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ORIGINAL RESEARCH

A novel multivariate STeady-state index during general ANesthesia (STAN)

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Abstract The assessment of the adequacy of general anesthesia for surgery, namely the nociception/anti-nociception balance, has received wide attention from the scientific community. Monitoring systems based on the frontal EEG/EMG, or autonomic state reactions (e.g. heart rate and blood pressure) have been developed aiming to objectively assess this balance. In this study a new multivariate indicator of patients' steady-state during anesthesia (STAN) is proposed, based on wavelet analysis of signals linked to noxious activation. A clinical protocol was designed to analyze precise noxious stimuli (laryngoscopy/intubation, tetanic, and incision), under three different analgesic doses; patients were randomized to receive either remifentanil 2.0, 3.0 or 4.0 ng/ml. ECG, PPG, BP, BIS, EMG and CO_2 were continuously recorded. ECG, PPG and BP were processed to extract beat-to-beat information, and CO_2 curve used to estimate the respiration rate. A combined steady-state index based on wavelet analysis of these variables, was applied and compared between the three study groups and stimuli (Wilcoxon signed ranks, Kruskal–Wallis and Mann–Whitney tests). Following institutional approval and signing the informed consent thirty four patients were enrolled in this study (3 excluded due to signal loss during data collection). The BIS index of the EEG, frontal EMG, heart rate, BP, and PPG wave amplitude changed in response to different noxious stimuli. Laryngoscopy/intubation was the stimulus with the more pronounced response ($P<0.05$). These variables were used in the construction of the combined index STAN; STAN responded adequately to noxious stimuli, with a more pronounced response to laryngoscopy/intubation (18.5–43.1 %, $P<0.05$), and the attenuation provided by the analgesic, detecting steady-state periods in the different physiological signals analyzed (approximately 50 % of the total study time). A new multivariate approach for the assessment of the patient steady-state during general anesthesia was developed. The proposed wavelet based multivariate index responds adequately to different noxious stimuli, and attenuation provided by the analgesic in a dose-dependent manner for each stimulus analyzed in this study.

Keywords Nociception · Pain · Anesthesia · Analgesia · Homeostasis · Wavelet transform · PKPD modeling · Steady-state

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1 Introduction

Pain is a multifaceted phenomenon, necessary for organism preservation, nonetheless this intrinsic defense mechanism may be undesirable in many clinical situations, making an adequate monitoring and treatment essential. One of these critical situations is during a surgical intervention, in which tissue damage leads to extensive physiological responses, such as increase in heart rate (HR) and blood pressure (BP), that need to be controlled by the use of potent analgesics.

Overdosing and underdosing has been related to patients' outcome, and the balance between anesthetics and noxious stimulation must be thoroughly examined [1, 2].

General anesthesia may be described as a neurophysiologic state defined by hypnosis, amnesia, paralysis and analgesia [3]. In order for the patient to be submitted to noxious stimuli the anesthesiologist needs to titrate the different anesthetic drugs to obtain an optimum equilibrium state. Several methods have been proposed to describe the nociception/anti-nociception balance (Noc/ANoc, balance between nociception or noxious activation and anti-nociception provided by anesthetics), but it still presents a research challenge.

Some of the proposed methods to assess the Noc/ANoc balance include the study of HR variability [4], photoplethysmography (PPG) wave amplitude [5], skin conductance [6], pupil diameter [7], EEG derived indexes variability [8–10], and electromiography (EMG) [11], although none has been widely disseminated. Some methods are combinations of variables with complementary information, and others are based solely on one physiological variable. All these physiological signals are conditioned by environmental factors and auto-regulation mechanisms (e.g. positioning). Some authors explored the homeostasis mechanisms to regulate HR and BP, that are altered in the presence of noxious stimulation and anesthetic drugs. In Rantanen et al. [12] the authors studied the fast and slow short-term HR variability related to respiration and modulated by the sympathetic/parasympathetic nervous systems (Poincaré analysis), in conjunction with the amplitude of the pulse wave photoplethismography (PPG), and in [13] the authors propose a method that relates the variations in BP and changes in RR intervals to evaluate the baroreflex response as a predictor of movement.

The objective during general anesthesia is to maintain the patient in homeostasis, and provide conditions for the clinical procedures to be performed. In this study, we propose to analyze different physiological variables usually monitored during general anesthesia, found to be related to noxious activation and analgesic dose. These variables were used in the development of a multivariate wavelet based indicator of the patient steady-state, which may carry information on the homeostasis and Noc/ANoc balance of the patient.

2 Materials and methods

Data were collected following institutional and Ethics Committee approval, at Hospital the Santo António (Centro Hospitalar do Porto, Portugal). Patients scheduled for urological procedures under general anesthesia were enrolled, after signing the informed consent.

2.1 Clinical protocol

The clinical protocol for this study was designed to evaluate autonomic responses to precise noxious stimuli (laryngoscopy/intubation, tetanic stimulus, and incision) under different analgesic doses, and develop a new multivariate indicator of patient's steady-state during anesthesia (STAN).

Adult patients scheduled for urological procedures under general anesthesia, ASA I–III, fulfilled the study requirements. Exclusion criteria were body weight 30 % above or lower the ideal weight for the corresponding height and gender, or counter-indication to the anesthetic technique.

The anesthetic technique was a total intravenous anesthesia (TIVA), administered through a target controlled infusion (TCI) of propofol and remifentanil, with Schnider and Minto's pharmacokinetic models (Orchestra Base Primea®, Fresenius Kabi) [14, 15]. Patients were randomly divided into three study groups considering the analgesic dose target for the precise stimuli (Group 1 2 ng/ml; Group 2 3 ng/ml; Group 3 4 ng/ml Ce). Induction was performed as follows: remifentanil infusion initiated with effect-site concentration (Ce) target steering; when remifentanil Ce reached steady-state, a propofol infusion at 200 ml/h was initiated until loss of response to verbal and mechanical stimulation; at this point propofol and remifentanil were controlled by effect-site TCI, aiming at a BIS range of 40–60 (manufacturer recommended range for general anesthesia). BIS sensor was placed on patient's forehead according to recommendations and contra-lateral to site of incision [16]. For each stimulus the remifentanil Ce was maintained in steady-state before and following stimulation (180 s), according to the study group dose (Fig. 1). Time from first laryngoscopy to intubation was registered and analyzed in the search for possible bias factors.

Following the analysis of the responses to precise noxious stimuli (laryngoscopy/intubation, tetanic and incision), and during the surgical procedure, analgesic doses were changed in ascending and descending steps of 0.5 ng/ml, according to clinical evaluation (Fig. 1).

BP was monitored non-invasively until insertion of a pressure transducer in the radial artery, preferably following induction of anesthesia. Data were collected and synchronized using the TCI software RugloopII Waves© (Demed, Belgium). Information considered relevant for the study was annotated, including loss of response to verbal and mechanical commands, recovery of consciousness, drugs' administration, movement, and stimulus onset,

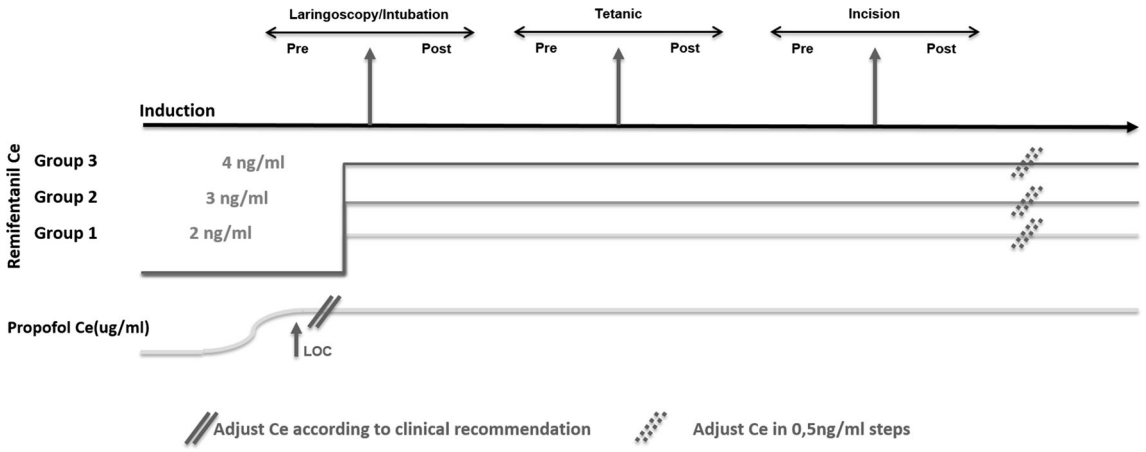

Fig. 1 Study timeline schematic representation; anesthesia induced and maintained with a TIVA TCI of propofol and remifentanil. Patients divided into three study groups according to the remifentanil effect-site concentration (Ce) for the the precise noxious stimuli (Group 1 2 ng/ml; Group 2 2 ng/ml; Group 3 4 ng/ml)

generating time stamps for each stimulus start and duration. Stimulus time stamps were used to produce a stimulus intensity trend, according to the estimated stimuli intensities described in [17].

Collected data included patients' demographic data, drugs infusion rate and concentrations, BIS, BIS Standard-Deviation (SD), frontal EMG, EMG SD, CO_2, ECG, BP and PPG waves. Data were analyzed off-line using Matlab®.

2.2 Data pre-processing

Data were pre-processed to extract relevant information linked to noxious activation. From the ECG, QRS complexes were detected, from the BP wave, systolic BP was extracted (SBP), from the PPG, wave amplitude was extracted (PPGA), and from the CO_2 curve, respiration rate (RespR) was estimated. The time series were then re-sampled using a cubic Hermite spline (1 Hz) producing a smooth continuous function for interpolation.

A high-pass Butterworth zero-phase filter of order 6, with cutoff frequency of 0.5 Hz, was used on the original ECG. From the filtered data, QRS peaks were detected, and the sequences of RR intervals obtained. A method with a time varying threshold of QRS complexes amplitude was used in this study. This method sets a recursive detection threshold (n_i) using the last detected complexes' amplitude according to Eqs. 1 and 2 [18].

$$n_i = \mu \tilde{z}_{e,i} \tag{1}$$

$$\tilde{z}_{e,i} = \tilde{z}_{e,i-1} + \alpha\left(z(\theta_i) - \tilde{z}_{e,i-1}\right),\ i \geq 1 \tag{2}$$

where θ_i is a detected QRS complex, $\tilde{z}_{e,i}$ is the previously calculated average, and $z(\theta_i)$ the amplitude of the most recently detected complex. μ represents the fraction used as threshold $(\mu = 0.7)$ and α the rate at which the threshold may change $(\alpha = 0.2)$.

This method was expanded to a time-dependent threshold as described in [18], improving erroneous detection of high amplitude T waves, with an eye-closing period. This period is usually between 160–200 ms, which is the time of absolute refraction during which the heart does not respond to electrical stimulation. Nevertheless, this period may be too long, missing ectopic beats. A waiting time during which no beat is detected (160 ms) was defined, followed by a linearly descending threshold.

Upon detecting the QRS complexes, the RR intervals sequence was extracted. The RR interval was defined as the time difference between two consecutive QRS complexes $(t_{R_i} - t_{R_{i-1}})$, and the HR sequence obtained by Eq. 3.

$$HR(t_{R_i}) = \frac{60}{t_{R_i} - t_{R_{i-1}}} \qquad (beats/min) \tag{3}$$

Following QRS peaks detection, RR intervals extraction and interpolation, the obtained RR sequence was still contaminated with outliers due to poor quality in the ECG data acquisition. The extracted sequence was post-processed for outlier detection and removal. The original extracted RR sequence was smoothed using the robust Loess method, a local regression with linear least squares, and a 2nd degree polynomial model, assigning lower weights to outlier values in the regression [19]. This method allows the construction of a smoother version of the original signal, diminishing the impact of outliers; to detect an outlier a comparison between the original and smoothed signal was performed: if the difference between the two sequences was above two standard-deviations of the median error observed in the population data, an outlier was identified and substituted by the corresponding point in the smoothed signal version.

A similar technique was applied to the remaining waves, extracting beat-to-beat information of the SBP and PPGA. Beat-to-beat PPGA was extracted considering the consecutively registered wave values at local minimum A (t_{A_i}) and local maximum B (t_{B_i}), given by Eq. 4, and shown in Fig. 2.

$$PPGA(t_{B_i}) = PPG(t_{B_i}) - PPG(t_{A_i}) \tag{4}$$

Figure 2 presents the synchronized waves from one of the data sets in the study, with correspondent extracted signal information.

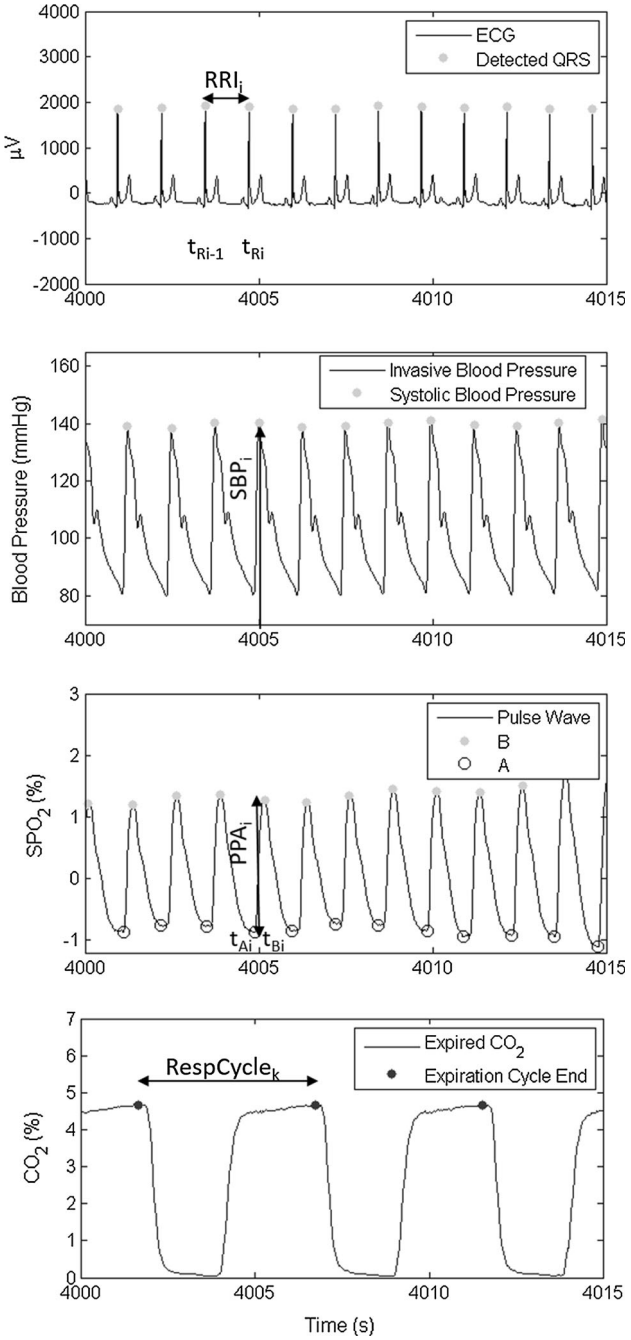

Fig. 2 Pre-processing of wave files collected during the study: electrocardiogram (ECG) and QRS complexes, blood pressure wave and systolic blood pressure peaks, photoplethysmography wave (PPG) and wave amplitude (A local minimum and B local maximum PPG points), and finally expired CO2 wave and corresponding periods of the respiratory cycle

2.3 Steady-state detection and wavelet analysis

When modeling a process it is important to obtain steady-state (SS) information of the process overall performance, including inputs and outputs of the system. In this study, we considered the patient as the system, drugs' doses and stimulus intensity as inputs, and the measurable physiological signals related to noxious activation the outputs. A wavelet based approach was employed for the SS detection of the analyzed signals, including the input drugs' infusion rates. Wavelets are currently widely used in several fields due to their properties, such as noise removal and feature extraction [20–23]. The method used was initially proposed in [20], and is summarized here with the correspondent and adequate modifications.

The concept behind multi-scale representation is to describe the signal as a limit of successive approximations (Eq. 5).

$$\begin{aligned} f(t) = f_0 &= \sum_{i\in I_0} c_{0,i}\varphi_{0,i} = \sum_{i\in I_1} c_{1,i}\varphi_{1,i} + \sum_{k\in k_0} d_{1,k}\psi_{1,k} = \ldots \\ &= \sum_{i\in I_j} c_{j,i}\varphi_{j,i} + \left(\sum_{k\in k_j} d_{j,k}\psi_{j,k} + \sum_{l=1}^{j}\sum_{k\in k_l} d_{l,k}\psi_{l,k}\right) \\ &= \underbrace{\sum_{i\in I_j} c_{J,i}\varphi_{J,i}}_{\substack{Low\ Frequency \\ Component\ Scale\ J}} + \underbrace{\sum_{j=1}^{J}\sum_{k\in k_i} d_{j,k}\psi_{j,k}}_{\substack{High\ Frequency \\ Components\ Scale\ 1\ to\ J}} \end{aligned} \tag{5}$$

where $\varphi_{j,i}$ and $\psi_{j,k}$ are the discretized dyadic scaling and wavelet functions, respectively.

Due to the known Wavelet Transform (WT) properties, the noise can be reduced using a soft threshold technique over the WT modulus (Eq. 6).

$$d'_{j,k} = \begin{cases} 0 & |d_{j,k}| \le \delta_j \\ sign(d_{j,k})\left(|d_{j,k}| - \delta_j\right) & |d_{j,k}| > \delta_j \end{cases} \tag{6}$$

where δ_j is the threshold value at scale j, $1 \le j \le J$, and $0 \le k \le K_j$.

At scale j = 1 the WT modulus is dominated completely by noise and the threshold value δ_1 can be assigned as the mean of the modulus maxima. The following threshold values are calculated as given by Eq. 7.

$$\delta_j = \delta_1 2^{(j-1)/2}, \quad 2 \le j \le J \tag{7}$$

Rapid changes in the signal may be detected using WT, since these changes in the signal are identified as a maximum in the corresponding WT. Two points, within a defined interval t_p, with a WT maximum and opposite signal identify an abnormality (Eqs. 8, 9).

$$\left|W_f(p_1)\right| \quad and \quad \left|W_f(p_2)\right| \ge T_1 \tag{8}$$

$$sign(W_f(p_1)).sign(W_f(p_2)) < 0, \quad p_2 - p_1 \le t_p \tag{9}$$

After detecting an abnormality, the duration of this event is determined as the nearest point t_a to the left of p_1 and the nearest point t_b to the right of p_2 that satisfy rules in Eqs. 10 and 11.

$$\left|W_f(t_a)\right| \quad and \quad \left|W_f(t_b)\right| \ge T_2 \tag{10}$$

$$\left|W_f(t_a - 1)\right| \quad and \quad \left|W_f(t_b + 1)\right| < T_2 \tag{11}$$

Threshold values T_1 and T_2 are computed from historic data as given in Eq. 12.

$$T_1 = 3\lambda_1 w, \quad T_2 = w \tag{12}$$

where w is the standard deviation of the wavelet modulus of historic measurements with noise eliminated, and λ_1 an adjustable parameter around 1.

A SS index β was used to measure the degree of SS of each signal, with $\beta = 0$ for unstable status, and $\beta = 1$ for SS. When trying to determine SS of a signal it is important to distinguish zero-crossing points of $W_j f(t)$. To do that the WT on $W_j f(t)$ is performed, obtaining a second order WT $WW_j f(t)$, proportional to the second derivative of $f(t)$.

The calculus of $\beta(t)$ was based on these notions, detecting rapid changes in $W_S f(t)$ and distinguishing zero-crossing points with $WW_S f(t)$ values. S is the characteristic scale, meaning the proper scale to analyze the WT where the WT represents the process variations properly (Eq. 13).

$$S = j = int\left(log_2 \frac{\tau}{t_s} + 0.5\right) \tag{13}$$

where t_s is the sampling interval, and τ the response time constant.

SS index is defined according to the following rules:

- if $|W_S f(t)| > T_u$ then $\beta(t) = 0$, where T_u is the identification WT modulus threshold for unsteady status;
- if $|W_S f(t - \Delta t)| < T_s$ then $\beta(t) = 1$, where T_s is the identification WT modulus threshold for steady status, and Δt a long enough time interval to identify SS;
- to detect zero-crossing points, the second order WT is used. If $|W_S f(t)| < T_s$ and $|WW_S f(t)| < T_w$ then $\beta(t) = 1$ where T_w is the second-order WT modulus threshold to identify zero-crossing point in the WT.

In other cases, the relations in Eqs. 14, 15, 16 and 17 are used.

$$\beta(t) = \xi[\theta(t)] \tag{14}$$

$$\theta(t) = |W_S f(t)| + \gamma |WW_S f(t)| \tag{15}$$

$$\gamma = \begin{cases} 0 & |WW_S f| \le T_w \\ (|WW_S f| - T_w)/2T_w & |WW_S f| \in]T_w, 3T_w[\\ 1 & |WW_S f| \ge 3T_w \end{cases} \tag{16}$$

$$\beta(t) = \begin{cases} 0 & \theta(t) \ge T_u \\ \xi[\theta(t)] & T_s < \theta(t) < T_u \\ 1 & \theta(t) \le T_s \end{cases} \tag{17}$$

where ξ is a smooth transfer function with range [0, 1] (Eq. 18).

$$\xi(x) = \frac{1}{2}\left[cos\left(\frac{x - T_s}{T_u - T_s}\pi\right) + 1\right] \tag{18}$$

The thresholds T_u, T_s and T_w were calculated from historic measurements, after manually selecting SS periods, and performing WT and second-order WT. Then the standard deviation of the WT modulus σ_{W_f} and the median of the second-order WT modulus σ_{WW_f} are obtained, and the thresholds defined as follows:

$$T_s = \sigma_{W_f}, \quad T_u = 3\lambda_2 \sigma_{W_f}, \quad T_w = \sigma_{WW_f} \tag{19}$$

where λ_2 is an adjustable parameter around 1.

The quadratic spline wavelet function and scaling function described in [23] were used.

2.4 Statistical analysis

Non-parametric paired sample tests were used for the comparison of observed values before and following stimulation, since measurements inside the same patient were being compared (Wilcoxon signed ranks). For the assessment of the analgesic impact, a non-parametric test for the comparison between different groups of patients was performed (Kruskal–Wallis and Mann–Whitney tests). $P < 0.05$ was considered significant. Data presented as mean ± standard-deviation.

3 Results

Thirty-four patients were enrolled in the study, however three were excluded from the analysis due to technical failure and signal loss during data collection. Surgical procedures included prostatectomy (13), nephrectomy (8), nephrolithotomy (5), cystectomy (2), urethral reconstruction (1), ureteropelvic junction repair (1), and pyelotomy (1). Five patients were eliminated from the analysis of response to precise noxious

stimuli due to protocol deviations: one case from Group 1, two cases from Group 2, and two cases from Group 3. The reasons for exclusion were the impossibility to maintain the patient without any outer stimulus following the precise noxious stimuli, which could bias the analysis, and signal loss from any of the variables analyzed. The final data set for this analysis was composed by 26 patients, nine in Group 1, nine in Group 2 and eight in Group 3.

Table 1 shows the demographic data of the final sample for precise stimuli analysis (no differences between groups). Location of the incision was (left, central, right): Group 1 3, 4, 2; Group 2 2, 7, 0; Group 3 3, 3, 2. In general time from first laryngoscopy to intubation was below 60 s, only two cases exceeded the one minute interval.

All variables were analyzed and compared within the same patient (stimulus analysis), and for the different groups of patients (analgesic dose analysis). HR, SBP, PPGA, BIS SD, EMG and EMG SD responded to stimulus and according to the remifentanil dose (Table 2). All these variables were included in the assessment of the Noc/ANoc balance and patient homeostasis. Statistical significant differences in amplitude responses considering the three noxious stimuli applied were also observed. Laryngoscopy/intubation was the stimulus with more pronounced response (increased amplitude response to stimulation), followed by incision, and tetanic stimulus. This result is corroborated by results presented in the literature [24–26].

3.1 Wavelet analysis and the steady-state index

The signals analyzed, and found to be related to noxious activation, were BIS, EMG, HR, SBP and PPGA. The respiration rate (RespR) was included in this analysis, since spontaneous ventilation may be a signal of interest to the anesthesiologist. Although ventilation was mechanically maintained in all patients, the anesthesiologist may change the ventilation conditions, which may alter the equilibrium state of the patient and induce changes in other physiological signals. Also, if the patient starts to recover from neuromuscular blockade, this may be translated into spontaneous breathing, and linked to arousal episodes. The following results include data for the respiration rate. Nevertheless when comparing the response to the laryngoscopy/intubation stimulus the respiration rate was removed from the analysis, since it would introduce bias due to the concomitant initiation of mechanical ventilation.

A training set of five patients randomly selected was used to adjust the wavelet thresholds of the eight analyzed signals: propofol Ce, remifentanil Ce, stimulus, BIS, EMG, HR, SBP, PPGA and RespR. For each data set, the output signals were visually inspected and sequences considered as in SS, selected to extract the thresholds later used in the SS index processing. Next, the method was applied to each signal individually, and individual SS indexes combined to produce the input (β_{In}, propofol Ce, remifentanil Ce, stimulus) and output (β_{Out} or STAN, BIS, EMG, HR, SBP, PPGA and RespR) SS indexes.

Individual $\beta(t)$ indexes were used to extract SS periods, by thresholding its value: if $\beta(t) \geq 0.9$ for more than 1 min then the signals were considered to be in SS. To validate the method, sequences that were manually annotated as in SS, and used to define the detection thresholds, were analyzed. Of the total time used in the threshold detection 91 % was found to be in SS ($\beta_{Signal_i} \geq 0.9,\ i = 1, \ldots, 8$), demonstrating that the method is adequately detecting SS sequences.

Table 1 Patients' demographic data (original and precise stimuli analysis sample)

	Global	Group 1	Group 2	Group 3
Original data set				
Gender (M/F)	18/13	5/5	8/3	5/5
ASA (I/II/III)	8/21/2	3/7/0	3/6/2	2/8/0
Age (years)	54.9 ± 13.4	58.2 ± 15.4	50.8 ± 13.8	56.1 ± 10.6
Weight (kg)	69.9 ± 12.3	66.0 ± 10.9	74.9 ± 14.4	68.5 ± 10.3
Height (cm)	165.0 ± 7.6	161.9 ± 2.6	168.4 ± 9.7	164.4 ± 7.5
LBM (kg/m^2)	25.6 ± 3.9	25.1 ± 3.6	26.3 ± 4.1	25.4 ± 4.1
Precise stimuli data set				
Gender (M/F)	15/11	4/5	7/2	4/4
ASA (I/II/III)	7/18/1	3/6/0	2/6/1	2/6/0
Age (years)	55.0 ± 12.4	57.0 ± 15.8	54.0 ± 11.1	53.9 ± 10.6
Weight (kg)	69.4 ± 12.2	63.4 ± 9.1	77.2 ± 12.9	66.8 ± 10.9
Height (cm)	164.5 ± 7.5	161.6 ± 2.5	168.7 ± 9.6	163.1 ± 7.6
LBM (kg/m^2)	25.6 ± 3.9	24.4 ± 3.1	27.1 ± 3.9	25.2 ± 4.6

Global and for each study group of remifentanil target effect-site concentration: Group 1 2 ng/ml, Group 2 3 ng/ml and Group 3 4 ng/ml (data as mean ± standard-deviation)

Table 2 Median values of the variables analyzed in the study, for each stimulus (average pre and post stimulation), divided according to the drug dose group: remifentanil effect-site concentration (RemiCe) of 2.0, 3.0, or 4.0 ng/ml

	Baseline	Laryngoscopy		Tetanic		Incision	
		Pre	Post	Pre	Post	Pre	Post
HR							
Group 1	67.78	63.98	71.66	60.58	59.68	58.69	59.00
Group 2	68.98	58.85	65.14	64.86	61.00	59.60	58.59
Group 3	82.61	59.38	65.71	63.81	63.48	62.72	62.35
SBP							
Group 1	126.34	91.66	108.16	103.37	100.97	104.90	108.07
Group 2	125.05	97.43	102.04	100.95	99.23	98.51	115.37
Group 3	120.54	101.26	96.76	101.28	95.02	96.83	104.75
PPGA							
Group 1	1.12	6.14	4.10	1.11	1.07	1.62	1.02
Group 2	1.53	5.75	5.18	6.38	7.32	6.52	2.33
Group 3	1.17	2.46	2.68	1.82	2.49	2.56	2.29
BIS							
Group 1	81.43	43.63	46.60	46.79	42.50	41.79	43.44
Group 2	95.81	50.51	47.00	42.42	43.17	42.63	43.78
Group 3	87.91	47.14	45.08	43.22	45.95	45.39	45.21
BIS SD							
Group 1	3.60	3.21	7.13	3.26	3.25	2.44	3.11
Group 2	1.93	2.52	4.88	2.79	3.28	2.94	3.33
Group 3	3.17	2.83	5.33	3.84	4.51	3.19	5.25
EMG							
Group 1	44.67	26.52	28.19	26.51	26.90	25.68	26.46
Group 2	48.62	27.23	27.67	26.70	26.93	25.90	25.94
Group 3	49.85	28.93	29.29	26.51	26.65	26.67	26.63
EMG SD							
Group 1	2.98	0.88	3.41	1.21	0.43	0.44	1.04
Group 2	3.76	1.63	2.85	0.40	1.56	0.33	0.34
Group 3	3.18	1.12	3.10	0.41	1.22	1.25	1.02

Figure 3 shows the developed SS index (β_{Out}, STAN) for one of the patients in the study.

The methodology was applied to all data sets (N = 31, Table 1), besides information regarding the subjects' homeostasis state (β_{Out}, STAN), the implemented methodology allows the inspection of whether or not the designed clinical protocol was efficient in the production of both periods in SS and dynamic conditions. The total time analyzed, considering the 31 data sets, was of 6684 min, with an average duration per case of 215 ± 76 min. Table 3 shows the time percentage that each physiological signal analyzed was in SS ($\beta(t) \geq 0.9$) and dynamic conditions, and also of input SS (β_{In}) and output SS (β_{Out} or STAN).

Input drugs' SS was not always followed by output SS, since different factors interfere with the patient's homeostasis, being noxious stimulation one of these factors. Also, it should be highlighted that SS does not necessarily mean the patient is in optimum equilibrium, but only that the patient is stable around a determined state of operation.

The response of STAN to precise noxious stimuli was inspected, under different analgesic drug doses. Table 4 and Fig. 4 respectively present the median and normalized values of the amplitude response to each stimuli (Table 1). Statistical differences were found between pre and post intubation periods, with a decrease in the SS index, in a dose-dependent manner. Also the decrease was significantly higher in the laryngoscopy/intubation stimulus, when compared to tetanic and incision amplitude responses. This is in agreement with the results obtained for each variable individually.

The methodology described in this paper may be used to obtain periods of SS both on input and output variables, and allow the construction of SS valid models (drug interaction surface models), relating each drug dose to the observed effect, considering different stimulation intensities.

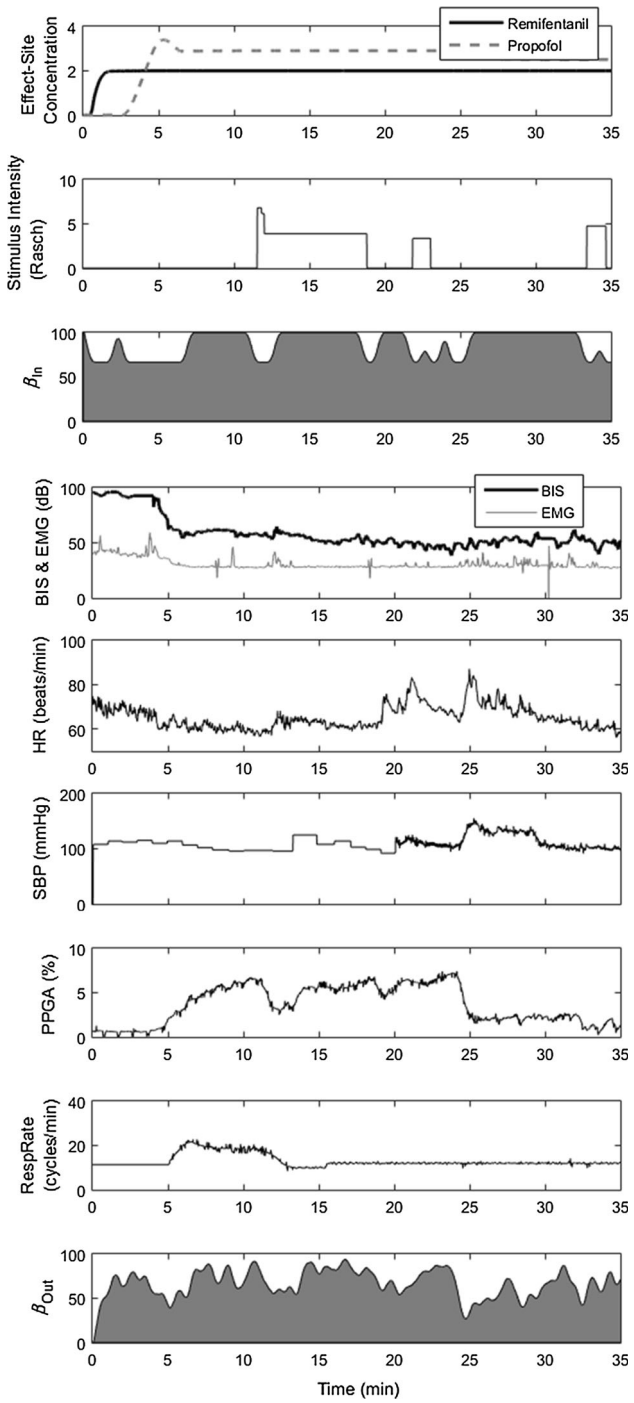

Fig. 3 Representation of the input and output steady-state indexes. The *bottom trend* may be interpreted as an steady-state index of the subject considering BIS, heart rate, systolic blood pressure, pulse wave amplitude and respiration rate (STAN)

4 Discussion

Despite the efforts of several researchers, the development of a Noc/ANoc indicator to titrate the analgesic drug during anesthesia is still a research challenge. The objective of this study was to develop a novel multivariate indicator of the patient steady-state using signals linked to noxious activation and shown to vary with different stimuli and analgesic doses. Developed indexes for the Noc/ANoc assessment during anesthesia use diverse approaches such as the standard-deviation of the BIS and EMG [16], RR variability [27], or combinations of RR interval and PPG amplitude [5, 12, 13]. The proposed index uses a new approach to detect variations of these signals outside a defined normal range (individually adjusted within the

Table 3 Percentage of total time (31 patients), that each signal was found to be in steady-state (SS) conditions using the proposed technique (data as mean ± standard-deviation)

Time Percentage in SS (N = 31)	
Remifentanil Ce	74.1 ± 7.8
Propofol Ce	79.5 ± 6.6
Stimulus	90.4 ± 3.1
β_{In}	59.5 ± 8.5
BIS	75.0 ± 9.7
EMG	67.0 ± 7.6
HR	32.6 ± 17.1
SBP	40.3 ± 19.3
PPGA	59.4 ± 28.6
RespR	88.4 ± 9.6
$\beta_{Out}(STAN)$	24.3 ± 14.2

Table 4 Amplitude responses of the proposed steady-state index to the precise stimuli, for each study group

	Baseline/pre-laryngo	Laryngoscopy	Tetanic	Incision
Group 1	23.7	−24.64	10.22	−3.68
Group 2	26.6	−12.22	−4.02	−3.84
Group 3	22.0	−10.05	−4.91	5.53

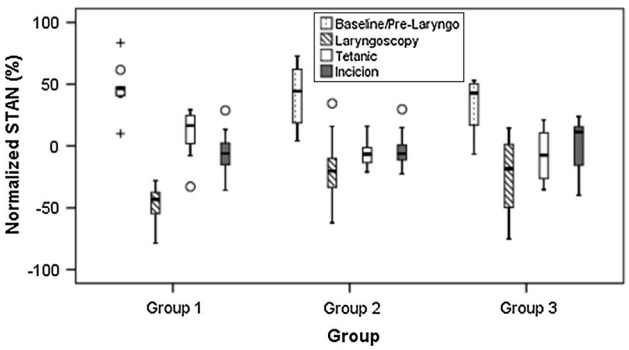

Fig. 4 Representation of the normalized amplitude responses of the proposed steady-state index (STAN) to the precise stimuli, for each study group

historical values), combining their information and allowing a detection of joint changes in these variables and the patient state.

Throughout daily activities, the body natural balance suffers constant interferences, automatically adjusting to maintain homeostasis [28]. During general anesthesia, the patient is subjected to the action of drugs and noxious stimulation, which interfere with the natural balance and also trigger compensatory mechanisms [12, 13, 27]; the clinician aims at maintaining the patient in a comfortable and stable condition, adjusting drug doses according to patients' needs, avoiding over/underdosing and its consequences [1, 2, 29–32]. In this study, these relations were investigated in response to drugs and stimuli inputs, to propose a measure of the patient SS.

In our work, BIS sensors were always placed contralateral to the surgical site of incision to assure maximum response, as described in previous studies [16]. We observed that the laryngoscopy/intubation was the stimulus with more pronounced response (increased amplitude response to stimulation), followed by incision, and tetanic stimulus. This result is corroborated by results presented in the literature [24–26]. The protocol allowed the collection of periods in dynamic and SS conditions, both containing useful information for the understanding of the relations between the different physiological signals linked to nociception. It was observed that considerable periods in dynamic conditions were obtained (approximately 50 % for each observed signal). The technique may be employed in search of combined periods of input and output SS, allowing the construction of surface models translating the relation between hypnotic and analgesic drugs and their impact on the output signals, under SS conditions, and under the influence of different stimuli intensities [33].

One of the limitations of our study, similarly to others in this field, is the difficulty in assessing stimulation intensity (patient is unconscious and unable to collaborate). We assumed that different stimuli have the same relation within and between subjects for comparison. The definition of the wavelet thresholds was retrieved following visual inspection, in a relatively small data set; this could be improved in future studies with a larger number of patients, and possibly with a calibration of the algorithm by a supramaximal stimulus, similar to what is used in the calibration of the neuromuscular blockade monitors, in order to achieve an individualized metric that is comparable between subjects. Finally, and although there is important information in the detection of the patient's global SS (even further in the detection of non-SS), it is not guaranteed that SS corresponds to an optimum patient condition, only that there is an equilibrium around some state of operation.

The concept of an index like the one we propose is to improve the simultaneous assessment of several variables on the patients state, and does not exclude attention to individual parameters. The STAN centralizes the information of all variables found to be related to noxious activation and analgesic dose, giving an idea of the variation of the signals in a certain moment in time (fast or slow varying), which may not be easily captured looking to the number on the screen or to a trend. It allows a fast extraction of the shift direction of all signals, defined according to the historically observed values.

5 Conclusion

A new measure of patients' steady-state during anesthesia (STAN) is proposed, as a method to evaluate patients' Noc/ANoc balance in response to changes in anesthetic doses and noxious stimulation. The STAN responded adequately to precise noxious stimulus and analgesic dose, and although the method allows the discern of patients' stability or instability, its main disadvantage is the fact that stability does not necessarily mean an optimum state. Further studies will be necessary to analyze the relation between these dynamic changes, stimuli intensity, and the analgesic dose to define the optimum state of operation. The main advantage of the proposed method is the automatic detection of dynamic changes and their direction, alerting the anesthesiologist for a shift in the patient's state that may require action.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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