Performance of the Parasympathetic Tone Activity (PTA) index to assess the intraoperative nociception using different premedication drugs in anaesthetised dogs

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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

The parasympathetic tone activity (PTA) index is based on heart rate variability and has been developed recently in animals to assess their relative parasympathetic tone. This study aimed to evaluate PTA index in anaesthetized horses with different health conditions and the performance of PTA variations (ΔPTA) to predict changes in mean arterial pressure (MAP).

Thirty-nine client-horses were anaesthetized for elective or colic surgery and divided into "Elective" and "Colic" groups. During anaesthesia, dobutamine was administered as treatment of hypotension (MAP < 60 mmHg).

In both groups, no significant variation of PTA and MAP were detected immediately before and after cutaneous incision. The PTA index increased 5 min before each hypotension, whereas it decreased 1 min after dobutamine administration. Horses of the Colic group had lower PTA values than those of the Elective group, whereas MAP did not differ between groups. 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%.

The PTA index in anaesthetized horses appears to be influenced by the health condition. The shift toward lower PTA values in colic horses may reflect a sympathetic predominance. An increase in PTA of >25% in 1 min showed an acceptable performance to predict 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.

Keywords: Anaesthesia, Horse, Autonomic Nervous System, Parasympathetic Tone Activity, Blood pressure.

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Conflict of interest

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

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Introduction

The assessment of intra operative nociception remains a challenge for the veterinary anaesthetist. For the anaesthetized patient, an inappropriate analgesia could lead to nociception and haemodynamic instability (Gruenewald and Ilies 2013). Recently, similarly to human medicine, the use of devices based on heart rate variability (HRV) has been proposed for veterinary purpose, including equine species (Stucke et al. 2015).

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 (Barnaby et al. 2002). Stress from various origin (including nociception, anxiety, aggression, etc…) can shift the autonomic balance towards a sympathetic nervous prevalence with a decrease in HRV (Tzelos et al. 2015). HRV has been used as a diagnostic and prognostic tool in a variety of conditions including anaesthesia (Stucke et al. 2015), aiming to optimize intraoperative haemodynamics (~~Huang et al. 2006~~). It is commonly used to characterize the relative activity of the sympathetic and parasympathetic nervous systems in animals and humans (Manzo et al. 2009) (~~Valenza et al~~. ~~2018)~~.

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 (Logier et al. 2010). The ANI index was validated to detect nociception during anaesthesia in human patients (Jeanne et al. 2009). The PTA index was evaluated to assess the analgesia/nociception balance and predict a haemodynamic reactivity in anaesthetized dogs (Mansour et al. 2017; Mansour et al.2020; Aguado et al. 2020; Hernández-Avalos et al. 2021).

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 (Latson and O’Flaherty 1993; Pearce 2002). 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 (Oel et al. 2014) (Gehlen et al. 2020) ~~(Latson et al. 1994~~).

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 PTA variations (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.

Materials and Methods

Animals

After obtaining the institutional approval of the ethical committee of VetAgro Sup (n°1514) as well as an 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.

In order to obtain a base-apex lead ECG, the electrodes were positioned as followed: the positive electrode (left arm) was placed over the left chest, at the level of the olecranon, the negative electrode (right arm) over the right jugular furrow. Invasive blood pressure measurement was performed using a transducer (TruWave; Edwards Lifesciences, Guyancourt, France) connected via a fluid-filled line to an arterial catheter. During surgical preparation, the left or right facial artery was cannulated aseptically using a 20 gauge, 36 mm catheter (Intraflon 2; Vygon, Ecouen, France). With the animal in dorsal recumbency, the transducer was positioned at the level of right atrium, considered at the level of the point of the shoulder. It was connected to the arterial catheter using noncompliant tubing filled with heparinized saline. Once the arterial cannula was in place and connected, before the start of measurements, the transducer was zeroed, and a fast-flush test was subjectively assessed to ensure that the degree of damping of the system was acceptable. This test was performed by flushing crystalloid fluid that fills the tubing/transducer system with 300 mmHg pressure via the flush system and ensuring the presence of two oscillations following release of the flush valve.

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.

The principle of the PTA index measurement and calculation is similar to ANI and has previously been described elsewhere (Jeanne et al. 2009; Logier et al. 2010; Mansour et al. 2017; Aguado et al. 2020). The PTA index is measured using a dedicated monitor (Physiodoloris, MDoloris medical system, Lille, France), based on ECG measurement, with a lead II ECG using a 3 lead-system. The signal acquisition is made via a 250 Hz ECG to evaluate heart rate variability. The algorithm for the PTA index calculation is succinctly described thereafter. The first step is the R waves detection and calculation of RR intervals. The RR series 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 (Logier et al. 2010) 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 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 cutaneous 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 variations of ANI over static values to detect haemodynamic reactions in human patients (Boselli et al. 2016), 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 change of MAP over the following 5 minutes.

Statistical analysis

Statistical analysis was performed using MedCalc[@] 12.1.4.0 (MedCalc Software®, Ostend, Belgium). 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 changes 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.

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 (Mazzeo et al. 2011) ~~(Oel et al. 2014)~~. To evaluate the ANS, HRV uses a frequency domain-based analysis (Akselrod et al. 1985) ~~(Stucke et al. 2015)~~). During anaesthesia, HRV has been used in humans for the prediction of blood pressure change (Huang et al. 2006; Hanss et al. 2008) (~~Ogawa et al. 2006~~) and the evaluation of analgesia nociception balance (Jeanne et al. 2009) ~~(Boselli et al. 2013)~~. 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 (Stucke et al. 2015). The normal resting horse is considered as having a prevailing parasympathetic tone, which was confirmed by HRV analysis (Kuwahara et al. 1996). A recent study in horses has reported that HRV can detect sympathovagal stimulation during ocular surgery (Oel et al. 2014). It has also been used as a prognostic information for postoperative horses with severe gastrointestinal disease (McConachie et al. 2016).

In addition to its use in the perioperative settings, HRV was utilized as an indicator of emotional state in race horses. One study aimed to analyze whether the balance of the autonomic system could impact the horses' racing performance; it revealed better racing results in horses with enhanced LF/HF (indicating an appropriate autonomic system balance) whereas the worst racing results were determined in horses with low LF (associated with a low sympathetic response). Therefore, it was concluded that emotional excitability influences horses' performance in sports and races (Janczarek et al. 2017). Another study using the heart rate and HRV as indicators of the emotional state of young racehorses undergoing relaxing massage during the full race season demonstrated changes in these parameters throughout the season (Kowalik et al. 2017). Moreover, one study focused on monitoring recovery and the possible overtraining status in horses by measuring HRV. It was found that horses were more relaxed during moderate exercise than standing still or anaerobic exercise (Kinnunen et al. 2006). Overall, in these studies, HRV appeared to effectively monitor the sympathovagal balance in horses, but it was assessed retrospectively.

The PTA index is similar to the ANI, validated in human medicine to predict intraoperative haemodynamic reactions (Boselli et al. 2016) and hypotension caused by spinal anaesthesia (Sakata et al. 2016). Recently, the 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 (Mansour et al. 2017; Aguado et al. 2020; Mansour et al. 2020), 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 (Bootsma et al. 1993).

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 (McConachie et al. 2016) (~~Gehlen et al. 2020~~). 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}, (Mansour et al. 2017). 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 (Kerr et al. 2004), morphine has a reported plasma half-life of elimination of 1.6 hours (Combie et al. 1983).

The variations of PTA observed during blood pressure changes 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 (Jeanne et al. 2012). 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 (Armour 1997).

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 (Carrara et al. 2020) ~~(Tanaka and Nishikawa 1999)~~ 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 (Schmidt et al. 2005) due to ineffective baroreflex failing to compensate the anaesthetics-induced hypotension (Huang et al. 2006). Our findings confirm thereby a previous report where horses with gastrointestinal disease had an increased sympathetic tone and a reduced HRV (McConachie et al. 2016).

The changes of MAP at the different time-points did not differ between 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 (Annane et al. 1999) (~~Silverstein et al. 2009~~).

The ROC analysis revealed an acceptable performance of the variation of PTA to predict a MAP change. 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 (Boselli et al. 2015; Boselli et al. 2016; Jendoubi et al. 2021). However, other studies failed to show such a similar performance for the ANI (Ledowski et al. 2014).

We acknowledge several limitations for this study. There was a lack of homogeneity in the inclusion criteria with different surgical stimulations and intestinal lesions in the Colic group, which could have biased the homogeneity of PTA measurements. In addition, 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. Furthermore, we didn't evaluate if dobutamine has a dose-dependent effect on PTA shift. Therefore, the variation in the results could be partly related to the use of various drugs. However, this study aimed to assess the influence of health status on the PTA index and had to be performed in a clinical setting so it was difficult to standardize administered drugs. Other factors may have also influenced the HRV analysis, including preoperative stress, the different ages and breeds (Michaloudis et al. 1998; Stucke et al. 2015; McConachie et al. 2016). Another limitation is that we were unable to provide a reference technique in order to analyze HRV and validate our results. The use of a reference method would have allowed to better evaluate both components of the ANS independently, and evaluate in particular the sympathetic response and compare it with the PTA values, which focuses on the parasympathetic component of the ANS to extrapolate the sympathetic response. 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 (Oberfeld and Franke 2013) and further studies should be investigated in a more standardized condition to evaluate the performance of the PTA index to anticipate nociception in horses.

Conclusion

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 changes were also associated with PTA variations. Clinically, the 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.

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Tables

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.

Figure legends

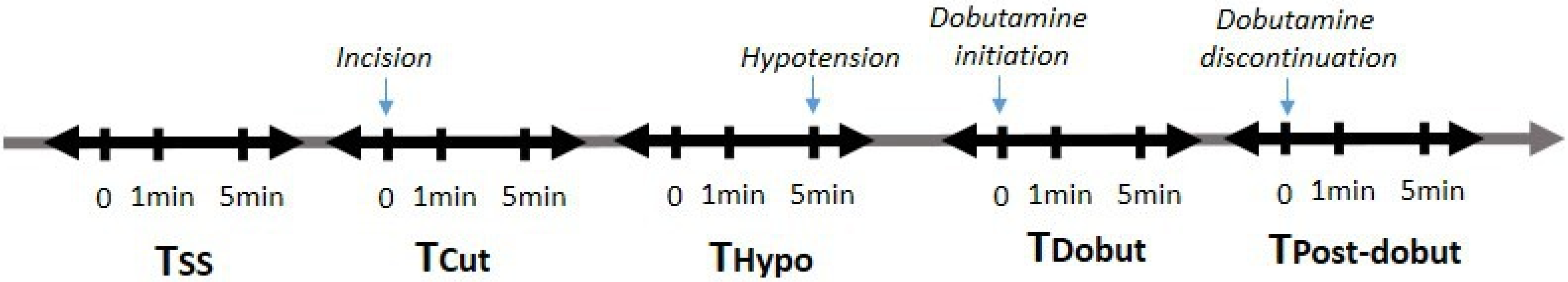
Figure 1. Schematic presentation of the predefined time-points. T_{SS}, steady-state period; T_{Cut}, period after noxious stimulation; T_{Hypo}, retrospective period before each hypotension; T_{Dobut}, period after each dobutamine initiation; $T_{Post\text{-}dobut}$, period after each dobutamine discontinuation.

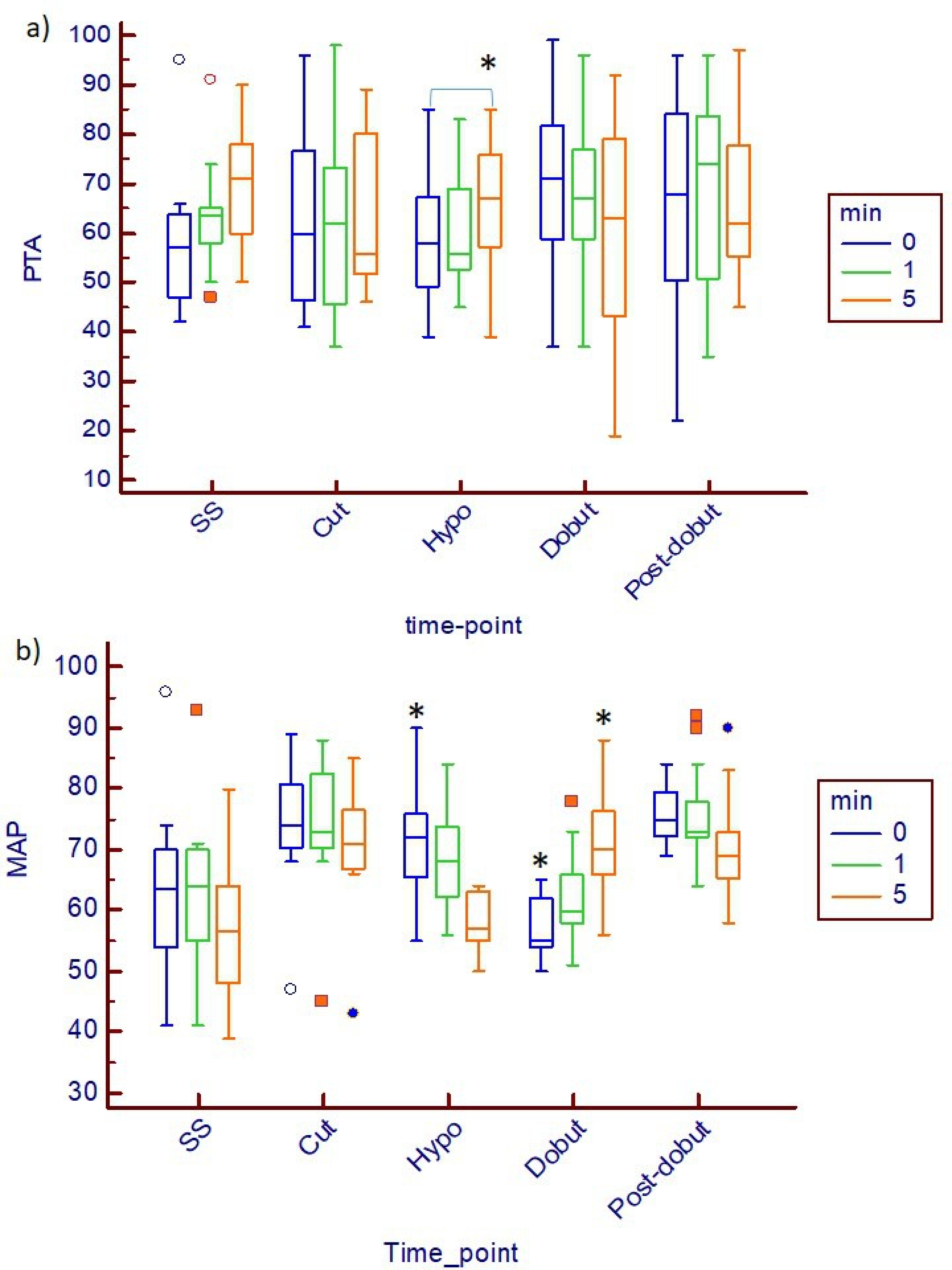
Figure 2. (a) PTA (Parasympathetic Tone Activity) and (b) MAP (Mean arterial pressure) evolution in Elective group at the predefined time-points. * indicates a significant difference ($p < 0.05$) of PTA and MAP between the predefined-time, 1 and 5 minutes thereafter. Values are expressed as median [IQR]. 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.

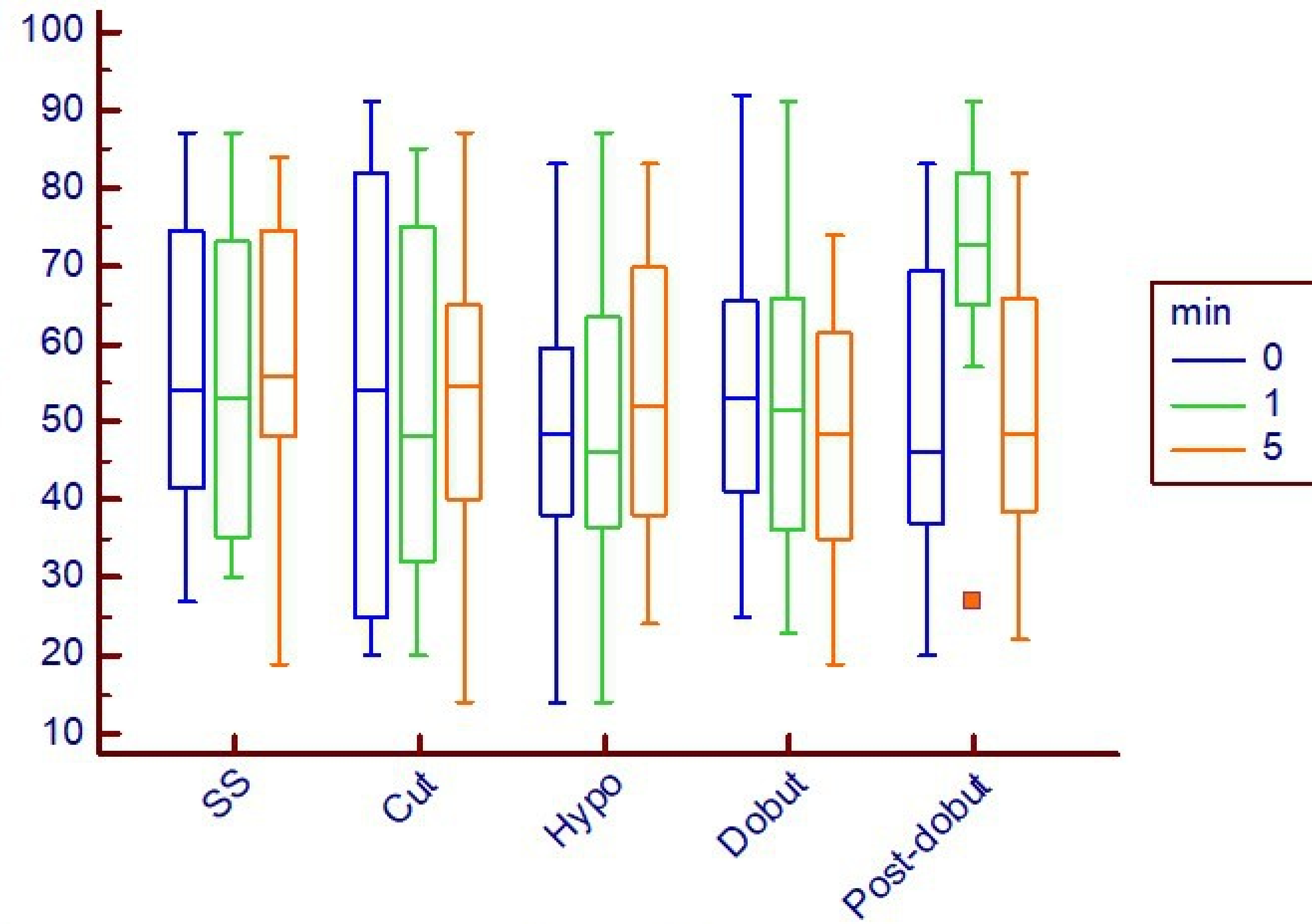
Figure 4. Time by group effect at the baseline (T0) of the predefined time-points of Elective group (closed circles ●) versus Colic group (open circles ○) for (a) Parasympathetic Tone Activity index values (PTA) and (b) mean arterial pressure (MAP). Values are expressed as median [IQR]. SS, steady-state; 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.


Incision
Hypotension
Dobutamine initiation
Dobutamine discontinuation
0 1min 5min
0 1min 5min
0 1min 5min
0 1min 5min
0 1min 5min
TSS
TCut
THypo
TDobut
TPost-dobut

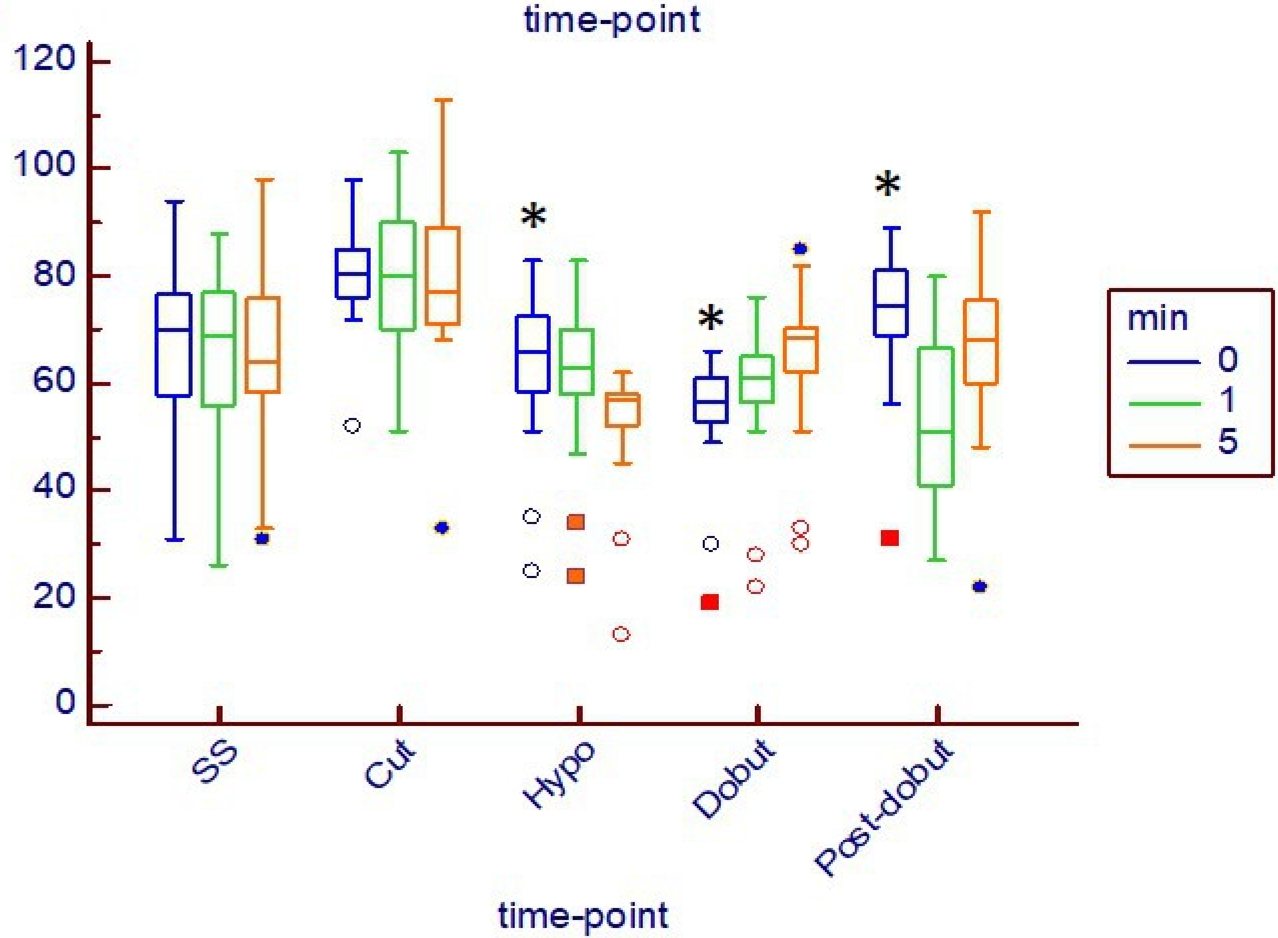

a)
PTA
100
90
80
70
60
50
40
30
20
10
SS
Cut
Hypo
Dobut
Post-dobut
time-point
min
0
1
5
*
b)
MAP
100
90
80
70
60
50
40
30
SS
Cut
Hypo
Dobut
Post-dobut
Time_point
min
0
1
5
*
*
*

a)



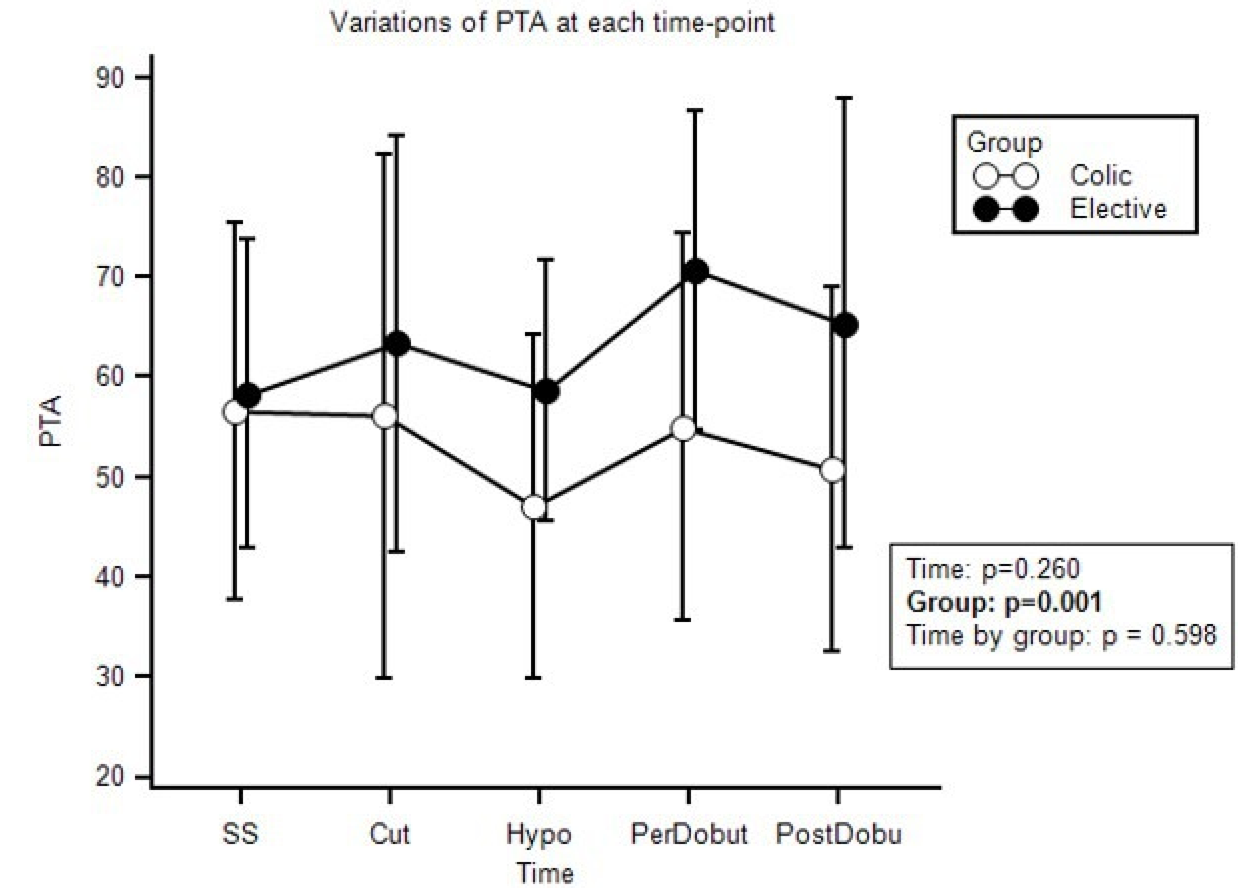
PTA
100
90
80
70
60
50
40
30
20
10
SS
Cut
Hypo
Dobut
Post-dobut
time-point
min
0
1
5

b)



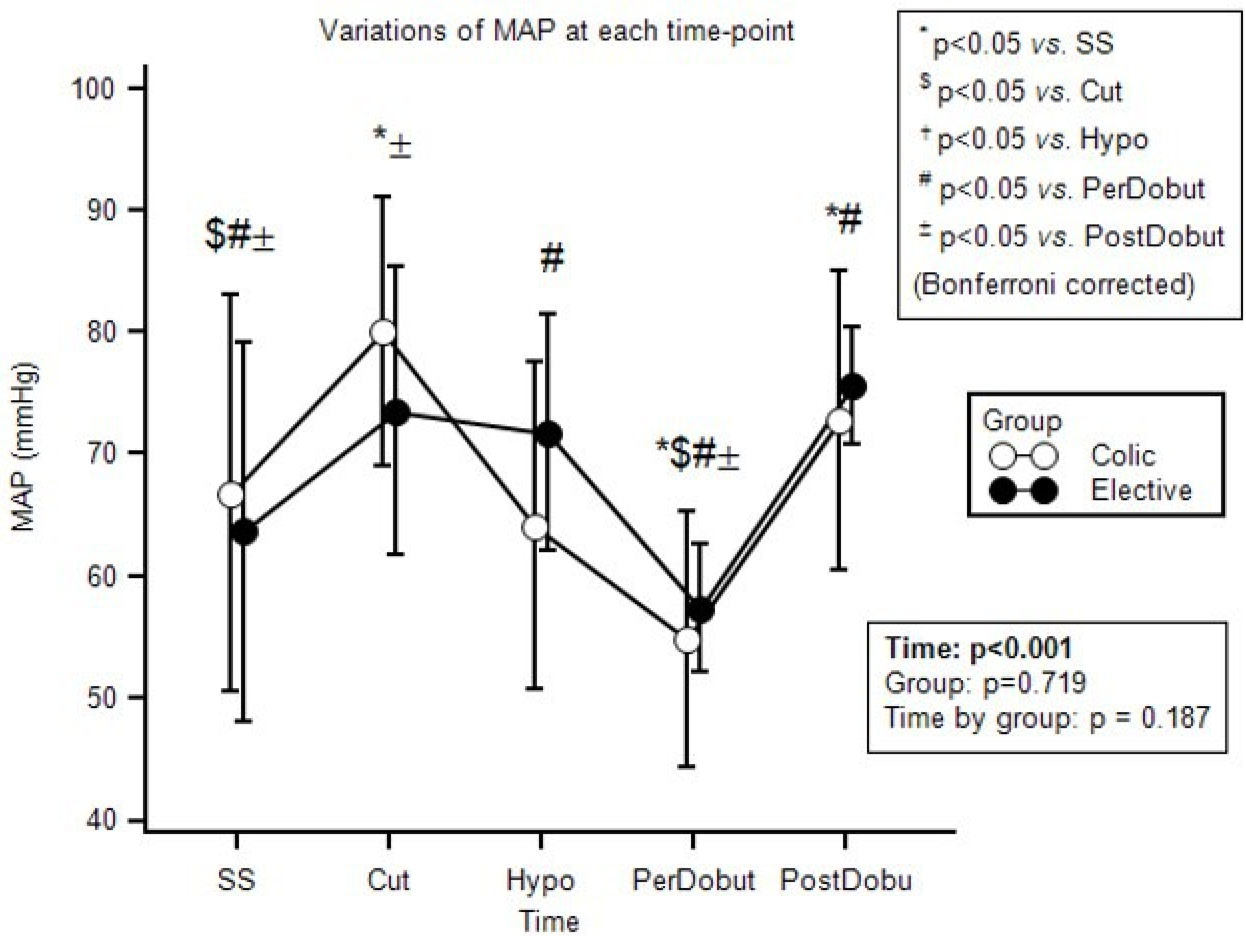
MAP
120
100
80
60
40
20
0
SS
Cut
Hypo
Dobut
Post-dobut
time-point
min
0
1
5

a)



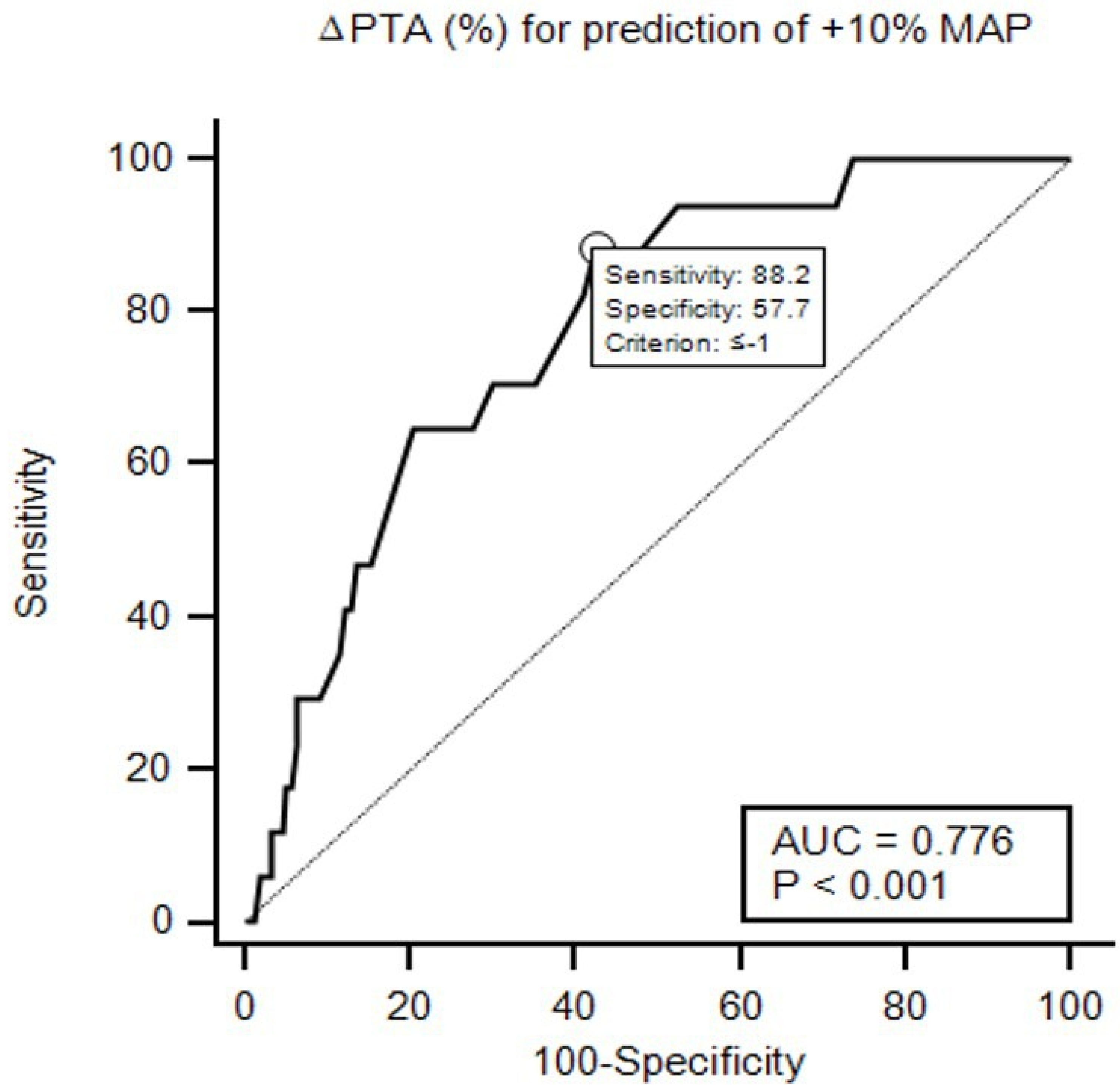
Variations of PTA at each time-point
Group
Colic
Elective
PTA
90
80
70
60
50
40
30
20
SS
Cut
Hypo
PerDobut
PostDobu
Time
Time: p=0.260
Group: p=0.001
Time by group: p = 0.598

b)



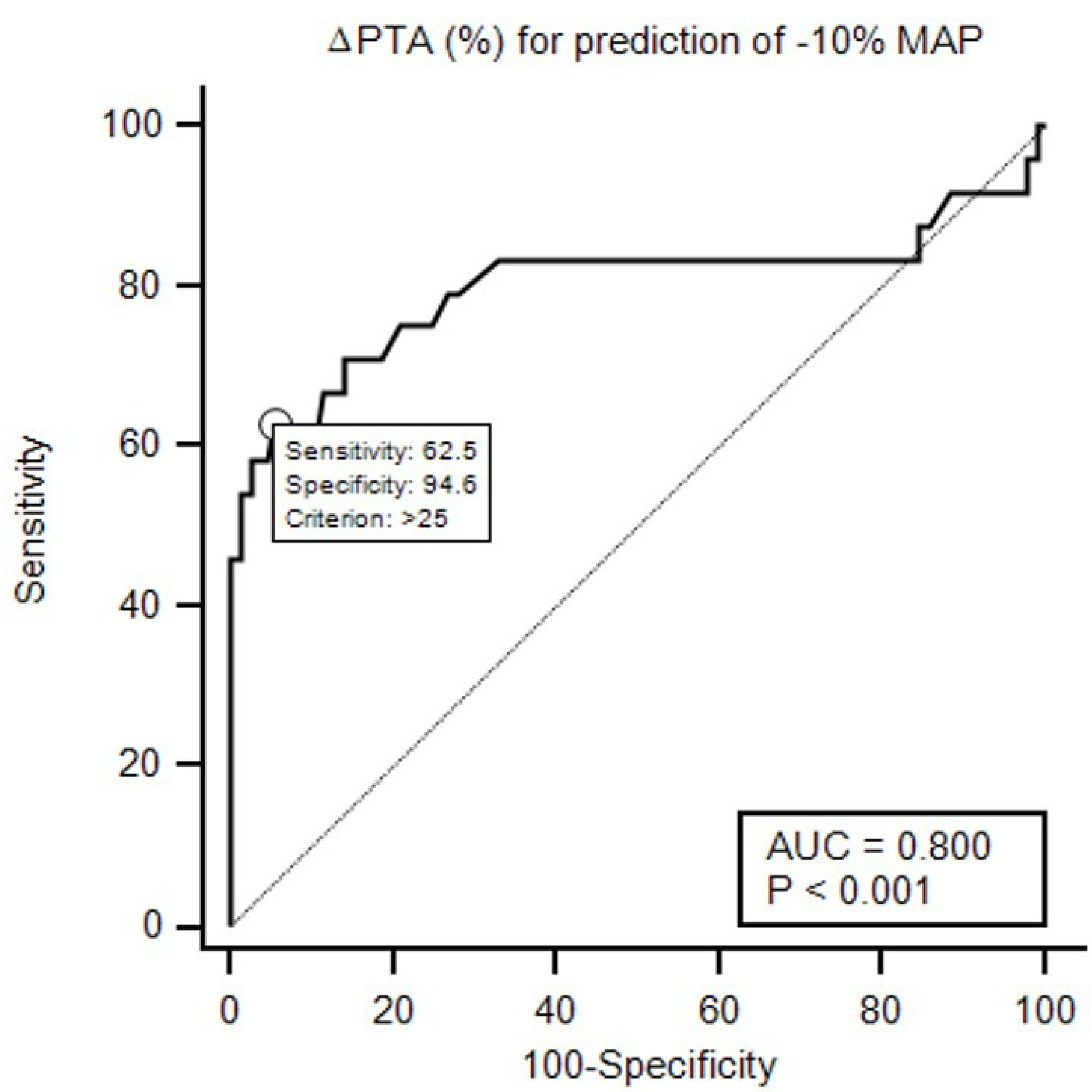
Variations of MAP at each time-point
* p<0.05 *vs.* SS
$ p<0.05 *vs.* Cut
+ p<0.05 *vs.* Hypo
# p<0.05 *vs.* PerDobut
± p<0.05 *vs.* PostDobut
(Bonferroni corrected)
MAP (mmHg)
100
90
80
70
60
50
40
$#±
*±
#
*$#±
*#
Group
Colic
Elective
Time: p<0.001
Group: p=0.719
Time by group: p = 0.187
SS
Cut
Hypo
PerDobut
PostDobu
Time

a)



ΔPTA (%) for prediction of +10% MAP
Sensitivity: 88.2
Specificity: 57.7
Criterion: ≤-1
AUC = 0.776
P < 0.001
Sensitivity
100-Specificity
0
20
40
60
80
100

b)



ΔPTA (%) for prediction of -10% MAP
Sensitivity: 62.5
Specificity: 94.6
Criterion: >25
AUC = 0.800
P < 0.001
Sensitivity
100-Specificity
0
20
40
60
80
100