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ORIGINAL RESEARCH

Two different methods to assess sympathetic tone during general anesthesia lead to different findings

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Abstract

Noxious stimulation influences the autonomic nervous system activity. Sympathetic tone monitoring is currently used to assess the adequacy of the balance between nociception and anti-nociception during general anesthesia. The Surgical Plethysmographic Index (SPI) and the EBMi software (Custos©) are commercial devices that use different algorithms to measure it. We aimed at determining whether those devices provide similar information during routine surgical procedures under general anesthesia. Data acquired during a previously published study in patients undergoing surgery under general anesthesia were retrospectively analyzed and passed through the EBMi software. The occurrence of EBMi alarms of increased sympathetic tone was compared to the occurrence of SPI values ≥ 60, a commonly recommended intraoperative SPI threshold. Trends in classical parameters of sympathetic tone during the 5 min preceding a SPI ≥ 60, namely blood pressure, heart rate, and plethysmographic pulse amplitude were assessed. SPI ≥ 60 episodes (n = 307) were more frequent than EBMi alerts (n = 240). Approximately 70% of EBMi alerts occurred during periods where the SPI was below 60. Among all episodes of SPI ≥ 60, absence of any EBMi alerts was much more frequent than the inverse. A majority, but not all SPI ≥ 60 episodes were consistently preceded by an increase in heart rate and/or a decrease in pulse amplitude. Blood pressure did not significantly change before SPI ≥ 60. Longer SPI ≥ 60 episodes were associated with lower anti-nociception anesthetic regimen. Different methods of sympathetic tone assessment during general anesthesia provide conflicting information. Prospective studies should be undertaken to clarify the clinical indications of both techniques.

Keywords Autonomic nervous system · Sympathetic tone · Monitoring · General anesthesia

Aline Defresne, Michael Harrison, Luc Barvais and Vincent Bonhomme have contributed equally to the present manuscript.

An abstract related to this work has been submitted to the ANZCA ASM 2018 (https://asm.anzca.edu.au/) for possible presentation, and its evaluation is still under progress.

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1 Introduction

As opposed to pain, nociception corresponds to the unconscious consequences of noxious stimulation on the body, including the autonomic nervous system (ANS) response. Depending on the nature and location of noxious stimulation, and on patient individuality, the relative contribution of the parasympathetic and sympathetic system to this ANS response may vary [1–4]. During anesthesia and surgery, in addition to noxious stimulation, the parasympathetic and sympathetic tones are influenced by several other factors, such as the administration of medications (including anti-nociceptive medications), temperature, intravascular volume, or lung ventilation [5]. Despite several existing potential confounders, some estimates of the parasympathetic or sympathetic tone have been proposed to monitor the balance between nociception and anti-nociception intraoperatively, and have been demonstrated to surpass simple monitoring of heart rate and blood pressure in that respect [6]. Proposed indexes are based on measurements performed at the level of the ANS target organs. Multiple parameters may enter their algorithm, including some derived from the cardiovascular system (for example blood pressure, heart rate, heart beat interval, plethysmographic pulse wave amplitude, or heart rate variability) [7], the eye (for example pupil diameter) [8], or the skin (for example skin conductance) [9].

Among the assessors of sympathetic tone, the Surgical Plethysmographic Index (SPI, GE Healthcare, Chicago, IL, USA) (Fig. 1) has a value ranging between 0 and 100, and combines a normalized heart beat-to-beat interval (HBI_{norm}) and a normalized plethysmographic pulse wave amplitude ($PPGA_{norm}$) according to the formula: $SPI = 100 - (0.7\ PPGA_{norm} + 0.3\ HBI_{norm})$ [7]. An increase in sympathetic tone provokes tachycardia, and a decrease in HBI_{norm}, as well as vasoconstriction, and a decrease in $PPGA_{norm}$. Both lead to an increase in SPI. Targeting an intra-operative SPI value between 20 and 50 has been demonstrated to reduce remifentanil consumption, improve hemodynamic stability, and prevent opioid under or over dosage in young healthy patients [10]. Another system, an Evidence-Based Monitoring software (EBMi)(Custos©, http://www.custos.co.nz) (Fig. 1) is designed to alert the clinician on possible pathophysiological changes during anesthesia [11–13]. Classical monitoring devices output an alert when parameter values at a given point in time overcome predefined thresholds. Contrarily, EBMi extracts routinely collected data from those monitors, weighs up the evidence of changes of several parameters over time, and suggests a diagnosis when identifying concordance in changes. This new type of alarm has the potential to improve diagnostic accuracy, by reducing the frequency of irrelevant alerts [12, 13]. Among EBMi possible alerts, the 'sympathetic response' alert corresponds to the conjunction of an upward trend of heart rate and blood pressure, and a downward trend in plethysmographic pulse wave amplitude. Fully describing the algorithm of the Custos© software is beyond the scope of this paper, but details on how 'sympathetic response' alerts are generated are provided below, in the Sect."2".

Given the fact that sympathetic tone can be assessed using several methods during anesthesia, one may wonder whether they provide concordant information, and alert the clinician at the same time. We have retrospectively analyzed data collected intraoperatively during a previously published study [3]. We focused on sustained relevant changes in a largely studied indicator of sympathetic tone, namely episodes of

Fig. 1 Screenshots of the GE Healthcare (Chicago, IL, USA; http://www3.gehealthcare.fr/fr-fr/products/categories/soins_peroperatoires/adequacy_of_anaesthesia#tabs/tab8E53EFB21C5F4E3F8A4CF04D562355E2) and Custos© (http://www.custos.co.nz/) websites describing the SPI and EBMi software, respectively. For Custos©, using the software implies going through a series of screens before obtaining the monitoring screen (**d**), including security warnings (**a**), type of monitor selection (**b**), and patient's characteristics (**c**). Reproduced with permission from the webmasters of the above-mentioned websites

SPI value over 60 for at least 20 s, and wanted to determine whether those episodes would have generated EBMi alerts, and were preceded by physiological changes in accordance with an increased sympathetic tone.

2 Methods

2.1 Patient recruitment and data recording

We used a dataset recorded in 44 patients during a previously published study [3]. All of them were aged over 18 years, and had ASA physical status I or II. Full details on inclusion and exclusion criteria, Ethics Committee approval, informed consent, study registration, study location, and start and end date of inclusion can be found in [3]. Out of the 46 patient data sets that were analyzed in the initial study, only 44 were included in the present one. The technical quality of two data sets was indeed not good enough to be included in the present analysis.

In those patients undergoing minor to moderate severity general surgery under general anesthesia and controlled mechanical lung ventilation through a tracheal tube, non-invasive systolic blood pressure (SBP), heart rate (HR), and SPI were continuously recorded from induction of anesthesia to the end of the procedure. The sampling rate of HR and SPI was 0.1 Hz (1 in 10 s), and approximately 0.0083 Hz (1 in 2 min) for BP. Anesthesia was induced and maintained using propofol and remifentanil target-controlled infusions. A single dose of muscle relaxant was given at induction to facilitate tracheal intubation. Throughout the procedure, propofol target concentrations were adjusted to keep the Bispectral Index between 40 and 60, while remifentanil target concentrations were adjusted to keep the SPI between 40 and 60 or stable hemodynamic parameters, at the discretion of the anesthesiologist in charge.

2.2 Input to and output from the EBMi software, and data analyses

Data were pre-processed before being passed through the EBMi software. The SPI data served to obtain pulse wave amplitude values in the form of $PPGA_{norm}$ (data conversion by KU). HR, and $PPGA_{norm}$ data were also decimated. Every tenth line of data was used as this corresponds to the format for the EBMi software. The output files were then analyzed for the incidence of changes in physiological variables that were assessed by both Length of Runs (LOR) analysis and a statistical assessment of changes in SBP.

In LOR, the median value for SBP, HR or $PPGA_{norm}$ for the preceding 5 min is calculated, and the current value is assessed as being below or above the median. Four sequential values on one side of the median are indicative of a significant upward (for SBP and HR) or downward (for $PPGA_{norm}$) trend (sigLOR), as described in [14]. The assessment of change in SBP also used a normalization of data to units of standard deviation as implemented into the EBMi software and described in detail in [12, 15]. A change in SBP is considered significant by the EBMi software when it exceeds two normalized standard deviations. An EBMi alert is generated when sigLOR for HR, SBP, and $PPGA_{norm}$ are recognized as concordant in indicating increased sympathetic tone (sigLOR alert), AND when change in SBP is considered significant. Simple trends in SBP (dSBP), HR (dHR) and $PPGA_{norm}$ ($dPPGA_{norm}$) during the preceding 5 min were also assessed by subtracting the median of the considered parameter over that 5 min from the actual value of the parameter at the time of SPI becoming ≥ 60.

All simple trends and their direction toward increased sympathetic tone (dSBP up, dHR up, $dPPGA_{norm}$ down, and their combinations), as well as the sigLOR and EBMi alerts were then compared to the indications given by the SPI. We considered that SPI corresponded to a clinically relevant high sympathetic tone when it was equal to or above 60 for at least 20 s. We looked at concordant sigLOR or EBMi alerts within 2 min before and 2 min after the occurrence of SPI $\geq$ 60. All analyses were performed for episodes of SPI $\geq$ 60 during 20–39 s, 40–59 s, and more than 59 s, as well as for all SPI $\geq$ 60 episodes pooled together. Episodes of SPI $\geq$ 60 for more than 20 s that were not preceded by at least 5 min of data recording were excluded from the analyses. EBMi and sigLOR alerts occurring during periods where the SPI was below 60 were also recorded, as were remifentanil estimated effect-site concentration (Ce_{remi}), propofol concentration (Ce_{propo}), and BIS at the time of SPI $\geq$ 60, sigLOR alerts, or EBMi alerts.

Proportions were compared using χ^2 tests and Bonferroni-corrected z-tests for post hoc comparisons. A two-tailed P value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using the IBM© SPSS© statistics software (Version 25, IBM corporation).

3 Results

The total duration of data collection was 130 h. There were 307 episodes where the SPI exceeded 60 for more than 20 s, in which 127 lasted between 20 and 39 s, 57 between 40 and 59 s, and 123 more than 59 s (Table 1). Overall, during the study period, there were appreciably fewer sigLOR alerts (n = 202) and EBMi alerts (n = 38) generated by the EBMi software, among which 147 (72%) sigLOR alerts and 26 (68%) EBMi alerts occurred during periods where the SPI was below 60.

The frequency of EBMi and sigLOR alerts during periods of SPI $\geq$ 60 was low (overall 3.9% and 13.9% for

Table 1 Contingency table showing count and proportion of events of interest within each group of SPI ≥ 60 observations

44 datasets — 130 h of recording

		20-39 seconds (n = 127)	40-59 seconds (n = 57)		≥60 seconds (n = 123)	All (n = 307)
Seven h and 50 min of SPI≥60	EBMi alerts	2 1.6 %	2 3.5 %	$\chi^2_{(4)}$ = 12.90 P = 0.012	8 6.5 %	12 3.9 %
	sigLOR alerts	14 11.0 %	11 19.3 %		30 24.4 %b	55 13.9 %
	No discernible pattern by EBMi software	111 87.4 %a	44 77.2 %		85 69.1 %	240 78.2 %
	Simple trend HR up (dHR)	70 55.1 %	29 50.1 %	$\chi^2_{(2)}$ = 0.31 P = 0.86	65 52.8 %	164 53.1 %
	Simple trend SBP up (dSBP)	50 39.4 %	19 33.4 %	$\chi^2_{(2)}$ = 1.42 P = 0.49	40 32.5 %	109 35.5 %
	Simple trend $PPGA_{norm}$ down ($dPPGA_{norm}$)	108 85.0 %	42 73.7 %	$\chi^2_{(2)}$ = 5.95 P = 0.05	108 87.8 %	258 84.0 %
	dSBP up, dHR up, and $dPPGA_{norm}$	25 19.7 %	8 14.0 %	$\chi^2_{(2)}$ = 0.95 P = 0.62	24 19.5 %	57 18.6 %
	dHR up and dSBP up	28 22.0 %	10 17.5 %	$\chi^2_{(2)}$ = 0.49 P = 0.78	25 20.3 %	63 20.5 %
	dHR up and $dPPGA_{norm}$ down	62 48.8 %	21 36.8 %	$\chi^2_{(2)}$ = 3.09 P = 0.21	62 50.4 %	145 47.2 %
	dSBP up and $dPPGA_{norm}$ down	42 33.1 %	15 26.3 %	$\chi^2_{(2)}$ = 1.25 P = 0.53	34 27.6 %	91 29.6 %
One hundred twenty two h and 10 min of SPI<60	EBMi alerts (n = 38)	26 68 %				
	sigLOR alerts (n = 202)	147 72 %				

Groups of observations are SPI ≥ 60. during 20–39 s, 40–59 s, and ≥ 60 s. Events of interest are the occurrence of EMBi alerts or sigLOR alerts during a period ranging from 2 min before to 2 min after the occurrence of SPI ≥ 60, simple trend of HR rising up (dHR up), of SBP rising up (dSBP up), PPGAnorm going down (dPPGAnorm down), or their combinations. A simple trend corresponds to the difference between actual value at the time of SPI > 60 and median during the preceding 5 min

Results of χ^2 tests comparing proportions between groups of observations are provided in the central column with degrees of freedom between brackets and P values

[a]Significantly higher proportion than in the group of observations of SPI ≥ 60 during 60 s or more

[b]Significantly higher proportion than in the group of observations of SPI > 60 during 20–39 s

EBMi and sigLOR alerts, respectively). sigLOR alerts were significantly more frequent for episodes where the SPI remained ≥ 60 for more than 59 s (Table 1). Among all episodes of SPI ≥ 60, the absence of any discernible pattern by the EBMi software was much more frequent than the occurrence of EBMi or sigLOR alerts.

When looking at simple trends of HR, SBP, and $PPGA_{norm}$ (Table 1; Fig. 2), episodes of SPI ≥ 60 were mainly preceded by an increase in HR (50.1 to 55.1% of the episodes) or a decrease in $PPGA_{norm}$ (73.7 to 89.8% of the episodes). The proportion of episodes combining classical changes of an increase in sympathetic tone, that is a preceding dHR up, dSBP up, and $dPPGA_{norm}$ down, was relatively low (between 14 and 19.7%). A combination of HR up and $PPGA_{norm}$ down (the parameters entering the SPI algorithm) preceding SPI ≥ 60 was only seen in approximately half of the episodes (48.8–50.4%).

The median dHR was positive and significantly different from 0, but small (Table 2). The median $dPPGA_{norm}$ was negative, significantly different from 0, and more marked than dHR. SBP did not significantly change before SPI ≥ 60 (Table 2; Fig. 2). Ce_{remi} was significantly lower and BIS significantly

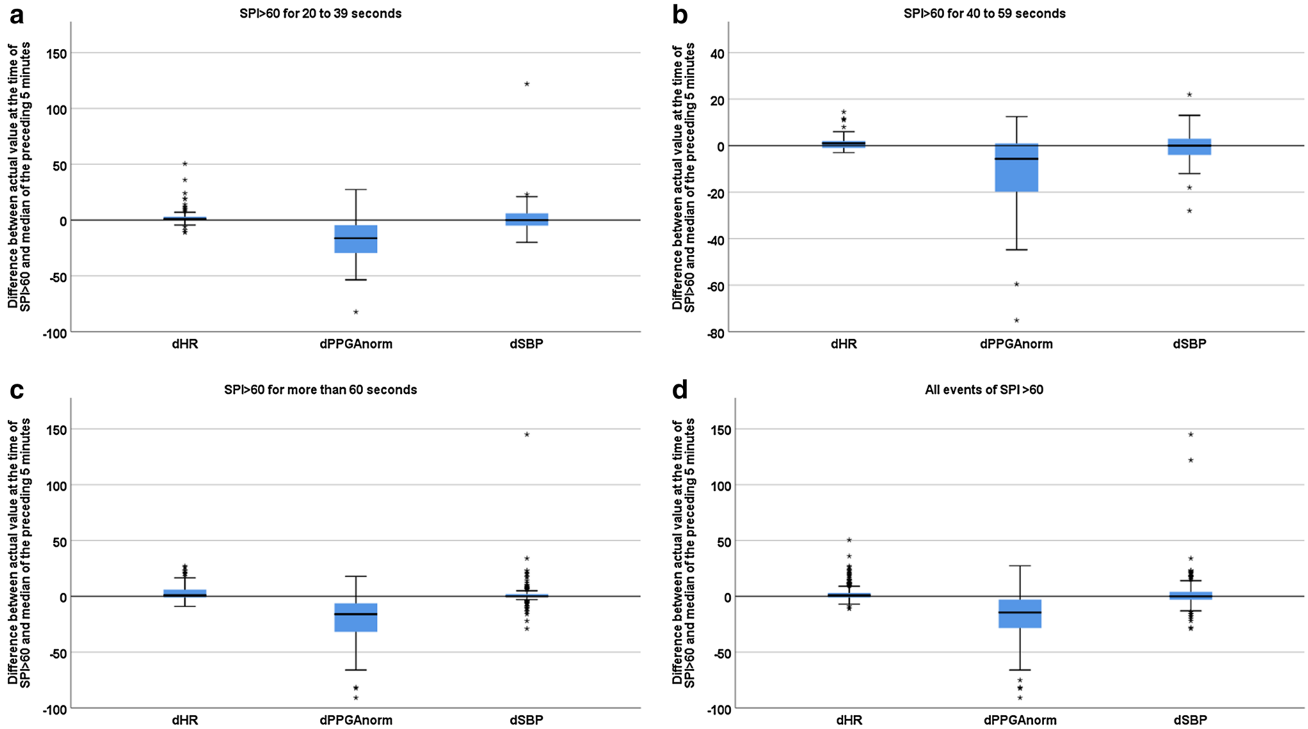

Fig. 2 Median (plain black line) of simple trends (difference of actual value at the time of SPI ≥ 60 and median during the preceding 5 min) for heart rate (dHR), systolic blood pressure (dSBP), and normalized pulse wave amplitude ($dPPGA_{norm}$) in the group of observations of SPI ≥ 60 during 20–39 s (**a**), 40–59 s (**b**), more than 60 s (**c**), and all observations pooled together (**d**). Error bars from below upwards correspond to minimum, 25 and 75 centiles, and maximum. Stars correspond to the individual values of outliers

Table 2 Recorded median (95% CI) simple trends in heart rate (dHR), systolic blood pressure (dSBP), normalized plethysmographic pulse amplitude ($dPPGA_{norm}$), remifentanil (Ce_{remi}) and propofol (Ce_{propo}) effect site concentrations, and Bispetral Index values (BIS) for episodes of SPI ≥ 60 for 20–39 s, 40–59 s, more than 59 s, all pooled episodes of SPI ≥ 60, sigLOR alerts, and EBMi alerts

	Ce_{remi}	Ce_{propo}	BIS	dHR	dSBP	$dPPGA_{norm}$
SPI ≥ 60 for 20–39 s	4.00 (3.10–4.19) b	2.30 (2.00–2.53)	49 (47–53) d	**1 (0.5–1.5) e**	0 (0–0.5)	**−16.3 (− 21.2 to − 10.7) e**
SPI ≥ 60 for 40–59 s	3.56 (3.00–5.00) b	2.23 (2.00–2.80)	51 (47–53) d	**1 (0.0–1.5) e**	0 (− 1 to 1)	**− 5.7 (− 12.5 to − 2.6) e**
SPI ≥ 60 for more than 59 s	**2.00 (1.17–3.02) a**	1.57 (1.20–2.00)	**63 (55–78) c**	**1 (0.5–2.0) e**	0 (0–1)	**− 16.4 (− 20.7 to − 13.0) e**
All pooled episodes of SPI ≥ 60				**1 (0.5–1.5) e**	0 (0–0.5)	**− 14.5 (− 17.3 to − 11.4) e**
LOR alerts	3.02 (3.01–3.93) b	2.50 (2.30–2.59)	47 (46–50) d			
EBMIs alerts	3.01 (1.67–4.00)	2.46 (2.00–2.80)	52 (44–61)			

a = Significantly lower than b

c = Significantly higher than d

e = Significantly different from 0

higher during episodes of SPI ≥ 60 for more than 59 s than during shorter episodes or at the moment of sigLOR alerts, although Ce_{propo} was similar (Table 2).

4 Discussion

The main finding of this retrospective analysis is that two different monitoring methods, claimed to assess the same physiological status, namely the sympathetic tone, do not react synchronously during surgery under general anesthesia. In face of this observation, one may wonder which monitoring system best reflects the sympathetic status of the patient. Unfortunately, our study does not allow answering this question. Indeed, we did not record one of the nociception-anti-nociception balance components, the intensity of surgical noxious stimulation, in our patients. We observed, however, that longer SPI ≥ 60 episodes occurred during relatively lighter depth of anesthesia, as indicated by the lower remifentanil concentrations and higher BIS values at those times. The SPI has been extensively studied with respect to the intraoperative nociception-anti-nociception balance, and has been demonstrated, when used to guide anti-nociceptive medication administration, to nicely reflect the nociception-anti-nociception balance, to predict the occurrence of movement in response to noxious stimulation, to ameliorate the individual tailoring of the anti-nociception level, to promote intraoperative hemodynamic stability, and to help predicting the moment of recovery [6, 7, 10, 16–18]. Its ability to reflect the nociception-anti-nociception balance may, however, be less strong when using peculiar combinations of agents [19], or in specific populations of patients [20]. The performance of the SPI may also be altered by several confounding factors, including the concomitant use of cardiovascular medications [21–23], the intravascular volume status [23–25], and cardiac pacing [22]. None of these confounding factors were controlled in the present study. Contrarily to SPI, the EBMi software has been much less extensively studied regarding its ability to reflect the nociception-anti-nociception balance during anesthesia, as well as the effect of confounding factors on their occurrence. However, the EBMi software alarms, by combining more pieces of evidence to suggest plausible diagnoses, namely trends in blood pressure, heart rate, and plethysmographic amplitude, may reveal more specific to nociception-anti-nociception balance monitoring in the future. Our observation, in the present study, of far fewer EBMi and sigLOR alerts than the number of SPI episodes over 60 is an argument in favor of this hypothesis. EBMi alerts at least seem to improve the advice of clinicians on otherwise undetected atypical changes in sympathetic tone, such as, for example, an increase in blood pressure without tachycardia, or an isolated decrease in plethysmographic pulse amplitude [11]. In this study, the fact that a substantial amount of EBMi alerts and sigLOR alerts occurred when the SPI value was below 60 further suggests a possible higher specificity of those alerts as compared to the SPI. Nevertheless, our results strongly support the need for prospective randomized controlled studies to formally compare the SPI with the EBMi sympathetic tone alarms, in addition to those studies that are needed to clinically validate the EBMi as a monitor of the nociception-anti-nociception balance.

Despite the noticed discrepancies between SPI and EBMi, episodes of SPI over 60 were preceded by logical changes in parameters that enter its algorithm. Changes in SPI were indeed mainly governed by changes in plethysmographic pulse amplitude, as shown by the marked negative trend in $PPGA_{norm}$, the small but significant positive trend in HR, and the more frequent incidence of $dPPGA_{norm}$ down. Of note, HR contributes to only 30% of the SPI value. The fact that changes in SBP did not precede a change in SPI is not surprising, insofar as this parameter is not part of SPI calculation, although an increase in blood pressure is frequently expected when sympathetic tone increases.

Our study has some limitations. First, its retrospective nature only allows the generation of hypotheses prompting specifically designed studies to address precise unresolved questions. The study was indeed not powered for the analyses we performed here, and we may have missed some significant changes in one parameter or the other. Second, insofar as original pulse wave tracings were not available to be passed through the EBMi software, we used $PPGA_{norm}$ values that were back-transformed from the SPI values instead. This may have introduced bias. Finally, we arbitrarily decided that a SPI value over 60 was indicative of raised sympathetic tone, and that a 5-min preceding length of time was adequate to look at parameter trends and perform LOR analyses. The SPI value of 60 was chosen according to the usually recommended intraoperative SPI threshold values, which range between 20 and 50 [10]. Hence, a SPI value over 60 (over the upper limit of the 20 to 50 range) during a relevant amount of time (more than 20 s) is certainly indicative of the most significant sympathetic events. The 5-min length for trends was chosen for the sake of comparisons with LOR analyses by the EBMi software, which is based on that time delay. It was also chosen in order to obtain reliable medians, while remaining within a time delay that has clinical relevance. With a sampling rate of 0.1 Hz, a 5-min period allows recording 30 values, which can be considered a reasonable amount for estimating medians. Five min is a common time interval between clinician interventions during anesthesia, in the absence of any emergency situation. However, choosing a longer or shorter length of time could have led to different results. Regarding EBMi, the necessary 5-min median for baseline and a minimum of four values that are consistently above or below the median before generating an alert lead to a minimum 40-s time delay for an alert. Attempting to detect changes earlier increases the risk of false alerts.

5 Conclusions

Our results clearly demonstrate that different methods of sympathetic tone assessment during general anesthesia may provide conflicting information, and that caution should be paid to its interpretation. Further work is needed to clarify the factors that may confound each of the used method, and clinical situations where the reliability of one technique surpasses the one of the other technique.

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Compliance with ethical standards

Conflict of interest Michael Harrison is one of the designers of the EBMi software. The other authors declare that they have no conflict of interest.

Ethical approval All procedures performed on human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study is a retrospective analysis of data acquired during a previously published study, for which Ethics Committee approval was obtained. The initial study was registered at Clinicaltrials.gov, NCT: 02884310; https://clinicaltrials.gov/ct2/show/NCT02884310. Although formal consent is not required for retrospective studies, informed consent was obtained from all individual participants included in the study.

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