Feasibility of Closed-loop Titration of Propofol and Remifentanil Guided by the Spectral M-Entropy Monitor

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ABSTRACT

Background: This randomized controlled trial describes automated coadministration of propofol and remifentanil, guided by M-Entropy analysis of the electroencephalogram. The authors tested the hypothesis that a novel dual-loop controller with an M-Entropy monitor increases time spent within predetermined target entropy ranges.

Methods: Patients scheduled for elective surgery were randomly assigned in this single-blind study using a computer-generated list, to either dual-loop control using a proportional-integral-derivative controller or skilled manual control of propofol and remifentanil using target-controlled-infusion systems. In each group, propofol and remifentanil administration was titrated to a state entropy target of 50 and was subsequently targeted to values between 40 and 60. The primary outcome was the global score, which included the percentage of state entropy or response entropy in the range 40–60, the median absolute performance error and wobble. Data are presented as medians [interquartile range].

Results: Thirty patients assigned to the dual-loop group and 31 assigned to the manual group completed the study. The dual-loop controller was able to provide induction and maintenance for all patients. The Global Score of State Entropy was better maintained with dual-loop than manual control (25 [19–53] *vs.* 44 [25–110], $P = 0.043$), and state entropy was more frequently maintained in the range of 40–60 (80 [60–85] *vs.* 60 [35–82]%, $P = 0.046$). Propofol (4.1 [2.9–4.9] *vs.* 4.5 [3.4–6.3] $mg \cdot kg^{-1} \cdot h^{-1}$) and remifentanil (0.18 [0.13–0.24] *vs.* 0.19 [0.15–0.26] $\mu g \cdot kg^{-1} \cdot min^{-1}$) consumptions and the incidence of somatic side effects were similar.

Conclusion: Intraoperative automated control of hypnosis and analgesia guided by M-Entropy is clinically feasible and more precise than skilled manual control.

What We Already Know about This Topic

- The use of electroencephalography to guide anesthetic administration remains controversial
- M-Entropy analysis provides dual analyses with differential sensitivities to hypnosis and analgesia

What This Article Tells Us That Is New

- Intraoperative automated propofol-remifentanil anesthesia guided by M-Entropy is clinically feasible and more precise than skilled manual control

IN 1950, Mayo *et al.* reported that electrocortical activity could be used to automatically titrate ether administration.[1] Subsequently, various signals including the median frequency of the electroencephalogram power spectrum[2] and

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auditory evoked potentials[3] have been used to guide automated administration of methohexital,[2] propofol,[3,4] or alfentanil.[5] Currently, the Bispectral Index Monitor (BIS Monitor, Aspect Medical Systems, Newton, MA) is the best-studied electroencephalographic monitor for the single feedback control of propofol[6–19] or remifentanil.[20]

M-Entropy analysis of the electroencephalogram (GE Healthcare, Helsinki, Finland) calculates two parameters. The first is state entropy (SE), a measure of the irregularity of frontal electroencephalogram activity within the frequency range of 0.8–32 Hz. SE is a surrogate measure of hypnotic depth and can identify varying levels of sedation[21] and predict volunteers' ability to recall auditory stimuli.[22] The second parameter, response entropy (RE), measures electroencephalogram and facial muscle electromyogram activity with a frequency range of 0.8–47 Hz.[23,24] The difference between RE and SE represents frequencies within the band between 32 and 47 Hz, corresponding to facial muscle electromyogram activity. During painful stimuli, an increase in RE above SE facial muscle activation may thus indicate that analgesia is inadequate[25] because facial muscle activity is a surrogate measure of depth of antinociception.[26] The fact that M-Entropy analysis provides distinct indications of hypnotic and analgesic status makes it a potential output for a previously developed dual closed-loop proportional-integral-derivative controller.[20]

Therefore, we used our dual-loop system to control administration of propofol and remifentanil using M-Entropy SE and RE. We compared manual *versus* closed-loop control during general anesthesia induction and maintenance. Specifically, we tested the hypothesis that the dual-loop controller with M-Entropy as output increases time spent within predetermined target SE and RE ranges.

Materials and Methods

Our prospective, randomized, single-blind clinical trial was approved by the Ethics Committee of our university (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Hôpital A. Paré, N°06 06 59, Boulogne Billancourt, France) and the relevant French regulatory office (Agence Française de Sécurité Sanitaire des Produits de Santé). It was registered with ClinicalTrials.gov, file number NCT00391885. The study was conducted in a single university hospital (Hôpital Foch, Suresnes France). Patients were informed of the nature of the study and gave their written informed consent during the preoperative visit performed by the investigators. Inclusion criteria were patients age 18–80 yr presenting for elective surgical procedures (lung, vascular, orthopedic, gynecologic, urologic, and otolaryngologic). Exclusion criteria were combined regional/general anesthesia, a history of psychiatric and/or neurologic disorder, presence of a pacemaker, or planned intracranial surgery.

Protocol

An intravenous cannula dedicated to propofol and remifentanil infusion pumps was connected *via* a three-way Smartsite® Needle-Free System (Alaris Medical Systems, San Diego, CA) with a priming volume of 0.3 ml to the pumps. Routine monitoring included core temperature and neuromuscular function at the adductor pollicis. The Entropy electrode was positioned on the patient's forehead and connected to the M-Entropy Module (GE-Healthcare, Helsinki, Finland). Just before induction of general anesthesia, patients were randomly assigned to the dual-loop controller or to skilled manual control based on the M-Entropy Module. The sequence of treatments was determined in blocks of 10 (five dual-loop and five manual group) using a random number computer-generator in a 1:1 ratio. Assignments were kept in sequentially numbered opaque envelopes until just before surgery. Investigators had considerable clinical experience titrating intravenous anesthesia using the spectral entropy monitor and target-controlled infusion systems.

All patients received total intravenous anesthesia in target-controlled Infusion mode using the population pharmacokinetic sets of Schnider *et al.*[27] for propofol and Minto *et al.*[28] for remifentanil to target the effect-site concentration. Infusion Toolbox 95 version 4.11 software[29] (Université Libre de Bruxelles, Brussels, Belgium) implemented in a personal computer served as a platform for calculating effect-site concentrations of propofol and remifentanil; displaying effect-site concentration estimates in real time; providing a user interface that permits entry of patients' demographic data (sex, age, weight, and height) and modifications to target concentrations; controlling the propofol and remifentanil infusion pumps (Alaris Medical, Hampshire, United Kingdom); and recording calculated effect-site drug concentrations, entropy, and hemodynamic data from an AS/5 GE-Healthcare S/5™ monitor at 5-s intervals.

In the manual group, clinicians chose propofol and remifentanil effect-site concentrations for induction according to their clinical judgment. During maintenance, anesthetic agents were adjusted to maintain a SE value as close to 50 as practical. Remifentanil was given to maintain the RE value between 40 and 60 or to avoid a difference between RE and SE more than 5. As clinically necessary, anesthesiologists could modify the drug target concentration once 95% equilibration of the effect site compartment was reached without the constraint of upper or lower limits for the two agents.

For the dual-loop group, the controller has a cascade structure with a proportional-integral-derivative algorithm associated with a target-controlled infusion device as shown in figure 1. This controller was similar to a published controller.[20] Users entered the patient's sex, age, weight, and height. For this study, the user could modify the minimum or the maximum concentration of propofol or remifentanil targets, or switch between dual-loop and manual control. Clinicians chose the initial propofol effect-site concentrations for induction according to their clinical judgment. The

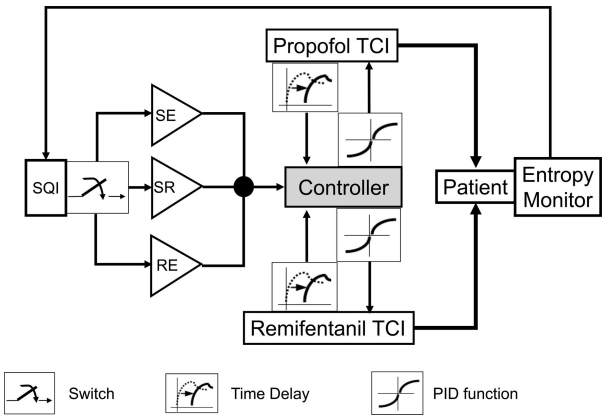

Fig. 1. The controller's main algorithm has a cascade structure including a dual proportional-integral-derivative (PID) and a target-controlled infusion (TCI) system for the administration of intravenous agents. The controller uses the parameters from the M-Entropy monitor, if the signal quality index (SQI) is more than 50%. The controller measures and calculates the error or the difference between the set point = 50 and the measured state entropy (SE), the difference between response entropy (RE) and SE and the percentage of suppression ratio (SR). If the error differs from 0, the controller determines a new propofol and remifentanil concentration proportional to the error with a gain constant or amplification of the feedback specific at each agent, proportional to the size and the sign of the error and specific to level of SE. The agent concentrations and the effect-site delays are calculated using the pharmacokinetic models of Schnider *et al.*[27] and Minto *et al.*[28] for propofol and remifentanil, respectively. The interaction rules between the two drugs avoid an opposite decision of infusion rates (*e.g.*, if the controller increases the propofol concentration then the remifentanil cannot decrease). The feed-forward term amplifies the correction of the two drugs when a measured SE or RE values greater than 60 is detected or the difference RE-SE greater than 5.

controller decides the first remifentanil concentration related to initial propofol concentration. The controller includes several main elements:

1. Calculation of the SE_{error} difference between the set point of 50 and the actual unfiltered SE value: it allows the titration until the target level of SE = 50 is obtained.
2. The "error" size, which determines which drug will be modified. If the SE_{error} is small, only the remifentanil is changed, and if the SE_{error} is higher than a threshold, the two drug concentrations are changed.
3. A proportional correction has been determined for each drug and for each SE_{error}. The controller continuously modifies the target concentration until a $SE_{error} = 0$ is obtained. The new target is modulated by the use of this accumulated error and provides the integral action of the controller.
4. Delay between each new modification of propofol or remifentanil concentration: it is determined by the time necessary for equilibration of the previous effect site compartment given by the pharmacokinetic models[27,28] (fig. 1).
5. A derivative term of the controller: check the profile every 5 s and decide on a rapid concentration correction.
6. Interaction rule between propofol and remifentanil: if the controller increases the remifentanil concentration successively more than three times then the controller increases the propofol concentration.
7. Safety feature: the system automatically maintains the calculated drug concentrations in the case of controller or Entropy dysfunction or low signal quality index less than 50%.

In both groups, the induction phase was defined from the start of propofol and remifentanil administration to SE <60 for 30 s; subsequent times until the end of surgery were considered to be the maintenance phase. Neuromuscular blockers were given to facilitate tracheal intubation followed by continuous or bolus administrations at the discretion of the anesthesiologist during the maintenance phase. Hemodynamic modifications were managed by administration of fluids, vasopressors, or antihypertensives.

Patients were ventilated with an air/oxygen mixture without nitrous oxide. Cardiovascular management, premedication, duration of anesthesia, blood loss, and somatic events (movements, grimacing, eye opening) were recorded. Surgery was classified as minor or major. Approximately 45 min before the scheduled end of surgery, intravenous analgesics were given to provide postoperative pain relief: morphine 0.05–0.15 mg/kg^{-1}, proparacetamol (1 g), nefopam (20 mg), and nonsteroidal antiinflammatory drugs at the discretion of the clinician. A neuromuscular antagonist was given if indicated. At the end of surgery, propofol and remifentanil infusions were stopped. Time to tracheal extubation was defined as the time from discontinuation of the infusions until tracheal extubation. All patients were visited and interviewed about intraoperative recall in the postanesthesia care unit and on the second or third postoperative day.[30]

The primary outcome was the Global Score[11] ($SE_{Global\ Score}$), which characterized the overall performance of the controller including the percentage of adequate anesthesia, defined as SE between 40 and 60 (SE_{40-60}) and oscillation of the SE determined by the median absolute performance error and the wobble.[31] The controller performance and the parameters were calculated according to the following equations:

The performance error, or PE, calculated as the difference between actual and desired values (set point): $PE_{ij} = ((SE_{measuredij} - SE_{set\ point})/SE_{set\ point}) \times 100$; the bias or median performance error (MDPE): $MDPE_i$ = median $[PE_{ij}, j = 1, \ldots, N_i]$; the inaccuracy or median absolute performance error (MDAPE): $MDAPE_i$ = median $[|PE_{ij}|, j = 1, \ldots, N_i]$; the wobble, which measures the intraindividual variability in performance error: $Wobble_i = [|Pe_{ij} - MDPE_i|, j = 1, \ldots, N_i]$, where: i = subject number, j = j^{th} (one) measurement of observation period, n = total number of measurements during observation period. The Global Score was calculated according to the following equation: $^{11}SE_{Global\ Score} = (MDAPE + Wobble)/SE_{40-60}$.

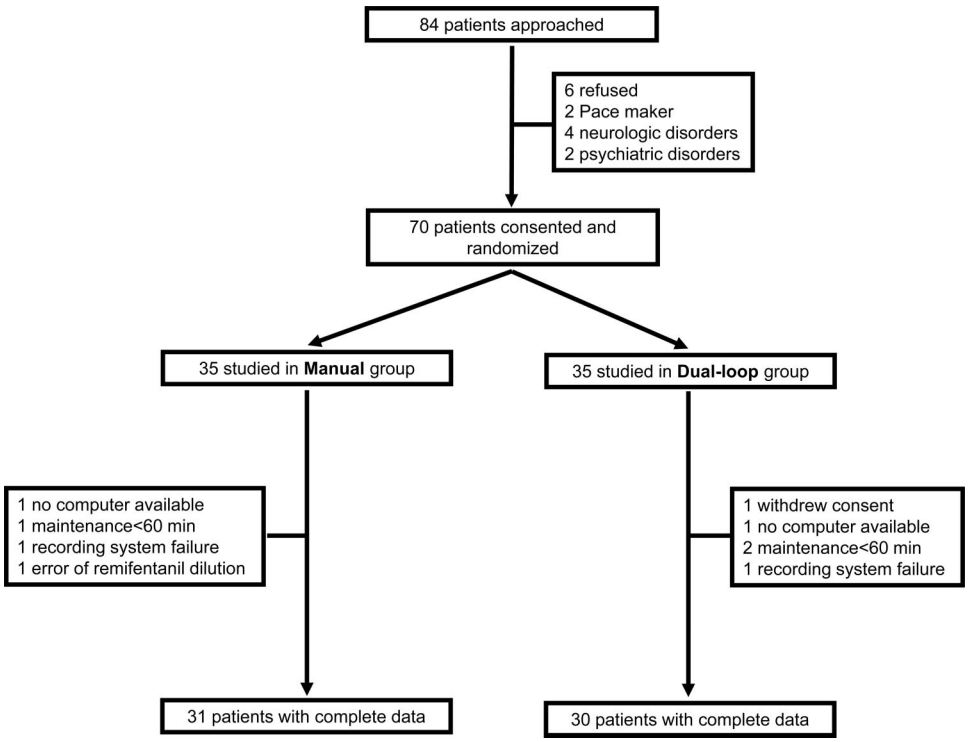

Fig. 2. Trial profile.

Excellent controller performance is characterized by a low median absolute performance error and wobble and high percentage of SE value in the range 40 and 60. Consequently, a low Global Score indicated superior performance.

Secondary outcomes included the percentage of adequate anesthesia, overshoot ($SE_{<40}$) and undershoot ($SE_{>60}$) periods, occurrence of suppression ratio (SR) defined as SR more than 10% lasting at least 1 min, Varvel parameters (PE, median performance error, median absolute performance error, wobble).[31] Secondary outcomes included also clinical data: drug consumption, number of somatic events (*i.e.*, movements, grimacing), time to tracheal extubation (*i.e.*, time from discontinuation of propofol and remifentanil infusions until extubation), and recall of intraoperative events as determined by a standardized interview performed in the postanesthesia care unit and on the second or third postoperative day.[30]

Data Analysis

A preliminary study indicated a mean Global Score for SE was roughly 50 ± 19 using manual propofol and remifentanil target-controlled infusion; we expected an improvement of at least 30% with our dual-loop controller. Based on these values, we estimated that a total of 54 patients (27 per group) would provide an 80% power at 5% two-sided type I error. We thus planned to recruit 70 patients to allow for dropouts. This trial was not overseen by an independent data safety monitoring board.

Data are presented as medians [interquartile ranges], percentages, or number of cases. Continuous data were compared by Mann–Whitney U tests. Categorical data were compared with Fisher exact tests. Difference in heart rate, systolic blood pressure, SE, and RE-SE were evaluated with repeated-measures ANOVA. Speed to tracheal extubation was compared using a Kaplan–Meier survival analysis, followed by a log-rank test. Significance was defined by P values less than 0.05 using a two-tailed test. Data analysis was performed using SPSS version 11.0 (SPSS Science Inc., Chicago, Il).

Results

Seventy patients were recruited between November 2006 and April 2007. Thirty-one patients in the manual group and 30 in the dual-loop group completed the study with useable data (fig. 2). Baseline characteristics were similar in the two groups (table 1). More than a third of the subjects took at least one cardiovascular medication preoperatively. One investigator (F.B.-L.) managed 80% of the patients in the manual group; N.L. and T.C. managed the others. The median SE and RE values from induction to discontinuation of propofol and remifentanil infusion are presented in figure 3.

Anesthetic induction was similar with dual-loop and manual induction (table 2). The dual-loop system maintained anesthesia for a total of 68 h, during which time 1,250 target modifications were made automatically (519 for the propofol and 731 for the remifentanil). In the dual-loop patients, no manual modifications were made. However, the remifentanil upper limit was increased (the maximum default concentration was 12 ng/ml^{-1}) for two patients

Table 1. Characteristics of Patients at Entry

	Manual (n = 31)	Dual-loop (n = 30)	*P* Value
Age (y)	55 [41–70]	56 [36–71]	0.76
Sex ratio (male/female)	16/15	14/16	0.80
Height (cm)	169 [162–177]	171 [160–177]	0.72
Weight (kg)	74 [62–82]	74 [60–83]	0.94
Major surgery	6 (19)	12 (40)	0.10
ASA physical status III–IV	2 (6)	4 (13)	0.42
Cardiovascular medication	9 (29)	12 (40)	0.42

Results expressed as median [interquartile range] or number (%). Cardiovascular medication: β blocker, calcium channel blocker, angiotensin converting enzyme inhibitor, or diuretics.

ASA = American Society of Anesthesiologists; Dual-loop = closed-loop control of propofol and remifentanil; Manual = manual control infusion group guided by the Spectral M-Entropy.

and the propofol lower limit was decreased in three patients (the minimum default concentration was 1.3 $\mu g/ml^{-1}$). Time to tracheal extubation was comparable in the two groups (table 3).

The fraction of time during which SE was adequate, SE_{40-60}, was significantly greater in the Dual-loop group 80% [60–85] than in the Manual group 60% [35–82]. Periods of excessive anesthesia ($SE_{<40}$) were shorter in the Dual-loop group, and the Global Score of SE was better (fig. 3 and table 4). In contrast, RE responses were similar in each group (fig. 3 and table 5). The occurrence of burst suppression ratio (table 4) and the amount administered and the median effect site-concentrations of propofol and remifentanil were similar between the two groups (fig. 3 and table 4).

Heart rate, noninvasive systolic blood pressure, SE, and RE-SE changes in response to stimulating events such as laryngoscopy or skin incision were similar in each group (fig. 4). There were no significant differences in the incidence of somatic events or in treatment of hypotension or hypertension (table 3). No cases of awareness with recall were detected.

Discussion

Despite numerous potential advantages of automated drug delivery, no fully automated system is currently approved or routinely used in anesthesia.[32] In addition, the only commercial automated propofol administration device nearing Food

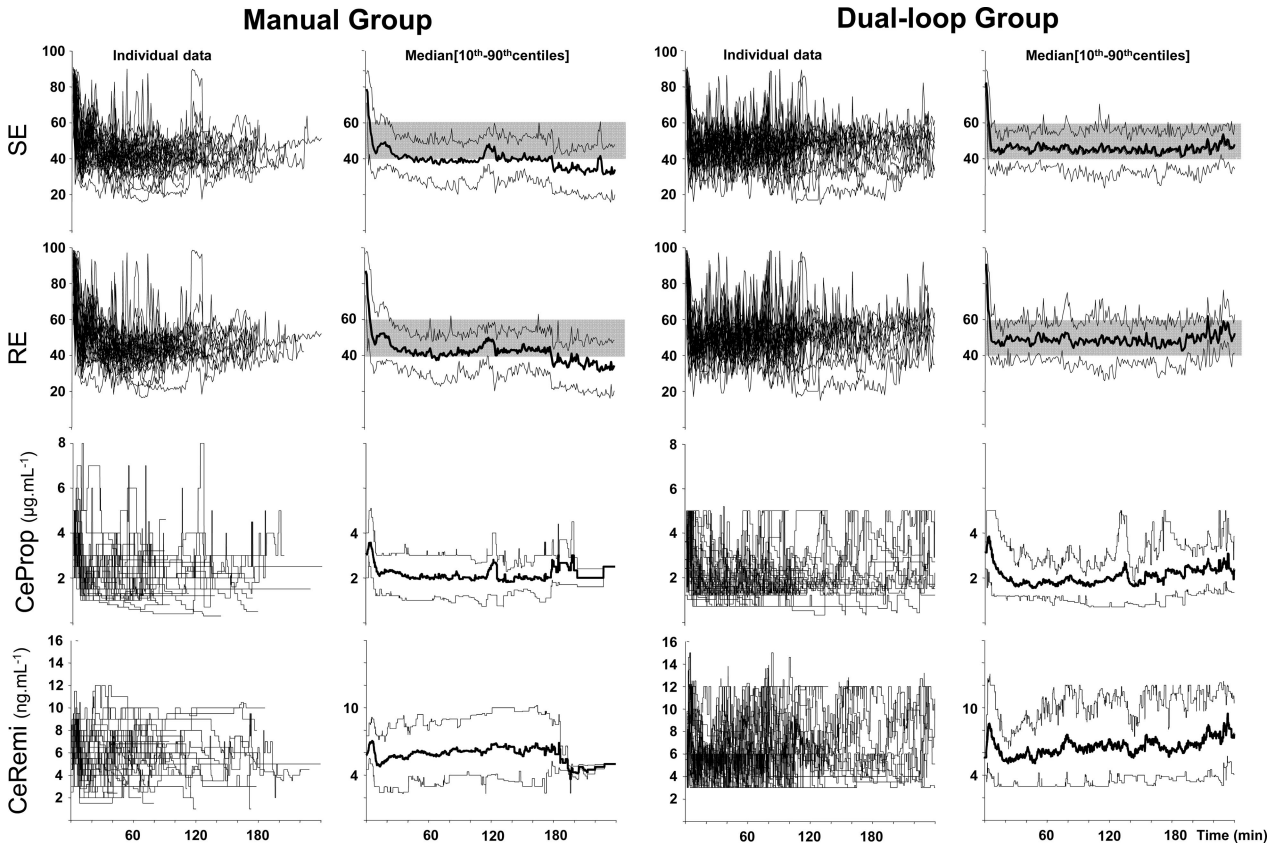

Fig. 3. State entrophy (SE) and response entropy (RE) values and calculated effect-site concentration of propofol (CeProp) and remifentanil (CeRemi) from induction to discontinuation of these drugs. All individual values are shown; data are averaged for graphical representation with a moving average filter of 1min duration. Median values (*thick line*) are presented with 10th and 90th percentiles (*thin line*). Dual-loop = closed-loop control of propofol and remifentanil; Manual = manual group guided by spectral entropy.

Table 2. Comparison of Anesthetic Procedure during the Induction Phase

	Manual (n = 31)	Dual-loop (n = 30)	*P* Value
Premedication (none/hydroxyzine)	4/27	2/28	0.67
Duration (s)	246 [134–318]	208 [151–311]	0.89
Propofol dose (mg/kg)	0.9 [0.6–1.4]	0.9 [0.6–1.4]	0.07
Remifentanil dose (mcg/kg)	1.8 [1.2–2.5]	1.1 [0.8–1.8]	0.72
Ephedrine bolus	8 (26)	6 (20)	0.76
$SE_{<40}$ (s)	31 [0–93]	41 [5–68]	0.96
$SE_{>60}$ (s)	0 [0–0]	0 [0–10]	0.71
Occurrence of SR	0	0	1

Data are presented as median [interquartile range] or number (%) of total patients of each group. Duration: defined as the time elapsed from the start of propofol administration to the moment when the SE value decreased and remained less than 60 for 30 s. $SE_{<40}$: duration of SE under 40 in a period of 3 min after the SE value fell and remained under 60. $SE_{>60}$: duration of SE greater than 60 in a period of 3 min after the SE value fell and remained under 60.

Dual-loop = closed-loop control of propofol and remifentanil; Manual = manual control infusion group guided by the Spectral M-Entropy™; SE = spectral entropy; SR = burst suppression ratio.

Table 4. Efficiency of the Control System for State Entropy during Maintenance of Anesthesia

	Manual (n = 31)	Dual-loop (n = 30)	*P* Value
$SE_{<40}$	37 [14–62]	16 [5–32]	0.029
$SE_{>60}$	5 [1–7]	7 [2–9]	0.21
$SE_{40–60}$	60 [35–82]	80 [60–85]	0.046
SE_{PE}	−14 [−20– (−4)]	−6 [−12– (−1)]	0.014
SE_{MDPE}	−16 [−24– (−10)]	−8 [−12– (−4)]	0.016
SE_{MDAPE}	18 [14–26]	12 [10–18]	0.022
SE_{Wobble}	8 [6–10]	8 [8–14]	0.40
$SE_{Global\ Score}$	44 [25–110]	25 [19–53]	0.043
SR	7 (23)	4 (13)	0.51

Data are presented as median [interquartile range] or number (%) of total patients of each group.

Dual-loop = closed-loop control of propofol and remifentanil; Manual = manual control infusion group guided by the Spectral M-Entropy™; SE = state entropy; $SE_{<40}$ = percentage of time during which the SE value was less than a value of 40; $SE_{>60}$ = percentage of time during which the SE value was greater than a value of 60; $SE_{40–60}$ = percentage of time during which the SE value was between 40 and 60 during the maintenance; $SE_{Global\ Score}$ = Global Score of SE; SE_{MDPE} = median performance error of SE; SE_{MDAPE} = median absolute performance error of SE; SE_{PE} = performance error of SE; SE_{Wobble} = wobble of SE; SR = burst suppression ratio occurrence.

and Drug Administration approval was designed for endoscopy with sedation provided by nonanesthesiologists.[33]

Numerous control algorithms have nonetheless been proposed, each using a single output to control administration of a single drug. For example, more than 400 patients have been anesthetized since 1998 with a closed-loop controller using the BIS Monitor as output.[6–20] In contrast, fully automated coadministration of a hypnotic and an opioid, such as in our study, remains rare. A closed-loop controller was described with the BIS Monitor and a fixed mixture of propofol and alfentanil.[7] Use of an isoboller controller has also been de-

Table 3. Comparison of Anesthetic Procedure during the Maintenance Phase

	Manual (n = 31)	Dual-loop (n = 30)	*P* Value
Duration of anesthesia (min)	95 [79–239]	116 [82–239]	0.185
Propofol			
Median dose ($mg \cdot kg^{-1} \cdot h^{-1}$)	4.5 [3.4–6.3]	4.1 [2.9–4.9]	0.10
Increment value ($\mu g/ml$)	0.55 [0.44–0.76]	0.42 [0.31–0.56]	0.016
Modifications per hour	8 [4–16]	21 [13–25]	<0.001
Median effect-site ($\mu g/ml$)	2.2 [1.7–2.5]	2.2 [1.7–2.5]	0.99
Remifentanil			
Median dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.19 [0.15–0.26]	0.18 [0.13–0.24]	0.47
Increment value (ng/ml)	1.1 [0.7–1.4]	1.2 [1.1–1.5]	0.039
Modifications per hour	10 (6–21)	28 (20–33)	<0.001
Median effect-site (ng/ml)	5.9 [4.8–7.6]	5.9 [5.0–6.7]	1.00
Ephedrine bolus	9 (29)	3 (10)	0.11
Antihypertensive therapy	6 (20)	2 (6)	0.25
Blood loss ≥500 ml	3 (10)	2 (6)	0.82
Lactated Ringer's solution $ml \cdot kg^{-1} \cdot h^{-1}$	12 [8–17]	9 [7–15]	0.13
Somatic events	4 (13)	2 (6)	0.67
Neuromuscular blocker boluses	24 (77)	22 (73)	0.77
Median normalized morphine (mg/kg)	0.09 [0.06–0.11]	0.07 [0.06–0.12]	0.71
Time to tracheal extubation (min)	8 ± 4	9 ± 4	0.13

Data are presented as median [interquartile range] or number (%) of total patients of each group. Time to tracheal extubation was defined as the time from discontinuation of propofol and remifentanil infusion until tracheal extubation.

Dual-loop = closed-loop control of propofol and remifentanil; Manual = manual control infusion group guided by the Spectral M-Entropy™.

Table 5. Efficiency of the Control System for Response Entropy during Maintenance of Anesthesia

	Manual (n = 31)	Dual-loop (n = 30)	*P* Value
$RE_{<40}$	23 [6–46]	12 [3–26]	0.12
$RE_{>60}$	10 [4–13]	11 [6–15]	0.38
$RE_{40–60}$	67 [42–84]	79 [57–84]	0.21
RE_{PE}	−7 [−15–1]	−1 [−7–4]	0.09
RE_{MDPE}	−10 [−18– (−2)]	−2 [−10–1]	0.11
RE_{MDAPE}	16 [10–26]	13 [10–19]	0.18
RE_{Wobble}	10 [8–12]	10 [8–14]	0.95
$RE_{Global\ Score}$	39 [24–91]	30 [22–63]	0.25

Data are presented as median [interquartile range].

Dual-loop = closed-loop control of propofol and remifentanil; Manual = manual control infusion group guided by the Spectral M-Entropy™; RE = response entropy; $RE_{<40}$ = percentage of time during which the RE value was less than a value of 40; $RE_{>60}$ = percentage of time during which the RE value was greater than a value of 60; $RE_{40–60}$ = percentage of time during which the RE value was between 40 and 60 during the maintenance; $RE_{Global\ Score}$ = global score of RE; RE_{MDPE} = median performance error of RE; RE_{MDAPE} = median absolute performance error of RE; RE_{PE} = performance error of RE; RE_{Wobble} = wobble of RE.

scribed, in which propofol and fentanyl administration was based on the midlatency auditory evoked potential and a fuzzy-logic algorithm that combined heart rate and mean arterial pressure.[34]

The dual-loop controller we used with M-Entropy is an extension of the controller developed in a previous study that used BIS as the output.[20] Propofol and remifentanil administration was based on the assumption that intraoperative BIS fluctuation is related to noxious stimuli intensity changes. The controller thus changed remifentanil more frequently than propofol, depending on the difference between the measured BIS and a designated setpoint. The trial demonstrated that the BIS can automatically guide propofol and remifentanil administration; specifically, BIS was more frequently between 40 and 60 with the dual-loop controller than with manual target control, and time to tracheal extubation was shorter.

Monitoring of anesthetic depth using M-Entropy can reduce propofol[35] or sevoflurane[36] consumption, speed emergence from general anesthesia,[35] guide anesthetic management in pediatric patients,[37] and reduce the risk of recall.[22] Our study demonstrates that coadministration of propofol and remifentanil can be guided by spectral M-Entropy during anesthesia induction and maintenance. Dual-loop and manual control performed similarly during induction of general anesthesia, but the controller improved the global score of SE, the fraction of adequate anesthesia (*i.e.*, $SE_{40–60}$), and simultaneously reduced the amount of excessive anesthesia (*i.e.*, $SE_{<40}$).

We currently have closed-loop controllers that use electrocortical activity provided by M-Entropy or BIS.[20] A potential advantage of M-Entropy is that it provides distinct signals (RE and SE) that distinguish need for a hypnotic or opioid. A further potential advantage of M-Entropy is that it may react more quickly to rapid changes of anesthesia depth[23,24] and a potential drawback to BIS is the inconstant time delay between electroencephalogram change and the index calculation.[38] However, neither system is linear or time-invariant during rapid changes in cortical activity[39] and comparably distinguish anesthesia depth.[21] Finally, how each monitor compares during electrocautery artifacts and clinical transients remains to be determined. It will thus be of obvious interest to directly compare the performance of each system in realistic clinical situations.

Mathews *et al.* used feed-back control based on the RE-SE difference to titrate remifentanil in 20 patients having orthopedic surgery.[26] A difficulty is that the RE-SE difference or muscle facial activity[25] response to noxious stimuli was altered[40] or suppressed by the use of a neuromuscular blocking agent.[41] In contrast, the SE arousal response after noxious stimuli remains intact during paralysis.[42] In the current study, the controller adjusted the hypnotic and antinociceptive medications using the SE_{error}; specifically, the RE-SE difference was used to amplify the correction thus preventing neuromuscular block from limiting controller function.

A limitation of any opioid control system is that there is no specific measure of intraoperative analgesia. Determining whether remifentanil administration was adequate with our closed-loop controller was thus challenging. For example, hemodynamic changes are not specific to analgesic need, but have nonetheless been used in closed-loop systems to titrate alfentanil[43] and remifentanil.[44] In the current study, which used electroencephalogram changes to titrate the deficit of antinociception, hemodynamic characteristics before and after painful stimuli suggest acceptable hemodynamic stability. But before being widely adopted, our M-Entropy closed-loop controller should be tested clinically under physiologically challenging conditions[45] including hypertension, hypotension, morbid obesity, in pediatric patients, and during major surgery such as cardiac surgery[16] or lung transplantation.[14] Several reasons can be advanced to explain why a closed-loop controller outperforms manual control to maintain the SE in the desired range: the investigators were influenced by nonelectroencephalogram components such as hemodynamic (*e.g.*, tachycardia, hypertension, hypotension) or intraoperative events (*e.g.*, painful stimuli, vascular clamping, blood loss) and investigators modified the target of anesthesia depth; the investigators' vigilance decreased with the duration of surgery. The titration was very active initially, then the number of concentration adjustments decreased over time, and anesthesia was too deep in the manual group despite a decrease of calculated drug concentrations compared with the initial period of anesthesia. But, after 3 h, we had only three cases in the manual group and we could not come to a definite conclusion (fig. 3). Finally, the current study demonstrated the interest of automated technology for monotonous and repetitive tasks. The human brain is more efficient in making complex decisions.[46]

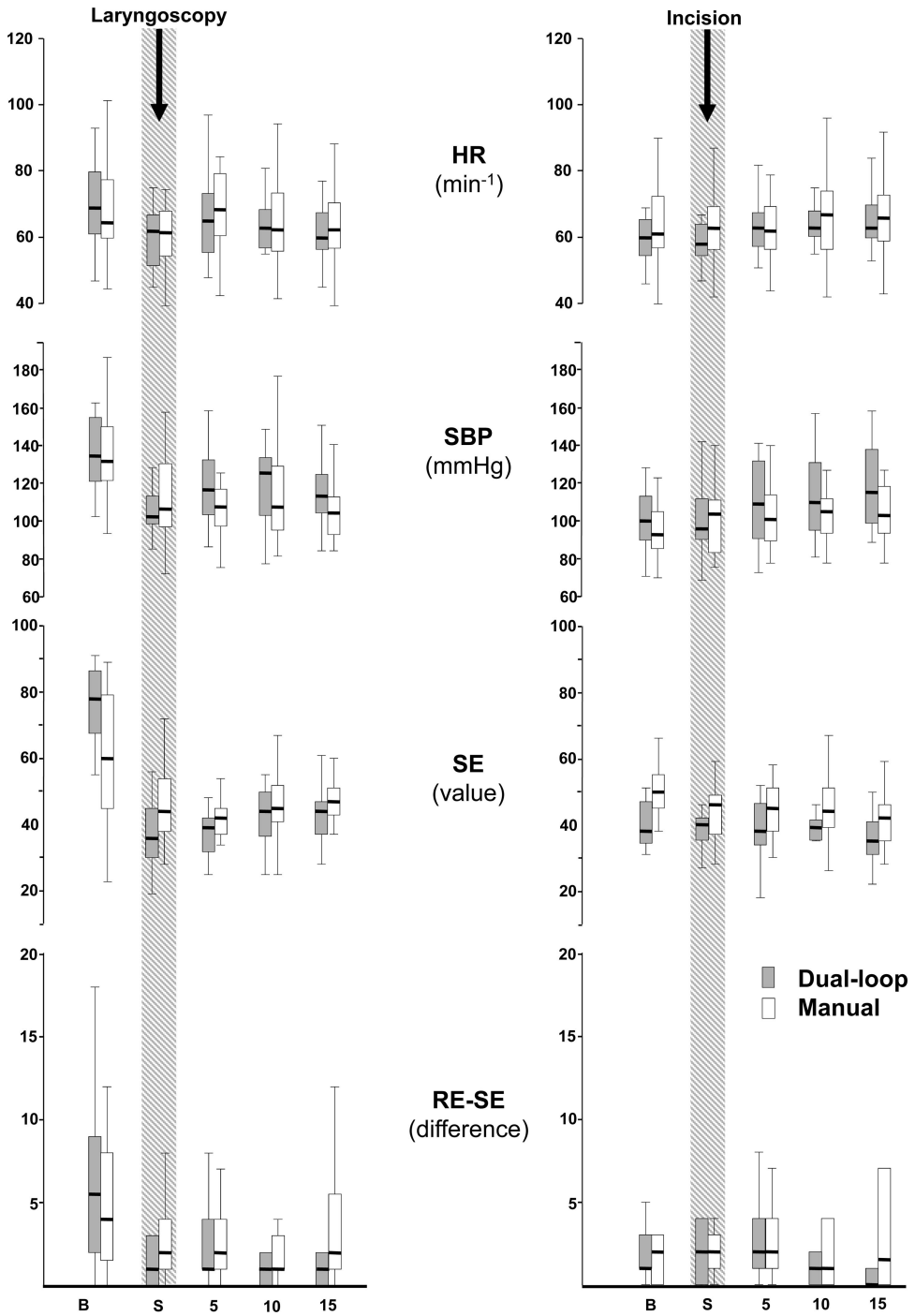

Fig. 4. Hemodynamic and entropy characteristics before and after painful stimuli. 5, 10, and 15 min after painful stimuli for dual-loop = closed-loop and manual groups. B = 5 min before stimuli; HR = heart rate; RE = response entropy; S = painful stimuli (laryngoscopy or incision); SBP = systolic blood pressure; SE = state entropy.

We make the assumption that tight control of SE or RE is preferable to greater variability; however, there is currently no evidence that tight control actually improves patient outcomes. Moreover, depth of analgesia can be evaluated by other methods such as fixed-order autoregressive moving average analysis of frontal electroencephalogram[47] or the Surgical State Index,[48] which are probably among the more specific measures of remifentanil effect. Whether these measures are comparable (or perhaps superior) outputs for closed-loop controllers remains unknown.

In conclusion, electrocortical activity, as provided by the Spectral M-Entropy monitor, is a surrogate measure of hypnosis and analgesia that allows simultaneous automated titration of propofol and remifentanil during induction and maintenance of general anesthesia. The Dual closed-loop controller outperforms manual control during maintenance of general anesthesia.

References

1. Mayo CW, Bickford RG, Faulconer AJ: Electroencephalographically controlled anesthesia in abdominal surgery. JAMA 1950; 144:1081–3
2. Schwilden H, Schttler J, Stoeckel H: Closed-loop feedback control of methohexital anesthesia by quantitative EEG analysis in humans. ANESTHESIOLOGY 1987; 67:341–7
3. Kenny GN, Mantzaridis H: Closed-loop control of propofol anaesthesia. Br J Anaesth 1999; 83:223–8
4. Schwilden H, Stoeckel H, Schttler J: Closed-loop feedback control of propofol anaesthesia by quantitative EEG analysis in humans. Br J Anaesth 1989; 62:290–6
5. Schwilden H, Stoeckel H: Closed-loop feedback controlled administration of alfentanil during alfentanil-nitrous oxide anaesthesia. Br J Anaesth 1993; 70:389–93
6. 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
7. Morley A, Derrick J, Mainland P, Lee BB, Short TG: Closed loop control of anaesthesia: An assessment of the bispectral index as the target of control. Anaesthesia 2000; 55:953–9
8. Struys MM, De Smet T, Versichelen LF, Van De Velde S, Van den Broecke R, Mortier EP: Comparison of closed-loop controlled administration of propofol using Bispectral Index as the controlled variable *versus* "standard practice" controlled administration. ANESTHESIOLOGY 2001; 95:6–17
9. Absalom AR, Sutcliffe N, Kenny GN: Closed-loop control of anesthesia using Bispectral index: Performance assessment in patients undergoing major orthopedic surgery under combined general and regional anesthesia. ANESTHESIOLOGY 2002; 96:67–73
10. Absalom AR, Kenny GN: Closed-loop control of propofol anaesthesia using bispectral index: Performance assessment in patients receiving computer-controlled propofol and manually controlled remifentanil infusions for minor surgery. Br J Anaesth 2003; 90:737–41
11. Liu N, Chazot T, Genty A, Landais A, Restoux A, McGee K, Lalo PA, Trillat B, Barvais L, Fischler M: Titration of propofol for anesthetic induction and maintenance guided by the bispectral index: Closed-loop *versus* manual control: A prospective, randomized, multicenter study. ANESTHESIOLOGY 2006; 104:686–95
12. Haddad WM, Bailey JM, Hayakawa T, Hovakimyan N: Neural network adaptive output feedback control for intensive care unit sedation and intraoperative anesthesia. IEEE Trans Neural Netw 2007; 18:1049–66
13. Puri GD, Kumar B, Aveek J: Closed-loop anaesthesia delivery system (CLADS) using bispectral index: A performance assessment study. Anaesth Intensive Care 2007; 35:357–62
14. Liu N, Chazot T, Trillat B, Michel-Cherqui M, Marandon JY, Law-Koune JD, Rives B, Fischler M, Foch Lung Transplant Group: Closed-loop control of consciousness during lung transplantation: An observational study. J Cardiothorac Vasc Anesth 2008; 22:611–5
15. De Smet T, Struys MM, Neckebroek MM, Van den Hauwe K, Bonte S, Mortier EP: The accuracy and clinical feasibility of a new bayesian-based closed-loop control system for propofol administration using the bispectral index as a controlled variable. Anesth Analg 2008; 107:1200–10
16. Agarwal J, Puri GD, Mathew PJ: Comparison of closed loop *vs.* manual administration of propofol using the Bispectral index in cardiac surgery. Acta Anaesthesiol Scand 2009; 53:390–7
17. Hegde HV, Puri GD, Kumar B, Behera A: Bi-spectral index guided closed-loop anaesthesia delivery system (CLADS) in pheochromocytoma. J Clin Monit Comput 2009; 23:189–96
18. Mendez JA, Torres S, Reboso JA, Reboso H: Adaptive computer control of anesthesia in humans. Comput Methods Biomech Biomed Engin 2009; 12:727–34
19. Hemmerling TM, Charabati S, Zaouter C, Minardi C, Mathieu PA: A randomized controlled trial demonstrates that a novel closed-loop propofol system performs better hypnosis control than manual administration. Can J Anaesth 2010; 57:725–35
20. Liu N, Chazot T, Hamada S, Landais A, Boichut N, Dussaussoy C, Trillat B, Beydon L, Samain E, Sessler DI, Fischler M: Closed-loop coadministration of propofol and remifentanil guided by bispectral index: A randomized multicenter study. Anesth Analg 2011; 112:546–57
21. Schmidt GN, Bischoff P, Standl T, Hellstern A, Teuber O, Schulte Esch J: Comparative evaluation of the Datex-Ohmeda S/5 Entropy Module and the Bispectral Index monitor during propofol-remifentanil anesthesia. ANESTHESIOLOGY 2004; 101:1283–90
22. Moller DH, Rampil IJ: Spectral entropy predicts auditory recall in volunteers. Anesth Analg 2008; 106:873–9
23. Vierti-Oja H, Maja V, Srkel M, Talja P, Tenkanen N, Tolvanen-Laakso H, Paloheimo M, Vakkuri A, Yli-Hankala A, Merilinen P: Description of the Entropy algorithm as applied in the Datex-Ohmeda S/5 Entropy Module. Acta Anaesthesiol Scand 2004; 48:154–61
24. Vakkuri A, Yli-Hankala A, Talja P, Mustola S, Tolvanen-Laakso H, Sampson T, Vierti-Oja H: Time-frequency balanced spectral entropy as a measure of anesthetic drug effect in central nervous system during sevoflurane, propofol, and thiopental anesthesia. Acta Anaesthesiol Scand 2004; 48:145–53
25. Wheeler P, Hoffman WE, Baughman VL, Koenig H: Response entropy increases during painful stimulation. J Neurosurg Anesthesiol 2005; 17:86–90
26. Mathews DM, Cirullo PM, Struys MM, De Smet T, Malik RJ, Chang CL, Neuman GG: Feasibility study for the administration of remifentanil based on the difference between response entropy and state entropy. Br J Anaesth 2007; 98:785–91
27. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ: The influence of age on propofol pharmacodynamics. ANESTHESIOLOGY 1999; 90:1502–16
28. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, Billard V, Hoke JF, Moore KH, Hermann DJ, Muir KT, Mandema JW, Shafer SL: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I Model development. ANESTHESIOLOGY 1997; 86:10–23
29. Cantraine FR, Coussaert EJ: The first object oriented monitor for intravenous anesthesia. J Clin Monit Comput 2000; 16:3–10
30. Leclerc C, Gerard JL, Bricard H: [Intraoperative memory. A study of its incidence in general anesthesia in 326 patients]. Ann Fr Anesth Reanim 2001; 20:592–9
31. Varvel JR, Donoho DL, Shafer SL: Measuring the predictive performance of computer-controlled infusion pumps. J Pharmacokinet Biopharm 1992; 20:63–94
32. Manberg PJ, Vozella CM, Kelley SD: Regulatory challenges facing closed-loop anesthetic drug infusion devices. Clin Pharmacol Ther 2008; 84:166–9
33. Pambianco DJ, Vargo JJ, Pruitt RE, Hardi R, Martin JF: Computer-assisted personalized sedation for upper endoscopy and colonoscopy: A comparative, multicenter randomized study. Gastrointest Endosc 2011; 73:765–72
34. Zhang XS RR, Huang JW: Closed-loop system for total intravenous anesthesia by simultaneously administering two anesthetic drugs. IEEE Eng Med Biol Mag 1998; 6:3052–5
35. Vakkuri A, Yli-Hankala A, Sandin R, Mustola S, Hymork S, Nyblom S, Talja P, Sampson T, van Gils M, Vierti-Oja H: Spectral entropy monitoring is associated with reduced propofol use and faster emergence in propofol-nitrous oxide-alfentanil anesthesia. ANESTHESIOLOGY 2005; 103:274–9
36. Aime I, Verroust N, Masson-Lefoll C, Taylor G, Lalo PA, Liu N, Fischler M: Does monitoring bispectral index or spectral

entropy reduce sevoflurane use? Anesth Analg 2006; 103: 1469–77

37. Klockars JG, Hiller A, Ranta S, Talja P, van Gils MJ, Taivainen T: Spectral entropy as a measure of hypnosis in children. Anesthesiology 2006; 104:708–17
38. Pilge S, Zanner R, Schneider G, Blum J, Kreuzer M, Kochs EF: Time delay of index calculation: Analysis of cerebral state, bispectral, and narcotrend indices. Anesthesiology 2006; 104:488–94
39. Bibian S, Dumont GA, Zikov T: Dynamic behavior of BIS, M-entropy and neuroSENSE brain function monitors. J Clin Monit Comput 2011; 25:81–7
40. Kawaguchi M, Takamatsu I, Kazama T: Rocuronium dose-dependently suppresses the spectral entropy response to tracheal intubation during propofol anaesthesia. Br J Anaesth 2009; 102:667–72
41. Aho AJ, Yli-Hankala A, Lyytikinen LP, Jäntti V: Facial muscle activity, Response Entropy, and State Entropy indices during noxious stimuli in propofol-nitrous oxide or propofol-nitrous oxide-remifentanil anaesthesia without neuromuscular block. Br J Anaesth 2009; 102:227–33
42. Aho AJ, Lyytikinen LP, Yli-Hankala A, Kamata K, Jäntti V: Explaining Entropy responses after a noxious stimulus, with or without neuromuscular blocking agents, by means of the raw electroencephalographic and electromyographic characteristics. Br J Anaesth 2011; 106:69–76
43. Luginbhl M, Bieniok C, Leibundgut D, Wymann R, Gentilini A, Schnider TW: Closed-loop control of mean arterial blood pressure during surgery with alfentanil: Clinical evaluation of a novel model-based predictive controller. Anesthesiology 2006; 105:462–70
44. Hemmerling TM: Automated anesthesia. Curr Opin Anaesthesiol 2009; 22:757–63
45. Glass PS, Rampil IJ: Automated anesthesia: Fact or fantasy? Anesthesiology 2001; 95:1–2
46. Battles JB, Keyes MA: Technology and patient safety: A two-edged sword. Biomed Instrum Technol 2002; 36:84–8
47. Liley DT, Sinclair NC, Lipping T, Heyse B, Vereecke HE, Struys MM: Propofol and remifentanil differentially modulate frontal electroencephalographic activity. Anesthesiology 2010; 113:292–304
48. Struys MM, Vanpeteghem C, Huiku M, Uutela K, Blyaert NB, Mortier EP: Changes in a surgical stress index in response to standardized pain stimuli during propofol-remifentanil infusion. Br J Anaesth 2007; 99:359–67