Autonomic Neuroscience: Basic and Clinical 195 (2016) 1–7

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Influence of thoracic epidural anesthesia on gastric oxygenation during hypothermia and hemorrhage☆

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ARTICLE INFO

Article history:
Received 6 November 2015
Received in revised form 26 January 2016
Accepted 27 January 2016

Keywords:
Sympathetic nervous system
Vasopressin receptor
Microcirculation
Hemorrhage
Hypothermia

ABSTRACT

Objective: Hypothermia preserves gastric mucosal microvascular oxygenation (μHbO_2) during hemorrhagic shock. Additionally, hypothermia activates the sympathetic nervous system that leads to the release of vasopressin. The aim of this study was to evaluate whether the effect of hypothermia is mediated via the sympathetic nervous system and/or via vasopressin.

Methods: In prospective and randomized experiments on five anesthetized dogs (foxhounds, cross-over design, 6 groups with n = 5 per group) we analyzed the effects of hemorrhage on μHbO_2 during mild hypothermia (HT, 34 °C), during additional thoracic epidural anesthesia (HT/TEA) and during additional vasopressin V1 receptor blockade (HT/VB). As control groups, effects of hemorrhage were studied under normothermia alone (NT), during additional thoracic epidural anesthesia (NT/TEA) and during additional vasopressin V1 receptor blockade (NT/VB).

Results: Hemorrhage decreased μHbO_2 from 81 ± 3 to 49 ± 8%. In contrast, in the presence of hypothermia, μHbO_2 was significantly higher during hemorrhagic shock (from 79 ± 3 to 66 ± 9%) despite a similar decrease in DO_2. The effect of hypothermia on μHbO_2 was reduced in the presence of thoracic epidural anesthesia or vasopressin receptor blockade.

Conclusions: Hypothermia preserves μHbO_2 during hemorrhagic shock. This effect is partially abolished during thoracic epidural anesthesia or during vasopressin receptor blockade. The sympathetic nervous system and the vasopressin V1 receptor are partially involved in mediating the effect of hypothermia on gastric oxygenation during hemorrhage.

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1. Introduction

The gastrointestinal mucosa is an effective barrier against endotoxins and bacteria located in the intestine. Perfusion of the mucosa is vital to maintain this barrier function (Magnotti and Deitch, 2005; Russell et al., 1995; Trzeciak et al., 2008). During hemorrhagic shock, insufficient microcirculatory oxygen supply leads to an impaired mucosal barrier function and has been shown to enable translocation of bacteria and bacterial toxins into portal venous and local lymphatic circulation (Deitch et al., 2004).

In this context, we have recently shown that hypothermia reduces detrimental effects of hemorrhage on regional mucosal oxygenation (Vollmer et al., 2013b). However, the exact underlying mechanisms remain unclear.

Hypothermia leads to sympathoadrenal activation (Frank et al., 2003) and subsequently to vasopressin release to the plasma (Lipinska et al., 2004). Thus, the effects of hypothermia during hemorrhagic shock might be mediated via activation of the sympathetic nervous system with subsequent release of vasopressin.

Therefore, the aim of our study was to clarify the influence of the sympathetic nervous system (inhibition via thoracic epidural anesthesia) and the vasopressin V1 receptor on the effect of hemorrhage on gastric mucosal oxygenation under normothermia and hypothermia. This question is addressed in an animal model with healthy dogs, since this allows us to evaluate the results in the context of our previous results (Vollmer et al., 2013b), allows measurement of gastric oxygenation under hypothermia and hemorrhage (Vollmer et al., 2013b) and allows us to analyze the effects of additional thoracic epidural anesthesia (Schwarte et al., 2004) and vasopressin receptor blockade (Vollmer et al., 2013a).

Abbreviations: μHbO_2, microvascular oxygen saturation; CO, cardiac output; DO_2, systemic oxygen delivery; Hb, hemoglobin concentration; HR, heart rate; HT, hypothermia; MAP, mean arterial pressure; NT, normothermia; rHb, relative hemoglobin concentration; SaO_2, arterial oxygen saturation; SV, stroke volume; SVR, systemic vascular resistance; TEA, thoracic epidural anesthesia; VB, vasopressin receptor blockade.

☆ The study was performed with institutional funding.

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http://dx.doi.org/10.1016/j.autneu.2016.01.004
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2. Methods

2.1. Animals

The data were derived from experiments on five dogs conducted in a prospective, randomized (covariate adaptive randomization (Suresh, 2011), to avoid a similar sequence of the respective experiments in each animal) cross-over design. The dogs (female foxhounds, weight 30.4 ± 1.3 kg, age 5.2 ± 0.9 years (mean ± SEM)) were derived from the breeding facility at the Central Animal Research Facility of the Heinrich-Heine-University Dusseldorf. They were treated in accordance with NIH guidelines for animal care. Dogs are housed at the Central Animal Research Facility with free access to water, daily feeding and daily free movement in groups outdoors. Experiments were performed with the approval of the local animal care and use committee (North Rhine-Westphalia State Agency for Nature, Environment and Consumer Protection, Recklinghausen, Germany; ref. 84-02.04.2011.A288). The study is reported according to the ARRIVE guidelines (Kilkenny et al., 2010) as detailed in the Supplemental material.

Prior to the experiments, food was withheld overnight with water ad libitum to ensure complete gastric depletion and to avoid changes in perfusion and oxygenation due to digestive activity, as described in detail previously (Vollmer et al., 2013b). Each dog underwent each experimental protocol in a randomized order and served as its own control. Experiments were performed at least 3 weeks apart to prevent carryover effects. The experiments started at 8:30 a.m. in the research laboratory of the department of anesthesiology and were performed under general anesthesia (induction of anesthesia with 4 mg/kg propofol, paralyzation with rocuronium 1 mg/kg + 0.6 mg/kg/h, maintenance with sevoflurane, end-tidal concentration 3.0%, 1.5 MAC in dogs (Kazama and Ikeda, 1988)). The animals were mechanically ventilated after endotracheal intubation ($FiO_2 = 0.3$; VT = 12.5 ml/kg, a normal tidal volume for dogs (Dyson, 2012)) with the respiratory frequency adjusted to achieve normocapnia (end-expiratory carbon dioxide $etCO_2 = 4.7$ kPa), verified by continuous capnography (Capnomac Ultima, Datex Instrumentarium, Helsinki, Finland). During baseline conditions, the dogs were placed on their right side and covered with warming blankets to maintain body temperature at 38 °C (continuous arterial measurement).

2.2. Measurements

The primary endpoint in this study is mucosal oxygenation, secondary endpoints are hemodynamic parameters. The aorta was catheterized and mean arterial pressure was measured continuously while blood samples were analyzed intermittently (Rapidlab 865, Siemens Healthcare Diagnostics GmbH, Eschborn, Germany). Cardiac output was determined via transpulmonary thermodilution (PiCCO 4.2 non-US, PULSION Medical Systems, Munich, Germany) at the end of each intervention, at least every 30 min, as previously described (Vollmer et al., 2013a; von Spiegel et al., 1996). Oxygen saturation was calculated for canine blood from pO_2 and adjusted to pH and temperature (Rossing and Cain, 1966). Arterial oxygen content ($C_aO_2 =$ hemoglobin·1.34·oxygen saturation + $pO_2 \cdot 0.0031$) and systemic oxygen delivery ($DO_2 = C_aO_2 \cdot CO$) were calculated subsequently.

Heart rate (HR) was continuously measured by electrocardiography.

2.2.1. Mucosal oxygenation

Microvascular oxygen saturation (μHbO_2) and regional hemoglobin volume (rHb) of the gastric mucosa were continuously assessed by a tissue reflectance spectrophotometry (O2C, LEA Medizintechnik, Gießen, Germany), as detailed previously (Brell et al., 2005; Frank et al., 1989; Vollmer et al., 2013a).

White light (450–1000 nm) is transmitted to the tissue of interest via a micro-lightguide and the reflected light is analyzed. The wavelength-dependent absorption and overall absorption of the applied white light can be used to calculate the percentage of oxygenated hemoglobin (μHbO_2) (Kuchenreuther et al., 1996). The overall extinction of light at the hemoglobin spectra is used to estimate the relative hemoglobin content (rHb) of the examined tissue representing microvascular vessel density and vessel filling.

The probe has a measuring depth of 100–140 μm and thus measurement is limited to the mucosal tissue. In addition, vessels with a diameter larger than 100 μm lead to a total absorption of white light (Gandjbakhche et al., 1999). Thus, only the mucosal microcirculation is taken into account.

Prior to each experiment, a calibration is performed with white light. During the experiments, the hemoglobin spectra are presented on the screen ensuring sufficient signal quality.

The flexible light-guide probe is introduced into the stomach via an orogastric silicone tube and positioned facing the greater curvature (Scheeren et al., 2002), a site representing the microcirculation of other gastrointestinal mucosa regions (Temmesfeld-Wollbruck et al., 1998). In order to achieve reliable data, insertion depth of the silicone tube and the probe as well was noted and kept constant in each animal. Though this cannot exclude the presence of microcirculatory heterogeneity in the gastric region, the baseline values were similar in each experiment indicating high reproducibility. Online evaluation of the signal quality throughout the experiments allows verification of the correct position of the probe tip. The μHbO_2 values reported are the means of the last 5 min (150 spectra, 2 s each) of the respective intervention under steady state conditions. The non-traumatic instrumentation and in particular non-traumatic access to the gastric mucosa allow the determination of mucosal microcirculation in the absence of surgical stress.

2.3. Induction of hypothermia

Detailed methods on the induction of hypothermia have been reported before (Vollmer et al., 2013b). Briefly, body temperature was reduced continuously over 90 min to achieve a core temperature of 34 °C. Body temperature was continuously measured via arterial catheter. When temperature fell below 34 °C, forced-air warming was used to maintain the body temperature at 34 °C.

2.4. Thoracic epidural anesthesia (TEA)

Under general anesthesia prior to baseline conditions, the epidural space was accessed under fluoroscopy at the L5/6 inter-vertebral segment (loss-of-resistance technique, 16G Tuohy-needle, Perican, B.Braun, Melsungen, Germany) and a radiopaque epidural catheter (Perifix, B.Braun) was advanced cranially to the Th10-level, as previously described (Schwarte et al., 2004). The final position of the catheter tip was confirmed by typical epidural spread of injected radiopaque dye (2 ml ACCUPAQUETM, GE Healthcare Buchler GmbH & Co. KG, Braunschweig, Germany).

To induce TEA later in the experimental protocol, a test dose of 2 ml lidocaine (Lidoject® 1%, HEXAL AG, Holzkirchen, Germany) was administered, followed by a further 10–12 ml (adapted to animal size). TEA was maintained by continuous infusion of 6 ml/h. This dosing regimen has been proven to achieve sufficient epidural anesthesia (Schwarte et al., 2004).

2.5. Vasopressin receptor blockade (VB)

Vasopressin V1 receptor blockade was induced by intravenous infusion of 35 μg/kg of [Pmp1,Tyr(Me)2]-Arg8-Vasopressin (Peptide Institute, Inc., 4-1-2 Ina, Minoh-shi, Osaka 562-8686, Japan), a selective V1 receptor antagonist (Howl and Wheatley, 1995; Kruszynski et al., 1980), as a single dose. Complete receptor blockade was confirmed by administration of vasopressin (250 mu, [Arg8]-Vasopressin, Sigma-Aldrich) at the end of each experiment. This dose had no effect on

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