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

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36

37

38 **Abstract**

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

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

46 In both groups, no significant variation of PTA and MAP were detected immediately before and
47 after cutaneous incision. The PTA index increased 5 min before each hypotension, whereas it
48 decreased 1 min after dobutamine administration. Horses of the Colic group had lower PTA
49 values than those of the Elective group, whereas MAP did not differ between groups. To predict
50 a 10% decrease in MAP, Δ PTA performance was associated with: AUC ROC [95% CI] =0.80
51 [0.73 to 0.85] ($p < 0.0001$), with a sensitivity of 62.5% and a specificity of 94.6% for a threshold
52 value of 25%.

53 The PTA index in anaesthetized horses appears to be influenced by the health condition. The
54 shift toward lower PTA values in colic horses may reflect a sympathetic predominance. An
55 increase in PTA of >25% in 1 min showed an acceptable performance to predict MAP decrease
56 of >10% within 5 min. Even though these results require further evaluation, this index may thus
57 help to predict potential autonomic dysfunctions in sick animals.

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

60

61

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68 Christelle Mansour was supported by the Lebanese University to accomplish her PhD studies in

69 France.

70

71 **Conflict of interest**

72 Christelle Mansour has received a travel grants from MDoloris Medical Systems for short

73 communications related to PTA.

74 Emmanuel Boselli has received honoraria and travel grants from MDoloris Medical Systems for

75 lectures related to ANI.

76 The other authors have no conflict of interest to disclose.

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85 **Introduction**

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

91 Spectral analysis of HRV is a non-invasive objective technique that examines the beat-to-
92 beat variations in heart rate (HR) and can characterize the autonomic nervous system activity
93 (Barnaby et al. 2002). Stress from various origin (including nociception, anxiety, aggression,
94 etc...) can shift the autonomic balance towards a sympathetic nervous prevalence with a
95 decrease in HRV (Tzelos et al. 2015). HRV has been used as a diagnostic and prognostic tool in
96 a variety of conditions including anaesthesia (Stucke et al. 2015), aiming to optimize
97 intraoperative haemodynamics (~~Huang et al. 2006~~). It is commonly used to characterize the
98 relative activity of the sympathetic and parasympathetic nervous systems in animals and humans
99 (Manzo et al. 2009) (~~Valenza et al. 2018~~).

100 Recently, a monitor has been launched to assess the sympathovagal balance in animals
101 (PTA Monitor®; MDoloris Medical Systems, Lille, France). It displays an index called PTA
102 (Parasympathetic Tone Activity), which is similar to the Analgesia Nociception Index (ANI).
103 These indexes assess the parasympathetic tone based on the qualitative and quantitative analysis
104 of the HRV. At each respiratory cycle, these indexes measure the relative parasympathetic tone
105 and its effect on the sinus node. The signal collected is simply an electrocardiogram (ECG)
106 which is automatically analyzed for the R-R interval over a period of time (Logier et al. 2010).
107 The ANI index was validated to detect nociception during anaesthesia in human patients (Jeanne

108 et al. 2009). The PTA index was evaluated to assess the analgesia/nociception balance and
109 predict a haemodynamic reactivity in anaesthetized dogs (Mansour et al. 2017; Mansour et
110 al.2020; Aguado et al. 2020; Hernández-Avalos et al. 2021).

111 The autonomic nervous system (ANS) is a major regulator of the cardiovascular system:
112 it maintains internal physiologic homeostasis, but can be altered by a variety of perioperative
113 factors, including anaesthetic drugs and clinical condition, with resulting haemodynamic changes
114 (Latson and O’Flaherty 1993; Pearce 2002). As horses are prone to develop pronounced
115 cardiovascular alterations during general anaesthesia, it is probable that their sympathovagal
116 balance can be modified during anaesthesia, which may interfere with HRV analysis.
117 Alternately, apart from the evaluation of analgesia nociception balance, monitoring the
118 sympathovagal balance during anaesthesia may provide useful information to early detect ANS
119 dysfunction and optimize the cardiovascular support of the anaesthetized horse (Oel et al. 2014)
120 (Gehlen et al. 2020) (~~Latson et al. 1994~~).

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

127

128 **Materials and Methods**

129 **Animals**

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

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

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

145

146 **Anaesthetic protocol**

147 Horses of the Elective group had free access to water and food was withheld for at least
148 six hours before anaesthesia, whereas horses of Colic group had no food or water restriction
149 before anaesthesia due to their emergency condition. After placement of a catheter into a jugular
150 vein, horses from the Elective group were premedicated with acepromazine (Calmivet,
151 Vetoquinol, Paris, France) 0.03 mg kg^{-1} intramuscularly (IM), followed 30 minutes later by a

152 combination of 0.6 mg kg⁻¹ of xylazine hydrochloride (Rompun™, Bayer, Lille, France) and 0.1
153 mg kg⁻¹ of morphine (Morphine chlorhydrate, Aguetant, Lyon, France) intravenously (IV).
154 Horses of the Colic group received 0.4 mg kg⁻¹ of xylazine hydrochloride combined to 0.1 mg kg⁻¹
155 of morphine IV as a premedication. Once sedation was achieved, anaesthesia was induced with
156 2.2 mg kg⁻¹ of ketamine hydrochloride (Imalgene 1000, Merial, Lyon, France) and 0.05 mg kg⁻¹
157 of diazepam (Diazepam TVM, TVM, Clermont-Ferrand, France) intravenously (IV).

158 After orotracheal intubation, horses were positioned in dorsal recumbency on the surgical
159 table and anaesthesia was maintained in both groups with sevoflurane (SevoFlo, Zoetis,
160 Malakoff, France) delivered in 60% O₂ using a large animal rebreathing circuit (Tafonius;
161 Vetronic Services Ltd, Abbotskerswell, UK). The horses were mechanically ventilated
162 (Tafonius; Vetronic Services Ltd, Abbotskerswell, UK) with an initial respiratory rate of 8
163 breaths minute⁻¹, a tidal volume (\dot{V}_T) of 10 mL kg⁻¹, adjusted to maintain a P_{E'}CO₂ of 4.6 to 6.0
164 kPa (35-45 mmHg). Ringer lactate solution was administered IV during anaesthesia at a rate of
165 10 mL kg⁻¹ h⁻¹. Horses of the Colic group received a lidocaine (Lurocaine, Vetoquinol, Paris,
166 France) infusion of 0.05 mg kg⁻¹ min⁻¹ preceded by a loading dose of 1.5 mg kg⁻¹ over 20
167 minutes. In case of a prolonged surgery, a supplementary bolus of morphine 0.1 mg kg⁻¹ IM was
168 given once intra-operatively, 2 hours after the initial dose. At the end of the anaesthesia, xylazine
169 (0.1-0.2 mg kg⁻¹) IV was administered in every horse of the “Elective” group, and in horses of
170 the Colic group according to the presence of early signs of excitation and / or consciousness.
171 Horses were then transferred to a padded recovery box. After removal of the endotracheal tube,
172 oxygen (15 L min⁻¹) was administered flow-by through a nasal tube during recovery. Horses of
173 both groups received flunixin meglumine (Finadyne, MSD Santé animale, Beaucouzé, France)
174 (1.1 mg kg⁻¹ IV) and antimicrobial agents adapted to the surgical condition.

175

176 **Monitoring**

177

178 Heart rate (HR), invasive blood pressure, respiratory rate, end-tidal carbon dioxide tension
179 ($P_E'CO_2$), end-tidal oxygen tension ($P_E'O_2$), end-tidal sevoflurane concentration ($P_E'Sevo$),
180 inspired oxygen fraction (FiO_2) and oxygen saturation of haemoglobin (SpO_2) were measured
181 continuously using a multi-parameter monitor (Tafonius; Vetronic Services Ltd, Abbotskerswell,
182 UK) and recorded manually every 5 minutes.

183 In order to obtain a base-apex lead ECG, the electrodes were positioned as followed: the
184 positive electrode (left arm) was placed over the left chest, at the level of the olecranon, the
185 negative electrode (right arm) over the right jugular furrow. Invasive blood pressure
186 measurement was performed using a transducer (TruWave; Edwards Lifesciences, Guyancourt,
187 France) connected via a fluid-filled line to an arterial catheter. During surgical preparation, the
188 left or right facial artery was cannulated aseptically using a 20 gauge, 36 mm catheter (Intraflon
189 2; Vygon, Ecoenen, France). With the animal in dorsal recumbency, the transducer was positioned
190 at the level of right atrium, considered at the level of the point of the shoulder. It was connected
191 to the arterial catheter using noncompliant tubing filled with heparinized saline. Once the arterial
192 cannula was in place and connected, before the start of measurements, the transducer was zeroed,
193 and a fast-flush test was subjectively assessed to ensure that the degree of damping of the system
194 was acceptable. This test was performed by flushing crystalloid fluid that fills the
195 tubing/transducer system with 300 mmHg pressure via the flush system and ensuring the
196 presence of two oscillations following release of the flush valve.

197 Arterial blood samples were taken from the facial artery at 1-hour intervals to determine
198 blood gas values (VetStat analyzer, Idexx, Hoofddorp, The Netherlands). The urinary bladder

199 was catheterized for passive urine collection until the end of anaesthesia. The PTA index was
200 monitored continuously during anaesthesia using a dedicated monitor (Physiodoloris®,
201 MDoloris Medical System, Lille, France).

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

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

209

210 **PTA measurement**

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

216 The principle of the PTA index measurement and calculation is similar to ANI and has
217 previously been described elsewhere (Jeanne et al. 2009; Logier et al. 2010; Mansour et al. 2017;
218 Aguado et al. 2020). The PTA index is measured using a dedicated monitor (Physiodoloris,
219 MDoloris medical system, Lille, France), based on ECG measurement, with a lead II ECG using
220 a 3 lead-system. The signal acquisition is made via a 250 Hz ECG to evaluate heart rate

221 variability. The algorithm for the PTA index calculation is succinctly described thereafter. The
222 first step is the R waves detection and calculation of RR intervals. The RR series are then filtered
223 with a real-time artefact-removal filter. The resulting RR series are resampled at 8Hz and then
224 filtered with a wavelet transform based band pass filter from 0.15 to 0.5Hz. This is based on the
225 principle that fluctuations in heart rate variability in high frequencies (0.15-0.5Hz) are
226 exclusively mediated by the parasympathetic nervous system whereas changes in low
227 frequencies (0.004-0.15Hz) are mediated by both parasympathetic and sympathetic activities
228 (Logier et al. 2010) and the algorithm aims at determining the parasympathetic activity
229 exclusively. The signal issued is called the “energy”. The energy curve is displayed on the
230 monitor’s screen and divided into four 16-seconds windows. The area under the curve (AUC) is
231 calculated for each window. The smallest of the four AUC is defined as the AUCmin.

232 The PTA index is calculated with the formula:

233 $PTA = [100 * (\alpha * AUCmin + \beta) / 12.8] * 100 / 163$; 100/163 is a coefficient determined for the
234 horse in order to obtain PTA values between 0 and 100.

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

240

241 **Study design**

242 For each anaesthetized animal, different predefined time-points of 5 minute-duration
243 were considered (figure 1): T_{SS} (steady-state time, immediately before cutaneous incision), T_{Cut}

244 (after surgical noxious stimulation defined as cutaneous incision), T_{Hypo} (retrospectively assessed
245 5 minutes before each hypotension), T_{Dobut} (after each dobutamine initiation) and $T_{Post-dobut}$ (after
246 each dobutamine discontinuation). These different time-points were designed to allow a
247 comparison between groups despite different clinical conditions and surgical procedures.

248 In order to assess the performance of the PTA index to predict a decrease or an increase
249 in MAP, PTA and MAP were recorded initially, 1 minute and 5 minutes thereafter for each
250 predefined time-point. Based on a recent report showing a better performance of the variations of
251 ANI over static values to detect haemodynamic reactions in human patients (Boselli et al. 2016),
252 variations of PTA (ΔPTA) and MAP (ΔMAP) were calculated at each time-point as follow:

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

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

255 Where X_0 , X_{1min} and X_{5min} are respectively the values of PTA and MAP at the predefined time, 1
256 min and 5 min thereafter.

257 This calculation was used *posteriori* to evaluate the performance of ΔPTA_{1min} to anticipate a
258 change of MAP over the following 5 minutes.

259

260 **Statistical analysis**

261 Statistical analysis was performed using MedCalc® 12.1.4.0 (MedCalc Software®,
262 Ostend, Belgium). Normality of distribution was assessed using the Shapiro-Wilk test. Normal
263 data were expressed as mean \pm standard deviation (SD) whereas skewed data were expressed as
264 median and interquartile range [IQR]. Demographic data was compared between groups using

265 Student's *t* test. An analysis of variance (ANOVA) for repeated measures was used to detect any
266 significant variations of PTA and MAP within 1 min and 5 min at each time-point for both Colic
267 and Elective groups. In case of significant variation, *post-hoc* Tukey multiple paired comparisons
268 were performed. Variations of PTA and MAP within time were compared between groups using
269 two-way ANOVA with Bonferroni correction for post hoc analysis. The performance of Δ PTA
270 to predict an increase or decrease of MAP within 5 minutes after predefined time-points was
271 assessed by calculation of the area under curve (AUC) of a receiver operating characteristic
272 (ROC) curve using pooled data from the defined times. The threshold value showing the best
273 sensitivity and specificity was determined using Youden index. A p-value < 0.05 was considered
274 statistically significant.

275

276 **Results**

277 **Animals**

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

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

287

288 **PTA and MAP evolution at the predefined time-points**

289 **Variation of parameters for horses of the Elective group**

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

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

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

297 At T_{Dobut} , a decrease in PTA was observed 1 min after initiation of dobutamine (-12.7%,
298 $p = 0.08$), whereas PTA_{5min} did not vary compared to PTA_0 . After dobutamine initiation, MAP
299 significantly increased at 1 min (+20%, $p = 0.009$) as well as at 5 min (+27%, $p < 0.0001$).

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

302

303 **Variation of parameters for horses of the Colic group**

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

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

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

310 At T_{Dobut} , a decrease in PTA was observed at 1 min (-9%, $p = 0.07$) as well as at 5 min (-
311 12.9 %, $p = 0.03$). MAP increased significantly at 1 min (8 %, $p < 0.0001$) as well as at 5 min
312 (21%, $p < 0.0001$) compared to MAP_0 .

313 At $T_{Post-dobut}$, no difference in PTA was found whereas a significant decrease in MAP (-
314 8%, $p < 0.0001$) was found 5 minutes after dobutamine discontinuation.

315

316 **Elective vs Colic group**

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

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

323 There was no significant difference in MAP values at each time-point between groups
324 (group effect, $p = 0.719$) and no interaction between time and groups (time by group effect, $p =$
325 0.187) (figure 4, b). Yet, in both groups, MAP was shown to be significantly the lowest at the
326 time of dobutamine administration (T_{Dobut}) (time effect, $p < 0.001$).

327

328 **Relationship between ΔPTA and ΔMAP at the predefined time-** 329 **points of each group**

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

338

339 **Discussion**

340

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

348 The analysis of heart rate variability (HRV) is a non-invasive simple method, which can
349 detect and record continuously the fluctuations in the autonomic input to the sinoatrial node and
350 the activity of the individual components of the ANS (Mazzeo et al. 2011) (~~Oel et al. 2014~~). To
351 evaluate the ANS, HRV uses a frequency domain-based analysis (Akselrod et al. 1985) (~~Stucke~~
352 ~~et al. 2015~~). During anaesthesia, HRV has been used in humans for the prediction of blood

353 pressure change (Huang et al. 2006; Hanss et al. 2008) (~~Ogawa et al. 2006~~) and the evaluation of
354 analgesia nociception balance (Jeanne et al. 2009) (~~Boselli et al. 2013~~). In anaesthetized animals,
355 the use of HRV analysis has been sparsely reported. In horses, HRV power spectrum has been
356 reported to the power spectrum of humans, rats and pigs (Stucke et al. 2015). The normal resting
357 horse is considered as having a prevailing parasympathetic tone, which was confirmed by HRV
358 analysis (Kuwahara et al. 1996). A recent study in horses has reported that HRV can detect
359 sympathovagal stimulation during ocular surgery (Oel et al. 2014). It has also been used as a
360 prognostic information for postoperative horses with severe gastrointestinal disease
361 (McConachie et al. 2016).

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

376 The PTA index is similar to the ANI, validated in human medicine to predict
377 intraoperative haemodynamic reactions (Boselli et al. 2016) and hypotension caused by spinal
378 anaesthesia (Sakata et al. 2016). Recently, the variation of the PTA index (Δ PTA) has been
379 evaluated in anaesthetized dogs, with an acceptable performance to predict haemodynamic
380 reactivity associated with intraoperative nociceptive stimuli (Mansour et al. 2017; Aguado et al.
381 2020; Mansour et al. 2020), but to our knowledge, this index has not been evaluated in
382 anaesthetized horse.

383 In the present study, predefined time-points were chosen to allow a comparison between
384 animals of different physical status undergoing different surgical procedures. The time-point T_{SS}
385 was designed to evaluate the stability of the signal without any surgical stimulation, whereas T_{Cut}
386 was designed to evaluate the potential influence of a nociceptive stimulation on PTA. The time-
387 points T_{Hypo} , T_{Dobut} and $T_{Post-dobut}$ were designed to assess the influence of hypotension and
388 administration of inotropes on the index (Bootsma et al. 1993).

389 At steady-state (T_{SS}), the absence of significant difference within each group was
390 expected, as no surgical or pharmacological stimulus was carried out during this time-point.
391 However, the lack of difference, specifically of PTA index, between groups is surprising as colic
392 horses are known to be in severe haemodynamic status and should have a higher activation of the
393 sympathetic nervous system compared to healthy horses (McConachie et al. 2016) (~~Gehlen et al.~~
394 ~~2020~~). Yet, we assume that the drugs administered to the colic horses preoperatively could have
395 reduced the sympathetic effects, pain and inflammatory reactions with the consequence of
396 increasing the PTA index in these horses at steady-state.

397 In comparison with previous results in dogs, no significant variation was registered at
398 T_{Cut} , (Mansour et al. 2017). This can be explained by the association of xylazine and morphine at

399 premedication which could have resulted in an adequate level of analgesia. Xylazine mediates a
400 sympatholytic action with a reported duration of action of 20 to 30 minutes (Kerr et al. 2004),
401 morphine has a reported plasma half-life of elimination of 1.6 hours (Combie et al. 1983).

402 The variations of PTA observed during blood pressure changes appeared to be inversely
403 related to those of arterial pressure, and thus, seem to follow modifications of the sympathovagal
404 balance. During hypotension, the increase in PTA reflects a shift toward a parasympathetic
405 predominance. Similar results have been reported in human medicine with the analgesia
406 nociception index (Jeanne et al. 2012). This shift was blunted by dobutamine initiation (T_{Dobut})
407 with a decrease in the PTA and a concomitant increase in blood pressure values noticed during
408 this time-point. We assume that dobutamine administration caused a shift toward sympathetic
409 predominance, as described after cardiac β_1 -adrenergic receptors stimulation (Armour 1997).

410 In general, lower PTA values were found in the horses of the Colic group, in comparison
411 with those of the Elective group. This is in accordance with a presumed autonomic dysfunction
412 and predominance of the sympathetic tone in Colic horses, associated with the stress response
413 due to the critical condition. Similar findings have been reported in an experimental model of
414 sepsis (Carrara et al. 2020) (~~Tanaka and Nishikawa 1999~~) and in human patients presented with
415 endotoxaemia; the patients presented an uncoupling of autonomic nervous system and
416 cardiovascular function leading to an impaired sympathetic modulation and regulation of blood
417 pressure (Schmidt et al. 2005) due to ineffective baroreflex failing to compensate the
418 anaesthetics-induced hypotension (Huang et al. 2006). Our findings confirm thereby a previous
419 report where horses with gastrointestinal disease had an increased sympathetic tone and a
420 reduced HRV (McConachie et al. 2016).

421 The changes of MAP at the different time-points did not differ between horses of the
422 colic group and those of the Elective group. These results are probably related to the blood-
423 pressure directed therapy that was guided to maintain MAP above 60 mmHg. An additional
424 potential explanation could be attributed to the sympathetic activation associated with the early
425 stages of sepsis (Annane et al. 1999) (~~Silverstein et al. 2009~~).

426 The ROC analysis revealed an acceptable performance of the variation of PTA to predict
427 a MAP change. This result is, to some extent, in agreement with several human studies that
428 reported a good performance of ANI to predict intraoperative haemodynamic reactivity and
429 hypotension in human patients (Boselli et al. 2015; Boselli et al. 2016; Jendoubi et al. 2021).
430 However, other studies failed to show such a similar performance for the ANI (Ledowski et al.
431 2014).

432 We acknowledge several limitations for this study. There was a lack of homogeneity in
433 the inclusion criteria with different surgical stimulations and intestinal lesions in the Colic group,
434 which could have biased the homogeneity of PTA measurements. In addition, even though
435 surgical procedures with the same recumbency were chosen to limit the influence of the posture,
436 the anaesthetic protocols were slightly different between group, with intravenous lidocaine that
437 was added in the Colic group and acepromazine that was used for horses of the Elective group.
438 Furthermore, we didn't evaluate if dobutamine has a dose-dependent effect on PTA shift.
439 Therefore, the variation in the results could be partly related to the use of various drugs.
440 However, this study aimed to assess the influence of health status on the PTA index and had to
441 be performed in a clinical setting so it was difficult to standardize administered drugs. Other
442 factors may have also influenced the HRV analysis, including preoperative stress, the different
443 ages and breeds (Michaloudis et al. 1998; Stucke et al. 2015; McConachie et al. 2016). Another

444 limitation is that we were unable to provide a reference technique in order to analyze HRV and
445 validate our results. The use of a reference method would have allowed to better evaluate both
446 components of the ANS independently, and evaluate in particular the sympathetic response and
447 compare it with the PTA values, which focuses on the parasympathetic component of the ANS to
448 extrapolate the sympathetic response. In consequence, and because of the small number of horses
449 in both groups, the results of MAP and PTA values at the measured time points are considered
450 questionable (Oberfeld and Franke 2013) and further studies should be investigated in a more
451 standardized condition to evaluate the performance of the PTA index to anticipate nociception in
452 horses.

453

454 **Conclusion**

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

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618 **Tables**

619 **Table 1. Demographic data**

620

	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*

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

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

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642 **Figure legends**

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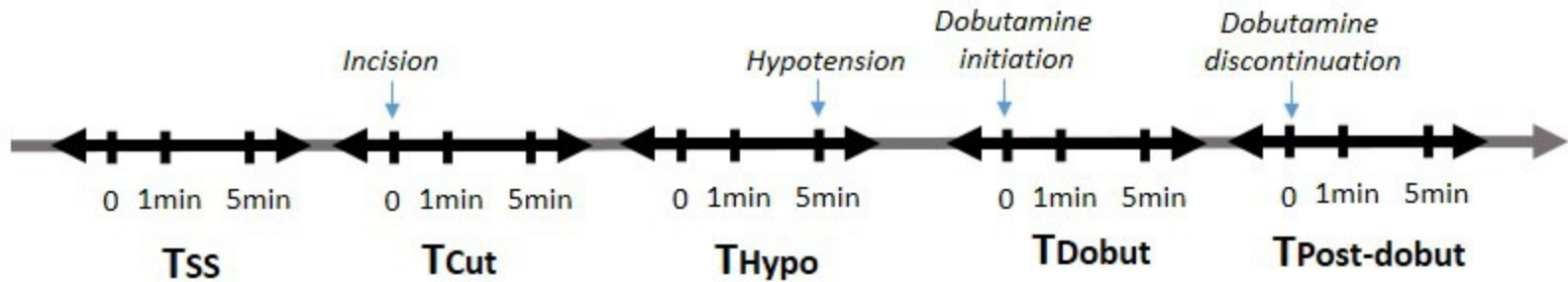
644 **Figure 1. Schematic presentation of the predefined time-points.** T_{SS}, steady-state period; T_{Cut},
645 period after noxious stimulation; T_{Hypo}, retrospective period before each hypotension; T_{Dobut},
646 period after each dobutamine initiation; T_{Post-dobut}, period after each dobutamine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

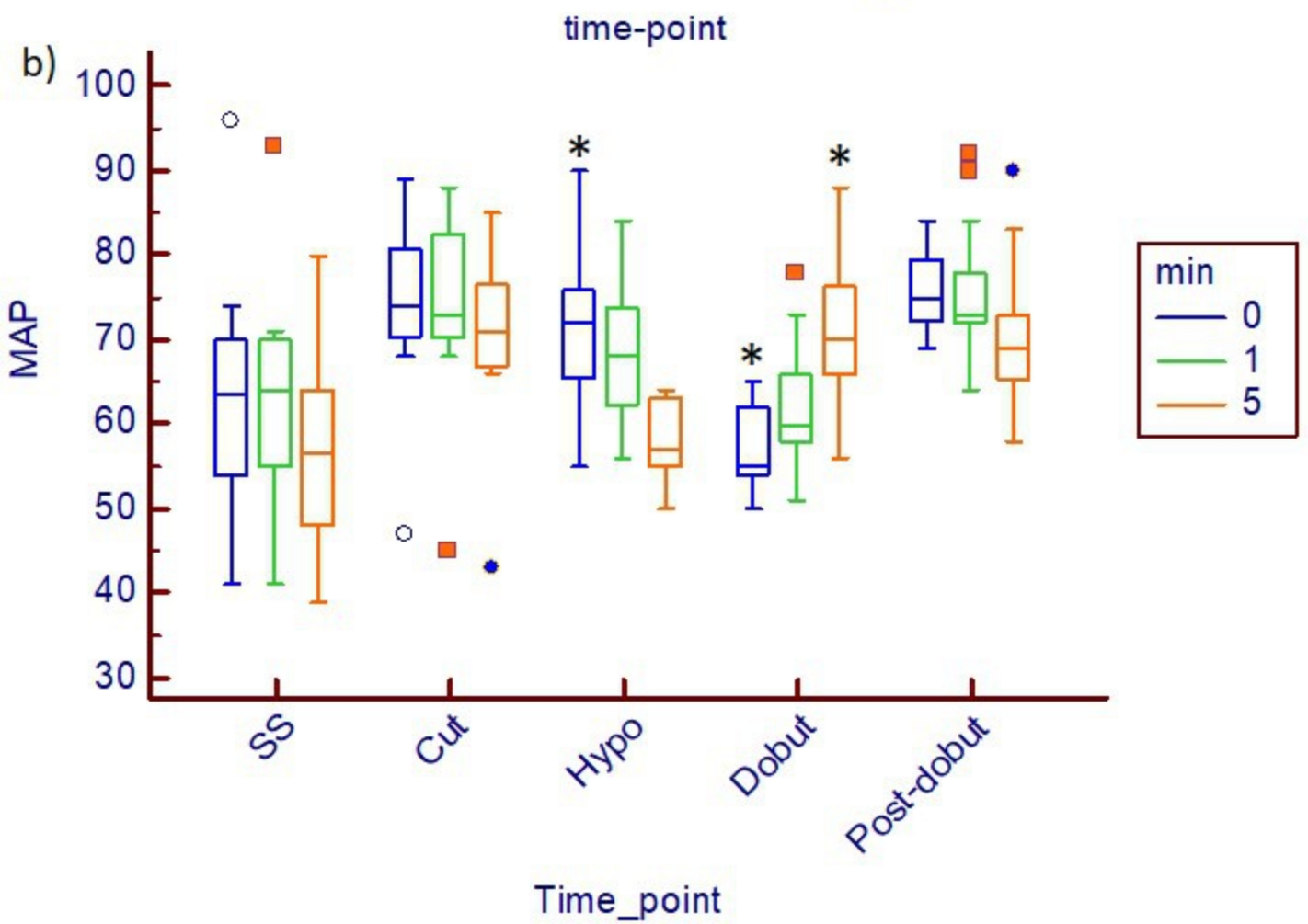
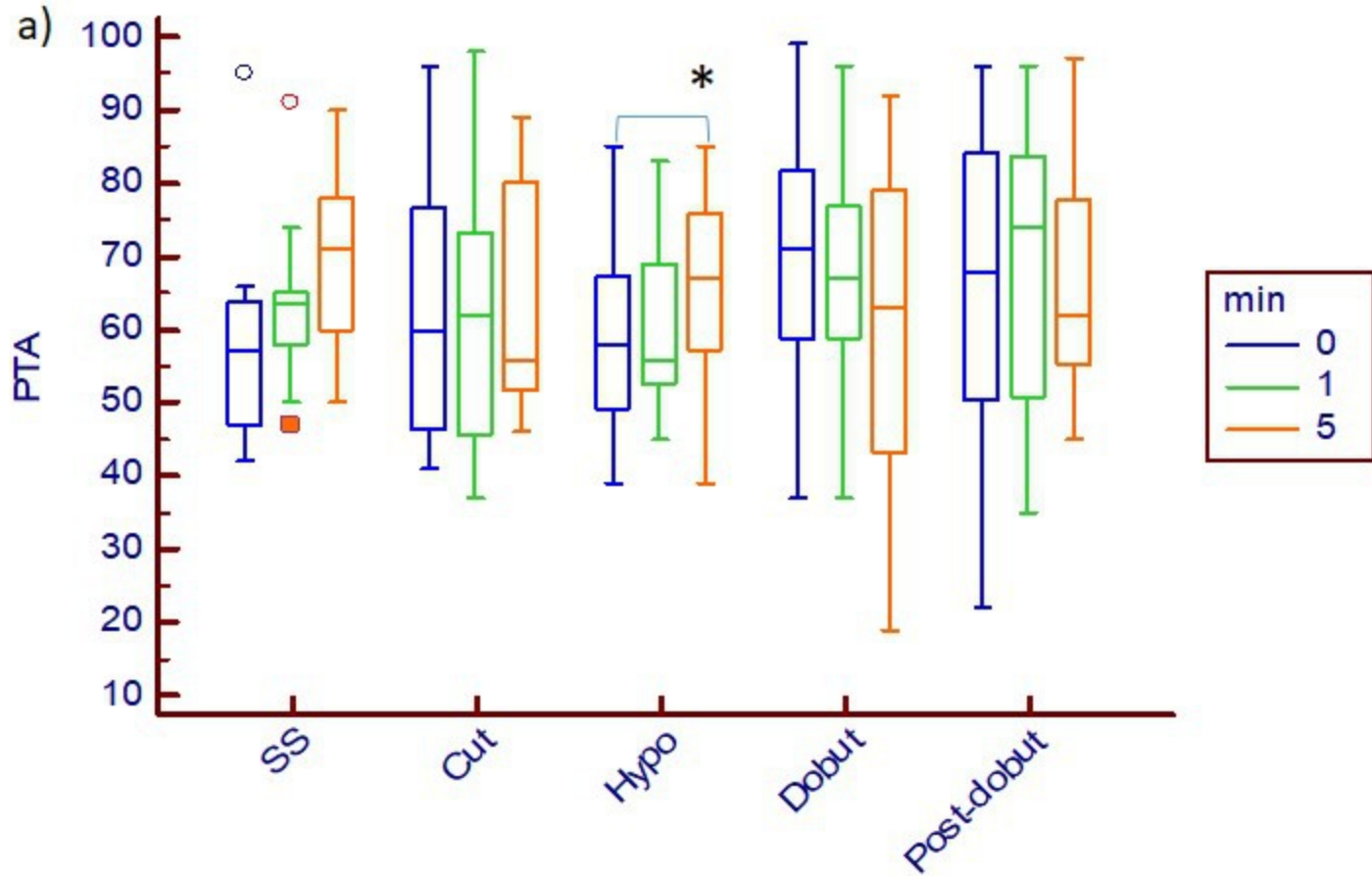
647 **Figure 2. (a) PTA (Parasympathetic Tone Activity) and (b) MAP (Mean arterial pressure)**
648 **evolution in Elective group at the predefined time-points.** * indicates a significant difference
649 ($p < 0.05$) of PTA and MAP between the predefined-time, 1 and 5 minutes thereafter. Values are
650 expressed as median [IQR]. SS, steady-state; Cut, after noxious stimulation; Hypo,
651 retrospectively before each hypotension; Dobut, after each dobutamine initiation; Post-dobut,
652 after each dobutamine discontinuation.

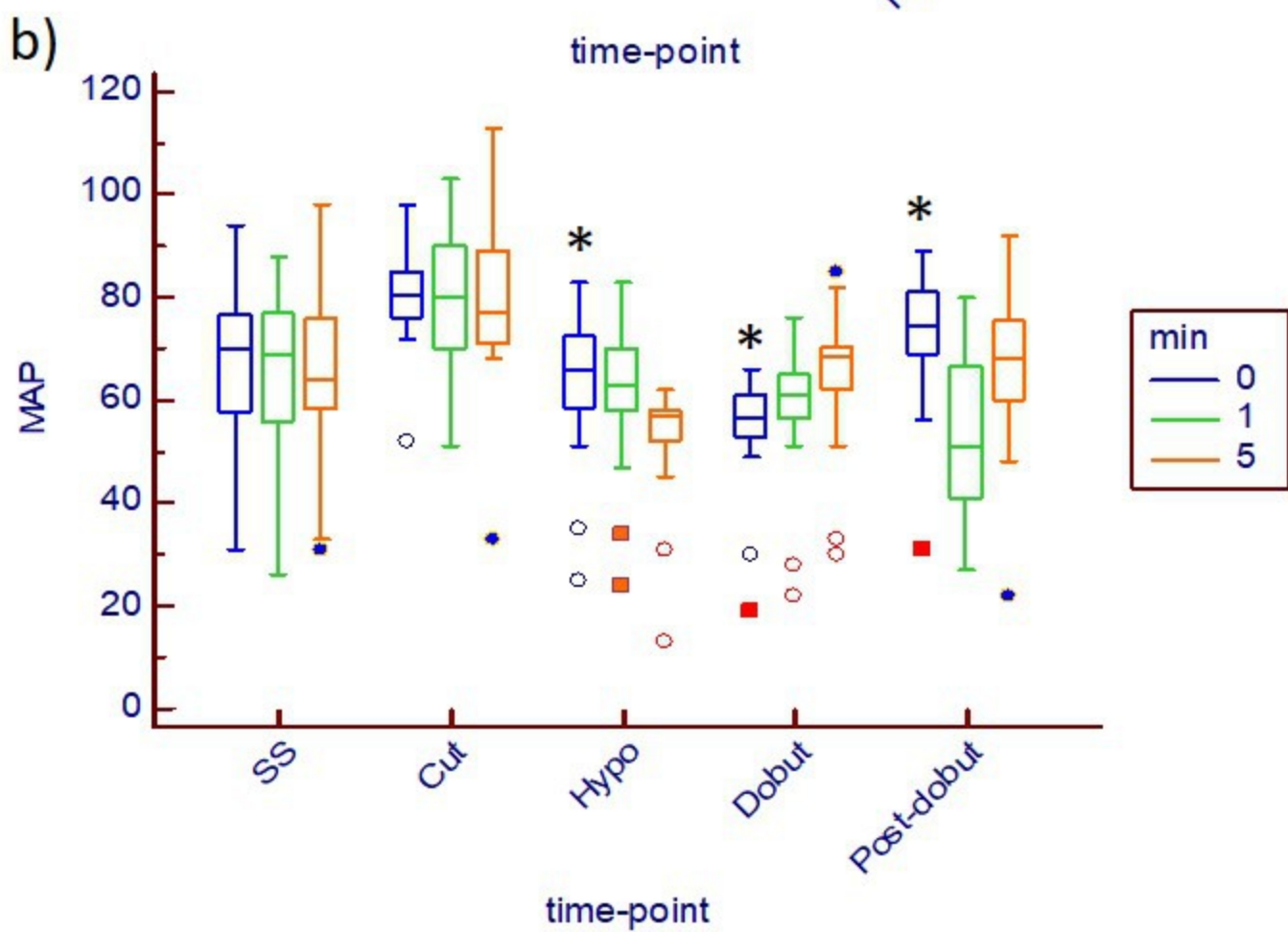
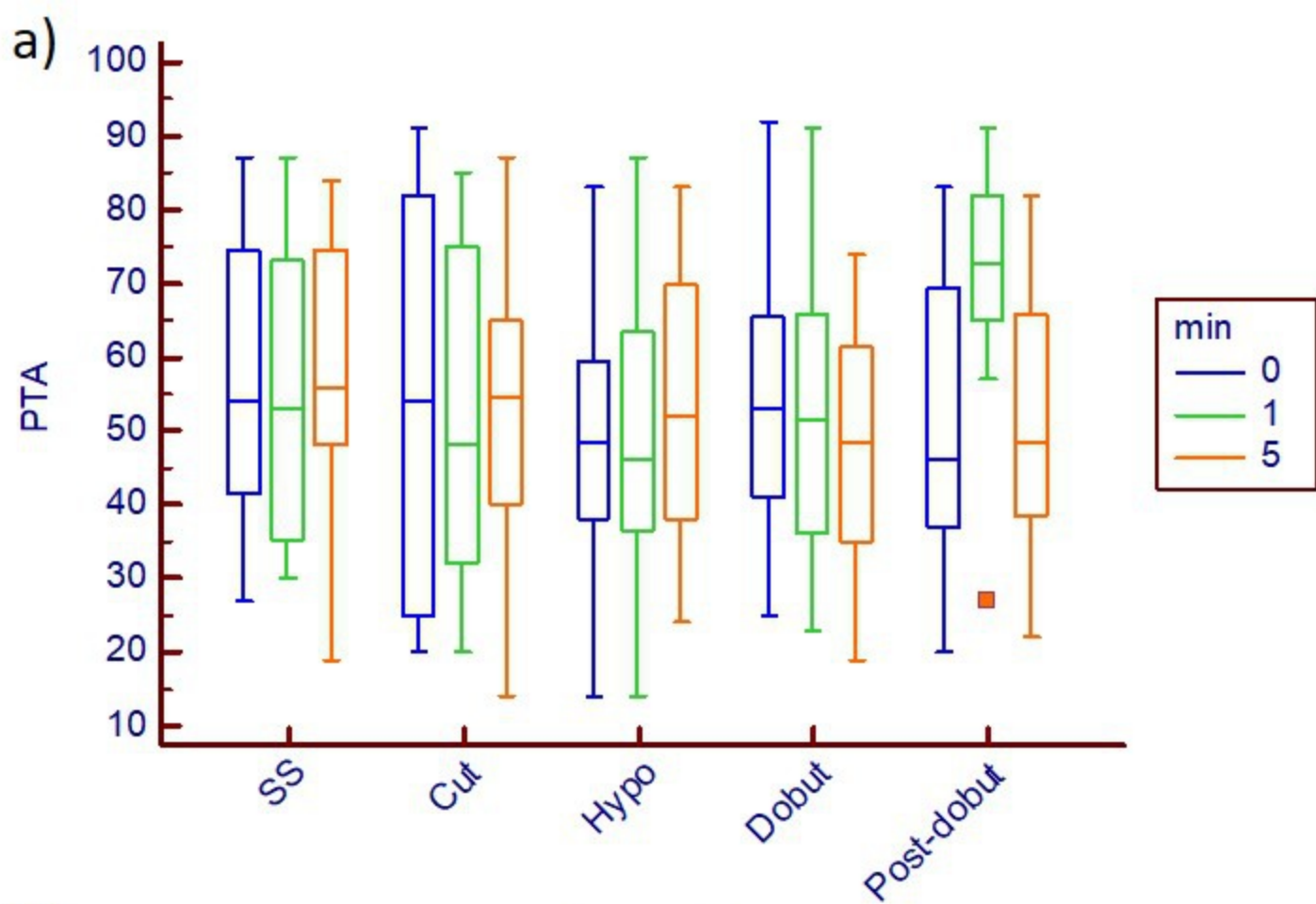
653 **Figure 3. (a) PTA (Parasympathetic Tone Activity) and (b) MAP (Mean arterial pressure)**
654 **evolution in Colic group at the predefined time-points.** * indicates a significant difference ($p <$
655 0.05) of PTA and MAP between the predefined-time, 1 and 5 minutes thereafter. Values are
656 expressed as median [IQR]. SS, steady-state; Cut, after noxious stimulation; Hypo,
657 retrospectively before each hypotension; Dobut, after each dobutamine initiation; Post-dobut,
658 after each dobutamine discontinuation.

659 **Figure 4. Time by group effect at the baseline (T0) of the predefined time-points of Elective**
660 **group (closed circles ●) versus Colic group (open circles ○) for (a) Parasympathetic Tone**
661 **Activity index values (PTA) and (b) mean arterial pressure (MAP).** Values are expressed as
662 median [IQR]. SS, steady-state; Cut, after noxious stimulation; Hypo, retrospectively before each
663 hypotension; Dobut, after each dobutamine initiation; Post-dobut, after each dobutamine
664 discontinuation.

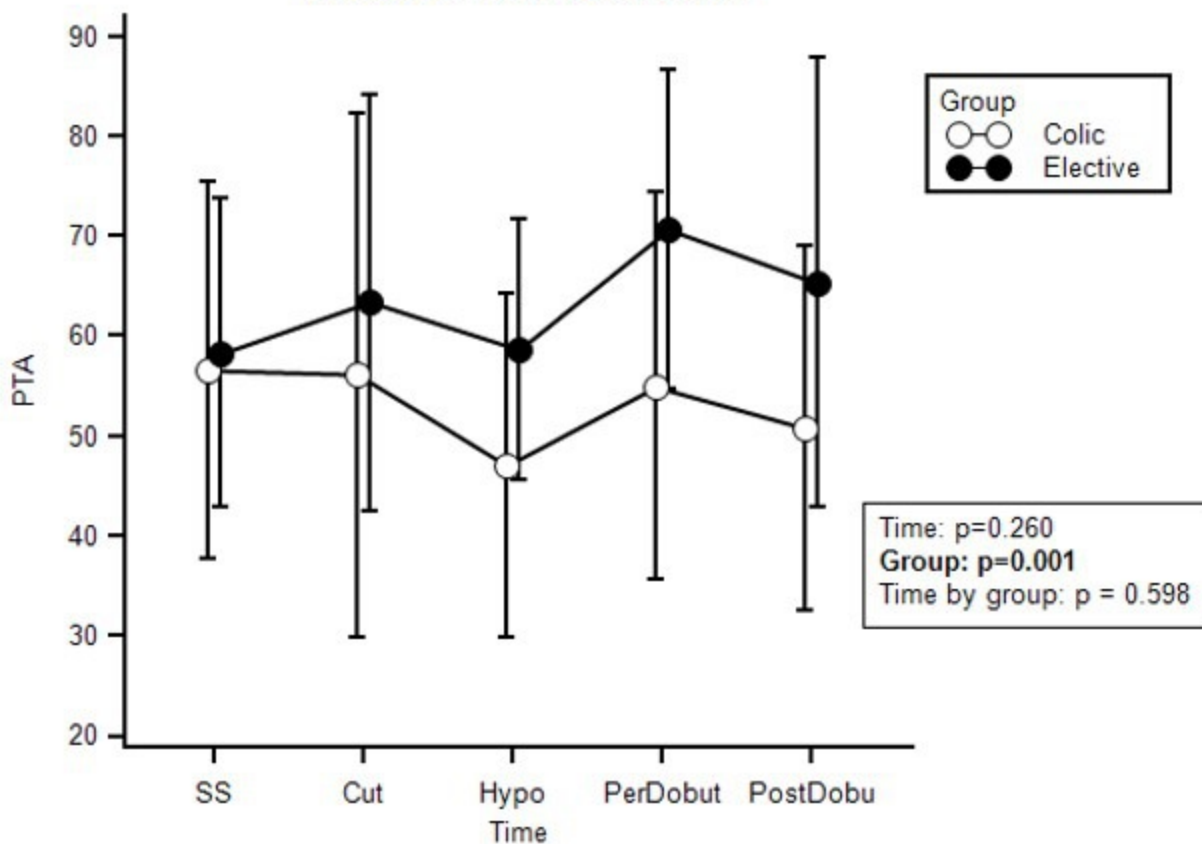
665 **Figure 5. Performance of PTA to predict 10% increase and decrease in MAP in both**
666 **groups. (a) 10% increase in MAP.** AUC ROC = 0.77 [0.70 to 0.83] ($p < 0.0001$), sensitivity =
667 88.2 %, specificity = 57.7 % and a threshold value of -1% for Δ PTA. **(b) 10% decrease in**
668 **MAP.** AUC ROC = 0.80 [0.73 to 0.85] ($p < 0.0001$), sensitivity = 62.5 %, specificity = 94.6 %
669 and a threshold value of 25% for Δ PTA.



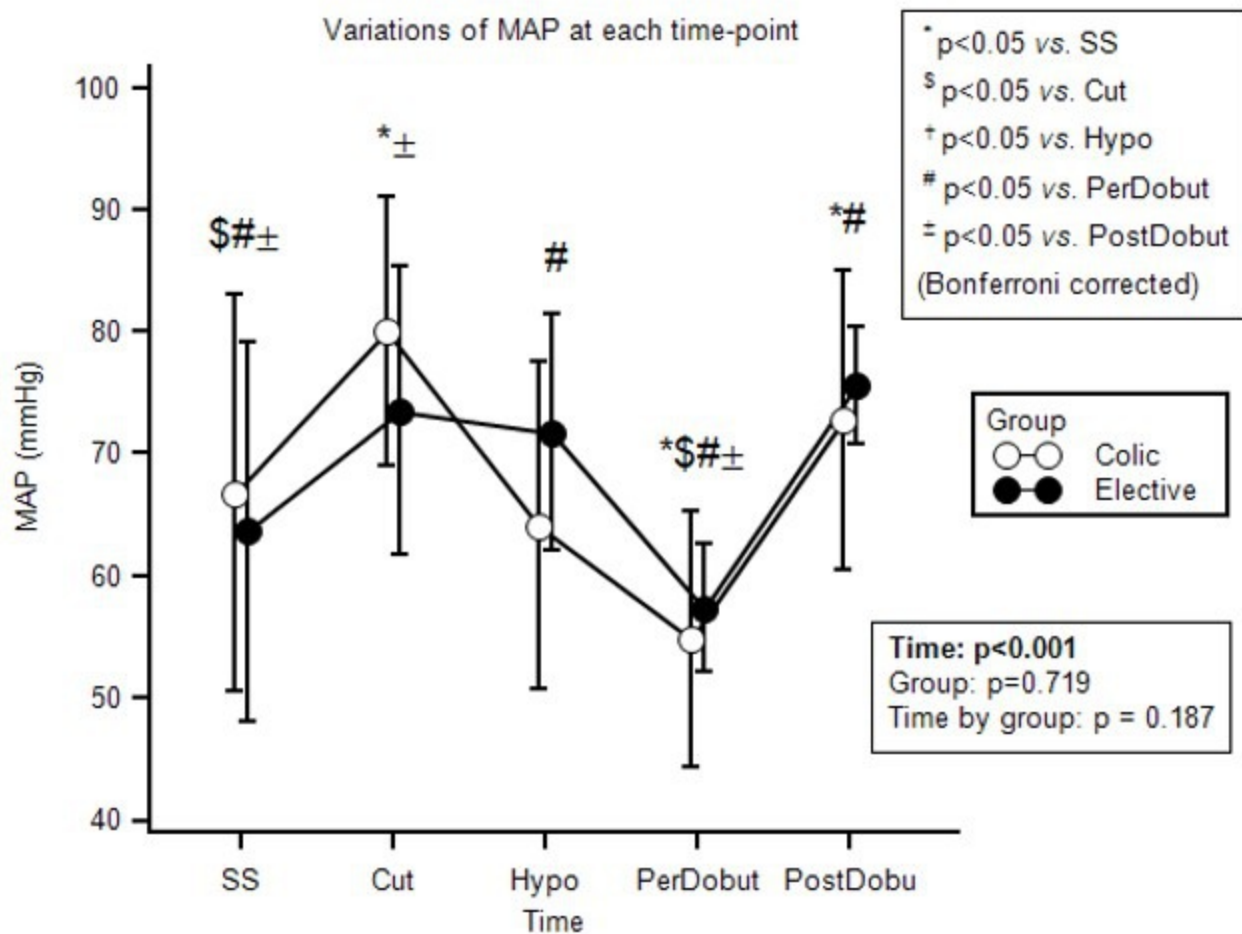




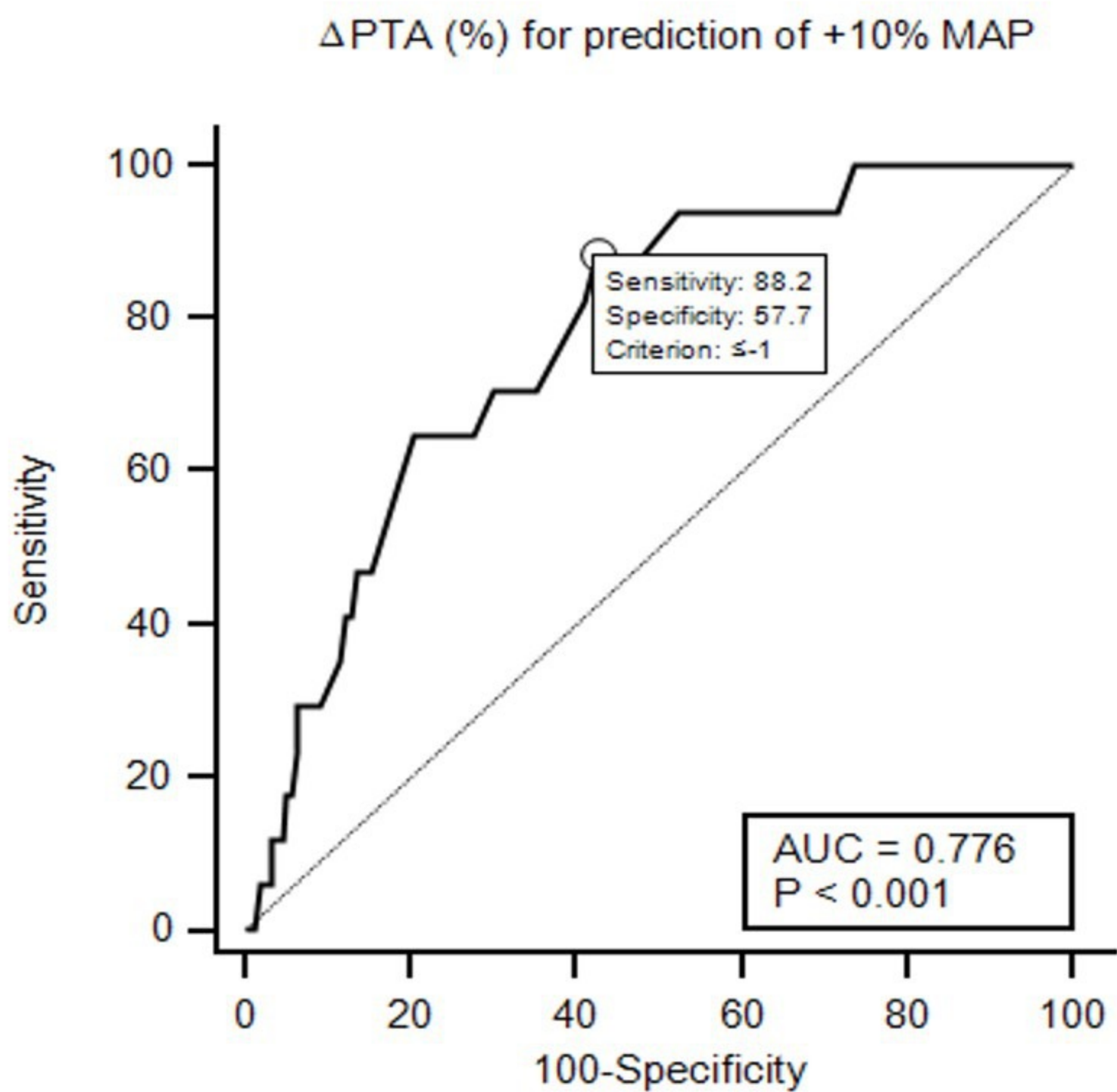
a) Variations of PTA at each time-point



b) Variations of MAP at each time-point



a)



b)

