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## Arginine vasopressin reduces intestinal oxygen supply and mucosal tissue oxygen tension

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Departments of <sup>1</sup>Anesthesiology and Critical Care Medicine, <sup>2</sup>General Surgery, and <sup>3</sup>Biostatistics and Documentation, Innsbruck Medical University, Innsbruck; and <sup>4</sup>Department of Anesthesiology and Critical Care Medicine, Krankenhaus der Barmherzigen Schwestern Ried, Ried, Austria.

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**Knotzer, H., W. Pajk, S. Maier, R. Ladurner, A. Kleinsasser, V. Wenzel, M. W. Dünser, H. Ulmer, and W. R. Hasibeder.** Arginine vasopressin reduces intestinal oxygen supply and mucosal tissue oxygen tension. *Am J Physiol Heart Circ Physiol* 289: H168–H173, 2005. First published March 11, 2005; doi:10.1152/ajpheart.01235.2004.— We investigated intestinal oxygen supply and mucosal tissue  $P_{O_2}$  during administration of increasing dosages of continuously infused arginine vasopressin (AVP) in an autoperfused, innervated jejunal segments in anesthetized pigs. Mucosal tissue  $P_{O_2}$  was measured by employing two Clark-type surface oxygen electrodes. Oxygen saturation of jejunal microvascular hemoglobin was determined by tissue reflectance spectrophotometry. Microvascular blood flow was assessed by laser-Doppler velocimetry. Systemic hemodynamic variables, mesenteric venous and systemic acid-base and blood gas variables, and lactate measurements were recorded. Measurements were performed at baseline and at 20-min intervals during incremental AVP infusion ( $n = 8$ ; 0.007, 0.014, 0.029, 0.057, 0.114, and 0.229  $IU \cdot kg^{-1} \cdot h^{-1}$ , respectively) or infusion of saline ( $n = 8$ ). AVP infusion led to a significant ( $P < .05$ ), dose-dependent decrease in cardiac index (from  $121 \pm 31$  to  $77 \pm 27$   $ml \cdot kg^{-1} \cdot min^{-1}$  at 0.229  $IU \cdot kg^{-1} \cdot h^{-1}$ ) and systemic oxygen delivery (from  $14 \pm 3$  to  $9 \pm 3$   $ml \cdot kg^{-1} \cdot min^{-1}$  at 0.229  $IU \cdot kg^{-1} \cdot h^{-1}$ ) concomitant with an increase in systemic oxygen extraction ratio (from  $31 \pm 4$  to  $48 \pm 10\%$ ). AVP decreased microvascular blood flow (from  $133 \pm 47$  to  $82 \pm 35$  perfusion units at 0.114  $IU \cdot kg^{-1} \cdot h^{-1}$ ), mucosal tissue  $P_{O_2}$  (from  $26 \pm 7$  to  $7 \pm 2$  mmHg at 0.229  $IU \cdot kg^{-1} \cdot h^{-1}$ ), and microvascular hemoglobin oxygen saturation (from  $51 \pm 9$  to  $26 \pm 12\%$  at 0.229  $IU \cdot kg^{-1} \cdot h^{-1}$ ) without a significant increase in mesenteric venous lactate concentration ( $2.3 \pm 0.8$  vs.  $3.4 \pm 0.7$  mmol/l). We conclude that continuously infused AVP decreases intestinal oxygen supply and mucosal tissue  $P_{O_2}$  due to a reduction in microvascular blood flow and due to the special vascular supply in the jejunal mucosa in a dose-dependent manner in pigs.

mucosal oxygen delivery; microcirculatory blood flow; Clark-type surface oxygen electrodes; reflectance spectrophotometry; jejunum

MUCOSAL CELLULAR FUNCTION is maintained by the microcirculation, which is responsible for an adequate oxygen delivery, nutrient supply, and waste removal system. Alterations in the mucosal microcirculation can result in decreased mucosal oxygenation, which, in turn, may predispose in severe tissue injury. Insufficient oxygen supply, particularly to the gastrointestinal mucosa, may result in tissue injury, mucosal barrier failure, and subsequent translocation of bacteria and endotoxins. These events may cause, or maintain, a systemic inflam-

matory response that is believed to initiate and/or perpetuate multiple organ dysfunction syndrome (1, 29).

The response of the splanchnic circulation to different systemic shock states is a vascular spasm, disproportionate to that of the systemic vasculature. This profound splanchnic vasoconstriction is mediated by an increase in sympathetic nervous system activity, activation of the renin-angiotensin system, and vasopressin (30). Arginine vasopressin (AVP) is a peptide hormone released from the posterior pituitary. Its primary function in the body is to regulate extracellular fluid volume by affecting renal handling of water. In addition, AVP increases mean arterial blood pressure by stimulation of vasopressin type 1 ( $V_1$ ) receptors. Because of its potent vasoconstrictor effect, AVP has made its way into the management of vasodilated states in critical care and emergency medicine (6, 20, 33).

Systemic hemodynamic effects of AVP administration have been investigated in several studies (7, 8, 28). Several negative aspects of AVP therapy were published (3, 21, 32), and it was shown that AVP causes a considerable reduction of intestinal blood flow (10, 19, 35, 38). Reports on gastrointestinal tissue oxygen supply are scarce, and little is known whether AVP causes reductions in mucosal tissue  $P_{O_2}$  ( $P_{O_{2\text{ muc}}}$ ) and increases the risk of ischemic injury in a dose-dependent manner. This is especially important because small dosages of AVP infusion may be beneficial (13, 26, 31), whereas large doses may have detrimental effects on the microcirculation. If the optimal strategy of an AVP infusion could be identified, both treatment success and patient safety may be improved.

The purpose of this study was to investigate effects of increasing dosages starting below and ending above the commonly used infusion rate of 2–4 IU/h AVP (6, 8) on jejunal tissue oxygen supply and jejunal microvascular blood flow in pigs. We hypothesized that there would be a significant decrease in intestinal oxygen supply and  $P_{O_{2\text{ muc}}}$  in high dosages of AVP, whereas there would be little or no effect in low to moderate dosages of AVP compared with control animals.

### MATERIALS AND METHODS

**Anesthesia and animal instrumentation.** The experimental protocol was approved by the Federal Ministry of Science and Research (Vienna, Austria). Sixteen domestic pigs (40–50 kg) were made to fast for 12 h but had free access to water. After the induction of anesthesia with ketamine hydrochloride (20 mg/kg im), animals were intubated and mechanically ventilated with a positive end-expiratory

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pressure of 5 mmHg. Tidal volume and respiratory frequency were adjusted to maintain a  $P_{CO_2}$  of 35–45 mmHg at baseline; the fractional inspiratory oxygen concentration was set at 0.3. Anesthesia was maintained using a continuous infusion of midazolam ( $0.5 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ) and fentanyl ( $10 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ). If hemodynamic variables or clinical evaluation indicated an inadequate depth of anesthesia, an additional bolus of midazolam and fentanyl was administered. All animals were infused with Ringer lactate solution and modified gelatine (mol wt 22,600; Braun; Melsungen, Germany) to keep central venous pressure between 10 and 12 mmHg constant throughout the experiment. After preparation of the right carotid artery and internal jugular vein, an arterial line and a 7.5-Fr pulmonary artery catheter (Baxter; Irvine, CA) were inserted. A midline laparotomy was then performed, and a 16-gauge catheter was placed in the superior mesenteric vein for intermittent blood sampling. To expose part of the mucosa for tissue oxygenation and laser-Doppler flow measurements, a 20-cm antimesenteric enterotomy was performed in the midjejunum about 100 cm distal of the flexura duodenojejunalis. The boundary of the mucosa was sutured on an oval opening of a cork plate. The intestine was reintroduced into the abdominal cavity with the exception of the exposed mucosa. The temperature of the preparation was maintained at  $38.5^\circ\text{C}$  by covering the preparation with an acrylic glass box, including a temperature sensor and a servo-controlled heated water bath.

**Hemodynamic and blood gas measurements.** Arterial, pulmonary artery, and central venous pressure were measured using three Statham P10EZ pressure transducers (Spectramed-Statham; Bithoven, The Netherlands). Cardiac output was determined using the thermodilution method. Heart rate (HR), blood pressure, and core temperature were continuously recorded. Zero reference for all pressures was the mid-chest position. Arterial and central venous as well as mesenteric venous blood gases and acid-base status were determined using an automatic blood gas analyzer (AVL 995, AVL; Graz, Austria). Hemoglobin oxygen saturation ( $\text{HbO}_2$ ) was measured with a hemoximeter (Cooximeter, AVL). Hemoglobin concentration was assessed using the cyanmethemoglobin method. Arterial and mesenteric venous lactate was measured with a lactate analyzer based on reflectance photometry (Accusport, Boehringer-Mannheim).

**Measurements of jejunal mucosal tissue oxygenation and microvascular blood flow.** Measurement of  $\text{Po}_2$  muc and microvascular  $\text{HbO}_2$  has been described in detail in previous studies (16, 17). Briefly,  $\text{Po}_2$  muc was measured by two Clark-type multiwire surface electrodes (Eschweiler; Kiel, Germany). These electrodes were calibrated using pure nitrogen and room air in a water bath warmed to  $38.5^\circ\text{C}$ . One electrode consists of eight platinum wires, each of which with a diameter of  $15 \text{ }\mu\text{m}$ , representing an individual measuring point and one Ag-AgCl reference electrode. An Erlangen microlight guide spectrophotometer (EMPHO II, BGT; Überlingen, Germany) was used for determination of jejunal microvascular  $\text{HbO}_2$ . The measuring principle is based on the use of one illuminating and six detecting microlight guides (each  $250 \text{ }\mu\text{m}$  in diameter) and a rapidly rotating bandpass interference filter disk for the generation of monochromatic light in 2-nm steps, within the spectral range of 502–628 nm, representing 64 different wavelengths. Jejunal microvascular blood flow was assessed by laser-Doppler velocimetry (Periflux 4001, Perimed; Järfella, Sweden). Laser-Doppler measurements are based on the principle that light, scattered by moving red blood cells, undergoes a frequency shift that is proportional to the velocity of red blood cells. The Periflux 4001 uses laser light with wavelengths of 770–790 nm. A fiber-optic guidewire (PF407, Perimed) conducts laser light to the tissue and carries backscattered light to a photo detector was placed on the mucosal surface. Jejunal microvascular blood flow was recorded in arbitrary perfusion units (PU). Calibration of the laser-Doppler flowmeter device was performed by using the manufacturer's original calibration kit (Perimed). Setting of the zero value was conducted on the surface of a white compact synthetic material ( $\text{PU} = 0$ ). The second value of the calibration curve ( $\text{PU} = 250$ ) was derived by

measurement in a motility standard fluid provided by the manufacturer (Perimed). The fraction of the scattered light that is Doppler shifted in this solution is exactly  $250 \pm 5 \text{ PU}$ . Each sensor was held in place by adhesion force, generated by a surrounding thin transparent silicon rubber patch ( $\sim 2 \text{ cm}$  in diameter) that was connected to the sensor via a small polyvinyl chloride cap.

**Experimental protocol.** Baseline measurements of systemic hemodynamic variables, arterial, mesenteric venous, mixed venous blood gas analysis, and  $\text{HbO}_2$  measurements,  $\text{Po}_2$  muc, and PU were performed after animal preparation and after a 30-min recovery period. Systemic oxygen delivery, oxygen consumption, and systemic and intestinal oxygen extraction ratio were calculated. Afterward, animals were randomized into an AVP group ( $n = 8$ ) and a placebo group ( $n = 8$ ). AVP animals were infused with increasing dosages in 20-min increments of AVP (0.007, 0.014, 0.029, 0.057, 0.114, and 0.229  $\text{IU}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ), which reflects a dosing regimen below and above the clinically used AVP dose of 2–4 IU/h, equivalent to 0.029 and 0.057  $\text{IU}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  in our study (6, 8). In placebo animals, measurements were repeated at 20, 40, 60, 80, 100, and 120 min without intervention but with infusion of an equal amount of saline. Lactate determinations of arterial and mesenteric venous blood were performed at baseline and at 60 and 120 min.

**Statistical analysis.** Systemic oxygen delivery, oxygen consumption, and systemic and mesenteric oxygen extraction ratio were calculated according to standard formulas.  $\text{Po}_2$  muc and  $\text{HbO}_2$  were recorded for a period of at least 100 s. Laser-Doppler flowmetry measurements were performed for a period of 300 s. Mean values of these variables were used for statistical comparison. Shapiro-Wilk's test was used to test the normality assumption, which was fulfilled in all measurements. For systemic hemodynamic variables, oxygen transport, systemic and mesenteric venous acid-base status, blood gas variables, arterial and mesenteric venous lactate concentrations, arterial and mesenteric venous lactate concentration differences,  $\text{Po}_2$  muc,  $\text{HbO}_2$ , PU, and intestinal oxygen extraction ratio, ANOVA for repeated measurements was performed to assess differences between and within groups.  $P < 0.05$  was considered statistically significant. In the case of significant differences, further comparisons were made with paired *t*-tests within groups to baseline and between groups at individual time points. The Bonferroni-Holm procedure was used for correction of multiple comparisons. Data are presented as means  $\pm$  SD.

## RESULTS

No differences on hemodynamic, acid-base, arterial lactate, and systemic oxygen transport variables in placebo and AVP animals were observed at baseline between groups (Table 1). A significant time effect was found in HR, mean arterial blood pressure, cardiac index, systemic oxygen delivery, and systemic oxygen extraction ratio between 0.007 and 0.229  $\text{IU}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  AVP. In AVP animals, a significant decrease in HR, cardiac index, and systemic oxygen delivery was found between 0.007 and 0.229  $\text{IU}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  AVP; mean arterial pressure and systemic oxygen extraction ratio increased significantly compared with baseline measurements between 0.007 and 0.229  $\text{IU}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  AVP. Significant changes in cardiac index at 0.007 and between 0.029 and 0.229  $\text{IU}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  AVP and systemic oxygen extraction ratio between 0.057 and 0.229  $\text{IU}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  AVP were found between groups.

There were no significant differences in mesenteric venous pH,  $\text{Po}_2$ ,  $\text{Pco}_2$ , lactate, intestinal oxygen extraction ratio, and jejunal microvascular blood flow between groups at baseline (Table 2). In AVP animals, mesenteric venous  $\text{Po}_2$  decreased significantly between 0.007 and 0.229  $\text{IU}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  AVP;



Table 1. Systemic hemodynamics, arterial blood gas analysis, arterial lactate concentrations, and systemic oxygen transport in control animals and animals receiving AVP

	Time, min							P Values	
	0	20	40	60	80	100	120	Time effect	Group effect
Dose, IU·kg <sup>-1</sup> ·h <sup>-1</sup>									
Control	0	0	0	0	0	0	0		
AVP	0	0.007	0.014	0.029	0.057	0.114	0.229		
HR, beats/min								<0.001	0.165
Control	94±20	90±18	88±16	86±16	83±15	86±17	83±15‡		
AVP	86±18	80±17‡	77±17‡	74±15‡	72±15‡	70±17‡	69±15‡		
MAP, mmHg								0.021	0.621
Control	98±7	99±5	98±7	100±9	103±8	107±8‡	104±9		
AVP	96±6	99±6‡	101±6‡	100±5‡	101±9	101±4‡	102±3‡		
MPAP, mmHg								0.671	0.233
Control	25±5	25±5	25±4	25±4	26±4	26±4	26±5		
AVP	24±5	23±4	23±3	22±3	23±3	23±4	22±3		
PCWP, mmHg								0.582	0.962
Control	13±3	14±3	14±3	14±3	15±2	14±3	13±3		
AVP	14±1	14±2	14±2	14±2	14±2	13±2	14±2		
CI, ml·kg <sup>-1</sup> ·min <sup>-1</sup>								<0.001	0.039
Control	135±36	136±40*	122±31	126±37*	120±32*	114±28*	112±31‡*		
AVP	121±31	99±23‡	93±23‡	88±26‡	85±29‡	81±31‡	77±27‡		
Arterial pH								0.593	0.283
Control	7.44±0.07	7.43±0.05	7.45±0.05	7.44±0.03	7.45±0.04	7.46±0.05	7.45±0.04		
AVP	7.46±0.06	7.47±0.05	7.47±0.05	7.48±0.06	7.47±0.05	7.47±0.06	7.47±0.07		
Arterial PCO <sub>2</sub> , Torr								0.504	0.996
Control	38±3	39±2	37±2	38±2	38±1	37±3	38±2		
AVP	40±5	37±4	38±3	38±4	38±5	37±5	39±6		
Arterial lactate concentration, mmol/l								0.329	0.970
Control	2.4±0.8	NM	NM	2.2±0.7	NM	NM	2.2±0.6		
AVP	2.3±1.2	NM	NM	1.8±0.3	NM	NM	2.6±0.7		
Do <sub>2</sub> sys, ml·kg <sup>-1</sup> ·min <sup>-1</sup>								<0.001	0.055
Control	15.5±3.7	14.9±3.7	13.1±3.4	14.2±4.9	13.2±5.0	12.6±4.3	12.2±2.9‡		
AVP	13.7±3.0	11.0±2.8‡	10.6±2.8‡	10.0±2.7‡	9.7±3.1‡	9.5±3.7‡	9.1±3.4‡		
Vo <sub>2</sub> sys, ml·kg <sup>-1</sup> ·min <sup>-1</sup>								0.083	0.648
Control	4.8±1.7	4.4±2.1	4.2±1.4	4.6±1.6	4.3±1.7	4.1±1.7	4.3±1.5		
AVP	4.4±0.9	3.8±0.6	4.0±0.7	4.2±0.6	4.0±0.8	4.0±0.9	4.2±0.8		
ER <sub>sys</sub> , %								<0.001	0.044
Control	29±6	30±13	33±11	34±12	33±10*	33±10*	35±10*‡		
AVP	31±4	36±5‡	39±6‡	43±8‡§	43±6‡§	44±8‡§	48±10‡§		

Values are means ± SD. Baseline time is 0 min. To convert Torr to kPa, multiply the value by 0.1333. AVP, arginine vasopressin; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; Do<sub>2</sub> sys, systemic oxygen delivery; Vo<sub>2</sub> sys, systemic oxygen consumption; ER<sub>sys</sub>, systemic oxygen extraction ratio; NM, not measured. \*Significantly different by uncorrected post hoc group comparison ( $P < 0.05$ ); ‡significantly different by uncorrected post hoc baseline comparison; §significantly different by Bonferroni-corrected post hoc baseline comparison ( $P < 0.0026$ ).

mesenteric venous PCO<sub>2</sub> increased at 0.229 IU·kg<sup>-1</sup>·h<sup>-1</sup> AVP; mesenteric venous oxygen extraction ratio increased at 0.057, 0.114, and 0.229 IU·kg<sup>-1</sup>·h<sup>-1</sup> AVP; and jejunal microvascular blood flow decreased significantly between 0.029 and 0.229 IU·kg<sup>-1</sup>·h<sup>-1</sup> AVP compared with baseline. Mesenteric venous PO<sub>2</sub> was significantly decreased and mesenteric venous oxygen extraction ratio was significantly increased between groups.

Figure 1 shows mean jejunal PO<sub>2</sub> muc and mean jejunal HbO<sub>2</sub> in control animals and animals receiving AVP. PO<sub>2</sub> muc at baseline was 30 ± 6 mmHg for controls and 26 ± 8 mmHg for AVP animals. HbO<sub>2</sub> was 55 ± 8% in controls and 51 ± 10% in AVP animals. Both parameters decreased significantly compared with baseline and compared with placebo animals. In animals receiving AVP, PO<sub>2</sub> muc and HbO<sub>2</sub> decreased significantly between 0.007 and 0.229 IU·kg<sup>-1</sup>·h<sup>-1</sup> AVP with a minimum value of 7 ± 3 mmHg and 26 ± 13%, respectively.

## DISCUSSION

We found that continuously infused AVP decreased jejunal microvascular blood flow, jejunal microvascular hemoglobin oxygen saturation, and PO<sub>2</sub> muc at incremental dosages of intravenous AVP infusion. Interestingly, distinct decreases in PO<sub>2</sub> muc were observed at dosages of 0.029 and 0.057 IU·kg<sup>-1</sup>·h<sup>-1</sup> AVP, which reflect dosages used in vasodilated shock patients. However, we observed no significant increase in mesenteric venous lactate concentration and pH, indicating some form of dysoxia in the whole gut wall of the jejunum.

The novel aspect of the present study is the direct measurement of tissue PO<sub>2</sub> and microvascular HbO<sub>2</sub> of the jejunal mucosa during continuous AVP administration in an autoperfused, innervated jejunal segment. AVP does not only decrease gut mucosal microvascular blood flow but also attenuates jejunal PO<sub>2</sub> muc. Effects of AVP to reduce gastrointestinal blood flow via vasoconstriction have been described in previous

Table 2. Jejunal mesenteric venous blood gas analysis, mesenteric venous lactate concentration, intestinal oxygen extraction ratio, and jejunal microvascular blood flow in control animals and animals receiving AVP

	Time, min							P Values	
	0	20	40	60	80	100	120	Time effect	Group effect
Dose, IU·kg <sup>-1</sup> ·h <sup>-1</sup>									
Control	0	0	0	0	0	0	0		
AVP	0	0.007	0.014	0.029	0.057	0.114	0.229		
Mesenteric venous pH								0.104	0.349
Control	7.39±0.07	7.39±0.06	7.40±0.05	7.39±0.05	7.41±0.03	7.40±0.05	7.40±0.05		
AVP	7.38±0.05	7.39±0.05	7.39±0.06	7.38±0.06	7.36±0.06	7.36±0.07	7.33±0.06		
Mesenteric venous PO <sub>2</sub> , Torr								<0.001	0.002
Control	52±4	49±5*	49±7	49±7*	48±6*†	49±5*†	49±5*†		
AVP	49±5	43±4‡	43±6‡	41±6‡	38±4‡§	35±5‡§	34±6‡§		
Mesenteric venous PCO <sub>2</sub> , Torr								0.045	0.091
Control	44±4	45±3	44±2	44±2	43±3	43±3	44±2		
AVP	46±4	44±9	45±4	46±5	49±7	48±8	54±9‡		
Mesenteric venous lactate concentration, mmol/l								0.401	0.115
Control	2.4±0.8	NM	NM	2.3±0.7	NM	NM	2.2±0.7		
AVP	2.3±0.8	NM	NM	2.7±1.6	NM	NM	3.4±0.7		
ER <sub>mv</sub> , %								<0.001	0.022
Control	27±7	30±8	30±9	31±10	31±9	30±9	37±16*		
AVP	32±8	34±9	36±6	39±8	44±15†	47±21†	58±7‡§		
PU								0.010	0.101
Control	160±46	159±48	149±50	154±51	150±51	146±42	138±50		
AVP	133±47	140±76	136±60	105±45†	86±36†	82±35†	103±51†		

Values are means ± SD. Baseline time is 0 min. To convert Torr to kPa, multiply the value by 0.1333. ER<sub>mv</sub>, mesenteric venous oxygen extraction ratio; Pu, perfusion units. \*Significantly different by uncorrected post hoc group comparison ( $P < 0.05$ ); †significantly different by Bonferroni-corrected post hoc group comparison ( $P < 0.0026$ ); ‡significantly different by post hoc baseline comparison ( $P < 0.05$ ); §significantly different by Bonferroni-corrected post hoc baseline comparison ( $P < 0.0026$ ).

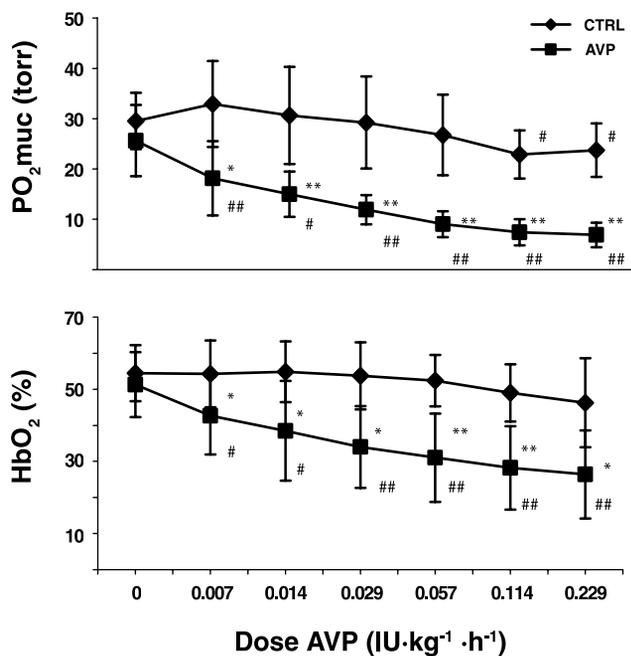


Fig. 1. Mean mucosal tissue oxygen tension (PO<sub>2</sub> muc; top) and mean microvascular hemoglobin oxygen saturation (HbO<sub>2</sub>; bottom) of the jejunum in controls (CTRL) and animals receiving arginine vasopressin (AVP). There were no significant differences in PO<sub>2</sub> muc and HbO<sub>2</sub> between groups at baseline. AVP significantly decreased PO<sub>2</sub> muc and HbO<sub>2</sub> in a dose-dependent manner compared with control animals and compared with baseline at dosages of 0.007, 0.014, 0.029, 0.057, 0.114, and 0.229 IU·kg<sup>-1</sup>·h<sup>-1</sup>. \*Significantly different by uncorrected post hoc group comparison ( $P < 0.05$ ); \*\*significantly different by Bonferroni-corrected post hoc group comparison ( $P < 0.0026$ ); #significantly different by uncorrected post hoc baseline comparison ( $P < 0.05$ ); ##significantly different by Bonferroni-corrected post hoc baseline comparison ( $P < 0.0026$ ).

investigations (9–11, 19, 38, 40). In fact, AVP has been traditionally employed to decrease perfusion of the hepatosplanchnic system in patients with bleeding esophageal varices (5). Similar to our observations, previous studies demonstrated that AVP not only reduces blood flow in a dose-dependent manner but also decreases small bowel PO<sub>2</sub> and diminishes the arteriovenous oxygen content difference in the gut (11, 22, 23, 34).

Several mechanisms may be responsible for the attenuation of PO<sub>2</sub> muc in our study: First, the PO<sub>2</sub> in a tissue is a function of 1) prevailing oxygen consumption, 2) diffusion distances from nearby capillaries or arterioles, and 3) oxygen delivery (15). Delivery of oxygen to the mucosal tissue layer, in turn, is a function of both blood flow and oxygen content of the supplied blood. In our investigation, we assume that oxygen consumption and the prevailing oxygen content were unchanged; thus the reason for the reduction in jejunal mucosal tissue oxygen supply is due to a decrease in jejunal blood flow and/or an increase in the diffusion distance, as precapillary arterioles are able to constrict completely. This evidence is confirmed by recent studies using intravital microscopy, showing a markedly vasoconstriction of arterioles in animal experiments (11, 40).

Second, in the mucosa of the small intestine, the effects of AVP on oxygen supply may also be influenced by the countercurrent exchange of oxygen within the villi (27). The circulatory anatomy of the villus is characterized by the presence of a parallel run of artery and vein within the villus. This arrangement permits shunting of oxygen from artery to vein, thereby producing a gradient in tissue PO<sub>2</sub> from the base to the apex. Tissue PO<sub>2</sub> at the base of the villus can exceed that at the apex by as much as 25 mmHg (2), indicating that the degree of shunting of oxygen is largely dependent on the blood flow

through the villus (24). A reduction in villus blood flow through AVP increases the degree of shunting and increases the oxygen gradient between the apex and the base of the villus in the small intestine.

Furthermore, our data indicate a redistribution of microcirculatory blood flow in favor of the muscularis and serosa of the jejunum. This assumption can be made as  $P_{O_2}$  of the mucosa decreased in a more distinctive way (maximum of 73% decrease from baseline) compared with jejunal microvascular  $HbO_2$  (49%) or the microcirculatory blood flow and the cardiac index (38% and 36%, respectively); in addition, we have to consider that both the laser-Doppler flowmeter and the EM-PHO II measures through the entire jejunal wall (25, 37). Therefore, these two measurement techniques detect parameters sampled from the microvasculature of the entire intestinal wall and are not restricted to the mucosal layer, whereas the  $P_{O_2}$  measured with Clark-type electrodes is limited to the villus tips and is equivalent to the oxygenation present in underlying cells because of the small catchment volume of  $\sim 25 \mu\text{m}$  in diameter of the  $P_{O_2}$  electrodes (12, 16). From this observation, it follows that AVP obviously markedly decreases villus blood flow, whereas the blood flow of the entire jejunal wall decreases to a lesser extent.

As shown in previous studies, AVP contracts precapillary arteriolar smooth muscles, which act as the final resistance vessels of the mesenteric circulation (10, 19). A recent study (11) demonstrated that a reduction in oxygen supply to the villus tip due to this vasoconstriction is accompanied by an increase in the arteriolar wall transmural  $P_{O_2}$  difference. This phenomenon indicates an increase of oxygen consumption by the muscle cells of the arteriolar wall. Therefore, less oxygen will be delivered to the villus tip of the jejunal mucosa.

Concerning hemodynamic variables and systemic oxygen transport variables, our results agree with a previous report (41). AVP at dosages of  $0.007$  to  $0.229 \text{ IU}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  decreased HR and cardiac index, whereas mean arterial blood pressure only slightly increased. This phenomenon of AVP is due to a strong reflex suppression of cardiac output, which is seen even in physiological AVP plasma concentrations (4), and demonstrates that our model reflects healthy pigs. Parallel to the decrease in cardiac index, systemic oxygen delivery decreased. Contrary to an endotoxic sheep model, we did not find that a decrease in systemic oxygen consumption indicated some degree of tissue ischemia (42). Systemic oxygen consumption remained unchanged at any AVP dose, with a concomitant increase of systemic oxygen extraction ratio over time. Additionally, we observed no increase in systemic lactate concentration as a marker of increased anaerobic metabolism.

There is a discrepancy between gastric tonometry-derived variables in vasodilated shock patients receiving AVP and our findings. In one study (6), gastrointestinal perfusion assessed by gastric tonometry was better after the initiation of AVP in such patients. However, it has to be considered that there may be differences in blood flow between the stomach and jejunum. Furthermore, gastric tonometry does not directly measure gastrointestinal perfusion and cannot be regarded as an accurate indicator of the splanchnic circulation under pathophysiological conditions (14).

Some limitations of our experiment should be noted. First, AVP is administered in healthy pigs, and we cannot conclude that the same mechanisms can be observed in a vasodilated

shock state, where the microcirculation is impaired. Second, the decrease of cardiac index due to reflex suppression of HR and concomitantly a decrease of systemic oxygen delivery was not corrected in this model.

Although our measurements were restricted to the jejunum, the probability of significant alterations in other segments of the gut mucosa is unlikely. However, AVP may have different perfusion and oxygen extraction effects in different vascular beds (39). For example, AVP induced concomitant forearm vasodilatation and digital vasoconstriction in healthy volunteers (18). Also, AVP-mediated  $V_1$  receptor stimulation can cause a vasodilatation in the rat carotid artery (36). In addition, effects of AVP on jejunal tissue oxygen supply under pathophysiological conditions like septic shock or endotoxemia are still lacking. Harmful effects of AVP on splanchnic organs may be outweighed by beneficial effects concerning patients with vasodilated shock refractory to adrenergic vasopressors (8). Finally, one has to consider that long-term effects of vasoactive drugs on jejunal and, in general, on splanchnic oxygen supply have not been investigated.

In conclusion, the present study shows that a continuous intravenous infusion of AVP decreased jejunal microvascular blood flow and jejunal mucosal tissue oxygen supply at dosages clinically administered ( $0.007$ – $0.229 \text{ IU}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ). Nonetheless, the lack of a significant change in mesenteric venous pH and lactate concentration indicates a sufficient compensatory mechanism to sustain oxygen supply by increasing intestinal oxygen extraction ratio. AVP is usually applied to patients suffering from vasodilated shock to raise systemic blood pressure and ensure an adequate tissue perfusion. This increase in blood pressure is accompanied by a reduction in microcirculatory blood flow, and our data imply that AVP may adversely affect intestinal tissue oxygenation. Further investigations will be needed to evaluate vasopressin effects on mucosal tissue oxygen supply under pathophysiological conditions.

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