

Propofol and Sufentanil Titration with the Bispectral Index to Provide Anesthesia for Coronary Artery Surgery

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Background: To provide anesthesia for cardiac surgery, hypnotics and opioids are frequently titrated on variables such as mean arterial pressure and heart rate. In this study conducted in patients scheduled to undergo coronary artery bypass grafting, propofol and sufentanil, both administered by computer-controlled infusion, were titrated on the Bispectral Index (BIS) values using a predefined algorithm.

Methods: After written informed consent, 110 patients, 95 men and 15 women aged 61 (9) yr [mean (SD)], were randomly allocated to receive predicted sufentanil effect site concentrations (Ce) of 0.5, 0.75, 1, 1.25, and 1.5 ng/ml, decreased by a third after sternotomy (groups 1-5). Target induction propofol concentration was 1.5 µg/ml and subsequently adjusted on BIS values. The following parameters were recorded: BIS values, predicted propofol Ce, the number of changes of propofol target, mean arterial pressure, heart rate, the number of bolus injection and doses of vasoconstrictor and vasodilator drugs, time to tracheal extubation, postoperative awareness and satisfaction scores, and cumulative morphine doses for the first postoperative day.

Results: One patient randomized to group 1 required 0.75 ng/ml sufentanil Ce instead of 0.5 ng/ml for increased BIS values on tracheal intubation. BIS values were similar in the five groups. The predicted propofol Ce values were different ($P < 0.05$; analysis of variance) among the five groups: 1.59 (0.47) to 1.23 (0.25) µg/ml in group 1 and group 4, respectively. Significantly fewer changes of propofol target were required in group 4 as compared to group 1. There were no differences among the five groups for mean arterial pressure, heart rate, time to tra-

cheal extubation, awareness, satisfaction scores, and morphine requirements.

Conclusion: These results suggest the BIS, as part of an algorithm that uses both the absolute BIS value and its increase following tracheal intubation, can be used to effectively titrate both propofol and sufentanil. A predicted sufentanil Ce of 1.25 ng/ml before and 0.8 ng/ml after sternotomy was associated with the lowest predicted propofol Ce and fewer changes of propofol target. Lower sufentanil concentrations required higher propofol concentrations and more frequent changes of the target propofol concentration and were associated with similar hemodynamic tolerance.

CORONARY artery bypass graft (CABG) surgery is a frequently performed procedure in developed countries. Several studies have convincingly demonstrated that patients presenting for CABG since 1990, as compared to previous reports, are older,¹ have more frequent and severe comorbidities, and have more altered cardiovascular reserve.^{2,3} In parallel, there is increased pressure on clinicians to decrease the duration of stay in the intensive care unit (ICU), the duration of stay in the hospital, and total cost,⁴ a strategy called "fast-track" cardiac surgery. Early tracheal extubation, obtained by optimized anesthetic technique, is part of this strategy,⁵ although this has not been found by all investigators.^{6,7}

To meet the challenges of early tracheal extubation, the initial high-dose opioid technique has been progressively abandoned, and in more recent studies cumulative opioid doses have been significantly reduced.⁸ This is consistent with a ceiling effect (observed at relatively low doses/concentrations) of opioids to attenuate cardiovascular responses to noxious stimuli⁹ and to potentiate the effects of hypnotics.¹⁰

A major problem of any anesthetic technique for cardiac surgery concerns the criteria on which anesthetic drugs are titrated. In older¹¹ and more recent^{12,13} studies, both opioids and hypnotics were titrated on the cardiovascular response to noxious stimuli. The limitations of such an approach are well documented,¹⁴ mainly because hemodynamic variables such as arterial blood pressure or heart rate are poorly correlated to anesthetic depth. Evidence exists that the Bispectral Index[®] (BIS[®]) monitor (Aspect Medical System, Newton, MA) improves titration of hypnotics^{15,16} even when they are administered by computer-controlled infusion.¹⁷ In addition, it was recently shown that the BIS[®] monitor could also be used to titrate *a posteriori* the concentration of opioids necessary to avoid patient movement as well as an increase of arterial blood pressure upon ap-



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Fig. 1. Study plan. Ce = predicted effect site concentration; CPB = cardiopulmonary bypass; ICU = intensive care unit; PO = *per os*.

	Premedication	Induction	Intubation	Skin incision followed by sternotomy	CPB	Skin closure	Sedation in ICU
Midazolam PO	0.1 mg/kg						
Propofol target		1.5 µg/ml adapted to obtain a BIS value between 50 and 60; minimum propofol target: 1 µg/ml					1 µg/ml
Ce sufentanil		Group 1: 0.5 ng/ml Group 2: 0.75 ng/ml Group 3: 1 ng/ml Group 4: 1.25 ng/ml Group 5: 1.5 ng/ml			Group 1: 0.35 ng/ml after sternotomy Group 2: 0.5 ng/ml Group 3: 0.65 ng/ml Group 4: 0.8 ng/ml Group 5: 1 ng/ml		
Pancuronium bromide		0.1 mg/kg			At the discretion of the anesthesiologist		

plication of a potent nociceptive stimulus such as tracheal intubation.¹⁸ Therefore, the possibility exists that both hypnotics and opioids could be titrated on the BIS values.

This study was designed to investigate the hypothesis that both propofol and sufentanil (both administered by computer-controlled infusion) can be titrated on a pre-defined algorithm that includes the absolute BIS value and its increase (hereafter called δ BIS) in response to a nociceptive stimulus such as tracheal intubation. Specifically, we made the hypothesis, based on previous experience, that propofol titration on the BIS would result in different propofol concentrations in the presence of different sufentanil concentration with similar hemodynamic tolerance. We describe the effects of such a titration technique on several surrogate endpoints such as predicted effect site concentration (Ce), number of changes of propofol target, cardiovascular stability, time to tracheal extubation, awareness, and patient satisfaction in patients presenting for elective CABG surgery with cardiopulmonary bypass (CPB).

Methods and Materials

After approval of the protocol for all the centers by the institutional review board of Hôpital Cochin (Paris, France) and informed written consent, 111 patients from 12 academic cardiac surgery centers in France (Appendix 1) were included from September 1999 to December 2000 into this prospective, randomized, open, multi-center study.

The inclusion criteria were the following: age between 18 and 75 yr; American Society of Anesthesiologists physical status class less than IV; first-time elective CABG surgery with CPB temperatures greater than 30°C and no other planned surgical procedures; and left ventricular ejection fraction greater than 40% as assessed by cineangiography, radionuclide ventriculography, or echocardiography. The exclusion criteria were the following: myocardial infarction and/or coronary angioplasty occurring

within 7 days before screening or unstable angina necessitating intravenous nitrates and/or heparin; unstable arrhythmia; the existence of a ventricular pacemaker; documented risk of difficult tracheal intubation; obesity as defined by body mass index (BMI) higher than 35; history of neurologic, muscular, pulmonary (oxygen saturation measured by pulse oximetry [SpO₂] < 90% at room air), renal (serum creatinine > 200 µM), or hepatic disease; alcohol or drug abuse; unstable diabetes mellitus; or allergy to one of the drugs used for the study. Women of childbearing age were not eligible if they did not have negative pregnancy test results. After having signed an informed consent and having met the above criteria, patients were randomly allocated (computer-generated random numbers in closed envelopes opened when the patient arrived in the operating room [OR]) to receive one of the five different concentrations of sufentanil: 0.5 ng/ml (group 1), 0.75 ng/ml (group 2), 1 ng/ml (group 3), 1.25 ng/ml (group 4), or 1.5 ng/ml (group 5). Sufentanil concentrations were decreased after sternotomy according to the study plan (fig. 1).

Anesthetic Management

Preinduction Period. Usual cardiac medications were given until the evening that preceded surgery. β -Adrenergic receptor antagonists were given on the morning of surgery. Midazolam (0.1 mg/kg) was given orally at least 60 min before surgery.

Two peripheral venous cannulae were inserted. One was used exclusively for propofol and sufentanil infusion, and the second was used for volume expansion and infusion of other drugs. The perfusion montage for propofol and sufentanil administration was standardized to have the lowest dead volume and attenuate interpatient variability. It used a connector (Braun, Meltzungen, Germany) with a dead volume of 1.4 ml directly connected to the intravenous canula at one extremity and a three-way stopcock at the other followed by a unidirectional valve (Vygon, Ecouen, France). Propofol and sufentanil syringes were linked to the three-way stop-

Table 1. Values Recorded Manually by the Investigators at Different Time Points

Time Points	MAP	HR	BIS	Ce Propofol	Ce Sufentanil
Baseline: preoperative visit	Yes	Yes			
Before induction	Yes	Yes	Yes		
BIS 60	Yes	Yes	Yes	Yes	Yes
Before laryngoscopy	Yes	Yes	Yes	Yes	Yes
During laryngoscopy	Yes	Yes	Yes	Yes	Yes
Before tracheal intubation	Yes	Yes	Yes	Yes	Yes
Two minutes after tracheal intubation	Yes	Yes	Yes	Yes	Yes
Before skin incision	Yes	Yes	Yes	Yes	Yes
Two minutes after skin incision	Yes	Yes	Yes	Yes	Yes
Before sternotomy	Yes	Yes	Yes	Yes	Yes
Two minutes after sternotomy	Yes	Yes	Yes	Yes	Yes
Aortic cannulation	Yes	Yes	Yes	Yes	Yes
Two minutes before CPB	Yes	Yes	Yes	Yes	Yes
Two minutes after CPB onset	Yes		Yes	Yes	Yes
Thirty minutes after CPB onset	Yes		Yes	Yes	Yes
Ten minutes after the end of protamine infusion	Yes	Yes	Yes	Yes	Yes
During sternal closure	Yes	Yes	Yes	Yes	Yes
During skin closure	Yes	Yes	Yes	Yes	Yes
Two hours after arrival in the ICU	Yes	Yes		Yes	
Onset of spontaneous ventilation	Yes	Yes			
Five minutes after tracheal extubation	Yes	Yes			

BIS = Bispectral Index values displayed by the BIS® monitor at a specific time point; BIS 60 = time point when the BIS value displayed by the monitor first reached 60 after onset of induction; Ce = effect site concentration; CPB = cardiopulmonary bypass; HR = heart rate; ICU = intensive care unit; MAP = mean arterial pressure.

cock through 1.5-m tubes (Fresenius Vial, Brézins, France) with 1.5 ml dead volume. All patients received 500 ml Ringer's lactate before induction of anesthesia over 15 min.

Hemodynamic Monitoring and Treatment of Hemodynamic Instability. Resting heart rate (HR) as well as systolic and diastolic arterial pressure levels were determined noninvasively at the preoperative anesthetic visit, and the calculated mean arterial pressure (MAP) was considered as baseline. Perioperative hemodynamic monitoring included electrocardiography with at least two leads (usually D_{II} and V₅) displayed continuously and invasive arterial pressure *via* an arterial canula inserted under local anesthesia before induction. Heart rate and arterial pressure were recorded at different time points during the study as indicated in the study plan (table 1).

Tachycardia was defined as HR greater than 90 beats/min and was treated with intravenous esmolol (0.25 mg/kg followed as necessary by a continuous infusion); bradycardia was defined as HR less than 45 beats/min and was treated with intravenous atropine (1 mg) or ephedrine (3 mg as a bolus, repeated as necessary). Arterial hypertension was defined as systolic arterial pressure greater than 140 mmHg lasting more than 3 min and was treated with intravenous nicardipine (0.5 mg, repeated as necessary). Arterial hypotension was defined as systolic arterial pressure less than 90 mmHg lasting more than 3 min and was treated with intravenous phenylephrine (50 µg) or ephedrine (3 mg, repeated as necessary). The lowest MAP value admitted during CPB was 50 mmHg.

Below this value, patients were treated with intravenous phenylephrine (100 µg) or ephedrine (6 mg, repeated as necessary). In addition, investigators were allowed to administer vasoactive drugs as required by the clinical context. Both the number of episodes of hemodynamic instability as defined above and the cumulative doses of vasoactive drugs were recorded. The changes in HR and MAP were analyzed as raw values and as ratios to the baseline (preoperative visit) values.

The use of the pulmonary artery catheter was not standardized because of differences among the centers. When inserted, cardiac index and pulmonary artery, central venous, and pulmonary artery occluded pressures were measured.

Induction of Anesthesia. After breathing 100% oxygen for 3 min through a facemask, anesthesia was induced as follows. Sufentanil and propofol infusions were started simultaneously. A laptop computer-controlled Graseby 3400® pump (SIMS Graseby Ltd., Watford, Herts, United Kingdom) was used to obtain the desired effect compartment concentration (Ce) of sufentanil using the STANPUMP® software (developed by Professor Steven Shafer, M.D., Ph.D., Department of Anesthesia, Stanford University, CA) and to apply the pharmacokinetic model of Gepts *et al.*¹⁹ Sufentanil was diluted at a concentration of 5 µg/ml in saline, and the maximum infusion rate of the pump (1,200 ml/h) was used.

Propofol infusion was performed with the Diprifusor® (Master TCI, Fresenius Vial, Brézins, France) and pre-filled tagged syringes (AstraZeneca, Rueil-Malmaison, France) at an initial target concentration of 1.5 µg/ml.

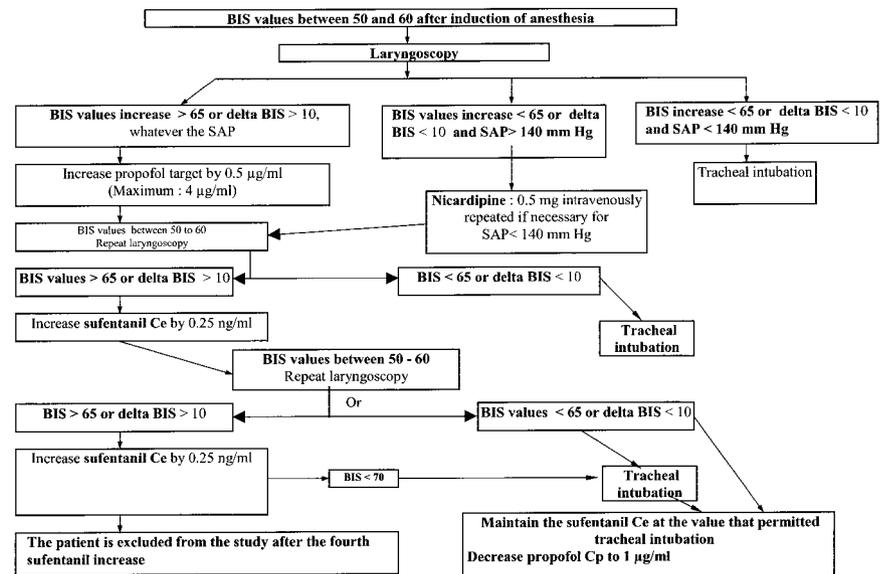


Fig. 2. Algorithm used to titrate propofol and sufentanil during anesthesia. BIS = Bispectral Index; Ce = predicted effect site concentration; delta BIS = increase of BIS values (between the value measured after as compared to before laryngoscopy); SAP = systolic arterial pressure.

The perfusion rate was 1,200 ml/h. After the start of the infusion, loss of consciousness (LOC) was tested every 15 s by verbal stimulation. The predicted plasma concentration (Cp) and Ce of propofol and sufentanil were recorded at LOC and when the BIS reached a value of 60. If LOC did not occur at the predicted propofol Ce of 1.5 µg/ml, the target concentration was increased every 3 min by 0.5 µg/ml until LOC occurred. Both infusion software programs recorded the rate of drug infusion and the predicted Cp and Ce. The predicted Ce values for propofol and sufentanil were recorded manually at the indicated time points according to the study plan (table 1). The number of changes of target for propofol from induction to skin closure and from induction to end of propofol infusion in the ICU were obtained from the Diprifusor[®] electronic files.

Tracheal Intubation. To facilitate tracheal intubation, pancuronium bromide (0.1 mg/kg) was injected immediately after LOC occurred. Tracheal intubation could be attempted only when the BIS value reached a value less than 60. The decision algorithm that was used to titrate sufentanil and propofol based on the BIS values is presented in figure 2. This algorithm for opioid titration on application of a nociceptive stimulus such as tracheal intubation was based on the data from Guignard *et al.*¹⁸ and Iselin-Chaves *et al.*²⁰

Maintenance of Anesthesia. After tracheal intubation, the sufentanil concentration was maintained at the randomized concentration or at the concentration that allowed tracheal intubation until the end of sternotomy, decreased as shown in figure 1 and stopped at skin closure. Propofol concentration was decreased by 0.2-µg/ml steps to a minimum of 1 µg/ml after tracheal intubation to maintain a BIS value between 50 and 60, a value commonly accepted as adequate anesthesia.¹⁷ Three minutes before skin incision, the propofol target

concentration was increased to the value that allowed tracheal intubation without increases in BIS values. To maintain BIS values between 50 and 60 during maintenance of anesthesia, the propofol target concentration was increased by 0.5 µg/ml or decreased by 0.2 µg/ml as necessary. Throughout the study, propofol target concentrations could not be lowered below 1 µg/ml even when BIS values were less than 50. Administration of pancuronium bromide was left at the discretion of the anesthesiologist performing the study and was based on train-of-four monitoring. The study design did not include adjustments of propofol or sufentanil concentrations because of CPB *per se* based on a previous study with a similar anesthesia protocol in cardiac surgery patients.²¹

BIS Monitoring. The BIS values were calculated online by the A2000 monitor (Aspect Medical Systems), versions 3.3 and 3.4 (updated during the study) using a BIS[®] sensor placed on either the right or the left hemisphere. For analysis purposes, BIS[®] versions were pooled. The smoothing time of the BIS[®] monitor was set at 30 s. All physicians involved in the study were trained in two sessions in the OR in one center (Hôpital Bichat, Paris, France) under the supervision of one author (D. L.) to interpret the BIS values, the signal quality index (SQI), and possible interference with the high-frequency signal (30–110 Hz; also called electromyographic signal) as displayed by the monitor. BIS values were recorded electronically from preinduction of anesthesia to skin closure. In addition to the electronically recorded files, BIS values were manually recorded at the indicated time points (table 1). The electronic clocks of the BIS[®] monitors were synchronized with those of the hemodynamic monitors and Diprifusor[®] pumps.

Off-line Analysis of BIS Values. The BIS values together with SQI, the electromyographic signal, and elec-

trode impedance were captured every 5 s on a laptop computer using the Terminal software included in Microsoft Windows 95® (Microsoft Corp., Redmond, WA), imported into an Excel file (Microsoft Corp.) and analyzed off-line. The first value that reached 60 after induction of anesthesia was the starting point of the analysis for the average BIS values after induction of anesthesia. Off-line analysis calculated the percentage of points (from the total number of points) in which the SQI was greater than 50 or greater than 80. The percentage of points with BIS values greater than 60 or greater than 70 was calculated after exclusion of SQI points < 50 using the filter function of the Excel software. A continuous BIS episode with values higher than 60 was arbitrarily defined if it lasted at least 3 min (*i.e.*, 36 time points). If the BIS values greater than 60 were discontinuous, an episode of BIS greater than 60 was counted if the number of points was at least 18 out of 36. The total number of episodes of BIS greater than 60 and their cumulative duration (in minutes) were recorded.

Surgery and Cardiopulmonary Bypass. Surgery was not standardized except that all patients were operated on through a median sternotomy incision. Each surgeon made the choices of the conduit graft, the grafted vessels, and the myocardial protection technique. The CPB technique was not standardized except that all centers used a cardiotomy reservoir, and a CPB temperature greater than 30°C was mandatory.

Postoperative Period. Postoperative sedation was performed for all patients with an initial propofol target concentration set at 1 µg/ml on arrival in the ICU (fig. 1). Propofol target concentrations were subsequently adapted to obtain a Ramsay score²² of 3–4, evaluated every 30 min until the end of propofol infusion. The minimum duration of sedation in the ICU was 2 h to allow patient rewarming and to verify that the criteria for tracheal extubation were fulfilled. Propofol infusion in the ICU was stopped when core temperature was 37°C or greater, there was no shivering or excessive bleeding through the chest tubes (defined as blood loss > 1 ml/kg/h for 2 consecutive hours), and when blood oxygenation was considered as correct according to the patient's preoperative respiratory function.

Protocol for Tracheal Extubation. A test of spontaneous ventilation was performed in all patients after the infusion of propofol was stopped in the ICU. The test was successful if the patient could maintain an SpO₂ value greater than 95% in 100% oxygen for at least 15 min with respiratory frequency greater than 12 breaths/min. In case of failure, this test was initially repeated every hour until tracheal extubation. In some patients in whom tracheal extubation was obviously delayed, the test was repeated at the discretion of the physician in charge of the patient.

The intervals between skin closure and the end of propofol infusion in the ICU on one side and eyes open-

ing, onset of spontaneous ventilation, and tracheal extubation on the other side were recorded. The cumulative doses of sufentanil (from induction to skin closure) and propofol (from induction to the end of propofol infusion in the ICU) were recorded for all patients.

Postoperative Analgesia. Morphine sulfate was used as the postoperative analgesic drug. The site of infusion (intravenous *vs.* subcutaneous) and the doses were not standardized, but titration to reach a visual analog scale value less than 40 out of 100 was mandatory for all centers. Propacetamol (2 g) was administered intravenously every 6 h after arrival in the ICU. The cumulative morphine doses for the first 24 postoperative hours were recorded in all patients.

Explicit Awareness. A questionnaire of explicit awareness (Appendix 2) was performed immediately after tracheal extubation and 3 days later. It was adapted from Sebel *et al.*²³ and modified to easily detect awareness during surgery (see Appendix 2 for explanations).

Patient and Nursing Team Satisfaction Questionnaires. A patient satisfaction questionnaire (Appendix 3) was performed immediately after tracheal extubation and 3 days after. A satisfaction questionnaire of the ICU personnel regarding the first 24 postoperative hours was performed (Appendix 4).

Statistical Analysis

Statistical analysis was performed with the SAS software (version 6.12 for Windows NT) or with Statview 5.0 software (both from SAS Institute Inc., Cary, NC). Results were expressed as mean and SD if distributed normally or as median and 25th–75th percentile if the normality test failed. When interpatient variability was considered to be (clinically) high, values were reported as median and range.

Normally distributed values were compared by analysis of variance with repeated measures when appropriate and the Bonferroni *post hoc* test for paired comparisons. Continuous variables that did not follow a normal distribution were analyzed with a nonparametric test (Kruskal-Wallis). Categorical variables were compared with the Fisher exact test. A *P* value of 0.05 or less on a two-tailed test was the threshold for statistical significance.

Unless specified otherwise, all statistical analyses are by intention to treat (ITT), *i.e.*, the sufentanil concentration to which the patient was randomized. Missing data were not replaced by any calculated variable, and the number of patients who were actually analyzed is indicated for each table. A per-protocol analysis (*n* = 103 patients; see following explanations) was also performed.

Results

Twelve centers included patients in this study. The number of patients included by each center is presented

Table 2. Demographic and Clinical Characteristics of the Patients Randomized to the Five Sufentanil Groups

	Group 1	Group 2	Group 3	Group 4	Group 5	P Value
Number of patients	21	22	23	21	23	NS
Sex, F/M	3/18	3/19	3/20	4/17	2/21	NS
Mean age (SD)	59.8 (12)	61.1 (8.9)	62.3 (8.6)	64 (9.2)	60.6 (8.6)	NS
Mean BMI (SD)	24.6 (3.2)	25.8 (4.7)	26.4 (3.3)	24.5 (2.5)	25.8 (3.2)	NS
ASA class II/class III	6/15	8/14	6/17	8/13	7/16	NS

Values are expressed as mean (SD).

ASA = American Society of Anesthesiologists. BMI = body mass index; NS = not significant.

in Appendix 1. One hundred eleven patients were included in the study and were randomly allocated (21 patients to group 1, 23 to group 2, 23 to group 3, 21 to group 4, and 23 to group 5) to receive one of the five sufentanil concentrations. Demographic and clinical characteristics of the randomized patients were similar for the five groups (table 2). There were no differences among the five groups regarding the sex ratio, age, BMI, or American Society of Anesthesiologists physical status.

For four patients (one from group 2, one from group 4, and two from group 5), there were technical problems regarding manipulation of the Stanpump[®] software and/or connection between the computer and the Graseby[®] infusion device. For the patient randomized to group 2, the technical problem occurred before induction of anesthesia, and this patient was not included in the analysis. The other three patients for whom there were technical problems were included in the analysis. Therefore, the ITT population represents 110 patients (21 patients allocated to group 1, 22 to group 2, 23 to group 3, 21 to group 4, and 23 to group 5).

Study Violations

Major Study Violations. One patient randomized to group 1 (76 yr), two patients randomized to group 2 (76 and 77 yr), and one patient randomized to group 4 (76 yr) were aged older than 75 yr but were included in the analysis. Two patients randomized to group 2 had a BMI higher than 35 (37 and 38) and were included in the analysis. One patient randomized to group 5 (1.5 ng/ml) received sufentanil at the predicted Ce of 1 ng/ml, before and upon sternotomy. Violations regarding age, BMI, and the change of sufentanil concentrations before sternotomy were considered to be major (n = 7), and all other violations (see next section) were considered to be minor. The per-protocol population was as follows: 19 patients for group 1, 19 patients for group 2, 23 patients for group 3, 20 patients for group 4, and 22 patients for group 5. The per-protocol population represents 103 patients (*i.e.*, 94% of the ITT population). Study violations occurred with similar frequency in all of the five groups.

Minor Study Violations.

Changes in the Premedication Regimen. Two patients (one in group 1 and one in group 4) received 0.5

mg alprazolam orally. Fourteen patients (group 1: 2 patients; group 2: 3 patients; group 3: 4 patients; group 4: 1 patient; group 5: 4 patients) received 6 mg bromazepam orally. Two patients (group 2: 1 patient; group 4: 1 patient) received 3 mg bromazepam orally. Two patients (1 from group 3 and 1 from group 5) received 7.5 mg zopiclone orally. Two patients (one from group 2 and one from group 5) received 100 mg hydroxyzine and 1 mg flunitrazepam orally. One patient from group 1 received 10 mg chlorazepate orally. Finally, two patients (one from group 4 and one from group 5) received intravenous midazolam after arrival in the OR and before anesthesia induction. The distribution of the minor study violations among the five groups is not statistically different.

Changes in Sufentanil Concentrations on Skin Closure. On skin closure, five other patients received lower (than randomized) sufentanil concentrations. One patient from group 1 received 0.32 ng/ml instead of 0.35 ng/ml; one patient from group 2 received 0.33 ng/ml instead of 0.5 ng/ml; two patients from group 4 received 0.71 and 0.5 ng/ml instead of 0.8 ng/ml; and one patient in group 5 received 0.5 ng/ml instead of 1 ng/ml.

Adverse Events

One patient randomized to group 1 (70 yr old, male, BMI = 23) died on day 5 after surgery; he was diagnosed with electromechanical dissociation. This patient was extubated on the day of surgery and was hemodynamically stable. Another patient randomized to group 2 had an ischemic stroke on day 3 after surgery. Both patients were included in the analysis.

Concentrations and Cumulative Doses of Sufentanil and Propofol

One patient randomized to group 1 (sufentanil Ce = 0.5 ng/ml) required an increase of sufentanil Ce to 0.75 ng/ml before and during sternotomy because of an increase in BIS value (see fig. 2 for definition of an increase in BIS value) on tracheal intubation. Propofol target, as well as predicted Cp and Ce, is shown in table 3. Target concentrations, Cp, and Ce were statistically different among the five groups (analysis of variance) with paired comparisons, showing a statistically significant difference between group 1 and group 4 ($P = 0.026$ for target

Table 3. Target, Predicted Plasma, and Effect Site Propofol Concentrations, and Cumulative Doses of Propofol and Sufentanil

	Group 1	Group 2	Group 3	Group 4	Group 5	P Value
No. of patients	21	21	23	21	22	
Propofol target concentrations, $\mu\text{g/ml}$ (OR and ICU)	1.56 (0.47)	1.40 (0.33)	1.44 (0.35)	1.23 (0.25)*	1.32 (0.28)	< 0.05
Predicted propofol Cp (OR and ICU)	1.59 (0.47)	1.42 (0.33)	1.47 (0.34)	1.24 (0.25)*	1.34 (0.27)	< 0.05
Predicted propofol Ce (OR and ICU)	1.59 (0.47)	1.43 (0.31)	1.45 (0.32)	1.23 (0.24)*	1.33 (0.25)	< 0.05
Cumulative doses of propofol, mg (OR)	1,201 (410)	1,078 (341)	1,091 (390)	854 (227)	1,061 (427)	0.11
Cumulative doses of propofol, mg (OR and ICU)	1,851 (563)	1,658 (428)	1,653 (617)	1,348 (445)*	1,558 (583)	< 0.05
Cumulative doses of sufentanil, μg	165 (20)	229 (38)	300 (49)	355 (56)	440 (107)	< 0.05
Duration (h:min) of propofol infusion (OR)	5:23 (1:06)	4:52 (0:43)	4:58 (1:07)	4:47 (0:51)	4:56 (1:38)	NS
Duration (h:min) of propofol infusion (OR and ICU)	8:16 (1:02)	9:04 (3:53)	8:00 (1:33)	8:31 (1:57)	7:50 (1:23)	NS
No. of changes of propofol target (OR and ICU)	21 [4–47]	12 [7–39]	15 [3–32]	12* [1–21]	13 [3–36]	< 0.05
No. of changes of propofol target (OR)	18 [3–34]	10 [4–35]	9 [1–27]	9* [1–15]	11 [1–29]	< 0.05

Values are expressed as mean (SD) or median [range].

* $P < 0.05$ as compared to group 1.

Ce = effect site concentration; Cp = plasma concentration; ICU = intensive care unit; OR = operating room; NS = not significant.

concentration, $P = 0.041$ for Cp, and $P = 0.019$ for Ce). The cumulative doses of propofol and sufentanil for each group are presented in table 3. There were no statistically significant differences ($P = 0.11$) for cumulative propofol doses in the OR, although a trend showing lower propofol doses in group 4 was observed. Nevertheless, the propofol cumulative dose for the whole study (OR and ICU) was significantly lower in group 4 despite comparable durations of propofol infusion.

Taken together, these results demonstrate that the lowest target and predicted propofol concentrations were observed in group 4, and this accounts for the significantly lower cumulative propofol dose in this group. Interestingly, the lowest median number of changes of propofol target was also observed in group 4 (table 3), suggesting more stable BIS values requiring

fewer adaptations of the propofol target to obtain the desired BIS values and sedation score.

BIS Values for the Five Groups

The average BIS values calculated after induction of anesthesia (first BIS value that reached 60 after induction), the percentage of points for which the SQI value was higher than 50 or 80, and the percentage of points for which the BIS value was higher than 60 or 70 or lower than 40 are presented in table 4. There were no statistically significant differences among the five groups, thus suggesting that the study design (*i.e.*, titration of propofol for BIS values < 60) was respected in all groups. The number of episodes with BIS values higher than 60 for more than 3 consecutive minutes is presented in table 4. For all of the five groups, there were

Table 4. Bispectral Index Values Obtained from the BIS[®] Electronic Files

	Group 1	Group 2	Group 3	Group 4	Group 5	P Value
No. BIS files/no. of patients	19/21	16/22	18/23	17/21	18/23	NS
BIS value	47 (6)	47 (6)	47 (6)	46 (5)	45 (5)	NS
Percent of points with SQI > 50	88 (4)	89 (4)	89 (4)	89 (4)	88 (6)	NS
Percent of points with SQI > 80	71 (6)	72 (5)	71 (7)	74 (5)	73 (8)	NS
Percent of points with BIS < 40	5.5 [1.25–14.7]	6.7 [2.9–12.7]	6.6 [0.7–19]	12.7 [1.9–20.8]	15.2 [4.4–32.8]	NS
Percent of points with BIS > 60	4.5 [2.2–12.1]	5.1 [1.9–8.9]	4.0 [2.7–5.9]	1.7 [0.2–4.1]	1.7 [0.2–3.0]	NS
Percent of points with BIS > 70	0.1 [0–0.9]	0.2 [0–0.9]	0.3 [0.03–0.9]	0.08 [0–0.3]	0.1 [0–0.4]	NS
No. of patients/no. of patients with BIS electronic files	12/19	11/16	12/18	5/17	8/18	NS
Percent of patients with at least one BIS episode > 60*	63	69	67	29	44	0.073
No. of BIS episodes > 60	38	31	23	10	34	NS
Cumulative time of episodes with BIS > 60	20 (16)	15 (11)	14 (12)	14 (16)	32 (40)	NS
	14 [3.9–55]	13 [3–37]	13 [3.2–44]	8 [5–44]	10 [3.4–117]	

Several electronic files were not recovered or were not recorded. The number of electronic files and the total number of patients randomized to the five sufentanil groups are presented. Values are expressed as mean (SD) or median [25th–75th percentile] when the distribution of values was not normal or when interpatient variability was considered to be (clinically) high.

* See the Materials and Methods section for the definition of episodes with Bispectral Index (BIS) values greater than 60.

NS = not significant; SQI = signal quality index.

Table 5. Intervals from Skin Closure or End of Propofol Infusion in the ICU to Eyes Opening, Onset of Spontaneous Ventilation, and Tracheal Extubation

Interval	Group 1	Group 3	Group 3	Group 4	Group 5	P Value
From skin closure to eye opening	231 [73–473]	186 [117–437]	203 [65–1,051]	212 [135–594]	230 [85–397]	NS
From end of propofol infusion to eye opening	5 [–135–75]	6.5 [–750–30]	5 [–240–90]	10 [–47–80]	10 [–155–90]	NS
From skin closure to onset of spontaneous ventilation	305 [135–1,187]	315 [165–977]	290 [190–1,154]	320 [135–1,535]	312 [170–1,296]	NS
From end of propofol infusion to onset of spontaneous ventilation	40 [–120–1,050]	65 [5–830]	48 [–30–1,185]	60 [–10–1,185]	67 [0–1,072]	NS
From skin closure to tracheal extubation	380 [172–1287]	373 [170–1,067]	383 [207–1,179]	380 [215–1,580]	411 [188–1,346]	NS
From end of propofol infusion to tracheal extubation	81 [7–1,150]	130 [8–920]	123 [0–950]	115 [20–1,230]	165 [8–1,122]	NS

Values represent minutes and are expressed as median [range].

ICU = intensive care unit; NS = not significant.

136 episodes with BIS values greater than 60 for more than 3 min. There were fewer such episodes in patients randomized to group 4, but the difference was not statistically significant ($P = 0.073$). The periods with episodes of BIS greater than 60, by decreasing frequency, were CPB (37.5% of all episodes with BIS values > 60), skin closure (20.5%), the interval between tracheal intubation and skin incision (14%), the post-CPB period before skin closure (11.7%), laryngoscopy/tracheal intubation (8.8%), and the interval between sternotomy and CPB onset (5.8%) and incision/sternotomy (1.4%).

Time to Onset of Spontaneous Ventilation and Tracheal Extubation

The intervals between skin closure or the end of propofol infusion in the ICU on one side and eyes opening, onset of spontaneous ventilation, and tracheal extubation were analyzed (table 5). There were no statistically significant differences among the five groups for any of the analyzed intervals.

Hemodynamic Tolerance

The values of MAP, HR (Web tables 1–4), and their ratio to the values measured at the preoperative visit (Web tables 5–8) for the different time points are presented in the Web Enhancement. When analyzed by ITT, there were no significant differences among the five groups concerning any of these parameters, and there was no interaction between the sufentanil group and time (repeated-measures analysis of variance). The analysis was performed for specific periods during anesthesia (e.g., from induction to skin incision) or surgery (e.g., from skin incision to sternotomy or during CPB), and there were no significant differences among the five groups for any specific period (results not shown). The analysis was also performed on a per-protocol basis and confirmed the results of the ITT analysis. These results indicate that MAP and HR were comparable over time among the five groups.

The number of episodes of arterial hypertension or hypotension, bradycardia, and tachycardia as well as the number of bolus injections of the different cardiac or vasoactive drugs are presented in the Web tables 9 and 10, respectively. There were no statistically significant differences among the five groups for the number of episodes of hemodynamic instability or any of the individual cardiovascular drugs.

Sedation in the ICU, Morphine Requirements, and Patients' and Nurses' Satisfaction Scores

For the whole patient population included in the five groups, 2 h after arrival in the ICU, the Ramsay score was 4.7 (1.4) [mean (SD)] (median value 5) and decreased to 3.7 (1.9) (median 3) 4 h after arrival in the ICU. There were no statistically significant differences among the five groups for the level of sedation (Kruskal-Wallis test).

Morphine requirements (median [range]) for the first 24 postoperative hours were 45 [5–129] mg for group 1, 40 [0–119] mg for group 2, 36 [0–74] mg for group 3, 30 [0–104] mg for group 4, and 36 [0–110] mg for group 5. The differences among the five groups were not statistically significant.

The mean (SD) values for patients' satisfaction scores (1 = not satisfied, 4 = very satisfied; Appendix 3) for the five groups at extubation and on postoperative day 3 were 3.8 (0.5) and 3.9 (0.4), respectively, and there were no statistically significant differences among the five groups, indicating similar quality of overall acceptance of the anesthetic protocol and postoperative period.

The mean (SD) values for ICU nurses' satisfaction scores (Appendix 4) were 1.2 (0.5) for item A, 1.2 (0.4) for item B, 1.8 (1) for item C, and 1.1 (0.2) for item D. There were no statistically significant differences among the five groups for the ICU nurse satisfaction scores. These results are consistent with the Ramsay score values and indicate a similar level of sedation for the five groups.

Table 6. Details Regarding BIS Values and Predicted Effect Sites for Propofol and Sufentanil for Patients Who Reported Recall/Dreaming during the Perioperative Period

Group	Age, yr	Sex	BMI	ASA Class	Premedication	No. of Episodes (n) with BIS Values > 60 and Periods during Anesthesia and Surgery	Duration of BIS Episodes with Values > 60	Ce Propofol, $\mu\text{g/ml}$	Ce Sufentanil, ng/ml
2	60	M	24	II	3 mg bromazepam	n = 4 5 min after sternotomy Sternal and skin closure: 3 episodes	3 min 20 s 18 min 40 s	1.3 1	0.66 0.5
4	68	M	25	II	6 mg bromazepam	n = 0 But 2 BIS values >60: BIS = 60.1 during skin incision BIS = 62.9 between end of CPB and skin closure	10 s	1.3	1.25 0.8
5	50	M	27	II	5 mg midazolam	n = 0 But 8 BIS values > 60 and 3 > 70: 5 min after tracheal intubation and before aortic cannulation	40 s	2.2	1.5
5	60	M	25	II	6 mg bromazepam	n = 8 Interval between tracheal intubation and skin incision Interval between sternotomy and aortic cannulation: 2 episodes Aorta manipulation for cannulation until onset CPB: 2 episodes During CPB Sternal and skin closure: 2 episodes	4 min 45 s 7 min 30 s 8 min 20 s 12 min 25 s 16 min 10 s	1.2 1	1 1.5 1.46 1 1

ASA = American Society of Anesthesiologists; BIS = Bispectral Index; BMI = body mass index; Ce = predicted effect site concentration; CPB = cardiopulmonary bypass.

The awareness scores (Appendix 2) obtained immediately after tracheal extubation (median [range]) were 1 [0–3] for group 1, 0.5 [0–7] for group 2, 1 [0–3] for group 3, 0 [0–4] for group 4, and 0.5 [0–6] for group 5. On postoperative day 3, the awareness scores were 1 [0–3] for group 1, 2 [0–3] for group 2, 1 [0–3] for group 3, 0 [0–2] for group 4, and 0 [0–4] for group 5. There were no statistically significant differences among the five groups for the awareness scores calculated after tracheal extubation or on postoperative day 3.

Only one patient randomized to group 5 reported dreaming on the two questionnaires. Three patients randomized to group 2, group 4, and group 5 reported dreams only on the questionnaire performed immediately after tracheal extubation. None of the four patients could attribute the dreams specifically as being during surgery. There were no statistically significant differences among the five groups for the percentage of patients who reported recall/dreams at any moment. Despite the dreams, three patients declared they were very satisfied with the anesthetic technique, and one patient stated that he was moderately satisfied.

The patients who reported dreams during the perioperative period, the periods when BIS values greater than 60 occurred, and the cumulative period of time with BIS values greater than 60 (analysis of the BIS[®] electronic file), together with predicted propofol and sufentanil Ce

values recorded manually by the investigators, are reported in table 6.

Discussion

To the best of our knowledge, this is the first randomized study performed in a cohort of patients who underwent CABG surgery with CPB who had a computer controlled infusion of propofol and sufentanil titrated on the BIS values and not on hemodynamic parameters. The patients included in the study are comparable to those included in large European²⁴ and North American studies²⁵ and are representative of low-risk patients who require first-time elective CABG surgery.

A predicted sufentanil Ce of 0.5 ng/ml was sufficient in all but one patient allocated to group 1 to avoid increases of BIS values (δ BIS) on laryngoscopy. Predicted sufentanil Ce of 1.25 ng/ml before sternotomy and predicted sufentanil Ce of 0.8 ng/ml from sternotomy to skin closure were associated with the lowest predicted propofol Ce, the lowest number of changes of propofol target and unexpectedly, with the lowest number of BIS episodes greater than 60 (table 4), although this did not reach statistical significance ($P = 0.073$). This sufentanil regimen was associated with a median interval between end of propofol infusion for ICU sedation and tracheal extu-

bation of 115 min as compared to 81 min for the lowest sufentanil concentration. Because of important interpatient variability, time to tracheal extubation was not significantly different among the groups. This is probably related to the fact that time to tracheal extubation depends on variables other than the cumulative opioid doses. Confounding variables could have been CPB or surgical techniques. This is nevertheless unlikely because we analyzed both the interval from skin closure to tracheal extubation and from end of propofol infusion in the ICU (a time point when criteria for tracheal extubation as defined in the Methods and Materials were met) to tracheal extubation (table 5). It is likely that factors related to the activity in the ICU could mask the benefits of lower cumulative sufentanil doses supposed to result in faster tracheal extubation.

What are the possible clinical implications of these results? When the BIS values are used as a measure of combined propofol-sufentanil pharmacodynamic effects, clinicians can choose lower or higher sufentanil concentrations. If a low sufentanil concentration is chosen and there are no increases in BIS values on laryngoscopy and tracheal intubation, there is probably no need to further increase the sufentanil concentration. A low sufentanil concentration would require more frequent adaptations of the propofol target to maintain BIS values within predefined targets. Higher sufentanil concentrations result in unchanged BIS values on laryngoscopy and tracheal intubation and require fewer adjustments of the propofol target. Higher sufentanil concentrations could be associated with a moderate increase of time to tracheal extubation, but our results do not support this possibility.

The highest sufentanil concentrations to which the patients were randomized in the current study are similar to the lowest concentrations reported by Jain *et al.*¹² and Thomson *et al.*²⁶ in cardiac surgery patients and correspond to the concentrations that were shown to possess a nearly maximum sparing effect on minimum alveolar concentration (MAC) in dogs.²⁷ Lower concentrations of opioids, as compared to those usually reported in anesthesia for cardiac surgery, are probably desirable given the recent observations that suggest that high opioid concentrations can induce persistent hypersensitivity and allodynia.^{28,29} In this respect, our observation that there is no measurable benefit of concentrations of sufentanil higher than 1.25 ng/ml before sternotomy and 0.8 ng/ml thereafter is important. The results of Thomson *et al.*²⁶ are consistent with this observation and suggest that there is no measurable benefit to use sufentanil concentrations higher than 1 ng/ml. Interestingly, only one patient from group 1 (allocated to receive a predicted sufentanil concentration of 0.5 ng/ml) required an increase of the sufentanil target concentration because of an increase in BIS values on tracheal intubation. This suggests that even lower sufentanil concentrations

would have provided similar outcomes. The optimal sufentanil concentration for cardiac surgery would be that concentration just greater than that which results in a high percentage of patients who require an increase of sufentanil concentration because of increases of BIS values on tracheal intubation.

An important and relatively unexpected result of our study is the low concentrations of propofol necessary to obtain what is considered adequate BIS values (*i.e.*, < 60) during anesthesia. The predicted concentrations of propofol obtained using a predefined algorithm based on BIS values were lower than those of any other published articles that investigated cardiac surgery patients. Indeed, Barvais *et al.*,³⁰ using the Diprifusor[®], reported average propofol target concentrations of 2.5 $\mu\text{g/ml}$ before skin incision and 4.95 $\mu\text{g/ml}$ before sternotomy. Jain *et al.*¹² designed their study to obtain predicted propofol C_e higher than 3 $\mu\text{g/ml}$. Therefore, the target propofol concentrations reported in the current study are probably among the lowest ever published, comparable only to those reported by Olivier *et al.*³¹ Such low concentrations of propofol were achievable only because hypnosis was titrated on the BIS values and should probably not be used in the absence of BIS monitoring because they are close to the propofol concentrations that prevent explicit recall in 50% of the patients.²⁰

Despite these low predicted propofol concentrations, average BIS values during maintenance of anesthesia were between 45 and 47, and BIS values greater than 60 were measured during less than 5% of anesthesia duration. This predicted propofol concentration-*versus*-BIS value relationship is different from that reported by Iselin-Chaves *et al.*²⁰ Our results are also different from those of Kazama *et al.*,³² who studied the propofol concentration-*versus*-BIS value relationship in a cohort that included older patients.

The unusual predicted propofol concentration-*versus*-BIS value relationship could be related to a combination of several factors. One factor is an unusual patient population in which chronic medication with cardiovascular drugs would decrease hypnotic requirements or displace to the left the propofol concentration-*versus*-BIS value/LOC relationship. Such an effect has been reported for β -adrenergic receptor antagonists given on an acute basis^{33,34} through mechanisms that are poorly understood and could be related to their effects on the cerebral circulation.³⁵ A second factor is a large difference between the predicted and the real propofol concentrations with the pharmacokinetic model of Diprifusor[®] either because of an unusual patient population or because of pharmacokinetic interactions between propofol and sufentanil. This pharmacokinetic model was studied in patients who underwent cardiac surgery with alfentanil as the opioid.³⁰ Barvais *et al.*³⁰ showed that the measured plasma propofol concentrations were approximately 20% higher than the predicted C_p . Even if

Table 7. Centers (Departments of Anesthesia and Intensive Care) Participating in the Study and Number of Patients Included per Center

No.	Center	Patients (n)
2	CHU de Nancy, Hôpital de Brabois, Vandoeuvre-les-Nancy	3
3	CHU de Bordeaux, Hôpital du Haut Lévêque, Pessac-Bordeaux	19
5	CHU de Nantes, Hôpital G. et R. Laennec, Nantes	15
6	CHU Bichat, Groupe Hospitalier Bichat, Paris	4
7	CHU de Lille, Hôpital Cardiologique, Lille	1
9	CHU de Dijon, Hôpital du Bocage, Dijon	9
10	CHU de Grenoble, Hôpital A. Michallon, Grenoble	12
11	CHU de Lyon, Hôpital Louis Pradel, Lyon	9
12	CHU d'Amiens, Hôpital Sud, Amiens	4
13	CHU de Toulouse, Hôpital Rangueil, Toulouse	25
14	CHU de Rennes, Hôpital Pontchaillou, Rennes	6
15	CHU Henri Mondor, Hôpital Henri-Mondor, Creteil-Paris	4

CHU = Centre Hospitalier Universitaire

the predicted C_p was 20% lower than the real propofol concentrations, this could still not explain the propofol concentration-*versus*-BIS value relationship that we report here. (3) A third factor is a pharmacodynamic interaction between sufentanil and propofol on the BIS values. Indeed, in group 4, despite a significantly lower predicted propofol C_e , the BIS values were less than 40 during 13% of the time. Therefore, we hypothesize that a pharmacodynamic sufentanil-propofol interaction is the main cause of the unusual propofol concentration-*versus*-BIS value relationship observed in this study. The commonly accepted knowledge is that low^{20,36,37} or even high¹⁸ concentrations of opioids would not change the hypnotic concentration-*versus*-BIS value relationship in the absence of nociceptive stimulation. This is probably true unless the opioid itself, at the concentrations being used, affects the electroencephalogram and therefore the BIS value. The EC_{50} of sufentanil that modifies the electroencephalogram was reported to be approximately 0.7 ng/ml.³⁸ Nevertheless, in our clinical experience, sufentanil at a predicted C_e of 1.5 ng/ml or even 2 ng/ml does not reproducibly decrease BIS values in the absence of a hypnotic agent. Interestingly, an effect of opioids on the BIS value in the presence of hypnotics has been found by some authors.^{39,40} The differences among the different articles are probably related to study design. Further investigations are necessary to document the effects of opioids on BIS values. In addition, the above-cited authors did not use the technique of BIS analysis performed in this study (*i.e.*, number of BIS values < 40 during several hours of BIS recordings), and comparisons are therefore difficult.

How low can "low" propofol concentrations be? Our results demonstrate (table 3) that with a predicted sufentanil C_e of 1.25 ng/ml and an average propofol C_e of 1.23 μ g/ml, BIS values were lower than 40 in up to 13% of the time and higher than 60 during only 1.7% of the BIS recording time. This observation could be interpreted as propofol overdose and could represent an incentive to lower propofol concentrations even further.

This does not seem reasonable, and therefore, we do not recommend propofol concentrations lower than 1.5 μ g/ml even with BIS monitoring.

Special Considerations Regarding BIS Monitoring When Using Low Propofol Concentrations

We were surprised when analyzing the electronic BIS recordings to observe BIS values greater than 60 in continuous 3-min periods in many patients. This 3-min interval was chosen arbitrarily based on the work of Flaishon *et al.*,¹⁴ who demonstrated that the return of consciousness on emergence from a bolus injection of a hypnotic is related to the BIS values and also to the duration of an increase in BIS value. Although the cumulative average duration of continuous 3-min episodes with BIS values greater than 60 was relatively short (approximately 20 min) and most of these "high" BIS values were less than 70, individual patients had intervals as long as 117 min of BIS values greater than 60, which can expose to inadequate hypnosis and perioperative recall. Interestingly, approximately 40% of BIS episodes with values greater than 60 occurred during CPB, an unexpected result given our previous experience²¹ and recent results that suggest that moderate hypothermia during CPB should moderately reduce BIS values.⁴¹ The most likely explanation is based on the observation that the investigators recorded hemodynamic instability during CPB only as arterial hypotension (results not shown). This indicates that clinicians are still reluctant to increase the hypnotic concentration in the presence of increased BIS values and low arterial blood pressure. The discordance between arterial blood pressure values and BIS values during CPB could be an incentive to monitor cardiac surgery patients with the BIS.

There are several limitations of this study. The study concentrated on surrogate endpoints and did not analyze endpoints such as biomarker elevation, myocardial ischemia, infarction, or mortality, mainly because published results do not suggest a major effect of the anesthetic technique on such endpoints with intravenous anes-

thetic drugs.¹² In addition, the study was not designed to have the statistical power to detect differences among the five groups for rare events such as perioperative awareness.

In summary, our results suggest that the BIS scale as part of an algorithm that includes both the absolute BIS value and the δ BIS on application of a nociceptive stimulus is a clinically useful titration tool of the combined effects of propofol and sufentanil. The titration algorithm used in this study resulted in unusually low predicted propofol concentrations probably related to a pharmacodynamic interaction between sufentanil and propofol on the electroencephalogram and BIS values.

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Appendix 1

Table 7 lists the centers (Departments of Anesthesia and Intensive Care) that participated in the study and the number of patients included from each center.

Appendix 2: Awareness Score

The questions for the Awareness Score were modified from Sebel.²³

1. What is the last thing you remember before you fell asleep?
2. What is the first thing you remember when you woke up?
3. Do you have any memories between these two events?
4. Did you dream during anesthesia and surgery?
5. What is the most unpleasant thought you had during the intervention?

For answers such as nothing, no, or none, the score was 0. For questions 1, 2, and 5, any other answer was given a value of 1. For questions 3 and 4, values of 5 and 4, respectively, were given to easily detect awareness during surgery. Thus, a score of 0 indicated lack of perioperative awareness, a score less than 3 was consistent with recall before or after surgery, and a score greater than 3 was consistent with recall during surgery.

Appendix 3: Patients' Satisfaction Score

Are you satisfied with your anesthesia?

- Very satisfied = 4
 Moderately satisfied = 3
 Not satisfied = 2
 Unsatisfied = 1

Appendix 4: Satisfaction Score of the Nursing Team

The questionnaire rated the following items:

A. Global evaluation of patient sedation and the way the patient underwent his or her stay in the intensive care unit

B. Global evaluation of the tolerance of the endotracheal tube and mechanical ventilation

C. Global evaluation of the communication with the patient during the first 24 postoperative hours

D. Global evaluation of the facility to provide care to the patient during the first 24 postoperative hours

For each item, a score was designed as follows:

Item A

1. Very easy: The patient is calm and cooperative.
2. Easy: The patient is calm unless stimulated.
3. Moderately difficult: The patient is agitated even when not stimulated.
4. Difficult: Frequent episodes of agitation when the patient must be contained.

Item B

1. Well tolerated
2. Moderately tolerated: The patient occasionally pushes the tracheal tube.
3. Not tolerated: The patient is agitated and wants to remove the endotracheal tube and an intervention from the nursing team is necessary.

Item C

1. Very easy: The patient answers questions and can clearly indicate what he or she wants.
2. Easy: The needs of the patient can be determined easily, with few questions.
3. Moderately difficult: The patient answers questions, but it is difficult to understand what he or she wants.
4. Difficult: The patient has difficulties in answering questions; it is very difficult to understand what he or she wants.
5. Impossible: The patient is too sedated to communicate.

Item D

1. It is easy to provide care because the patient is cooperative.
2. It is relatively difficult to provide care to the patient and obtain the patient's cooperation.
3. It is difficult to provide care because the patient is not cooperative.

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