Performance of the Parasympathetic Tone activity (PTA) index to predict changes in mean arterial pressure in anaesthetized horses with different health conditions

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Abstract

Background: The parasympathetic tone activity (PTA) index is based on heart rate variability recently and has been developed in animals to assess their relative parasympathetic tone and their analgesia nociception balance. The present study aimed to evaluate the variation of PTA in anaesthetized horses according to haemodynamic status and health conditions and to determine the performance of dynamic variations of PTA (ΔPTA) to predict mean arterial pressure (MAP) variations.

Results: Thirty-nine client-horses admitted to the Veterinary Campus of Lyon were anaesthetized for elective or emergency surgery and divided into "Colic" and "Elective" groups. During anaesthesia, dobutamine was administered as treatment of hypotension (MAP < 60 mmHg). No significant variation of PTA and MAP were detected immediately before and after the time of cutaneous incision. PTA increased 5 min before each hypotension (+15% in Elective and +11.4% in Colic group), conversely, PTA decreased 1 min after the administration of dobutamine (-12.7% in Elective and -9% in Colic group). Horses of the Colic group had lower PTA values than those in Elective group, whereas MAP didn't differ between groups. Globally, to predict a 10% increase in MAP, ΔPTA performance was associated with: AUC ROC [95% CI] = 0.77 [0.70 to 0.83] ($p<0.0001$), with a sensitivity of 88.2% and a specificity of 57.7% for a threshold value of −1%. Besides, to predict a 10% decrease in MAP, ΔPTA performance was associated with: AUC ROC [95% CI] =0.80 [0.73 to 0.85] ($p<0.0001$), with a sensitivity of 62.5% and a specificity of 94.6% for a threshold value of 25%.

Conclusions: The PTA index in anaesthetized horses appears to be influenced by the haemodynamic status and the health condition. The shift toward lower PTA values in colic horses may potentially reflects a sympathetic tone predominance. Of clinical significance, a PTA increase of >25% in 1 min showed an acceptable performance to predict a MAP decrease of >10% within 5 min. Even though these results require further evaluation, this index may thus help to predict potential autonomic dysfunctions in sick animals.

Background

The assessment of intra operative nociception remains a challenge for the veterinary anaesthetist. For the anaesthetized patient, an inappropriate analgesia nociception balance could lead to pain, haemodynamic instability, and possible analgesic overdose [1]. Recently, similarly to human medicine, the use of devices based on heart rate variability (HRV) has been proposed for veterinary purpose, including equine species [2].

Spectral analysis of HRV is a non-invasive objective technique that examines the beat-to-beat variations in heart rate (HR) and can characterize the autonomic nervous system activity [3]. Stress from various origin (including nociception, anxiety, aggression, etc…) can shift the autonomic balance towards a sympathetic nervous prevalence with a decrease in HRV [4]. HRV has been used as a diagnostic and prognostic tool in a variety of conditions including anaesthesia [2], aiming to optimize intraoperative haemodynamics [5]. It is commonly used to characterize the relative activity of the sympathetic and parasympathetic nervous systems in animals and humans [6].

Recently, a monitor has been launched to assess the sympathovagal balance in animals (PTA Monitor®; MDoloris Medical Systems, Lille, France). It displays an index called PTA (Parasympathetic Tone Activity), which is similar to the Analgesia Nociception Index (ANI). These indexes assess the parasympathetic tone based on the qualitative and quantitative analysis of the HRV. At each respiratory cycle, these indexes measure the relative parasympathetic tone and its effect on the sinus node. The signal collected is simply an electrocardiogram (ECG) which is automatically analyzed for the R-R interval over a period of time [7]. ANI index was validated to detect nociception during anaesthesia in human patients [8]. PTA index was evaluated to assess the analgesia/nociception balance and predict a haemodynamic reactivity in anaesthetized dogs [9].

The autonomic nervous system (ANS) is a major regulator of the cardiovascular system: it maintains internal physiologic homeostasis, but can be altered by a variety of perioperative factors, including anaesthetic drugs and clinical condition, with resulting haemodynamic changes [10] [11]. As horses are prone to develop pronounced cardiovascular alterations during general anaesthesia, it is probable that their sympathovagal balance can be modified during anaesthesia, which may interfere with HRV analysis. Alternately, apart from the evaluation of analgesia nociception balance, monitoring the sympathovagal balance during anaesthesia may provide useful information to early detect ANS dysfunction and optimize the cardiovascular support of the anaesthetized horse [12].

To our knowledge, no study has been carried out to evaluate the performance of the PTA index in anaesthetized horses. The present study aimed to evaluate the variation of PTA in anaesthetized horses according to different intraoperative and health conditions and to determine the performance of dynamic variations of PTA (ΔPTA) to predict an increase or a decrease of MAP. We hypothesized that the PTA index would vary in conjunction with cardiovascular changes and could help to predict mean arterial pressure (MAP) changes in anaesthetized horses.

Statistical analysis

Statistical analysis was performed using MedCalc@ 12.1.4.0 (MedCalc SoftwareÒ, Ostend, Belgium). The number of horses in each group was chosen arbitrarily. Normality of distribution was assessed using the Shapiro-Wilk test. Normal data were expressed as mean ± standard deviation (SD) whereas skewed data were expressed as median and interquartile range [IQR]. Demographic data was compared between groups using Student's *t* test. An analysis of variance (ANOVA) for repeated measures was used to detect any significant variations of PTA and MAP within 1 min and 5 min at each time-point for both Colic and Elective groups. In case of significant variation, *post-hoc* Tukey multiple paired comparisons were performed. Variations of PTA and MAP within time were compared between groups using two-way ANOVA with Bonferroni correction for post hoc analysis. The performance of ΔPTA to predict an increase or decrease of MAP within 5 minutes after predefined time-points was assessed by calculation of the area under curve (AUC) of a receiver operating characteristic (ROC) curve using pooled data from the defined times. The threshold value showing the best sensitivity and specificity was determined using Youden index. A p-value < 0.05 was considered statistically significant.

Results

Animals

No significant difference in age, sex and weight was found between groups whereas the total surgical time was significantly longer in Colic group ($p = 0.003$) (table 1).

Colic group (24 horses) included horses admitted for colic surgery, whereas Elective group (15 horses) comprised healthy horses admitted for elective surgery. Elective surgeries in the latter group consisted of castration ($n = 9$), cutaneous surgery (sarcoidosis $n = 3$, epidermoid carcinoma $n = 1$), abdominal hernia ($n = 2$). Among horses of Colic group, nineteen horses recovered from anaesthesia and five were euthanized prior to the end of surgery. All horses, except of 1 horse in Colic group, developed episodes of hypotension (MAP □ 60 mmHg) that required the administration of dobutamine.

PTA and MAP evolution at the predefined time-points

Variation of parameters for horses of the Elective group

For each predefined time-point of interest in the “Elective group”, the initial PTA and MAP as well as their evolution at 1 and 5 min thereafter are shown in figure 2.

During T_{SS} and $T_{Cut,}$ no significant variation occurred for PTA or MAP.

During T_{Hypo}, no significant difference was observed between PTA_{1min} and PTA_0. However, at 5 min, a significant increase in PTA of 15 % ($p = 0.03$) was observed compared to PTA_0. In addition, the results showed a significant decrease in MAP_{1min} (-4 %, $p = 0.03$) and MAP_{5min} (-20 %, $p < 0.0001$) compared to MAP_0.

At T_{Dobut}, a decrease in PTA was observed 1 min after initiation of dobutamine (-12.7%, $p = 0.08$), whereas PTA_{5min} did not vary compared to PTA_0. After dobutamine initiation, MAP significantly increased at 1 min (+20%, $p = 0.009$) as well as at 5 min (+27%, $p < 0.0001$).

After dobutamine discontinuation ($T_{Post\text{-}dobut}$), no significant change occurred in PTA, whereas a decrease of 8% of MAP was noticed after 5 min ($p = 0.002$).

Variation of parameters for horses of the Colic group

For each surgical time-point of interest in the “Colic group”, the initial PTA and MAP as well as their evolution at 1 and 5 min thereafter are shown figure 3.

During T_{SS} and $T_{Cut,}$ no significant difference was found neither in PTA or MAP, whereas a decrease of 8% compared to MAP_0 was noticed for MAP_{5min} at T_{SS} ($p = 0.059$).

At T_{Hypo}, an increase of PTA was noticed within 5 min (11.4 %, $p = 0.057$), whereas MAP_{5min} decreased significantly (-13%, $p < 0.0001$).

At T_{Dobut}, a decrease in PTA was observed at 1 min (-9%, $p = 0.07$) as well as at 5 min (-12.9 %, $p = 0.03$). MAP increased significantly at 1 min (8 %, $p < 0.0001$) as well as at 5 min (21%, $p < 0.0001$) compared to MAP_0.

At $T_{Post\text{-}dobut}$, no difference in PTA was found whereas a significant decrease in MAP (-8%, $p<0.0001$) was found 5 minutes after dobutamine discontinuation.

Elective vs Colic group

Figure 4 (a and b) compares PTA and MAP values at each predefined time-point between Elective group and Colic group.

The PTA values were significantly lower in the Colic group compared to the Elective group (group effect, $p = 0.001$) (figure 4, a). However, there was no significant PTA variations within time for both groups (time effect, $p = 0.260$) and no interaction between time and groups (time by group effect, $p = 0.598$) (figure 4, a).

There was no significant difference in MAP values at each time-point between groups (group effect, $p = 0.719$) and no interaction between time and groups (time by group effect, $p = 0.187$) (figure 4, b). Yet, in both groups, MAP was shown to be significantly the lowest at the time of dobutamine administration (T_{Dobut}) (time effect, $p<0.001$).

Relationship between ΔPTA and ΔMAP at the predefined time-points of each group

The ROC analysis of the pooled data of ΔPTA at each predefined time-points assumed to anticipate an increase or decrease in MAP was performed with the totality of horses. The ΔPTA was associated with an AUC ROC [95% CI] of 0.77 [0.70 to 0.83] ($p < 0.0001$), showing an acceptable performance to predict an increase of 10% in MAP with 88.2% sensitivity and 57.7% specificity for a threshold value of -1% (figure 5). On the other hand, ΔPTA was associated with an AUC ROC [95% CI] of 0.80 [0.73 to 0.85] ($p < 0.0001$), showing an acceptable performance to predict a decrease of 10% in MAP with 62.5% sensitivity 94.6% specificity for a threshold value of +25% (figure 5).

Discussion

This study describes the variations of the PTA index in anaesthetized horses according to haemodynamic variations and to their physical status. The main findings revealed significant variations of the PTA index during hypotension and administration of dobutamine. Horses of the Colic group demonstrated lower PTA values for several predefined time-points in comparison with those of the elective group, whereas MAP did not differ between groups. Finally yet importantly, the PTA index showed an acceptable performance to predict MAP changes: An increase of 25% in PTA index within 1 min could predict a 10% decrease in MAP after 5 min. In addition, a 1% decrease in PTA index within 1 min could predict a 10% increase in MAP after 5 min, however, this finding is not clinically relevant.

The analysis of heart rate variability (HRV) is a non-invasive simple method, which can detect and record continuously the fluctuations in the autonomic input to the sinoatrial node and the activity of the individual components of the ANS [13] [14]. To evaluate the ANS, HRV uses a frequency domain-based analysis [2]. During anaesthesia, HRV has been used in humans for the prediction of blood pressure variation [15], quality of recovery and the evaluation of analgesia nociception balance [16] [17]. In anaesthetized animals, the use of HRV analysis has been sparsely reported. In horses, HRV power spectrum has been reported to the power spectrum of humans, rats and pigs [2]. The normal resting horse is considered as having a prevailing parasympathetic tone, which was confirmed by HRV analysis [18]. A recent study in horses has reported that HRV can detect sympathovagal stimulation during ocular surgery [14]. It has also been used as a prognostic information for postoperative horses with severe gastrointestinal disease [19].

The PTA index is similar to the ANI, validated in human medicine to predict intraoperative haemodynamic reactions [17] [20] and hypotension caused by spinal anaesthesia [21]. Recently, the dynamic variation of the PTA index (ΔPTA) has been evaluated in anaesthetized dogs, with an acceptable performance to predict haemodynamic reactivity associated with intraoperative nociceptive stimuli [22] [23], but to our knowledge, this index has not been evaluated in anaesthetized horse.

In the present study, predefined time-points were chosen to allow a comparison between animals of different physical status undergoing different surgical procedures. The time-point T_{SS} was designed to evaluate the stability of the signal without any surgical stimulation, whereas T_{Cut} was designed to evaluate the potential influence of a nociceptive stimulation on PTA. The time-points T_{Hypo}, T_{Dobut} and $T_{Post\text{-}dobut}$ were designed to assess the influence of hypotension and administration of inotropes on the index [24].

At steady-state (T_{SS}), the absence of significant difference within each group was expected, as no surgical or pharmacological stimulus was carried out during this time-point. However, the lack of difference, specifically of PTA index, between groups is surprising as colic horses are known to be in severe haemodynamic status and should have a higher activation of the sympathetic nervous system compared to healthy horses [25]. Yet, we assume that the drugs administered to the colic horses preoperatively could have reduced the sympathetic effects, pain and inflammatory reactions with the consequence of increasing the PTA index in these horses at steady-state.

In comparison with previous results in dogs, no significant variation was registered at T_{Cut}, [22]. This can be explained by the association of xylazine and morphine at premedication which could have resulted in an adequate level of analgesia. Xylazine mediates a sympatholytic action with a reported duration of action of 20 to 30 minutes [26], morphine has a reported plasma half-life of elimination of 1.6 hours [27].

The variations of PTA observed during blood pressure variations appeared to be inversely related to those of arterial pressure, and thus, seem to follow modifications of the sympathovagal balance. During hypotension, the increase in PTA reflects a shift toward a parasympathetic predominance. Similar results have been reported in human medicine with the analgesia nociception index [28] [29]. This shift was blunted by dobutamine initiation (T_{Dobut}) with a decrease in the PTA and a concomitant increase in blood pressure values noticed during this time-point. We assume that dobutamine administration caused a shift toward sympathetic predominance, as described after cardiac β1-adrenegic receptors stimulation [30].

In general, lower PTA values were found in the horses of the Colic group, in comparison with those of the Elective group. This is in accordance with a presumed autonomic dysfunction and predominance of the sympathetic tone in Colic horses, associated with the stress response due to the critical condition. Similar findings have been reported in an experimental model of sepsis [31] and in human patients presented with endotoxaemia; the patients presented an uncoupling of autonomic nervous system and cardiovascular function leading to an impaired sympathetic modulation and regulation of blood pressure [32] due to ineffective baroreflex failing to compensate the anaesthetics-induced hypotension [5]. Our findings confirm thereby a previous report where horses with gastrointestinal disease had an increased sympathetic tone and a reduced HRV [19].

The variations of MAP at the different time-points did not differ horses of the colic group and those of the Elective group. These results are probably related to the blood-pressure directed therapy that was guided to maintain MAP above 60 mmHg. An additional potential explanation could be attributed to the sympathetic activation associated with the early stages of sepsis [33].

The ROC analysis revealed an acceptable performance of the dynamic variation of PTA to predict a MAP variation. This result is, to some extent, in agreement with several human studies that reported a good performance of ANI to predict intraoperative haemodynamic reactivity and hypotension in human patients [7] [20]. However, other studies failed to show such a similar performance for the ANI [34].

We acknowledge several limitations for this study. There was a lack of homogeneity in the inclusion criteria, leading to different surgical stimulations, and different intestinal lesions in the Colic group, which could have biased the homogeneity of PTA measurements. However, one main objective of the study was to assess the influence of health status on the PTA index, which had to be performed in a clinical setting. In addition, several other factors may have influence the HRV analysis, including posture, medication, preoperative stress, noxious stimulation and different ages and breeds [2] [19] [35]. Even though surgical procedures with the same recumbency were chosen to limit the influence of the posture, the anaesthetic protocols were slightly different between group, with intravenous lidocaine that was added in the Colic group and acepromazine that was used for horses of the Elective group. In consequence, and because of the small number of horses in both groups, the results of MAP and PTA values at the measured time points are considered questionable [36] and further studies should be investigated in a more standardized condition to evaluate the performance of the PTA index to anticipate nociception in horses.

Conclusions

In the present study, the values of the PTA index were influenced by the health status of the animal, with emergency conditions associated with lower values, corresponding to higher sympathetic tone. Moreover, intraoperative blood pressure variations were also associated with PTA variations. Clinically, the dynamic variation of PTA showed an acceptable performance to predict a decrease in MAP. These results are in accordance with the influence of the sympathovagal balance on HRV. Further studies are needed in particular to evaluate the effects of different intraoperative drugs on the PTA performance in horses, but also to assess if this index could serve as a prognosis factor with regard to critically ill animals.

Methods

Animals

After obtaining the institutional approval of the ethical committee of VetAgro Sup (n°1514) as well as the informed consent of the owners, this study prospectively enrolled thirty-nine client-owned horses (10 stallions, 17 geldings and 12 mares; mean age 10 ± 7 years; mean body weight 484 ± 96 kg). These horses were admitted to the Equine Hospital of VetAgro Sup (Veterinary Campus of Lyon, France) for elective surgery (castration and cutaneous surgery) or emergency colic surgery. Horses anaesthetized for elective surgery were determined to be healthy, based on preanaesthetic physical examination, and graded 1 and 2 on the American Society of Anaesthesiologists (ASA) physical status classification, whereas horses admitted for colic surgery were classified ASA 3 to 5 E.

Foals were not included in the study and horses requiring an intraoperative α_2-agonists or ketamine continuous infusion or cardiopulmonary resuscitation were excluded.

The animals were assigned to two groups: horses requiring an emergency colic surgery were included in the “Colic group”, whereas those admitted for elective surgery were defined as “Elective group”. After the surgery, horses were hospitalized in the Equine Hospital of VetAgro Sup until full recovery.

Anaesthetic protocol

Horses of the Elective group had free access to water and food was withheld for at least six hours before anaesthesia, whereas horses of Colic group had no food or water restriction before anaesthesia due to their emergency condition. After placement of a catheter into a jugular vein, horses from the Elective group were premedicated with acepromazine (Calmivet, Vetoquinol, Paris, France) 0.03 mg kg^{-1} intramuscularly (IM), followed 30 minutes later by a combination of 0.6 mg kg^{-1} of xylazine hydrochloride (Rompun™, Bayer, Lille, France) and 0.1 mg kg^{-1} of morphine (Morphine chlorhydrate, Aguettant, Lyon, France) intravenously (IV). Horses of the Colic group received 0.4 mg kg^{-1} of xylazine hydrochloride combined to 0.1 mg kg^{-1} of morphine IV as a premedication. Once sedation was achieved, anaesthesia was induced with 2.2 mg kg^{-1} of ketamine hydrochloride (Imalgene 1000, Merial, Lyon, France) and 0.05 mg kg^{-1} of diazepam (Diazepam TVM, TVM, Clermont-Ferrand, France) intravenously (IV).

After orotracheal intubation, horses were positioned in dorsal recumbency on the surgical table and anaesthesia was maintained in both groups with sevoflurane (SevoFlo, Zoetis, Malakoff, France) delivered in 60% O_2 using a large animal rebreathing circuit (Tafonius; Vetronic Services Ltd, Abbotskerswell, UK). The horses were mechanically ventilated (Tafonius; Vetronic Services Ltd, Abbotskerswell, UK) with an initial respiratory rate of 8 breaths $minute^{-1}$, a tidal volume ($\dot{V}_T$) of 10 mL kg^{-1}, adjusted to maintain a $P_E'CO_2$ of 4.6 to 6.0 kPa (35-45 mmHg). Ringer lactate solution was administered IV during anaesthesia at a rate of 10 mL kg^{-1} h^{-1}. Horses of the Colic group received a lidocaine (Lurocaine, Vetoquinol, Paris, France) infusion of 0.05 mg kg^{-1} min^{-1} preceded by a loading dose of 1.5 mg kg^{-1} over 20 minutes. In case of a prolonged surgery, a supplementary bolus of morphine 0.1 mg kg^{-1} IM was given once intra-operatively, 2 hours after the initial dose. At the end of the anaesthesia, xylazine (0.1-0.2 mg kg^{-1}) IV was administered in every horse of the "Elective" group, and in horses of the Colic group according to the presence of early signs of excitation and / or consciousness. Horses were then transferred to a padded recovery box. After removal of the endotracheal tube, oxygen (15 L min^{-1}) was administered flow-by through a nasal tube during recovery. Horses of both groups received flunixin meglumine (Finadyne, MSD Santé animale, Beaucouzé, France) (1.1 mg kg^{-1} IV) and antimicrobial agents adapted to the surgical condition.

Monitoring

Heart rate (HR), invasive blood pressure, respiratory rate, end-tidal carbon dioxide tension ($P_E'CO_2$), end-tidal oxygen tension ($P_E'O_2$), end-tidal sevoflurane concentration ($P_E'Sevo$), inspired oxygen fraction (FiO_2) and oxygen saturation of haemoglobin (SpO_2) were measured continuously using a multi-parameter monitor (Tafonius; Vetronic Services Ltd, Abbotskerswell, UK) and recorded manually every 5 minutes. Arterial blood samples were taken from the facial artery at 1-hour intervals to determine blood gas values (VetStat analyzer, Idexx, Hoofddorp, The Netherlands). The urinary bladder was catheterized for passive urine collection until the end of anaesthesia. The PTA index was monitored continuously during anaesthesia using a dedicated monitor (Physiodoloris®, MDoloris Medical System, Lille, France).

Signs of anaesthetic depth were monitored every 5 minute, and presence or absence of spontaneous palpebral reflex and nystagmus was recorded, as well as skeletal muscle relaxation. Ketamine 0.5 mg kg^{-1} IV was injected in case of signs of insufficient depth anaesthesia.

In case of hypotension, defined as MAP < 60 mmHg, anaesthesia depth was lightened if possible and a dobutamine continuous infusion (Dobutamine Aguettant, Laboratoires Aguettant, Lyon, France) was administered at a dose-rate of 2 to 10 μg kg^{-1} min^{-1} IV, with step-incremental doses until a MAP above 60 mmHg was reached.

PTA measurement

The PTA monitor uses the ECG signal to evaluate HRV. It records a base-apex surface ECG (lead II), using a 3-electrode/wire system with flattened crocodile clips attached to the skin. In our setting, the clips were moistened with electrode gel to maintain electrical contact; the red and yellow electrodes were positioned at the level of the right and left jugular groove respectively, the black electrode was placed over the right olecranon.

Briefly, the signal acquisition is made via a 250 Hz ECG to evaluate heart rate variability. To calculate the PTA index, the ECG signal needs to be analyzed in a frequency domain. The first step is the R waves detection and calculation of RR intervals. This leads to RR series that are then filtered with a real-time artefact-removal filter. The resulting RR series are resampled at 8Hz and then filtered with a wavelet transform based band pass filter from 0.15 to 0.5Hz. This is based on the principle that fluctuations in heart rate variability in high frequencies (0.15-0.5Hz) are exclusively mediated by the parasympathetic nervous system whereas changes in low frequencies (0.004-0.15Hz) are mediated by both parasympathetic and sympathetic activities [7] and the algorithm aims at determining the parasympathetic activity exclusively. The signal issued is called the “energy”. The energy curve is displayed on the monitor’s screen and divided into four 16-seconds windows. The area under the curve (AUC) is calculated for each window. The smallest of the four AUC is defined as the AUCmin. The PTA index is then calculated with the formula:

PTA= $[100 * (\alpha * AUCmin + \beta)/12.8] * 100/163$; 100/163 is a coefficient determined for the horse in order to obtain PTA values between 0 and 100.

The PTA monitor continuously displays an instantaneous index (PTAi) calculated over the last 56 seconds and an average measurement (PTAm) over the previous 176 s. PTA values are scored between 0 and 100: a value of 100 corresponds to a maximum parasympathetic tone; conversely, a value of 0 corresponds to a decreased parasympathetic tone with maximum sympathetic tone.

Study design

For each anaesthetized animal, different predefined time-points of 5 minute-duration were considered (figure 1): T_{SS} (steady-state time, immediately before cutaneous incision), T_{Cut} (after surgical noxious stimulation defined as cutan3eous incision), T_{Hypo} (retrospectively assessed 5 minutes before each hypotension), T_{Dobut} (after each dobutamine initiation) and $T_{Post\text{-}dobut}$ (after each dobutamine discontinuation). These different time-points were designed to allow a comparison between groups despite different clinical conditions and surgical procedures.

In order to assess the performance of the PTA index to predict a decrease or an increase in MAP, PTA and MAP were recorded initially, 1 minute and 5 minutes thereafter for each predefined time-point. Based on a recent report showing a better performance of the dynamic variations of ANI over static values to detect haemodynamic reactions in human patients [20], dynamic variations of PTA (ΔPTA) and MAP (ΔMAP) were calculated at each time-point as follow:

Over 1 minute period: $\Delta X_{1min} = [(X_{1min} - X_0) / (X_{1min} + X_0)/2]*100$.

Over 5 minutes period: $\Delta X_{5min} = [(X_{5min} – X_0) / (X_{5min} + X_0)/2]*100$.

Where $X_{0,}$ X_{1min} and X_{5min} are respectively the values of PTA and MAP at the predefined time, 1 min and 5 min thereafter.

This calculation was used *posteriori* to evaluate the performance of ΔPTA1min to anticipate a variation of MAP over the following 5 minutes.

Abbreviations

PTA: Parasympathetic Tone Activity

MAP: Mean Arterial Pressure

T_{SS}: steady-state, before surgical stimulus

T_{Cut}: after surgical stimulation

T_{Dobut}: retrospectively assessed 5 minutes before hypotension

T_{Hypo}: after dobutamine initiation

$T_{Post\text{-}Dobut}$: after dobutamine discontinuation

ANS: Autonomic Nervous System

HRV: Heart Rate Variability

ANI: Analgesia Nociception Index

AUC: area under curve

ROC curve: receiver operating characteristic curve

VLF: Very Low Frequency

LF: Low Frequency

HF: High Frequency

ΔPTA: Dynamic variation of the Parasympathetic Tone Activity Index

ΔMAP: Dynamic variation of the Mean Arterial Pressure

ΔHR: Dynamic variation of the Heart Rate

ASA: American Society of Anesthesiologists

IM: Intramuscular

IV: Intravenous

HR: Heart Rate

Vt: Tidal Volume

P_E'Sevo: End-tidal sevoflurane concentration

$P_E'CO_2$: End-tidal carbon dioxide tension

FiO_2: inspired fraction of oxygen

Declarations

Ethics approval and consent to participate

This prospective clinical study was approved by the ethical committee of VetAgro Sup (n°1514).

A written informed consent was obtained from the owners before using the animals in the study.

Consent for publication

“Not applicable”.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

Christelle Mansour has received a travel grants from MDoloris Medical Systems for short communications related to PTA.

Emmanuel Boselli has received honoraria and travel grants from MDoloris Medical Systems for lectures related to ANI.

The other authors have no conflict of interest to disclose.

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Authors' contributions

All authors of the manuscript have read and agreed to its content.

CM: collected, analyzed and interpreted the horses' data and wrote the manuscript.

RM: helped in data collection.

BS: helped in data collection.

RC: assisted in data interpretation.

BA: contributed in data analysis.

JMBG: supported in writing the manuscript.

EB: advised in data interpretation.

SJ: major contributor in writing the article and data collection, analysis, and interpretation.

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References

[1] M. Gruenewald and C. Ilies, “Monitoring the nociception-anti-nociception balance,” *Best Pract. Res. Clin. Anaesthesiol.*, vol. 27, no. 2, pp. 235–247, Jun. 2013.

[2] D. Stucke, M. Große Ruse, and D. Lebelt, “Measuring heart rate variability in horses to investigate the autonomic nervous system activity – Pros and cons of different methods,” *Appl. Anim. Behav. Sci.*, vol. 166, pp. 1–10, May 2015.

[3] D. Barnaby *et al.*, “Heart rate variability in emergency department patients with sepsis,” *Acad. Emerg. Med. Off. J. Soc. Acad. Emerg. Med.*, vol. 9, no. 7, pp. 661–670, Jul. 2002.

[4] T. Tzelos, K. J. Blissitt, and R. E. Clutton, “Electrocardiographic indicators of excitability in horses for predicting recovery quality after general anaesthesia,” *Vet. Anaesth. Analg.*, vol. 42, no. 3, pp. 269–279, May 2015.

[5] C.-J. Huang, C.-H. Kuok, T. B. J. Kuo, Y.-W. Hsu, and P.-S. Tsai, “Pre-operative measurement of heart rate variability predicts hypotension during general anesthesia,” *Acta Anaesthesiol. Scand.*, vol. 50, no. 5, pp. 542–548, May 2006.

[6] G. Valenza, L. Citi, J. P. Saul, and R. Barbieri, “Measures of sympathetic and parasympathetic autonomic outflow from heartbeat dynamics,” *J. Appl. Physiol. Bethesda Md 1985*, vol. 125, no. 1, pp. 19–39, 01 2018.

[7] R. Logier *et al.*, “PhysioDoloris: a monitoring device for analgesia / nociception balance evaluation using heart rate variability analysis,” *Conf. Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE Eng. Med. Biol. Soc. Annu. Conf.*, vol. 2010, pp. 1194–1197, 2010.

[8] M. Jeanne, R. Logier, J. De Jonckheere, and B. Tavernier, “Validation of a graphic measurement of heart rate variability to assess analgesia/nociception balance during general anesthesia,” *Conf. Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE Eng. Med. Biol. Soc. Annu. Conf.*, vol. 2009, pp. 1840–1843, 2009.

[9] C. Mansour *et al.*, “Performance of the Parasympathetic Tone Activity (PTA) index to assess the intraoperative nociception using different premedication drugs in anaesthetised dogs,” *Int. J. Vet. Sci. Med.*, vol. 8, no. 1, pp. 49–55, Jan. 2020.

[10] W. Pearce, “The Cardiovascular Autonomic Nervous System and Anaesthesia,” *South. Afr. J. Anaesth. Analg.*, vol. 8, no. 3, pp. 8–24, Jul. 2002.

[11] T. W. Latson and D. O’Flaherty, “Effects of surgical stimulation on autonomic reflex function: assessment by changes in heart rate variability,” *Br. J. Anaesth.*, vol. 70, no. 3, pp. 301–305, Mar. 1993.

[12] T. W. Latson, T. H. Ashmore, D. J. Reinhart, K. W. Klein, and A. H. Giesecke, “Autonomic reflex dysfunction in patients presenting for elective surgery is associated with hypotension after anesthesia induction,” *Anesthesiology*, vol. 80, no. 2, pp. 326–337, Feb. 1994.

[13] A. T. Mazzeo, E. La Monaca, R. Di Leo, G. Vita, and L. B. Santamaria, “Heart rate variability: a diagnostic and prognostic tool in anesthesia and intensive care,” *Acta Anaesthesiol. Scand.*, vol. 55, no. 7, pp. 797–811, Aug. 2011.

[14] C. Oel, H. Gerhards, and H. Gehlen, “Effect of retrobulbar nerve block on heart rate variability during enucleation in horses under general anesthesia,” *Vet. Ophthalmol.*, vol. 17, no. 3, pp. 170–174, May 2014.

[15] Y. Ogawa *et al.*, “Different effects on circulatory control during volatile induction and maintenance of anesthesia and total intravenous anesthesia: autonomic nervous activity and arterial cardiac baroreflex function evaluated by blood pressure and heart rate variability analysis,” *J. Clin. Anesth.*, vol. 18, no. 2, pp. 87–95, Mar. 2006.

[16] R. Hanss *et al.*, “Does heart rate variability predict hypotension and bradycardia after induction of general anaesthesia in high risk cardiovascular patients?,” *Anaesthesia*, vol. 63, no. 2, pp. 129–135, Feb. 2008.

[17] E. Boselli *et al.*, “Prospective observational study of the non-invasive assessment of immediate postoperative pain using the analgesia/nociception index (ANI),” *Br. J. Anaesth.*, vol. 111, no. 3, pp. 453–459, Sep. 2013.

[18] M. Kuwahara *et al.*, “Assessment of autonomic nervous function by power spectral analysis of heart rate variability in the horse,” *J. Auton. Nerv. Syst.*, vol. 60, no. 1, pp. 43–48, Aug. 1996.

[19] E. L. McConachie, S. Giguère, G. Rapoport, and M. H. Barton, “Heart rate variability in horses with acute gastrointestinal disease requiring exploratory laparotomy,” *J. Vet. Emerg. Crit. Care San Antonio Tex 2001*, vol. 26, no. 2, pp. 269–280, Apr. 2016.

[20] E. Boselli, R. Logier, L. Bouvet, and B. Allaouchiche, “Prediction of hemodynamic reactivity using dynamic variations of Analgesia/Nociception Index (ΔANI),” *J. Clin. Monit. Comput.*, vol. 30, no. 6, pp. 977–984, Dec. 2016.

[21] K. Sakata, N. Yoshimura, K. Kito, K. Tanabe, and H. Iida, “Abstract PR216: Prediction of Hypotension During Spinal Anesthesia for Cesarean Section By Heart Rate Variability.,” *Anesth. Analg.*, vol. 123, p. 279, Sep. 2016.

[22] C. Mansour *et al.*, “Evaluation of the Parasympathetic Tone Activity (PTA) index to assess the analgesia/nociception balance in anaesthetised dogs,” *Res. Vet. Sci.*, vol. 115, pp. 271–277, Dec. 2017.

[23] D. Aguado, R. Bustamante, V. García-Sanz, P. González-Blanco, and I. A. Gómez de Segura, “Efficacy of the Parasympathetic Tone Activity monitor to assess nociception in healthy dogs anaesthetized with propofol and sevoflurane,” *Vet. Anaesth. Analg.*, vol. 47, no. 1, pp. 103–110, Jan. 2020.

[24] M. Bootsma, C. A. Swenne, F. P. van Rugge, and E. E. van der Wall, “The sympathovagal balance during control and dobutamine stress MRI,” in *Proceedings of Computers in Cardiology Conference*, Sep.

1993, pp. 317–320.

[25] H. Gehlen, J. Loschelder, R. Merle, and M. Walther, “Evaluation of Stress Response under a Standard Euthanasia Protocol in Horses Using Analysis of Heart Rate Variability,” *Anim. Open Access J. MDPI*, vol. 10, no. 3, Mar. 2020.

[26] C. L. Kerr, W. N. McDonell, and S. S. Young, “Cardiopulmonary effects of romifidine/ketamine or xylazine/ketamine when used for short duration anesthesia in the horse,” *Can. J. Vet. Res. Rev. Can. Rech. Veterinaire*, vol. 68, no. 4, pp. 274–282, Oct. 2004.

[27] J. D. Combie, T. E. Nugent, and T. Tobin, “Pharmacokinetics and protein binding of morphine in horses,” *Am. J. Vet. Res.*, vol. 44, no. 5, pp. 870–874, May 1983.

[28] M. Jeanne, C. Clément, J. De Jonckheere, R. Logier, and B. Tavernier, “Variations of the analgesia nociception index during general anaesthesia for laparoscopic abdominal surgery,” *J. Clin. Monit. Comput.*, vol. 26, no. 4, pp. 289–294, Aug. 2012.

[29] Y. Fujiwara *et al.*, “A greater decrease in blood pressure after spinal anaesthesia in patients with low entropy of the RR interval,” *Acta Anaesthesiol. Scand.*, Aug. 2007.

[30] J. A. Armour, “Intrinsic cardiac neurons involved in cardiac regulation possess alpha 1-, alpha 2-, beta 1- and beta 2-adrenoceptors,” *Can. J. Cardiol.*, vol. 13, no. 3, pp. 277–284, Mar. 1997.

[31] M. Tanaka and T. Nishikawa, “Arterial baroreflex function in humans anaesthetized with sevoflurane,” *Br. J. Anaesth.*, vol. 82, no. 3, pp. 350–354, Mar. 1999.

[32] H. Schmidt *et al.*, “Autonomic dysfunction predicts mortality in patients with multiple organ dysfunction syndrome of different age groups,” *Crit. Care Med.*, vol. 33, no. 9, pp. 1994–2002, Sep. 2005.

[33] D. C. Silverstein, A. Pruett-Saratan II, and K. J. Drobatz, “Measurements of microvascular perfusion in healthy anesthetized dogs using orthogonal polarization spectral imaging: Microvascular perfusion measurements in normal dogs,” *J. Vet. Emerg. Crit. Care*, vol. 19, no. 6, pp. 579–587, Dec. 2009.

[34] T. Ledowski, L. Averhoff, W. S. Tiong, and C. Lee, “Analgesia Nociception Index (ANI) to predict intraoperative haemodynamic changes: results of a pilot investigation,” *Acta Anaesthesiol. Scand.*, vol. 58, no. 1, pp. 74–79, Jan. 2014.

[35] D. Michaloudis *et al.*, “The influence of premedication on heart rate variability,” *Anaesthesia*, vol. 53, no. 5, pp. 446–453, May 1998.

[36] D. Oberfeld and T. Franke, “Evaluating the robustness of repeated measures analyses: The case of small sample sizes and nonnormal data,” *Behav. Res. Methods*, vol. 45, no. 3, pp. 792–812, Sep. 2013.

Table

Table 1. Demographic data

	n (horses)	Gender	Age (years)	Weight (kg)	Total length of surgery (min)
Elective	24	8 G, 3 S, 4 M	7 ± 8	448 ± 107	121 ± 42
Colic	15	3 G, 15 S, 6 M	10 ± 6	505 ± 105	176 ± 74*

G, gelding; S, stallion; M, mare.

* indicates a significant difference (p<0.05) between Elective and Colic group.

Figures

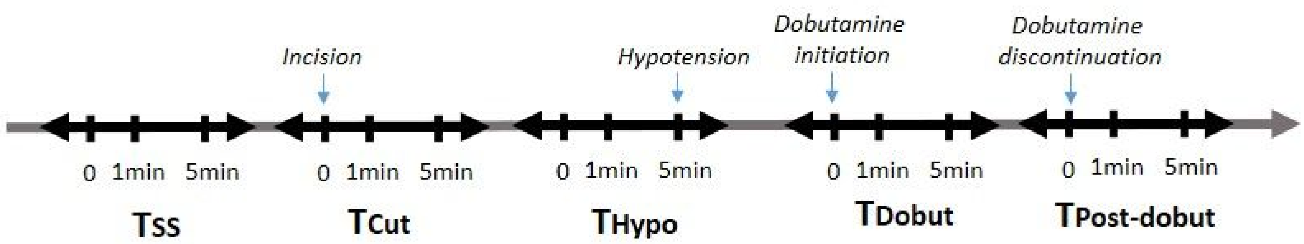

Figure 1

Schematic presentation of the predefined time-points. TSS, steady-state period; TCut, period after noxious stimulation; THypo, retrospective period before each hypotension; TDobut, period after each dobutamine initiation; TPost-dobut, period after each dobutamine discontinuation.

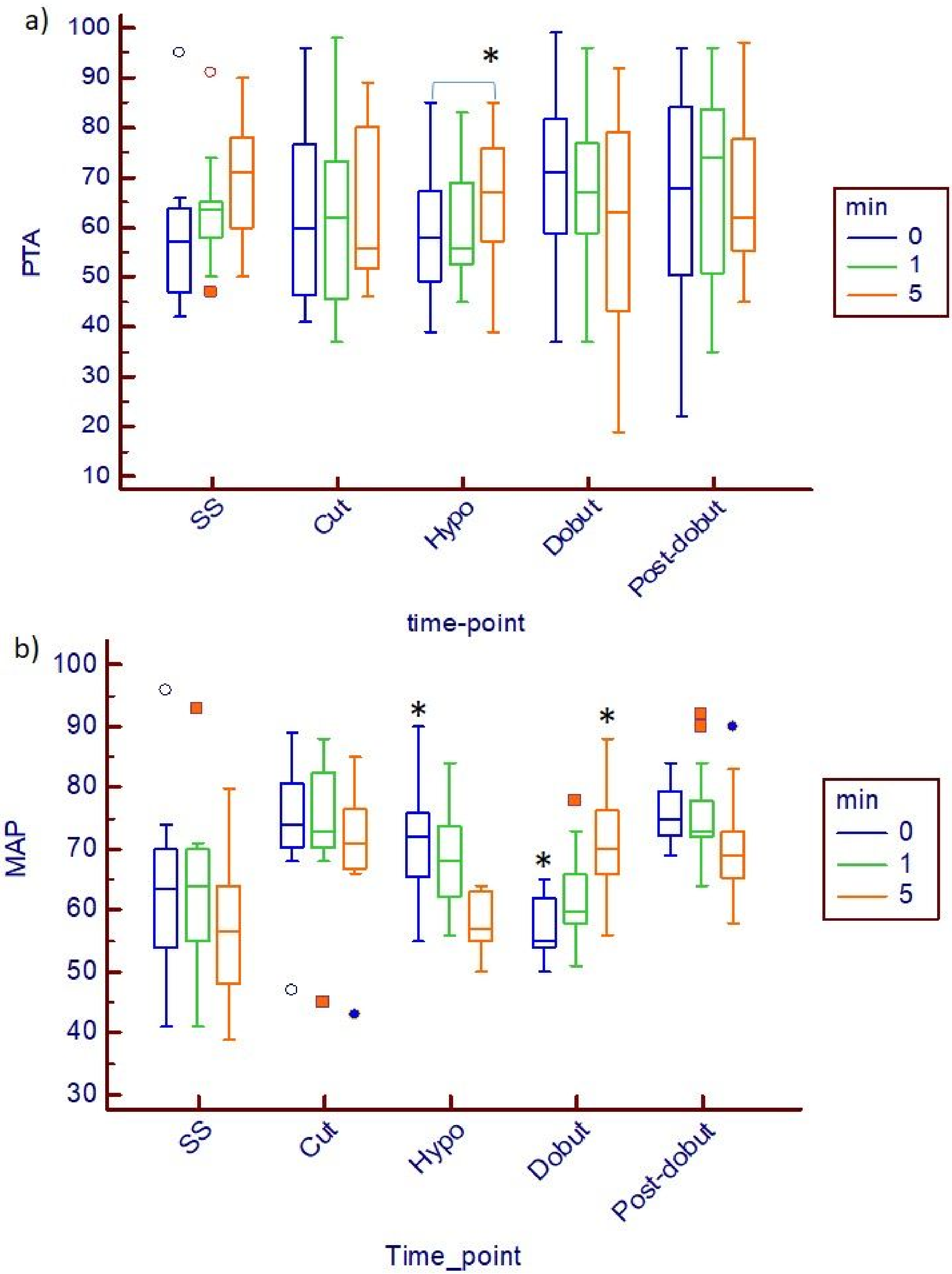

Figure 2

(a) PTA (Parasympathetic Tone Activity) and (b) MAP (Mean arterial pressure) evolution in Elective group at the predefined time-points. * indicates a significant difference ($p < 0.05$) of PTA and MAP between the predefined-time, 1 and 5 minutes thereafter. Values are expressed as median [IQR]. SS, steady-state; Cut, after noxious stimulation; Hypo, retrospectively before each hypotension; Dobut, after each dobutamine initiation; Post-dobut, after each dobutamine discontinuation.

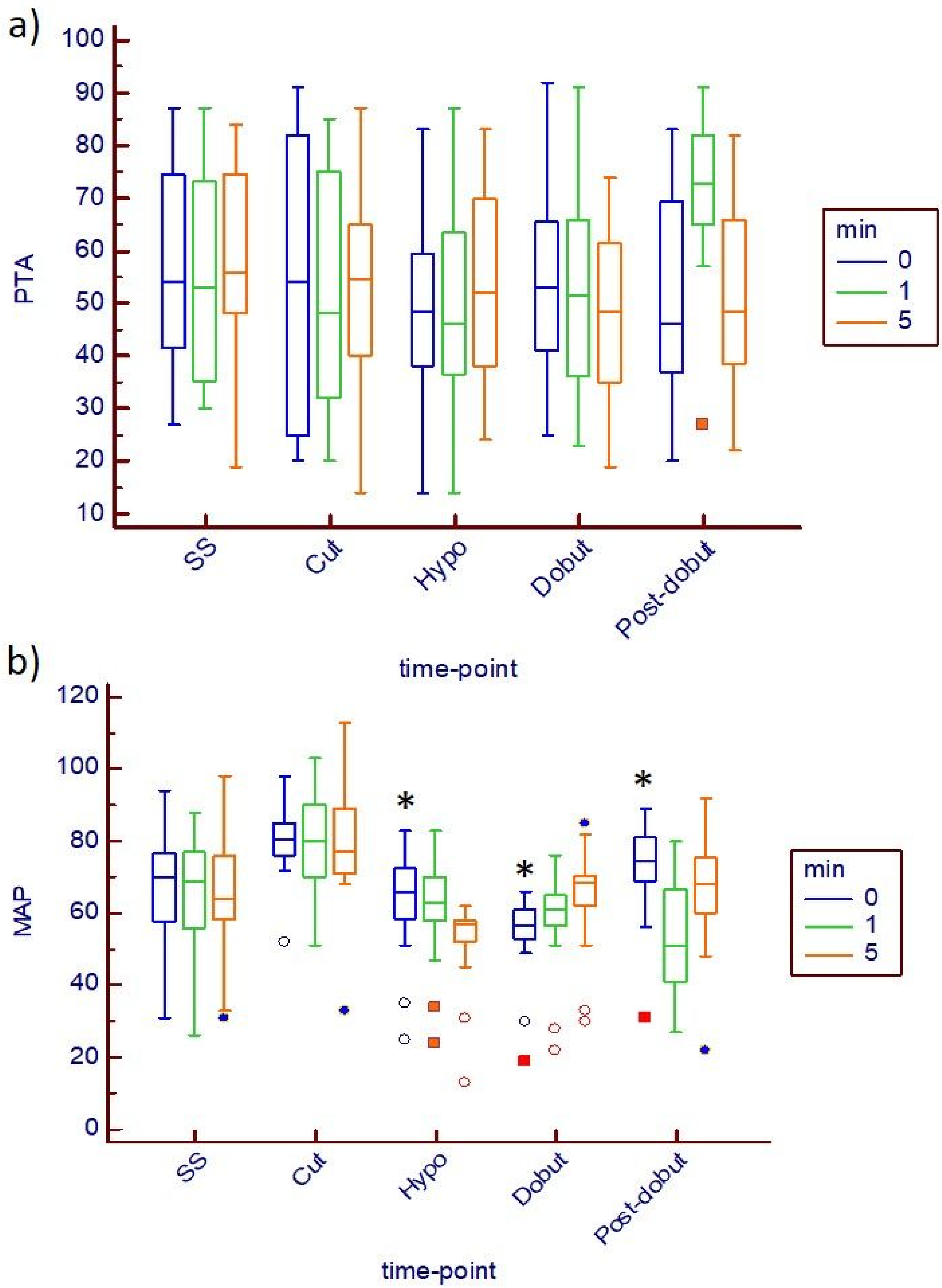

Figure 3

(a) PTA (Parasympathetic Tone Activity) and (b) MAP (Mean arterial pressure) evolution in Colic group at the predefined time-points. * indicates a significant difference ($p < 0.05$) of PTA and MAP between the predefined-time, 1 and 5 minutes thereafter. Values are expressed as median [IQR]. SS, steady-state; Cut, after noxious stimulation; Hypo, retrospectively before each hypotension; Dobut, after each dobutamine initiation; Post-dobut, after each dobutamine discontinuation.

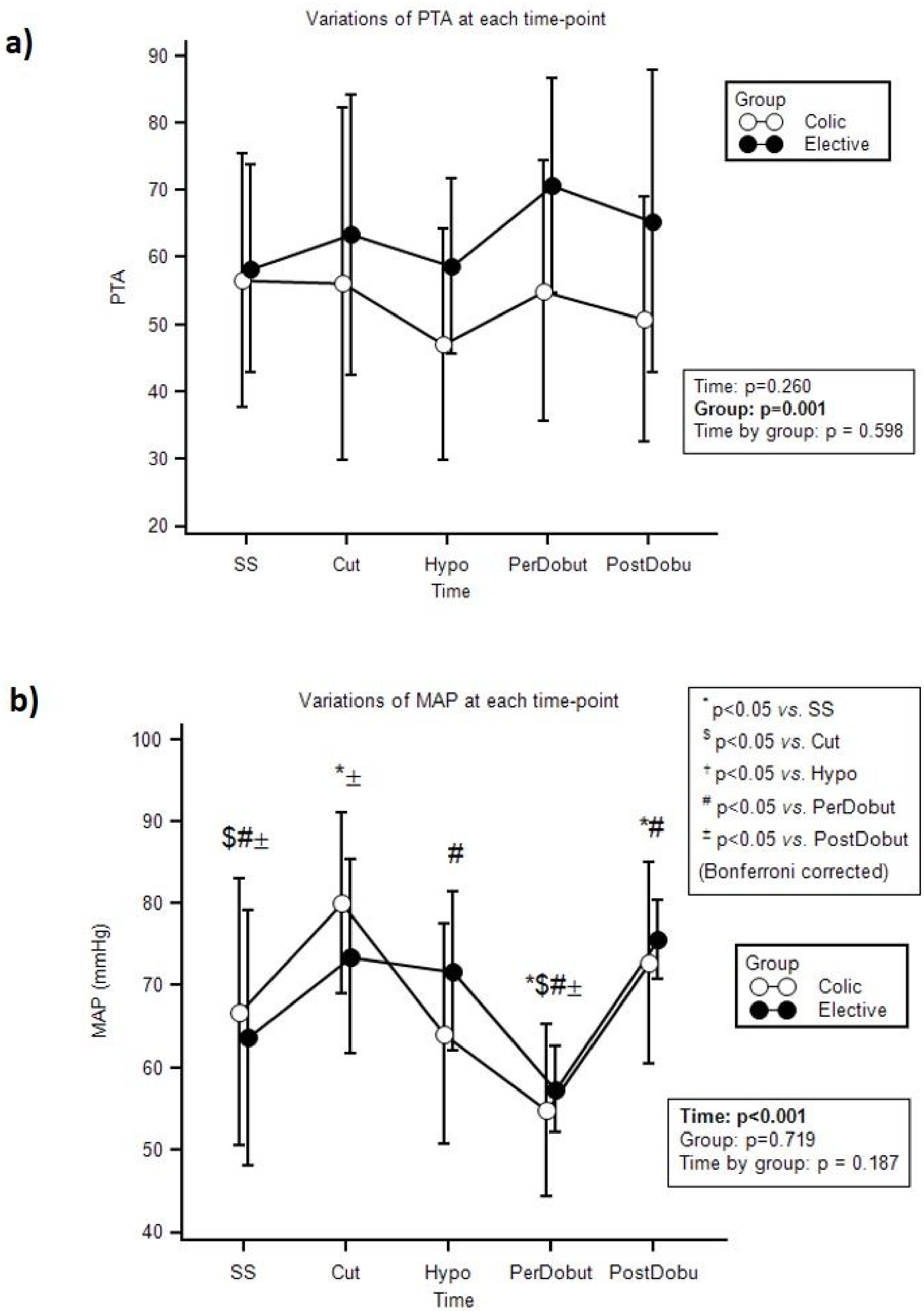

Figure 4

Time by group effect at the baseline (T0) of the predefined time-points of Elective group (closed circles ●) versus Colic group (open circles ●) for (a) Parasympathetic Tone Activity index values (PTA) and (b) mean arterial pressure (MAP). Values are expressed as median [IQR]. SS, steady-state; Cut, after noxious stimulation; Hypo, retrospectively before each hypotension; Dobut, after each dobutamine initiation; Post-dobut, after each dobutamine discontinuation.

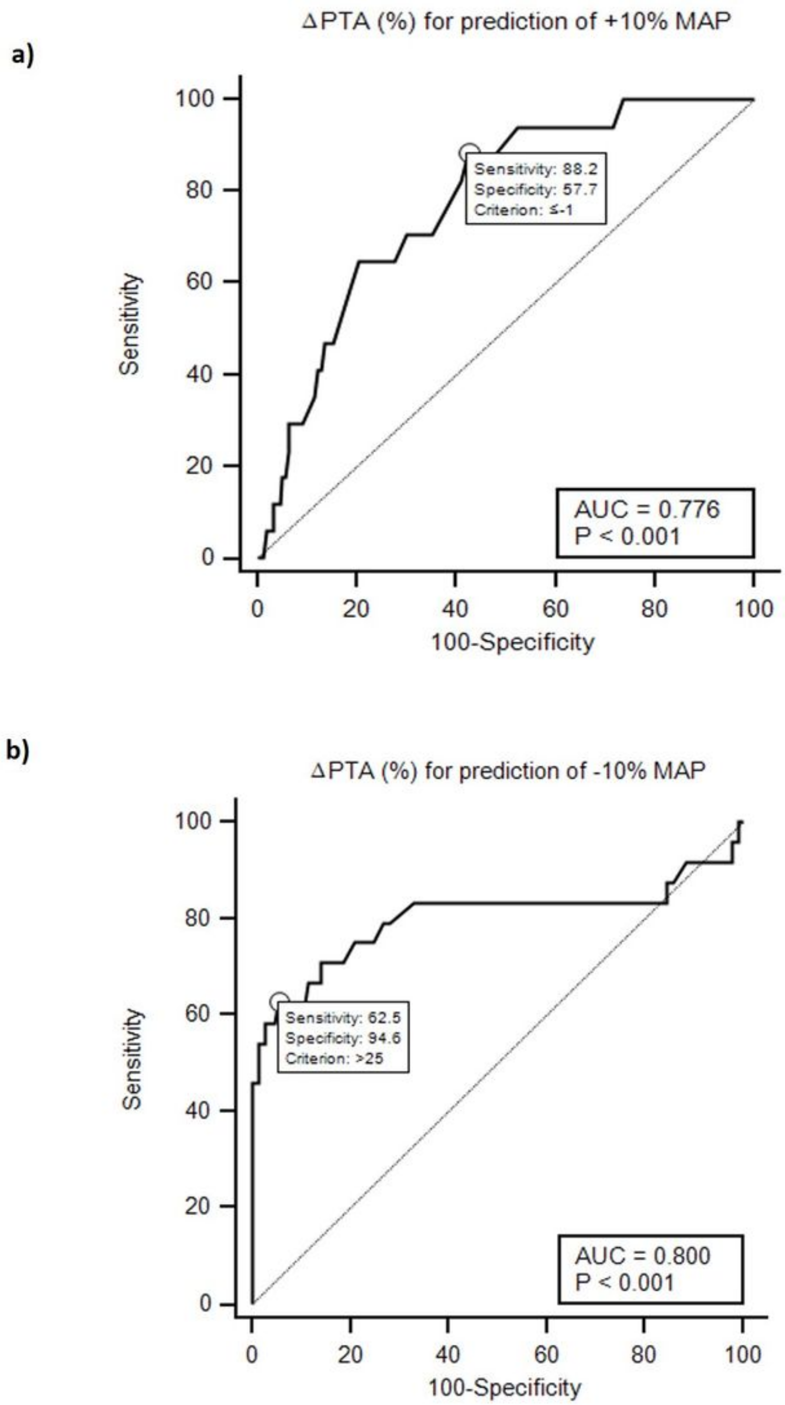

Figure 5

Performance of PTA to predict 10% increase and decrease in MAP in both groups. (a) 10% increase in MAP. AUC ROC = 0.77 [0.70 to 0.83] ($p < 0.0001$), sensitivity = 88.2 %, specificity = 57.7 % and a threshold value of -1% for ΔPTA. (b) 10% decrease in MAP. AUC ROC = 0.80 [0.73 to 0.85] ($p < 0.0001$), sensitivity = 62.5 %, specificity = 94.6 % and a threshold value of 25% for ΔPTA

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