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A New Closed-Loop Control System for Isoflurane Using Bispectral Index Outperforms Manual Control

Stephan Locher, M.D.,* Konrad S. Stadler, M.Sc., Ph.D.,§ Thomas Boehlen, M.D.,* Thomas Bouillon, M.D.,* Daniel Leibundgut, M.Eng.,† Peter M. Schumacher, M.Sc., Ph.D.,† Rolf Wymann, M.D.,* Alex M. Zbinden, M.D., Ph.D.‡

Background: **Automatic control of depth of hypnosis using the Bispectral Index (BIS) can help to reduce phases of inadequate control. Automated BIS control with propofol or isoflurane administration *via* an infusion system has recently been described, a comparable study with isoflurane administration *via* a vaporizer had not been conducted yet. Our hypothesis was that our new model based closed-loop control system can safely be applied clinically and maintains the BIS within a defined target range better than manual control.**

Methods: **Twenty-three patients, American Society of Anesthesiologists risk class I–III, scheduled for decompressive spinal surgery were randomized into groups with either closed-loop or manual control of BIS using isoflurane. An alfentanil target-controlled infusion was adjusted according to standard clinical practice. The BIS target was set to 50 during the operation. The necessity of human intervention in the control system and events of inadequate sedation (BIS <40 or BIS >60) were counted. The number of phases of inadequate control, defined as BIS ≥65 for more than 3 min, were recorded. The performance of the controller was assessed by several indicators (mean absolute deviation and median absolute performance error) and measured during the skin incision phase, the subsequent low flow phase, and the wound closure phase. Recovery profiles of both groups were compared.**

Results: **No human intervention was necessary in the closed-loop control group. The occurrence of inadequate BIS was quantified with the mean and median values of the area under the curve and amounted to 0.360 and 0.088 for the manual control group and 0.049 and 0.017 for the closed-loop control group, respectively. In the manual control group nine phases of inadequate control were recorded, compared with one in the closed-loop control group, 10.3% to 0.5% of all observed anesthesia time. During all phases the averages of the performance parameters (mean absolute deviation and median absolute performance error) were more than 30% smaller in closed-loop control than in manual control ($P < 0.05$ between groups).**

Conclusions: **Closed-loop control with BIS using isoflurane can safely be applied clinically and performs significantly better than manual control, even in phases with abrupt changes of stimulation that cannot be foreseen by the control system.**

THE Bispectral Index (BIS) results from processing the phase and frequency relations of the component frequencies in the electroencephalogram.[1] It correlates better with the hypnotic state of anesthesia than with the analgesic state.[2] Whether it can measure depth of hypnosis independently of the drugs used is under discussion.[3–5] As it is a single composite measure that is available online it has been repeatedly used to automatically control hypnosis by delivering hypnotic agents.[6–9]

Automatic closed-loop control systems act similarly to anesthesiologists. A system processes information coming from the patient and the anesthesia system, compares it to a set point that defines the desired output level, and uses the difference to adjust the output so that the desired set point is reached and maintained.[10] These adjustments can be made more frequently by a computer than by manual control. In closed-loop control an algorithm can integrate pharmacokinetic and pharmacodynamic models of the agents to continuously predict and customize target organ concentrations and expected effects. This should lead to improved stability and predictability of the controlled value and thus eventually to better anesthesia outcome compared with manual control.

Provided that BIS is a reliable indicator of depth of hypnosis, closed-loop control using BIS can help to avoid 1) phases of inadequate control with associated hemodynamic and stress responses and the subsequent risk of recall[11] and 2) phases of excessive hypnosis associated with hypotension and delayed emergence. Thus, closed-loop control systems have a potential to improve quality of anesthesia, freeing the physician for more demanding human tasks. Furthermore, automated systems are not subject to fatigue,[12,13] thus maintaining the same high vigilance throughout a surgical procedure.

The rapid development of control and system theory with parallel progress in computer technology has resulted in several studies on the automatic control of sedation[14] and hypnosis[6–9] based on BIS as the controlled variable and using continuous propofol infusion. Volatile anesthetics have been used less frequently under conditions of automated control. Ross *et al.*[15] and Morley *et al.*[8] describe the use of a syringe pump that injected liquid isoflurane into the inspiratory limb of a breathing circuit; this method is unlikely to be approved for routine use because of its inherent safety risks. The administration of volatile anesthetics with the use of vaporizers, as done in our study, has been rarely described,[16] probably because modified vaporizers with an added external servomotor are not readily available.

In the previously mentioned studies measurement artifacts pose an inherent safety risk. Because the controllers depend on a single input signal, the disturbance of

* Staff Anesthesiologist, † Engineer, ‡ Professor, Department of Anesthesiology, Research Section, University of Berne, Switzerland. § Engineer, Automatic Control Laboratory, Swiss Federal Institute of Technology (ETH), Zurich, Switzerland.

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Address reprint requests to Dr. Schumacher: Department of Anesthesiology, University Hospital Berne, 3010 Berne, Switzerland. Address electronic mail to: peter.schumacher@dkf.unibe.ch.

this signal may greatly affect controller performance. On the other hand, when volatile anesthetics are used the end-tidal anesthetic gas concentration is routinely available and provides additional information on the arterial blood concentration of the volatile anesthetic. Our newly designed controller uses both measurements: the end-tidal concentration measurement and the BIS measurement. This recently patented controller (DE 100 15 026 C2 and United States No. 09/815,092) has a cascade structure with outer and inner control loops. The outer control loop adjusts the end-tidal volatile concentration to obtain a desired BIS concentration. The inner control loop adjusts the vaporizer to obtain the desired end-tidal concentration. A model based state feedback control algorithm is used to obtain optimal control despite temporary disturbance of the signals. A detailed description appears in the Appendix.

The goal of this study was to evaluate this system clinically and to compare it with manual control. Our hypothesis was that the set point precision of closed-loop control as quantified by performance parameters is at least 30% better than that of manual control. Furthermore we expected that our closed-loop control system should reduce the duration of time of BIS values outside the boundary (defined as phases of inadequate control) by a factor higher than three times, even in a clinical setting with variable disturbances.

Materials and Methods

Clinical Study Design

After approval from the governmental Ethics Committee of the Canton of Berne (Switzerland) informed written consent from 23 patients of American Society of Anesthesiologists physical status I or II was obtained. All patients were aged between 18 and 65 yr and scheduled to undergo elective decompressive spinal surgery. Exclusion criteria were a history of cerebral vascular insult, transient ischemic attacks, a diagnosis of dementia, a history of coronary artery disease in the last 12 months or a successful percutaneous transluminal coronary angioplasty less than 6 months before, or insufficiently treated arterial hypertension (diastolic pressure values $>$100 mm Hg or systolic pressure values $>$180 mm Hg).

All patients received 7.5 mg midazolam orally as premedication 30 to 60 min before surgery. Standard monitoring with electrocardiogram, pulse oximeter, noninvasive blood pressure, and Bispectral Index was installed in each patient. The BIS® electrodes (Aspect Medical Systems Inc., Natick, MA) were attached to the forehead according to the manufacturer's instructions. An intravenous catheter was placed in the forearm vein for drug and fluid administration.

Anesthesia was induced with 1.5–2.0 mg/kg propofol. After loss of consciousness, the accelerometer TOF-Watch SX (Organon Teknika BV., RM Boxtel, The Netherlands) was calibrated according to manufacturer specifications. After a bolus of 0.3 mg/kg mivacurium for muscle relaxation, a target-controlled infusion of alfentanil was started using a Harvard-22 syringe pump (Harvard Clinical Technology, Inc., South Natick, MA) driven by the STANPUMP software (Steven L. Shafer, M.D., Department of Anesthesia, Stanford University, Stanford, CA, Version 1.21.1998)‖ with an initial target plasma concentration set to 180 ng/ml.

After tracheal intubation, isoflurane was administered to reach BIS of 50 using a fresh gas flow of 3 l/min and 100% oxygen. Target end-tidal CO_2 was 35 mm Hg. Neuromuscular blockade was maintained by a mivacurium infusion of 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$. Ringer's lactate was infused at 2 $ml \cdot kg^{-1} \cdot h^{-1}$. Patients were kept normothermic using forced air warming blankets.

Before moving to the operating room, patients were randomly allocated to either the manually controlled (MC) or the computer controlled (CC) group. The isoflurane vaporizer was set to keep the BIS value at 50 in the MC group by a clinical staff member (a different person for each trial) and in the CC group by the automatic closed-loop control system. Staff members were instructed to maintain BIS values ideally at 50 but not to exceed either the lower (40) or higher (60) limit. The study was performed in the neurosurgery department, where all anesthetists are familiar with BIS monitoring. Manual or computer control was started 5 min after moving the patient into the prone position. The patients were moved to the operating room with fully connected and running anesthesia machine, monitoring, data acquisition, and controller in the CC group. For safety reasons all trials were supervised by an investigator and a research engineer.

Individual limits for blood pressure and heart rate were set by the staff anesthesiologist in a range $\pm$20% of the values determined during the premedication visit the day before surgery. Blood pressure was measured noninvasively every 5 min. If, during manual or computer control, blood pressure or heart rate reached their respective limits and evidence for normovolemia was given, the target alfentanil concentration was adjusted stepwise by $\pm$50 ng/ml by the staff member. For safety reasons the study was aborted if limits were violated for more than 5 min. The initially set fresh gas flow of 3 l/min was kept constant during skin incision with 40% oxygen in air. Five minutes after skin incision or when stable clinical parameters were reached, fresh gas flow was reduced to 1 l/min. At the end of surgery (*i.e.*, at the beginning of skin closure) all drug infusions were stopped, BIS target value was set to 60, and fresh gas

‖ STANPUMP program is available from the author at http://anesthesia.stanford.edu/pkpd/target%20control%20drug%20delivery/STANPUMP. Accessed December 2003.

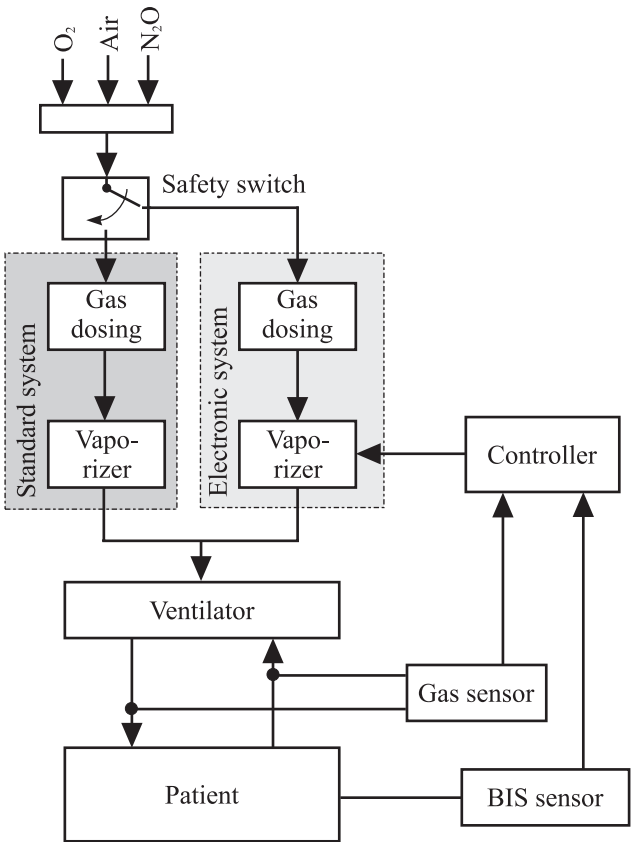

Fig. 1. System design overview of the extended anesthesia workplace. The safety switch is an electrical push button to switch the gas supply back to the standard dosing system.

flow were increased to 3 l/min. During skin closure the staff members in the manual group were instructed to maintain BIS ideally at 60. After the patient was transferred back to bed, isoflurane was turned off and fresh gas flow was adjusted to 10 l/min of pure oxygen.

System Specification

An extended Cicero anesthesia workstation (Dräger Medical, Lübeck, Germany) equipped with an isoflurane vaporizer (Dräger Vaporizer 19.3) and hemodynamic, gas, and respiratory monitoring (Dräger PM8060) was used (fig. 1). The processed electroencephalogram was derived from an A-2000 BIS® Monitor (Aspect Medical Systems Inc., software version 3.11); the delay was set to 15 s.

Between the fresh gas supply from the pipelines and the inlet to the breathing system an additional electronically driven gas dosing system was installed in parallel to the standard system. It consisted of a Dräger 19.3 isoflurane vaporizer driven by an external servomotor and two Hi-Tech mass flow controllers (Bronkhorst Hi-Tech, Ruurlo, Netherlands) for oxygen and air to supply a precise flow of gases. We refer to this dosing system as the "actuator" of the control system.

For safety reasons, an emergency shut-down button was integrated to enable the anesthetist to switch back from the actuator to the standard gas dosing system in case of a critical situation, when the regular deactivation of the controller would not have been possible.

The control algorithms were implemented on a VME-board Power personal computer using the real-time operating system XO/2 (Institute of Robotics, Swiss Federal Institute of Technology, Zurich, Switzerland).# Dedicated parts of the program were used to send data for display and storage to a standard personal computer *via* an Ethernet link. Every 5 s from several minutes before induction until the recovery of the patient all sensory data were stored on the personal computer.

The implemented controller used a cascade structure. The outer cascade is a standard proportional-integral controller, which provides the end-tidal anesthetic target fraction reference (F_E,ISO_{ref}) for the inner controller. This inner controller has a model based state feedback design with an additional safety override structure to ensure constraints on end-tidal anesthetic fraction (F_E,ISO). For the safety override structure the end-tidal minimum and maximum concentrations were set to 0.4 vol.% and 1.8 vol.%, respectively. For further details see the Appendix.

The measurements of F_E,ISO, the inspired isoflurane fraction ($F_I ISO$), and especially BIS are prone to artifacts. Artifacts in the isoflurane concentration can be caused by disconnection of the gas sampling line or self-calibration of the gas-sampling module. A valid measurement was assumed when F_E,ISO and $F_I ISO$ were between 0 and 5 vol.%. Disconnected or badly conducting electrodes or electrocautery may cause artifacts in the BIS. A valid BIS was assumed when the corresponding signal quality index was greater than 30. If a faulty isoflurane measurement was detected, the controller used the model estimate instead of the actual measurement. As the patient model does not estimate BIS, the controller of the outer cascade was automatically switched off and the reference for the end-tidal fraction of the inner cascade drifted to a safe, predefined value until the BIS measurements were valid again. This safe value was defined by the anesthesiologist before induction and could be adjusted if necessary during the procedure. During artifact periods the anesthetist was notified with a warning that included the length of the period.

Before its clinical application, the complete system including the controller had been carefully tested and optimized using a hardware-in-the-loop simulator.** The same setup was also used to teach the investigators how to handle the system. A detailed description appears in the Appendix.

XO/2 is available from the authors at http://www.xo2.org. Accessed March 2003.

** Stadler K, Frei CW, Hausheer D, Sierra R, Leibundgut D, Glattfelder AH, Zbinden AM: Simulating a Patient Undergoing Anesthesia for Controller Development and Educational Purposes. Available at: http://control.ee.ethz.ch/research/publications/publications.msql?id=1179. Accessed March 2003.

Performance Analysis

Set Point Precision Comparison. Controller performance was assessed by comparing the measured BIS values of the controlled variable and the preset BIS values (set point). The parameters were calculated for three phases.

1) The skin incision phase with a BIS set point of 50 and a fresh gas flow of 3 l/min included the period 5 min before and 5 min after skin incision.

2) The low flow phase with a BIS set point of 50 included the subsequent period where a total fresh gas flow of 1 l/min was used. This period lasted until the beginning of wound closure, when the BIS target was set to 60. A minimum observation period of 20 min was required because of the system dynamics of the patient and dosing system. If the low flow phase was shorter than 20 min the patient data were excluded from the analysis.

3) The wound closure phase included the period from 5 min after the BIS set point was changed to 60 until isoflurane administration was stopped. Five minutes delay after set point change was chosen to exclude the transient phase from the static set point precision evaluation.

Set point precision was assessed using different methods: the mean absolute difference (MAD) between measured and set point BIS values resulting in Equation 1:

$$MAD_i = \frac{1}{N_i} \sum_{j=1}^{N_i} | BIS_{measured}(i, j) - BIS_{reference}(i, j) |$$

where N_i = total number of measurements during observation period for subject i.

Additional parameters as proposed by Varvel *et al.*[17] were used to assess set point precision: the performance error (PE) calculated as the weighted difference between actual and desired values, (Equation 2); bias (median performance error, MDPE) (Equation 3); inaccuracy (median absolute performance error, MDAPE) (Equation 4); wobble (Equation 5).

Equation 2:

$$PE_{ij} = \frac{BIS_{measured_{ij}} - BIS_{reference_{ij}}}{BIS_{reference_{ij}}} \times 100$$

Equation 3:

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

Equation 4:

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

Equation 5:

$$wobble_i = \text{median}[|PE_{ij} - MDPE_i|, j = 1,. . .,N_i]$$

where: i = subject number, j = j^{th} (one) measurement of observation period, N = total number of measurements during observation period.

For each i^{th} subject all parameters were calculated. Divergence, another parameter given by Varvel, was not calculated because of the feedback structure of the controller, which by definition corrects any divergence over time (as opposed to an open-loop target-controlled infusion system).

We used standard statistical methods for population estimates and group comparison for all Varvel parameters.

Response to Stimulus. The skin incision was used as a standardized stimulus, and the hemodynamic and BIS response was recorded. The data of the skin incision phase, defined as 5 min before and after skin incision, were filtered using a moving median filter with a length of 1 min. The filtered value before skin incision was then compared with the maximum of the filtered data after skin incision. In addition the reaction of the controller (manual and automatic) to the BIS change was recorded and the corresponding system gain was calculated. The gain was defined as the change of end-tidal fraction *versus* the change of BIS (plus set point deviation before stimulation data points) expressed as the slope of the linear least squares fit.

Safety. To calculate the safety parameters all measured values within the period between 5 min after starting of manual or computer control (*i.e.*, after reaching steady state) and the end of the low flow phase were used for analysis. Inadequate sedation was expressed as area under the curve of the BIS values above 60 or less than 40, respectively. The resulting areas were then divided by the duration of the measuring period to obtain the mean area under the curve. Mean area under the curve was also calculated for heart rate and mean arterial blood pressure values outside ±20% of baseline. Phases of inadequate control were defined as periods with a BIS value of 65 and above for more than 3 min. The number of such incidents was recorded, and the duration of all incidents as well as the ratio to anesthesia time was determined.

Outcome. Recovery parameters such as time from stopping the isoflurane administration until opening eyes, extubation, and orientation (stating date of birth) were recorded. Patients were postoperatively interviewed for quality of anesthesia and occurrence of awareness. The occurrence of postoperative nausea and vomiting and other incidents was recorded.

Statistical Analysis

A power analysis for unequal variances with a significance level of 0.05 and a power of 0.8 was calculated after the first studies for the reduction of the mean absolute difference parameter by 30% in the CC group with resulting N's equal to 11 and 4 for the MC and CC groups, respectively. The group size was then defined as 10 for both groups because we wanted to perform the same number of experiments in both groups. Data are presented as mean ± SD or median (range) and, where applicable, confidence intervals are given. Differences between the groups (tables 1 and 2) were determined using Student *t* test or the Mann-Whitney *U*-test depend-

Table 1. Demographic Data

	MC Group (n = 10)	CC Group (n = 10)
Age [yr]	40.5 (32–56)	48.5 (29–59)
Body Mass Index	24.5 (18–32)	27.0 (23–33)
Sex [female/male]	6/4	3/7

Data are shown as median (range).

MC = manual control; CC = closed-loop control.

ing on normality of data. For comparison of variance a variance ratio test (F test) was performed with $P < 0.05$ ($F_{0.95}$).

Results

Twenty of 23 consenting patients were included in the group comparison. Two patients randomized to the CC group had to be excluded because of too short low flow phases (9 and 12 min). One patient was excluded because the override safety structure of the controller became active; as this patient had a very low isoflurane requirement, the predefined lower end-tidal concentration limit of 0.4 vol.% was reached and the controller switched from BIS to end-tidal control. Thus the controller was not allowed to reach the target BIS.

There were no significant differences between either the demographic data (table 1) or the clinical data (table 2) of the two groups except for the alfentanil concentration in the low flow phase. In the MC group the alfentanil target concentration for the low flow phase was increased in four patients; in the CC group the target concentration was increased in two and decreased in three patients. As shown in table 2 this leads to statistically significant higher effect compartment concentrations of alfentanil in the MC group during the low flow phase, whereas the difference between the groups during the skin incision phase was not significant. No experiment had to be aborted as a result of hemodynamic parameters being out of bounds for more than 5 min.

Table 2. Clinical Data

	MC Group (n = 10)	CC Group (n = 10)
Anesthesia duration (min)	120.1 ± 31.3	138.3 ± 24.4
LFP duration (min)	46.5 ± 19.8	59.6 ± 24.8
WCP duration (min)	11.0 ± 4.7	12.5 ± 4.8
Recovery time until eye opening (min)	8.2 ± 6.2	8.9 ± 2.7
Recovery time until extubation (min)	10.3 ± 5.8	10.3 ± 2.5
Recovery time until orientation (min)	13.5 ± 6.6	12.0 ± 3.4
F_E, ISO during SIP (vol. %)	0.84 ± 0.19	0.72 ± 0.20
F_E, ISO during LFP (vol. %)	0.78 ± 0.17	0.81 ± 0.17
F_E, ISO during WCP (vol. %)	0.74 ± 0.17	0.83 ± 0.10
Alfentanil C_e during SIP (ng/ml)	184.4 ± 24.9	169.3 ± 20.8
Alfentanil C_e during LFP (ng/ml)	204.3 ± 46.2*	162.2 ± 39.9*

Data are shown as mean ± SD.

F_E, ISO = end-tidal isoflurane concentration; LFP = low flow phase; SIP = skin incision phase; WCP = wound closure phase.

* $P < 0.05$ between groups.

Table 3. Experience Levels of the Anesthetists for the Manual Control Group

	Experiments by Anesthesiologists	Experiments by Anesthesia Nurses
Experience level 8 years and more	3	2
Experience level 4 to 8 years	2	1
Experience level 2 to 4 years	2	–

Table 3 shows the experience level of the staff members participating in the MC group of the study.

Set Point Precision Comparison

The set point precision quantified by the performance parameters are shown in table 4 for the skin incision phase, the low flow phase, and the wound closure phase. The results of the CC group showed a significantly better performance during all phases with respect to the two performance parameters mean absolute difference and median absolute performance error and for wobble during the wound closure phase ($P < 0.05$). Median performance error and wobble for the skin incision phase and the low flow phase showed no significant differences. The results of the MC group show a much higher variability of the data: the standard deviations of all listed performance parameters for the skin incision phase, the low flow phase, and the wound closure phase are 1.9 (0.7–3.8) times greater than the corresponding values for the CC group. Except for wobble parameter and mean absolute difference during the skin incision phase and the wound closure phase this difference is statistically significant ($F_{0.95}$). Figure 2 shows all the BIS values from induction to emergence of anesthesia for both groups.

The transition between the low flow phase and the wound closure phase with a BIS set point change of 50 to 60 lasted 3.8 ± 1.4 min in the CC group with little to no overshoot. Excessive overshoot would clearly influence the set point precision indicators, which is not the case. No consistent method to quickly achieve the new set point could be found in the MC group; therefore no meaningful transition time can be given.

Response to Stimulus

Figure 3 shows the response to the skin incision for both groups for the heart rate and BIS. The increase in heart rate was 3.0 (0.0–18.0) beats/min for the MC group and 2.3 (0.0–25.0) beats/min for the CC group.

Table 4. Control Performance Parameters

	MC group (n = 10)	CC group (n = 10)
Skin incision phase (BIS setpoint = 50)		
MAD (BIS values)	5.95 ± 1.86 (4.80–7.10)*	3.93 ± 1.15 (3.22–4.65)*
MDAPE (%)	11.96 ± 4.31 (9.29–14.63)*†	6.95 ± 2.28 (5.53–8.37)*†
MDPE (%)	−0.72 ± 12.62 (−8.54–7.10)†	−1.01 ± 3.31 (−3.06–1.04)†
Wobble (%)	5.79 ± 2.23 (4.41–7.17)	6.60 ± 2.45 (5.08–8.12)
Low flow phase (BIS setpoint = 50)		
MAD (BIS values)	5.50 ± 1.83 (4.37–6.64)*†	4.25 ± 0.83 (3.74–4.77)*†
MDAPE (%)	10.86 ± 4.61 (8.00–13.72)*†	7.47 ± 1.90 (6.29–8.65)*†
MDPE (%)	4.83 ± 8.58 (−0.49–10.15)†	−0.75 ± 2.45 (−2.27–0.77)†
Wobble (%)	7.05 ± 1.54 (6.10–8.00)	7.33 ± 1.87 (6.17–8.49)
Wound closure phase (BIS setpoint = 60)		
MAD (BIS values)	5.75 ± 3.05 (3.87–7.64)*	3.38 ± 2.11 (2.07–4.68)*
MDAPE (%)	8.72 ± 5.45 (5.34–12.09)*†	4.20 ± 2.77 (2.48–5.92)*†
MDPE (%)	−2.21 ± 7.87 (−7.09–2.67)†	1.73 ± 2.72 (0.04–3.41)†
Wobble (%)	5.89 ± 3.40 (3.78–8.00)*	3.42 ± 2.35 (1.96–4.87)*

Data shown as mean ± SD (confidence interval).

BIS = bispectral index; MAD = mean absolute difference; MDAPE = median absolute performance error; MDPE = median performance error.

* $P < 0.05$ between groups; † significant difference of variances ($F_{0.95}$).

Data shown as median (range). This small response indicates an adequate analgesia for the patients in both groups in most cases. BIS showed a response with an increase of 5.7 (1.8–11.3) and 7.7 (0.0–17.6) in the MC and CC groups, respectively (median [range]).

Figure 4 shows the system gain, which is very consistent for the CC group but does not reflect selective reactions in the MC group. In this group, on average end-tidal fraction increased by 0.05 vol.% independently of the change in BIS. In the CC group the change in end-tidal fraction was usually achieved within 1 min as a response to the BIS change.

Safety

The occurrence of inadequate BIS is shown in figure 5. The safety data are summarized in table 5. Although the median of the mean areas under the curve for BIS above 60 in the CC group is five times smaller than the same value of the MC group, there is no statistically significant difference mainly because of the high variance of the data.

The measurements for hemodynamic stability showed no significant differences between the groups.

In the MC group nine phases of inadequate control were recorded with an overall duration of 78.1 min of 757.1 min of observed anesthesia time (10.3%). In the CC group one phase of inadequate control was recorded with an overall duration of 4.8 min of 895.9 min of observed anesthesia time (0.5%).

As mentioned above, in one patient experiment (not included in the group comparison) the safety structure of the end-tidal override controller was activated because of a low isoflurane requirement of the patient. Figure 6 shows a sample recording with the end-tidal isoflurane concentration reaching the preset lower limit

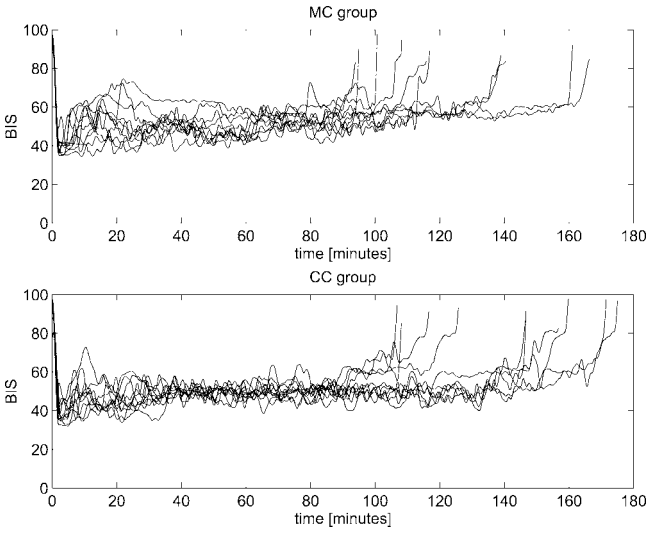

Fig. 2. Individual bispectral index (BIS) data for manual control and computer control groups. All data from induction to emergence of anesthesia are shown; data are averaged for the graphical representation with a moving average filter of 1-min length.

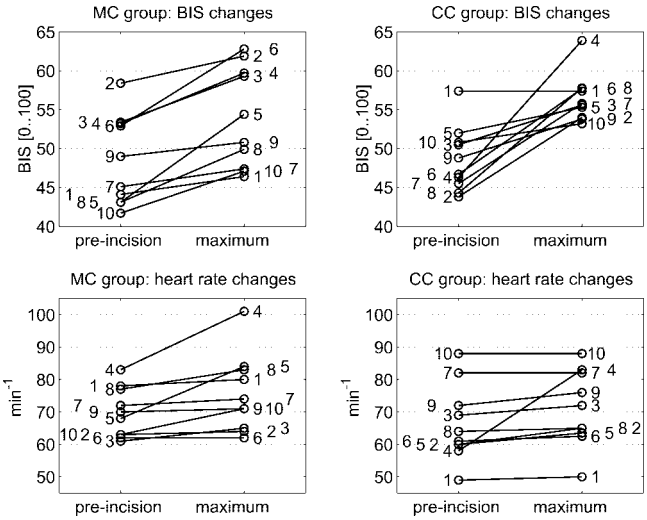

Fig. 3. Response to skin incision for bispectral index and heart rate for each patient.

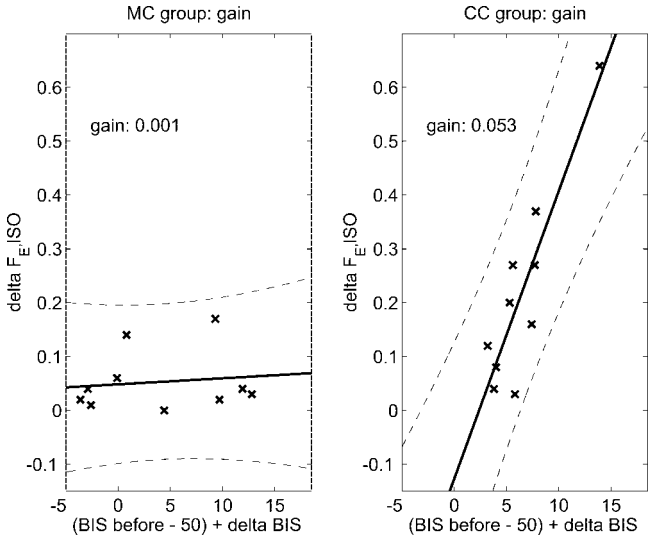

Fig. 4. System gain as response to skin incision defined as the slope of the linear least squares fit of the change of end-tidal isoflurane fraction (ΔF_E,ISO) plotted against the change of bispectral index (ΔBIS) plus the set point deviation before stimulation. Each cross represents one patient; dashed lines indicate the 95% confidence interval.

of 0.4 vol.%. This limit was well maintained by the controller, allowing no further reduction even though the measured BIS was less than 40. Figure 6 also shows a change of this lower target concentration by 0.1 vol.% and the reaction of the controller to this change (onset time was approximately 3 min).

Figure 7 shows an example of artifact handling. During a phase of missing BIS signal the controller used the predefined safe value for setting the end-tidal isoflurane concentration.

No human intervention was necessary during automatic control; controller operation was stable and safe.

Outcome

The recorded recovery times do not show a significant difference between the two groups (table 2). The standard deviations of the two groups differ by a factor of 2.3 for opening of the eyes and extubation and 1.9 for orientation recovery time. Comparing variances gives a statistically significant lower variance for all recovery times in the CC group ($F_{0.95}$).

Generally the quality of the anesthesia was considered to be good by both groups of patients. No cases of awareness were recorded in either group. Postoperative nausea and vomiting was recorded in two cases of the MC group and in one case of the CC group. In one case in the MC group a postoperative gastric reflux was observed.

Discussion

This study showed significantly better control performance for an automatic model based control system as compared with human control for isoflurane administration using BIS as the controlled variable. No human intervention was necessary, as the system performed with stability and robustness for two different set point values and fresh gas flows. The set point precision comparison showed a significant reduction for all the measures for inaccuracy in CC group by more than 30%, except for the mean absolute difference in the low flow phase (23%). All listed performance parameters of the MC group had an average of two times larger variability. Furthermore, an impressive reduction in phases of inadequate control (by a factor of 20) was reached in the CC group, thereby reducing the risk of inadequate anesthesia.[11]

An accepted method to assess the performance parameters was proposed by Varvel *et al*. for open-loop computer controlled infusion pumps. They defined these performance measures to optimize the prediction quality of pharmacokinetic models and therefore proposed a population estimation based on the work of Sheiner.[18] The goal of this study was to estimate the variability of

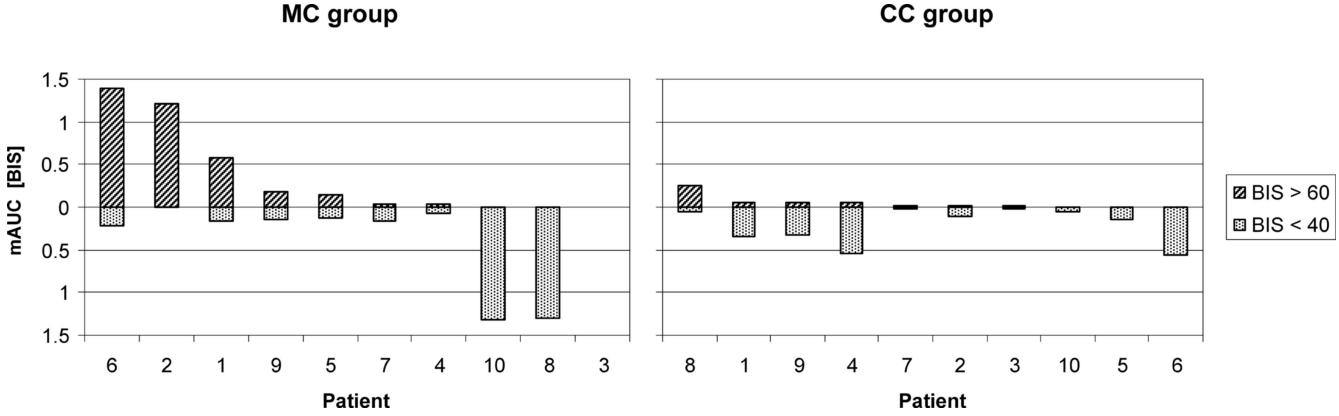

Fig. 5. Mean area under the curve (mAUC) for inadequate bispectral index values from 5 min after control start until beginning of skin closure. A bispectral index value above 60 or less than 40 was considered as inadequate. Each bar represents one patient experiment, sorted by mAUC of bispectral index >60. The area was defined by the curve above 60 or less than 40 respectively and was scaled with the total observation time.

Table 5. Safety data

	MC Group (n = 10)	CC Group (n = 10)
BIS deviations		
mAUC BIS >60	0.088 (0.002–1.401)	0.017 (0.001–0.254)
mAUC BIS <40	0.150 (0.000–1.312)	0.126 (0.018–0.563)
PIC incidents	9	1
PIC relative duration	10.3%	0.5%
Hemodynamic stability		
mAUC of heart rate beyond ±20% of baseline	1.84 ± 5.30	0.57 ± 0.98
mAUC of MAP beyond ±20% of baseline	5.29 ± 4.31	5.90 ± 7.18

Data shown as median (range) or mean ± SD.

BIS = bispectral index; mAUC = mean area under the curve; PIC = phase of inadequate control.

* $P < 0.05$ between groups.

the controller performance, not to use the data for modeling purposes. Therefore the population estimates (*i.e.*, the controller performance of each group) of the Varvel parameters was calculated using standard descriptive statistics (mean, SD).

The controller showed consistent and safe performance even when the BIS signal was temporarily invalid, mainly because of the newly conceived cascade structure of the controller, which uses both the BIS and the end-tidal concentration measurement. The cascade design (fig. 8) has additional advantages. In case of an invalid BIS signal (*e.g.*, as a result of artifacts) the inner control loop for the end-tidal isoflurane concentration takes over the control. Even with a missing end-tidal measurement, the controller maintains system stability using the estimated value of the observer-based state feedback controller. An additional advantage of the cascade controller is the override structure, which was introduced to ensure a minimum and maximum end-tidal isoflurane concentrations. As an additional safety layer this can help to prevent light anesthesia with the associated risks of hypertension, tachycardia, and increased stress response and also avoid administration of excessive gas concentrations. Indeed, a patient requiring very low end-tidal isoflurane concentrations to achieve the desired BIS value was anesthetized in override end-tidal control mode, and the controller did not decrease to less than the predefined lower end-tidal isoflurane concentration of 0.3 vol.%. Even though BIS was between 35 and 45 over longer periods of time, a prolonged emergence could not be observed and the patient was clinically stable at all times. An additional beneficial feature is the feed-forward term (see Appendix for description). As rapid BIS changes caused by an arousal require fast controller reaction, the feed-forward term amplifies the vapor settings and thereby minimizes the wash-in time of the volatile anesthetic into the breathing system and the patient. The consistent system gain as shown in case of the standardized skin incision stimulation was only possible thanks to the fast dynamics essentially provided by this feed-forward term. The cascade design, the override structure, and the feed-forward term are features that contribute to the safety of closed loop systems as called for by Glass and Rampil[19] for adoption in daily practice.

Previous authors have presented studies with automatic control of sedation or hypnosis.[6,9] However, these studies, covering only stable phases after beginning of

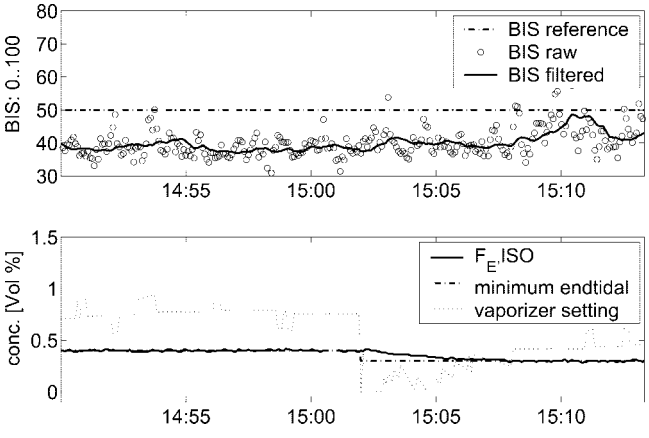

Fig. 6. End-tidal override controller: Despite a bispectral index value less than the set point, the controller kept a minimal end-tidal concentration of 0.4 vol.% constant. At 15:02 the minimally allowed end-tidal target concentration was decreased to 0.3 vol.% by the anesthesiologist, which was followed by the controller. A slightly higher bispectral index value can subsequently be observed.

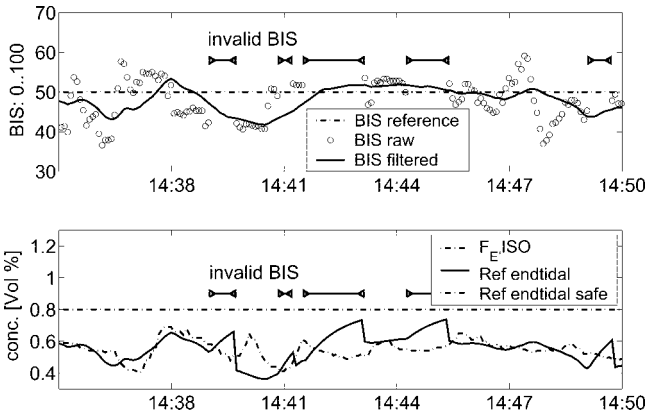

Fig. 7. Example data trace of artifact handling: during phases of invalid bispectral index measurements the controller allowed the end-tidal concentration to approach a safe predefined and patient dependent value.

surgery or under presence of peridural anesthesia,[7,8] had insufficient controller performance[8] or had no manual control group.[7,9] All control systems except that of Morley *et al.*[8] used propofol. Our system is the first to use volatile anesthetics and to take advantage of the end-tidal measurement, which provides a better estimation of blood concentration than model prediction calculation.

A disadvantage of volatile anesthetics is the limited speed with which the concentration at the effect site can be increased. As discussed by Olofson *et al.*[20] this lag is mainly caused by the breathing system's gas-delivery system. Taking into account the time of onset of anesthetic action, they found analogous values for isoflurane and propofol. However, a recently marketed anesthesia system for volatiles (Zeus; Dräger Medical) has very short lag times and allows for the rapid increase of inspired concentration.††

The success of automatic control is ultimately related to the quality of the input signal to the controller. A good correlation between the occurrence of recall under isoflurane anesthesia and the BIS has been shown.[4,5,21] We consider BIS to be the best established among all potential electroencephalogram surrogate parameters for assessing depth of hypnosis.

A comparison of closed-loop control to manual control is always subject to several variable factors: instruction of the person who performs the control task, training, experience and motivation, type of practice guideline used, difficulty of the case, and other less tangible factors. In addition the study may be criticized for the lack of blinding of anesthesia personnel. To reduce this potential bias, a double-blind and double-dummy design could help; however, the technical and organizational effort of such a setup would surpass the possibilities of our University Hospital environment. In this study we tried to involve randomly chosen anesthesiologists and anesthesia nurses with different experience levels (table 3). Thus, variability in the MC group reflects within and between anesthetist variability. The preconceived isoflurane concentration for adequate hypnosis had some guiding influence on the more experienced providers confirming the findings of Pavlin *et al.*[22] To minimize or offset effects of bias, we attempted to stimulate general interest in achieving good control results. However, the anesthesiologist certainly acts differently as an automatic controller when confronted with a set point deviation. Most obvious was the transition phase between the low flow phase and the wound closure phase when the BIS set point was increased form 50 to 60. The automatic controller immediately closed the vaporizer until the required end-tidal fraction matched the new BIS set point and then maintained this end-tidal concentration with a corresponding vaporizer setting. In the manual group every anesthesia provider maintained the same vaporizer setting for a while and then only gradually reduced the setting, resulting in an unspecific and meaningless transition time. Another example of different behavior is shown by the gain (fig. 4) in the MC group where no consistent reaction to an increase of BIS as response to the skin incision could be found. On average, isoflurane dosing was increased independently of the change in BIS induced by the skin incision. The automatic controller in the CC group, on the other hand, showed a very consistent behavior and responded quickly and appropriately to the BIS change. As a consequence the closed-loop system was more stable with respect to maintaining the desired BIS values, even in phases with abrupt changes of stimulation, like the skin incision, which could not be anticipated by the control system. This cannot be attributed to different concentrations of opioids, as the alfentanil concentrations were similar during the skin incision phase and even higher during the low flow phase in the MC group as compared with the CC group (table 2). Nevertheless, the relatively high opioid concentrations reduced the stress on the controllers in both groups. In further studies, the use of less or shorter-acting opioids should be investigated.

More important than surrogate parameters of control and monitoring are the true clinical outcome parameters. Recovery times were not significantly different, but the variance for the recovery parameters was significantly decreased in the CC group, which reflects the more consistent control in this group. The less scattered recovery characteristics in the CC group could be interpreted as evidence for better predictability of recovery, which allows for better planning of the recovery phase.

We do not know how these times are related to duration of postanesthesia care unit stay, time to oral intake, and time to home-readiness, which are reportedly not related to the immediate recovery times.[23] To investigate these parameters and other outcome parameters such as the occurrence of awareness, further studies in larger and more varying populations are needed.

In conclusion, we have shown the superiority of an automatic control system for depth of hypnosis using BIS as the controlled variable and isoflurane gas concentration as the adjusted variable over manual control. The new technology with the cascade controller appears to be an attractive way to take advantage of the additional measurement of the end-tidal concentration, thus avoiding adverse effects of measurement artifacts. Although this study suggests potential advantages in true clinical outcome parameters, larger clinical studies will have to be performed in varying patient populations to show the benefits of such systems in terms of patient outcome and cost savings.

Appendix

The controller uses a cascade structure (fig. 8), which separates regulation of the pharmacodynamic and phar-

†† Personal communication, Ralf Dittmann, M.Sc., Head of Research and Development, Dräger Medical, Lübeck, Germany, January, 2003.

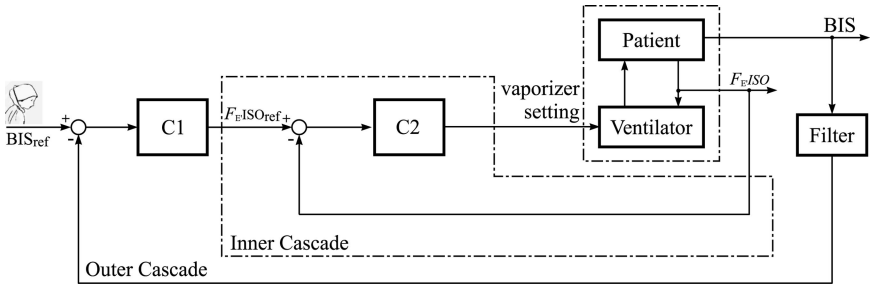

Fig. 8. Cascade control structure consisting of an outer cascade to control bispectral index (C1) and an inner cascade to control F_E,ISO (C2). The artifact handling structure with safe end-tidal input value is not shown.

macokinetic effects of isoflurane on BIS. The outer cascade is a standard proportional-integral (PI) controller (C1), providing the end-tidal anesthetic target fraction reference (F_E,ISO_{ref}) for the inner cascade to obtain the desired BIS value. The latter (controller C2, fig. 8) is a model based state feedback controller, which sets the vaporizer to obtain the desired F_E,*ISO*. It has an additional override structure to ensure constraints on F_E,*ISO*.

Model

The pharmacokinetic model of isoflurane described by Sieber *et al.*[24] was adapted; this consists of a physiologic model describing the time-course of the partial pressure of isoflurane in 12 body compartments and an equation for the anesthetic partial pressure in the respiratory circuit. The model used in our new controller differed only in the assumption of a constant cardiac output. The cardiac output was set according to Brody's relation[25] $CO = 0.2 \cdot m^{3/4}$, where m is the body weight in kg. The linear model is described by a set of ordinary differential equations of the form

$$\dot{\hat{x}}(t) = A \cdot \hat{x}(t) + B \cdot u(t)$$

$$\hat{y}(t) = C \cdot \hat{x}(t) + D \cdot u(t)$$

where $\hat{x}(t)$ is the estimated state vector and $\dot{\hat{x}}(t)$ the corresponding time derivative, u(t) is the control input and $\hat{y}(t)$ is the estimated measurement output. In this case x(t) represents a vector composed of the partial pressure of isoflurane in the 12 different body compartments and the respiratory system, u(t) represents the vaporizer setting and $\hat{y}(t)$ is a vector composed of the estimated measurements of inspired and end-tidal isoflurane concentration. The system coefficient matrices A, B, C, D depend on fresh gas flow, respiratory frequency and tidal volume set by the anesthesiologist. Therefore, A is a 13 by 13 matrix describing the influence between the state variables ($\hat{x}(t)$). No pharmacodynamic model for isoflurane effects on BIS was used.

Cascade Controller

In figure 8 the patented (DE 100 15 026 C2 and United States No. 09/815,092) cascade structure of the controller is shown. The cascade control structure was adopted from Gentilini *et al.*[26] and significantly modified. The outer cascade is a standard proportional-integral controller (C1), which provides the end-tidal isoflurane concentration reference (F_E,ISO_{ref}) for the controller of the inner cascade (C2) according to the BIS reference (BIS_{ref}) and actual BIS measurement. Because of patient variability and the nonlinear effects of isoflurane on BIS measurements, which were not considered by the model, the controller C1 was tuned moderately (*i.e.*, a slow reaction was expected) to increase robustness. Every 5 s the controller C2 calculates a new vaporizer setting according to F_E,ISO_{ref} and the measured F_E,*ISO*. The controller C2 is shown in figure 9. It is a model based state feedback controller adopted from Sieber *et*

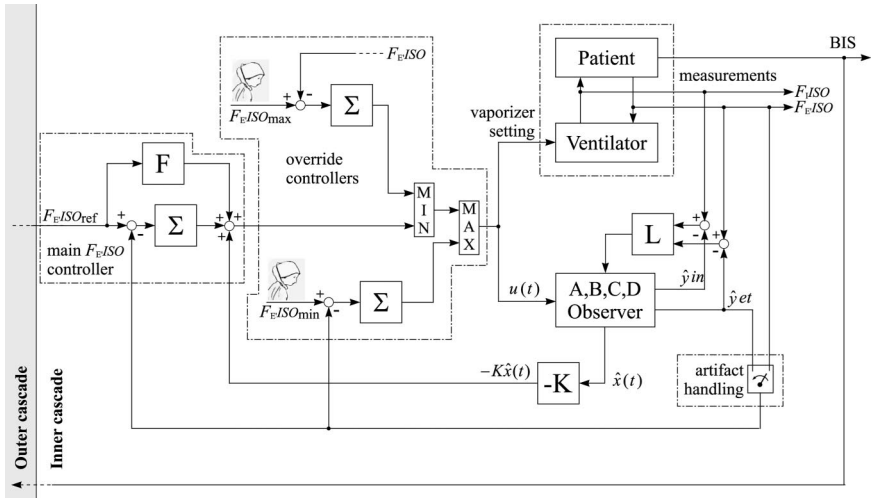

Fig. 9. Structure of the model based state feedback controller (inner cascade) consisting of an observer (with state feedback K and correction gain L), a main F_E,ISO controller, override controllers for constraint handling, and artifact handling procedures.

al.[24] and extended by several features. The control output is composed of an integrator term (Σ), a feed-forward term (F), and a linear combination of the system states, which can be written as $-K \cdot \hat{x}(t)$. The coefficient K is a constant matrix. For safety reasons the feed-forward term is mandatory, as rapid BIS changes caused by an arousal require fast controller reaction. Small changes of F_E,ISO_{ref} will be amplified by F such that the vaporizer setting will increase rapidly. This is necessary; as the respiratory system with its gas volume of approximately 6 l causes a significant time delay at low fresh gas flows (1 l/m), the feed-forward term minimizes the wash-in time.

The feed-forward term increases noise sensitivity considerably. Therefore a special filter was designed (based on empirical evidence) for the BIS measurement. In general the mean BIS value of the last 3 min was used by controller C1 to derive the end-tidal reference. Furthermore, it detected deviations larger than 15 from the mean BIS over the previous 3 min (BIS > mean BIS + 15) or BIS measurements higher than 70. In both cases the current BIS measurement, instead of mean BIS, was used for control. The integrator term (Σ) mainly compensates for modeling errors and therefore for the interpatient and intrapatient variability. With state feedback not just a first order derivative action as in standard proportional-integral-derivative controllers but rather derivatives up to an order equal to the number of states in the state vector can be used. The derivative of a state provides information of the future trend of that state. A state feedback controller therefore uses the information of the future trend of all states, whereas a proportional-integral-derivative controller uses only the information of the future trend of the last state, which corresponds to the measurable state. Considerably more aggressive controller designs without significant loss of robustness are possible. The inner cascade, which relies on measurable pharmacokinetics, therefore compensates for the slow responsiveness of the outer cascade. Because in most cases the system states (*i.e.*, the isoflurane partial pressure within an organ) cannot be measured, an observer (parallel model of the system to be controlled) is used to estimate the system states. The system states estimate $\hat{x}(t)$ can be used in the control algorithm instead of the actual system states x(t). Generally, the model and the reality will differ, as the model is always an abstraction of the latter. To achieve fast convergence of $\hat{x}(t)$ towards x(t) a correction gain L is introduced that corrects the state estimate $\hat{x}(t)$ based on the difference between the measurements y(t) and the measurement estimates of the parallel model $\hat{y}(t)$. In this case y(t) and $\hat{y}(t)$ are vectors consisting of the inspired and the end-tidal isoflurane concentration measurements and their estimations, respectively. Typically L is a constant gain, which is tuned such that the rate of convergence is faster than the desired response of the controller.

For safety reasons an override structure was added to controller C2 with additional controllers for a lower and an upper constraint on the end-tidal isoflurane concentration. The anesthesiologist sets an upper and lower acceptable limit of the end-tidal isoflurane concentration (F_E,ISO_{max}, F_E,ISO_{min}). The override structure switches automatically between the controllers in case F_E,ISO_{min} or F_E,ISO_{max} is reached. Therefore the override structure prevents overdosing and underdosing.

Artifact Handling

The measurements of F_E,ISO, F_IISO, and especially BIS are prone to artifacts. Artifacts in the isoflurane concentration can be caused by temporary disconnection of the gas sampling line or self-calibration of the gas-sampling module. A valid measurement was assumed when F_E,ISO and F_IISO were within 0 and 5 vol.%. Disconnected electrodes, poor signal quality of the electroencephalogram measurement used for deriving BIS or electrocautery cause artifacts on the BIS. A valid BIS was assumed when the corresponding signal quality index was larger than 30. If a faulty isoflurane measurement was detected, the controller used the estimate instead of the actual measurement. As the patient model does not estimate BIS, the controller of the outer cascade was switched off and the reference value of the inner cascade drifted to a safe, predefined value. During artifact periods the anesthetist was notified with a warning that included the length of the artifact period.

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