Total Intravenous Anaesthesia (TIVA) with propofol-fentanyl and propofol-midazolam combinations in spontaneously-breathing goats

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Abstract

Objective To compare the efficacy and cardiopulmonary effects of propofol and fentanyl, with propofol and midazolam for total intravenous anaesthesia.

Study Design Prospective, randomized, crossover experimental study.

Animals Six healthy goats; 3 does and 3 wethers.

Methods Goats received either fentanyl 0.02 mg kg^{-1} (treatment FP) or midazolam 0.3 mg kg^{-1} (treatment MP) intravenously. One minute later anaesthesia was induced with propofol, then maintained by constant rate infusion of propofol 12.0 mg kg^{-1} $hour^{-1}$ and

fentanyl 0.02 mg kg^{-1} $hour^{-1}$ (treatment FP) or propofol 12.0 mg kg^{-1} $hour^{-1}$ and midazolam 0.3 mg kg^{-1} $hour^{-1}$ (treatment MP) for 90 minutes. Response to noxious stimulus was tested every 10 minutes and propofol dose adjusted to prevent purposeful movement. Cardiopulmonary parameters were measured continuously, and arterial blood-gas analysis performed intermittently. Recovery was timed and quality scored. Results are presented as median (IQR).

Results Differences in the propofol induction dose [4.00 (3.96–4.01) and 3.97 (3.91–4.00) mg kg^{-1} for treatments FP and MP, respectively] were not significant. Quality of induction in both groups was smooth. The median propofol dose for maintenance was less (p = 0.004) with treatment FP (12.0 mg kg^{-1} $hour^{-1}$) than MP (18.0 mg kg^{-1} $hour^{-1}$). Cardiopulmonary function was well maintained with both treatments. Recovery times in minutes from the end of anaesthetic infusion for treatments FP and MP respectively were; to extubation 3.0 (3.0–3.0) and 4.5 (3.3–5.0); to sternal position, 4.5 (3.3–5.0) and 5.0 (5.0–6.5) and to standing 13.0 (10.3–15.0) and 15.0 (11.3–17.3). Quality of recovery was acceptable in both groups, but abnormal behavioural signs were observed after treatment FP.

Conclusions and clinical relevance Total intravenous anaesthesia with propofol and fentanyl or propofol and midazolam, at the doses studied, in spontaneously-breathing, oxygen-supplemented goats is practicable. Recovery from the fentanyl-propofol combination is not always smooth.

Keywords goat, anaesthesia, fentanyl, midazolam, propofol, constant rate infusion

Introduction

Use of propofol as the sole agent for total intravenous anaesthesia (TIVA) is unsatisfactory, since the dosages required to eliminate responses to surgery might cause significant cardiopulmonary depression (Smith 1994). There is a paucity of information on TIVA in ruminants; however, in goats, propofol in combination with ketamine caused a degree of immobility and cardiopulmonary effects comparable to those associated with sevoflurane anaesthesia (Larenza et al. 2005).

Propofol is the most suitable of the induction drugs for administration as a constant rate infusion (CRI) due to its short context-sensitive half-time (Bettschart-Wolfensberger et al. 2000). Fentanyl, a short-acting μ opioid agonist, is used for treatment of moderate to severe pain in dogs and humans (Carroll et al. 1999). There is very little information in the literature on the use of fentanyl in goats; however, fentanyl has been reported to have a short half-life following intravenous administration to goats, thus necessitating its use by means of CRI (Carroll et al. 1999). Midazolam, a water-soluble benzodiazepine, is used as a sedative, muscle relaxant and an anticonvulsant in human patients (Cao et al. 2002). Midazolam's sedative effects are due to its agonist actions at gamma-aminobutyric acid (GABA) receptors (Cao et al. 2002). In goats, midazolam administered at 0.3 mg kg^{-1} caused clinically significant sedation and a 40% reduction in the dose of propofol required for induction of anaesthesia (Dzikiti et al. 2009)

In the present study, we assessed the anaesthetic efficacy and cardiopulmonary effects of TIVA from propofol co-administered with either fentanyl or midazolam, in goats. We tested the hypothesis that TIVA with either propofol-fentanyl or propofol-midazolam would produce similar anaesthestic and cardiopulmonary effects.

Materials and method

This study was approved by the Faculty's Animal Use and Care Committee (Protocol Number: V045/06). Six, adult, mixed-breed goats (three does and three wethers) were used. The goats were determined to be healthy based on physical examination, a complete blood count and serum biochemical analysis. The age of the goats ranged between 20.0 and 21.0 months while the weight ranged between 39.6 and 46.5 kg. Each goat was studied on two occasions, receiving each treatment in a randomized manner with a four-week washout between treatments. Food and water were withheld for 18 – 24 hours before anaesthesia.

Study protocol

Baseline rectal temperature was measured by a digital thermometer, and heart rate and respiratory rate were measured by thoracic auscultation for one minute before the goats were placed on a custom-made sling-cum-table for ease of restraint. A 24-SWG catheter (Jelco, Medex Medical Ltd, Rossendale, Great Britain) was inserted into an auricular artery and connected to a calibrated strain gauge transducer (DTX Plus transducer, BD Medical, Johannesburg, South Africa) for measurement of systolic, diastolic and mean arterial pressures. The arterial pressure readings were obtained from a multi-parameter monitor (Cardiocarp/5, Datex-Ohmeda Corporation, Helsinki, Finland), which had been calibrated against a mercury column within a month of commencement of the study. The scapulohumeral joint and the point of the sternum were used as zero reference points for transducer calibration to atmospheric pressure in sternally and laterally recumbent goats, respectively., An 18-SWG catheter (Jelco, Medex Medical

Ltd, Rossendale, Great Britain) was inserted into each cephalic vein for administration of drugs and intravenous fluids, respectively.

Fentanyl, 0.02 mg kg^{-1}, or midazolam, 0.3 mg kg^{-1}, were administered intravenously over a one minute period. The degree of sedation was assessed one minute later, immediately before the administration of propofol, using a 0 – 2 scale, where 0 = no sedation, 1 = moderate sedation: the goat assumed sternal recumbency, 2 = heavy sedation: the goat failed to maintain sternal recumbency and unable to hold its head up. Propofol was administered initially as a bolus at 2.0 mg kg^{-1} over 15 seconds and this was followed by incremental dosages at 0.5 mg kg^{-1} every 15 seconds until the goats were judged to be anaesthetized sufficently to allow placement of an endotracheal tube, as determined by presence of a weak palpebral reflex and relaxation of the jaws. Immediately after tracheal intubation, the goats were placed in left lateral recumbency and the dose of propofol required for induction recorded. The goats were then connected to a circle breathing system (Anaesthesia System, Clinicare, Crest Health Technology, Chatham, UK) with an oxygen flow rate of 2 L min^{-1}. The goats breathed spontaneously, but were to be mechanically ventilated if the end-tidal carbon dioxide partial pressure ($PE´CO_2$) increased to 55 mmHg or if the peripheral oxygen saturation (SpO_2), read from an infrared probe (describe) on the tongue, decreased below 90%. Quality of induction was scored using a 0-2 scale where: 0 = excitement, jumps or attempts to stand after becoming recumbent, unable to place orotracheal tube; 1 = slightly prolonged (>2 minutes) induction or mild excitement; 2 = smooth induction, no excitement, orotracheal intubation easy.

A CRI, of propofol (12.0 mg kg^{-1} hr^{-1}) with either with fentanyl (0.02 mg kg^{-1} hr^{-1}) (Group FP) or midazolam (0.3 mg kg^{-1} hr^{-1}) (Group MP) was started immediately after induction. Propofol for CRI was drawn up to fill a 60 mL syringe; while fentanyl or midazolam were mixed with normal saline to 60 mL in a separate syringe. The drugs

were delivered using syringe-driving pumps (Perfusor Compact, BBraun, Melsungen, Germany). The accuracy of the pumps was checked before the study by measuring the volume of solution delivered over time into a graduated cylinder. Ringer's lactate was infused at 4 mL kg^{-1} hr^{-1} by a volumetric pump (Infusomat, BBraun, Melsungen, Germany).

Instrumentation for recording of clinical parameters was set up using a multi-parameter monitor (Cardiocarp/5, Datex-Ohmeda Corporation, Helsinki, Finland). The ECG was monitored continuously using a lead II tracing. A pulse oximeter probe was placed on the tongue to estimate haemoglobin saturation and calculate heart rate. Inspired and expired partial pressures of CO_2 and oxygen were obtained from a flow sensor and a side-stream gas sampler placed between the endotracheal tube and the Y-piece of the breathing system. The flow rate through the gas sampling line was 200 mL $minute^{-1}$. Respiratory rate was calculated from the capnogram. The gas analyzer had been calibrated with calibration gas composed of 3% isoflurane in 5.0% CO_2, 55.0% O_2, 33.0% N_2O and N_2 as balance (Datex-Ohmeda Corporation, Helsinki, Finland) within a month of commencement of the studies and automatically self-calibrated to atmospheric air at the beginning of the experiment. Temperature was measured by an electronic oesophageal probe placed as close to the base of the heart as possible. This was done by marking from outside how far the temperature probe had to be placed to reach the point of the elbow. Oesophageal temperature was maintained between 37.5 and 39.5ºC using a forced warmed air blanket (Bair Hugger, Augustine Medical, Eden Prairie, USA). Clinical parameters were recorded at 3 and 10 minutes after induction and every 10 minutes thereafter.

Anaesthetic depth was assessed, by the same person, every 10 minutes, immediately after recording the cardiopulmonary parameters, by application of a noxious stimulus. The noxious stimulus consisted of clamping a claw with Vulsellum forceps, closed tightly

to the second ratchet, for 60 seconds or until purposeful movement occurred. The four claws on the two uppermost limbs were clamped consecutively in a clockwise fashion. Purposeful movement was defined as gross movement of the head or limbs. If purposeful movement occurred, the propofol infusion rate was increased by 10% and held constant for at least 10 minutes, otherwise, it was decreased by 10% and the stimulus was re-applied. In the event that the goat swallowed or moved spontaneously, a bolus of propofol (1.0 mg kg^{-1}) was to be administered.

Arterial blood samples were collected anaerobically into heparinised 1 mL syringes immediately prior to sedation (baseline), and at 3, 30 and 60 minutes after induction. Syringes were sealed and placed in ice, and analysis occurred within 30 minutes of collection. From these samples, PaO_2, $PaCO_2$, pH and bicarbonate concentration were determined by use of a pre-calibrated machine (Rapidlab ^{TM} 348 Analyser, Siemens Diagnostics, Midrand, South Africa).

Administration of anaesthestic agents was discontinued after 90 minutes and the goats were allowed to recover. The endotracheal tube was removed once the swallowing reflex was regained. Times (minutes) to extubation, sternal recumbency, and standing were recorded. All times were determined as the interval between the termination of anaesthesia and the occurrence of a particular event. Quality of recovery was scored using a 0 – 2 scale where: 0 = restlessness, 1 = relatively smooth, with some restlessness, 2 = smooth.

Statistical analysis

Data were analysed using the R statistical software (The R Foundation for Statistical Computing, Vienna, Austria). All data were assumed to be non-parametric because of the small sample size and are expressed as median and inter-quartile ranges.

Data on sedation scores, propofol induction doses, induction scores, propofol doses required for maintenance of anaesthesia, time to extubation, time to sternal position, time to standing and recovery scores were tested for statistical differences between the 2 groups using the Wilcoxon matched-pairs signed rank test.

Repeatedly measured data (cardiopulmonary parameters and arterial blood gas data) were tested for statistically significant differences between and within groups using repeated measures analysis of variance (ANOVA) by ranks. Where differences existed between groups, post-hoc (pair-wise Wilcoxon test with a Bonferroni adjustment for multiple testing) was conducted to identify any two different time points. Two arterial blood sample results (one at baseline and one at 30 minutes after induction) from Group MP were considered to be outliers, suggesting contamination of the blood sample with atmospheric air and were therefore excluded from statistical analysis. Exclusion of a data point has the advantage of narrowing the confidence interval, but it negatively impacts on statistical power as it brings in some bias which might have led to a wrong conclusion. In this instance only value is excluded on each of the two time points and hence complete case analysis is not expected to bias the results by a large extend. A value of $p<0.05$ was considered significant.

Results

The goats consistently exhibited heavy sedation following intravenous administration of either fentanyl or midazolam. The sedation scores were 2 (1.5 – 2.0) for both groups. There was no significant difference in median propofol doses for induction which were 4.00 (3.96-4.01) and 3.97 (3.91-4.00) mg kg^{-1} for Group FP and Group MP, respectively. Induction was smooth on all occasions (i.e. induction score of 2 for each goat). A median propofol dose of 12.0 mg kg^{-1} $hour^{-1}$ was required for maintenance of anaesthesia in

Group FP and this was significantly less than ($p = 0.004$) the dose of 18.0 mg kg^{-1} $hour^{-1}$ observed in Group MP. No additional boluses of propofol were required.

The cardio-respiratory data did not differ significantly between groups. Respiratory rates were statistically significantly less at all time points when compared to baseline readings in both groups. No goat required artificial ventilation as intervention for hypoventilation ($PE´CO_2 > 55$ mmHg or $SpO_2 < 90\%$). There were no significant differences between or within groups for blood-gas parameters. The oesophageal temperatures of the goats were maintained within the pre-determined range (37.5-39.5ºC) and there were no significant differences between groups at any time point. The temperature readings observed in Group FP were significantly less ($p < 0.05$) than baseline readings from 30 minutes of anaesthesia onwards, and in Group MP they were significantly less than baseline readings from 70 minutes of anaesthesia onwards (Table 1).

Copius salivation was observed in all goats, and regurgitation was observed in one goat from Group FP. Median time to extubation was 3.0(3.0-3.0) and 4.5(3.3-5.0) minutes for Group FP and Group MP, respectively. Median time to sternal position was 4.5(3.3-5.0) and 5.0(5.0-6.5) minutes for Group FP and Group MP, respectively. Median time to standing was 13.0(10.3-15.0) and 15.0(11.3-17.3) minutes for Group FP and Group MP, respectively. The scores for quality of recovery from anaesthesia were 0.5(0-2) and 2(2-2) for Group FP and Group MP, respectively; however, there was no difference ($p > 0.05$) between groups. Nevertheless, 4 out of 6 times, goats recovering from fentanyl-propofol anaesthesia showed abnormal behavioural signs such as exaggerated tail-wagging, nibbling at surrounding objects and restlessness. There were no significant differences between groups in terms of time to extubation, sternal position and standing.

Discussion

Total intravenous anaesthesia using propofol combined with either fentanyl or midazolam for induction and maintenance of general anaesthesia produced adequate immobilization of goats, although recovery from anaesthesia in Group FP was characterized by abnormal behavioural signs.

The dosages of fentanyl and midazolam were chosen because they had been shown to reduce isoflurane minimum alveolar concentration by about 30% in unpublished studies from the authors' laboratory. There is no study documenting the sedative effects of intravenously administered fentanyl in goats. Fentanyl has been administered to goats intravenously for its anti-nociceptive effects (Carroll et al. 1999), but its sedative effects were not described. Likewise, there is no information on the effect of fentanyl on the propofol induction and maintenance dose in goats. Morphine, a μ opioid agonist like fentanyl, was reported to decrease isoflurane minimum alveolar concentration by 30% after administration at 2 mg kg^{-1} as single intravenous dose (Doherty et al. 2004. Midazolam has been reported to produce sedation in goats (Stegmann & Bester, 2001; Dzikiti et al. 2009) and decrease the induction dose of propofol in goats (Dzikiti et al. 2009). In a previous study, the maximal sedative effects of midazolam were observed at 5 minutes following intravenous administration (Stegmann & Bester, 2001). Although midazolam induced heavy sedation in the present study, it was likely that the maximal effect of midazolam was not achieved by the time propofol was administered. Also, the median induction dose of propofol (3.97 mg kg^{-1}) in Group MP was greater than the mean propofol induction dose (3.2 mg kg^{-1}) previously reported after intramuscular administration of midazolam (Dzikiti et al., 2009), which is further evidence that the maximal sedative effects of midazolam were not achieved by one minute. In an earlier study by Dzikiti et al., 2009 using the same goats as in the present study, a mean

propofol dose of 5.3 mg kg^{-1} was needed for induction in non-premedicated goats and a median propofol dose of 5.1 mg kg^{-1} was reported in the study by Pablo et al., 1997. In the study reported here, propofol provided a smooth induction of general anesthesia. Similar results were also achieved in sedated goats (Dzikiti et al 2009) and even unsedated goats (Prassinos et al. 2005; Dzikiti et al 2009). Previous studies have reported adverse effects such as apnoea and myoclonus in some goats following induction of general anaesthesia with propofol (Pablo et al. 1997; Bettschart-Wolfensberger et al. 2000; Dzikiti et al. 2009). No such adverse effects were observed immediately after induction of anaesthesia in the present study.

The proposed dose of propofol for maintenance of anaesthesia (12.0 mg kg^{-1} $hour^{-1}$) proved to be sufficient to prevent purposeful movement to noxious stimulation when combined with fentanyl, but a propofol dose of 18.0 mg kg^{-1} $hour^{-1}$ was required when combined with midazolam. In retrospect, use of a higher dose of midazolam might have allowed a smaller dose of propofol to be used for maintenance of anaesthesia, since the sedative effects of midazolam have been reported to be dose-dependent (Stegmann & Bester 2001). The propofol infusion rates were chosen based on the results of a pilot study by our laboratory which showed that propofol administered at 12.0 mg kg^{-1} $hour^{-1}$ reduced isoflurane minimum alveolar requirements by about 60%. A weakness of the present study is that the plasma concentration of propofol was not measured and thus the possibility exists that there was a difference in propofol plasma concentrations between the groups. However, this is not considered likely as a randomized crossover design was used and the goats' body mass was calculated on each occasion. Increasing the propofol rate by 10% for 10 minutes appeared to increase the plasma concentration as this maneuver was effective in preventing purposeful movement on the subsequent stimulation, although the data from this study cannot substantiate that the propofol plasma concentration had changed within the 10-minute period.

Total intravenous anaesthesia with fentanyl-propofol or midazolam-propofol has minimal negative impact on cardiopulmonary function based on cardiovascular and respiratory findings of this study. Although respiratory rate decreased in comparison to baseline values in both groups during maintenance of anaesthesia, SpO_2, $PE´CO_2$, and PaO_2 remained normal throughout the anaesthetic procedure.

In the present study, recovery times were short for both groups, and consistent with data available for premedicated, goats (Dzikiti et al. 2009). Recovery from anaesthesia was smooth and uneventful in all goats recovering from midazolam-propofol anesthesia, but abnormal behavioural signs and restlessness were observed in 4 of the 6 goats recovering from fentanyl-propofol anaesthesia. The latter finding is consistent with a previous report on the effects of fentanyl in goats (Carroll et al. 1999). It might be prudent to sedate the goats with effective sedatives like midazolam during the recovery period to ameliorate fentanyl's excitatory effects. This may improve quality of recovery by calming the goat while providing more time for metabolism and excretion of fentanyl. Adverse effects such as myoclonus, that have have been reported previously in goats recovering from a single dose propofol (Dzikiti et al. 2009), were not observed in the present study probably because the goats were recovering from a lower plasma concentration of propofol, following CRI. Had the present study included a control group, in which only propofol CRI was administered and another group, in which propofol was combined with both fentanyl and midazolam CRI, answers to whether the excitatory effects of fentanyl during recovery from anaesthesia can be ameliorated by midazolam or whether myoclonus is only observed with high doses of propofol in goats could have been obtained.

The advantages of TIVA in comparison to inhalation anaesthesia include absence of pollution of working environment and requirement of minimal equipment which allows its use in remote settings (Larenza et al. 2005). Fentanyl has benefits of analgesic effects in

addition to sedation. Midazolam causes mild cardiopulmonary depression, but lacks analgesic effects (Cao et al. 2002).

The results of this study indicate that TIVA achieved by co-administration of propofol and either fentanyl or midazolam for induction and maintenance of anaesthesia in spontaneously-breathing, oxygen-supplemented goats is satisfactory, but caution must be exercised with the fentanyl-propofol combination as recovery from anaesthesia might be rough.

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Table 1 Physiological parameters [median (inter-quartile range)] during total intravenous anaesthesia with fentanyl and propofol (Group FP) or midazolam and propofol (Group MP) in goats breathing 100% oxygen.

Variable	Unit	Group	Time (minutes)					
			Baseline	3	10	30	60	90
Heart Rate	beats min^{-1}	FP	80 (80-80)	84 (81-92)	80 (67-84)	70 (61-72)	65 (56-67)	58 (56-64)
		MP	74 (72-79)	102 (97-110)	101 (94-105)	97 (87-99)	91 (85-100)	92 (83-100)
SAP	mmHg (kPa)	FP	124 (116-128) 16.5 (15.4-17.0)	109 (101-115) 14.5 (13.5-15.3)	111 (101-117) 14.7 (13.5-15.6)	104 (100-112) 13.8 (13.3-14.9)	101 (99-107) 13.5 (13.2-14.3)	104 (95-105) 13.8 (12.7-14.0)
	mmHg (kPa)	MP	120 (118-121) 15.9 (15.8-16.1)	123 (108-131) 16.4 (14.4-17.5)	113 (107-118) 15.1 (14.3-15.7)	109 (103-110) 14.5 (13.7-14.6)	109 (96-118) 14.5 (12.8-15.8)	114 (101-127) 15.1 (13.4-17.0)
DAP	mmHg (kPa)	FP	85 (70-91) 11.4 (9.4-12.1)	77(67-82) 10.3 (8.9-10.9)	81 (75-84) 10.8 (9.9-11.2)	77 (69-81) 10.3 (9.2-10.8)	72 (66-75) 9.5 (8.8-9.9)	74 (64-80) 9.9 (8.5-10.6)
	mmHg (kPa)	MP	84 (82-92) 11.2 (10.9-12.3)	98 (73-104) 13.0 (9.7-13.9)	84 (78-90) 11.2 (10.4-12.0)	79 (69-84) 10.5 (9.2-11.2)	80 (68-90) 10.7 (9.1-11.9)	85 (76-98) 11.3 (10.1-13.0)
MAP	mmHg (kPa)	FP	105 (95-110) 14.0 (12.6-14.7)	92 (84-94) 12.3 (11.1-12.5)	96 (87-100) 12.7 (11.6-13.4)	90 (85-95) 11.9 (11.3-12.7)	84 (80-91) 11.1 (10.7-12.1)	85 (80-93) 11.3 (10.7-12.3)
	mmHg (kPa)	MP	102 (97-104) 13.5 (12.9-13.8)	109 (88-116) 14.5 (11.8-15.5)	98 (92-102) 13.1 (12.3-13.7)	94 (85-95) 12.5 (11.4-12.7)	94 (81-102) 12.5 (10.8-13.5)	99 (88-111) 13.1 (11.6-14.8)
SpO_2	%	FP	-	99 (98-100)	100 (96-100)	99 (98-100)	100 (100-100)	100 (98-100)
		MP	-	100 (100-100)	100 (99-100)	99 (98-100)	99 (98-99)	99 (98-100)
f_R	Breaths min^{-1}	FP	28 (28-34)	6 (5-7)*	5 (3-6)*	6 (5-10)*	9 (6-12)*	8 (6-9)*
		MP	30 (28-30)	10 (5-17)*	13 (9-14)*	15 (13-16)*	15 (15-17)*	15 (14-18)*
$PE'CO_2$	mmHg (kPa)	FP	- -	33.5 (30.5-35.8) 4.5 (4.1-4.8)	32.0 (31.0-35.3) 4.3 (4.1-4.7)	29.5 (29.0-33.8) 3.9 (3.8-4.5)	31.0 (29.5-33.3) 4.1 (3.9-4.8)	32.0 (29.8-32.8) 4.3 (3.9-4.4)
	mmHg (kPa)	MP	- -	33.5 (30.8-34.8) 4.5 (4.1-4.6)	33.5 (31.5-35.5) 4.5 (4.2-4.7))	32.5 (32.0-33.0) 4.3 (4.2-4.4)	32.5 (32.0-34.5) 4.3 (4.2-4.6)	31.5 (30.0-35.0) 4.2 (4.0-4.7)
P_aO_2	mmHg (kPa)	FP	80 (75-105) 10.6 (9.9-14.0)	277 (271-288) 37.4 (36.2-38.5)	-	315 (307-335) 42.1 (41.0-44.7)	338 (311-356) 45.1 (41.5-47.4)	-
	mmHg (kPa)	MP	83 (82-85) 11.1 (10.9-11.3)	286 (271-293) 38.1 (36.1-39.0)	-	300 (277-305) 40.0 (37.0-40.7)	307 (299-325) 41.0 (39.9-43.4)	-
P_aCO_2	mmHg (kPa)	FP	28.8 (24.7-32.3) 3.8 (3.3-4.3)	42.7 (39.8-44.3) 5.7 (5.3-5.9)	-	38.7 (36.8-40.3) 5.2 (4.9-5.4)	38.8 (36.4-42.5) 5.2 (4.9-5.7)	-
	mmHg (kPa)	MP	32.0 (30.3-34.0) 4.3 (4.0-4.5)	33.9 (33.8-37.6) 4.5 (4.5-5.0)	-	38.7 (35.1-39.2) 5.2 (4.7-5.2)	39.8 (38.8-42.3) 5.3 (5.2-5.6)	-
pH_a		FP	7.47 (7.43-7.48)	7.34 (7.32-7.35)	-	7.38 (7.36-7.39)	7.39 (7.39-7.39)	-

		MP	7.43 (7.43-7.44)	7.36 (7.34-7.38)	-	7.35 (7.34-7.37)	7.36 (7.33-7.38)	-
HCO_3^-	mmol L^{-1}	FP	20.8 (17.5-21.2)	21.6 (21.0-22.5)	-	22.5 (22.3-23.0)	23.3 (22.8-24.0)	-
		MP	22.6 (22.0-23.8)	18.9 (17.9-21.1)	-	22.2 (21.4-22.9)	22.2 (21.2-22.5)	-
Temp	(ºC)	FP	39.1 (38.9-39.4)	38.8 (38.7-38.8)	38.6 (38.5-38.6)	38.4 (38.3-38.5)	38.2 (38.1-38.4)	38.1 (38.0-38.3)
		MP	39.2 (39.2-39.6)	38.8 (38.6-39.1)	38.8 (38.6-39.1)	38.8 (38.5-39.0)	38.6 (38.3-39.1)	38.5 (38.1-39.0)

*: significantly different ($p<0.05$) from baseline reading within group