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Titration of Propofol for Anesthetic Induction and Maintenance Guided by the Bispectral Index: Closed-loop versus *Manual Control*

A Prospective, Randomized, Multicenter Study

Ngai Liu, M.D., Thierry Chazot, M.D.,* Antoine Genty, M.D.,† Alain Landais, M.D.,‡ Aymeric Restoux,§ Kathleen McGee, M.D.,‖ Pierre-Antoine Laloë,§ Bernard Trillat, M.Sc.,# Luc Barvais, M.D.,** Marc Fischler, M.D.††*

Background: **This report describes a closed-loop titration of propofol target control infusion based on a proportional-differential algorithm guided by the Bispectral Index (BIS) allowing induction and maintenance of general anesthesia and compares this to manual propofol target control infusion.**

Methods: **One hundred sixty-four patients scheduled to undergo elective minor or major surgery were prospectively randomized in a multicenter study into the closed-loop (n = 83) or manual target control infusion group (n = 81). The goal was to reach a BIS target of 50 during induction and to maintain it between 40 and 60 during maintenance. For both groups, remifentanil target control infusion was adjusted manually, and ventilation was without nitrous oxide.**

Results: **Closed-loop control was able to provide anesthesia induction and maintenance for all patients. During induction, propofol consumption was lower in the closed-loop group (1.4 ± 0.5 *vs.* 1.8 ± 0.6 mg/kg; $P < 0.0001$), but the duration was longer (320 ± 125 *vs.* 271 ± 120 s; $P < 0.0002$). Adequate anesthesia maintenance, defined as the BIS in the range of 40–60, was significantly higher in the closed-loop group (89 ± 9 *vs.* 70 ± 21%; $P < 0.0001$), with a decrease of the occurrence of BIS less than 40 (8 ± 8 *vs.* 26 ± 22%; $P < 0.0001$). Time from discontinuation of propofol infusion to tracheal extubation was shorter in the closed-loop group (7 ± 4 *vs.* 10 ± 7 min; $P < 0.017$). Unwanted somatic events and hemodynamic instability were similar.**

Conclusion: **Automatic control of consciousness using the BIS is clinically feasible and outperforms manual control.**

ELECTROENCEPHALOGRAPHIC monitoring may be used to assess the effect of anesthetic drugs on the central nervous system.[1] More recently, Bispectral Index (BIS) monitoring has emerged as a convenient and versatile tool to titrate hypnotic agents[2,3] and to reduce drug consumption, therefore allowing faster recovery[2,4–6] while avoiding side effects such as hemodynamic instability[7] or awareness.[8] BIS is a dimensionless number scaled from 100 to 0, with 100 representing an awake electroencephalogram and 0 representing electrical silence.[1] Because it is a single composite measure monitored continuously, it has been used to control depth of hypnosis automatically.[9–12] Closed-loop systems are not subject to fatigue, thus maintaining the same efficiency throughout a surgical procedure,[13] while freeing the physician for more demanding human tasks.[12,14] However, in these studies, induction of general anesthesia was performed manually, closed-loop control being used only during stable phases of surgery. The number of cases studied was small, and control groups were generally omitted[10,12,15] or BIS monitoring was not used.[11]

Anesthesiologists often compare themselves to pilots who use automated flight control. Autopilot systems are routinely used in the airline industry to reduce the workload during busy periods and certain types of human error during takeoff, cruising, and landing. Because closed-loop control has the potential to improve the quality of anesthesia, we have created a system that controls a target-controlled infusion (TCI) of propofol, a system that is titrated to the BIS. The system induces and maintains general anesthesia using a proportional-differential algorithm. To our knowledge, there is no study in the literature reporting a closed-loop system using the BIS allowing total control of hypnosis throughout anesthesia, whereas Kenny and Mantzaridis[16] have described the first closed-loop anesthesia from induction to maintenance using auditory evoked potential index as the control variable.

The current clinical study was designed to evaluate our propofol–BIS closed-loop system during induction, maintenance, and emergence from anesthesia and to compare it with manual control. In particular, we expected that our closed-loop system would reduce time spent with BIS values outside predetermined limits and would enable faster recovery times without increasing the incidence of adverse events.

Materials and Methods

The ethics committee of our university (Comité Consultatif de Protection des Personnes dans le Recherche Biomédicale, Hôpital Ambroise Paré, Boulogne Billan-

* Staff Anesthesiologist, § Resident in Anesthesia, †† Professor in Anesthesiology and Chairman, Department of Anesthesiology, # Informatics Engineer, Hôpital Foch. † Staff Anesthesiologist, Clinique Saint Augustin, Bordeaux, France. ‡ Chairman, ‖ Staff Anesthesiologist, Department of Anesthesiology, Hôpital V. Dupouy, Argenteuil, France. ** Professor in Anesthesiology and Chairman, Department of Anesthesiology, Hôpital Erasme, Brussels, Belgium.

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Address correspondence to Dr. Fischler: Department of Anesthesiology, Hôpital Foch, 40 rue Worth, 92151 Suresnes, France. m.fischler@hopital-foch.org.

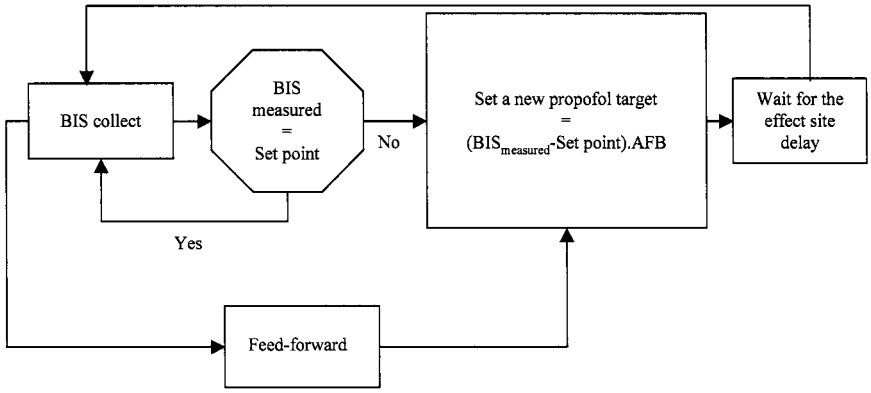

Fig. 1. The main algorithm. Effect site delay was calculated using the pharmacokinetic model of Schnider *et al.*[19] The feed-forward term amplified the correction of the propofol target when a measured Bispectral Index (BIS) value greater than 60 was detected. AFB = amplification of the feedback.

court, France) approved this prospective, randomized, multicenter, clinical study. Patients were informed of the nature of the study and gave their written, informed consent. Patients selected for the study presented for various elective surgical procedures requiring general anesthesia of at least 30 min. The patient had to be aged between 18 and 100 yr with an American Society of Anesthesiologists (ASA) physical status of I–III. Patients presenting psychiatric, supraspinal neurologic disorders and those equipped with a pacemaker or scheduled to undergo cardiac or cranial neurosurgical procedures were excluded. Patients were randomized to one of two groups (manual TCI or closed-loop group). The sequence of treatments was determined in blocks of 10 in each participating center (5 manual TCI and 5 closed-loop group) using a random number generator.

Anesthesia Protocol

In both groups, patients received a propofol-and-remifentanil TCI administered using the Infusion ToolBox 95 version 4.8 computer-controlled infusion system (Department of Computer Science, Faculty of Medicine, Free University of Brussels, Brussels, Belgium).[17] The population pharmacokinetic sets of Minto *et al.*[18] and Schnider *et al.*[19] were selected for remifentanil and propofol, respectively. Infusion ToolBox steered two Asena GH® infusion pumps (Alaris Medical UK Ltd., Basingstoke, Hampshire, United Kingdom) and recorded the BIS obtained from an A-2000 XP (version 3.11) BIS® monitor (Aspect Medical System, Newton, MA). A standard personal computer running with Windows 98® (Microsoft, Redmond, WA) was used to provide a user interface and to control communication with the BIS® monitor and the infusion pumps *via* an RS232 serial port. Data from the BIS® monitor and the two infusion pumps was stored on the personal computer at 5-s intervals from induction to recovery.

For the closed-loop group, the control algorithm was based on an empirical proportional-differential control algorithm allowing the titration of propofol until the target level of BIS = 50 was obtained. In closed-loop mode, the system calculates the BIS "error" (difference between the target and actual BIS value). The BIS "error" is used by the proportional differential control algorithm to calculate a new propofol target. The delay between each modification of propofol target was determined by the time necessary for 95% equilibration of the effect site compartment using the pharmacokinetics model of Schnider *et al.* The gain constants or amplification of the feedback used in the control algorithm was determined empirically and tested in an open-loop pilot study: The algorithm calculated a new target of propofol, and the target was modified after manual validation. Fine-tuning had been tested in a previous pilot study in 20 subjects. A feed-forward term was implemented in the algorithm because rapid BIS changes caused by an arousal require fast controller reaction. Every 5 s, the feed-forward term amplified the correction of the new propofol target when a measured BIS value greater than 60 was detected (fig. 1). The user entered the sex, age, weight, and height of the patient, and the induction phase was commenced. After tracheal intubation, the user entered "End of induction," and the system switched automatically to the maintenance phase. A valid BIS measurement was assumed when the signal quality was greater than 50. During poor signal quality, the target of propofol was not modified until the BIS values were valid again. The minimum value and the maximum value (default value) of the propofol target were 1 and 5 μg/ml, but the user could modify these values. Throughout the procedure, the user could adjust the propofol target if necessary or switch between closed-loop control and manual control. The investigators were trained to use the closed-loop controller during 1 day of clinical demonstration. All investigators had clinical experience in titrating anesthesia using the BIS, propofol, and remifentanil TCI before the study.

For the manual TCI group, during the induction phase, the anesthesiologists were instructed to titrate the propofol target to achieve a BIS value of 50, sufficient to allow tracheal intubation, as rapidly as possible, without adverse hemodynamic effects. The anesthesiologist could only increase propofol target after 95% equilibration of the effect site compartment was obtained. During

maintenance, the anesthesiologists were instructed to adjust the propofol target to maintain a BIS value as close as possible to 50 and between 40 and 60.

In both groups, on arrival in the operating room, an intravenous cannula, dedicated to TCI infusion, was connected *via* a three-way Smartsite® Needle-Free System (Alaris Medical Systems, San Diego, CA) with a priming volume of 0.3 ml to the pumps. Routine monitoring was commenced (pulse oximetry, electrocardiography, noninvasive or invasive [as necessary] blood pressure). Before starting BIS recording, we verified that electrode impedance was below 5 kΩ and that the BIS sampling rate was 256 Hz.

For both groups, remifentanil TCI and muscle relaxants were administered at discretion by the anesthesiologists throughout the procedure. Signs of inadequate analgesia were treated with increased remifentanil target. Hypotension and bradycardia were managed by appropriate dose reduction of remifentanil, adjustments of fluid status, or administration of atropine. All patients were mechanically ventilated without nitrous oxide. Cardiovascular treatment, premedication, duration of anesthesia, fluid infusion, blood loss, somatic events (movement, grimacing, eye opening), and use of a vasopressor (ephedrine) or antihypertensive therapy were recorded. The type of surgery was classified as minor or major. Approximately 20 min before the scheduled end of surgery, titration of the following drugs was started for postoperative intravenous analgesia: 0.1–0.15 mg/kg morphine, proparacetamol, nefopam, and nonsteroidal antiinflammatory drugs. Neuromuscular blockade reversing agent was administered as necessary. Patients were kept normothermic using a forced air warming blanket associated with a fluid warming device as necessary. At completion of the surgical procedure, propofol and remifentanil were stopped. Time to tracheal extubation was defined as the time from discontinuation of propofol infusion until tracheal extubation. The speed of recovery was defined as follows: excellent: time to tracheal extubation less than 5 min; good: time to tracheal extubation less than 10 min; and poor: time to tracheal extubation greater than 10 min. All patients were visited and interviewed about intraoperative recall in the postanesthesia care unit and on the second or third postoperative day.

Performance Analysis

Performance was assessed in both groups by comparing the actual measured BIS value to the preset BIS. BIS values with a signal quality index below 50% were removed from the data analyzed. The parameters were calculated for two phases: the induction phase and the maintenance phase.

Induction Phase. For the induction phase, we measured the duration of induction, defined as the time elapsed from the start of propofol administration to the moment when the BIS value fell to and remained under 60 for 30 s. Overshoot and undershoot of BIS were defined as episodes of the BIS value under 40 or above 70, respectively, and were calculated (in seconds) for each patient during the first 3 min after the time when the BIS value fell and remained under 60 for 30 s.

Maintenance Phase. For the maintenance phase, adequate control of BIS was defined as maintaining BIS between 40 and 60 and was calculated as a percentage of the maintenance duration. Precision of the system was validated using the parameters proposed by Varvel *et al.*[20] Performance error (PE) was calculated as the difference between actual and desired values. Bias or median performance error (MDPE) described whether the measured values were either above or below the target ones and thus represented the direction (undershoot or overshoot) of the PE. Inaccuracy or median absolute performance error (MDAPE) described the size of the errors. Wobble measured the intraindividual variability in PE. We have calculated another parameter, the global score (GS), which characterized the overall performance of the system. Excellent performance is characterized by low MDAPE and wobble values and a high percentage of BIS values between 40 and 60 and consequently a low value of GS. Equations and explanations of these parameters are provided in the appendix.

Statistical Analysis

In a pilot study, the percentage of adequate anesthesia (defined as BIS between 40 and 60) was above 65% using manual propofol TCI guided by the BIS, and we expected an improvement of greater than 33% using the closed-loop system. We calculated that a total of 148 patients (74 per group) were required to achieve 80% power at 5% two-sided type I error. We planned to recruit 180 patients to allow for patients' dropping out and for missing data.

Data are presented as mean ± SD, percentage, or number of cases. Continuous data were compared by means of the Student *t* test. Categorical data were compared by means of the chi-square test or Fischer exact test as appropriate. Three-way analyses of variance were used to test for differences in demographic features and for all anesthesia efficacy end points defined for this study between the three centers. Times from discontinuation of propofol infusion until tracheal extubation were compared using a Kaplan-Meier survival analysis followed by log-rank test. Probability values under 0.05 were considered significant. Data analysis was performed using SPSS® version 11.0 (SPSS Science Inc., Chicago, IL).

Results

One hundred eighty patients undergoing various surgical procedures (thoracic, vascular, urologic, gyneco-

Table 1. Demographics

	Manual TCI (n = 81)	Closed-loop (n = 83)	*P* Value
Age, yr	59 ± 16	58 ± 15	NS
Sex ratio, M/F	32/49	31/52	NS
Height, cm	167 ± 14	167 ± 21	NS
Weight, kg	70 ± 15	73 ± 13	NS
Major surgery, %	42	48	NS
ASA physical status III, %	4	16	0.016
Cardiovascular treatment, %	28	35	NS

Data are presented as mean ± SD, number, or % of total patients in each group.

ASA = American Society of Anesthesiologists; cardiovascular treatment = β blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor, or diuretics; closed-loop = closed-loop group; manual TCI = manual target-controlled infusion group guided by the Bispectral Index; NS = not significant.

logic, abdominal, and otolaryngic) were enrolled at three sites, 90 in the manual TCI group and 90 in the closed-loop group. Sixteen patients were excluded for protocol violations (duration of surgery < 30 min, 4 patients; lack of recorded end points, 6 patients; use of nitrous oxide, 4 patients; combined locoregional anesthesia, 2 patients). Therefore, the study population consisted of 81 in the manual TCI group and 83 in the closed-loop group.

Fifteen anesthesiologists and 22 anesthetic nurses participated in this study. No significant site differences were found regarding the demographic variables (age, weight, height), except for ASA physical status classification. The number of ASA physical status III patients was higher in the closed-loop group ($P < 0.016$). No significant site differences or group-by-site interaction was found for the end point measures. There was no consistent evidence of site-related differences in the overall outcome. Therefore, results from the pooled data from all sites combined for the manual TCI and closed-loop groups are presented. Demographics, types of surgery, and cardiovascular treatments for the two groups are presented in table 1.

Induction Phase

Anesthesia induction was successfully provided for all the patients of the closed-loop group. The amount of propofol was larger in the manual TCI group than in the closed-loop group (1.8 ± 0.6 *vs.* 1.4 ± 0.5 mg/kg; $P = 0.0001$). Induction was faster in the manual TCI group (271 ± 120 *vs.* 320 ± 125 s; $P = 0.0002$), but overshoot of BIS was more pronounced in this group (29 ± 50 *vs.* 12 ± 26 s; $P = 0.005$). The amount of infused remifentanil and the use of ephedrine were similar in both groups. These results are presented in table 2.

Maintenance and Recovery Phases

The time spent with low signal quality (< 50) was similar between the two groups during maintenance (2 ± 2 *vs.* 3 ± 2%, manual TCI *vs.* closed-loop groups, respectively). All of the BIS values from induction to discontinuation of propofol infusion are presented for both groups in figure 2; typical best- and worst-case performances for both groups are presented in figure 3. The closed-loop system maintained anesthesia during a total of 185 h, during which 5,273 propofol target modifications were made automatically. Only 4 modifications were made manually in 4 patients of the closed-loop group compared with 1,543 manual modifications in the manual TCI group. Propofol target modifications were made significantly more frequently in the closed-loop group and with smaller adjustments when compared with the manual TCI group (table 3).

The incidence of adequate BIS level was significantly higher in the closed-loop group (89 ± 9%) compared with the manual TCI group (70 ± 21%). The incidence of BIS levels higher than 60 were similar in the two groups, but the incidence of too-deep anesthesia (BIS < 40) was significantly less frequent in the closed-loop group (8 ±

Table 2. Clinical Data and Performance of Induction Phase

	Manual TCI (n = 81)	Closed-loop (n = 83)	*P* Value
Premedication, none/hydroxyzine/diazepam	9/50/22	10/54/19	NS
Duration of induction, s	271 ± 120	320 ± 125	0.0002
Propofol induction dose, mg/kg	1.8 ± 0.6	1.4 ± 0.5	< 0.0001
Propofol target, μg/ml	3.8 ± 1.2	3.2 ± 1.0	< 0.0001
Remifentanil induction dose, μg/kg	2.5 ± 1.2	2.7 ± 1.1	NS
Remifentanil target, $\mu g \cdot kg^{-1} \cdot min^{-1}$	6.0 ± 2.2	6.1 ± 2.2	NS
Use of neuromuscular blocker, %	91	90	NS
Ephedrine bolus, %	16	12	NS
Antihypertensive therapy, %	0	1	NS
Overshoot BIS < 40, s	29 ± 50	12 ± 26	0.005
Undershoot BIS >70, s	7 ± 18	10 ± 24	NS

Data are presented as mean ± SD, number, or % of total patients in each group.

Closed-loop = closed-loop group; duration of induction = time elapsed from the start of propofol administration to the moment when the Bispectral Index (BIS) value fell to and remained under 60 for 30 s; manual TCI = manual target-controlled infusion group guided by BIS; NS = not significant; overshoot BIS < 40: duration of BIS under 40 in a period of 3 min after the BIS value fell and remained under 60; undershoot BIS > 70: duration of BIS greater than 70 in a period of 3 min after the BIS value fell and remained under 60.

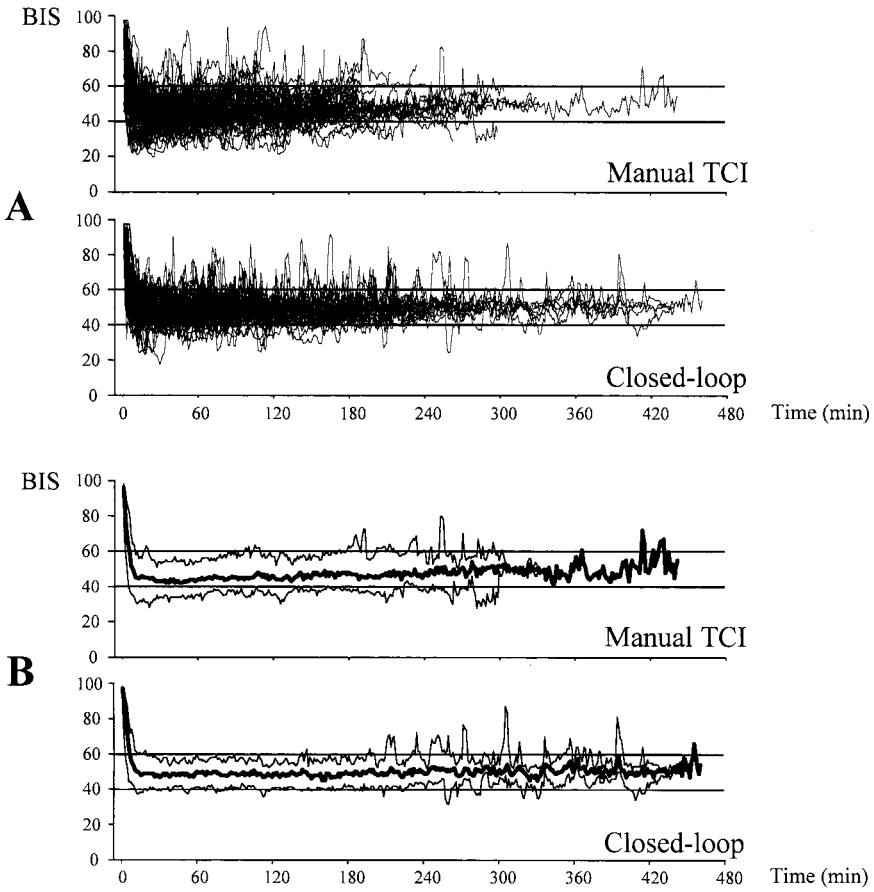

Fig. 2. Bispectral Index (BIS) values from induction to discontinuation of propofol infusion for manual target-controlled infusion (TCI) and closed-loop groups. (*A*) All individual data are shown; data are averaged for graphical representation with a moving average filter of 1-min duration. (*B*) Median BIS values (*thick line*) are presented with 10th and 90th percentiles (*fine lines*).

8%) than in the manual TCI group (26 ± 22). All control performance parameters were significantly better in the closed-loop group (table 4 and figs. 4 and 5).

The average normalized lactated Ringer's infusion was similar in the two groups (table 3). In the patients with blood loss greater than 500 ml, the colloid infusion was more important (531 ± 644 *vs.* 41 ± 141 ml; $P < 0.001$). In the closed-loop group, the percentage of patients with blood loss greater than 500 ml was higher.

The need for ephedrine bolus and somatic events were similar in the two groups (table 3). Two patients in each group needed 0.5 mg atropine for treatment of bradycardia.

The average normalized morphine amounts administered for postoperative analgesia were similar (0.12 ± 0.06 *vs.* 0.13 ± 0.05 mg/kg, manual TCI *vs.* closed-loop groups, respectively).

Speed of tracheal extubation, defined as the time from discontinuation of propofol infusion to tracheal extubation, was shorter in the closed-loop group than in the manual TCI group. These results are presented in table 3 and figure 6, which shows a Kaplan-Meier survival analysis comparison of the cumulative probability of patients remaining intubated after discontinuation of propofol administration. The distributions were different between the two groups ($P < 0.0003$).

There were no significant differences in the incidence of somatic events, hypertension (defined as the need for hypotensive therapy), or hypotension (defined as the use of ephedrine) (table 3). No cases of awareness were recorded.

Discussion

In the current study, we have demonstrated that our closed-loop system guided by the BIS allowed the titration of propofol during induction and maintenance of anesthesia. The system was studied in patients undergoing routine surgery who were ventilated without nitrous oxide. The closed-loop system decreases consumption of propofol, as well as BIS overshoot during the induction phase. It increases the time of adequate BIS control, decreases the period of too-deep anesthesia, and allows faster extubation. Control performance was better than manual TCI control during maintenance. These end points were achieved without increase of unwanted hemodynamic instability or somatic events compared with manual control.

Previous studies, using closed-loop propofol–BIS systems, were performed during minor surgery in patients with an ASA physical status of I or II.[10,11,15,21] Only one study had a control group with BIS monitoring (version 3.1)[10] in which anesthesia was maintained with a propofol–alfentanil mixture. No clinical advantage was found

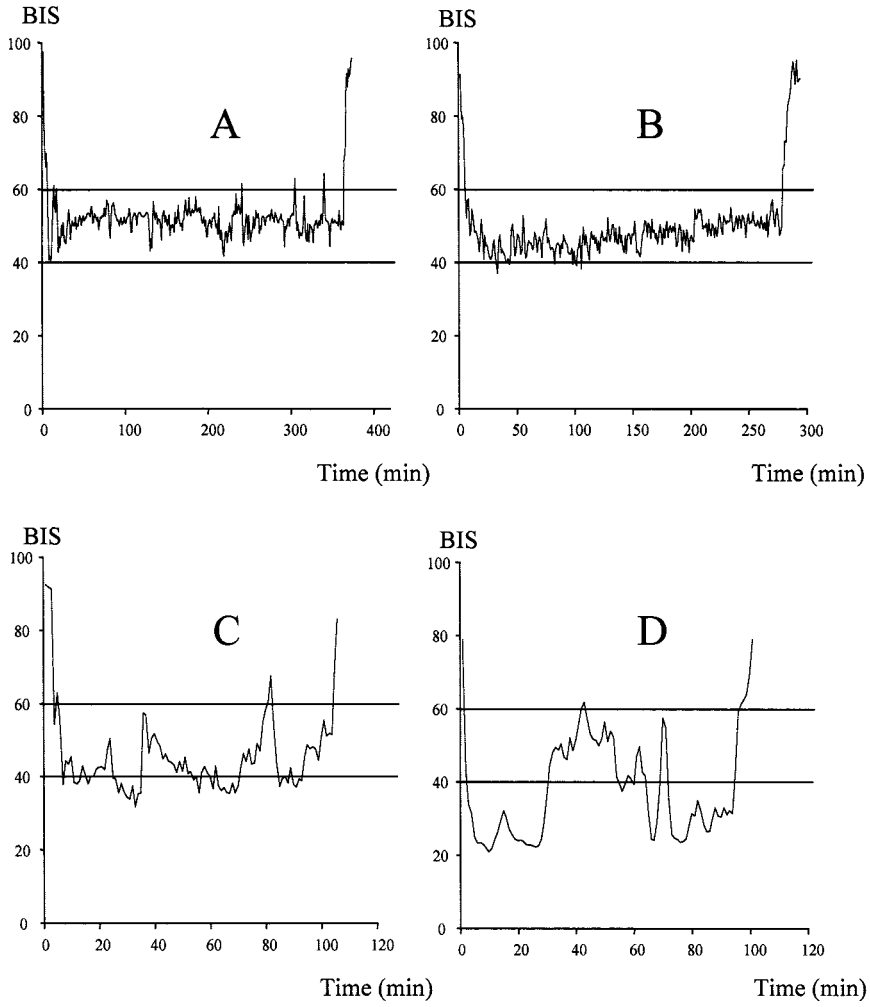

Fig. 3. Typical examples. (*A*) Best closed-loop patient. Male patient who underwent a cystectomy with a blood loss of 800 ml, 98% of the anesthesia duration with a Bispectral Index (BIS) between 40 and 60, median performance error (MDPE): 4.2, median absolute performance error (MDAPE): 5.4, wobble: 3, global score (GS): 9. (*B*) Best manual target-controlled infusion. Male patient who underwent a prostatectomy with a blood loss of 400 ml, 96% of the anesthesia duration with a BIS between 40 and 60, MDPE: −5.2, MDAPE: 7.2, wobble: 6.6, GS: 14. (*C*) Worst closed-loop patient. Male tetraparetic patient who underwent a cervical laminectomy in the sitting position, 64% of the anesthesia duration with a BIS between 40 and 60, MDPE: −16.7, MDAPE: 17.5, wobble: 8.3, GS: 41. (*D*) Worst manual target-controlled infusion patient. Female patient who underwent a hysterectomy, 34% of the anesthesia duration with a BIS between 40 and 60, MDPE: −35.8, MDAPE: 35.8, wobble: 16.8, GS: 153.

between closed-loop and manual control of anesthesia. The main problem in this study seems to be the use of the BIS as a monitor of both analgesia and depth of hypnosis, and this could explain the high incidence of episodes of light anesthesia. BIS monitoring assesses the hypnotic component of anesthesia.[3] Moreover, the number of patients studied with use of a closed-loop system was generally small (10 patients,[9,11,12] 16 pa-

Table 3. Clinical Data of Maintenance

	Manual TCI (n = 81)	Closed-loop (n = 83)	*P* Value
Mean duration of anesthesia, min	126 ± 63	134 ± 86	NS
Average normalized propofol, mg · kg^{-1} · h^{-1}	4.80 ± 1.90	4.40 ± 1.62	NS
Average normalized remifentanil, μg · kg^{-1} · min^{-1}	0.22 ± 0.10	0.22 ± 0.09	NS
Ephedrine bolus, %	30	22	NS
Antihypertensive therapy, %	1	7	NS
Number of modifications of propofol target per h	11 ± 7	33 ± 10	< 0.0001
Mean increment value of propofol target, μg/ml	0.69 ± 0.34	0.30 ± 0.11	< 0.0001
Number of modifications of remifentanil target per hour	10 ± 6	10 ± 6	NS
Blood loss of more than 500 ml, %	7	22	0.014
Lactated Ringer's infusion, ml · kg^{-1} · h^{-1}	7.3 ± 3.1	7.9 ± 3.9	NS
Somatic events, %	14	13	NS
Neuromuscular blocker, %	54	53	NS
Time to tracheal extubation, min	10 ± 7	7 ± 4	0.017
Time to tracheal extubation, %			
Excellent	14	35	
Good	53	51	0.001
Poor	33	14	

Data are presented as mean ± SD or % of total patients of each group.

Closed-loop = closed-loop group; Manual TCI = manual target-controlled infusion group guided by the Bispectral Index; NS = not significant; time to tracheal extubation = time from discontinuation of propofol infusion until tracheal extubation (time to tracheal extubation is reported in absolute values [minutes] and as excellent [time of tracheal extubation < 5 min], good [time of tracheal extubation < 10 min], or poor [time of tracheal extubation > 10 min]).

Table 4. Efficiency of the Control System during Maintenance of Anesthesia

	Manual TCI (n = 81)	Closed-loop (n = 83)	*P* Value
BIS < 45, %	55 ± 31	31 ± 17	< 0.0001
BIS < 40, %	26 ± 22	8 ± 8	< 0.0001
BIS > 60, %	4 ± 5	3 ± 3	NS
45 < BIS < 60, %	41 ± 20	66 ± 18	< 0.0001
40 < BIS < 60, %	70 ± 21	89 ± 9	< 0.0001
PE, %	−8.91 ± 9.46	−1.92 ± 4.72	< 0.0001
MDPE, %	−9.75 ± 11.02	−3.32 ± 5.37	< 0.0001
MDAPE, %	15.53 ± 7.00	9.94 ± 3.40	< 0.0001
Wobble, %	9.19 ± 4.32	8.10 ± 2.46	< 0.031
GS	50 ± 62	21 ± 8	< 0.0001

Data are presented as mean ± SD.

BIS < 45 = percentage of time when the Bispectral Index (BIS) value was below 45; BIS < 40 = percentage of time when the BIS value was below 40; BIS > 60 = percentage of time when the BIS value was greater than 60; 45 < BIS < 60 = percentage of time when the BIS value was between 45 and 60; 40 < BIS < 60 = percentage of time when the BIS value was between 45 and 60; closed-loop = closed-loop group; GS = global score; manual TCI = manual target-controlled infusion group guided by the BIS; MDAPE = median absolute performance error; MDPE = median performance error; NS = not significant; PE = performance error.

tients,[21] 20 patients,[15] and 30 patients[10]). In an editorial, Glass and Rampil[22] stated that closed-loop systems needed to be tested on a broad range of surgery and in extreme circumstances to fully establish the safety, efficiency, and utility of closed-loop anesthesia. Our closed-loop controller was tested in several circumstances, including major surgery with some hemorrhagic events, in sick or elderly patients, with variable durations of surgery (table 3) and with several different users. We have demonstrated the feasibility of closed-loop systems in routine care.

The feasibility of automated induction using the BIS was demonstrated in a preliminary report.[23] Our study is in agreement with the finding that closed-loop titration of general anesthesia induction, guided by the BIS, can be performed with hemodynamic stability similar to that

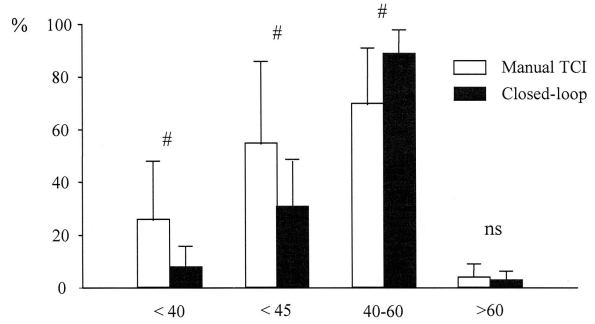

Fig. 4. Efficiency of the system during maintenance of anesthesia. # *P* < 0.0001. BIS < 40 = percentage of time when the Bispectral Index (BIS) value was under 40; BIS < 45 = percentage of time when the BIS value was under 45; 40 < BIS < 60 = percentage of time when the BIS value was between 40 and 60; BIS > 60 = percentage of time when the BIS value was greater than 60; closed-loop = closed-loop group; manual TCI = manual target-controlled infusion group guided by the BIS; NS = not significant.

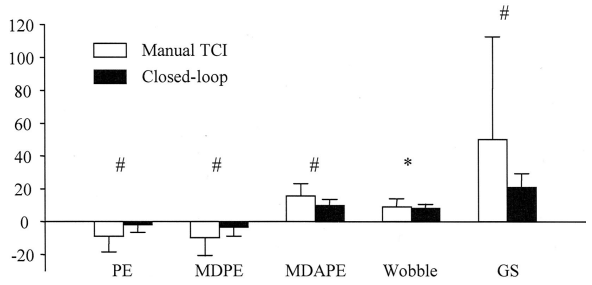

Fig. 5. Control performance during maintenance of anesthesia. * *P* < 0.05; # *P* < 0.0001. Closed-loop = closed-loop group; manual TCI = manual target-controlled infusion group guided by the Bispectral Index; GS = global score; MDAPE = median absolute performance error; MDPE = median performance error; PE = performance error.

found with manual control. However, better hemodynamic stability could have been expected in the manual TCI group, because the anesthesiologist in charge had access to the patient's history and to hemodynamic parameters before and during induction, allowing him or her to react more precisely to sudden decreases in blood pressure during titration and to decrease the propofol target for patients who were under cardiovascular medication. For the closed-loop group, BIS was the only feedback control. This study demonstrates that the closed-loop system can achieve induction, despite limited patient covariables.

During any surgical procedure, the intensity of surgical stimulation and thus the need for anesthetics vary greatly. In addition, some patients have unpredictably low or high anesthetic requirements, and anesthesia results from the dynamic balance between need and delivery. Manual TCI titration using BIS requires continuous control and vigilance on the part of the anesthesiologist to obtain the benefit such monitoring can provide. Propofol consumption during the maintenance phase (table 3) was similar to that found in the study by Kreuer *et al.*[7] (4.8 mg · kg^{-1} · h^{-1}), which used a similar dose of remifentanil (0.22 μg · kg^{-1} · min^{-1}) in patients scheduled to undergo minor orthopedic surgery. Our maintenance propofol doses were lower than in the study by Gan *et al.*[2] (6.9 mg · kg^{-1} · h^{-1}), where pa-

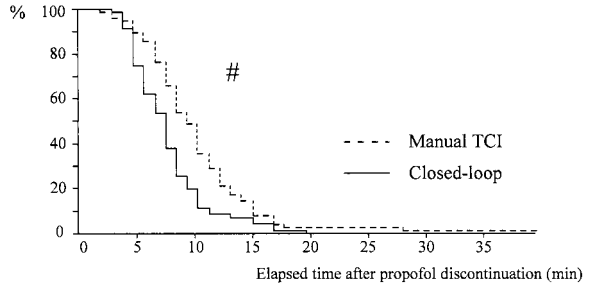

Fig. 6. Comparison of the cumulative probability of remaining intubated patients after the discontinuation of propofol administration. # *P* < 0.0003. Closed-loop = closed-loop group; manual TCI = manual target-controlled infusion group guided by the Bispectral Index.

tients received alfentanil–nitrous oxide analgesia, or the study by Struys *et al.*[11] (6.4. $mg \cdot kg^{-1} \cdot h^{-1}$ for the closed-loop group and 6.5 $mg \cdot kg^{-1} \cdot h^{-1}$ for the standard practice group), which used a continuous infusion of remifentanil (0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The high rate of manual target modifications per hour and the low amount of propofol used for induction and maintenance (tables 2 and 3) demonstrated that titration in the manual TCI group was performed actively, like a challenge (human *vs.* machine), to maintain the BIS within the required limits. The manual TCI group was an active control group, by a Hawthorne effect (*i.e.*, an increase in worker productivity produced by the psychological stimulus of being singled out and made to feel important).[24] The rate of target modifications would probably be lower in routine care. Therefore, significant investigator bias can be excluded as a confounding factor for the explanation of the current results.

Adequate control of maintenance, defined as keeping the BIS value in the range of 40–60 (table 4 and figs. 2A and B), was better in the closed-loop group, as seen with a decrease in episodes of too-deep anesthesia. The proportion of time spent at BIS values under 45 was high (55%) in the manual TCI group, compared with the study by Kreuer *et al.*,[7] who found a value of 36.6%. Recently, in a prospective observational study, Monk *et al.*[25] demonstrated that "cumulative deep hypnotic time" (quantified as the total amount of time in hours with the BIS inferior to 45) increases the risk of mortality at 1 yr by 24.4%. This finding was supported by a preliminary report[26] confirming that low intraoperative BIS levels were associated with increased postoperative mortality at 1 and 2 yr. For both groups (table 4), the incidence of too-deep anesthesia with a BIS value below 45 seems to be high. However, in these studies, BIS values were recorded manually every 5 min and not with a computer, every 5 s, as in our study. The lack of measurement precision may explain the low percentage of too-deep anesthesia in previous studies. The incidence of too-deep anesthesia episodes, BIS below 45 or 40, decreases by two or three times, respectively, in the closed-loop group compared with the manual TCI group. Closed-loop systems can be an alternative to help avoid episodes of too-deep anesthesia. Further studies are needed to determine whether intraoperative management with a closed-loop system can improve the long-term outcome in high-risk patients.

The goals of automated control are to keep the average value of the controlled variable within defined limits and minimize oscillations to an acceptable level.[27] These criteria were given by MDPE, MDAPE, and wobble and were summarized by the GS. These parameters were significantly better in the closed-loop group, as compared with the manual TCI group (fig. 5 and table 4). In fact, MDPE, MDAPE, or wobble cannot be interpret alone and depend on the level of BIS value. GS avoids a misinterpretation of closed-loop performances (see appendix). For MDAPE and wobble, slightly better results were obtained in previous studies.[11,12,15] However, in our study, analgesia was not performed using high fixed doses of remifentanil during gynecologic laparotomy[11] or using epidural analgesia[12] but was adjusted throughout the procedure. Analgesia plays a major role in the need for hypnotic agents and the oscillation of the BIS value.[28,29] Indeed, when the dose of analgesic administered is sufficient to inhibit autonomic response to noxious stimuli, the required propofol concentration is only that needed to achieve loss of consciousness. The BIS® monitor does not monitor analgesia directly, but the oscillation of the BIS, after surgical stimulation, may indirectly reflect the analgesic state. For example, if a patient has inadequate analgesia, and there are significant painful stimuli, pain may cause cortical activation and the BIS may increase. Finally, in a patient who has insufficient analgesia, BIS oscillation given by the MDAPE or wobble can reflect the shifting balance between sensory suppression and repeated stimulation. For both groups, the number of target modifications and the amount of administered remifentanil were similar and cannot explain the difference between the two groups regarding the performances of the system. The closed-loop system allows more frequent and appropriate change of drug delivery with small adjustments in propofol concentration (table 3), achieving an MDAPE and wobble (table 4) under 10 and a GS of 21. Closed-loop systems can titrate propofol to a desired BIS index better than manual control during induction and maintenance. Closed-loop systems could be a valuable tool to assist the anesthesiologist in handling cumbersome and monotonous processes and decrease the workload.[30] However, the clinician must be present constantly to overlook the control system and will always hold the ultimate responsibility for patient safety.

Although a better hypnotic level was achieved in the closed-loop group during maintenance, the use of ephedrine bolus was similar in the two groups (30 *vs.* 22%, manual TCI and closed-loop groups, respectively). The use of vasopressors was lower than in the study by Kreuer *et al.*,[7] which found an incidence of 42% during minor orthopedic surgery. We have not demonstrated better hemodynamic stability with the use of the closed-loop system. However in the closed-loop group, the number of patients with an ASA physical status of III was higher (table 1) and the intraoperative blood loss was more important (table 3), but the use of vasoactive agents was similar. This suggests that patient care was improved by use of the closed-loop system, because the physician was more vigilant and had more time to adjust the fluid volume status during hemorrhagic periods. Further studies are needed to confirm the hypothesis that the closed-loop system can improve patient care by freeing the physician.

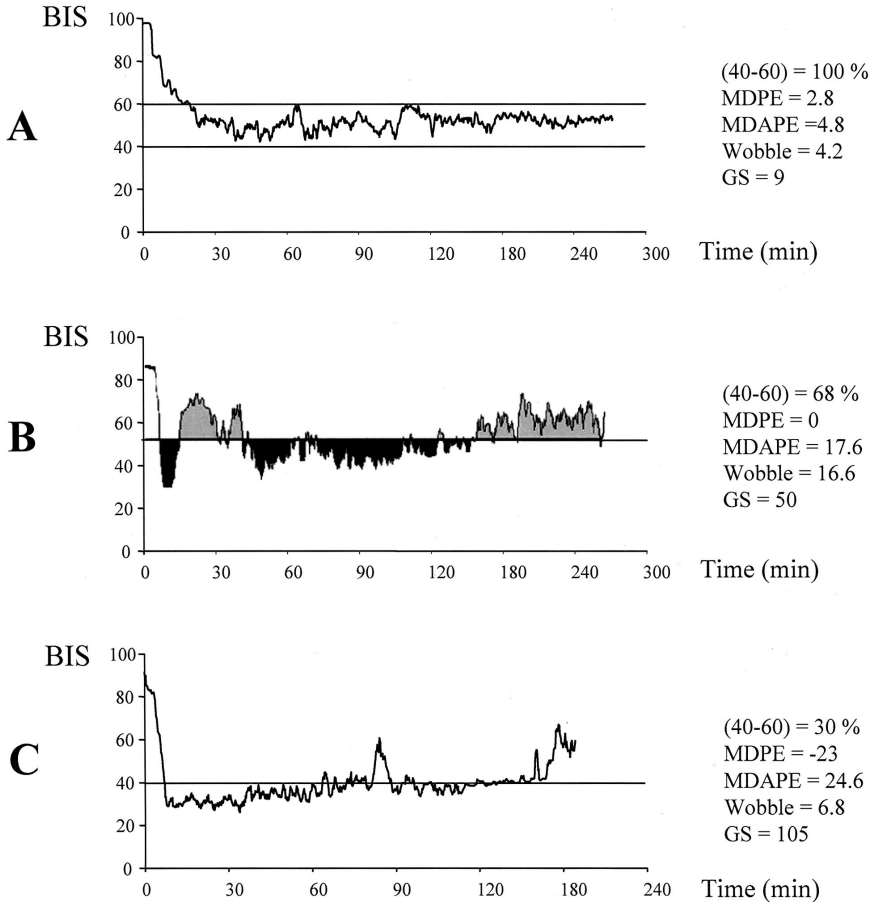

Fig. 7. Clinical examples for the performance interpretation. (*A*) Example of a closed-loop patient. The Bispectral Index (BIS) value was included during 100% of the maintenance phase in the range of 40–60. Median performance error (MDPE), median absolute performance error (MDAPE), and wobble were low. The global score (GS) of 9 was low, and we can conclude that the performance was excellent in this case. (*B*) Example of a manual target-controlled infusion patient. The BIS value had a large oscillation with the value variation above and below 50. The bias or MDPE was excellent and equal to zero because the positive (*gray area*) and negative (*black area*) errors cancelled each other out, but the inaccuracy or MDAPE and the wobble were high. Finally, the calculated GS was poor. (*C*) Example of a manual target-controlled infusion patient. The intraindividual variability or wobble was low or excellent, but the BIS value was below 40 during 70% of the maintenance phase, and the GS was consequently poor. 40 < BS < 60 = percentage of time when the BIS value was between 40 and 60 during maintenance.

The incidence of somatic events was no different between the two groups (14 and 13%, manual TCI and closed-loop groups, respectively). The closed-loop incidence was lower than in the study by Gan *et al.*[2] (39%) and similar to the study of Drover *et al.*[31] (14%), which both used the Patient State Index monitor. In standard clinical practice, the incidence of somatic events varied from 23%[31] to 31%[2] in these studies.

Patients in the closed-loop group emerged faster from anesthesia than those in the manual group (fig. 6). The speed of extubation in the closed-loop group (7 ± 4 min) was similar to that found by Struys *et al.*[11] (6.9 min). The closed-loop presented greater predictability, which allowed for better planning of the recovery phase. Only 14% of all patients in the closed-loop group required a long time (> 10 min) to extubation, compared with 33% in the manual group (table 3). This result was obtained without a specific emergence phase to facilitate rapid recovery (*i.e.*, adjusting propofol infusion to achieve BIS value in the range of 60–75 during skin closure) for both groups. By using a specific emergence phase, the time from stopping propofol infusion until tracheal extubation varies from 4.1 ± 2.8 min[7] to 7.3 min.[2] We plan to implement a specific emergence phase in our closed-loop system to allow extubation for all patients in less than 10 min.

The significant number of investigators, whether anesthesiologist or nurse anesthetist, having used the closed-loop control demonstrated the ease of use of the system. Although our system was only a prototype, it demonstrated that the closed-loop anesthesia device is not only a research tool but also a clinical tool.

In conclusion, we have demonstrated in a large population of patients that our closed-loop system seems to be clinically feasible, reliable, and safe throughout anesthesia, when compared with a manual titration of propofol TCI guided by the BIS. The behavior of the controller was observed in various clinical situations with different users. Total control of consciousness by a computer, using short-acting drugs, a BIS® monitor, and an original closed-loop algorithm provides a future orientation of anesthesia resembling the autopilot in the aircraft industry. In continuing this parallel, the use of closed-loop systems in anesthesia may be safer for patients, just as hull loss rates are lower for advanced-technology aircraft.[32]

Appendix

To determine the controller performance, the parameters proposed by Varvel *et al.*[20] were calculated according to following equations:

- The performance error (PE), calculated as the difference between actual and desired values (set point):

$$PE_{ij} = ((BIS_{measuredij} - BIS_{set\ point})/BIS_{set\ point}) \times 100;$$

- the bias or median performance error (MDPE):

$$MDPE_i = \text{median } [PE_{ij}, j = 1, \ldots, N_i];$$

- the inaccuracy or median absolute performance error (MDAPE):

$$MDAPE_i = \text{median } [|PE_{ij}|, j = 1, \ldots, N_i];$$

- the wobble, which measures the intraindividual variability in performance error:

$$Wobble_i = [|PE_{ij} - MDPE_i|, j = 1, \ldots, N_i];$$

where i = subject number, j = jth (one) measurement of observation period, and N = total number of measurements during the observation period. The global score (GS) was calculated according to following equation:

GS = (MDAPE + Wobble)/% of time BIS value between 40 and 60.

Three clinical examples are given to explain how to interpret these performance parameters and to avoid misinterpretation (fig. 7). These cases illustrate that MDPE, MDAPE, or wobble cannot assess the manual or closed-loop system's performance alone— hence the need for an overall performance score, namely the GS.

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