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CLINICAL INVESTIGATIONS

Model-based automatic feedback control versus human control of end-tidal isoflurane concentration using low-flow anaesthesia

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We studied the clinical use of an automatic feedback control system to adjust the end-tidal anaesthetic concentration with a low-flow method. The end-tidal controller uses two input signals (the end-tidal and inspiratory concentrations) to control the isoflurane concentration in the fresh gas flow, using a model-based algorithm. We studied 22 ASA I–III patients during elective surgery lasting more than 2 h. The anaesthetist was asked to make four step changes of the target end-tidal concentration (+0.3, +0.6, –0.3, –0.6 vol%), either manually (Group A) or by setting the target value for the feedback controller (Group B), and then the control was changed and the step changes were repeated, in a crossover design. Eighty step changes with each control method were compared in terms of response time, maximal overshoot and stability. The automatic control system was more accurate and stable than the human controller for step increases and step decreases, with less overshoot/undershoot and greater stability [e.g. maximal overshoot 14.7 (SD 3.7)% and 18 (8.1)% respectively for +0.6 vol% step changes, and 19.8 (3.7)% and 30.7 (13.2)% respectively for +0.3 vol% step changes]. However, the automatic control system showed a faster response time than the manual method only with large increasing steps (e.g. 149 (32) s and 205 (57) s respectively for +0.6 vol% step changes) and was not different from manual control for decreasing steps. Automatic control of the end-tidal isoflurane concentration can be better than human control in a clinical setting, and this task could be done automatically.

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Computers are increasingly used for delivering anaesthesia and monitoring patients. Automatic control systems will probably soon help to improve safety and reduce repetitive tasks.[1–4]

Minimal and low-flow techniques of general anaesthesia are gaining popularity for different reasons. Cost and environmental issues[5 6] favour low-flow systems.[7] On the other hand, low-flow systems require more expertise, and because the changes in the fresh gas concentration have a delayed effect on the end-tidal concentration of inhalation agents, more adjustments of the vaporizer setting are needed. Automatic control of end-tidal anaesthetic concentration could facilitate low-flow anaesthesia and prove cost-effective.

The ideal variable for the control of anaesthesia is still a matter of debate. An indirect variable (e.g. mean arterial pressure, heart rate) is often chosen, and the EEG-derived bispectral index (BIS) has been used recently in a closed-loop feedback control system.[8] Another easily measurable variable is the end-tidal concentration of an inhalation anaesthetic. It closely represents the brain concentration and can easily be measured breath-to-breath by a non-invasive procedure. In clinical practice, a certain level of anaesthesia is sought by observing the end-tidal concentration of the volatile agent by adjusting the inspired anaesthetic concentration manually. Previous studies have shown that, by controlling the end-tidal concentration of the anaesthetic, induction is shortened and arterial and brain concentrations

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are more stable.[9] During the induction of anaesthesia, the inspired concentration is often set well above the desired brain tension to speed the induction process (the over-pressure technique).[10]

We set a control system to adjust the end-tidal anaesthetic concentration for a variety of surgical interventions and patient characteristics, and compared it with manual control.

Methods

Patients

With institutional ethics committee approval and written, informed consent from the subjects, we studied 22 ASA I–III patients (18–75 yr) undergoing elective surgical procedures (neurosurgery, ENT, abdominal and orthopaedic surgery). We excluded patients with a history of coronary artery disease or with arterial hypertension that was poorly controlled.

The patients were given lorazepam 1–2 mg orally 30 min before induction of anaesthesia. An i.v. cannula was placed in a peripheral vein, and we monitored 3-lead ECG, arterial pressure (either non-invasively or invasively, at the discretion of the anaesthetist), and pulse oximetry. Anaesthesia was performed by experienced anaesthetists with more than 2 yr of training.

The patients were assigned randomly (by lot) to one of two treatment groups for the first phase of anaesthesia. Group A patients were anaesthetized by manual adjustment of the concentration of isoflurane. Group B patients were anaesthetized with an automatic feedback control system to adjust the end-tidal isoflurane concentration.

The anaesthetist was asked to make four step changes of the target end-tidal isoflurane concentration, either manually or by setting the target value for the feedback controller, after the beginning of surgery. The anaesthetists were in a realistic clinical situation and had to make the changes as best they could while fulfilling other clinical tasks. Before the first step change and after each subsequent step, an equilibration period of approximately 10 min was allowed so that a constant end-tidal concentration could be maintained. The end-tidal target concentration was increased in two steps (+0.3 and +0.6 vol%) and decreased in two steps (–0.3 and –0.6 vol%).

The sequence of the four step changes was chosen by the anaesthetist according to clinical needs and anticipated surgical stimulation, but the chosen step had to be sustained for a minimum time of 10 min. If the mean arterial blood pressure decreased by more than 20% after an increasing step-change, a single dose of ephedrine (5 mg i.v.) was allowed or an equivalent decreasing step-change of the end-tidal isoflurane concentration was sought. If the mean arterial pressure increased by more than 20% after a decreasing step change, additional fentanyl (1–2 μg kg^{-1}) was given.

After this first phase of four step changes, the method of adjusting the end-tidal isoflurane concentration was changed to the other method for a second phase, i.e. patients randomized to Group A (manual control) were now assigned to the automatic feedback control system for the next four step changes, and vice versa for Group B patients.

After a total of eight changes, the study finished and control continued with the second method. All the changes were made within the first 2 h of surgery. All changes were within a range of 0.3–1.2 vol% of the end-tidal isoflurane concentration.

Anaesthesia was induced with fentanyl (2 μg kg^{-1}) and thiopental (3–5 mg kg^{-1}). The trachea was intubated after muscle relaxation with vecuronium (0.1 mg kg^{-1}). Additional doses of vecuronium were given to maintain 0–2 responses of TOF stimulation at the ulnar nerve. After tracheal intubation, controlled ventilation was adjusted to maintain the end-tidal carbon dioxide at 4.5% (fixed respiratory rate of 10 per min, tidal volume variable), and anaesthesia was maintained with 70% N_2O in oxygen, isoflurane and boluses of fentanyl (1–2 μg kg^{-1}) as necessary.

After tracheal intubation, the fresh gas flow was set to 6 litre min^{-1}. Ten minutes later the flow was reduced to 1 litre min^{-1} and at the end of the surgery it was reset to 6 litre min^{-1} in both groups. The control system was started after the beginning of the operation. An equilibration period of 10 min was allowed for initialization of the controller before step changes of the end-tidal isoflurane concentration were undertaken. The sampling frequency for data collection was 10 per min, corresponding to a respiratory rate of 10 per min.

The control system

We used the Cicero workstation (Drägerwerke, Germany) with an isoflurane vaporizer (Dräger Vapour 19.3). It is able to monitor the following values: ECG, arterial pressure, pulse oximetry and sidestream measurements of oxygen, nitrous oxide, isoflurane and other inhalation agents. For safety reasons, isoflurane, nitrous oxide and oxygen concentrations were also measured with a sidestream anaesthetic gas analyser (Datex Capnomac; AVL, Switzerland). Both sampling lines were connected to a stopcock at the breathing filter (HME filter, nos 22 and 25; PALL, Switzerland) fitted to the endotracheal tube. All analysers were calibrated before use, according to the instructions of the manufacturers.

The end-tidal controller is a model-based state feedback controller (see Appendix A), uses two input signals (end-tidal and inspiratory isoflurane concentrations) and produces one output signal—the isoflurane concentration in the fresh gas supply, i.e. the vaporizer setting. The Dräger 19.3 vaporizer is adjusted by an external servo-motor. The servo-motor itself is driven by an analogue amplifier controlled by a PID (Proportional Integral Derivative; for explanation see

Appendix A), which in turn is controlled by a conventional electronic interface. The vaporizer and the PID control system are calibrated so that known concentrations are delivered in response to the input voltage. Two Hi-Tech (Bronkhorst Hi-Tech, Ruurlo, Netherlands) nitrous oxide and oxygen mass flow controllers are used to supply a precise flow of gases. They are able to deliver gas flows between 0 and 10 litre min^{-1} with $\pm 1\%$ accuracy. The anaesthetist can control the feedback system with a touchscreen panel. This panel has buttons for the selection of the end-tidal isoflurane concentration and the fresh gas flow. The Cicero vaporizer and flowmeters are bypassed when the feedback control system is operating. However, the anaesthetist can revert to manual control at any time.

The control algorithms are implemented on a VME-board power PC using the real-time programming language XOberon (Institute of Robotics, Swiss Federal Institute of Technology, Zurich, Switzerland). Dedicated parts of the program are used to send data for display and storage to a standard PC via an Ethernet link.

Table 1 Patient characteristics and duration of surgery. Values are mean (SD)

	Group A: manual control first	**Group B: automatic control first**
Sex		
Male	7	5
Female	4	6
Age (yr)	40.18 (19–68)	53.64 (31–75)
Weight (kg)	75.64 (17.33)	70.36 (14.35)
Duration of surgery (min)	233.64 (121.94)	204.09 (63.95)

Data analysis

The control of the end-tidal isoflurane concentration was judged by comparing the step changes of the target end-tidal isoflurane concentration under the two modes of control (manual/automatic feedback), using the following performance criteria (Tables 2 and 3).

1. Response time: time to reach the target value:

(a) increasing step change: time to reach the target value, from 10 to 90% of the step height (e.g. for an increasing step change of 0.6%, from 0.5 to 1.1%, the response time would be defined as the time to reach 1.04% from 0.56%);

(b) decreasing step change: time to reach the target value, from 10 to 90% of the step height (e.g. for a decreasing step change of 0.3%, from 0.8 to 0.5%, the response time would be defined as the time to reach 0.53 from 0.77%).

2. Maximal overshoot/undershoot: maximum amount the system overshoots or undershoots its target value, expressed as a percentage of the step height. Observation starts after the target value has been reached for the first time.

3. Stability: deviation of the measured end-tidal isoflurane concentration from the target value, expressed as percentage frequency distributions of the deviation (measured minus desired) of the end-tidal isoflurane concentration. Observation starts after the target value has been reached for the first time.

The number of changes of the vapour setting ($\geqslant$0.05 vol%) was also recorded.

Numerical variables in the two groups were compared by the paired *t*-test when data were normally distributed, otherwise the Wilcoxon signed rank test was used. A P value <0.05 was considered statistically significant. The statistical package used was Sigma Stat, version 2.0 (Jandel Corporation, San Rafael, California, USA).

Table 2 Increasing step changes of F_E. Values are mean (SD). The sampling frequency for data collection was 10 per min, corresponding to a respiratory rate of 10 per min. Response time=time to reach the target value, from 10 to 90% of the step height. Maximum overshoot=maximum amount the system overshot its target value, expressed as a percentage of the step height. Stability=deviation of the measured end-tidal isoflurane concentration from the target value, expressed as percentage frequency distributions of the deviation (measured minus desired) of the end-tidal isoflurane concentration. *$P<0.05$

	Intended +0.3 vol% step change		**Intended +0.6 vol% step change**	
	Automatic control	**Manual control**	**Automatic control**	**Manual control**
Response time (s)	116 (20)*	71 (34)*	149 (32)*	205 (57)*
Maximal overshoot (%)	19.8 (3.7)*	30.7 (13.2)*	14.7 (3.7)	18 (8.1)
Number of changes of vapour setting	49.9 (7.4)*	14.7 (13.9)*	66.3 (11.9)*	14.4 (7.7)*

Table 3 Decreasing step changes of F_E. Values are mean (SD). The sampling frequency for data collection was 10 per min, corresponding to a respiratory rate of 10 per min. *$P<0.05$

	Intended –0.3 vol% step change		**Intended –0.6 vol% step change**	
	Automatic control	**Manual control**	**Automatic control**	**Manual control**
Response time (s)	248 (169)	320 (260)	485 (230)	492 (190)
Maximal overshoot (%)	9.5 (3.3)*	14.2 (6.3)*	4.8 (1.7)*	7.2 (4.1)*
Number of changes of vapour setting	20.2 (14.3)*	8.7 (6.2)*	12.7 (7.7)	9.6 (4.1)

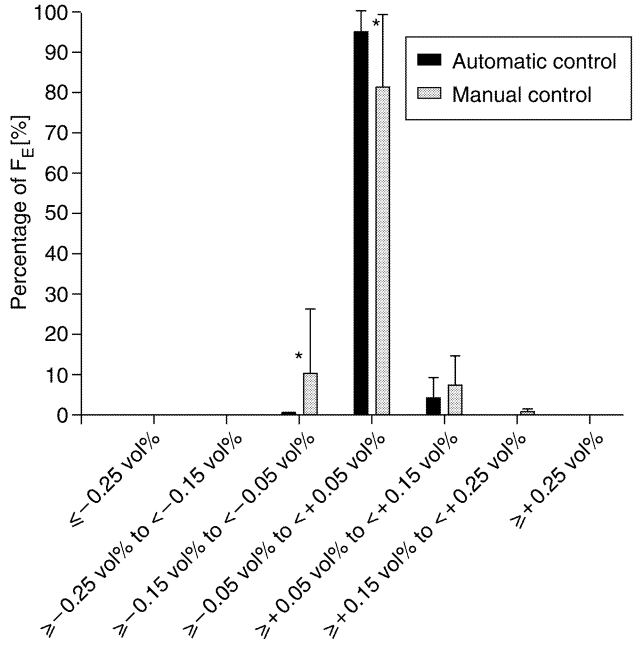

Fig 1 Target increases of +0.3 vol%. Stability of control obtained with manual control (shaded bars) and automatic control (black bars). The distribution histogram shows the proportion of samples that deviated from the intended value by increasing amounts. Mean and SD in each column. *P<0.05.

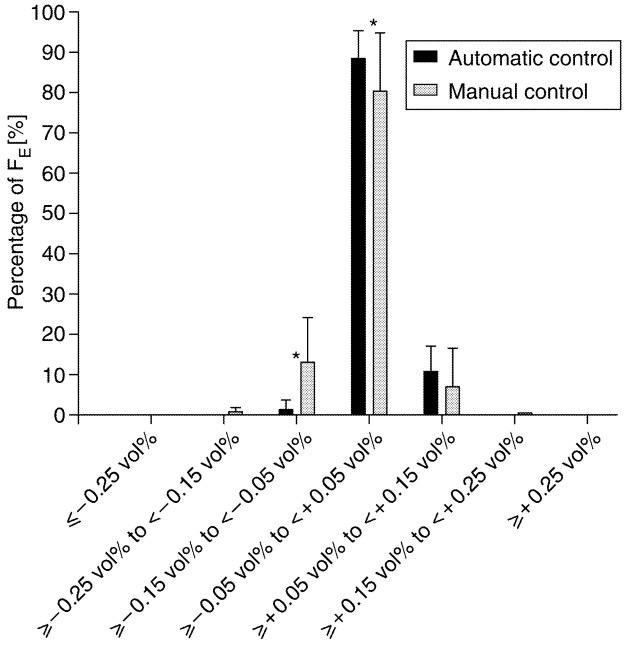

Fig 2 Target increases of +0.6 vol%. Stability of control obtained with manual control (shaded bars) and automatic control (black bars). The distribution histogram shows the proportion of samples that deviated from the intended value by increasing amounts. Mean and SD in each column. *P<0.05.

Results

The two groups were similar with respect to sex, age, weight and duration of surgery (Table 1).

In both groups, two patients had only one series of step changes because the operation finished early. The remaining 18 patients were studied after the protocol, i.e. they all had four step changes performed in the manual and in the automatic mode. Therefore, a total of 80 step changes were analysed in each group.

The performance of the feedback control was superior to that of the manual control in terms of overshoot and stability, with increasing as well as decreasing step changes (Tables 2 and 3 and Figs 1, 2, 3 and 4). The response time for the increasing step changes was shorter in the automatic mode for the larger steps only; for the smaller steps it was shorter in the manual mode. The response time for the decreasing step changes did not differ statistically between the two groups.

The automatic control of the end-tidal isoflurane concentration resulted in higher numbers of changes of the vapour setting, for increasing as well as decreasing step changes (only with decreasing steps of 0.6 vol% was the difference not statistically significant).

We observed a total of 19 artefacts during the automatic control mode. These artefacts were caused by the calibration process and were all handled successfully by the end-tidal controller. Figure 5 shows an untreated artefact during a pilot study. Figure 6 shows a suppressed artefact in a study patient.

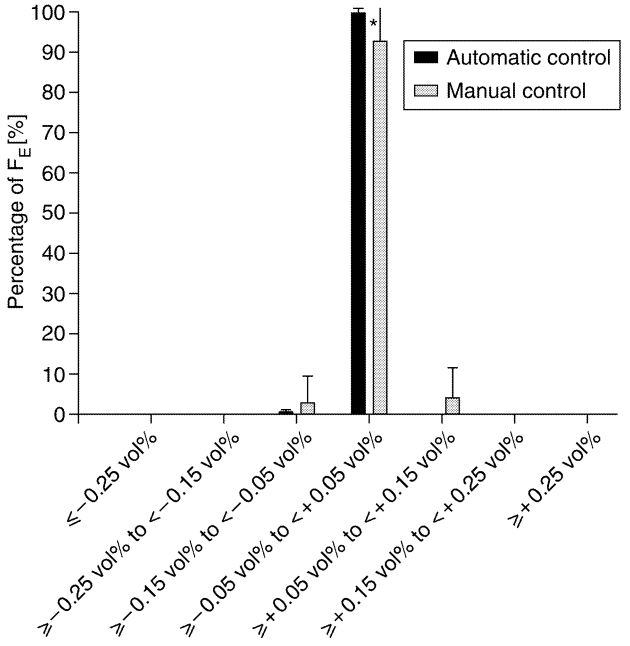

Fig 3 Target decreases of –0.3 vol%. Stability of control obtained with manual control (shaded bars) and automatic control (black bars). The distribution histogram shows the proportion of samples that deviated from the intended value by increasing amounts. Mean and SD in each column. *P<0.05.

One patient in Group A and two patients in Group B required ephedrine to treat a decrease in mean arterial blood pressure of more than 20%.

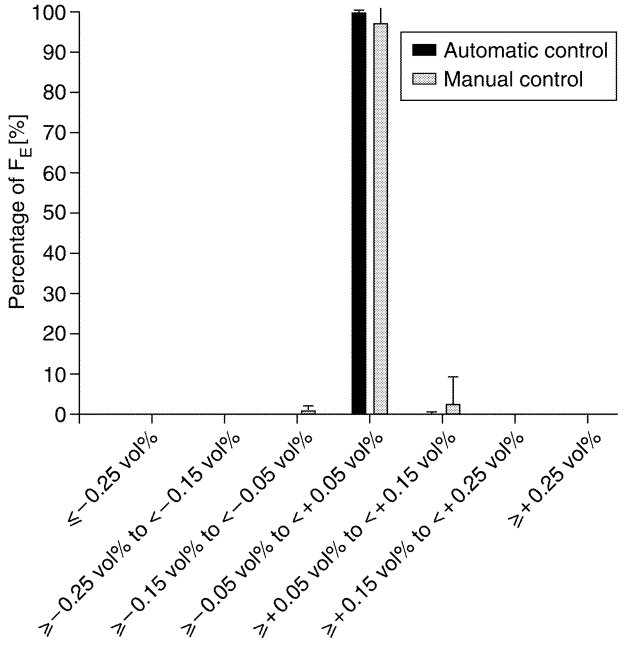

Fig 4 Target decreases of –0.6 vol%. Stability of control obtained with manual control (shaded bars) and automatic control (black bars). The distribution histogram shows the proportion of samples that deviated from the intended value by increasing amounts. Mean and SD in each column.

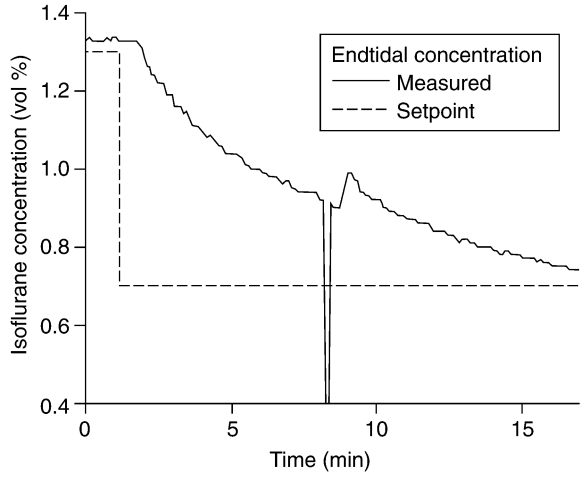

Fig 5 Example of an untreated calibration artefact, occurring during a decreasing step change in a pilot study. Because of the artefact, the end-tidal controller overshot the target value for a short period.

Discussion

The automatic control system of end-tidal isoflurane was generally faster, more stable and more accurate than human control.

The response time for increasing step changes was faster with automatic control than with manual control except for the small (+0.3 vol%) step changes. The slower response time of the automatic control for the small step changes was caused by the control algorithm, which only allowed a stepwise increase in the vaporizer setting, whereas with manual control the vaporizer setting was often immediately turned up to the maximum position. In a control system, there is a trade-off between the response time and the overshoot/stability of control. We judged that stability and accuracy of control should have priority over speed. Nevertheless, for the larger increasing step changes, the automatic control was faster and more reliable. With decreasing step changes there was no difference in the response time of the two modes. This is no surprise, as the rate of decrease of the end-tidal isoflurane concentration is determined by patient uptake and cannot be influenced directly unless the fresh gas flow is adjusted.

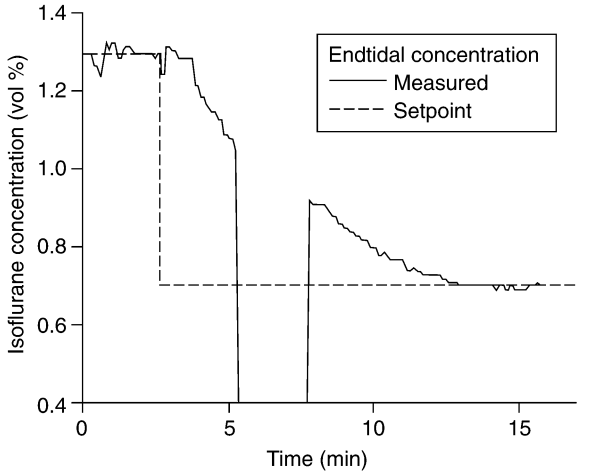

Fig 6 Example of the successful suppression of a calibration artefact, occurring during a decreasing step change in a study patient. Despite a prolonged calibration process, of approximately 2 min, the end-tidal isoflurane controller was not disturbed by the temporary lack of incoming data and the end-tidal isoflurane concentration slope continued to fall as if no data loss had occurred.

Stability and accuracy are the important clinical features of an automatic control system. Large changes in the control variable can either jeopardize the patient by an overdose or expose the patient to the risk of awareness. The clinical significance of the better performance of the automatic controller lies in the more reliable avoidance of minimal and maximal values of the control variable, whereas in the mid-range it does not make a great difference.

The model used in this study, with its 12 physiological compartments, is fairly complex. A less complex model derived from input/output measurements, like the one described by Yasuda and colleagues,[11] could perhaps give similar results. However, we plan to extend the automatic control application to children and less fit patients, for whom physiologically based models are easier to adjust to specific patient characteristics.

Complex control systems should reduce work and increase safety, but they will not do so in all situations or circumstances. An important safety issue is the handling of artefacts. Measurement artefacts can degrade controller performance or lead to hazardous situations for the patient.

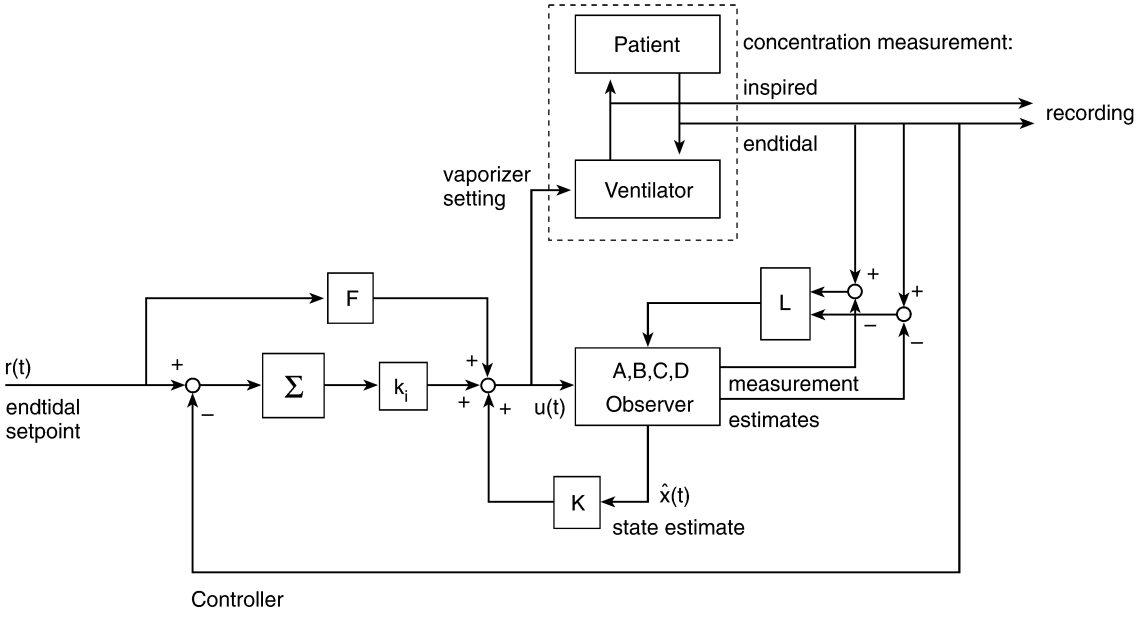

Fig 7 Structure of the model-based feedback controller. It consists of three components: an observer (with the state feedback K and the correction gain L), the integrator **Σ** and the feedforward term F.

Artefacts are quite common in clinical practice—for example, kinking of the gas sample tube. In our case, non-linear weighting of the error signal was used to make the model-based control algorithms tolerant of measurement artefacts.[12] When activated, the controller was able to suppress the influence of any artefact that occurred during the study.

Efforts to reduce the cost of inhalation agents by encouraging clinicians to use low fresh gas flows have not been very successful in the long term,[13 14] mostly because of lack of continued feedback. Carefully constructed practice guidelines seem to be promising,[15 16] but they can be difficult to introduce and are not in widespread use. A feedback control system for the end-tidal concentration of an inhalation agent would encourage low-flow systems and could be cost-effective.

Human control and intervention are still required to specify the appropriate depth of anaesthesia and to respond to crises. However, liberating the anaesthetist from those tasks that can be automated should improve safety by allowing the anaesthetist more time for other aspects of anaesthesia care.

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Appendix A

Model-based state feedback controller (Fig. 7)

Linear dynamic systems may be described by differential equations of the form

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

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

where $\mathbf{x}(t)$ is the state vector, $\dot{\mathbf{x}}(t)$ is the time derivative of $\mathbf{x}(t)$, $u(t)$ is the control input and $\mathbf{y}(t)$ is the measurement output. In our case, $\mathbf{x}(t)$ represents the partial pressure in the different body compartments and the breathing system and $u(t)$ represents the vaporizer position: $\mathbf{y}(t)$ is a vector composed of the measurements of inspired and expired isoflurane concentrations. The coefficients **A**, **B**, **C** and **D** are constant matrices. For details of the model, see Appendix B. Linear systems are idealizations since most real-world dynamic processes, and in particular physiological processes, are non-linear. However, most non-linear systems can be approximated by linear systems in a narrow working range. Even with larger working ranges it is often possible to achieve good controller performance with controller designs based on linearizations. The term 'state feedback' is used to describe a control algorithm in which the control signal is computed as a linear combination of various system states. Mathematically, the relationship between the controller output and the system states can be written as

$$u = -\mathbf{K}\mathbf{x}(t)$$

where **K** is again a constant matrix. This generic model-based state feedback controller is augmented with a feedforward term (F) and an integrator (Σ).[17 18] The feedforward term accounts, for example, for the steady-state vaporizer position required to achieve a certain end-tidal target value. The integral term mainly compensates for modelling errors. Through these modifications, the state

feedback control algorithm has some similarities to a classical PID controller. In such a controller, the control action has three components: (i) an action which is proportional (hence 'P') to the error between the set point and the system output; (ii) an action proportional to the integral (hence 'I') of this error; and (iii) an action that is proportional to the derivative (hence 'D') of this error. In the case of the augmented state feedback controller, the feedforward term (F) plays an analogous role as the P part. The integral term acts identically in both types of controller. The state feedback acts like a derivative term. The important difference is that it does not introduce just first-order derivative action but rather derivatives up to an order equal to the number of states in the state vector $\mathbf{x}(t)$. This makes it possible to design considerably more aggressive controllers.

Because in most cases the states of the system (e.g. the partial pressure of isoflurane within an organ) cannot be measured, an 'observer' (parallel model of the system to be controlled) is used to compute an estimate of the states ($\hat{\mathbf{x}}(t)$). This state estimate is then used in the control algorithm instead of the actual state. The state estimates usually differ from the true states because an observer cannot fully describe the reality and the initial conditions are not known precisely. To achieve fast convergence of the state estimates towards the true states, a correction gain (L) is introduced. This gain leads to correction of the state estimates based on the difference between the measurements and the predictions of the parallel model. Note that in our case the measurements refer to the measurement vector $\mathbf{y}(t)$, which contains the inspired as well as the end-tidal isoflurane concentration measurement. Typically, L is a constant gain which must be chosen so that the rate of convergence of the state estimation is faster than the desired response of the controller. Using a non-linear-modified gain, however, artefacts can be rejected easily.[12]

Appendix B

Model

The pharmacokinetic and pharmacodynamic model description was obtained by adjusting the compartmental model for halothane described by Smith and colleagues[19] to isoflurane and by augmenting it with a dynamic representation of the respiratory circuit. The adjustment to isoflurane was done by means of published isoflurane partition coefficients.[20] The physiological model part describes the time-course of the partial pressure of isoflurane in 12 body compartments. Nine compartments represent different organs grouped according to their pharmacokinetic properties with respect to isoflurane. One compartment represents the gas exchange in the lung, and an arterial and a venous compartment are introduced to interconnect the lung and the body compartments. Together with the equation for the anaesthetic partial pressure in the respirator circuit, the state vector $\mathbf{x}(t)$ is derived as follows:

$$\mathbf{x}(t) = [p_1(t) \ \ldots \ p_9(t) \ p_{Lung}(t) \ p_{Art}(t) \ p_{Ven}(t) \ p_{Resp}(t)].$$

The dynamics of the pressure in a body compartment is described by

$$\dot{p}_i(t) = \frac{\lambda_b q_i(t)}{\tilde{V}_i}[p_{Art}(t) - p_i(t)]$$

where λ_b is the solubility of isoflurane in blood, $q_i(t)$ is the blood flow through the compartment, and $\tilde{V}_i$ is a virtual distribution volume obtained as the sum of the blood and tissue volumes of the compartment, weighted with their respective solubilities. The partial pressure dynamics in the lung is given by

$$\dot{p}_{Lung}(t) = \frac{1}{\tilde{V}_{Lung}}[\lambda_b CO(t)\{p_{Ven}(t) - p_{Lung}(t)\} + q_{AV}\{p_{Resp}(t) - p_{Lung}(t)\}]$$

where $CO(t)$ is cardiac output and q_{AV} is the alveolar ventilation, which is given by

$$q_{AV} = f_R(V_A - V_{AD})$$

where f_R is the respiratory frequency.

The equation for the arterial partial pressure is

$$\dot{p}_{Art}(t) = \frac{\lambda_b CO(t)}{\tilde{V}_{Art}}[l_s p_{Ven}(t) + (1 - l_s)p_{Lung}(t) - p_{Art}(t)]$$

where l_s is the shunt in the lung. The venous partial pressure is

$$\dot{p}_{Ven}(t) = \frac{\lambda_b}{\tilde{V}_{Vent}}[\sum q_i(t)p_i(t) - CO(t)p_{Ven}(t)].$$

The above equations suggest that $CO(t)$ and $q_i(t)$ are measurable as time evolves. This is not the case. Pharmacodynamic relations are used instead to compute these quantities. The corresponding equations are

$$CO(t) = CO_0(1 + \alpha_1 p_1 + \alpha_2 p_2 + \alpha_3 p_{Art})$$

for the cardiac output and

$$g_i(t) = g_{i,0}(1 + \beta_i p_i)$$

for the conductivities of the different body compartments, from which $q_i(t)$ may be computed.

Finally, the dynamic equation of the respirator circuit is given by

$$\dot{p}_{Resp}(t) = \frac{FF}{V_R}p_{Vap}(t) + q_{AV}[p_{Lung}(t) - p_{Resp}(t)] - \frac{FF - \Delta(t)}{V_R}p_{endt}(t)$$

where FF is the fresh gas flow, V_R is the circuit volume, $p_{Vap}(t)$ is the vaporizer setting, and $\Delta(t)$ is the net uptake of

gas. The quantities FF and $p_{Vap}(t)$ are known because they are set, and $\Delta(t)$ is available from the literature.[21] $p_{endt}(t)$ is the end-tidal concentration, and is given by

$$p_{endt}(t) = \frac{V_{AD}}{V_A} p_{Resp}(t) + \left(1 - \frac{V_{AD}}{V_A}\right) p_{Lung}(t)$$

where V_A is the total alveolar space and V_{AD} is the alveolar deadspace. For the design of the controller, linearizations of these equations yield the system matrices **A**, **B**, **C** and **D**. To give a more detailed description of the model in terms of parameters and validations is beyond the scope of this appendix. The interested reader is referred to reference 22 for such details.

References

1 O'Hara DA, Bogen DK, Noordergraaf A. The use of computers for controlling the delivery of anesthesia. *Anesthesiology* 1992; **77**: 563–81

2 Fukui Y, Smith NT, Fleming RA. Digital and sampled-data control of arterial blood pressure during halothane anesthesia. *Anesth Analg* 1982; **61**: 1010–5

3 Meier R, Nieuwland J, Zbinden AM, Hacisalihzade SS. Fuzzy logic control of blood pressure during anesthesia. *IEEE Control Syst* 1992; **12**: 12–7

4 Zbinden AM, Feigenwinter P, Petersen-Felix S, Hacisalihzade S. Arterial pressure control with isoflurane using fuzzy logic. *Br J Anaesth* 1995; **74**: 66–72

5 Dale O, Dale T. Anesthetic gases, the ozone layer and the greenhouse effect. How harmful are the anesthetic emissions for the global environment? *Tidsskr Nor Laegeforen* 1991; **111**: 2115–7

6 Langbein T, Sonntag H, Trapp D, Hoffmann A, Malms W, Roth EP, *et al*. Volatile anaesthetics and the atmosphere: atmospheric lifetimes and atmospheric effects of halothane, enflurane, isoflurane, desflurane and sevoflurane. *Br J Anaesth* 1999; **82**: 66–73

7 Cotter SM, Petros AJ, Doré CJ, Barber ND, White DC. Low-flow anaesthesia. *Anaesthesia* 1991; **46**: 1009–12

8 Mortier E, Struys M, De Smet T, Versichelen L, Rolly G. Closed-loop controlled administration of propofol using bispectral analysis. *Anaesthesia* 1998; **53**: 749–54

9 Westenskow DR, Zbinden AM, Thomson DA, Kohler B. Control of end-tidal halothane concentration. Part A: *Anaesthesia* breathing system and feedback control of gas delivery. *Br J Anaesth* 1986; **58**: 555–62

10 Westenskow DR, Jordan WS, Hayes JK. Feedback control of enflurane delivery in dogs—inspired compared to end-tidal control. *Anesth Analg* 1983; **62**: 836–40

11 Yasuda N, Lockhart SH, Eger EI, Weiskopf RB, Johnson BH, Freire BA, *et al*. Kinetics of desflurane, isoflurane and halothane in humans. *Anesthesiology* 1991; **74**: 489–98

12 Frei CW, Bullinger E, Gentilini A, Glattfelder AH, Sieber TJ, Zbinden AM. Artifact tolerant controllers for automatic drug delivery in anesthesia. *Crit Rev Biomed Eng* 1998; **26**: 331–2

13 Johnstone RE, Jozefczyk KG. Costs of anesthetic drugs: experiences with a cost education trial. *Anesth Analg* 1994; **78**: 766–71

14 Body SC, Fanikos JR, DePeiro D. Individualized feedback of volatile agent use reduces fresh gas flow rate, but fails to favorably affect agent choice. *Anesthesiology* 1999; **90**: 1171–5

15 Szocik JF, Learned DW. Impact of a cost containment program on the use of volatile anesthetics and neuromuscular blocking drugs. *J Clin Anesth* 1994; **6**: 378–82

16 Lubarsky DA, Glass PSA, Ginsberg B. The successful implementation of pharmaceutical practice guidelines. *Anesthesiology* 1997; **86**: 1145–60

17 Franklin GF, Powell JD, Emami-Naeini A. *Feedback Control of Dynamic Systems*. Reading, Massachusetts: Addison-Wesley, 1994; 778

18 Kailath T. *Linear Systems*. Englewood Cliffs, New Jersey: Prentice Hall, 1980; 682.

19 Smith NT, Zwart A, Beneken JEW. Interaction between the circulatory effects and the uptake and distribution of halothane: use of a multiple model. *Anesthesiology* 1972; **37**: 47–58

20 Zbinden AM. Pharmacokinetics of inhaled anaesthetics. *Baillière's Clin Anaesthesiol* 1991; **5**: 543–66

21 Baum J. *Die Narkose mit Frischgasfluss*. Bibliomed–Medizinische Verlagsgesellschaft, 1993

22 Frei CW. *Fault Tolerant Control Concepts Applied to Anesthesia*. PhD thesis, Swiss Federal Institute of Technology, 2000