Experimental Research
Changes of local brain tissue oxygen pressure after vasopressin administration during spontaneous circulation*

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Summary

Background. Brain tissue oxygen pressure (PbtO2) correlates to cerebral blood flow (CBF) during spontaneous circulation, with one important regulator being nitric oxide (NO). Although it is established that arginine vasopressin (AVP) improves CBF and global cerebral oxygenation during cardiopulmonary resuscitation, it is unknown whether similar beneficial effects are present during spontaneous circulation. The purpose of this study was to investigate the effects of AVP with and without pre-treatment with the NO synthase inhibitor N-omega-nitro-L-arginine methyl ester (L-NAME) on local brain tissue oxygenation in a beating heart model.

Methods. Following approval of the Animal Investigational Committee, nine healthy piglets underwent general anaesthesia, and were instrumented with a probe in the cerebral cortex to measure PbtO2. Each animal was assigned to receive AVP (0.4 U·kg⁻¹), and after a wash-out period, L-NAME (25 mg·kg⁻¹ over 20 min) followed by AVP (0.4 U·kg⁻¹). After each AVP administration, nitroglycerine (25 μg·kg⁻¹ over 1 min) as a NO donor was infused to test the vascular reactivity independently from NOS inhibition.

Findings. Three minutes after administration of AVP, PbtO2 increased significantly (P < .05; mean ± SEM, 31 ± 11 versus 43 ± 14 mm Hg, +39%), compared with baseline. After pre-treatment with L-NAME, the changes of PbtO2 after AVP were not significant (32 ± 11 versus 28 ± 10, −13%) when compared with the baseline.

Conclusion. In this beating heart porcine model, local brain tissue oxygenation was improved after AVP alone, but not after inhibition of NO synthesis with L-NAME.

Keywords: Cerebral cortex; cerebral vasospasm; cerebrovascular disorders; NG-Nitroarginine methyl ester; nitric oxide; vasopressin.

Introduction

In patients undergoing cardiopulmonary resuscitation (CPR), circulating endogenous arginine vasopressin (AVP) concentrations were high, and levels in successfully resuscitated patients were significantly higher than in patients who died [14]. This may indicate that the human body discharges AVP in life-threatening situations such as cardiac arrest to preserve cardiocirculatory homeostasis. Thus, AVP has been shown to improve circulation during CPR, and haemorrhagic [30] or septic shock [18]. Focusing on cerebral circulation, AVP improves cerebral perfusion pressure (CPP), cerebral blood flow, and oxygen delivery during CPR [13], and haemorrhagic or vasodilatory shock [29, 31].

The vascular effects of AVP are heterogeneous [28]; first, activation of endothelial V1-receptors leads to vasoconstriction and therefore increases systemic vascular resistance, shifting blood to the heart and the brain. Secondly, a V1-receptor mediated release of nitric oxide (NO) can cause vasodilatation, which has been reported for coronary [16], pulmonary [5] and cerebral [26].

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Abbreviations

AVP Arginine vasopressin; CBF Cerebral blood flow; CPP Cerebral perfusion pressure; ICP Intracranial pressure; L-NAME N-omega-nitro-L-arginine methyl ester; MAP Mean arterial blood pressure; NO Nitric oxide; PbtO2 Brain tissue oxygen pressure.
arteries. During impaired circulation, this may maintain vital tissue perfusion and oxygenation, respectively, by a selective balance of regional vasoconstriction and vasodilation in regions with a high oxygen supply/demand ratio. Due to these effects, AVP may be an interesting agent in a variety of settings. For example, if AVP provokes vasodilatation in a patient with a spasm of the cerebral vasculature, the greater cerebral perfusion and oxygen delivery may be beneficial [12]. However, the effects of AVP on cerebral oxygenation during normal sinus rhythm remain unclear.

A potential method to obtain information about local cerebral oxygenation is a direct measurement of brain tissue oxygen pressure (PbtO2) [8]. During normal sinus rhythm, PbtO2 correlates to cerebral blood flow in patients with and without traumatic brain injury [4, 22], as well as in animal models of cerebral ischaemia [21]. The present experiment was designed as a pilot study to evaluate the effects of AVP on local cerebral oxygenation 1). alone, and 2). after pre-treatment with a NO-synthase (NOS) inhibitor in a porcine model of spontaneous circulation. Subsequently, nitroglycerine was used as a direct NO-donor to test the vascular reactivity independently from NOS inhibition. If the effect of AVP is mediated by endothelial NO, then this should be ameliorated or even prevented by NOS inhibition. If the mechanism of AVP administration in this setting could be better understood, possible extrapolation into clinical practice could be tested or even implemented. Our hypothesis was that AVP would improve local cerebral oxygenation compared with the baseline.

**Methods and materials**

**Surgical preparation and measurements**

This project was approved by the Austrian Federal Animal Investigation Committee, and the animals were managed in accordance with the American Physiologic Society and institutional guidelines. The study was performed according to the Ustein-style guidelines [10] on nine healthy swine (Tyrolean domestic pigs), ranging from 12- to 16-weeks of age of either gender, weighing 35 to 45 kg. Anaesthesia was used in all surgical interventions, all unnecessary suffering was avoided, and research was terminated if unnecessary pain or fear resulted. Our animal facilities meet the standards of the American Association for Accreditation of Laboratory Animal Care. The animals were fasted overnight, but had free access to water. The pigs were premedicated with azaperone (neuroleptic agent; 4 mg · kg⁻¹ im) and atropine (0.1 mg · kg⁻¹ im) 1 hr before surgery, and anaesthesia was induced with a bolus dose of ketamine (20 mg · kg⁻¹ im), propofol (1-2 mg · kg⁻¹ iv), and piritramide (30 mg iv) given via an ear vein [32]. After endotracheal intubation during spontaneous ventilation, the pigs were ventilated with a volume-controlled ventilator (Dräger, EV-A, Lübeck, Germany) with 35% oxygen at 20 breaths/min, and with a tidal volume adjusted to maintain normocapnia (PaCO2 35 to 40 mm Hg). Anaesthesia was maintained with a continuous infusion of propofol (6 to 8 ml · kg⁻¹ · hr⁻¹); muscle relaxation was provided by a continuous infusion of pancuronium (0.2 ml · kg⁻¹ · hr⁻¹). Ringer’s solution (6 ml · kg⁻¹ · hr⁻¹), and a 3% gelatine solution (4 ml · kg⁻¹ · hr⁻¹) were administered in the preparation phase. A standard lead II electrocardiogram (ECG) was used to monitor cardiac rhythm; depth of anaesthesia was controlled according to blood pressure, heart rate, and electroencephalography (Neurotrac, Engström, Munich, Germany). If cardiovascular variables or electroencephalography indicated a reduced depth of anaesthesia, additional propofol and piritramide was given. In our experience, the pigs do not respond to painful or auditory stimuli under this anaesthetic regimen when the paralysing agent is withheld, and the loading dose of ketamine and propofol subsides. Before trepanation, 5 ml local anaesthetic (bupivacaine 0.5%) was infiltrated into the skin overlying the skull between the eyes to provide additional anaesthesia. For brain access, a multiluminal probe introducer (Licox, GMS, Kiel-Miekendorf, Germany) was inserted via a 5.3 mm skull burr hole (10 mm paramedian and 10 mm cranial of the coronal suture) for measurement of PbtO2 adjusted to brain temperature, and intracranial extraparenchymal pressure (ICP; Ventrix, Integra NeuroSciences, Plainsboro, NJ, USA). Animal preparation was started with the skull preparation to allow the cerebral tissue to recover for 60 min from surgery. One 7F saline-filled catheter was advanced via femoral cut down into the thoracic aorta for measurement of aortic blood pressure, and withdrawal of arterial blood samples. A 7.5F catheter was inserted into the superior vena cava via cut down in the neck in order to measure right atrial pressure and core temperature, and for drug administration. The intravascular catheters were attached to pressure transducers (model 1290A, Hewlett Packard, Bochlingen, Germany) which were aligned at the level of the right atrium; all pressure tracings were recorded with a data acquisition system (Devetron port 2000, Graz, Austria). Body temperature was maintained between 38.0 to 39.0°C with a heating blanket. Blood gases were measured with a blood gas analyser (Rapidlab 865, Bayer, Vienna, Austria), and end-tidal carbon dioxide was measured with an infrared absorption analyser (suction rate, 200 ml/min; Sirecust 960, Siemens, Erlangen, Germany).

**Experimental protocol**

After the preparation phase, cerebral (PbtO2, Tmean, ICP, CPP) and haemodynamic (MAP, HR, PaCO2) parameters, and arterial blood gases (PaO2, PaCO2, pH) were measured, and 5000 U heparin were administered intravenously to prevent intracardiac clot formation. All parameters were in stable condition over five minutes, when the experiment was started with administration of arginine vasopressin (AVP; Pitressin®, Parke-Davis, Karlsruhe, Germany, 0.4 U · kg⁻¹), followed by measurement of the parameters after 0.5, 1, 1.5, 2, 3, 5, 8, 10, 15, 20, and 25 min. Subsequently, nitroglycerine (Nitronal®, Pohl-Boskamp, Germany, 25 µg · kg⁻¹ over 1 min) was given, followed by measurement of the parameters after 0.5, 1, 1.5, 2, 3, 5, and 10 min (= Non pre-treatment phase). After the NO-synthase inhibitor L-NAME (N-omega-nitro-L-arginine methyl ester, 25 mg · kg⁻¹) was infused during a period of 20 min, administration of AVP and nitroglycerine was repeated as described above (= Pre-treatment phase). The time intervals were selected according to the plasma half-life of AVP, L-NAME, and nitroglycerine (approx. 8 min, 25 hr, and 2 min, respectively), in order to minimise pharmacological hold over effects. At each baseline before drug administration, arterial blood gases were measured. (Fig. 1) All drugs were diluted to 10 ml with normal saline, and injected separately via the right atrial catheter followed by a 20 ml saline flush.