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Instantaneous monitoring of heart beat dynamics during anesthesia and sedation

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Abstract

Anesthesia-induced altered arousal depends on drugs having their effect in specific brain regions. These effects are also reflected in autonomic nervous system (ANS) outflow dynamics. To this extent, instantaneous monitoring of ANS outflow, based on neurophysiological and computational modeling, may provide a more accurate assessment of the action of anesthetic agents on the cardiovascular system. This will aid anesthesia care providers in maintaining homeostatic equilibrium and help to minimize drug administration while maintaining antinociceptive effects. In previous studies, we established a point process paradigm for analyzing heartbeat dynamics and have successfully applied these methods to a wide range of cardiovascular data and protocols. We recently devised a novel instantaneous nonlinear assessment of ANS outflow, also suitable and effective for real-time monitoring of the fast hemodynamic and autonomic effects during induction and emergence from anesthesia. Our goal is to demonstrate that our framework is suitable for instantaneous monitoring of the ANS response during administration of a broad range of anesthetic drugs. Specifically, we compare the hemodynamic and autonomic effects in study participants undergoing propofol (PROP) and dexmedetomidine (DMED) administration. Our methods provide an instantaneous characterization of autonomic state at different stages of sedation and anesthesia by tracking autonomic dynamics at very high time-resolution. Our results suggest that refined methods for analyzing linear and nonlinear heartbeat dynamics during administration of specific anesthetic drugs are able to overcome nonstationary limitations as well as reducing inter-subject variability, thus providing a potential real-time monitoring approach for patients receiving anesthesia.

Keywords: Autonomic nervous system; Electrocardiogram; Electroencephalogram; Heart rate variability; Respiratory sinus arrhythmia; Anesthesia; Sedation; Propofol; Dexmedetomidine; Instantaneous point process monitoring

Background

Despite recent technological advances in anesthetic delivery and monitoring systems and the growing body of information on molecular mechanisms of anesthetic actions, most anesthesia care providers monitor drug-induced altered states of arousal with basic clinical signs (e.g., heart rate, blood pressure). Due to the high prevalence of anesthesia-related morbidity, more precise monitoring tools are required. In particular, the administration of anesthetic agents can result in hypotension, hypoxia, and cardiac dysrhythmias. Post-operative recall of intraoperative events, including sleep

disturbances, dreams, nightmares, flashbacks and anxiety, as well as post-traumatic stress disorder [1], is also an important source of anesthesia-related morbidity. It is estimated that the incidence of awareness under anesthesia is experienced by 20,000 to 40,000 individuals a year in the United States [2]. On the other hand, small surgical operations, as well as most nonsurgical procedures, do not require loss of consciousness and may be performed without discomfort using reduced doses of anesthetic agents than are currently used.

It is known that anesthesia-induced altered states of arousal depend on drugs having their effect in specific brain regions. For instance, propofol (PROP) is a GABA-A agonist that primarily targets pyramidal neurons in the lower output layers of the cortex. It elicits reductions in cortical and subcortical responses to auditory and noxious stimuli. In particular, progressive failure to perceive or respond to auditory or noxious stimuli is associated with a reduction in functional connectivity between the putamen and other brain regions [3]. Varying the concentration of propofol differentially modulates brain activation [4,5], suggesting that the effects on the brain are also likely reflected in autonomic nervous system (ANS) outflow dynamics. Dexmedetomidine (DMED) is an α2 adrenergic agonist that binds to the receptors in the locus ceruleus with the downstream effect leading to activation of the ventrolateral preoptic nucleus (VLPO). The active VLPO facilitates GABA-A and galanin-mediated inhibition of the midbrain, hypothalamic, and pontine arousal nuclei, promoting altered arousal [6]. It is well established that changes in neurophysiological recordings such as the electroencephalogram (EEG) can provide a reliable, empirical characterization of anesthesia-induced loss of consciousness [7,8]. Systematic EEG changes have long been known to occur at different levels of intravenous and inhaled anesthetics, including increases in frontal EEG power [9-15], shifting of the power spectrum towards lower frequencies [16], changes in coherence [11,17], and in deep anesthesia, burst-suppression and isoelectricity [18]. These developed metrics could be used in conjunction with ANS measures for a novel multimodal assessment of ANS reactions to pain during sedation.

The ANS is known to regulate physiological homeostasis and the organism's response to environmental and psychological stressors. Innervation of the heart from the ANS sympathetic branch causes increases in heart rate and vascular constriction. Conversely, the vagus nerve, the main parasympathetic innervation of the heart, causes a decrease in heart rate. Anesthetic agents target important brain areas involved in the central autonomic network, particularly the brainstem centers processing and integrating information to generate ANS outflow to multiple organs [6]. As a consequence, virtually every drug used for sedation has an effect on the ANS, a critical factor to take into account when assessing nociceptive levels. The effect of anesthetic agent on the ANS varies due to the different neural mechanisms of anesthetic action [6]. For instance, propofol attenuates autonomic tone and baroreflex responses to hypotension resulting in a decrease in blood pressure that is largely due to vasodilatation [19-22]. On the other hand, dexmedetomidine reduces systemic sympathetic tone without altering baroreflex sensitivity [22-31].

Heart rate variability (HRV) is conventionally defined as the variation in instantaneous heart rate around its mean [32]. It is considered to be an important quantitative

marker of cardiovascular regulation by the ANS [32]. Frequency analysis of HRV allows for the estimation of the balance between the sympathetic and the parasympathetic nervous systems. The specific type of general anesthetic agent used has been shown to have a differential effect on the change of HRV when measured after induction of general anesthesia [33]. A recent review article by Mazzeo and colleagues [34] summarizes some of the most relevant findings and limits of HRV as a diagnostic and prognostic tool in anesthesia and concludes that 'investigation of HRV as a method of monitoring the depth of anesthesia, assessing the response to painful stimuli, did not yield uniform results and needs more extensive investigations.' Several other important studies have considered HRV to quantify anesthesia [35-51], demonstrating the usefulness of HRV measures. In particular, time-varying identification methods have provided successful characterization of PROP and DMED effects on the ANS [19,20,24,28,44,51]. Several other studies have considered ANS measures in an attempt to monitor pain during anesthesia [52-63]. However, ANS measures have yet not been able to provide strong predictive power due to high inter-individual variability and large random variations within subjects. Due to differences in study populations and settings, and important limitations in accounting for confounders, such as assisted ventilation, compensative drug administration, or surgical stimulation, a comprehensive comparative assessment of the proposed parameters is indeed quite problematic.

The presented work is aimed at combining novel instantaneous measures of autonomic activity to provide instantaneous monitoring of the ANS response with sedation. In particular, we have devised a novel assessment of ANS outflow based on instantaneous measures of autonomic tone able to track fast hemodynamic and autonomic effects during induction and emergence from altered arousal. In previous studies, we established a paradigm for using point process methods for analyzing heartbeat dynamics [64,65]. We have also assessed sympathovagal indices of heart rate variability, as well as baroreflex and respiratory sinus arrhythmia [66-70], and we have successfully applied these methods to protocols including induction and emergence from anesthesia [71-75]. We have further identified specific measures of complexity and nonlinearity associated with loss of consciousness during anesthesia [75]. Most importantly, these methods can track autonomic dynamics in real time. In this study, we present exemplary analyses from a multimodal (EEG, ECG, respiration) characterization in study participants undergoing PROP and DMED administration. Furthermore, in order to validate the proposed algorithms' ability to track pharmacological interventions in the operating room (OR) or the intensive care unit (ICU), we focus on how specific features of our framework are able to characterize instantaneous signatures of the hemodynamic and autonomic effects of the anesthetics before and during loss of consciousness.

Methods

Experimental protocol

We have considered experimental datasets from healthy volunteer subjects participating in two studies approved by the Massachusetts General Hospital (MGH) Institutional Review Board.

Study 1 Propofol was intravenously infused in six healthy subjects using a computer-controlled delivery system running STANPUMP connected to a Harvard 22 syringe pump (Harvard Apparatus, Holliston, MA, USA). Five effect-site

target levels (L1 to L5, step propofol concentration increase of 5 mcg/ml) were each maintained for 15 min, respectively, and then step-wise decreased by 5 mcg/ml per epoch during E6, E7, and E8 before full emergence from anesthesia. Along the experiment, subjects listened to pre-recorded auditory stimuli and were instructed to press a button to differentiate between sounds. We used the loss of button responses as a marker of loss of consciousness (LOC). EEG, capnography, pulse oximetry, ECG, and arterial BP were recorded and monitored continuously at 500 Hz throughout the study. Study participants were also fitted with a respiration belt and a piezo-electric pulse transducer for monitoring. Bag-mask ventilation with 30% oxygen was administered as needed in the event of propofol-induced apnea. Because propofol is a potent peripheral vasodilator, phenylephrine was administered intravenously to maintain mean arterial BP within 20% of the baseline when needed. This first study includes results from baseline and increasing propofol concentration levels of two male and four female subjects between 20 and 32 years old.

Study 2 Dexmedetomidine was intravenously infused in six healthy subjects using a Medfusion® 3500 syringe infusion pump (Smiths Medical, Dublin, OH, USA). EEG, capnography, pulse oximetry, and ECG were recorded and monitored continuously during the study protocol. EEG was sampled at 1,000 Hz, ECG at 240 Hz. In specific instances, respiration belts were used to record lung volume changes at 240 Hz. The dexmedetomidine infusion started with a loading dose of 1 mcg/kg over 10 min followed by an intravenous infusion of dexmedetomidine to be maintained at a maximum of 0.7 mcg/kg/h. This second study includes results from the first 28 min of administration of three male and three female subjects between 21 and 29 years old.

Preprocessing analysis

R wave peaks are detected from the ECG signal using an automatic algorithm. The R wave markers are tested to eliminate artifacts and correct eventual undetected beats or beats erroneously detected by the automatic peak detection procedure. Ectopic beat classification is also carried out with our specifically tailored routines [76]. Respiration, when recorded, is low-pass filtered at 10 Hz.

Point process assessment of HRV

The R wave events are a sequence of discrete occurrences in continuous time and hence, they can be analyzed meaningfully and continuously monitored using a probabilistic model of a dynamical system observed through a point process. In this model, the observation equation summarizes the stochastic properties of the observed heart beat point process while the essential features of the parasympathetic and sympathetic activity are concisely summarized in a history-dependent, autoregressive (AR), time-varying structure [64,65], allowing for definition of the *instantaneous RR and HR mean and variance*, the instantaneous very low frequencies (VLF: 0 to 0.04 Hz), low frequencies (LF: 0.04 to 0.15 Hz), high frequencies (HF: 0.15 to 0.4 Hz) indices in absolute ($ppVLFa$, $ppLFa$, $ppHFa$) and normalized ($ppLFu$, $ppHFu$) spectral power, and the ratio between LF and HF ($ppLF/HF$). Vagal activity is the major contributor to the HF

component. Some studies suggest that LF, when expressed in normalized units, is a quantitative marker of sympathetic modulation [77,78], while other studies have found that LF reflects both sympathetic and vagal activity [79,80]. The LF/HF ratio is considered to reflect the sympathovagal balance. A thorough review of standard measures is presented in [32] and [81].

There are several advantages of using a point process framework to assess HRV: (a) the model overcomes stationarity requirements for standard HRV analysis; (b) previous methods compute similar estimates either on a beat-to-beat basis or in continuous time by preprocessing and filtering of the original R-R interval series not justified by a physiological model of heart beat generation; (c) point process models include goodness-of-fit analyses supporting accurate description of the heartbeat stochastic structure; (d) point process instantaneous HRV indices can be computed simultaneously from a single statistical framework, they are computed in continuous time, and they can be extracted at any time resolution to track very fast dynamics; (e) our previous studies have shown that summaries comparable to standard HRV analysis (e.g., SDNN and LF/HF) can be obtained by averaging the instantaneous point process indices (static measures), which therefore encompass information from standard analysis; and (f) only instantaneous dynamics have been proved effective in characterizing central autonomic activity [82]. These results suggest that static and dynamic measures derived from point process models are good candidates for a more accurate, comprehensive description of ANS outflow dynamics [64,65].

Nonlinear assessment

The point process framework also allows for inclusion of nonlinear structures and for definition of novel indices of nonlinear HRV dynamics, such as the bispectrum [67] and the *instantaneous dominant Lyapunov exponent* (*IDLE*) [75]. Results suggest that such quantification provides important information, which is independent from the standard autonomic assessment and is significantly correlated with loss of consciousness. In addition, we have demonstrated [67] that nonlinear indices such as detrended fluctuation analysis (DFA) and approximate entropy (ApEn) can be more accurately estimated by applying those methods to the instantaneous point process series, thus avoiding the need for long (e.g., 24 h) recordings.

RSA assessment

We use an extension of the statistical point process model that we recently developed [68] to assess instantaneous estimates of respiratory sinus arrhythmia (RSA) from both ECG and respiration. Where respiratory information is available, we compute two RSA measures: the *RSA gain* at maximum coherence and RSA gain at maximum frequency. The instantaneous RSA assessments provide information that complements the standard HRV measures, particularly in the high frequency (HF) range, as well as indices such as the analgesia nociception index (ANI) and the surgical stress index (SSI) [53,56,57]. Importantly, only our new measures of RSA make it possible to reliably evaluate RSA in waning breathing conditions or whenever subjects show slow or unusual respiratory patterns [68].

EEG assessment

As described in detail in [15], we computed spectrograms using the multitaper method, implemented in the Chronux toolbox (http://chronux.org). The spectral analysis parameters were as follows: window length $T = 4$ s with 3-s overlap, time-bandwidth product TW = 3, number of tapers $K = 5$. Although not shown, eigenvector decomposition analysis of the cross-spectral matrix was performed to identify the principal modes of oscillation. Further modal projection analysis characterized how power within these principal modes changed as a function of time. The relationship between low-frequency phase (0.1 to 1 Hz) and alpha/beta (8 to 14 Hz) amplitude was extracted from the phase-amplitude histogram. These established EEG signatures help to characterize unconsciousness, track the transitions into and out of unconsciousness, and provide a means to monitor and predict the hypnotic state of patients under sedation and general anesthesia.
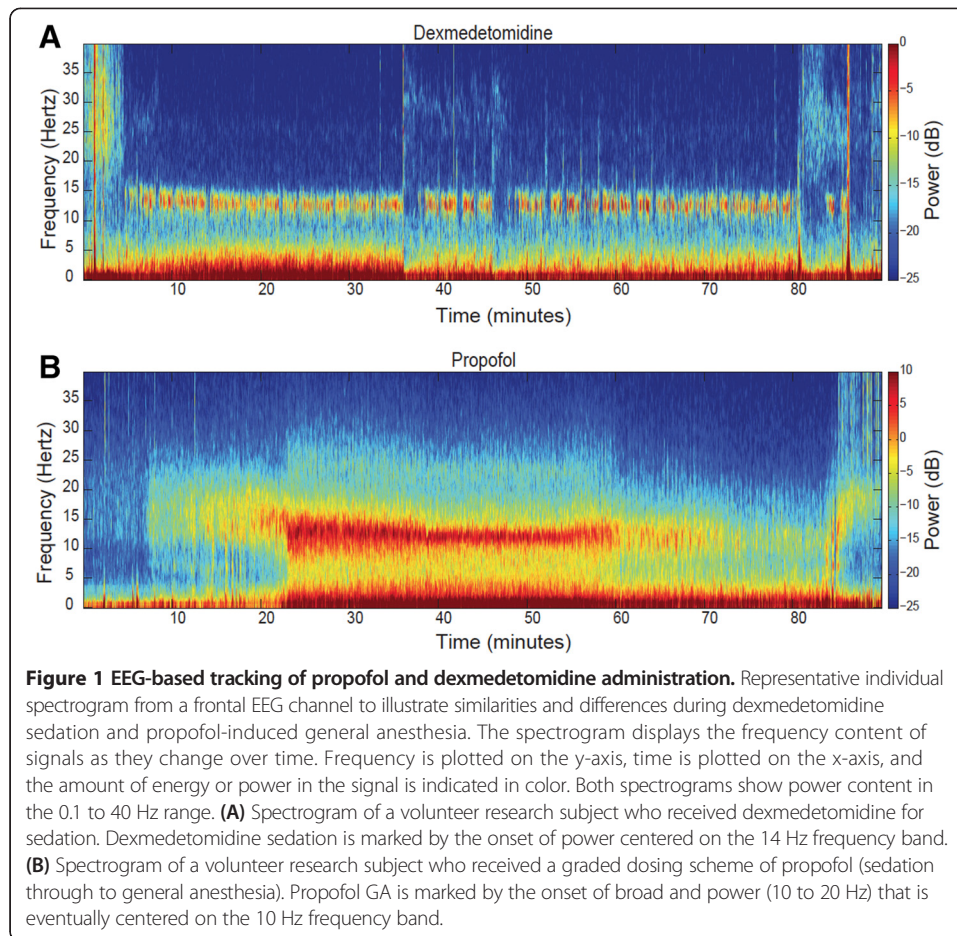
Results

Tracking levels of consciousness

The precise dynamics and relative timing of EEG changes during the transition between consciousness and unconsciousness have been recently described in previous works by Cimenser et al. and Purdon et al. [13-15]. These experiments found that responses to auditory stimuli show continuous changes in probability of response. Responses to salient stimuli (the sound of one's name) are lost later than responses to less salient stimuli (clicking noises). These features persist and strengthen with increasing concentrations of propofol and lead to burst suppression at sufficiently high doses. During emergence from anesthesia, this sequence reverses. Two patterns of phase-amplitude modulation were also discovered. The 'peak-max pattern' occurs in the unconscious state and is similar in character to slow oscillations observed during slow wave sleep. The 'trough-max pattern' is observed during the transitions to and from unconsciousness with propofol, whereas weaker and intermittent transitions into and out of unconsciousness are reported for DMED (see two exemplary spectrograms in Figure 1).

Tracking ANS outflow dynamics

Figure 2 shows tracking results from two recordings performed under the two considered studies, demonstrating how analysis of ANS outflow dynamics is able to provide critical information about autonomic effects by the two anesthetic agents. It is important to note that, as the two protocols have very different administration procedures, the tracking results are proposed together for methodological demonstration purposes and are not aimed at yielding specific comparative inferences between the two drugs.

In particular, PROP increases cardiovascular instability due to its hypotensive vasodilatatory effects, visible shortly after administration in mean RR, mean HR, ppHF, and ppLF. Hypotension usually requires further interventions such as, in the presented case, phenylephrine administration and assisted ventilation. These are mainly reflected in the respiratory coupling with heart rate (ppRSA). Excluding compensatory effects, a progressive long-term decrease along PROP administration in ppHF and ppLF suggests an increasingly poor autonomic tone, possibly associated with the significant baroreflex depression by PROP reported previously in Chen et al. [73]. The high hypnotic effect

Figure 1 EEG-based tracking of propofol and dexmedetomidine administration. Representative individual spectrogram from a frontal EEG channel to illustrate similarities and differences during dexmedetomidine sedation and propofol-induced general anesthesia. The spectrogram displays the frequency content of signals as they change over time. Frequency is plotted on the y-axis, time is plotted on the x-axis, and the amount of energy or power in the signal is indicated in color. Both spectrograms show power content in the 0.1 to 40 Hz range. **(A)** Spectrogram of a volunteer research subject who received dexmedetomidine for sedation. Dexmedetomidine sedation is marked by the onset of power centered on the 14 Hz frequency band. **(B)** Spectrogram of a volunteer research subject who received a graded dosing scheme of propofol (sedation through to general anesthesia). Propofol GA is marked by the onset of broad and power (10 to 20 Hz) that is eventually centered on the 10 Hz frequency band.
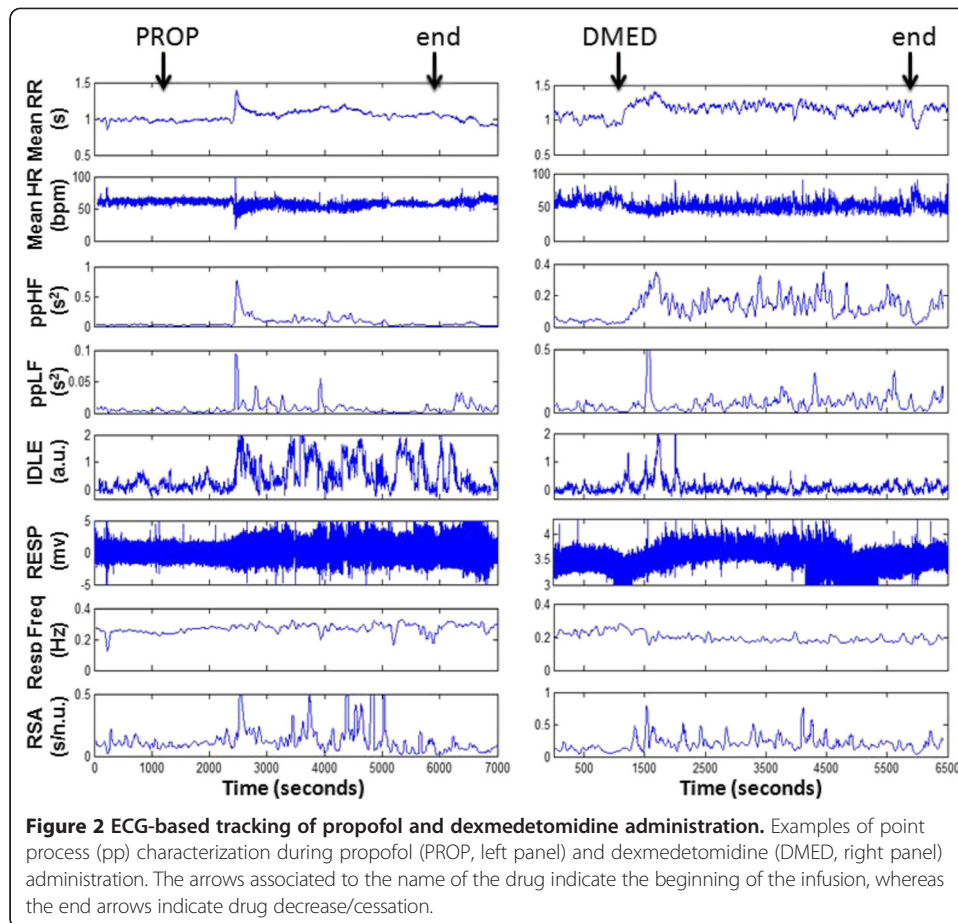
of PROP, leading to loss of consciousness as confirmed by EEG assessment, is reflected in the nonlinear IDLE index.

As a comparative example, the high bradycardic effect of DMED is clearly reflected in the RR and HR instantaneous assessment. ppHF increases as soon as DMED is administered and oscillates at significantly higher values, confirming the low sympathetic and predominant vagal activation effect. A sustained ppLF further confirms that baroreflex activation is maintained under administration [10]. On final note, respiratory frequency decreases and becomes more regular all along DMED administration. We further provide more details separately for each drug in the next paragraphs.

The importance of using multimodal approaches, including respiration

Figure 3 shows two examples focusing on the transition during DMED administration. These examples confirm that the mean RR and mean HR (Figure 3A,B) generally reflect a higher bradycardic effect during DMED administration, confirmed by the increase of the instantaneous vagally mediated HF HRV power (Figure 3C) and RSA gain (Figure 3F). Our results show that, generally, ppHF increases as soon as the drug is given (see example in Figure 3C), confirming the predominantly vagal activation effect. Such effect is not always observed, as shown in the second example (Figure 3G,H,I,J,K,L). In this case, the absence of the ppHF increase is clearly due to a progressive waning in respiratory variability (Figure 3L).

Figure 2 ECG-based tracking of propofol and dexmedetomidine administration. Examples of point process (pp) characterization during propofol (PROP, left panel) and dexmedetomidine (DMED, right panel) administration. The arrows associated to the name of the drug indicate the beginning of the infusion, whereas the end arrows indicate drug decrease/cessation.
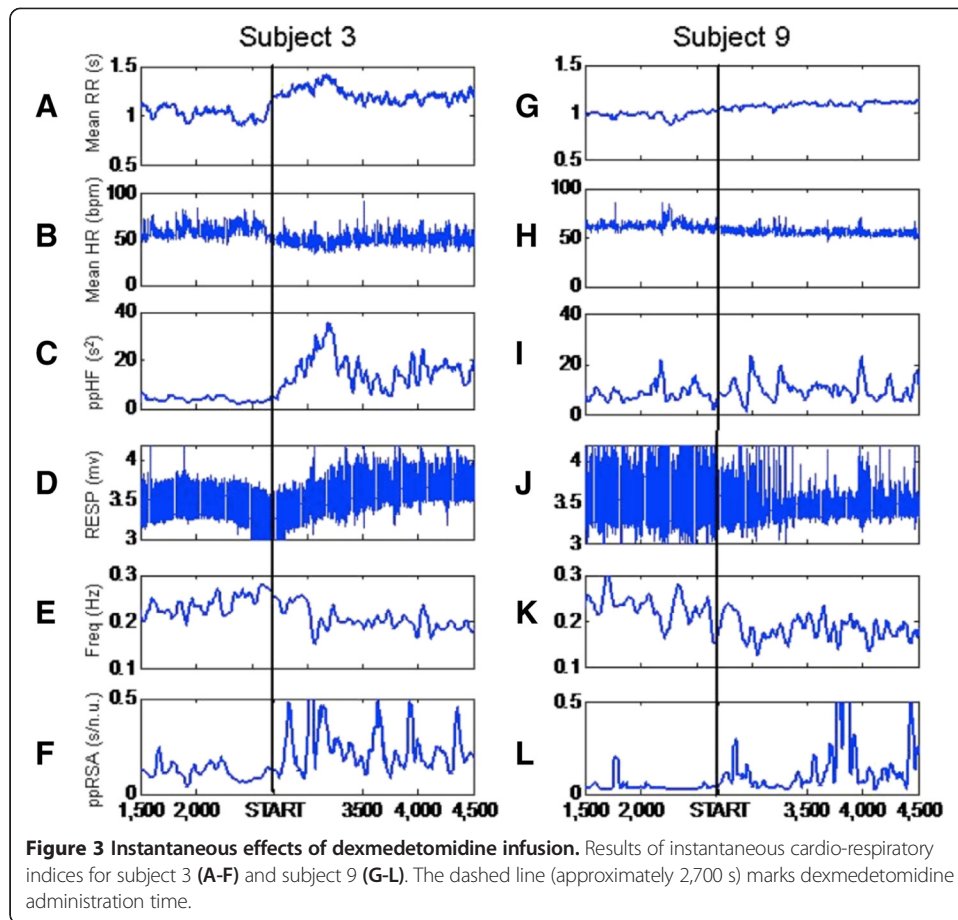
On the other hand, the RSA gain normalizes the RSA effect by respiratory power, as demonstrated by the increase in vagal activation in all subjects (including our examples in Figure 3F and 3L). Finally, it is important to note that respiration becomes more regular as drug administration progresses. This is validated by the lower variability of the respiratory rate around its mean value (see examples in Figure 3E,K).

Towards instantaneous signatures of ANS dynamics during sedation

In this section, we present a more detailed individual dynamics as function of the drug administration level, focusing on the linear and nonlinear HRV point process indices separately for each drug.

Although our aims are focused on the dynamics, we accompany the dynamical study with a brief statistical summary based on averaging our instantaneous indices. Tables 1 and 2 report median and median absolute deviation for the main instantaneous indices obtained from the ECG and averaged for each group and stages. The first segment is chosen within the baseline recording stage prior to the administration for both protocols (between 5 and 15 min). Five levels are considered for PROP (15 min each). Two levels are considered for DMED: 8 min within the 10 min bolus administration (1 min after marker), and 18 min at low-level maintained administration (100 s after marker). To give a more multifaceted portrayal, in Figures 4 and 5, we are showing results from

Figure 3 Instantaneous effects of dexmedetomidine infusion. Results of instantaneous cardio-respiratory indices for subject 3 **(A-F)** and subject 9 **(G-L)**. The dashed line (approximately 2,700 s) marks dexmedetomidine administration time.

a single subject side to side with the dynamics averaged for all six subjects (appropriately aligned according to the experiment markers). The single subject indices give an idea on how single events other than drug administration changes affect the dynamics, whereas the averaged signatures, along with their confidence intervals (median absolute deviations), facilitate a clearer interpretation of the common changes due to change in drug levels as well as the degree of inter-subject variability for each index.

Propofol signatures (Figure 4)

These results pertain to the part of *study 1* from baseline, to level 1 (L1), up to level 5 (L5), the highest level of PROP administration, and do not consider dynamics of emergence from anesthesia. In the subject portrayed on the left in Figure 4, the first three levels (baseline, L1, and L2) clearly confirm a sharp decrease in HRV, both in the LF and HF range, confirming the high decrease in autonomic tone, both vagal and sympathetic, with PROP. The relevant increase in variability at the beginning of level 3 is concomitant to administration of phenylephrine (arrow in the individual mean RR plot). In particular, the resulting vasoconstriction drives the autonomic balance towards parasympathetic action along the rest of the administration levels (bradycardia accompanied by high levels of ppHF together with a relevant, slow decrease in sympathovagal balance). Note that drug-induced physiological instability is not sensed by the nonlinear index IDLE even at the individual level, which maintains sustained levels up to mid-

Table 1 Statistical analysis with propofol administration

PROP	Baseline	L1	L2	L3	L4	L5
Mean RR (ms)	948.9 ± 186.1	894.9 ± 197.5	880.3 ± 170.2	941.2 ± 164.8	1,047.4 ± 166.6	1,067.5 ± 203.7
Mean HR (bpm)	63.7 ± 11.88	67.49 ± 12.82	68.49 ± 13.66	64.10 ± 10.33	58.07 ± 9.12	56.85 ± 11.02
Var RR (ms^2)	1194.5±	486.44 ± 366.47	292.98 ± 195.91	1,100.2 ± 851.37	492.06 ± 316.92	1,397.6 ± 1182.6
Var HR (bpm^2)	2.50 ± 1.22	2.49 ± 0.63	1.46 ± 0.97	4.67 ± 4.07	2.57 ± 1.87	3.02 ± 1.58
ppLF (ms^2)	1,080.7 ± 900.81	499.31 ± 309.57	262.70 ± 119.02	1,202.9 ± 1065.8	934.04 ± 478.23	1,170.4 ± 978.74
ppLFn	0.5834 ± 0.0492	0.5338 ± 0.1334	0.6508 ± 0.1663	0.7301 ± 0.0510	0.5635 ± 0.2059	0.4225 ± 0.1452
ppHF (ms^2)	941.83 ± 273.91	533.83 ± 445.82	237.49 ± 163.70	642.57 ± 500.73	299.24 ± 97.62	1,204.4 ± 1056.7
ppHFn	0.4166 ± 0.0492	0.4662 ± 0.1334	0.3492 ± 0.1663	0.2699 ± 0.0510	0.4365 ± 0.2059	0.5775 ± 0.1452
LF/HF	1.9064 ± 0.6756	1.0035 ± 0.4972	2.1198 ± 1.2618	2.8623 ± 1.6639	2.0781 ± 1.5195	0.9315 ± 0.4612
IDLE	0.0085 ± 0.0469	0.0058 ± 0.0607	0.0391 ± 0.0761	0.1033 ± 0.0342	0.1262 ± 0.0300	0.1002 ± 0.0801

Median ± median absolute deviation of the main cardiovascular instantaneous point process autonomic indices. Six subjects, PROP study 1.

**Table 2 Statistical analysis with dexmedetomidine administration**

DMED	Baseline	Bolus	Maintenance
Mean RR (ms)	985.8 ± 66.7	1,067.3 ± 101.4	1,049.4 ± 66.0
Mean HR (bpm)	61.48 ± 4.09	56.49 ± 4.96	57.51 ± 3.55
Var RR (ms^2)	899.78 ± 284.96	1,035.7 ± 445.75	467.09 ± 193.95
Var HR (bpm^2)	4.4436 ± 0.6607	3.3026 ± 0.5365	1.27 ± 0.029
ppLF (ms^2)	1,480.9 ± 517.31	1,573.2 ± 465.20	638.66 ± 313.80
ppLFn	0.5972 ± 0.0918	0.4340 ± 0.2498	0.5328 ± 0.1038i
ppHF (ms^2)	849.45 ± 223.67	10.30.1 ± 409.63	503.11 ± 273.61
ppHFn	0.4028 ± 0.0918	0.5660 ± 0.2498	0.4672 ± 0.1038
LF/HF	1.7550 ± 0.8124	0.9188 ± 0.5079	1.7286 ± 0.5964
IDLE	0.0409 ± 0.0214	0.1064 ± 0.0825	0.0242 ± 0.0482

Median ± median absolute deviation of the main instantaneous point process cardiovascular indices. Six subjects, DMED study 2.

level 4, and then it shows its most significant increase simultaneously with the reported loss of consciousness (arrow in the individual IDLE plot). The respective averaged signatures among all six subjects (Figure 4, right column) evidence the overall trends associated with the drug levels (appropriately aligned for each subject), thus 'blurring' the instantaneous effects of phenylephrine, which happens intermittently and at different times for each subjects. Of note, the measures with highest inter-individual variability, mirrored by a wider median absolute deviation region (in gray) are the mean RR and HR, followed by their respective variances. Conversely, the measures with least inter-subject variability are the two normalized LF and HF powers and, most of all, the IDLE index of complexity. The IDLE is also showing the most coherent (increasing) trends associated with the level of drug when looking at the average and, at the same time, significant increases at the moment of loss of consciousness when looking at each subject individually.

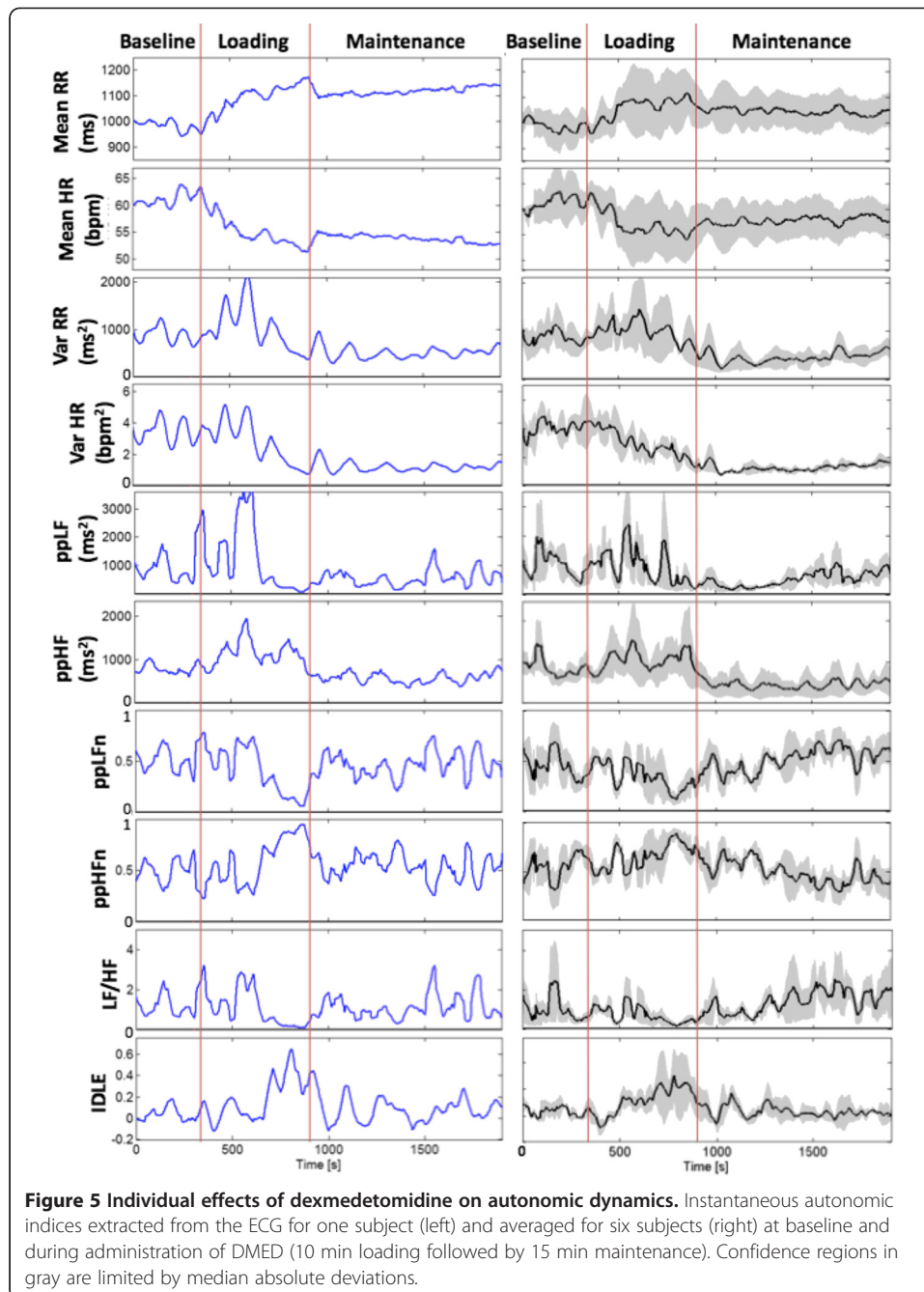### Dexmedetomidine signatures (Figure 5)

These results pertain to the part of *study 2* including baseline, 10 min of loading dose and 18 min of the following maintenance epoch. The marked bradycardic effect of the bolus dose is clear both at the individual and group level (increasing mean RR, decreasing mean HR). Bradycardia levels stabilize during maintenance. As the system is clearly migrating to a different state during loading, HRV (Var RR, Var HR, and ppLF) increases relevantly in the initial minutes and then tends to reach minimum levels by the end of the loading dose. On the other hand, ppHF increases at the start of administration and stays elevated for the entire 10 min of loading. As a consequence, the sympathovagal balance steadily decreases to minimum levels up to the end of the loading phase. The switch in balance during the maintenance period, along with HRV remaining at low levels, is quite probably due to the respiratory waning effect (not reportable for all subjects, see previous section for exemplary cases). Of note, the individual is losing consciousness at minute 8 of the loading epoch, regaining intermittent responsiveness from minute 11 after loading starts, whereas the average range of loss of consciousness for the group goes between 7 to 12 min after loading starts. Importantly, sharp increases in IDLE values can be observed around the range of loss of consciousness both for the individual and the group dynamics.
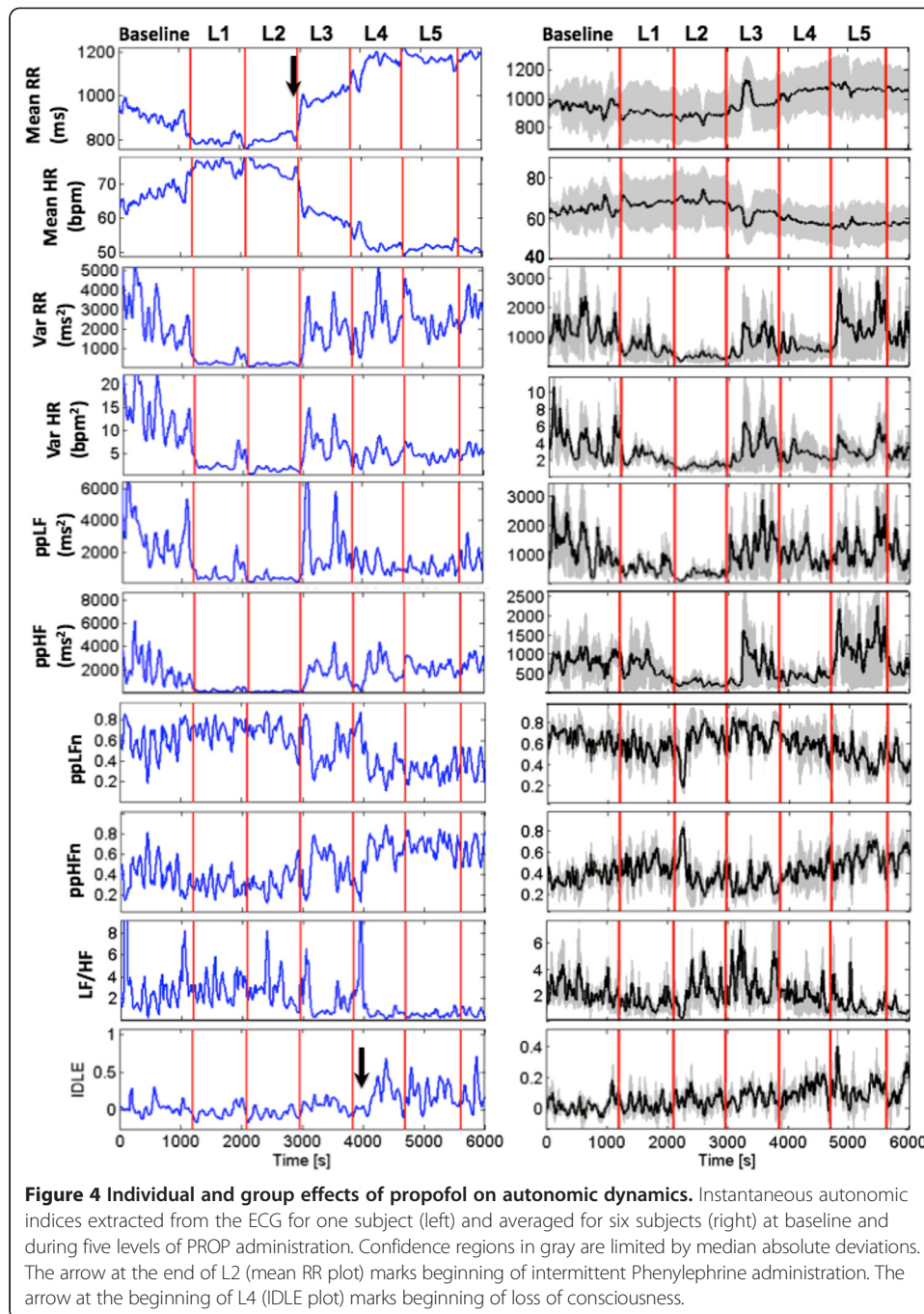
Figure 4 Individual and group effects of propofol on autonomic dynamics. Instantaneous autonomic indices extracted from the ECG for one subject (left) and averaged for six subjects (right) at baseline and during five levels of PROP administration. Confidence regions in gray are limited by median absolute deviations. The arrow at the end of L2 (mean RR plot) marks beginning of intermittent Phenylephrine administration. The arrow at the beginning of L4 (IDLE plot) marks beginning of loss of consciousness.

Discussions and conclusions

Our ongoing efforts are aimed at paving the way for a novel moment-to-moment ANS assessment in different states of sedation. Our main hypothesis is that different levels of sedation and analgesia affect the underlying neural processes and are reflected in different objective physiological signatures. As such, neural pathways are also differently affected, and specific physiological signatures of sedation could potentially be disentangled through appropriate experimental protocols and accurate noninvasive physiological assessments.

Figure 5 Individual effects of dexmedetomidine on autonomic dynamics. Instantaneous autonomic indices extracted from the ECG for one subject (left) and averaged for six subjects (right) at baseline and during administration of DMED (10 min loading followed by 15 min maintenance). Confidence regions in gray are limited by median absolute deviations.

Within a multimodal framework including EEG, cardiovascular and respiratory assessment, we have devised a point process framework able to successfully characterize the variations in heartbeat dynamics when applied to PROP and DMED administration protocols. Previous results from our groups and other authors have stressed the importance of dynamic autonomic monitoring during anesthesia, and particularly during PROP and DMED [13,15,19,20,34,44,46-48,51,53,54,72,73,75]. In this presentation, we provide further evidence that our refined methods for analyzing the heartbeat dynamics during administration of specific anesthetic drugs are able to overcome nonstationary limitations, thus providing new real-time monitoring approaches to patients receiving anesthesia.

In particular, we show the application of instantaneous linear and nonlinear estimates of heartbeat dynamics as measures defined in the time and frequency domain as well as the instantaneous dominant Lyapunov exponent [75,83-85]. As a result, our framework is able to examine the complex evolution of the unevenly sampled heartbeat dynamics series during anesthesia and sedation, in continuous time without the use of interpolation filters. Remarkably, most other nonlinearity and complexity indices are derived from non-parametric models, whereas our model is purely parametric and the analytically derived indices can be evaluated in a dynamic and instantaneous fashion. The proposed framework also allows for the inclusion of covariates as the respiration activity, thus being able to estimate other meaningful measures as the instantaneous RSA. We believe these strengths enable our method as a useful anesthesia and sedation assessment tool taking into account also the nonlinear dynamics of heartbeat intervals in a highly non-stationary environment. Moreover, goodness of fit measures such as Kolmogorov-Smirnov (KS) distance and autocorrelation plots quantitatively allow to verify the model fit as well as to choose the proper model order, which represents another open issue of current parametric approaches.

In the results from the first experimental study, we show that PROP signatures are initially (first two administration levels) characterized by a marked decrease in HRV, both in LF and HF, confirming previous findings, and pointing at a general loss of autonomic tone (both sympathetic and vagal) possibly connected with simultaneous baroreflex deactivation/resetting. The observed delayed compensatory variations of HRV can be attributed to sympathetic activation due to vasodilatory effect, as well as vagal activation due to intermittent phenylephrine administration. Vagal predominance is observed during loss of consciousness. Our comparison between individual signatures and signatures obtained from all subjects demonstrates that overall trends, devoid of fast transient effect present on individual dynamics, can be observed particularly in normalized measures. Most importantly, increased IDLE complex dynamics elicited by increasing drug administration levels are highly correlated with the hypnotic effect (as measured by auditory test and confirmed by EEG metrics) for the individual and with the level of administration for the group signature. In the results from the second experimental study, we show that DMED signatures are characterized by a marked sympathetic deactivation and by sustained vagal activation, clearly visible in HRV dynamics during the first loading stage, so less during maintenance levels, where respiration waning effects are more predominant. Importantly, the IDLE complex dynamic increases in accordance with the incidence of loss of consciousness (predominantly during the initial bolus administration). The reduced hypnotic effect compared with PROP (also demonstrated by EEG signatures) is also confirmed by relatively low IDLE levels during maintenance. Although we do not provide p values from statistical inference tests (because of the reduced number of subjects involved in the study), we show consistent trends in all the linear and nonlinear heartbeat features (see Figures 4 and 5) and, thus, provide important insights to the different cardiovascular dynamics during anesthesia and sedation as shown in an instantaneous fashion.

The main challenge of the proposed study, and all HRV studies in general, is the high inter-individual variability, mainly due to the complexity of the cardiovascular control responses to intrinsic or induced perturbations of the system, particularly with drug administration. Such variability has been the prominent limitation preventing previous

studies to go beyond statistical summaries indicating only general trends within a limited population, and to provide a personalized tracking of sedation. Moreover, another limitation of our methodology can be related to the need of a preliminary calibration phase before it can be effectively used to estimate the instantaneous measures. Like other parametric methods, in fact, a tuning of model parameters such as model order and time-window W size for the local-likelihood parameter estimation. To this extent, in the presented application, we were able to obtain reproducible and reliable results by using standard values such a $W = 90$ s, as well as optimal model orders by minimizing the KS statistics.

Given these limitations, we will center our future studies on two principles: (a) the high variability reflected in the resulting statistical predictions, and physiological interpretations must be accompanied by a multiorgan approach and a careful choice of complementary information; and (b) a powerful and reliable classification algorithm is required to use dimensionality towards optimal discrimination. We believe that validation of accurate and reliable scales based on the instantaneous identification, together with the careful choices in sedation levels (which are the results of our extensive preliminary investigations) will provide a more sensitive assessment and interpretation of the results. In particular, differently than previous investigations, we will consider EEG and HRV measures together and feed them to a classifier to find the most efficient combination signature. Most importantly, we will be able to consider a novel measure of RSA, which accounts for respiratory pattern variations in assessing sympathovagal dynamics. Our future studies will determine by which degree a combined index of the ANS measures is able to accurately quantify sedation in controlled scenarios, also estimating recently proposed instantaneous nonlinear measures based on high-order spectral analysis and entropy [70,83-90]. We will devise classifiers which might provide enough power to produce a combination of measures of autonomic outflow validating the assessment for each single subject, thus paving the way for the feasibility for a real-time monitoring tool able to track sedation in uncontrolled scenarios.

Abbreviations
ANI: analgesia nociception index; ANS: autonomic nervous system; AR: autoregressive; DMED: dexmedetomidine; ECG: electrocardiogram; EEG: electroencephalogram; HR: heart rate; HRV: heart rate variability; HF: high frequencies; ICU: intensive care unit; IDLE: instantaneous dominant Lyapunov exponent; LF: low frequencies; LOC: loss of consciousness; PP: point process; PROP: propofol; RSA: respiratory sinus arrhythmia; SSI: surgical stress index; VLF: very low frequencies.

Competing interest
The authors declare that they have no competing interests.

Authors' contributions
All authors read and approved the final manuscript.

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