Experimental Evaluation of Analgesia With an Event-Based PID Control Strategy for Anesthesia

Michele Schiavo, Nicola Latronico, Massimiliano Paltenghi, and Antonio Visioli

***Abstract*—The recent introduction of the Conox monitoring system in the clinical practice of total intravenous anesthesia (TIVA) has opened new research opportunities. Indeed, it provides the qCON and the qNOX indexes, which give a measure of hypnosis and analgesia, respectively. This letter presents the first experimental results of closed-loop anesthesia performed by using the Conox monitoring system. In particular, we exploited the qCON as the feedback variable for an event-based PID multiple-input single-output (MISO) controller and we recorded the qNOX to evaluate analgesia. Clinical experiments have been performed on four patients undergoing general anesthesia for elective plastic surgery. The controller demonstrated a satisfactory performance in maintaining qCON within the desired range for all patients. An optimal qNOX level has also been achieved in three out of four cases, while, in one patient, the qNOX level indicated a slight excess of analgesia. These findings suggest that the proposed MISO architecture is effective in providing adequate levels of hypnosis and analgesia and that, in future works, the qNOX information could be leveraged in the controller design to enhance analgesia control.**

***Index Terms*—Anethesia control, PID control, event-based control.**

I. Introduction

IN THE clinical practice of total intravenous anesthesia (TIVA) the anesthesiologist must manually regulate the infusion rates of specific anesthetic drugs to obtain on the patient suitable levels of depth of hypnosis (DoH) and analgesia. Propofol is commonly used to induce hypnosis while the short-acting opioid remifentanil is used as analgesic. In this context, a lot of research effort has been put in the development of closed-loop control systems in the last two decades [1] as they offers numerous benefits both for patients and clinical practitioners. Indeed, thanks to the feedback principle, they enhance drug dosing precision and improve patient safety while reducing clinicians workload. In fact, they represent a technological advancement with respect to the well-known target-controlled infusion (TCI) devices [2]. Indeed, these devices are model-based systems that work in open loop and the anesthesiologist needs to manually adjust the target concentration to compensate for unavoidable model uncertainties. Initially, single-input single-output (SISO) control solutions for closed-loop propofol administration have been proposed by exploiting as feedback variable one of the reliable measurements of DoH based on processed-electroencephalography (pEEG) that are commercially available, such as the widely used Bispectral Index (BIS, Aspect Medical Systems, Norwood, USA) [3]. In this context, noteworthy experimental results have been obtained with PID-based control solutions [4], [5], [6]. However, the experimental results obtained with SISO control confirmed that also analgesia must be properly controlled to guarantee a consistent clinical performance [5]. Indeed, the TIVA control problem is inherently multiple-input multiple-output (MIMO) [7] as the interaction between propofol and remifentanil is characterized by a synergistic behavior, impacting both therapeutic actions and side-effects. In this context, MIMO control structures should, in principle, provide the best results. However, their development has been hindered since, to date, there is not a reliable feedback signal for analgesia. Thus, multiple-input single-output (MISO) control architectures that exploit solely a measurement of DoH to control the administration of both propofol and remifentanil have been proposed. Noteworthy experimental results have been obtained with rule-based control [8], positive control [9], PID-based control [10], [11] and habituating control [12]. Pioneering experimental results with an MIMO rule-based controller have been obtained by employing, as indicators of analgesia, the Analgoscore, which is derived from the measurements of heart rate (HR) and mean arterial pressure (MAP) [13], [14], or an index derived

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from the elaboration of facial electromyography (EMG) [15]. However, the use of hemodynamic variables and of EMG to estimate analgesia lacks of sensitivity and specificity, as these measurements are affected by many confounding factors that can alter their interpretation. Other hemodynamic-based estimators of analgesia, such as ANI [16] and NOL [17] have been proposed but the lack of clinical evidence regarding their reliability has prevented the further development of MIMO control structures. The recent introduction of the qNOX index provided by the Conox monitoring system (Fresenius Kabi, Bad Homburg, Germany) could open new research opportunities in this context. The novelty with respect to the estimators of analgesia previously proposed lies in the fact that the qNOX index is derived from pEEG, which reflects the autonomic nervous system activity. This latter is less affected by confounding factors and thus, in principle, should provide a direct measurement of the pain/nociception level [18]. Clinical studies showed that the qNOX is able to quantify the probability of response to nociceptive stimulation disregarding the concentrations of anesthetics and its use in administering TIVA can reduce the total number of adverse events [19], [20]. Thus, it can be seen as an arousability measure that carries information about the adequacy of analgesic coverage. However, caution should be taken before relying on the Conox to develop an MIMO control system where the administration of remifentanil is fully driven by the qNOX as conflicting results have been obtained in clinical studies performed in the context of cardiac surgery [21], [22]. The Conox also provides the qCON index that is an indicator of DoH whose effectiveness and reliability has been demonstrated in several studies [18], [23], [24], [25], [26]. However, to date, there are no closed-loop systems based on the Conox in the literature. This is probably due to its relatively recent introduction with respect to other monitoring systems. Only an advisory tool for target-controlled infusion of propofol based on the qCON, which requires the manual intervention of the anesthesiologist, has been proposed [27].

In this letter we present the preliminary experimental results obtained on four patients with an event-based PID MISO control system for closed-loop anesthesia used in combination with the Conox monitoring system. In a previous study, the considered control system has already proven to be effective with BIS [28]. Here, qCON has been used as the feedback variable in place of BIS to evaluate the robustness of the controller with respect to the use of a different DoH measure. This is relevant from a practical point of view, since it is important to provide control solutions able to deliver a satisfactory clinical performance regardless the employed monitoring system. The qNOX index has been recorded with the aim to assess the capability of the proposed MISO approach to provide an adequate level of analgesia and to gather preliminary information regarding its suitability to be used as a feedback variable to implement MIMO control strategies.

II. Methodology

A. Control Problem Formulation

The TIVA control problem can be divided into two main phases: induction and maintenance. From the perspective of control system design, the induction phase is a set-point following task, where the considered DoH index must be driven from its initial value, typically near 100 for an awake patient, to the desired value, which is usually equal to 50. To reduce patient's discomfort, this task should be completed in the shortest possible time (and, in any case, at most in 5 minutes) but, at the same time, it is important to avoid undershoots below 30 since they could provoke side-effects related to drug overdosing. The maintenance phase is a disturbance rejection task where the DoH index should be kept in a range between 40 and 60 for as much time as possible despite the presence of nociceptive stimuli. The same applies to qNOX, since values within this range should, according to the manufacturer, indicate a low probability of response to nociceptive stimulation. The design of control systems for TIVA is a challenging task since the considered process is affected by a highly nonlinear behavior and by a great uncertainty. Indeed, for DoH, the relationship between drugs infusion and pEEG is usually described through an MISO Wiener structure where two linear pharmacokinetic/pharmacodynamic (PK/PD) models are connected in parallel and coupled with a static nonlinear function. The linear PK/PD models describe the relationship between the infusions of propofol and remifentanil ($u_p(t)$ and $u_r(t)$) and the resulting concentrations in the effect-site compartment ($C_{e,p}(t)$ or $C_{e,r}(t)$), which represents the brain. Usually, the Schnider [29] and the Minto [30] models are used for propofol and remifentanil, respectively. The nonlinear part of the model is an interaction surface that relates $C_{e,p}(t)$ and $C_{e,r}(t)$ to the pEEG value [31]. It is worth noting that the parameters of this surface are affected by a great uncertainty deriving partly from the great inter-patient variability in the response to drug administration and partly from the kind of pEEG employed [31], [32].

B. Control System Architecture

The event-based PID MISO control scheme considered in this letter has been originally developed by using the BIS as feedback variable in [33]. The event-based mechanism has been developed with the aim to obtain a piece-wise constant drug infusion profile that mimics the behavior of the anesthesiologist. This is achieved by filtering small variations of the pEEG, which are usually caused by measurement noise, while maintaining the ability to promptly reacting to larger pEEG variations that are associated to an actual alteration of DoH. In a clinical experiment performed on fourteen patients the controller delivered a satisfactory performance and demonstrated a consistent behavior that makes it easy and intuitive for the anesthesiologist to supervise [28]. A schematic representation of the control architecture is given in Figure 1 where $qCON(t)$ is the measurement provided by the Conox monitor and $\overline{qCON}$ is the target value, which is equal to 50. The $qCON_f(t)$ is the $qCON(t)$ signal filtered by the event generator, which triggers an event when the following condition occurs:

$$\left| \int_{t_{last}}^{t} qCON(t) - qCON_f(t_{last})dt \right| > \Delta_i \tag{1}$$

where $qCON_f(t_{last})$ is the output of the event generator provided when the last event was triggered at time t_{last}.

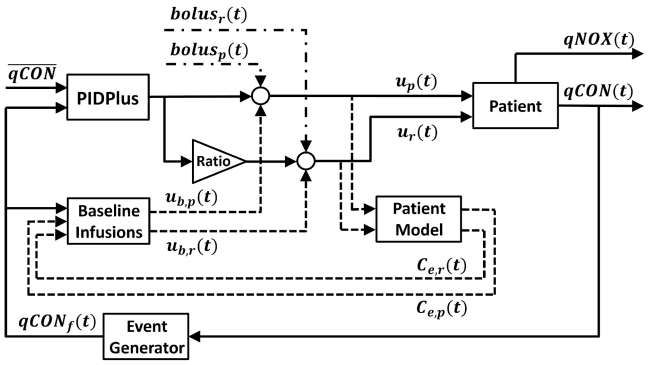

Fig. 1. Block diagram of the event-based PID MISO control scheme.

The threshold Δ_i is the tuning parameter that determines the filtering effect of the event generator. In particular, by increasing the value of this parameter it is possible to obtain a smoother infusion profile by filtering more the noise. However, excessively high values of this parameter worsen the ability to detect changes due to actual variations of DoH. As a safety measure, an event is also generated if a maximum timeout of 20 seconds is reached between the generation of two consecutive events. Note that, the selection of Δ_i and of the maximum timeout is not trivial. For more details regarding their tuning the reader is referred to [33]. The value $qCON_f(t)$ is sent to the PIDPlus controller, which is specifically designed to handle non-periodic sampling, when an event is triggered, and it is computed as:

$$qCON_f(t) = \frac{\int_{t_{last}}^{t} qCON(t)dt}{t - t_{last}}. \tag{2}$$

The MISO control is achieved by imposing a *ratio*, whose value has been fixed equal to 2 as in [10], between the control actions $u_p(t)$ and $u_r(t)$. In addition to the PIDPlus control action, a 1 mg/kg propofol bolus ($bolus_p(t)$) and a 1 μg/kg remifentanil bolus ($bolus_r(t)$) are automatically administered in feedforward when the controller is started to ensure a short induction time. Moreover, the effect-site concentrations of propofol ($C_{e,p}(t)$) and of remifentanil ($C_{e,r}(t)$) are estimated by using the linear PK/PD models of Schnider [29] and Minto [30], respectively. If the value of $C_{e,p}(t)$ (or $C_{e,r}(t)$) goes below a safety threshold and $qCON_f(t)$ is above 40, a baseline infusion rate of propofol $u_{b,p}(t)$ equal to 6 mg/kg/h (or of remifentanil $u_{b,r}(t)$ equal to 0.15 μg/kg/min) is administered to guarantee that a minimum amount of drug is always infused, thus reducing the risk of underdosing. To ensure patient's safety, $u_{b,p}(t)$ and $u_{b,r}(t)$ are also administered, thus overriding the PIDPlus controller, if the qCON signal quality index (SQI) drops below 40. This safety measure has been taken since low SQI values are associated with an unreliable qCON measure that, if fed back to the controller, could increase the risk of under/overdosing. The tuning parameters for the induction and maintenance phases of the event-based PID controller employed for the experiments are shown in Table I, note that a gain-scheduling approach is used. It is worth noting that the same tuning parameters of the event-based controller that were used in [28] with the BIS have been employed here with the qCON. Indeed, it has been proven in clinical studies that the qCON correlates well with the BIS [18], [23]. Moreover, changing the DoH sensor implies only a modification of the nonlinear part of the Wiener model considered and not of the linear PK/PD parts. In other words, changing the BIS with the qCON can be seen as a perturbation on the nonlinear static gain. Thus, with this experiment, we test the robustness of the controller tuning with respect to model uncertainty.

TABLE I
TUNING PARAMETERS OF THE EVENT-BASED PID CONTROLLER

	K_p $[mg/s]$	T_i $[s]$	T_d $[s]$	Δ_i
Induction	0.0087	197.47	29.18	15
Maintenance	0.0083	287.62	6.25	20.57

TABLE II
PATIENTS DEMOGRAPHIC INFORMATION AND TYPE OF SURGERY

Patient	Age	Height [cm]	Weight [kg]	Gender	Surgery
1	64	162	74	F	Breast implant replacement
2	83	150	50	F	Skin tumor resection
3	81	170	85	M	Skin tumor resection and microsurgical flap
4	35	168	53	F	Reconstructive breast surgery

TABLE III
VALUES OF THE CONSIDERED PERFORMANCE INDEXES

Patient	*Induction time* [s]	*Lowest qCON*	$qCON$ $40-60$ [%]	$qNOX$ $40-60$ [%]
1	80	40	90.9	94.6
2	114	42	74.9	75.2
3	114	34	83.8	16.1
4	120	46	64.7	76.2

III. EXPERIMENTAL RESULTS

The clinical experiments were performed on four patients undergoing TIVA for plastic surgery after obtaining approval by the Ethics Committee of Brescia (number of the study: NP-2861). Details regarding their demographic information and the description of the surgical procedure are given in Table II. The same clinical protocol described in [10] was used. The Conox monitor was used to acquire qCON and qNOX, a Dräger Infinity Delta monitor (Drägerwerk, Lübeck, Germany) was used to record hemodynamic variables and two Alaris GH (Becton Dickinson, Franklin Lakes, USA) syringe pumps were used as actuators to administer propofol and remifentanil. The results achieved by the controller during the induction and the maintenance phases are shown in Table III. The induction time is defined as the time interval between the beginning of infusions and the time when the qCON goes below 60 and stays there for the next 30 seconds. The lowest qCON is the minimum observed value of the qCON in the 60 seconds following the induction time. The time percentages of qCON and qNOX inside the recommended range from 40 to 60 are calculated on the duration of maintenance, which is the interval between induction time and the instant when the automatic control is turned off at the end of surgery. From the results shown in Table III it is possible to observe that the control specification for the induction phase were satisfied for all patients. Indeed, anesthesia was always induced within 2 minutes and qCON undershoots below 30 never occurred. As regards the maintenance phase remarkable results

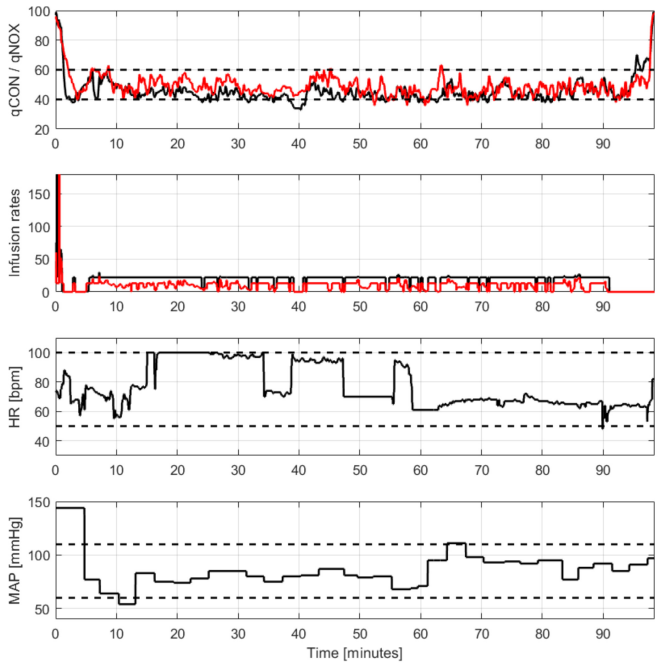

Fig. 2. Clinical variables trends of patient 1. From top to bottom: qCON and qNOX (black and red solid lines, respectively); propofol and remifentanil infusion rates (black and red solid lines, respectively) expressed in ml/h; heart rate (black solid line); noninvasive mean arterial pressure (black solid line). The black horizontal dashed lines mark the ranges of clinically recommended values. The spikes in the heart rate plot are due to artifacts caused by the electrocautery device.

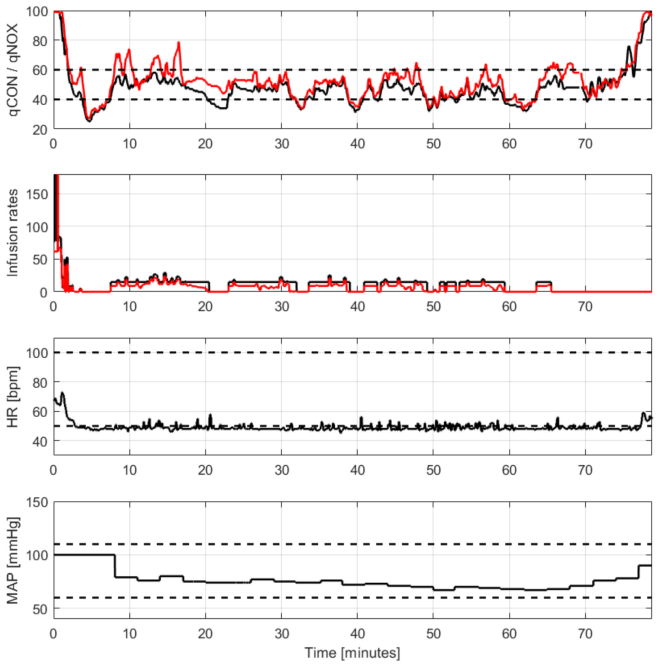

Fig. 3. Clinical variables trends of patient 2. From top to bottom: qCON and qNOX (black and red solid lines, respectively); propofol and remifentanil infusion rates (black and red solid lines, respectively) expressed in ml/h; heart rate (black solid line); noninvasive mean arterial pressure (black solid line). The black horizontal dashed lines mark the ranges of clinically recommended values.

were obtained in terms of percentage of maintenance time in which the qCON and the qNOX were maintained within the recommended range ($qCON$ $40-60$ and $qNOX$ $40-60$), with the exception of patient 3. The individual clinical variable plots for each patient enrolled are shown in Figures 2-5. In the plots, the horizontal dashed lines represent the ranges of clinically recommended values that are 40-60 for qCON and qNOX, 50-100 beats per minutes (bpm) for HR and 60-110 mmHg for the mean arterial pressure (MAP). By observing the qCON/qNOX plots we can observe different behaviors among the enrolled patients. As regards patient 1, during the first 55 minutes of surgery the qNOX was greater than the qCON, then, in the second part of surgery, the values of the two indexes were similar. For patient 2 the qNOX values were a little bit above 60 during the first minutes of surgery. For patient 3 the qNOX primarily remained below 40, as also witnessed by the low value of $qNOX$ $40-60$. For patient 4 both qCON and qNOX remained below the recommended threshold between minute 30 and 80. However, it is worth noting that those values were not reliable since the SQI was low in that time range due to the electrocautery interference. Indeed, in that time range also the infusion rates remained constant and equal to the baseline infusion rates since the safety mechanism described in Section II-B was activated. Then, around minute 100 there was a sudden increase of qCON and qNOX due to an abrupt surgical stimulation (prosthesis insertion), which however was quickly compensated by the PIDPlus controller without causing excessive undershoot. The infusion rates plots show that very smooth and piece-wise

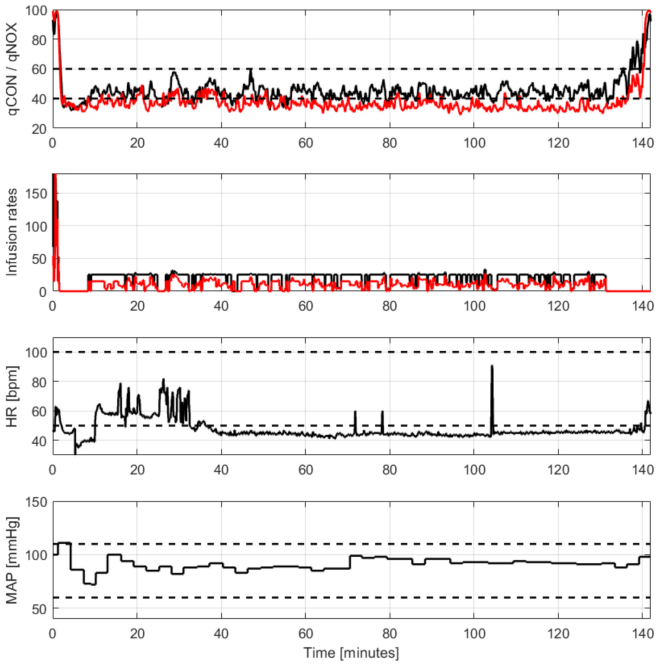

Fig. 4. Clinical variables trends of patient 3. From top to bottom: qCON and qNOX (black and red solid lines, respectively); propofol and remifentanil infusion rates (black and red solid lines, respectively) expressed in ml/h; heart rate (black solid line); noninvasive mean arterial pressure (black solid line). The black horizontal dashed lines mark the ranges of clinically recommended values. The spikes in the heart rate plot are due to artifacts caused by the electrocautery device.

constant infusion profiles have been obtained. Indeed, the infusion rates were mainly modulated around their baseline values and adjustments were made only when necessary,

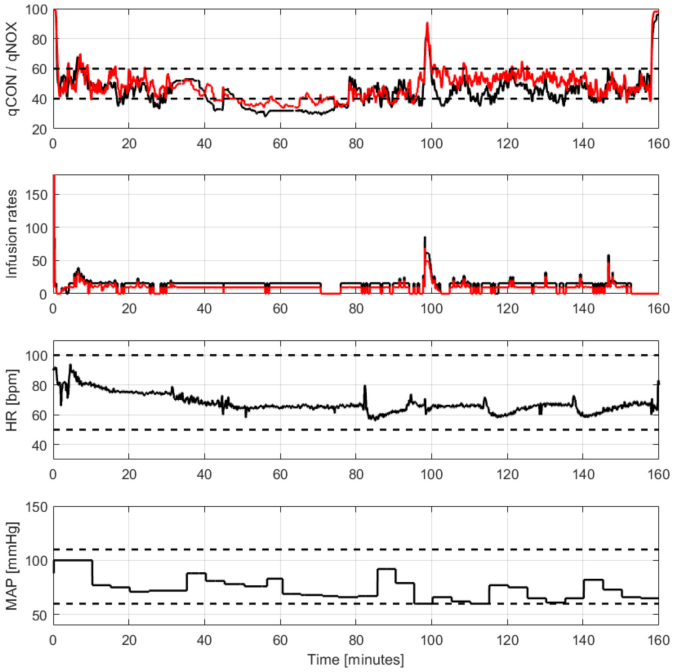

Fig. 5. Clinical variables trends of patient 4. From top to bottom: qCON and qNOX (black and red solid lines, respectively); propofol and remifentanil infusion rates (black and red solid lines, respectively) expressed in ml/h; heart rate (black solid line); noninvasive mean arterial pressure (black solid line). The black horizontal dashed lines mark the ranges of clinically recommended values.

thus filtering out the qCON variations provoked by noise. However, this was not paid at a cost of a sluggish response as shown in Figure 5 where the event-based controller showed, around minute 100, its capabilities to quickly react to qCON variations due to an actual alteration of DoH. As regards the hemodynamic variables they remained stable throughout the whole surgical procedure for all the patients enrolled. The MAP always remained within the clinically recommended range. The HR of patients 2 and 3 was slightly below the recommended range but this did not caused any issue form a clinical point of view.

IV. Discussion

In the previous section the experimental results obtained on four patients have been presented. Although the number of patients considered is too limited to carry out an exhaustive performance analysis, useful insights can be extrapolated. The event-based PID MISO controller that uses qCON as feedback signal performed well for all the patients enrolled. The controller was able to autonomously induce and maintain anesthesia and manual interventions by the attending anesthesiologist were never required. Moreover, the controller always provided an adequate anesthetic state of the patient in terms of qCON and hemodynamic stability. By observing the control actions it also appears that the use of qCON in combination with the event-based controller allows a smooth and piecewise constant infusion profile to be obtained. Thus, the systems is predictable and easy to supervise from an anesthesiologist perspective since it is able to mimic very well the behavior of the human operator. This is relevant since the goal of closed-loop anesthesia system is not to replace the anesthesiologist but to provide them a supporting tool, thus this can favour their acceptance and diffusion in the clinical practice. It is worth stressing that this behavior is not obtained by sacrificing the disturbance rejection performances. The results obtained in terms of qCON control confirmed that the tuning parameters obtained by considering the BIS remain suitable also when the DoH sensor is changed, thus showing the robustness of the tuning approach employed. The results obtained can also be seen as a good validation study of the proposed MISO architecture for propofol and remifentanil coadministration. Indeed, in previous clinical experiments the DoH was assessed with the BIS and analgesia was inferred by observing the time courses of the hemodynamic variables. In this experiment it has been shown that the controller not only performs well in terms of DoH but also in terms of analgesia, as suggested by the good performance obtained in terms of qNOX. The results also suggest that the qNOX could be suitable to be employed as a feedback variable to develop MIMO control solutions. Indeed, among the patients enrolled the qNOX showed different behaviors that seems to reflect patients' analgesia/nociception balance. For example, in patient 1 both qCON e qNOX remained within the recommended range and assumed similar values. This was also accompanied by HR and MAP values in the recommended range, thus indicating a good analgesia/nociception balance. In patient 2 the qNOX assumed values above the recommended threshold concurrently with the beginning of the surgical stimulation. In patient 3 the qNOX remained below the recommended threshold for most of the time of anesthesia. This was also accompanied by a low value of HR. Thus, this could indicate a slight excess of analgesia with the possibility of reducing the infusion of remifentanil. Finally, in patient 4 the qNOX show an increase from minute 100 to minute 140, concurrently to the painful stimulation caused by the insertion of the breast prosthesis and by the skin suturing. Thus, this could indicate an insufficient analgesia that could be compensated by increasing the infusion of remifentanil. It is worth stressing that in these experiments only patients undergoing elective plastic surgery have been considered. Thus, these observations have not a general validity and future studies should be performed in other surgical contexts. However, the results obtained using qCON confirm those of previous works utilizing BIS in terms of maintaining an adequate level of hypnosis. The event-based controller effectively filters the noise, as already demonstrated in [28] with the BIS, while maintaining a performance comparable to that achieved in [11] with a standard PID controller, which, in turns, demonstrated its ability to outperform manual control [10].

V. Conclusion

This letter presents the first experimental results of closed-loop anesthesia performed by using the Conox monitoring system. To this end, an event-based PID MISO controller originally designed to work with the BIS has been used by substituting this latter with the qCON index provided by the

Conox. The qNOX index has also been recorded to assess the performance of the controller in terms of analgesia. Four patients undergoing general anesthesia for elective plastic surgery were involved in the experiment. The satisfactory control performance obtained in terms of qCON shows that the proposed event-based PID controller is robust with respect to the perturbation introduced by the use of a DoH sensor different from that used for its tuning. The performance obtained in terms of qNOX shows that the proposed MISO architecture is effective in providing an adequate level of analgesia. Future works should exploit the qNOX information in the controller design to enhance the performance in terms of analgesia control.

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