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 ($PbtO_2$) 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 $PbtO_2$. Each animal was assigned to receive AVP ($0.4 \, U \cdot kg^{-1}$), and after a wash-out period, L-NAME ($25 \, mg \cdot kg^{-1}$ over 20 min) followed by AVP ($0.4 \, U \cdot kg^{-1}$). After each AVP administration, nitroglycerine ($25 \, \mu g \cdot kg^{-1}$ 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, $PbtO_2$ increased significantly ($P < .05$; mean $\pm$ SEM, 31 ± 11 versus $43 \pm 14 \, mm \, Hg$, +39%), compared with baseline. After pre-treatment with L-NAME, the changes of $PbtO_2$ 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.

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.

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]

arteries. During impaired circulation, this may maintain vital tissue perfusion and oxygenation, respectively, by a selective balance of regional vasoconstriction and vaso-dilatation 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 pro-vokes 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 ($PbtO_2$) [8]. During normal sinus rhythm, $PbtO_2$ 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 reac-tivity 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 Investi-gation Committee, and the animals were managed in accordance with the American Physiologic Society and institutional guidelines. The study was performed according to the Utstein-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; $4 \, mg \cdot kg^{-1}$ im) and atropine ($0.1 \, mg \cdot kg^{-1}$ im) 1 hr before surgery, and anaesthesia was induced with a bolus dose of ketamine ($20 \, mg \cdot kg^{-1}$ im), propofol ($1–2 \, mg \cdot kg^{-1}$ 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 (Draeger, EV-A, Lübeck, Germany) with 35% oxygen at 20 breaths/min, and with a

tidal volume adjusted to maintain normocapnia ($PaCO_2$ 35 to 40 mm Hg). Anaesthesia was maintained with a continuous infusion of propofol (6 to $8 \, ml \cdot kg^{-1} \cdot hr^{-1}$); muscle relaxation was provided by a continuous infusion of pancuronium ($0.2 \, ml \cdot kg^{-1} \cdot hr^{-1}$). Ringer's solution ($6 \, ml \cdot kg^{-1} \cdot hr^{-1}$), and a 3% gelatine solution ($4 \, ml \cdot kg^{-1} \cdot hr^{-1}$) were administered in the preparation phase. A standard lead II electro-cardiogram (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 infil-trated into the skin overlying the skull between the eyes to provide additional anaesthesia. For brain access, a multiluminal probe introdu-cer (Licox, GMS, Kiel-Mielkendorf, Germany) was inserted via a 5.3 mm skull burr hole (10 mm paramedian and 10 mm cranial of the coronary suture) for measurement of $PbtO_2$ adjusted to brain tempera-ture, 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 caval 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, Böblingen, Germany) which were aligned at the level of the right atrium; all pressure tracings were recorded with a data acquisition system (Dewetron 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 ($PbtO_2$, T_{brain}, ICP, CPP) and haemodynamic (MAP, HR, $P_{et}CO_2$) parameters, and arterial blood gases (PaO_2, $PaCO_2$, 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, $0.4 \, U \cdot kg^{-1}$), fol-lowed 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, $25 \, \mu g \cdot kg^{-1}$ 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, $25 \, mg \cdot kg^{-1}$) was infused during a period of 20 min, administration of AVP and nitro-glycerine 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.
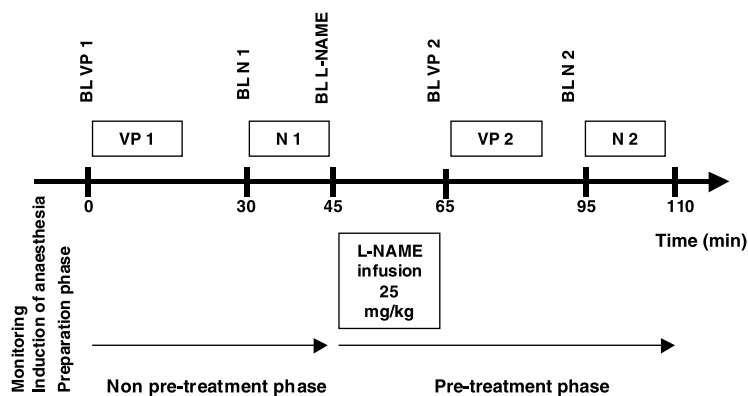
Fig. 1. Experimental protocol. *BL*: Baseline; *VP 1*: 1st Vasopressin $0.4 \, U \cdot kg^{-1}$; *N 1*: 1st Nitroglycerine $25 \, \mu g \cdot kg^{-1}$; *VP 2*: 2nd Vasopressin $0.4 \, U \cdot kg^{-1}$; *N 2*: 2nd Nitroglycerine $25 \, \mu g \cdot kg^{-1}$

After finishing the experimental protocol, the animals were euthanised with an overdose of propofol, fentanyl, and potassium chloride. All pigs were then subjected to necropsy to check for correct positioning of the catheters, and damage to internal organs.

Statistical analysis

The Kolmogorov-Smirnov test was performed to assess the distribution of the data. One way analysis of variance for repeated measures with post hoc Bonferroni correction was used to determine statistical significance of cerebral and haemodynamic variables, as well as blood gases; values are expressed as mean ± SEM. Statistical significance was considered at $P < .05$.

Results

Baseline values of $PbtO_2$, brain temperature, and end-tidal CO_2 did not differ significantly either before the first AVP, first nitroglycerine, L-NAME, second AVP, or second nitroglycerine administration. Baseline values of PaO_2, $PaCO_2$, and pH were comparable before each drug administration, respectively (Tables 1, 2).

After AVP without L-NAME pre-treatment, CPP (calculated by MAP minus ICP) increased significantly ($P < .001$), compared to baseline (Fig. 2), and also

Table 1. *Haemodynamic and cerebral variables at baseline, during administration of vasopressin, and nitroglycerine, respectively, before and after pre-treatment with L-NAME*

	BL VP		3′ VP	8′ VP	BL N	1′ N	3′ N	BL L-NAME
$PbtO_2$, mm Hg	BL 1	BL VP						
Before pre-treatment	30 ± 11	31 ± 11	43 ± 14*	37 ± 12*	34 ± 11	34 ± 11	35 ± 11	33 ± 11
After L-NAME pre-treatment	32 ± 11		28 ± 10	29 ± 10	33 ± 10	32 ± 9	34 ± 8	–
MAP, mm Hg								
Before pre-treatment	87 ± 3		160 ± 6†	142 ± 7†	105 ± 4	88 ± 4	98 ± 4	106 ± 3
After L-NAME pre-treatment	135 ± 4§		174 ± 4†	153 ± 10*	127 ± 5	98 ± 7‡	117 ± 6	–
ICP, mm Hg								
Before pre-treatment	12 ± 1		11 ± 1	12 ± 1	13 ± 1	15 ± 2	13 ± 1	14 ± 1
After L-NAME pre-treatment	13 ± 1		13 ± 1	12 ± 1	13 ± 1	18 ± 2‡	14 ± 1	–
CPP, mm Hg								
Before pre-treatment	75 ± 3		148 ± 6*	130 ± 7*	92 ± 4	74 ± 5‡	85 ± 4	92 ± 3
After L-NAME pre-treatment	122 ± 4§		161 ± 3*	140 ± 9*	114 ± 5	80 ± 6‡	103 ± 5	–
HR, beats/minute								
Before pre-treatment	92 ± 4		90 ± 2	94 ± 2	90 ± 2	103 ± 5	98 ± 6	94 ± 3
After L-NAME pre-treatment	93 ± 3		86 ± 7	89 ± 2	102 ± 6	106 ± 4	101 ± 4	–
$P_{et}CO_2$, mm Hg								
Before pre-treatment	39 ± 1		23 ± 1†	35 ± 1*	39 ± 0	39 ± 0	39 ± 1	40 ± 1
After L-NAME pre-treatment	39 ± 1		21 ± 1†	31 ± 2*	40 ± 1	42 ± 1	40 ± 1	–
T_{brain}, °C								
Before pre-treatment	39 ± 0		39 ± 0	39 ± 0	39 ± 0	39 ± 0	39 ± 0	39 ± 0
After L-NAME pre-treatment	39 ± 0		39 ± 0	39 ± 0	39 ± 0	39 ± 0	39 ± 0	–

Values are mean ± SEM. *BL VP* indicates measurement before vasopressin (*BL 1* indicates $PbtO_2$ baseline 5 min before *BL VP*); *3′VP* 3 min after vasopressin; *BL N* before nitroglycerine; *1′ N* 1 min after nitroglycerine administration, respectively; *BL L-NAME* before L-NAME infusion. *$P < .05$ vs. BL VP; †$P < .001$ vs. BL VP; ‡$P < .05$ vs. BL N; §$P < .05$ vs. BL L-NAME.

Table 2. *Baseline values of arterial blood gases*

	Baseline				
	VP1	N1	L-NAME	VP2	N2
PaO$_2$, mm Hg	151 ± 7	140 ± 4	134 ± 8*	142 ± 6	137 ± 6
PaCO$_2$, mm Hg	38 ± 1	40 ± 1	40 ± 1	39 ± 1	40 ± 1
pH, arterial	7.49 ± 0	7.43 ± 0	7.44 ± 0	7.47 ± 0	7.38 ± 0

Values are mean ± SEM. *VP1* indicates measurement before first vasopressin administration; *N1* first nitroglycerine; *L-NAME* L-NAME infusion; *VP2* second vasopressin; *N2* second nitroglycerine administration. *$P < .05$ vs. VP1.
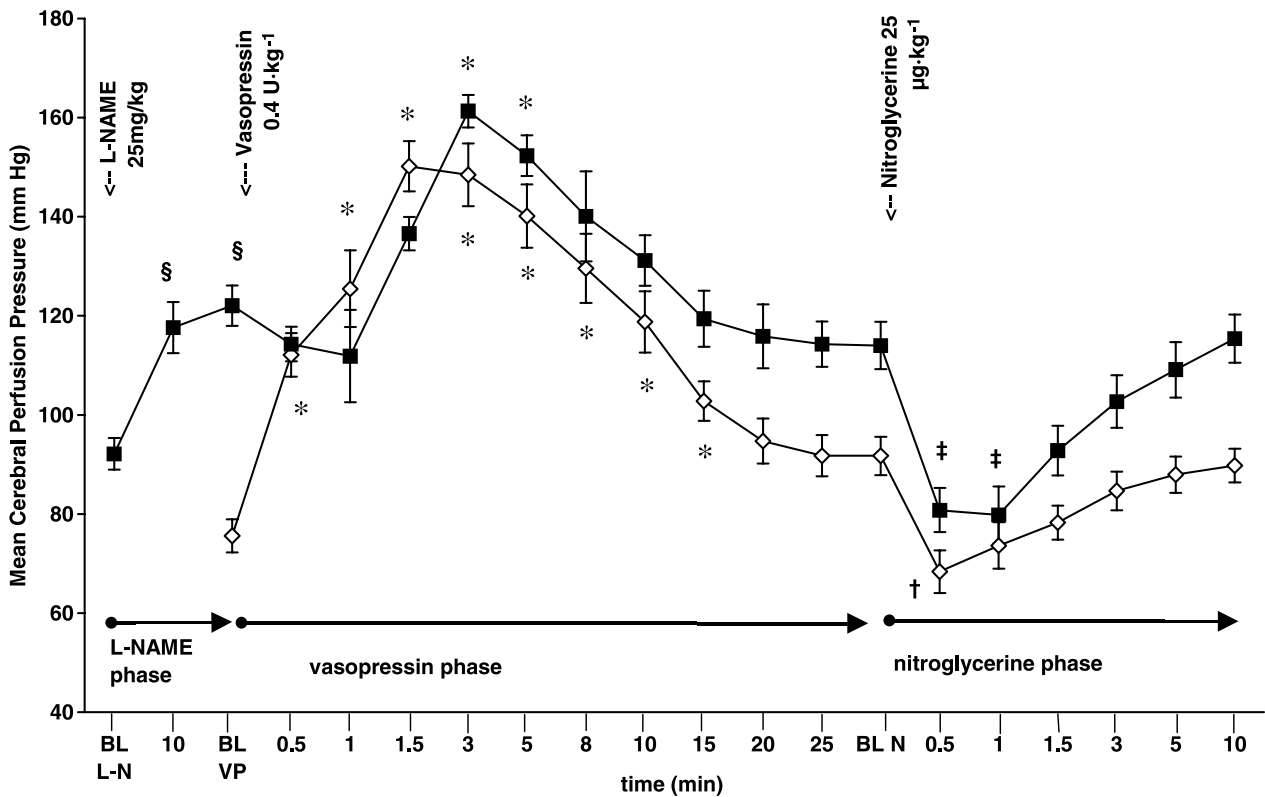

Fig. 2. CPP (mm Hg) after vasopressin with (-■-) and without (-◇-) pre-treatment with the NOS inhibitor L-NAME. *BL*: Baseline; *L-N*: L-NAME; *VP*: Vasopressin; *N*: Nitroglycerine. Data are given as mean ± SEM. *$P < .001$ vs. BL VP; †$P < .05$ vs. BL N; ‡$P < .001$ vs. BL N; §$P < .01$ vs. BL L-NAME. Note that the timeline is not subject to scale, and the y-axis does not start at zero

resulted in a significant ($P < .05$) long-lasting increase of PbtO$_2$, compared to baseline (Fig. 3). CPP decreased initially after nitroglycerine ($P < .05$), and then returned to baseline values (Fig. 2). There were no significant changes of PbtO$_2$ after nitroglycerine without L-NAME pre-treatment. During pre-treatment with L-NAME, mean CPP increased significantly ($P < .01$; Fig. 2), with no changes of PbtO$_2$ during this phase (Fig. 3). After pre-treatment with L-NAME, AVP again increased CPP significantly ($P < .001$), compared to baseline (Fig. 2), while PbtO$_2$ showed no significant differences when

compared to baseline (Fig. 3). CPP decreased initially after nitroglycerine ($P < .05$), and then returned to baseline values (Fig. 2). There were no significant changes of PbtO$_2$ after nitroglycerine with L-NAME pre-treatment.

Nitroglycerine increased ICP significantly ($P < .001$) after pre-treatment with L-NAME; there were no further differences in ICP whether the animals were pre-treated with L-NAME, or not (Fig. 4).

Necropsy confirmed appropriate catheter positions, and revealed no injuries of intrathoracic organs in any animal.
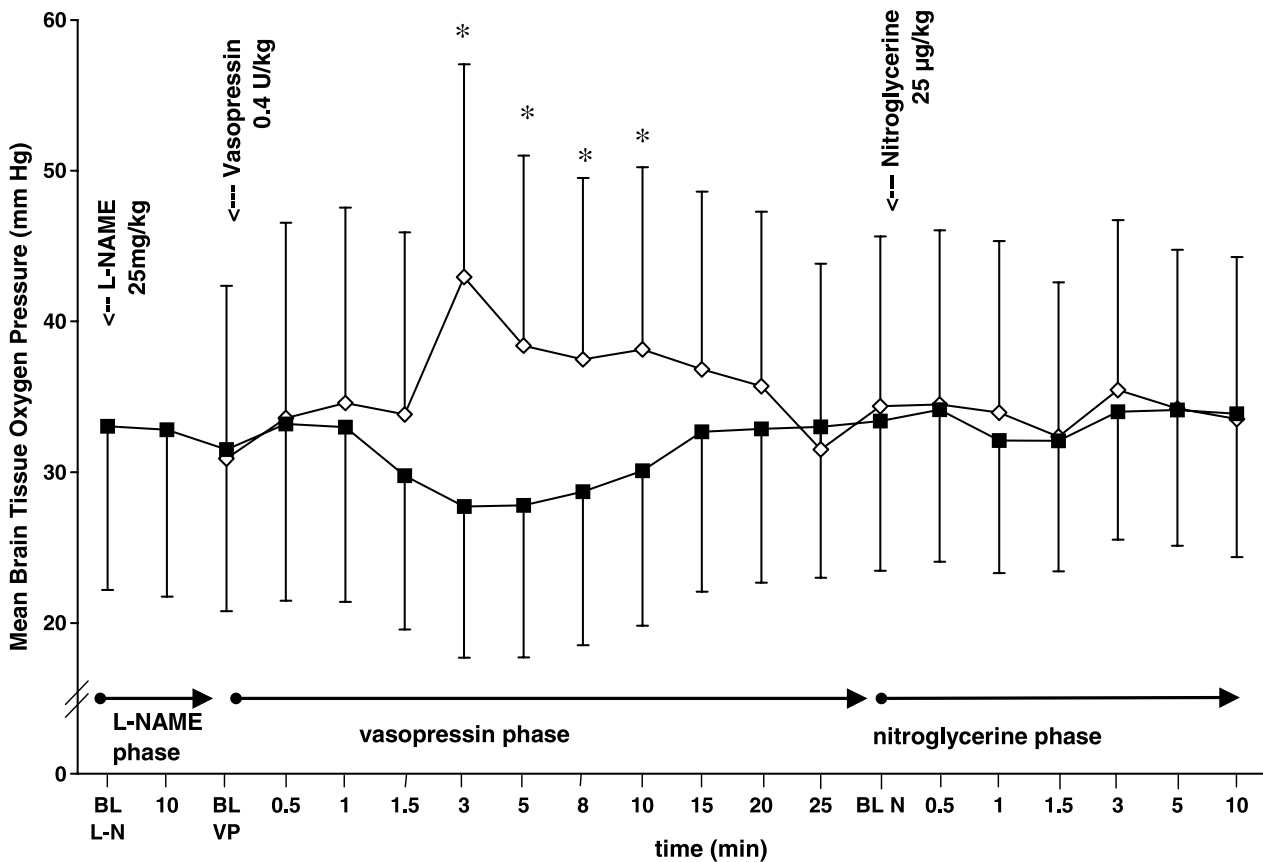
Fig. 3. PbtO$_2$ (mm Hg) after vasopressin with (-■-) and without (-◇-) pre-treatment with the NOS inhibitor L-NAME. *BL*: Baseline; *L-N*: L-NAME; *VP*: Vasopressin; *N*: Nitroglycerine. Data are given as mean ± SEM. $^*P < .05$ vs. BL VP. Note that the timeline is not subject to scale

Discussion

Similar to the finding that AVP improves global cerebral oxygenation during cardiopulmonary resuscitation (CPR) [13, 20], we were able to show that AVP improved local PbtO$_2$ during spontaneous circulation.

The reported effects of AVP on the cerebral vasculature are heterogeneous; some investigators showed an increase of cerebral vascular resistance by vasoconstriction due to AVP similar to the peripheral vascular bed [6, 7], others found evidence that AVP mediates vasodilatation [1, 17, 26]. Importantly, the results showed differences in both regional and species-dependent sensitivity, and responsiveness of the cerebral vasculature. For instance, AVP provoked vasodilatation of large cerebral vessels, but increased resistance of small cerebral vessels [24]. Furthermore, the vasodilatory effect of AVP in the major cerebral arteries might be dose-dependent [25], and might even shift to vasoconstriction, if the concentration of AVP is increased [27]. These heterogeneous effects may also be explained by the underlying mechanism of action of AVP. Pre-treatment with an unspecific NO synthase (NOS) inhibitor abolished the vasodilatory response to AVP, and suggests that cerebral arteries are able to dilate via an AVP-mediated release of endothelial NO. This is in accordance with our findings that AVP alone improved local PbtO$_2$, but had no effect or even decreased PbtO$_2$ after inhibition of NO synthesis with L-NAME; in particular, since AVP increased CPP with and without L-NAME in a comparable fashion. Furthermore, we did not observe an increase of PbtO$_2$ during the phase of L-NAME pre-treatment, even though CPP increased significantly. This is in agreement with both animal and human studies which have shown that infusion of a NOS inhibitor increases MAP and therefore CPP, but results in a decrease of CBF of 15–60% [19, 33]. Even though raising CPP may improve local PbtO$_2$ in a lesioned brain [23], this should have no substantial impact on our healthy infant pigs with no cerebral pathology and a fully developed [2], and postulated intact autoregulation of cerebral perfusion, with PbtO$_2$ and CBF being independent of CPP [15]. Additionally, the effects of NO, donated by nitroglycerine, on CPP
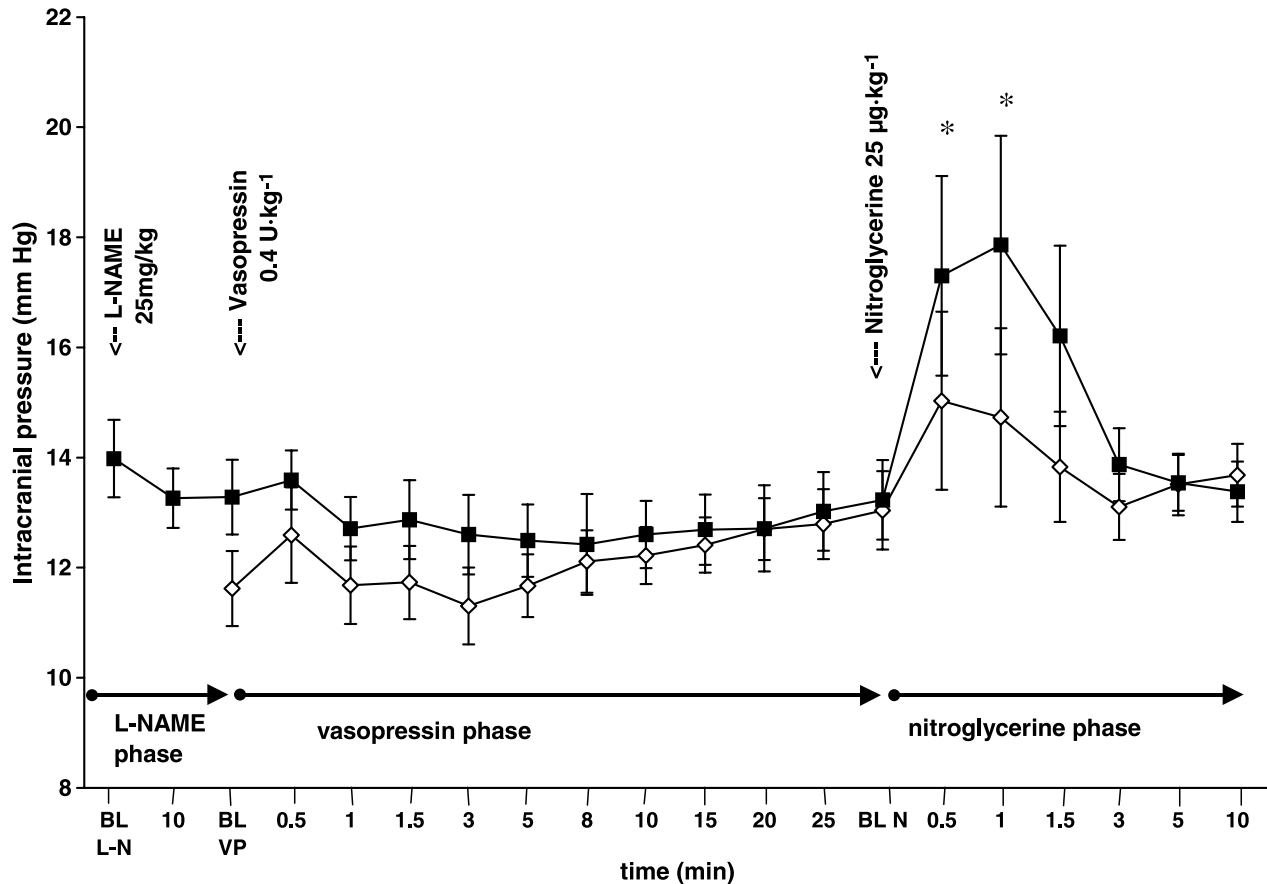
Fig. 4. ICP (mm Hg) after vasopressin with (-■-) and without (-◇-) pre-treatment with the NOS inhibitor L-NAME. *BL*: Baseline; *L-N*: L-NAME; *VP*: Vasopressin; *N*: Nitroglycerine. Data are given as mean ± SEM. *$P < .001$ vs. BL N. Note that the timeline is not subject to scale, and the y-axis does not start at zero

and PbtO$_2$ were comparable and independent of inhibition by NOS. We therefore suggest that the observed changes of PbtO$_2$ after AVP are not only due to an increased CPP, but also due to a NO-mediated vasodilatation, which results in an increased CBF as shown in other investigations [13, 20, 21].

Three isoforms of the NO generating enzyme, endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS), have been investigated so far, and a different distribution in the cerebral vasculature has been shown. With regard to the AVP effect, eNOS is predominantly found in endothelial cells which are associated with smooth muscle cells, but rarely found in pial arteries or microvessels [3]. Although we did not perform stereotactic placement of the oxygen probes in our study, these histological findings might support our results, since we have investigated an eNOS enriched region of the brain, as the tip of the probe was placed in the cortex and the oxygen sensitivity was averaged over a probe area of 13 mm^2. The changes of ICP that

were associated with administration of AVP were transient, and should have no clinical impact. The increase of ICP after nitroglycerine due to an increased CBF is known as a potential problem [11]; particularly, if the decrease of MAP due to peripheral vasodilatation is not controlled. Although we observed a transient decrease of MAP, PbtO$_2$ was not affected.

The net effect of AVP on local PbtO$_2$ during stable haemodynamic conditions may therefore result from two different mechanisms: 1). increased flow, as a consequence of dilated large cerebral vessels provoked by the release of NO from the endothelium, and 2). decreased flow in constricted small vessels.

Some limitations of this study should be noted. Different vasopressin receptors in pigs (lysine vasopressin) and humans (arginine vasopressin), may result in a different haemodynamic response to exogenously administered AVP. However, the circulatory effects of AVP, as administered in the present investigation, may be even greater in humans than in pigs. Since we were unable to

measure CBF using radioactive microspheres due to limitations posed by government regulations, we cannot comment on effects of drugs given throughout the study on cerebral perfusion. Furthermore, this study lacks dose-response data; therefore, we are unable to report whether different drug doses would have yielded other results. Hence, further investigations with clinical scenarios are needed to evaluate the benefit of different AVP doses on cerebral outcome.

Measurement of $PbtO_2$ with a probe placed in the cerebral cortex is a local method and may therefore underestimate global ischaemia due to heterogeneity of the brain. However, parameters of global cerebral oxygen supply and demand balance are limited in detecting regional differences because of mixed blood effects [8]. Additionally, especially in animal preparations, a wide range of normal $PbtO_2$ values is well known [9], because of the close relationship of tissue, vasculature, and cerebrospinal fluid. Therefore, the displayed absolute values are subjected to high standard deviations. Finally, each animal served as its own control rather than employing a separate control group; however, the schedule of drug administration was controlled to minimise previous hold over effects.

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

Acknowledgements

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Comment

This manuscript investigates the effects of vasopressin administration on tissue PO$_2$ and CPP in uninjured brains of healthy piglets. Attempting to further evaluate the mechanisms underlying observed changes, experiments were repeated following administration of L-NAME as inhibitor of NO synthetase. Vascular reactivity was further tested by administering nitro-glycerine.

The results fairly convincingly demonstrate an increase in PbtO$_2$ following vasopressin administration, which can be blocked by pre-treatment with L-NAME. The observed increase is accompanied by a rise of CPP. Interpretation of the results is however not so simple.

Several limitations of the study are acknowledged by the authors, including the absence of actual CBF measurements. Furthermore it is regrettable that only one baseline value is presented and evidence is lacking on the stability of PbtO$_2$ prior to initiating the experimental protocol. This is particularly relevant as a "run in time" has been reported in the use Licox catheters, during which period PbtO$_2$ increases to stable levels. Whether the observed increase in PbtO$_2$ actually should be considered beneficial to the brain is doubtful, as the occurrence of vasodilation in cerebral arterioles may have increased the "catchment area" of the probe, and led to higher averaged values. The additional value of administering nitro-glycerine is not clear, particularly as the half life of vasopressin (as stated by the authors) is 8 minutes, and thus reversal of an effect of vasopressin is not to be expected.

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