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Temporal and concentration effects of isoflurane anaesthesia on intestinal tissue oxygenation and perfusion in horses

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ABSTRACT

The aim of this study was to assess the effect of duration of anaesthesia and concentration of isoflurane on global perfusion as well as intestinal microperfusion and oxygenation. Nine Warmblood horses were premedicated with xylazine; anaesthesia was induced with midazolam and ketamine, and maintained with isoflurane. Horses were ventilated to normocapnia. During 7 h of anaesthesia, mean arterial blood pressures (MAP), heart rate, central venous pressure, pulmonary artery pressure, expiratory isoflurane concentration (E_TIso) and cardiac output using lithium dilution were measured; cardiac index (CI) was calculated. Intestinal microperfusion and oxygenation were measured using laser Doppler flowmetry and white-light spectrophotometry. Surface probes were placed via median laparotomy on the serosal and mucosal site of the jejunum and the pelvic flexion of the colon.

After 3 h of constant E_TIso (1.4%), E_TIso was increased in 0.2% increments up to 2.4%, followed by a decrease to 1.2% and an increase to 1.4%. The CI and MAP decreased continuously with increasing E_TIso to 40 ± 5 mL/kg/min and 52 ± 8 mmHg, respectively. Microperfusion and oxygenation remained unchanged until an E_TIso of 2.0% resulted in CI and MAP of 48 ± 5 mL/kg/min and 62 ± 6 mmHg, respectively, and then decreased rapidly. When E_TIso decreased back to baseline, CI, MAP, microperfusion and oxygenation recovered to baseline. Isoflurane concentration but not duration of isoflurane anaesthesia influenced central and intestinal oxygenation and perfusion in healthy horses. Under isoflurane, intestinal perfusion appeared to be preserved until a threshold MAP or blood flow was reached.

Introduction

In anaesthetised horses, the physiological function of the gastrointestinal tract is compromised, but information on the effect of general anaesthesia on gastrointestinal microperfusion is limited. In humans, splanchnic perfusion and oxygenation are impaired early in the course of reduced systemic O_2 transport, which might occur during anaesthesia (Gelman and Mushlin, 2004; Giglio et al., 2009), and impairment of splanchnic perfusion and/or oxygenation can contribute to alterations in intestinal motility (Buell and Harding, 1989) as well as disruption of the intestinal mucosal barrier (Fink et al., 1991), leading to septicaemia and ileus.

Laser Doppler flowmetry and radionuclide-labelled microspheres have been used to study relative changes in microvascular blood flow in the skeletal muscle of anaesthetised horses (Raisis et al., 2000; Edner et al., 2002). These studies demonstrated that inhalant anaesthesia resulted in a dose-independent decrease in skeletal muscle blood flow. However, none of the studies investigated the effects of anaesthesia on perfusion of other peripheral organs. Spectrophotometry provides information about tissue oxygenation and is used as an indirect measure of perfusion. The technique has been used to measure haemodynamic variables and oxygenation in the hooves of conscious horses (Hinckley et al., 1995) and in the skeletal muscle of anaesthetised horses (Pringle et al., 2000). Using these techniques, muscle ischaemia could be differentiated from hypoxaemia, and muscle deoxygenation associated with clinically relevant hypoxaemia was reported in anaesthetised horses.

The aim of the present study was to evaluate the effects of prolonged isoflurane anaesthesia at various concentrations on global perfusion, oxygenation, microperfusion and oxygenation of the gastrointestinal tract, using surface lightguide tissue spectrophotometry combined with laser Doppler flowmetry.

Materials and methods

Animals

The study was reviewed by the Ethics Committee for Animal Experiments of Lower Saxony, and approved (approval number 33.14-42502-04-11/0572; date of approval 1 October 2011) according to Article 8, German Animal Welfare Act (Tierschutzgesetz).

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Nine research horses weighing 546 ± 27 kg (mean ± standard deviation, SD) and aged 11 ± 5 years were used in this study. All horses had chronic, unresolved orthopaedic diseases that were refractory to treatment. Owners were informed about the study and provided their consent. General anaesthesia was induced before euthanasia. The horses were kept in box stalls and had free excess to hay and water. Eight hours before the induction of anaesthesia, horses were allowed access to water but not food. All horses were part of a terminal, experimental surgery study and were euthanased with pentobarbital 70 mg/kg (Euthadorm 400, CP-Pharma).

Anaesthesia

Premedication was with xylazine 0.8–1.1 mg/kg IV (Xylapan, Vetoquinol) and anaesthesia induced with a combination of intravenous (IV) midazolam 0.05 mg/kg (Midazolam-ratiopharm 15 mg/3 mL, Ratiopharm) and ketamine 2.2 mg/kg (Narketan, Vetoquinol). Anaesthesia was maintained with isoflurane (Isofluran, CP-Pharma) in 100% O_2. Lactated Ringer's solution (Ringer–Laktat–Lösung, B. Braun) was administered at 10 mL/kg/h.

Following the induction of anaesthesia and endotracheal intubation, horses were positioned in dorsal recumbency and ventilated immediately with a pressure limited and pressure cycled large animal ventilator (Vet.-Tec. Model JAVC 2000 J.D. Medical Distributing). Horses were ventilated using intermittent positive pressure ventilation with peak inspiratory pressure (PIP) of 25 cm H_2O. Respiratory rate (f_R) was adjusted to maintain arterial partial carbon dioxide pressure ($PaCO_2$) at 40–45 mmHg (5.3–6 kPa).

Instrumentation

Before anaesthesia, catheters were placed in both jugular veins, the right atrium and the pulmonary artery. The skin over the right and left jugular veins was clipped and aseptically prepared. After infiltration of the skin with mepivacaine hydrochloride (Scandicain 2%, AstraZeneca), a 12 G catheter (EquiCath Fastflow, B. Braun) was placed into the left jugular vein for drug administration. Two introduction ports were also placed into the right jugular vein under local anaesthesia, one at the mid-cervical region and the other close to the superior thoracic aperture. A balloon-tipped catheter (Balloon Wedge Pressure Catheter, Arrow) with a length of 160 mm was placed via the right jugular vein into the pulmonary artery to measure pulmonary artery pressure (PAP). A second balloon-tipped catheter was placed via the right jugular vein into the right atrium to measure central venous pressure (CVP). Correct placement of these catheters was verified by pressure curves as well as by transthoracic ultrasound.

After induction of anaesthesia and during the instrumentation period, the transverse facial artery was cannulated with a 20G catheter (Venocan IV Catheter, Kruuse) for invasive blood pressure monitoring and arterial blood sampling. Catheters were connected to calibrated pressure transducers (Gould Statham Transducer, PD 23 ID) via fluid-filled low compliance extension lines. The pressure transducers were positioned at the level of the sternal manubrium. Combined spectrophotometry and laser-Doppler flow probes of a micro-lightguide spectrophotometer O2C (Oxygen to See, LEA Medizintechnik) were placed via median laparotomy on the serosal surface and were inserted into the lumen on the mucosal site of the jejunum and the pelvic flexion of the colon. Probes with a penetration depth of 2.5 mm (LF2, LEA Medizintechnik) were used on the serosal site. A probe with a penetration depth of 1 mm (LF5, LEA Medizintechnik) was inserted into the lumen of the small and large intestine and placed on the mucosal site.

Measured variables

Recording and evaluation of the data started 60 min after induction of anaesthesia. Mean arterial blood pressures (MAP), PAP, CVP, heart rate (HR), f_R and expiratory isoflurane concentration (E_TIso) were measured continuously with the Cardiocap 5-monitor (Datex-Ohmeda) and recorded.

Cardiac output (CO) measurements were performed by lithium dilution (LiDCOplus Hemodynamic Monitor, LiDCO). Software to accommodate LiDCOplus for measurements in large animals (LiDCOplus V4 Vet Configuration) was installed. Blood haemoglobin and plasma Na concentration were entered into the LiDCOplus monitor. A bolus of 2.25 mmol of LiCl was delivered manually through the drug catheter into the jugular vein. The LiCl was injected 5 s after initiating measurement to allow 12 s of stable baseline measurement, as required for accurate CO calculation.

During anaesthesia, arterial blood samples were taken every 20 min and arterial pH, arterial partial O_2 pressure (PaO_2, mmHg) and $PaCO_2$, as well as haemoglobin concentrations and arterial O_2 saturation, were measured immediately after sampling (AVL995, AVL Medizintechnik). The O_2 content of arterial blood (CaO_2; mL/100 mL blood) and O_2 delivery to peripheral tissue (DO_2, mL/min) were calculated using standard equations:

$$CaO_2 = (1.34 \times [Hb] \times SaO_2) + (0.003 \times PaO_2)$$

$$DO_2 = CaO_2 \times CO$$

where [Hb] is haemoglobin concentration (g/100 mL blood), SaO_2 is % saturation of Hb with O_2, and CO is expressed in mL/min.

Tissue oxygenation and blood flow

Tissue oxygenation (sO_2 in %) and blood flow (flow) were measured by a micro-lightguide spectrophotometer (O2C) and data were sampled with 20 Hz. Measurements were performed every 20 min for at least five consecutive breaths over at least 40–50 s. Tissue depths at relevant sampling sites were confirmed by ultrasound investigation (Logiq E9, Fa. GE Healthcare; ultrasonic probe 6–15 MHz).

Experimental protocol

After 60 min of equilibration and instrumentation, six baseline measurements were performed at a stable plane of anaesthesia with E_TIso of 1.4% every 20 min over 2 h. Thereafter, isoflurane concentration was increased in 0.2% steps up to 2.4%, followed by decreases to 1.8%, 1.6% and 1.4%. Measurements were performed at the end of a 20 min equilibration period at each target isoflurane concentration. After another 60 min with constant E_TIso of 1.4% and three baseline measurements, isoflurane was reduced to 1.2% for two measurements (40 min), followed by a third period of 1 h and three measurements at E_TIso of 1.4% (Fig. 1).

The following parameters were measured every 20 min, after the target isoflurane concentration was reached: CO, MAP, CVP, PAP and HR, PaO_2 and $PaCO_2$, tissue oxygenation and tissue blood flow at the stomach, jejunum and colon (Fig. 1).

Statistical analysis

Statistical significance was set at $P < 0.05$. Analyses were carried out with commercially available statistical software (SAS, version 9.1.3; GraphPad Prism 5, GraphPad Software). For analysis of the linear model, the procedure MIXED was used. Normal distribution of model residuals of dependent variables was confirmed by visual assessment of q–q plots and by Shapiro–Wilks tests. Data are presented as means ± SD. Two-way ANOVA and Tukey's post-hoc tests were used to compare measured parameters by period of time (repeated measurements). Correlations between parameters MAP, CI, E_TIso and tissue flow were tested using Pearson correlation testing. Non-linear curve fitting was used to construct the curve that had the best fit to the data points (Fig. 4), to demonstrate correlations between tissue flow and MAP and tissue flow and CI.

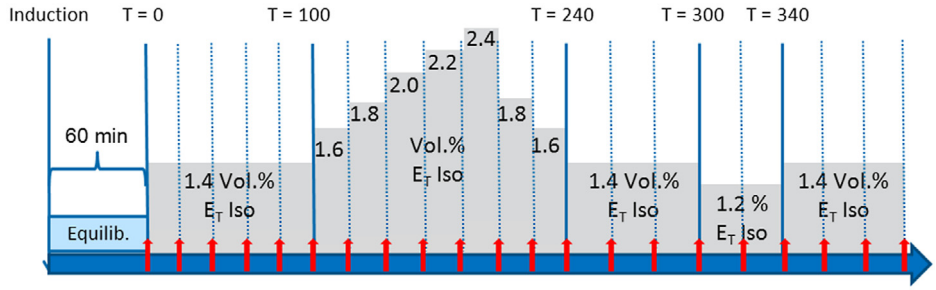

Fig. 1. Time-line of the experimental protocol. Sixty minutes after induction of anaesthesia, isoflurane concentration is increased and decreased stepwise with baseline measurements in between. The red arrows indicate time points when following parameters were measured: CO, MAP, CVP, PAP and HR, PaO_2 and $PaCO_2$, tissue oxygenation and tissue blood flow. Equilib, equilibration period.