# The Analgoscore™: a novel score to monitor intraoperative nociception and its use for closed-loop application of remifentanil

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*Abstract - Purpose.* **Measuring pain during general anesthesia is difficult because communication with the patient is impossible. The focus of this project is the evaluation of an objective score ('Analgoscore'™) of intraoperative nociception based on mean arterial pressure (MAP) and heart rate (HR). The Analgoscore is used for closed-loop application of remifentanil.**

*Methods.* **The Analgoscore™ ranges from -9 (too profound analgesia) to 9 (too superficial analgesia) in increments of 1, with -3 to +3 representing excellent pain control, -3 to -6 and 3 to 6 good pain control, and -6 to -9 and 6 to 9 insufficient pain control. According to the zone of pain, a remifentanil infusion was either closed-loop-administered (Closed-loop-group) or manually administered by the same anesthesiologist (Control group). The percentage of anesthetic time within the different control zones was recorded as well as the variability of MAP and HR and compared between the two groups. Data presented as means ± standard deviation.**

*Results.* **In the closed-loop group, 16 patients (5 f, 11 m; age 49 ± 21 y) underwent anesthesia of 111 ± 44 min, and received a dose of remifentanil of 0.13 ± 0.08 µg/kg/min. During 84%, 14% and 0.5% of the total anesthesia time, the Analgoscore™ showed excellent, good or insufficient pain control, respectively. During 70% of the time, MAP ranged from -5% to 5%, during 21% of the time it ranged from - 10% to -5% and from 5% to 10% and during 9% of the time, it ranged from -20% to -10% and from 10% to 20% below or above the target values. Heart rate was within 10% of target value in 99% of the total anesthesia time. Artifacts were recorded only 1.5% of the time.**

**The control group of eleven patients (4 f, 7 m; age 57 ± 16 y) underwent anesthesia of 110 (25) min; remifentanil of 0.17 (0.1) µg/kg/min was infused. Excellent control was obtained 79% of the time, whereas good control and insufficient control yielded 16% and 0%, respectively. Artifacts were recorded 5% of the time.**

*Discussion.* **The Analgoscore™ is a novel score of intraoperative nociception based on blood pressure and heart rate. Remifentanil was successfully closed-loop-administered using this score. The closed-loop system provided equal hemodynamic stability to meticulous manual administration of remifentanil.**

*Index terms* – **pain, intraoperative, remifentanil, Analgoscore, analgesia, closed-loop**

## I. INTRODUCTION

Pain control during general anesthesia is not easy since the patient cannot talk. However, indirect parameters, such as reactions of the autonomic nerve system, especially changes in heart rate or blood pressure are routinely used by clinicians in the attempt to determine pain during unconsciousness [1-6]. The clinician adjusts analgesia interpreting heart rate and blood pressure changes based on his judgment, his experience and also surgical variables, such as an estimation of the degree or presence of a surgical stimulus causing pain at any given time during surgery. Opioids, used during surgery for pain control, are known to effectively block changes in heart rate or blood pressure during periods of surgical stimuli [7].

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Although heart rate or blood pressure have been used in surgeries to assess pain [8-13] there is an absence of studies to establish any kind of 'intraoperative pain score', equivalent to the visual pain score widely used to assess pain in the conscious patient. At present, most studies have solely used either heart rate or blood pressure but not a combination of both to estimate intraoperative pain [12, 14, 15]. In order to translate mean arterial pressure (MAP) or heart rate (HR) variations into a surrogate of intraoperative nociception, signal processing and interpretation of the data is necessary.

The use of closed-loop systems might improve the quality of drug administration [16]. These automated drug delivery systems use an input variable (e.g. anesthetic depth or blood pressure or the degree of neuromuscular blockade) to control the output (drug delivery rate) [17] and try to maintain a preset target of the controlled input variable. Many closed-loop systems have been implemented to control the infusion of hypnotic or muscular relaxant drugs due to the availability of new monitors of depth of anesthesia or neuromuscular blockade. However, the application of closed-loop control for opioids faces the problem of lack of an optimal method of measuring intraoperative pain [18]. Thus, the focus of this feasibility study is the evaluation of a novel, objective score (called Analgoscore™) of intraoperative nociception to which an expert-based, adaptative system is linked to administer remifentanil in patients undergoing orthopedic, urologic, ENT or general surgery.

## II. METHODS

### A. *Analgoscore™ algorithm*

Depending on the type of surgery and the patient's general condition, the anesthetist defined target values for MAP and HR during surgery. These target values are based on the desired form of anesthesia, type of surgery or preoperative status of a patient. Some volatile anesthetics, such as desflurane, are known to increase HR and decrease MAP, some surgeries, e.g. ENT surgery, requires controlled hypotension resulting in lower than normal MAP, some patients might suffer from hypertension, therefore higher than normal MAP values are expected. These clinical situations are adjusted for either automatically by using the appropriate menus of the user interface or by manually adjusting MAP and HR targets before surgery. Mean arterial pressure, measured non-invasively, and HR are acquired using a standard vital sign monitor (Welch Allyn, Inc., Skaneateles Falls, NY, USA). Based on these target values of MAP and HR, the Analgoscore™ defines three areas of pain control. The range of the Analgoscore™ is defined from -9 (too profound analgesia) to 9 (insufficient analgesia) in increments of 1. Three control areas were defined with -3 to +3 representing excellent pain control, -3 to -6 and 3 to 6 good pain control, and -6 to -9 as well as 6 to 9 inadequate pain control (Figure 1). The score is calculated by comparing the offset percentage between target and measured values using expert based rules (Table I).

The algorithm modeling this procedure is illustrated in Figure 2 and is repeated every minute throughout the surgery to adjust the infusion rate of remifentanil. Several correction factors then act to modify and validate a new infusion rate. The amount of remifentanil infused is calculated dynamically based on algorithms according to the score. Since MAP or HR can be influenced by other reasons than changes in analgesia, hypovolemia was defined as a predominant increase of HR without increase of MAP, and vagal reactions (e.g. caused by pneumoperitoneum during laparoscopic surgery) defined as a predominant decrease of HR with no decrease of MAP (Figure 3). When such situations occurred, the clinician was advised and a pre-defined infusion rate of remifentanil 0.01 μg/kg/min administered.

TABLE I.
RULES FOR SCORE DETERMINATION

| **MAP** / **HR** | <20% | <15% | <10% | <5% | **MAP** | >5% | >10% | >15% | >20% |
|---|---|---|---|---|---|---|---|---|---|
| <35% | -9 | -8 | -6 | -5 | -4 | Vagal Reaction | | | |
| <25% | -8 | -7 | -5 | -4 | -3 | | | | |
| <15% | -6 | -5 | -4 | -3 | -2 | | | | |
| <10% | -5 | -4 | -3 | -1 | -1 | | | | |
| **HR** | -4 | -3 | -2 | -1 | 0 | 1 | 2 | 3 | 4 |
| >10% | Hypotension caused by volume depletion | | | | 1 | 1 | 3 | 4 | 5 |
| >15% | | | | | 2 | 3 | 4 | 5 | 6 |
| >25% | | | | | 3 | 4 | 6 | 7 | 8 |
| >35% | | | | | 4 | 5 | 6 | 8 | 9 |

MAP = mean arterial pressure; HR = heart rate


Figure 1. Illustration of user interface; different areas define different zones of pain control. The range of the Analgoscore™ is defined from -9 (too profound analgesia) to 9 (insufficient analgesia) in increments of 1. Three control areas were defined with -3 to +3 representing excellent pain control, -3 to -6 and 3 to 6 good pain control, and -6 to -9 as well as 6 to 9 inadequate pain control. These areas are color-coded. In addition, there is a numeric display of the exact Analgoscore™ value. Different other parameters are displayed: last, new infusion rate of remifentanil in µg/kg/min and in ml/h (pump display). The target values for mean arterial pressure (MAPc) and heart rate (HRc) are displayed as well as the actual heart rate and mean arterial blood pressure every min. On the left side of the interface, trends for Analgoscore™, infusion rate, bispectral index (BIS) and PMG (phonomyography) as an example of parameters reflecting either depth of anesthesia or neuromuscular blockade.

Table II shows how the remifentanil rate is modified by a correction factor (CF) according to the generated Analgoscore™. This factor is also combined to K1 and K2 factors (factors to account for trends in offset from target values over time) to engender the new remifentanil infusion rate as follows:

$$NewInfusion = PreviousInfusion \times CF \times K_1 \times K_2$$

where:

$$K1 = \begin{cases} 2 & MeanSlope > 1 \\ 1.25 & 0.5 < MeanSlope \le 1 \\ 1.10 & 0 < MeanSlope \le 0.5 \\ 1 & MeanSlope = 0 \\ 0.90 & -0.5 < MeanSlope \le 1 \\ 0.75 & -1 \le MeanSlope < -0.5 \\ -1 & MeanSlope < -1 \end{cases}$$

and,

$$K2 = \begin{cases} 1.5 & 6 \le Score < 9 \\ 1.25 & 3 \le Score < 6 \\ 1 & 0 \le Score < 3 \\ 0.75 & -3 \le Score < 0 \\ N/A & -9 \le Score < -3 \end{cases}$$

An IBM-compatible Pentium IV notebook computer running Windows XP (Microsoft, Redmond, WA, USA) is used to implement the algorithm, provide the graphical user interface (Figure 1) and control the communication with the vital sign monitor and the infusion pump via serial RS-232 ports. Remifentanil is administered using a Graseby 3400 infusion pump (Graseby Medical, Watford, UK). The control algorithm is developed with LabVIEW National Instruments (National Instruments Corporation, Austin, Texas) and with Visual Basic (Microsoft, Redmond, WA, USA).

TABLE II.
INFUSION RATE VARIATION

| Analgoscore™ | Infusion Modification | CF |
|---|---|---|
| -9 to -2 | No infusion | |
| -1,0, 1 | No change | 1 |
| 2 | ↑20% | 1.2 |
| 3 | ↑30% | 1.3 |
| 4 | ↑40% | 1.4 |
| 5 | ↑50% | 1.5 |
| 6 | ↑60% | 1.6 |
| 7 | ↑70% | 1.7 |
| 8 | ↑80% | 1.8 |
| 9 | ↑90% | 1.9 |

CF = Correction factor

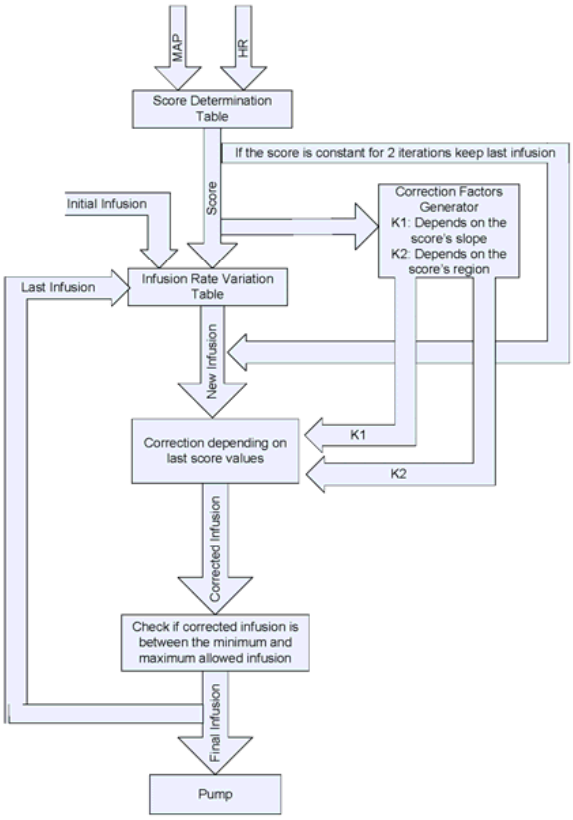


Figure 2. Closed-loop algorithm. A score is determined based on heart rate and mean arterial pressure patient values. Correction factors are then calculated following the variation of the score over time in order to determine the remifentanil infusion rate.

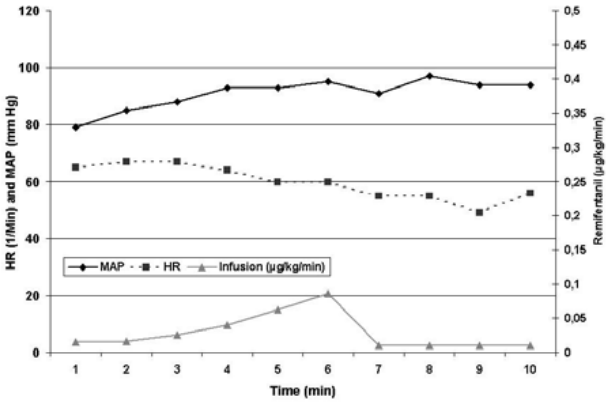


Figure 3. Vagal reaction. The figure shows a representative situation where pneumoperitoneum during laparoscopic prostatectomy increases arterial pressure and decreases heart rate. During this time, no score is determined and remifentanil is infused at a pre-defined rate.

### B. Clinical protocol

The study was approved by the ethics committee and written patient consent obtained. Patients undergoing general, urologic, ENT and orthopedic surgery of moderate trauma were included. Patients on beta-blockers were excluded from the study. In all patients, general anesthesia was induced using remifentanil 0.25 µg/kg/min for 2 min, followed by remifentanil 0.1 µg/kg/min, propofol 1.5 mg/kg and rocuronium 0.3 mg/kg after which a laryngeal mask airway was inserted. Unconsciousness was maintained using sevoflurane at 1 MAC (age-adjusted) throughout surgery in a breathing gas of 50% oxygen-air. Intermittent positive pressure ventilation was maintained throughout surgery to maintain an end-tidal CO2 of 30-35 mmHg. Mean arterial pressure and HR were determined once every min and an Analgoscore™ reading obtained at this time interval. Mean arterial pressure and HR were considered 'stable' if they were within 20% of the target value.

Remifentanil was closed-loop administered in 16 patients (Closed-loop group).

In a control group of 10 patients, the Analgoscore™ was calculated and displayed; an anesthesiologist with more than 10 years of experience of continuous administration of remifentanil for surgery and not involved in the study was asked to administer remifentanil for patients undergoing general or orthopedic surgery of moderate trauma to maintain the Analgoscore™ as often within the range of -3 to 3 around a target value of 0.

### C. Performance analysis

Using the method of Varvel et al. [19] the controller performance was obtained by measuring the variation of MAP and HR from the target values specified by the anesthetist. The performance error (PE) is given by:

$$PE = \frac{(\text{Measured Value - Target Value})}{\text{Target Value}} \times 100$$

Consequently, the median performance error (MDPE) which is a measure of bias and shows if the measured variables are above or below the target values is calculate:

$$MDPE_i = Median\{PE_{ij}, j = 1,..., N_i\}$$

where $N_i$ if the number of acquisitions for the ith patient and j is the acquired sample.

As for the median absolute performance error (MDAPE), it reflects the inaccuracy of the control system for the $i^{th}$ patient.

$$MDAPE_i = Median\{|PE|_{ij}, j = 1,..., N_i\}$$

In this context, wobble is a measure of the variability of $PE_{ij}$ in the $i^{th}$ individual:

$$Wobble_i = Median\{|PE_{ij} - MDPE_i|, j = 1,..., N_i\}$$

As for divergence, it reflects the evolution of the controller's performance through time (worsening or improvement). It is the slope obtained from linear regression of the subject's absolute PE against time. A positive slope indicates a gradually widening gap between the measured and targeted values whereas a negative value shows that the measured value tends to converge to the target values.

The percentage of time during which different zones of analgesia control occurred was calculated.

Results are presented as means ± standard deviation. Parameters between the two groups are compared using the Mann-Whitney U test for continuous data and the Chi-square test for categorical data; P<0.05 considered statistically significant.

## III. Results

In the Closed-loop group, sixteen patients (5 f, 11 m; age: 49 ± 21 y; weight: 70 ± 11kg) (Table III) underwent anesthesia of mean duration of 111 ± 44 min, and received a mean dose of remifentanil of 0.13 ± 0.08 µg/kg/min. Table IV shows the type of surgery performed, the time in min of each procedure and the variation of the Analgoscore™ in the different control

TABLE III.
PATIENT CHARACTERISTICS

| | Closed-loop Group | Control Group | P value |
|---|---|---|---|
| **Age (y)** | 48.87 ± 21.36 | 56.90 ± 15.75 | 0.374 |
| **Weight (Kg)** | 70.12 ± 11.39 | 86.30 ± 16.56 | 0.007 |
| **Sex (F/M)** | 5/11 | 4/7 | 0.782 |

Data as mean ± SD

regions for each patient. The Analgoscore™ showed excellent control during 84%, good control during 14% of the time, insufficient control was observed only 0.5% of the surgery time while 1,5% of the time was associated to other causes (i.e. with hypovolemia or vagal-type reactions) (Figure 4).

The results of the MDPE, MDAPE, divergence and wobble for the MAP and HR are shown in Table V. Wobble varied between 1.43% and 11.67% for MAP and between 0.95% and 6.67% for HR. For 8/16 and 11/16 patients, respectively, MAP and HR converged to the target values (negative divergence values). Mean arterial pressure was within the target values at -5% to 5% for 70% of the time while during 21% of the time, it ranged from -10% to -5% and from 5% to 10% and during 9% of the time it ranged from -20% to -10% and from 10% to 20% relatively to the targeted values. As for HR, it was 64% of the time between -5% and 5%, during 35% of the time it varied from -10% to -5% and from 5% to 10% and during 1% of the time it varied from -20% to -10% and from 10% to 20% below or above the targeted values. Only during 1.7% of the total surgery time, the infusion of remifentanil was given at a fixed minimal dose of 0.01 μg/kg/min because MAP and HR patterns indicative of either a vagal reaction or hypovolemia could be detected.

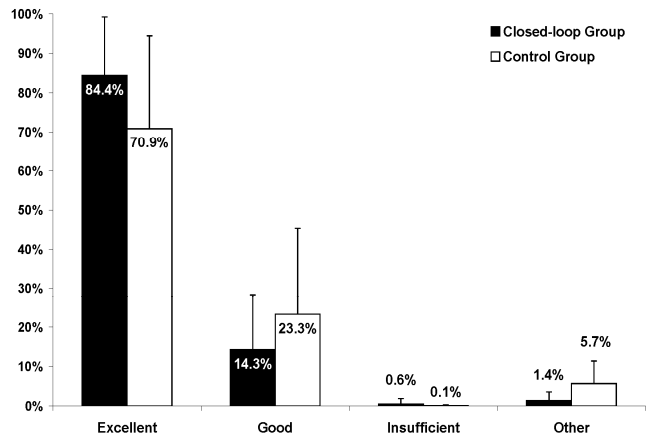


Figure 4. Analgesia control over time. The figure shows the percentage of time during which different areas of analgesia control occurred for all surgeries ('Excellent' represents an Analgoscore between –3 and 3; 'Good' represents an Analgoscore ranging from –6 to –3 or from 3 to 6 and 'Insufficient' control represents an Analgoscore ranging from –9 to –6 or from 6 to 9). 'Other' refers to periods where no score was determined since either 'vagal-type reactions' (decrease of heart rate, solely) or 'hypovolemia' (increased heart rate, solely) occurred.

In the Control group, 11 patients (Table III) underwent anesthesia of 110 (25) min with remifentanil infusion of mean 0.17 (0.1) μg/kg/min. Excellent control was obtained 71% of the time, whereas good control and insufficient control yielded 23% and 0% respectively. Artifacts were recorded 6% of the time.
The performance indices for mean arterial pressure and heart rate are given in Tables VI and VII, respectively. No differences between both groups were noted.

## IV. DISCUSSION

A novel score of nociception during unconsciousness was established using MAP and HR; in relation to subjectively chosen target values, a score between -9 and 9 is defined. Using an expert-based, adaptative closed-loop system, remifentanil was successfully administered with this score staying in a green area (-3 to 3, defined as excellent pain control, best balance between remifentanil dose and hemodynamic stability) during more than 80% of the time. The closed-loop system's performance was as good as manual control by an experienced anesthesiologist.

Assessing pain during general anesthesia is not an easy task. Communication with the patient is impossible, indirect parameters have to be used to estimate the amount of pain. Subjective estimation is mainly based on recording trends of blood pressure, heart rate or reactions of the sympathetic nervous system, such as sweating, involuntary movements or eye lacrimation. The interpretation of these parameters and the subsequent administration of analgesics are based on subjective decision-making of each

TABLE IV.
ANALGESIA CONTROL OVER TIME FOR EACH SURGERY IN THE CLOSED-LOOP GROUP

| ID | Surgery | Duration (min) | Excellent | Good | Insufficient | Other |
|---|---|---|---|---|---|---|
| 1 | Partial Mastectomy | 40 | 65% | 33% | 2% | 0% |
| 2 | Fracture right ankle | 85 | 56% | 41% | 0% | 3% |
| 3 | Skin transplantation | 169 | 89% | 11% | 0% | 0% |
| 4 | Skin transplantation | 83 | 98% | 0% | 0% | 2% |
| 5 | Percutaneous nephrostomy | 110 | 100% | 0% | 0% | 0% |
| 6 | Peripheral vascular grafts | 120 | 98% | 1% | 0% | 1% |
| 7 | Prostatectomy (laparoscopic) | 107 | 76% | 22% | 2% | 0% |
| 8 | Reconstruction anterior knee ligament | 59 | 69% | 31% | 0% | 0% |
| 9 | Partial nephrectomy (laparoscopic) | 154 | 64% | 36% | 0% | 0% |
| 10 | Partial mastectomy | 85 | 95% | 5% | 0% | 0% |
| 11 | Intestinal resection | 188 | 95% | 11% | 0% | 5% |
| 12 | Skin transplantation | 56 | 100% | 0% | 0% | 0% |
| 13 | Tympanoplasty | 168 | 79% | 17% | 0% | 4% |
| 14 | Tympanoplasty | 136 | 78% | 10% | 5% | 7% |
| 15 | urethroplasty | 80 | 93% | 7% | 0% | 0% |
| 16 | Skin transplantation | 132 | 96% | 4% | 0% | 0% |

TABLE V.
CONTROLLER PERFORMANCE FOR EACH PATIENT IN THE CLOSED-LOOP GROUP

| | MAP | | | | HR | | | |
|---|---|---|---|---|---|---|---|---|
| **ID** | **MDPE** | **MDAPE** | **Divergence** | **Wobble** | **MDPE** | **MDAPE** | **Divergence** | **Wobble** |
| 1 | 22.86 | 22.86 | -0.19 | 11.43 | 1.54 | 3.08 | 0.04 | 1.54 |
| 2 | 13.33 | 13.33 | 0.40 | 11.67 | -5.17 | 5.17 | -0.02 | 3.45 |
| 3 | 7.94 | 7.94 | -0.05 | 6.35 | 0.00 | 2.86 | -0.02 | 2.86 |
| 4 | 0.00 | 8.33 | 0.02 | 8.33 | -8.57 | 8.57 | -0.03 | 0.95 |
| 5 | -1.33 | 2.67 | 0.03 | 2.67 | 0.00 | 1.33 | 0.03 | 1.33 |
| 6 | 1.97 | 6.58 | 0.04 | 5.92 | -9.09 | 9.09 | 0.08 | 4.24 |
| 7 | -8.22 | 10.96 | 0.01 | 5.48 | -5.00 | 8.33 | -0.06 | 6.67 |
| 8 | -6.85 | 6.85 | 0.02 | 4.11 | -12.07 | 12.07 | 0.14 | 3.87 |
| 9 | -11.43 | 14.29 | 0.02 | 12.86 | -3.45 | 5.17 | -0.10 | 5.17 |
| 10 | -8.22 | 8.22 | -0.04 | 2.74 | -3.33 | 3.33 | -0.01 | 1.67 |
| 11 | 9.15 | 9.86 | 0.01 | 6.34 | 1.33 | 6.67 | 0.12 | 6.67 |
| 12 | -2.86 | 2.86 | -0.05 | 1.43 | -15.63 | 15.63 | -0.18 | 1.56 |
| 13 | -1.43 | 7.14 | -0.03 | 7.14 | 0.00 | 4.69 | -0.04 | 4.69 |
| 14 | -14.29 | 15.00 | -0.15 | 4.29 | 1.43 | 2.86 | -0.12 | 2.86 |
| 15 | -7.14 | 8.06 | 0.00 | 3.92 | -6.90 | 6.90 | -0.05 | 3.45 |
| 16 | -9.46 | 10.81 | 0.01 | 4.05 | -4.84 | 4.84 | -0.02 | 1.61 |

MAP = mean arterial pressure; HR = heart rate; MDPE = median performance error; MDAPE = median absolute performance error

anesthesiologist: it is based on his experience, his anesthetic preferences, his knowledge of pharmacokinetics and specific, patient-related data, such as preoperative blood pressure or surgery-related parameters, such as the degree and timing of surgical stimuli.

More objective decision-making has been proposed; however, only one study tested the control of MAP and HR in clinical conditions. Carregal et al. [14] proposed a closed loop system using HR and MAP to regulate alfentanil infusions. They weighted the parameters as 5/6 for the MAP and 1/6 for HR. The system was tested in 8 patients for a total surgical time of 373 minutes. They determined the mean dose of alfentanil, the hemodynamic stability and the number of alfentanil boli given additionally whenever the MAP was outside 20% of the target value. Criteria to abandon the automated alfentanil application was MAP below or above of 15% of target value for at least 12 min. They found that MAP stayed within 15% of the target value for 89.5% of the total time and no MAP above or below the target value during the total surgical time. However, they do not present any specific results for HR variability.

The Analgoscore™ could be a simple measure of intraoperative nociception as indicated by stable heart rate and blood pressure. In fact, it reflects a common practice of clinicians who – in the absent of any other simple parameters indicating the degree of pain during general anesthesia – use their empirical assessment of periods of possible surgical pain stimuli and changes in hemodynamic variables, such as blood pressure and heart rate, to adjust the dose of remifentanil. The Analgoscore™ is given between -9 and 9. Several 'areas' are created reflecting excellent, good or insufficient control of pain. The Analgoscore™ was used to administer remifentanil in a closed-loop form. During the vast majority of the operating time, excellent or good analgesia could be achieved. In comparison to the results of Carregal et al. [14], the Analgoscore™ provided a better hemodynamic stability with MAP within 10% of target value in 91%

TABLE VI.
PERFORMANCE INDICES FOR MEAN ARTERIAL PRESSURE

| | Closed-loop Group | Control Group | P value |
|---|---|---|---|
| **MDPE [%]** | -0.99 ± 10.01 | -0.29 ± 11.83 | 0.856 |
| **MDAPE [%]** | 9.73 ± 4.95 | 11.88 ± 7.55 | 0.429 |
| **Wobble [%]** | 6.17 ± 3.39 | 7.99 ± 2.66 | 0.056 |
| **Divergence [%/min]** | 0.004 ± 0.12 | -0.078 ± 0.20 | 0.481 |

Data as mean ± SD
MDPE = median performance error; MDAPE = median absolute performance error

TABLE VII.
PERFORMANCE INDICES FOR HEART RATE

| | Closed-loop Group | Control Group | P value |
|---|---|---|---|
| **MDPE [%]** | -4.36 ± 5.12 | -1.27 ± 6.30 | 0.229 |
| **MDAPE [%]** | 6.28 ± 3.76 | 6.80 ± 3.87 | 0.743 |
| **Wobble [%]** | 3.28 ± 1.84 | 4.36 ± 2.37 | 0.182 |
| **Divergence [%/min]** | -0.022 ± 0.09 | 0.053 ± 0.24 | 0.512 |

Data as mean ± SD
MDPE = median performance error; MDAPE = median absolute performance error

of the surgical total time of 1772 minutes and HR within 10% of target value in 99% of the total control time. The better hemodynamic stability might be due to better controller performance as well as the use of the more rapid acting remifentanil (in comparison to alfentanil in Carregal's study).

Varvel et al. [19] originally described the performance parameters for target control infusion system. These criteria have also been applied for studying the performance of closed-loop systems after some modification. Therefore, MDPE is a signed value; it represents the direction (over-prediction or under-prediction) of performance error (PE) rather than size of errors, which is represented by MDAPE [17]. The MDPE of -0.99 for MAP indicates that our closed-loop application had a slight negative bias i.e. the median measured MAP were always 1% lower than target MAP. An MDAPE value of 6.28% for HR indicates that 50% of HR values were within 6.28% of the set target HR. Wobble measures the total intra- individual variability in PE which was higher in the Control group (but did not reach statistical significance). Divergence measures the expected systemic time-related changes in performance. A positive value indicates progressive widening of the gap between target and measured value (divergence), whereas a negative value reveals that the measured values converge on the predicted values (convergence). The absolute value indicates the speed of convergence or divergence [17]. A mean divergence of -0.022 for HR in the Closed-loop group indicates that our system had a slight tendency to decrease the performance error with time.

In this study, surgery of moderate trauma was selected. Care was taken to select similar procedures for both groups. The procedures were selected according to our clinical experience and surgeries where the same amount of intraoperative analgesia was usually given per time period and where similar postoperative pain levels could be expected. In all patients, the same type of induction and the same amount of drugs for induction was given. In addition, patients on beta-blockers were excluded from this study. An adaptation of the algorithm is currently undertaken to take into account that patients on beta-blockade will react hemodynamically different to surgical stress. Future studies should also focus on the use of our setup for surgeries of different pain intensity and using different induction modes and analgesic agents.

In conclusion, we present a novel score of nociception during general anesthesia which successfully drives a closed loop system for the administration of remifentanil. Its performance is similar to manual administration.

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