Anesthesiology 2001; 95:6–17

Comparison of Closed-loop Controlled Administration of Propofol Using Bispectral Index as the Controlled Variable versus *"Standard Practice" Controlled Administration*

Michel M. R. F. Struys, M.D., Ph.D., Tom De Smet, M.Sc.,† Linda F. M. Versichelen, M.D.,‡ Stijn Van de Velde, M.B.,§ Rudy Van den Broecke, M.D.,‖ Eric P. Mortier, M.D., D.Sc.#*

Background: **This report describes a new closed-loop control system for propofol that uses the Bispectral Index (BIS) as the controlled variable in a patient-individualized, adaptive, model-based control system, and compares this system with manually controlled administration of propofol using hemodynamic and somatic changes to guide anesthesia.**

Methods: **Twenty female patients, American Society of Anesthesiologists physical status I or II, who were scheduled for gynecologic laparotomy were included to receive propofol–remifentanil anesthesia. In group I, propofol was titrated using a BIS-guided, model-based, closed-loop system. The BIS target was set at 50. In group II, propofol was titrated using classical hemodynamic signs of (in)adequate anesthesia. Performance of control during induction and maintenance of anesthesia were compared between both groups using BIS as the controlled variable in group I and the reference variable in group II, and, conversely, the systolic blood pressure as the controlled variable in group II and the reference variable in group I. At the end of anesthesia, recovery profiles between groups were compared.**

Results: **Although patients undergoing manual induction of anesthesia in group II at 300 ml/h reached a BIS level of 50 faster than patients undergoing open-loop, computer-controlled induction in group I, manual induction caused a more pronounced initial overshoot of the BIS target. This resulted in a more pronounced decrease in blood pressure in group II. During the maintenance phase, better control of BIS and systolic blood pressure was found in group I compared with group II. Recovery was faster in group I.**

Conclusion: **A closed-loop system for propofol administration using the BIS as a controlled variable together with a model-based controller is clinically acceptable during general anesthesia.**

This article is accompanied by an Editorial View. Please see: Glass PSA, Rampil IJ: Automated anesthesia: Fact or fantasy? ANESTHESIOLOGY 2001; 95:1–2.

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THE use of closed-loop systems might improve the quality of drug administration.[1] A number of basic components are required to develop a satisfactory closed-loop drug delivery system: (1) a system under control, which is the patient; (2) a controlled variable that measures the relevant drug effect; (3) a set point for this variable, which is the chosen target value specified by the user; (4) an actuator, which is, in this case, the infusion pump driving the administration of drug; and (5) a controller to control the actuator, which comprises an algorithm to translate a measured value of the controlled variable to a particular action for the actuator to steer the controlled variable closer to the target value.[2]

Since the pioneering work of Bickford,[3] various parameters, such as the median frequency of the electroencephalogram[4] or auditory evoked potentials,[5] have been applied as controlled variables for closed-loop control of intravenous hypnotic anesthetic drugs. More recently, the Bispectral Index (BIS; Aspect Medical Systems, Inc., Newton, MA), a single composite electroencephalogram measure, has been designed to track electroencephalographic changes associated with different anesthetic states.[6,7]

A satisfactory controller is needed during closed-loop control.[2] In closed-loop control, the input (*i.e.*, propofol infusion) at any particular time depends on the previous system output (*i.e.*, BIS). When the input to the system is controlled using a behavioral model of a reference system, then the controller is said use model-based control. For hypnotics, combined pharmacokinetic–pharmacodynamic models have been described[8] and tested.[9–12] When the model-based control system uses the measured output of the system not only to determine the next input, but also to update the model describing the systems' input–output relation, then the system is defined as model-based and adaptive.[13] Adaptive, model-based control has been demonstrated by Schwilden *et al.*[4] as an effective method to manage the dose–response (*i.e.*, input–output) relation of propofol.

* Staff Anesthesiologist, † Consulting Engineer, ‡ Staff Anesthesiologist and Associate Professor, § Medical Student, # Staff Anesthesiologist and Professor and Chairman, Department of Anesthesia, ‖ Staff Gynecologist, Department of Gynecology, Ghent University Hospital.

Received from the Department of Anesthesia, Ghent University Hospital, Gent, Belgium. Submitted for publication August 2, 2000. Accepted for publication March 2, 2001. Support was provided solely from institutional and/or departmental sources. Presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 14–18, 2000. Dr. Struys, Dr. De Smet, and Dr. Versichelen own propriety rights on the closed-loop algorithms. Tom De Smet is a consultant for Aspect Medical Systems, Newton, Massachusetts.

Address correspondence to Dr. Struys: Department of Anesthesia, Ghent University Hospital, De Pintelaan 185, B-9000, Gent, Belgium. Address electronic mail to: Michel.Struys@rug.ac.be. Reprints will not be available from the authors. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

Previously described closed-loop systems for the administration of hypnotic drugs were never compared with manually controlled anesthesia (*i.e.*, "standard practice"). Therefore, the purpose of this study was to describe a new closed-loop control system for propofol that uses BIS as the controlled variable in a patient-individualized, adaptive, model-based control system, and to compare its performance with manually controlled administration of propofol using hemodynamic and somatic changes to guide anesthesia. This study complies with the recently proposed performance specifications for feedback control systems in anesthesia.[14]

Methods and Material

System Specifications

Data Management, Monitored Variables, and Actuator Control. In all patients, our setup used RUGLOOP (Ghent University, Gent, Belgium) running on a Pentium II–based computer system to steer the infusion pump and to record the BIS signal, blood pressure, and all other relevant physiologic data. All data were stored on hard disk. BIS (version 3.4) was derived from the frontal electroencephalogram (At-Fpzt) as calculated by the A-2000 BIS Monitor (Aspect Medical Systems, Inc.). Blood pressure, heart rate, end tidal carbon dioxide, and oxygen saturation were acquired using the Datex AS3 monitor (Datex, Helsinki, Finland).

RUGLOOP is a general infusion pump control and data management system, written by two of the authors (T.D.S. and M.S.). It is written in Visual C++ (Microsoft, Redmond, WA) for the Windows 95/NT operating system and is freely available on the internet.** It is able to deliver a computer-controlled infusion, targeting either the plasma or effect-site concentrations using a combination of compartmental pharmacokinetic and effect-site models.[12] The algorithms to target the plasma[15] and the site of drug effect[16] in RUGLOOP are adapted from STANPUMP, written by Dr. S. L. Shafer and available on the internet.††

The Controlled Variable. In the closed-loop group, BIS was used as the controlled variable. The A-2000 BIS Monitor also calculates a Signal Quality Index (0–100). The suppression ratio is the percentage of isoelectric electroencephalogram within the previous minute. When detected artifacts within the electroencephalogram caused the Signal Quality Index to decrease below 15%, then the system stopped adjusting and maintained the current concentration, as further described below.

In the standard-practice group, anesthesia was conducted using several criteria for inadequate anesthesia, as described below. The systolic blood pressure (SYS) was considered the main controlled variable.

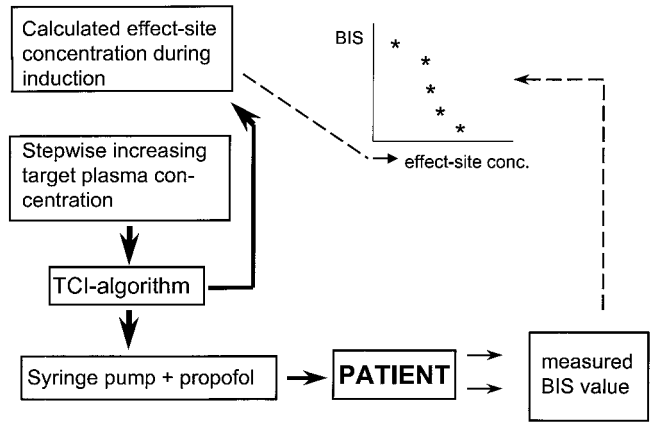

Fig. 1. Flow chart of the steering method during induction. During induction, an automatically stepwise increasing plasma concentration is administered using a target-controlled infusion (TCI) system (RUGLOOP) for propofol (straight line). The corresponding effect-site concentration is calculated and plotted *versus* the effect. The effect of this effect-site concentration on the Bispectral Index (BIS) is measured and sent to the computer (dotted line). After loss of consciousness, the increase in effect-site concentration is stopped by the anesthetist, and the computer estimates the pharmacodynamic curve (effect *vs.* effect-site concentration). Thereafter, the loop is closed and the target set point is entered in the controller.

The Closed-loop Controller. In the closed-loop group, RUGLOOP was used to manage the control algorithms as well. The measured BIS was transferred to the control algorithm that attempts to minimize the error between the measured BIS value and the target BIS value selected by the anesthesiologist. The algorithm calculated an adequate propofol effect-site concentration from the measured BIS using a specific patient-individualized, model-based, adaptive control method. This effect-site concentration was used as input to the RUGLOOP internal computer-controlled infusion system. The effect-site concentration was computed to yield a time to peak effect of 1.6 min after bolus injection, as published by Schnider *et al.*[10]

The controller was based on a pharmacodynamic model represented by a sigmoidal E_{max} model called the Hill curve.[17]

The initial patient-specific pharmacodynamic profile was calculated automatically during induction by correlating all predicted propofol effect-site concentrations with the corresponding BIS values. To obtain this information, the patient received a propofol infusion using open-loop, plasma target controlled infusion. RUGLOOP calculated the corresponding effect-site concentration concurrently. Every 50 s, the target concentration was increased automatically by 0.5 μg/ml. Once the target BIS level was achieved, the induction sequence was terminated, the pharmacodynamic model was calculated from paired assessments of BIS and predicted effect-site concentrations, and the feedback loop was closed. During maintenance, RUGLOOP switched the target-controlled infusion from targeting the plasma compartment

** RUGLOOP is available from the authors at http://allserv.rug.ac.be/~mstruys.
†† STANPUMP is available from the authors at http://pkpd.icon.palo-alto.med.va.gov.

to the effect compartment. The methods are plotted in figure 1 and described in Appendix A, which is available on the ANESTHESIOLOGY Web site.

The closed-loop controller used this patient-individualized pharmacodynamic relation calculated during induction to manage the control action and to generate the target value for the internal computer-controlled infusion system.

During closed-loop control, the controller minimized the difference between measured and desired effect. Small adjustments in the infusion rate occur while the patient state remains near the set point. Larger changes in patient state (*e.g.*, acute drug tolerance or arousal caused by perceived stimulation) are modeled by the controller as changes in the patient's dose–effect characteristics. As a remedy, Hill curve calculated during induction is adjusted to reflect the change in patient dynamics. The approach taken here is to shift the induction Hill curve[17]; figure 2A shows this curve calculated during induction. The specific chosen target BIS value is shown as E_I with the corresponding effect-site concentration, C_1. With small changes in effect-site concentration, corresponding changes in BIS can be noticed, moving along the operating curve in figure 2A. However, if, while operating at C_I (corresponding to the target BIS), a perceived stimulation would elevate BIS to E_S, this results in a mismatch between the current effect-site concentration and the measured effect according to the curve. The mismatch is resolved by sliding the pharmacodynamic relation to the right until the curve aligns with the measured effect, E_S, as shown in figure 2B. The new, increased target effect-site concentration is derived from the translated curve as the concentration corresponding to the target effect, E_I, *i.e.*, the desired effect can be reached by increasing the effect-site concentration by the same value as would be necessary to go from the measured effect to the desired effect during induction

$$\text{Ceffect}_{T1} = \text{Ceffect}_{T0} + H^{-1}\,(\text{Desired effect}) - H^{-1}\,(\text{Measured effect}_{T0}) \quad (1)$$

where H^{-1} stands for the inverse Hill–curve relation. Mathematically, the surgical manipulations are regarded as pushing the induction Hill curve to the right such that the current effect-site concentration equals the one for the measured effect during induction. Figure 3 shows the complete closed-loop feedback controller mechanism during maintenance.

A disadvantage of this approach is that the controller works independently from the increasing or decreasing trend in the controlled variable, as well as independent from the rate of change of the trend. This may produce overshoot in the correction of the effect-site concentration, causing oscillations and instability during anesthesia. These effects were observed using mathematical simulations of the controller.[18]

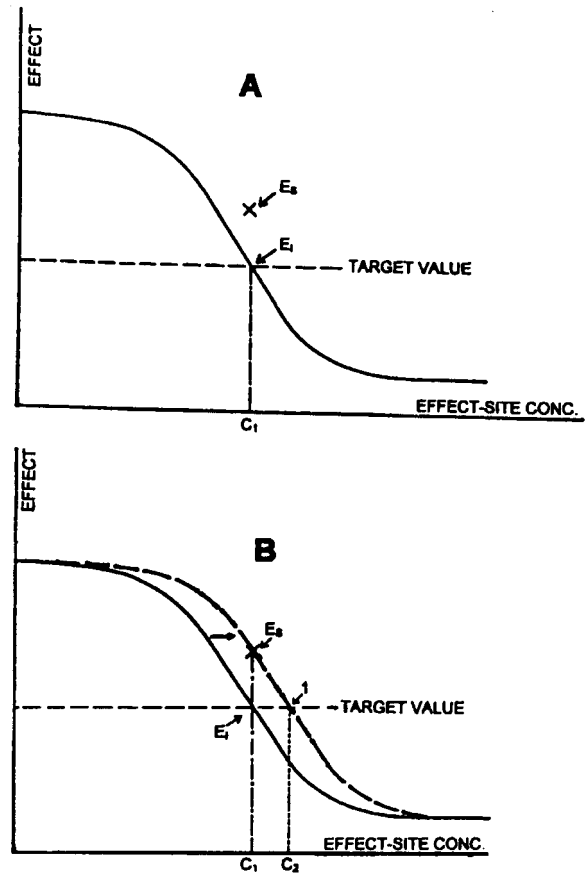

Fig. 2. (*A*) Theoretical example of a pharmacodynamic curve (effect *vs.* effect-site concentration) calculated during induction. A target value for the controlled variable is shown as the desired set point. E_I indicates the crossing point between the original curve and the target at a specific time. C_1 is the effect-site concentration actually required to equal the effect and the target value without stimulus. If, because of surgical stimulus, the measured effect increases (*i.e.*, E_S), there will be a mismatch between the measured effect and the target effect value. (*B*) The original curve (straight line) is moved horizontally to cross the newly measured effect E_S. The projection of the crossing point (1) of the new curve (dotted line) and the target value onto the x-axis gives the new desired effect-site concentration (C_2) to theoretically reach again the target value.

Therefore, an extra control action is implemented, using the difference between two consecutive measured BIS values multiplied by a differential factor

$$(\text{BIS}_{T1} - \text{BIS}_{T0}) \times \text{differential factor} \quad (2)$$

A differential factor of 0.05 was applied based on the results of our simulations.[18]

The Control of the Standard Practice Group. In the standard practice group, propofol was titrated using standard practice guidelines, as described below. The criteria for inadequate anesthesia described by Ausems *et al.*[19] were used: (1) increase in SYS to more than 15 mmHg above the baseline for that patient (measured the evening before surgery); (2) tachycardia higher than 90 beats/min in the absence of hypovolemia; (3) other autonomic signs such as sweating or flushing; and (4)

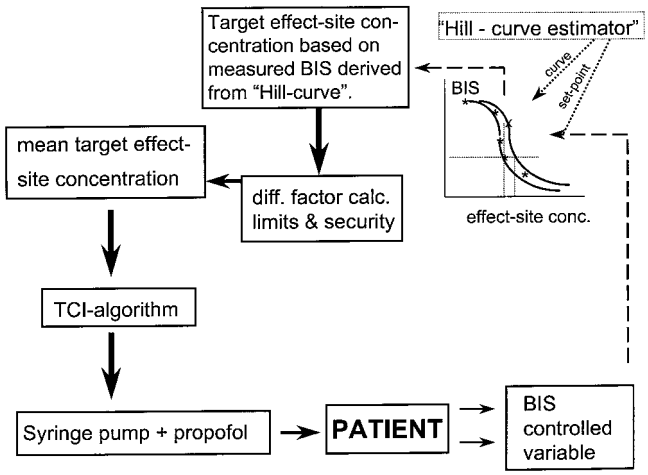

Fig. 3. Flow chart of the controller during maintenance. At each time the required effect-site concentration is calculated by the controller. This value is sent to an additional algorithm taking the differential factor and the safety limits into account. The result of these calculations is the required effect-site concentration sent to the RUGLOOP target-controlled infusion (TCI) algorithm.

somatic responses such as movement or swallowing. Signs of an excessive level of anesthesia were defined as: (1) a decrease in SYS to more than 15 mmHg below the baseline for that patient (measured the evening before surgery); and (2) bradycardia lower than 40 beats/min.

The Actuator. The actuator in a closed-loop system for the administration of intravenous drugs is a syringe pump. The Fresenius Modular DPS Infusion Pump connected to a Fresenius Base A (Fresenius Vial Infusion Systems, Brézins, France) was selected because of its high accuracy in both infused volume and infusion rate. A computer can monitor and drive the pump at infusion rates between 0 and 1,200 ml/h *via* an RS-232 interface.

Clinical Study

After obtaining approval from the Institutional Ethics Committee of Ghent University Hospital (Gent, Belgium), informed consent was obtained from 20 female patients, American Society of Anesthesiologists physical status I and II, aged 18–60 yr, who were scheduled for gynecologic laparotomy. Exclusion criteria included weight less than 70% or more than 130% of ideal body weight, neurologic disorder, and use of psychoactive medication, including alcohol. Patients were randomly allocated to one of the two groups. All patients received diazepam 10 mg orally 1 h before surgery as premedication. Two minutes before induction, a continuous infusion of remifentanil (0.50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ before intubation, 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ thereafter) was started in all patients. In the closed-loop controlled group (group I), propofol was administered using the previously described closed-loop system. Initial target concentration of propofol was set to a plasma concentration of 3 μg/ml. This target was automatically increased in a stepwise manner by 0.5-μg/ml increment concentration, every 50 s until a target BIS was reached. Thereafter, the loop was closed automatically, and the target-controlled infusion system reverted to delivering to a target effect-site concentration as dedicated by the targeted effect (BIS) value. The target BIS was fixed at 50. In the standard-practice group (group II), manually controlled administration of propofol was used. Propofol was administered at 300 ml/h[20] until loss of consciousness, defined as failure to respond to verbal command, and was evaluated every 5 s. Thereafter, a continuous infusion of propofol was started at an initial rate of 10 $mg \cdot kg^{-1} \cdot h^{-1}$. Propofol administration was increased or decreased by 2 $mg \cdot kg^{-1} \cdot h^{-1}$ after one of the signs of inadequate anesthetic depth, as previously described. After loss of consciousness, all patients received a bolus dose of rocuronium (0.5 mg/kg) to facilitate intubation.

The time and BIS were recorded at the moment of loss of consciousness. We also calculated the propofol induction dose as the amount of propofol delivered to the patients up to the time of loss of consciousness and the total dose used for the entire procedure.

Heart rate, end tidal carbon dioxide, oxygen saturation, and BIS were acquired every 10 s. Artifacts in the BIS caused by poor signal quality were automatically detected and excluded from further analysis. Blood pressure was acquired every 1 min.

At the end of surgery (*i.e.*, end of skin closure), all infusions were stopped, and recovery parameters (time until spontaneous respiration, opening eyes, extubation, and saying name and date of birth) were recorded.

Evaluation of the Controller Performance

Controller performance metrics are usually calculated on the measured values of the controlled variable *versus* its target value and compared with control performance data in a reference group. Because the controlled variable was different between groups, we decided to use the controlled variable of each group as a reference variable for the other group. BIS was defined as the controlled variable in group I and as a reference variable in group II, using 50 as the target value in both groups. SYS was considered as the main controlled variable in group II and as a reference variable in group I, using the baseline pressure as the target value in both groups.

The performance of the controllers was evaluated during three periods: induction, the period surrounding initial skin incision, and during recovery. The initial performance for BIS at induction was studied by using the following parameters: (1) BIS_{LOC} = BIS at the moment of loss of consciousness; (2) $T_{BIS\ TARGET}$ = observed time required for reaching the target BIS value; (3) $t_{PEAK,BIS}$ = observed time required for reaching maximal drug effect (lowest BIS value); (4) BIS_{PEAK} = observed BIS value at $t_{PEAK,\ BIS}$; and (5) t_{EQ} = observed time

required for reaching the target value after the initial overshoot, also called time to steady state.

For SYS, three initial performance parameters were calculated, taken within the first 10 min of the anesthesia: (1) SYS_{LOC} = SYS at the moment of loss of consciousness; (2) $t_{PEAK,\ SYS}$ = observed time required for reaching maximal drug effect (lowest SYS value); and (3) SYS_{PEAK} = observed SYS value at $t_{PEAK,\ SYS}$.

The ability of the controllers to react to a perturbation after achieving the target level was evaluated using the period surrounding skin incision. The average BIS and SYS over the minute preceding incision was defined as the baseline values. The maximum and minimum BIS and SYS values measured until 5 min after skin incision were considered to be the extreme responses to this noxious stimulus.

Acceptable control of BIS was defined as maintaining BIS between 40 and 60. Acceptable control of SYS was defined as maintaining SYS within15 mmHg of baseline. The percent of time of acceptable BIS control and acceptable SYS control was calculated for each patient. Based on the method of Varvel *et al.*[21], previously applied by Kansanaho *et al.*[22] for the performance of a closed-loop system for muscles relaxants, the overall performance of both control and reference variables was characterized on the basis of following parameters for the period when the variable was being controlled (*i.e.*, after BIS reached 50 in group 1 [or after the patient lost consciousness in group II] until drug administration was stopped).

First, using all observations within the period, the performance error (PE) was calculated according to the following formula

$$PE = \frac{(\text{measured value} - \text{t arg etvalue})}{\text{t arg etvalue}} \times 100 \quad (3)$$

Subsequently, bias (median performance error [MDPE]), inaccuracy (median absolute PE [MDAPE]), divergence, and wobble were calculated.[22] MDPE is a measure of bias and describes whether the measured values are systematically either above or below the target value. MDPE was calculated from the following equation:

$$MDPE_i = \text{median}\{PE_{ij},\ j - 1, \ldots, N_i\} \quad (4)$$

where N_i is the number of values PE obtained for the i^{th} subject.

Median absolute PE reflects the inaccuracy of the control method in the i^{th} subject

$$MDAPE_i = \text{median}\{|PE|_{ij},\ j - 1, \ldots, N_i\} \quad (5)$$

where N_i is the number of values $|PE|$ obtained for the i^{th} subject.

Divergence describes the possible time-related trend of the measured effects in relation to the targeted values. It is defined as the slope of the linear regression equation of $|PE|$ against time and is expressed in units of percentage divergence per minute. A positive value indicates progressive widening of the gap between targeted and measured values, whereas a negative value reveals that the measured values converge on the predicted values.

Wobble is another index of the time-related changes in performance and measures the intrasubject variability in PEs. In the i^{th} subject, the percentage of wobble is calculated as follows

$$wobble_i = \text{median}\{|PE_{ij} - MDPE_i|,\ j = 1, \ldots, N_i\} \quad (6)$$

Table 1. Demographic Data

	Group I (n = 10)	Group II (n = 10)
Age (yr)	42 ± 8	46 ± 4
Weight (kg)	67 ± 10	59 ± 9
Height (cm)	166 ± 6	163 ± 5

Data are shown as mean ± SD.

Statistical Analysis

Data are presented as mean ± SD or as median (range). Differences between the groups were determined using a Mann–Whitney U test. Continuous data were analyzed using analyses of variance for repeated measures. If significant, a *post hoc* test (Tukey) was applied for paired data. Kaplan-Meier survival analysis was applied to compare recovery parameters (time until spontaneous breathing, time until opening eyes, time until extubation, and time until orientation) between groups. Significance level was set at 5%.

Results

Population demographics for both groups are shown in table 1. There were no significant differences between both groups. No patients were excluded from the anal-

Table 2. Clinical Data

	Group I (n = 10)	Group II (n = 10)
Induction time (s)	120 ± 55	128 ± 44
Propofol induction dose (mg)	87 ± 16	79 ± 18
BIS at LOC	81 ± 8	82 ± 8
Intubation time (s)	285 ± 84	297 ± 77
Incision time (s)	1,497 ± 315	1,232 ± 293
Duration of anesthesia (s)	6,798 ± 2,085	6,896 ± 2,018
Recovery time until spontaneous respiration (s)	281 (257)	547 (2,285)
Recovery time until opening of the eyes (s)	336 (250)*	567 (2,285)*
Recovery time until extubation (s)	415 (240)*	580 (2,296)*
Recovery time until orientation (s)	461 (372)	592 (2,291)

* $P < 0.05$ between groups.

BIS = Bispectral Index; LOC = loss of consciousness.

Table 3. Control Quality during Induction

	Group I (n = 10)	Group II (n = 10)
$T_{BIS\ TARGET}$ (s)	241 ± 94*	176 ± 36*
BIS_{PEAK}	42 ± 4*	36 ± 4*
$T_{PEAK,\ BIS}$ (s)	290 ± 96*	516 ± 271*
T_{EQ}	336 ± 114*	1,410 ± 1,050*
SYS_{LOC} (mmHg)	122 ± 17	115 ± 26
SYS_{PEAK} (mmHg)	93 ± 8*	81 ± 8*
$T_{PEAK,\ SYS}$ (s)	402 ± 69*	672 ± 260*

* $P < 0.05$ between groups.

$T_{BIS\ TARGET}$ = observed time required for reaching the target Bispectral Index (BIS) value; BIS_{PEAK} = observed BIS value at $T_{PEAK,\ BIS}$; $T_{PEAK,\ BIS}$ = observed time required for reaching maximal drug effect (lowest BIS value); T_{EQ} = observed time required for reaching the target value after the initial overshoot; SYS_{LOC} = systolic blood pressure (SYS) at the moment of loss of consciousness; SYS_{PEAK} = observed SYS value at $T_{PEAK,\ SYS}$; $T_{PEAK,\ SYS}$ = observed time required for reaching maximal drug effect (lowest SYS value).

ysis. All data captured by the recording system were included in the analysis. The observations made at the time of loss of consciousness are shown in table 2. Induction times, BIS values at loss of consciousness, and induction doses of propofol were similar in both groups. Other clinical parameters during the maintenance of anesthesia, such as time to intubation and incision, were not significantly different in both groups. In addition, the duration of anesthesia did not differ statistically between groups. The performance during the induction phase is shown in table 3. Manually controlled induction in group II reached the target level of BIS (50) faster than open-loop computer-controlled induction in group I. However, the duration and magnitude of the initial overshoot in BIS was more pronounced in the standard practice than in the closed-loop group. For SYS, the baseline values were 122 ± 15 mmHg in group I *versus* 121 ± 14 mmHg in group II. A more pronounced decrease in blood pressure was observed in group II (table 3).

The relative behavior of the controlled variables at incision, BIS in group I and SYS in group II, in relation to their target value are shown in figures 4A and 4B, respectively. In group I, a significant initial increase in BIS is observed after incision, followed by a significant decrease in BIS values. In group II, only a significant increase after incision was observed, however, with a large variability in results.

The trends of BIS, BIS error, SYS, and SYS error are shown in figures 5 and 6 for groups I and II, respectively. Individual BIS data during induction, maintenance, and recovery are shown in figures 5A and 6A for all patients from groups I and II, respectively. For group I, the individual errors between target and measured BIS during the period of control are plotted in figure 5B. For group II, the individual errors between the reference BIS of 50 and the measured BIS are plotted in figure 5B. When defining an adequate level of anesthesia as having

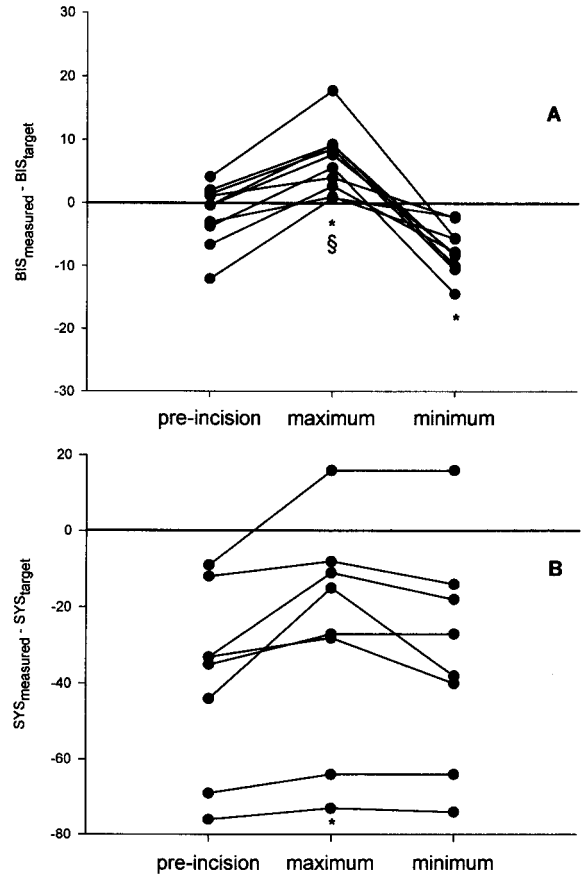

Fig. 4. Individual behavior of the controlled variable for each patient ((*A*) Bispectral Index [BIS] in group I and (*B*) systolic blood pressure [SYS] in group II) in relation to their target value. **P* < 0.05 compared with preincision baseline; §*P* < 0.05 between maximum and minimum postincision values.

a BIS between 40 and 60,[23], the incidence of accurate BIS level was significantly higher when BIS was used as controlled variable in group I (89 ± 10%) compared with the reference BIS levels in group II (49 ± 29%). Significantly higher incidences of too low BIS levels (BIS < 40) were recorded in group II (44 ± 31%) than in group I (9 ± 10%). BIS levels higher than 60 were less frequent in group I (2 ± 2%) than in group II (7 ± 16%).

Trends of SYS during induction, maintenance, and recovery are shown in figures 5C and 6C for groups I and II, respectively. Likewise, errors between measured and target SYS during the period of control are plotted in figures 5D and 6D for groups I and II, respectively. Although SYS was the controlled variable in group II, adequate hemodynamic stability (within the 15-mmHg range around baseline) occurred more frequently in group I (51 ± 27%) compared with group II (34 ± 31%; $P < 0.05$). The incidence of too low SYS (group I: 41 ± 33%; group II: 64 ± 31%) and the incidence of too high SYS (group I: 7 ± 11%; group II: 1 ± 2%) were both significantly different between groups ($P < 0.05$).

Individual patient trends of propofol effect-site concentrations are shown in figures 7A and 7B for groups I

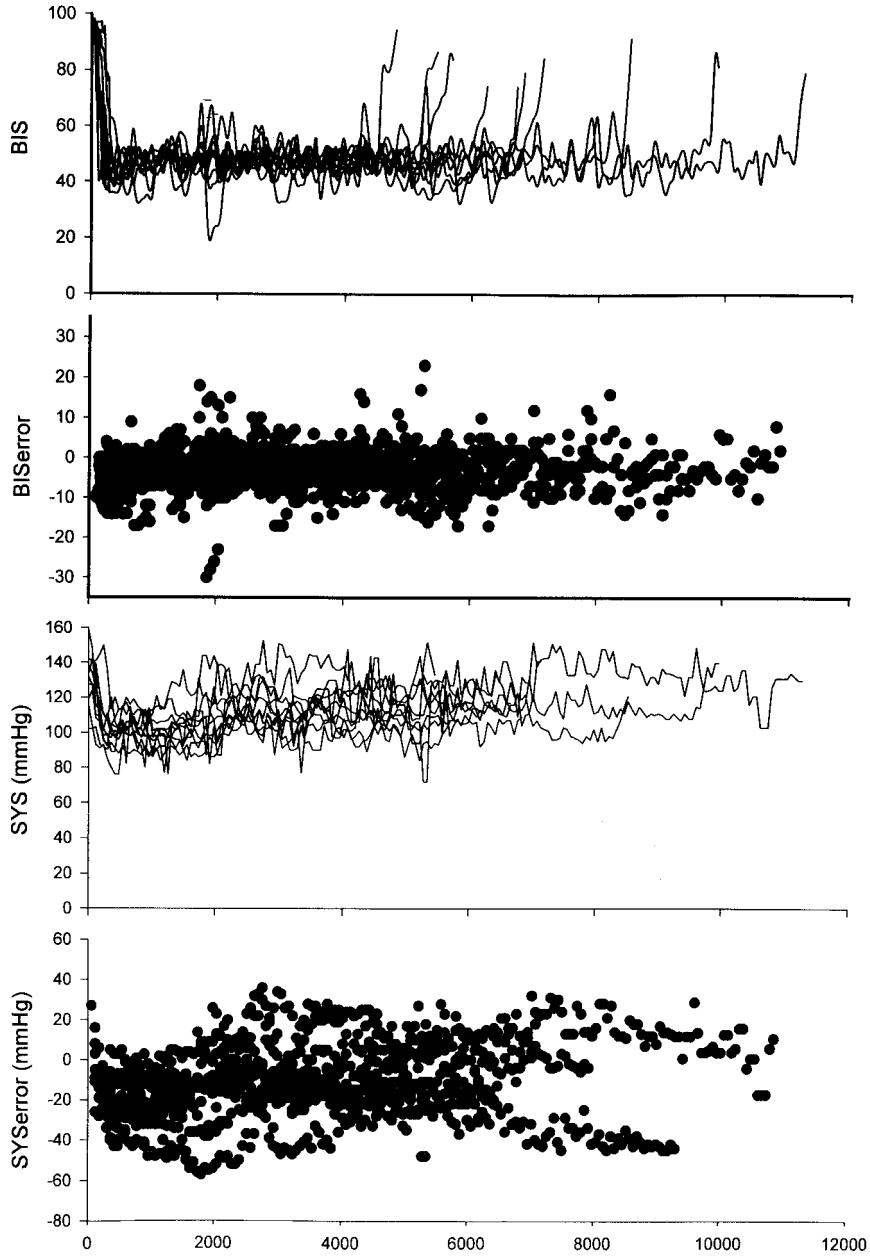

Fig. 5. Individual data from the closed-loop controlled group (group I) during anesthesia. (*A*) Individual Bispectral Index (BIS) data; (*B*) individual BIS error calculated as the difference between BIS targeted and BIS measured (averaged every minute for the figure); (*C*) Individual systolic blood pressure (SYS; acquired every minute); (*D*) individual SYS error calculated as the difference between SYS baseline and SYS measured (averaged every minute for the figure).

and II, respectively. The total amount of propofol used in both groups was 6.39 ± 1.13 mg · kg^{-1} · h^{-1} for group I and 6.48 ± 1.59 mg · kg^{-1} · h^{-1} for group II, without statistical difference between groups.

At the end of surgery, all infusions were stopped, and recovery parameters were recorded. As shown in table 2, significantly faster median recovery times were observed for time until opening of the eyes and extubation in the closed-loop group I than in the standard-practice group II. In addition, the variability (range) for all recovery parameters in group II was much higher than in group I. Figures 8A–D show the percent of subjects within a group that had not yet met the end point at a certain time point for the four end points of recovery: return of spontaneous respiration, opening eyes, extubation, and recovery, respectively. The data show that, with the exception of one fast responder in group II, subjects in the standard-practice group (group II) take longer to respond than the subjects in the closed-loop group (group I).

Discussion

The purpose of the current study was to describe a new closed-loop feedback control system for propofol administration using the BIS as the controlled variable together with a patient-individualized, adaptive, model-based controller, and to compare this closed-loop system with a manually controlled administration of propofol using standard practice guidelines.

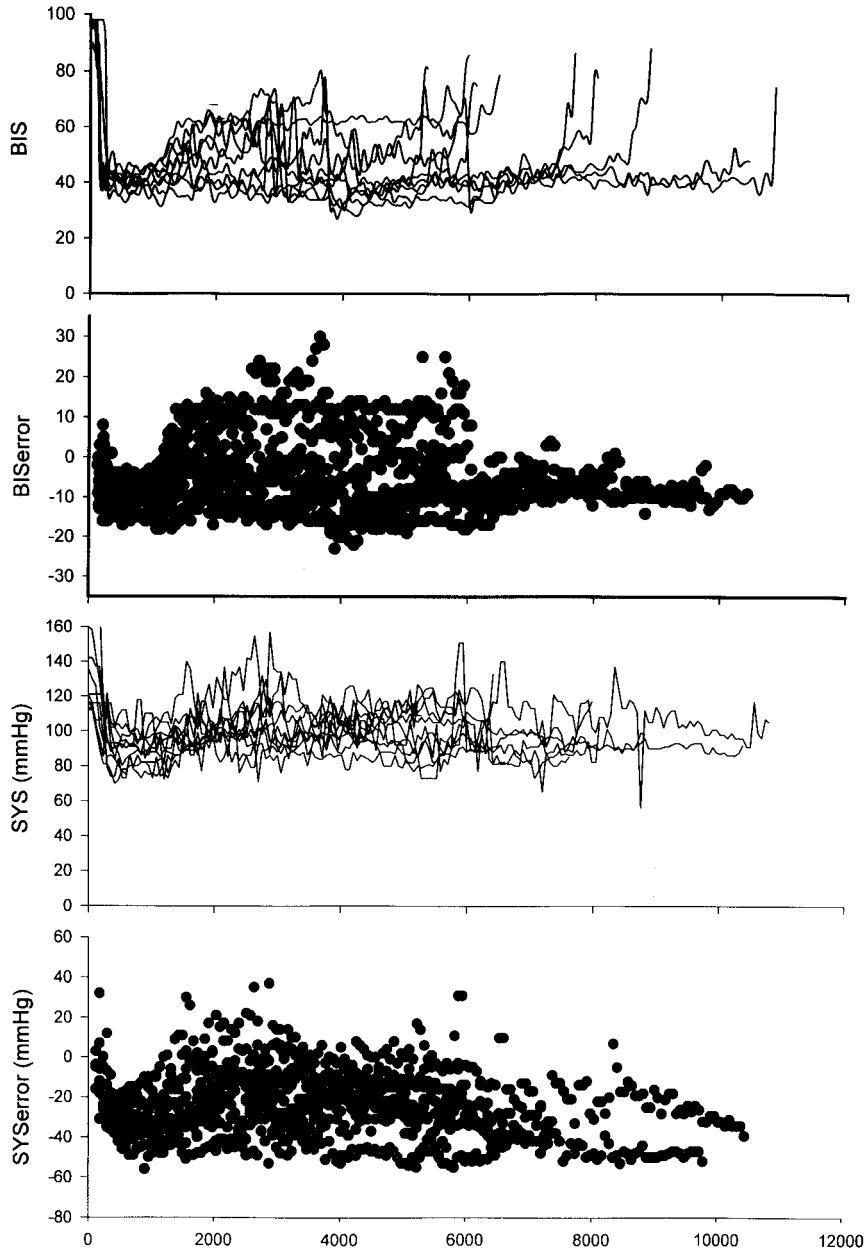

Fig. 6. Individual data from the closed-loop controlled group (group II) during anesthesia. (*A*) Individual Bispectral Index (BIS) data; (*B*) individual BIS error calculated as the difference between BIS targeted and BIS measured (averaged every minute); (*C*) individual systolic blood pressure (SYS; acquired every minute); (*D*) individual SYS error calculated as the difference between SYS baseline and SYS measured (averaged every minute for the figure).

One can argue about the methodology for our standard-practice group. Given the nature of the procedures in the anesthetics, one could probably design a comparison group to show almost anything wanted. When designing an "effect-control" *versus* an "effect-site-control" study, one might choose an effect compartment target controlled *versus* closed-loop controlled infusion study, as this compares the ability of the clinician to titrate to a predicted effect *versus* the best available measured effect. If one desired to see whether the automated system is better than the trained, vigilant human, then it would have been better to allow the standard-practice group to attempt to control the BIS. However, our aim was to compare effect-guided closed-loop control, as a unitary new method for drug administration with present-day practice, and, therefore, propofol administration in the standard-practice group was titrated as previously described.

Closed-loop systems are aimed at reaching and maintaining the desired drug effect. Therefore, the drug effect should be measured adequately. Many different quantitative electroencephalographic measures have been developed to estimate the drug effect of propofol. Billard *et al.*[24] studied the performance of delta power, spectral edge 95%, and BIS (version 1.1) and found a good performance of the BIS in modeling propofol drug effect. More recently, Leslie *et al.*[25] found a good correlation between BIS (version 3.0) and the hypnotic effect of propofol. Other investigators have confirmed these findings.[26–28] Unfortunately, the BIS is calculated using a

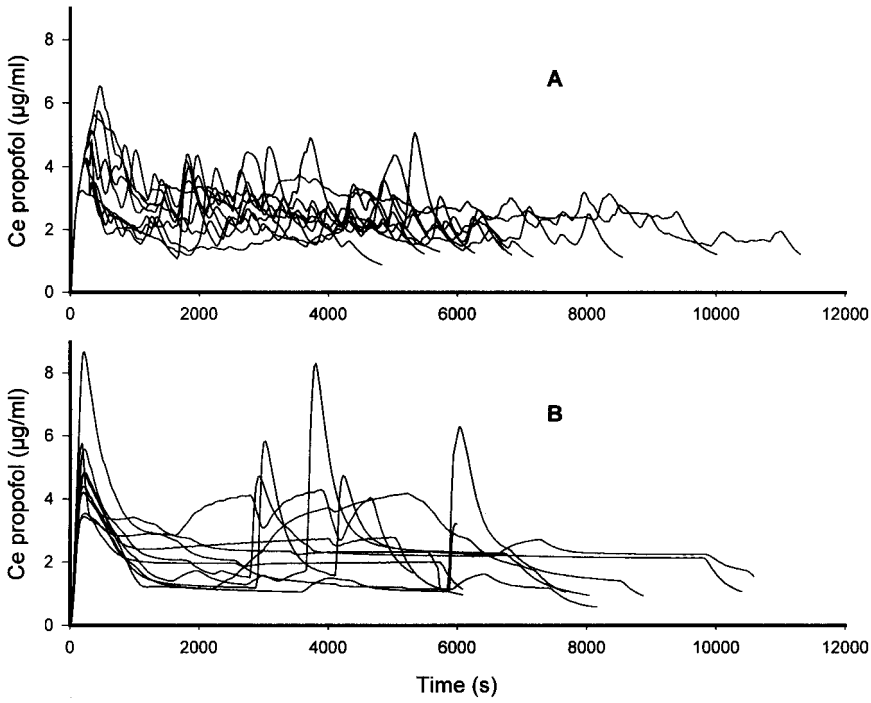

Fig. 7. Individual propofol effect-site concentrations during induction, maintenance, and recovery in group I (*A*) and group II (*B*).

30-s rolling window and thus lags behind the current status of the patient by approximately 15 s. This delay in BIS is one of the elements, among others, that contributes to global controller instability. The additional control algorithm, described in equation 2, was implemented to improve the controller stability.

In our study, a model-based adaptive controller was used. There are many examples of automatically controlled drug administration, based on different levels of control and different control methods.[2] A general PID (*e.g.*, proportional– integral– derivative) controller is sometimes proposed. This control method calculates the infusion rate by a straightforward mathematical formula based on the difference between the measured effect value and the chosen target effect value set by the user. PID controllers are essentially "ignorant" in that they lack knowledge of the complicated drug metabolism and the resulting time course between dosing and effect. In addition, tuning the values for the three terms (P, I and D) when the physiologic response of the subject is unknown, is very difficult.[13] Model-based adaptive control may help to refine the administration of intravenous hypnotics, as proposed by Schwilden *et al.*[4,29] Model-based control of drugs in response to a clinical effect (*i.e.*, surgical manipulations) is based on knowledge of the fate of the drug and its effect in the human body. Because of the large interindividual pharmacologic variability, it is better to have an adaptive controller to adapt the controller toward the individual patient. A model-based, adaptive controller compares the predicted values of the control signal (*e.g.*, BIS) against the actual values of the control signal and modifies the model parameters accordingly.

In the current study, a model-based adaptive control system integrating a previously published method for effect-compartment–controlled target controlled infusion was used to model the pharmacokinetic–pharmacodynamic relation.[12] Effect-compartment modeling is motivated by the observed hysteresis between measured blood drug concentrations and any currently measured index of drug effect. The hysteresis between pharmacokinetics and pharmacodynamics can be quantified by a rate constant, k_{e0}. The time course of drug effect parallels the time course of the effect-site concentration. Therefore, it becomes appealing to be able to quantitatively control the drug concentration in the effect compartment rather than the central compartment.[30,31]

For correlating the effect-site concentration with the clinical effect (BIS), a patient individualized curve was defined during the initial phase. This was also performed to minimize the problem of the large pharmacodynamic variability among patients. This variability might cause a problem when these combined pharmacokinetic–pharmacodynamic models, using mean population pharmacokinetic as well as mean population pharmacodynamic values, are applied for a particular dosage regimen in an individual patient.[32] Few data are found in the literature[33] concerning the use of patient-individualized pharmacodynamics in control strategies, and we therefore proposed a specific control method in this study. Previously, Schwilden *et al.* described a closed-loop feedback control system for methohexital[29] and propofol[4] anesthesia applying an online change in pharmacokinetic parameters. The difference with our controller is that we initially attempt to adapt all pharmacodynamic parameters to our patient. During the case, we shift the phar-

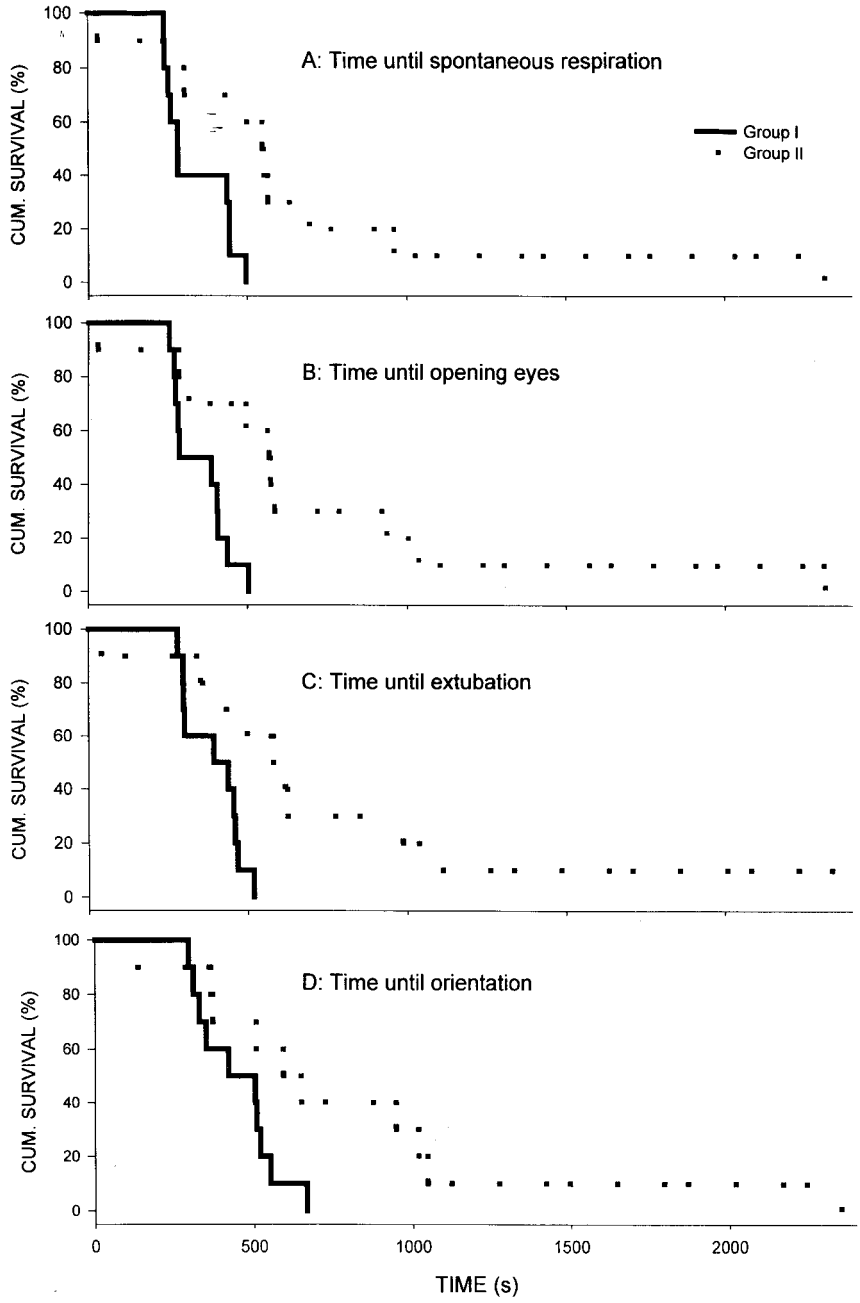

Fig. 8. (*A–D*) The percent of subjects within a group that have not yet met the end point at a certain time point (in seconds) for the four end points of recovery: return of spontaneous respiration, opening eyes, extubation, and recovery, respectively.

macodynamic curve horizontally, which is a different way of calculating the new model parameters compared with the methodology used by Schwilden *et al.*, who tried to fit the current effect on the curve by modifying the pharmacokinetic parameters. Our controller maintains the original pharmacokinetic model of drug but imposes a new target concentration. The difference in the adaptive methods is that, during the absence of variable values because of poor signal quality, we are still using the original pharmacokinetic model, whereas Schwilden *et al.* used a modified model at that time.

Differences in performance of this closed-loop system were found compared with the manually controlled administration. When comparing BIS or SYS as a control variable in one group relative to itself as a reference variable in the other group, more accurate control time was found in the closed-loop group for both variables. When comparing BIS with SYS as a controlled variable, clearly better performance time was found for BIS (figs. 5 and 6). Various reports are found in the literature supporting the concept that hemodynamic parameters are poor measures of anesthetic depth.[34]

The onset of clinical effect as measured by BIS was similar in both groups. Both groups lost consciousness at a similar time and BIS value using similar doses of propofol. However, the initial overshoot (BIS_{PEAK}) and time to steady state (t_{EQ}) were clearly more pronounced in the manually controlled group than in the closed-loop con-

Table 4. Performance of Control

	Performance of BIS		Performance of SYS	
	Used as Controlled Variable	Used as Reference Variable	Used as Reference Variable	Used as Controlled Variable
	Group I (n = 10)	Group II (n = 10)	Group I (n = 10)	Group II (n = 10)
PE (%)	−6.23 ± 10.44*†	−13.49 ± 21.74*	−7.40 ± 14.5*	−18.9 ± 13.06*†
MDPE (%)	−6.6 ± 2.63†	−6.1 ± 17	−7.36 ± 3.28*	−18.93 ± 2.92*†
MDAPE (%)	7.7 ± 2.49*†	18 ± 4.5*	10.49 ± 2.14*	18.93 ± 2.92*†
Divergence (%/min)	0.024 ± 0.029*†	−0.129 ± 0.177*	0.0007 ± 0.0009*	0.00001 ± 0.001*†
Wobble (%)	5.90 ± 2.33†	7.10 ± 5.74	6.51 ± 2.97	5.12 ± 1.38†

* $P < 0.05$ between groups for Bispectral Index (BIS) and for systolic blood pressure (SYS). † $P < 0.05$ between controlled parameters (*i.e.*, BIS in group I *versus* SYS in group II).

PE = prediction error; MDPE = median prediction error; MDAPE = median absolute performance error.

trolled group. During the first 10 min of anesthesia, a more pronounced decrease in blood pressure was observed in group II. One can argue that these differences may not be a result of any issue of control, but rather dictated by the rate of drug administration. However, Kazama *et al.*[35] recently concluded that an infusion rate of less than 80 $mg \cdot kg^{-1} \cdot h^{-1}$ did not reveal significant blood pressure changes during induction. In our study, the selected infusion rate of 300 ml/h in group II, as recently stated by Ludbrook *et al.*[20] to be hemodynamically stable, resulted for all patients in an induction rate of less than 80 $mg \cdot kg^{-1} \cdot h^{-1}$.

As shown in figure 4A, surgical incision caused an initial increase in BIS level in all group I patients slightly above the target BIS. This increase was corrected by the closed-loop controller without a large overshoot. In group II, a large variability in results at incision was observed (figure 4B). The behavior of control in both groups can be illustrated by depicting the time course of propofol effect-site concentration, as plotted in figures 7A and 7B for groups I and II, respectively. In group I, the continuous adaptation of the effect-site concentration reveals that closed-loop controller provided continuous control action. It can be observed in figure 7B that fewer control actions were seen in group II patients. Of course, it must be stated that the control behavior has to be correlated to the clinical setting like the applied remifentanil concentration and the selected targets of the respective control variables. Because this is the first study comparing closed-loop with manual control for hypnotics, it was impossible to solve all issues in a single study. Therefore, the closed-loop controller was always targeted to the same BIS level and no stress tests were performed on the controller to evaluate, for example, changes in the performance of the controller with changes in target BIS level. More research is required to study the behavior of this closed-loop algorithm during "extreme" conditions.

The characteristics of the closed-loop controller were compared with the manual control techniques using the performance parameters proposed by Varvel *et al.*[21] These parameters were originally developed for describing the performance of target controlled infusion systems but were already applied by Kansanaho *et al.*[22] for studying the preformance of a closed-loop system for muscles relaxants. As shown in table 4, the performance error (PE) was calculated for each BIS and SYS measurement. First, both controlled variables (BIS and SYS) were compared with their own reference. For BIS, an overall smaller PE was found during closed-loop control. Subsequently, the values of PE were used for intersubject data analysis. The $MDPE_i$ was similar in both groups; however, the $MDAPE_i$ was clearly larger in the standard practice group (group II). Note that $MDPE_i$ is a signed value and thus represents the direction (overprediction or underprediction) of the PE rather than the size of the errors, which is represented by $MDAPE_i$.[21] Finally, performance characteristics were also described by $divergence_i$ and $wobble_i$. $Divergence_i$ reflects the gradual worsening of performance of control over time. $Wobble_i$ represents the variability of the PE in a specific individual. It should be clear that the definitions of $wobble_i$ and $divergence_i$ overlap somewhat. Some of the variability in PEs measured by $wobble_i$ is caused by time-related trends in those errors, which is measured by $divergence_i$. $Wobble_i$ measures the total intraindividual variability in PEs, which is directly related to the ability to achieve a stable controlled variable value during control, whereas $divergence_i$ measures the expected systematic time-related changes in performance.[21] However, statistical differences were found between groups and between variables (table 4); we believe that the similarities between the two groups in terms of $wobble_i$ and $divergence_i$ are far more interesting than the very small and subtle differences.

A potential advantage of this model-based controller compared with PID controllers is its stability with respect to artifacts. In case of sensor failure, PID or "on–off" controllers cannot predict the future dose requirements. Our model-based controller can, however, open the loop when the input signal is biased and steer on effect compartment controlled infusion until the artifact

is solved. Therefore, no instability was observed in the BIS when long, sustained periods of electrosurgery eliminated the controlled variable.

Significantly better recovery profiles were observed in the closed-loop controlled group for time until opening of the eyes and extubation. In addition, a large variability (range) in recovery times were observed in the standard-practice group. When looking to the survival curves plotted in figure 8, we observed that, with the exception of the fast responder in the control group, subjects in the control group take longer to respond. This is powerful when concerned about quick and predictable operating room scheduling. For example, using the time-until-orientation curve, we see that at 10 min, the 90% of the patients in the closed-loop group are oriented, whereas only 50% are oriented in the standard-practice group.

In conclusion, we have demonstrated that the proposed closed-loop system for propofol administration using the BIS as the controlled variable together with a model-based controller is clinically acceptable during general anesthesia when compared with manually controlled titration of propofol using standard practice guidelines. More research is required to observe the behavior of the controller during various clinical situations.

The authors thank Scott Greenwald, Ph.D. (Aspect Medical Systems, Inc., Newton, MA) for assistance during manuscript preparation.

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