effective attenuation of the neurohumoral stress response with propofol–remifentanil did not prevent a cytokine response to CABG/CPB. Reducing the propofol administration rate according to BIS also failed to affect the plasma IL-6 and IL-10 response, although we have shown in previous studies that propofol has a permissive effect on tumor necrosis factor α release, i.e., an "upstream" cytokine that regulates IL-6 and IL-10 gene expression, by human peripheral blood mononuclear cells in vitro.[19]

Computerized infusion systems using internal pharmacokinetic models are becoming increasingly popular in cardiac surgery,[29] although their benefit with respect to required doses of propofol[30] or maintenance of a stable anesthetic depth, when compared with titration against traditional clinical signs,[31] has been questioned. Advantages over manual application include the rapid achievement of a desired blood concentration while avoiding "overshoot" seen with bolus administration. In addition, they may provide advisory information regarding calculated blood and effect site concentrations. Nevertheless, all pharmacokinetic models, such as the pharmacokinetic model of Marsh et al.[16] incorporated into the Diprifusor TCI used in the current study, have an inherent prediction error. This error may result in systematic overestimation or underestimation for certain patient populations, leading to an inappropriate infusion rate of propofol in elderly patients,[24] but this unavoidable prob-

lem may also change during the course of surgery as observed in the current study. Although the Diprifusor TCI constantly underestimated measured plasma propofol concentrations before CPB, the precision of predicted plasma concentrations was better after weaning from CPB, which might reflect, for example, increases of cardiac output after CPB as a typical confounding factor. In any case, a Diprifusor-predicted target concentration of 3 μg/ml propofol resulted in measured propofol concentrations in our patient population between 0.7 and 6.5 μg/ml and BIS values below 40. Therefore, an inadequately deep plane of anesthesia was observed in approximately 50% of the patients in the TCI group. Conversely, a reduction of propofol infusion rates below a target concentration of 3 μg/ml was possible in 16 of 20 patients when the propofol infusion rate was adjusted according to BIS readings. Interestingly, none of the patients reported intraoperative recall, not even those in whom actual plasma concentrations below 1.5 μg/ml were measured. Therefore, our data support the notion that titration of propofol based on pharmacodynamic effects, such as electroencephalographic suppression, is superior to administration based on pharmacokinetic modeling.

A variety of electroencephalogram-derived parameters and monitoring devices are now being evaluated with respect to measuring anesthetic depth. Among these, the BIS® monitor can currently be considered the accepted standard, although other algorithms and devices may provide similar information.[11] Interestingly, the differences in BIS between the study groups of the current investigation were fairly small, reaching statistical difference only in the late phase of the investigation, although a 30% reduction of propofol consumption was achieved. This reflects primarily two phenomena: All data were analyzed on an intent-to-treat basis, and the study protocol prevented a reduction of propofol administration below a predicted target of 1 μg/ml, resulting in BIS values repeatedly less than 40 in two patients of the BIS group. Because adjustments of the infusion rate were made intermittently every 5–10 min, outliers could be observed between adjustments. Similarly, 10 of 20 pa-

tients in the TCI group had BIS values in the target range of 40–50. Moreover, in the range of 35–55, the BIS algorithm results in a broad plateau underestimating any changes in the plasma or effect site concentration of an anesthetic.[11,32] Consequently, substantial changes in propofol infusion rates or anesthetic depth might result in only moderate changes of the numerical values in this given BIS range. This relation, together with the study design, which involved repeated adjustments of the propofol infusion rates over time, would also explain the delayed evolving difference between the BIS values in the two study groups. Conversely, our current data reflect a substantial interindividual variability with respect to the required plasma propofol concentration to achieve a given BIS value, which may result in part from the high number of confounding variables, such as changes in cardiac output or body temperature in this particular patient population.

In summary, total intravenous anesthesia using propofol and remifentanil substantially attenuates the stress response to cardiac surgery. Titration of propofol based on BIS monitoring under these conditions allows for a reduction in drug consumption, which is paralleled by a similar decrease in propofol plasma concentrations compared with TCI. However, titration of propofol did not induce an augmented release of stress hormones in response to CABG in the presence of a potent narcotic, *i.e.*, background remifentanil infusion in the current study.

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