The Measurement of Neurovegetative Activity During Anesthesia and Surgery in Swine: An Evaluation of Different Techniques

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In this study we evaluated, in 10 sevoflurane-anesthetized pigs undergoing abdominal surgery, different techniques for measuring autonomic nervous system (ANS) activity: ANSiscope™ index, spectral analysis of heart-rate variability, hemodynamic variables, and plasma catecholamines and cortisol levels. Animals underwent a 120-min anesthesia during which unilateral ovariectomy was performed. Cardiovascular and respiratory responses were monitored. ANSi scope™ indices (ANSindex™ sympathetic, ANSindex™ parasympathetic and balANSindex™) were used to monitor ANS activity. Spectral analysis was performed using an autoregressive model with a parametric method. The low frequency (LF) and high frequency (HF) components were used to interpret the power spectral density of short-term electrocardiograms (ECGs). The relationship LF/(LF+HF) reflects sympathetic activity, HF/(LF+HF) indicates parasympathetic activity, and the LF/HF ratio gives the predominance of the system. Plasma concentrations of adrenaline, noradrenaline, and cortisol were determined at different times. Correlation ($P < 0.01$) was found between the balANSindex™ and adrenaline levels and between LF/HF ratio and plasma adrenaline concentrations. Moreover, a significant ($P < 0.01$) correlation was found between the balANSindex™ and LF/HF ratio. However, no correlation was seen between the registered ANSiscope indices and hemodynamic variables. The correlation seen in this study suggests that the balANSindex™ could be a useful tool to monitor ANS activity during anesthesia and surgery.

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A variety of techniques have been used to assess sympathetic nervous system (SNS) activity, but in many cases the assessment is indirect and often obtained in the absence of related functional information. Probably the most widely used indicator of SNS activity is the measurement of plasma catecholamine concentrations (1).

Attenuation of sympathetic nerve activity during anesthesia is usually assessed by monitoring cardiovascular reactions. The beat-to-beat fluctuation in heart rate (HR) is closely linked to the activity of autonomic nerves. In the past 2 decades, spectral analysis of HR variability (HRV) has enabled continuous noninvasive quantification of cardiac autonomic function (2,3). Previous analysis indicates that HRV may be a useful tool for evaluating autonomic functions (4) or stress responses (5).

A new system for representing and measuring the autonomic nervous system (ANS), the ANSiscope™ (Dyansys, Inc., Burlingame, California), has been devised. It is based on a discriminating analysis of fractal characteristics found in the time-series between R wave intervals of the electrocardiogram (ECG). The system discriminates the component resulting from the activity of the sympathetic subsystem from the component resulting from the parasympathetic subsystem.

The ANSiscope™ computes a trajectorial representation of the sympathovagal balance named the balANSindex™. From this representation, the center of gravity can be computed (balANSindex™ corresponding to the distance from the origin), and it allows measurement of sympathetic or parasympathetic predominance. This balANSindex™ has values comprised between –50 and 50, negative values indicating

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a predominance of parasympathetic activity and positive values a predominance of sympathetic activity. A healthy volunteer at rest will have a balANSindex™ around –15, showing a predominance of parasympathetic activity.

The ANSiscope™ has shown promise in diabetes-related disorders (6).

ANS monitoring using the ANSiscope™ may allow the anesthesiologist to better determine correct drug dosage. The ANSiscope™ shows the state of the sympathovagal balance and thus may be used in the operating room to monitor the effectiveness of anesthesia in real time.

The aim of this pilot study was to compare different available methods to monitor ANS activity in sevoflurane-anesthetized animals undergoing abdominal surgery. We investigated the relationship between plasma catecholamines and cortisol levels, which are related to sympathetic activation, ANSiscope™ indices and spectral analysis of HRV, as a reflection of ANS activity, and hemodynamic variables of the subject's physiological responses to surgery.

Methods

The experimental protocol was approved by the Institutional Ethical Committee for Animal Research. Ten healthy female Large White pigs were used. Their mean weight was 21.0 ± 1.4 kg.

One day before the experimental anesthetic episode, each pig was anesthetized with sevoflurane and a 20-gauge catheter was placed in the external iliac artery through a femoral approach (7) and fixed to the skin. Similarly, on that same day a vascular sheath was placed in the jugular vein using the Seldinger technique.

The ANSiscope™ monitoring system has a single 3-lead ECG. Electrodes for the ECG module were placed on each pig in accordance with a standard (i.e., lead-III) configuration. The ECG signal is digitized with a sampling rate of 200 Hz. The QRS complex detection is performed leading to the RR-intervals signal. From this RR-intervals chaotic time-series, a phase-space is reconstructed in which changes in the state of the ANS become explicit as a velocity from negative to positive values, from parasympathetic predominance (manifested by slow HR) to sympathetic predominance (manifested by rapid HR). This reconstruction takes advantage of changes on multiple time scales. The obtained phase space describes the force of change applied (constant times of the acceleration) as a function of this velocity. Points reached in this two-dimensional space together form the sympathovagal balANS™, it expresses the global ANS outcome. To acquire independent measurements of sympathetic and parasympathetic activities, the following equation is solved with every point obtained at the time of the latest heart beat:

$$(p,q)_{PhaseSpace} = C \cdot \left(\frac{\sum}{2}, \frac{\Delta}{2}\right)\left(\left(\frac{SP}{2} + D\right) - PSP\right),$$

where SP and PSP are respectively the sympathetic and parasympathetic local degrees of activity, S and D are respectively the sum and difference of values for the last two heart beats, and C and D are constants to be defined. This equation expresses a summation law, i.e., how the two activities of the ANS subsystems add up to one global predominance for the ANS, with the overall antagonism of these subsystems respected. This approach of extraction of autonomic information from the interval tachogram represents scale-covariance, is non-model driven, and belongs essentially to the time-domain. The SP and PSP degrees of activity are termed ANSindices™, and the balANS index™ corresponds here to the distance from the points' center of gravity to the origin.

The ANSindex™ sympathetic, ANSindex™ parasympathetic and balANSindex™ computed at each R wave were recorded continuously beginning during the conscious state and continuing through induction, maintenance, and recovery from anesthesia.

Spectral analysis of HRV using an autoregressive model with a parametric method was performed as described by Malik et al. (8).

For each event time, we have taken 300 RR intervals just after the event. In a spectrum calculated from that short term recording of 300 RR intervals, 3 main spectral components are distinguished: very low frequency (LF), LF, and high frequency (HF) components. The very LF component should be avoided when interpreting the power spectral density of short-term ECGs. Vagal activity is the major contributor to the HF component (9). Previous studies suggest that LF is a quantitative marker of sympathetic activity (9). The LF/HF ratio is considered by some investigators to mirror the sympathovagal balance or to reflect sympathetic modulators (9).

Animals were premedicated with IM diazepam (Valium; Roche Pharma, Madrid, Spain) (0.1 mg/kg) and ketamine (Ketolar; Pfizer, Madrid, Spain) (10 mg/kg). Anesthesia was induced with sevoflurane (5%) in oxygen (5 L of oxygen/min). When lack of jaw tone, loss of swallowing, lack of head shaking, loss of palpebral and pain reflexes, and ventromedial rotation of the eyes were all detected, an endotracheal tube was inserted. The tube was then connected to a semiclosed circular anesthetic circuit attached to a ventilator (Ventilator 7800; Ohmeda, Madrid, Spain). Sevoflurane (Sevorane; Abbott Laboratories, Madrid, Spain) administration started at 5%, which enabled us to rapidly achieve 1.25 MAC (1 MAC = 2.66%) (10) with an oxygen flow rate of 3 L/min. Once 1.25 MAC was

reached (3.3% end-tidal sevoflurane), the vaporizer setting was adjusted as needed to maintain this concentration. Muscle relaxation was obtained by injection of vecuronium (0.1 mg/kg) (Norcuron, Organon Española, Barcelona Spain) every 30 min.

Intermittent positive pressure ventilation was used during the procedure to maintain the end-tidal CO_2 concentration between 35 and 40 mm Hg.

The pigs were placed in dorsal recumbence, and unilateral ovariectomy was performed through a midline approach with a 10-cm long infraumbilical incision. This procedure was always performed by the same surgeon using the same technique to achieve reproducible stimulation.

During surgery, continuous infusion of physiologic saline solution at a rate of 10 $mL \cdot kg^{-1} \cdot h^{-1}$ was administered. At the end of surgery, the vaporizer was switched off and fresh gas flow rate was increased to 10 L/min of 100% oxygen. Tracheal extubation was done when pigs regained swallowing reflexes and were considered recovered and fully conscious by the ability to stand and walk.

Bispectral index (BIS) (A-1050TM, version 3.05.05; Aspect Medical Systems, Newton, MA) was registered using gel-coated disposable silver-silver-chloride electrodes (Zipprep; Aspect Medical Systems) located according to a previously described montage (11). ECG was performed (model 86S; Hewlett-Packard, Geneva, Switzerland) (lead II) with the electrodes placed in the interdigital spaces of all 4 limbs and pulse-oximetry with a probe (Clip Tip sensor, Oximeter Sensor; Datex-Ohmeda, Louisville, CO) placed on the tongue. Other variables registered were rectal temperature, tidal volume, end-tidal concentration of sevoflurane, end-tidal CO_2 concentration, and respiratory rate (Ohmeda RGM 5250; Ohmeda, Madrid, Spain). Muscle relaxation was observed and monitored by train-of-four (TOF-Guard, Biometer International A/S, Odense, Denmark).

Arterial blood pressure, central venous pressure, and HR were also measured using a blood pressure module (Press M 1006B; Hewlett-Packard) connected to a system for monitoring hemodynamic variables.

Arterial blood pressure was obtained by connecting the catheter previously inserted in an external iliac artery to the monitoring system via a transducer (Ohmeda transducer DT-XX; Ohmeda).

Under sterile conditions a 7F Swan-Ganz catheter (CritiCath™ SP5107, Becton Dickinson Infusion Therapy Systems Inc., Singapore) was placed through a femoral vein approach. The placement of the tip of the Swan-Ganz catheter was confirmed through monitoring of pressure waveforms. Pulmonary artery occlusion pressure (wedged pressure), cardiac output calculated by thermodilution, and central venous pressure were measured.

Through the jugular sheath, venous blood was sampled at different times. At each interval, 5 mL of blood was collected using a cold syringe. Venous blood samples were collected in tubes containing EDTA.

Tubes of blood were centrifuged immediately at 4°C, and plasma was harvested, frozen, and stored at −20°C until hormone assays.

The plasma cortisol concentration was measured using radio-immunoassay. For plasma cortisol, intra-assay variation ranged between 3 and 5%, inter-assay variation ranged from 4% to 5.2%, with a detection limit of 5.52 nmol/L.

Plasma concentrations of adrenaline and noradrenaline were measured by enzyme immunoassay (Immuno-Biological Laboratories Hamburg, Germany). The sensitivity of the adrenaline assay was 10 pg/mL. Intra-assay variation ranged between 4.1 and 8.3% and inter-assay variation ranged from 12.4% to 16%. For plasma noradrenaline, intra-assay variation ranged between 4.8 and 10% and inter-assay variation ranged from 12% to 16.5%, with a detection limit of 20 pg/mL.

All the recorded data were computerized and means were calculated for the following times: baseline (conscious state) (T1); immediately after anesthetic induction (T2); immediately after tracheal intubation (T3); 30 s before skin incision (T4); during skin incision (T5); during ovarian pedicle traction (maximal nociceptive stimulus) (T6); during peritoneum closure (T7), and at the end of surgery and cessation of anesthetic administration (T8). The ANSiscope™ indices were also measured 24 h after the end of surgery (T9).

Plasma hormone concentrations were measured at baseline (conscious state), 30 s after induction, during skin incision, during ovarian pedicle traction, during peritoneal closure, and 24 h after the end of surgery.

Statistical analysis was performed with the SPSS 10.0 statistical package for Windows (SPSS Inc, Chicago, IL). Results were expressed as mean ± SD. A Kolmogorov-Smirnov test (13) was used to determine that data were normally distributed. Changes in BIS, ANSiscope™ indices, hemodynamic variables, and hormone concentrations at each time point were analyzed using one-way analysis of variance for repeated measures followed by the Tukey test to examine deviation from control values. A Bonferroni procedure for multiple comparisons was conducted to minimize the possibility of finding significant results by chance. Stepwise multiple-regression analysis was performed to evaluate the relationship between the ANSiscope™ indices and hemodynamic variables, the ANSiscope™ indices and hormone concentrations, the LF/HF ratio and BalANSindex™, and between the LF/HF ratio and hormone concentrations. Values of $P < 0.05$ were considered significant.

Table 1. Autonomic Nervous System (ANS)index™ Sympathetic, ANSindex™ Parasympathetic, balANSindex™ and Bispectral Index (BIS) in Pigs Anesthetized with Sevoflurane and Undergoing Surgery

Times	ANSindex™ sympathetic	ANSindex™ parasympathetic	balANSindex™	BIS
1 (baseline)	2.6 ± 3.9	2.8 ± 4.3	−9.8 ± 6.0	96.9 ± 1.6
2 (after anesthetic induction)	20.7 ± 10.1*	1.3 ± 2.9	10.0 ± 14.3*	56.2 ± 9.0*
3 (after tracheal intubation)	19.5 ± 16.1*	1.1 ± 3.0	18.9 ± 16.9*	55.7 ± 10.8*
4 (before skin incision)	23.7 ± 16.2*	−0.4 ± 0.8*	19.0 ± 17.8*	47.0 ± 18.2*
5 (during skin incision)	33.6 ± 7.0*	−0.3 ± 0.4*	34.3 ± 7.51*	45.4 ± 13.5*
6 (during ovarian pedicle traction)	30.7 ± 7.2*	0.4 ± 1.3	30.0 ± 10.0*	51.1 ± 16.4*
7 (during peritoneum closure)	33.0 ± 9.2*	0.0 ± 0.7	35.2 ± 9.0*	50.3 ± 16.8*
8 (end of surgery)	33.6 ± 11.1*	−0.2 ± 0.6	29.8 ± 16.5*	53.4 ± 16.2*
9 (24 h after surgery)	30.0 ± 7.4*	−0.3 ± 0.5*	29.5 ± 7.5*	98.2 ± 1.3

Data are expressed as mean ± SD.
* Significant changes from baseline ($P < 0.05$).

Results

Temperature was maintained stable as was P_{ETCO_2} between 35–40 mm Hg and Spo_2 was > 97% in all pigs. Blood loss was minimal for all procedures.

A significant ($P < 0.001$) decrease in BIS was detected after anesthetic induction, but no further significant changes were seen during anesthetic maintenance (Table 1). No movements were observed in any pig during anesthesia. Anesthetic depth, as determined by clinical observation was consistent with a surgical plane of anesthesia.

The changes observed in all the measured variables are reflected in Tables 1–3 . In brief, these changes are summarized below.

Before Surgery (Times 1 to 4)

The ANSindex™ sympathetic, balANSindex™, and LF/(LF+HF) increased significantly ($P < 0.001$)and the HF/(LF+HF) quotient decreased significantly after sevoflurane induction, but hemodynamic variables, cortisol, and catecholamine concentrations did not change significantly. The LF/HF ratio increased significantly after tracheal intubation.

During Surgery (Times 5 to 8)

The ANS index™ sympathetic and the quotient LF/(LF+HF) remained increased through the surgery. The HF/(LF+HF) quotient remained decreased from baseline through the whole procedure. The LF/HF ratio increased significantly during skin incision, ovarian pedicle traction, and during peritoneum closure. BalANSindex™ values increased significantly ($P < 0.001$) during skin incision. Similarly, a significant ($P < 0.001$) increase in plasma cortisol, adrenaline, and noradrenaline was seen immediately after incision, with the maximum hormone values being found at the moment of ovarian pedicle traction.

No significant changes were detected in hemodynamic variables during skin incision or during maximal nociceptive stimulus throughout the surgical procedure, except for a significant increase noted in wedged pulmonary pressure ($P < 0.001$) during abdominal incision. This high value was maintained all through surgery.

Time 9

The ANSindex™ sympathetic and the balANSindex™ remained significantly higher than baseline 24 h after surgery whereas the ANSindex™ parasympathetic stayed significantly lower. Catecholamine levels remained high but cortisol levels reverted to normal.

No correlation was detected in this study among any of the registered ANS indices™ and hemodynamic variables. A significant ($P < 0.01$) correlation was found, however, between the balANSindex™ and plasma adrenaline concentrations (Fig. 1) but not between balANSindex™ and cortisol concentration (Table 4). The same tendency was seen at all studied intervals between balANSindex™ and catecholamines concentrations.

A significant ($P < 0.01$) correlation was found between the balANSindex™ and LF/HF ratio and between LF/HF ratio and plasma adrenaline concentrations but not between LF/HF ratio and noradrenaline and cortisol concentrations (Table 4, Figs. 1 and 2).

Moreover a significant ($P < 0.01$) correlation was observed between the ANSindex™ sympathetic and adrenaline plasma levels, whereas no correlation was found between this index and noradrenaline and cortisol values. On the other hand, a correlation was found between ANSindex™ parasympathetic and plasma noradrenaline ($P < 0.01$) (Table 4).

Discussion

The present study detected a correlation between the balANSindex™ and catecholamine concentrations

Table 2. Low Frequency (LF)/(LF+ High Frequency (HF)), Which Gives Sympathetic Activity, HF/(LF+HF), Which Gives Parasympathetic Activity, and LF/HF Ratio, Which Gives the Predominance of the System in Pigs Anesthetized with Sevoflurane and Undergoing Surgery

Times	LF/(LF+HF)	HF/(LF+HF)	LF/HF ratio
1 (baseline)	28.3 ± 15.1	48.7 ± 7.3	0.62 ± 0.38
2 (after anesthetic induction)	53.3 ± 15.2*	33.1 ± 9.9*	1.81 ± 0.81
3 (after tracheal intubation)	66.6 ± 18.0*	24.4 ± 12.7*	4.37 ± 3.83*
4 (before skin incision)	56.1 ± 8.3*	32.9 ± 6.4*	1.80 ± 0.56
5 (during skin incision)	64.7 ± 7.3*	27.3 ± 5.4*	2.54 ± 0.84*
6 (during ovarian pedicle traction)	68.7 ± 8.3*	26.0 ± 4.3*	2.78 ± 0.94*
7 (during peritoneum closure)	68.1 ± 4.7*	26.9 ± 2.8*	2.54 ± 0.28*
8 (end of surgery)	59.6 ± 8.4*	32.0 ± 3.8*	1.92 ± 0.44

Data are expressed as mean ± SD.
* Significant changes from baseline ($P < 0.05$).

Table 3. Plasma Concentrations of Adrenaline, Noradrenaline and Cortisol in Pigs Anesthetized with Sevoflurane and Undergoing Surgery

Sample Times	Adrenaline (pg/mL)	Noradrenaline (pg/mL)	Cortisol (μg/dL)
Baseline	403.0 ± 81.2	488.0 ± 55.1	24.7 ± 3.7
30 s after induction	481.0 ± 66.6	565.2 ± 69.0	20.1 ± 5.1
During skin incision	600.8 ± 78.0*	635.6 ± 74.6*	44.1 ± 31.2*
During ovarian pedicle traction	642.3 ± 84.4*	632.4 ± 96.4*	42.7 ± 26.6*
Suture and surgical wound closure	612.9 ± 113.5*	673.8 ± 96.4*	57.6 ± 45.3*
24 h after surgery	571.0 ± 79.0*	632.4 ± 91.6*	18.2 ± 7.9

Data are expressed as mean ± SD.
* Significant changes from baseline ($P < 0.05$).

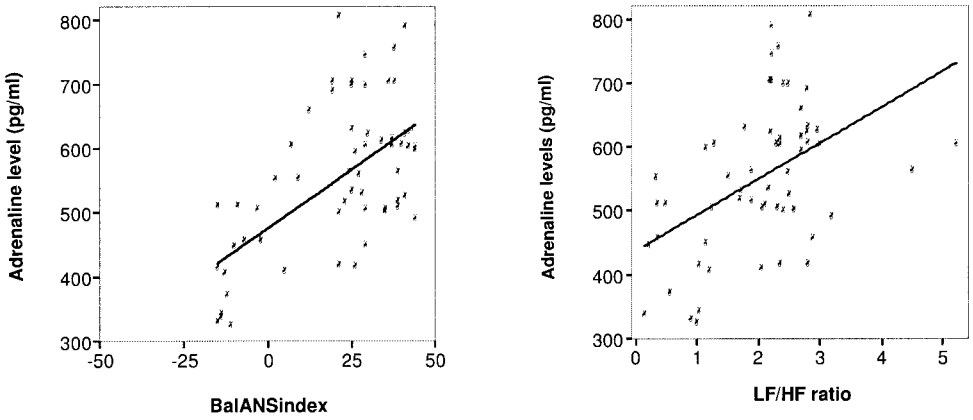

Figure 1. Graphical representation of the regression analysis performed between adrenaline levels and bal autonomic nervous system (ANS)index™ and between adrenaline and low and high frequency (LF/HF) ratio. Regression equation adrenaline = 475.42 + 3.66BalANS-index; $R^2 = 0.37$ adrenaline = 436.90 + 56.44 LF/HF ratio; $R^2 = 0.22$.

and between the balANSindex™ and HF/LF ratio during anesthesia.

On the other hand, no correlation was seen between both indexes and cortisol concentrations. The endocrine rapid response to stress is mainly associated with activation of the adrenal medulla and the SNS, with increased catecholamine levels, whereas stimulation of the pituitary-adrenocortical system and cortisol release represent a slower reaction (1). The balANSindex™ could be an earlier marker of sympathetic activity than changes in cortisol concentration.

In our opinion, the increase in hormone concentrations, ANS index™ sympathetic, HF/LF ratio, and balANSindex™ during surgery were related to the surgical trauma, (14) and they were accompanied by a substantial ANS activation secondary to either a stress response or pain. Values for the ANS index™, spectral analysis variables, and hormone concentrations obtained at that time reflect the fact that the anesthetic protocol we used was not successful in minimizing stress responses of the ANS to the surgery. Similarly, the increases shown in catecholamines, ANSindex™

Table 4. Results from Multiple-Regression Analysis of balANSindex™, ANSindex™ Sympathetic and ANSindex™ Parasympathetic with Levels of Cortisol, Adrenaline, and Noradrenaline and Between LF/HF Ratio with balANSindex™ and Levels of Cortisol, Adrenaline, and Noradrenaline

balANSindex™	Variable	Coefficient	SE	R^2	*P* value
	Intercept	−51.005	12.755		0.000
	Cortisol	0.0306	0.078	0.05	0.699
	Adrenaline	0.0726	0.023	0.37	0.003
	Noradrenaline	0.0544	0.028	0.31	0.050
ANSindex™ sympathetic	Intercept	−20.112	9.344		0.036
	Cortisol	−0.0151	0.057	0.05	0.792
	Adrenaline	0.0446	0.017	0.30	0.011
	Noradrenaline	0.0345	0.020	0.25	0.097
ANSindex™ parasympathetic	Intercept	7.801	2.048		0.000
	Cortisol	0.010	0.013	0.01	0.418
	Adrenaline	−0.052	0.004	0.08	0.890
	Noradrenaline	−0.012	0.004	0.17	0.012
LF/HF ratio	Intercept	1.392	0.146		0.000
	balANSindex™	0.031	0.005	0.38	0.000
LF/HF ratio	Intercept	−0.624	0.721		0.390
	Cortisol	0.000	0.004	0.04	0.985
	Adrenaline	0.003	0.001	0.22	0.004
	Noradrenaline	0.002	0.001	0.18	0.248

ANS = autonomic nervous system; LF = low frequency; HF = high frequency.

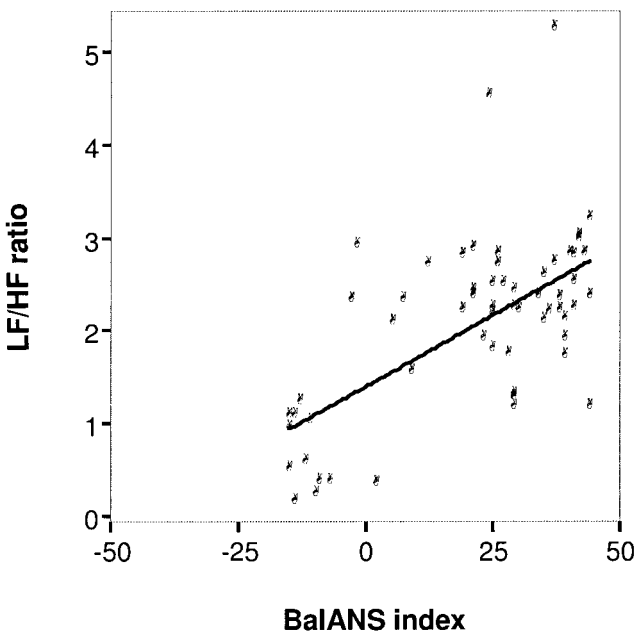

Figure 2. Graphical representation of the regression analysis performed between low and high frequency (LF/HF) ratio and bal autonomic nervous system (ANS)index™. Regression equation: LF/HF ratio = 1.39 + 0.03BalANSindex; R^2 = 0.38.

sympathetic and balANSindex™ during recovery of consciousness reflect a significant activation of the ANS during anesthetic recovery. However, this increase in the indices and in catecholamine concentrations was not followed by clinical signs suggestive of stress or pain during surgery or anesthetic recovery, nor did we detect hemodynamic changes at these times. This supports the assumption that HR and clinical signs are not good indicators of ANS stimulation during anesthesia, and these data are therefore not sufficient to determine the degree of stress in patients.

These results are consistent with prior studies in the same setting (15). It has been proposed (16) that HRV modifications can be used as an indicator of postoperative recovery.

The similarity between ANS indices during ovarian pedicle traction and 24 hours after surgery may be explained by considering that during surgical stimulus the animal was anesthetized and 24 hours later the measurements were taken in conscious animals with a surgical wound.

A slight increase in catecholamine levels was seen in this study immediately after induction, along with an increase on the balANSindex™, and a concurrent increase in the ANS index™ sympathetic, LF/(LF+HF) and HF/LF ratio. At the same time HF/(LF+HF) decreased. These changes suggest that sevoflurane anesthetic induction causes a sympathomimetic activation (9). The results obtained in the present study are in accordance with other studies conducted while inducing anesthesia with isoflurane (17). The sympathoadrenal activation shown by ANSiscope™ and spectral analysis of HRV were not associated in this study to a hemodynamic response, in contrast with the data reported for isoflurane and desflurane (18). In humans,

the initial administration of desflurane prompts a transitory, but substantial, increase in HR and arterial blood pressure (19) that is associated with sympathetic stimulation. The changes observed in ANSiscope™ indices, hormones levels, and spectral analysis after induction may be associated with the administration of ketamine as a preanesthetic medication. This drug has a sympathomimetic action, thus decreasing the variability of R-R intervals. Theoretically, administration of ketamine should have caused an increase in the ANSindex™ sympathetic and in the LF/(LF+HF), so the increase observed in this index between baseline (registered in the conscious animal and before any preanesthetic medications) and immediately after anesthetic induction (i.e., after administration of ketamine), may have been related to this premedication (20). In our opinion this may reflect that ANSiscope™ does not only reflect the sympathetic activation caused by the external stimulus but it also reflects the sympathetic activation caused by drugs.

Our study did not reveal a correlation between ANSiscope™ indices and hemodynamic variables. Previous studies conducted with a different, early version of the monitor that also measured the reactivity of the ANS in real time through fractal analysis of HRV (15,21)[1] reflected that the measured index could be a marker of stress responses to a nociceptive stimulus that would be evident sooner than changes in HR or arterial blood pressure. The period that elapses between changes in the proprietary index and hemodynamic changes may account for the lack of correlation in our study. In our opinion, this difference in the time frame between changes in the proprietary index and hemodynamic changes may make the ANSiscope™ a valuable therapeutic tool. It is possible that the anesthetic protocol used, given the known cardiovascular effects of sevoflurane, could have masked any HR and arterial blood pressure changes in response to surgery.

In our opinion, the main limitations of this pilot study are that despite having found significant correlations among several of the studied variables (Table 4), these correlations are weak as indicated by the R^2 values. Moreover, further studies including direct measurements of ANS activities are needed to fully determine the clinical usefulness of the monitor.

In the study reported here, we used an electrode configuration for BIS that is normally used in human medicine (11). Our clinical experience with this electrode arrangement has always yielded good-quality recordings in pigs. BIS data have not been validated in animals and hence the interpretation of these data must extrapolate from human data.

In a previous study performed by our group (12), BIS was useful for predicting changes in anesthetic depth at clinically used dosages of sevoflurane at varying MAC concentrations.

We used intermittent positive-pressure ventilation in all pigs to avoid chemoreflex activation secondary to hypoventilation-induced hypercapnia and hypoxemia. Moreover, variables were measured as soon as possible after anesthetic induction (i.e., a time when capnic changes are minimal). Variables of mechanical ventilation (tidal volume and respiratory rate) were set near values observed for conscious pigs. In conscious subjects, reduction of tidal volume is associated with a reduction in HF spectral energy and, through a complex dynamic interaction, causes an increase in the LF components (22). This implies that changes in HRV during induction of anesthesia depend on drug-induced modifications of ANS activity as well as their effects on respiration.

In the pilot study reported here, the correlations seen suggest that the balANSindex™ could be a useful tool to monitor ANS activity during anesthesia and surgery. However, we did not detect a correlation between hemodynamic variables and the ANSindex™. To fully validate this monitoring system further studies are needed, using the technique described by Ebert and Muzi (23) that obtain direct measurements of SNS and parasympathetic nervous systems activity. In this way the sensitivity and the specificity of the ANSindices™ could be verified.

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