

# Moderate-dose Vasopressin Therapy May Impair Gastric Mucosal Perfusion in Severe Sepsis

## A Pilot Study

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### ABSTRACT

**Background:** The effects of moderate-dose vasopressin on gastric mucosal perfusion and its relation to global and hepatosplanchnic hemodynamic and oxygen transport variables were investigated in patients with severe sepsis.

**Methods:** Vasopressin was administered at a dose of  $0.04 \text{ IU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  over 4 h in 12 patients with severe sepsis who were receiving norepinephrine. During the study period, the norepinephrine infusion rate was reduced to keep mean arterial blood pressure constant. Hepatosplanchnic blood flow, oxygen delivery, and oxygen consumption (*via* hepatic venous catheterization using the Fick principle and continuous indocyanine green infusion technique), global hemodynamics (transpulmonary thermodilution method), and the difference between the gastric mucosal and arterial carbon dioxide tension ( $\text{PCO}_2\text{-gap}$ ) were measured at baseline and 4 h after the start of the vasopressin infusion.

**Results:** The administration of  $0.04 \text{ IU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  vasopressin over 4 h was associated with minimal changes in global hemodynamics. Heart rate decreased slightly from 99 [81–115] (median [interquartile range]) to 96 [74–109] beats/min ( $P = 0.016$ ) and cardiac index from  $3.7 [2.8\text{--}4.7]$  to  $3.5 [2.7\text{--}3.6] \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  ( $P = 0.003$ ). Global oxygen delivery index decreased significantly from 461 [375–637] to 419 [352–551]  $\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  ( $P = 0.002$ ), whereas hepatosplanchnic blood flow and oxygen uptake remained unchanged. Gastric mucosal  $\text{PCO}_2\text{-gap}$  increased significantly from 13.3 [8.0–16.7] to 17.1 [10.3–28.7] mmHg

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Received from the Klinik für Anästhesiologie und Intensivtherapie, Friedrich-Schiller-Universität Jena, Jena, Germany. Submitted for publication September 23, 2010. Accepted for publication January 25, 2011. Support was provided solely from institutional and/or departmental sources.

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### What We Already Know about This Topic

- Vasopressin has been suggested as a supplementary vasopressor in patients with vasodilatory shock.
- In septic states, high-dose vasopressin has been shown to exert negative effects on global hemodynamics.

### What This Article Tells Us That Is New

- Administration of moderate vasopressin doses in severe sepsis allows norepinephrine dosages to be reduced and does not impair hepatosplanchnic perfusion. However, gastric mucosal perfusion is decreased.

( $P = 0.002$ ), suggesting that blood flow may have been redistributed away from the gut mucosa.

**Conclusions:** Vasopressin at a dosage of  $0.04 \text{ IU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  may impair gastric mucosal perfusion with minimal global hemodynamic effects.

**S**EPSIS is the 10th most common cause of death in industrialized countries, and is the leading cause of death in the intensive care unit.<sup>1</sup> Approximately 751,000 cases of severe sepsis occur annually in the United States.<sup>2</sup> A German survey in 2007 revealed that severe sepsis and/or septic shock occurred in 75,000 inhabitants (110 cases per 100,000 population) and sepsis in 79,000 inhabitants (116 cases per 100,000 population), therefore contributing to 60,000 deaths annually in Germany.<sup>3</sup> Maintenance of adequate tissue oxygen transport can be considered a primary objective in the management of patients with severe sepsis. Vasopressor therapy is a mainstay in achieving this goal. Unfortunately, global hemodynamic parameters, which represent the main target of vasopressor therapy, do not correlate with microvascular perfusion.<sup>4</sup> For this reason, assessment of the possible deleterious effects of vasopressor agents on tissue oxygenation at the microvascular level is essential.

Vasopressin has been used as a supplementary vasopressor in patients with advanced vasodilatory shock.<sup>5–9</sup> Vasopressin restores vascular tone in catecholamine-resistant shock states. This may be achieved by activation of vasopressin (V1) re-

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ceptors, modulation of potassium-adenosine triphosphate channels, modulation of nitric oxide, and potentiation of adrenergic and other vasoconstrictor agents.<sup>10</sup> Because of its vasoconstrictive effects in the splanchnic area, vasopressin has been widely used for the management of gastrointestinal bleeding in patients with cirrhosis.<sup>11,12</sup> It has not yet been determined whether the effects of vasopressin on splanchnic blood flow may be more pronounced than those of other vasoconstrictors (*e.g.*, norepinephrine) in patients with severe sepsis and septic shock.

In a previous study,<sup>13</sup> we examined the effects of high-dose vasopressin on global hemodynamics and hepatosplanchnic blood flow in sepsis when norepinephrine was replaced completely by vasopressin. We found that hepatosplanchnic blood flow was preserved despite a substantial reduction in cardiac output, but that the difference between the gastric mucosal and arterial carbon dioxide tension [ $(\text{PCO}_2\text{-gap})$ ] was increased, suggesting that gastric mucosal perfusion was impaired by high-dose vasopressin. Whether such potentially harmful effects also exist when vasopressin is used in lower doses has not yet been satisfactorily studied. It has been demonstrated that septic states cause an absolute or relative vasopressin deficiency.<sup>5,14</sup> However, it remains unclear whether vasopressin administered in lower doses to offset such a deficiency is associated with more beneficial effects than when it is used as a vasopressor.

The aim of our study was, therefore, to assess the effects of moderate doses of vasopressin on global hemodynamics, hepatosplanchnic blood flow, and gastric mucosal  $\text{PCO}_2$ .

## Materials and Methods

The study was approved by our institutional research review committee (Ethik-Kommission der FSU Jena, Jena, Germany), and informed consent was received from each patient's next of kin before inclusion. Twelve consecutive patients were included in this pilot study within 24 h of development of severe sepsis, defined according to the definition of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Criteria.<sup>15</sup>

### General Management

All patients were treated with mechanical ventilation during the study period with an inspiratory:expiratory ratio of 1:1.5, a positive end-expiratory pressure of 6–10 cm  $\text{H}_2\text{O}$ , and a constant inspired fraction of oxygen. Patients were sedated using continuous infusions of midazolam (maximum dose 9.0 mg/h) or propofol (maximum dose 300 mg/h) and sufentanil (maximum dose 75  $\mu\text{g}/\text{h}$ ). Ventilatory parameters and dose of analogosedation were kept constant during all measurements. All patients were treated with  $\text{H}_2$  receptor antagonists (ranitidine), and enteral nutrition was stopped at least 2 h before the start of the study. All patients had arterial and central venous lines in place. According to our internal intensive care unit guidelines, all patients were treated with dobutamine (2.0–6.0  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). The infusion rate

of dobutamine was not changed during the study period. The management of severe sepsis was in accordance with the guidelines of the German Sepsis Society and the German Society of Intensive Care.<sup>16</sup>

### Measurement of the Study Parameters

Radial artery pressures and central venous pressures were measured with reference to the midaxillary line (transducer 5265 039, Viggo-Spectra-med, Balthoven, The Netherlands). Cardiac output was measured using the transpulmonary thermodilution method using 15 ml of cooled (6–12 °C) saline solution and an arterial thermosensor in the femoral artery (PiCCO™ system, Pulsion Medical Systems, Munich, Germany). Blood samples for blood gas estimations were drawn in duplicate, stored on ice, and processed within 30 min. Arterial and hepatovenous oxygen tension, pH and lactate concentration (ABL 3, Radiometer, Copenhagen, Denmark), and hemoglobin and oxygen saturation (Hemoximeter Osm 3, Radiometer) were measured immediately after sampling. Global oxygen consumption ( $\text{VO}_2$ ) was calculated using a metabolic monitor (Deltatrac II, Datex-Ohmeda, Helsinki, Finland). Urine output was monitored hourly throughout the study period.

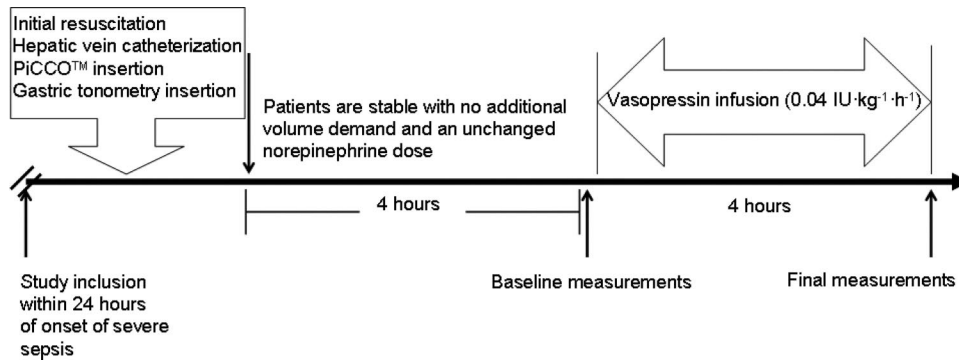
Using continuous radiologic monitoring, a 7.5-F catheter was inserted into the hepatic vein *via* the right internal jugular vein or the right femoral vein, and the position was verified radiologically. Hepatosplanchnic blood flow was evaluated by a continuous infusion of indocyanine green (ICG, Pulsion Medical Systems, Germany).<sup>17</sup> This technique enables measurement of total hepatosplanchnic venous blood flow. The dye used is a monosodium salt of ICG prepared in freeze-dried form and dissolved in sterile water. A 30-mg bolus of ICG was injected *via* the central venous line and followed by a continuous ICG infusion (30 mg/h). To keep the volume of redistribution constant, no additional fluids were infused during the measurements. ICG was assayed spectrophotometrically at 805 nm on plasma samples. For each measurement, three samples were taken from the hepatic vein catheter and arterial line at an interval of 1 min and the results of the ICG measurements were averaged. Hepatosplanchnic blood flow was calculated using the equation<sup>18</sup>:

$$\text{SBF} = C_i / (C_a - C_{iv}) \cdot (1 - \text{hematocrit})$$

where SBF is the splanchnic blood flow (l/min),  $C_i$  is the ICG concentration of infusate (mg/l), and  $C_a$  and  $C_{iv}$  are the ICG concentrations in the radial artery and hepatic vein (mg/l), respectively. Fractional splanchnic blood flow (fSBF) was calculated using the equation:

$$\text{fSBF} = \text{SBF} / \text{cardiac output} \cdot 100.$$

Oxygen content was calculated as (hemoglobin [mg/dL] · 1.39 · hemoglobin oxygen saturation) + (arterial partial pressure of oxygen [mmHg] · 0.0031). Total body and splanchnic oxygen delivery ( $\text{DO}_2$ ) rates were calculated by multiplying the



**Fig. 1.** Schematic representation of the study protocol. PiCCO™ (Pulsion Medical Systems, Munich, Germany).

arterial oxygen content with the appropriate flow parameters. Splanchnic  $\text{VO}_2$  was calculated by multiplying the hepatic venous oxygen-content difference with the appropriate splanchnic blood flow.

Gastric mucosal  $\text{PCO}_2$  was determined by air tonometry (Tonometrics catheter, 16 F, Tonocap monitor, Datex-Ohmeda, Helsinki, Finland) every 10 min. The  $\text{PCO}_2$ -gap was calculated as the difference between gastric mucosal  $\text{PCO}_2$  and  $\text{PCO}_2$  in the corresponding arterial blood sample.

### Study Protocol

Before data collection was started, all patients were stabilized by volume loading, predominantly using a balanced electrolyte solution (Jonosteril®, Fresenius Kabi, Germany), until there was no further increase in cardiac output and targeting a central venous pressure of 8 mmHg. The norepinephrine dose was increased to achieve a mean arterial pressure of at least 70 mmHg. Measurements began when the patients were stable (no additional volume demand and an unchanged norepinephrine dose for 4 h) to avoid possible confounding effects of changes in therapy and fluctuation in hemodynamic parameters (fig. 1). After baseline measurements were obtained, arginine vasopressin ( $0.04 \text{ IU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) was administered and norepinephrine dose was reduced in increments of 10% to achieve the baseline mean arterial pressure. After 4 h all measurements were repeated, and the vasopressin infusion was terminated. All measurements were taken with the patients in the supine position, and no interventions were performed during this period apart from adjustment of vasopressor dosage according to the study protocol.

### Statistical Analysis

All values are presented as median [interquartile range]. Paired data obtained before and 4 h after vasopressin infusion were compared with the Wilcoxon signed rank nonparametric test (Medcalc®, version 4.16e, Medcalc Software, Mariakerke, Belgium). All statistical tests were two-tailed and statistical significance was considered at  $P < 0.05$ .

## Results

### Characteristics of the Study Group

Twelve patients with severe sepsis were included in a consecutive series design study. Patients were between 40 and 89 yr

old with an Acute Physiology and Chronic Health Evaluation (APACHE)-II score between 18 and 36 on admission to the intensive care unit. Patient demographics, including norepinephrine and dobutamine dosages, are summarized in table 1. Administration of vasopressin ( $0.04 \text{ IU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) enabled norepinephrine dosage to be significantly reduced, from a median of  $0.23 [0.19-0.85]$  to  $0.11 [0.08-0.36]$   $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  ( $P = 0.002$ ), whereas the mean arterial pressure remained constant (table 2). No additional fluids were given during the study period apart from the basic crystalloid infusions (range: 80–250 ml within 4 h).

### Effect of Moderate-dose Vasopressin Infusion on Global Hemodynamics

Infusion of vasopressin and reduction of norepinephrine caused minimal changes in global hemodynamics (table 2). Heart rate decreased significantly from 99 [81–115] to 96 [74–109]  $\text{min}^{-1}$  ( $P = 0.016$ ). Cardiac index decreased significantly from  $3.7 (2.8-4.7) \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  to  $3.5 (2.7-3.6) \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  ( $P = 0.003$ ) (table 2 and fig. 2). Intrathoracic blood volume index and central venous pressure remained unchanged (table 2). In parallel with cardiac output, global  $\text{DO}_2$  index decreased significantly from 461 (375–637) to 419 (352–551)  $\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  ( $P = 0.002$ ), whereas global  $\text{VO}_2$  index did not change after vasopressin infusion.

### Effect of Moderate-dose Vasopressin on Regional Parameters and Gastric Mucosal Perfusion

Total hepatosplanchnic blood flow (fig. 3), fractional splanchnic blood flow as part of cardiac output, splanchnic  $\text{DO}_2$ , splanchnic  $\text{VO}_2$ , and hepatic venous oxygen saturation did not change significantly after vasopressin infusion (table 2). Hepatosplanchnic oxygen extraction (fig. 4) and hepatic ICG extraction (fig. 5) showed marked interindividual variability after vasopressin infusion but remained globally unchanged. However, gastric mucosal  $\text{PCO}_2$ -gap increased significantly from  $13.3 [8.0-16.7]$  to  $17.1 [10.3-28.7]$  mmHg ( $P = 0.002$ ) (fig. 6). Only four patients received propofol in our study (table 1). Gastric mucosal  $\text{PCO}_2$ -gap increased after administration of vasopressin in patients who were sedated using midazolam ( $14 [7.2-16.7]$  to  $17.1 [9-27.9]$  mmHg,  $P = 0.028$ ) and in those who were sedated using propofol ( $11.1 [6.7-24.5]$  to  $20.9 [9.7-38.4]$  mmHg,  $P = 0.066$ ).

**Table 1.** Patients' Characteristics and Demographic Data

#	Sex	Age (yr)	Diagnosis	APACHE II Score	ICU LOS (Days)	Sedation		Duration of Shock(h)	Norepinephrine, $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	Dobutamine, $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	Outcome
						Medication	Dosage				
1	F	64	Peritonitis	31	23	Midazolam/ Sufentanil	6 mg/h 75 $\mu\text{g}/\text{h}$	87	0.83	2.3	Died
2	M	59	Peritonitis	27	4	Midazolam/ Sufentanil	9 mg/h 75 $\mu\text{g}/\text{h}$	17	0.90	5.9	Died
3	M	54	Spondylodiskitis	29	2	Midazolam/ Sufentanil	9 mg/h 75 $\mu\text{g}/\text{h}$	20	0.31	2.0	Died
4	F	62	Peritonitis	28	20	Midazolam/ Sufentanil	9 mg/h 50 $\mu\text{g}/\text{h}$	96	0.23	6.0	Died
5	F	89	Peritonitis	20	6	Propofol	200 mg/h	60	0.19	2.4	Died
6	M	74	Peritonitis	33	2	Midazolam/ Sufentanil	9 mg/h 75 $\mu\text{g}/\text{h}$	29	1.40	2.3	Survived
7	M	81	Mediastinitis	28	1	Midazolam/ Sufentanil	9 mg/h 75 $\mu\text{g}/\text{h}$	12	0.16	3.2	Survived
8	M	60	Peritonitis	30	1	Midazolam/ Sufentanil	9 mg/h 75 $\mu\text{g}/\text{h}$	20	0.26	2.8	Survived
9	F	77	Pacer infection	18	3	Propofol	120 mg/h	16	0.26	2.1	Survived
10	F	40	Peritonitis	26	6	Propofol/ Sufentanil	160 mg/h 30 $\mu\text{g}/\text{h}$	37	0.92	3.8	Survived
11	M	68	Peritonitis	26	10	Midazolam/ Sufentanil	6 mg/h 50 $\mu\text{g}/\text{h}$	22	0.13	2.8	Survived
12	F	75	Mediastinitis	36	2	Propofol/ Sufentanil	200 mg/h 30 $\mu\text{g}/\text{h}$	18	0.21	2.2	Survived

APACHE = Acute Physiology and Chronic Health Evaluation Score; F = female; ICU = intensive care unit; LOS = length of stay; M = male.

Arterial lactate concentration (1.9 [1.4–2.7] to 2.0 [1.5–2.3] mM), hepatovenous lactate concentration (1.6 [0.9–1.2] to 1.7 [1.0–1.3] mM), and hourly urine production (74 [57–130] *versus* 107 [60–180] ml/h) did not change significantly during or after administration of vasopressin.

## Discussion

The major finding of our study is that administration of a moderate so-called substitution dose of vasopressin in severe sepsis enabled norepinephrine dosages to be reduced, but did not reduce total hepatosplanchnic perfusion and minimally

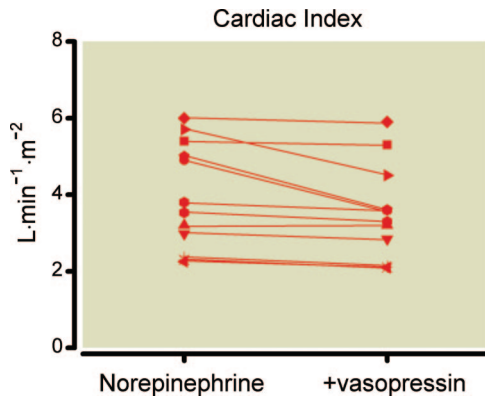
decreased cardiac output and global  $\text{DO}_2$ . However, gastric mucosal perfusion decreased markedly as evidenced by an increase in the gastric mucosal  $\text{PCO}_2$ -gap after vasopressin infusion.

In a previous study, we showed that use of vasopressin as a vasopressor in higher dosages was associated with negative effects on global hemodynamics.<sup>13</sup> In the current study, using a lower dosage of vasopressin, global hemodynamic effects were minimal, including a slight decrease in heart rate and cardiac index. In a state of relative vasopressin deficiency, vasopressin acts as a vasopressor; however, it has no positive inotropic or

**Table 2.** Global Hemodynamics and Hepatosplanchnic Oxygen Transport Variables before and after Vasopressin Administration

	Norepinephrine	Norepinephrine + Vasopressin	Significance
Mean arterial pressure, mmHg	81 [78–86]	82 [79–85]	0.415
Central venous pressure, mmHg	10 [8–15]	12 [7–17]	0.537
Cardiac index, $\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$	3.7 [2.8–4.7]	3.5 [2.7–3.6]	0.003
Heart rate, beats/min	99 [81–115]	96 [74–109]	0.016
Oxygen delivery index, $\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$	461 [375–637]	419 [352–551]	0.002
Oxygen consumption index, $\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$	126 [123–149]	124 [117–146]	0.05
Hemoglobin, mg/dl	8.6 [7.4–9.7]	8.5 [7.5–9.3]	0.741
Arterial oxygen saturation, %	97 [95–99]	98 [96–99]	0.658
Hepatosplanchnic oxygen delivery, ml/min	55 [43–110]	77 [43–117]	0.929
Hepatosplanchnic oxygen consumption, ml/min	30 [21–36]	35 [23–44]	0.239
Hepatic venous saturation, %	50 [42–63]	48 [37–55]	0.336

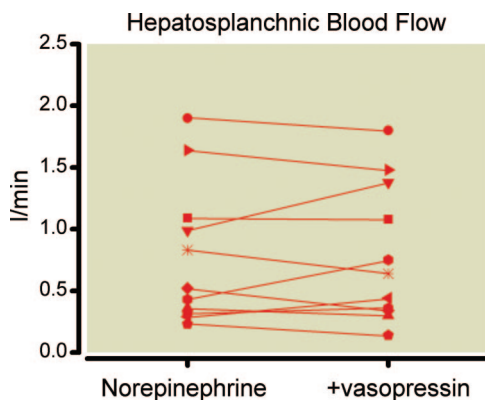
Data are presented as median [25–75% interquartile range].



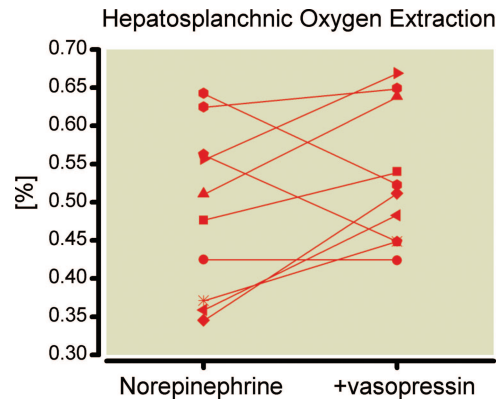
**Fig. 2.** Changes in cardiac index ( $\text{L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ) in individual patients before and 4 h after the start of vasopressin infusion.

chronotropic properties, in contrast with norepinephrine in higher dosages.<sup>13</sup> The reduction in cardiac index and heart rate may, therefore, be due to the reduction in the norepinephrine dosage after the vasopressin infusion. The reduction in global  $\text{DO}_2$  observed in our study had no significant effect on global  $\text{VO}_2$  or arterial lactate concentration.

In experimental studies, vasopressin has been convincingly shown to have vasoconstrictive effects on gut perfusion. In pigs, administration of vasopressin was associated with a significant decrease in blood flow in the superior mesenteric artery after cardiopulmonary resuscitation.<sup>19</sup> In our study, however, vasopressin infusion at a dosage of  $0.04 \text{ IU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  had no effect on total hepatosplanchnic blood flow or fractional hepatosplanchnic blood flow, similar to our previous observation using higher vasopressin dosages.<sup>13</sup> Nevertheless, we used a liver vein catheter for measurement of hepatosplanchnic blood flow, a technique that only enables calculation of the net flow through the liver and does not allow differentiation between mucosal, hepatoarterial, and portal venous flows. Despite the relatively invasive nature of this procedure, it is considered the only method by which hepatosplanchnic flow can be measured in clinical practice without surgical intervention.<sup>20</sup> In our study it was important to differentiate the possible influence of vasopressin ad-



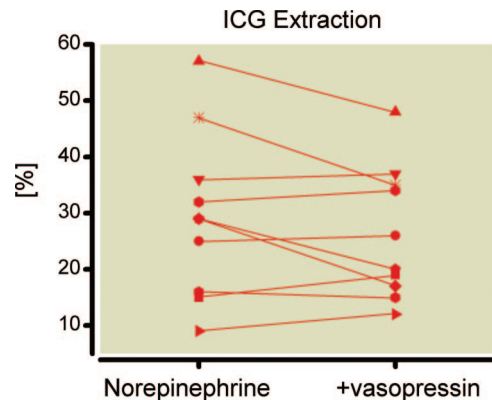
**Fig. 3.** Changes in hepatosplanchnic blood flow (l/min) in individual patients before and 4 h after the start of vasopressin infusion.



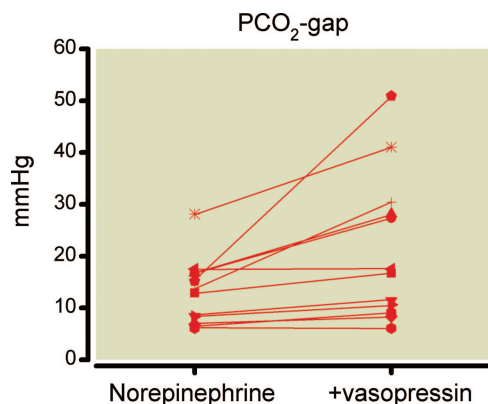
**Fig. 4.** Changes in hepatosplanchnic oxygen extraction (%) in individual patients before and 4 h after the start of vasopressin infusion.

ministration on tissue perfusion at the global, regional, and local mucosal levels. Therefore, measurement of the regional hepatosplanchnic flow was essential.

Importantly, we observed a significant increase in gastric mucosal  $\text{PCO}_2$ -gap in our patients after vasopressin infusion, denoting impaired gastric mucosal perfusion. These data are in accordance with our previous observation using a higher vasopressin dosage.<sup>13</sup> Intestinal and gastric mucosal vasoconstriction were recently demonstrated in cardiac surgery patients for a dose range of 1.2–4.8 IU vasopressin per hour.<sup>21</sup> Impaired gut mucosal perfusion has also been demonstrated in septic rats.<sup>22</sup> However, Dünser *et al.*<sup>23</sup> and Patel *et al.*<sup>24</sup> reported no increase in gastric mucosal carbon dioxide production using similar vasopressin dosages. The differences with our findings can perhaps be explained by the increased mean arterial pressure<sup>23</sup> or the concomitant use of dopamine<sup>24</sup> in contrast with dobutamine that was used in our study. Our own results support those of van Haren *et al.*,<sup>25</sup> who demonstrated that a so-called substitution dose of 0.04 IU/min led to supranormal plasma vasopressin levels of more than 200 pg/ml, and that there was a correlation between plasma vasopressin levels and mucosal  $\text{PCO}_2$ -gap.



**Fig. 5.** Changes in hepatic indocyanine green (ICG) extraction (%) in individual patients before and 4 h after the start of vasopressin infusion.



**Fig. 6.** Changes in gastric mucosal  $PCO_2$ -gap (mmHg) in individual patients before and 4 h after the start of vasopressin infusion.

The increase in gastric mucosal  $PCO_2$ -gap after vasopressin infusion in our patients despite the preserved hepato-splanchnic flow may be explained by redistribution of flow. Our results also emphasize the heterogeneity of tissue perfusion in patients with severe sepsis, previously reported using other techniques.<sup>26</sup> It is also important to stress that these alterations were independent of global hemodynamic measurements, confirming the results of previous reports.<sup>4,26–28</sup>

Gastric mucosal tonometry is one of the only techniques that can be used at the bedside to assess gastrointestinal mucosal perfusion, but it has important limitations, and whether it can be a useful tool in the intensive care unit is still unclear.<sup>29,30</sup> Lang *et al.* reported in a rat model that changes in blood flow with sepsis varied among the different splanchnic organs.<sup>31</sup> In stable patients with sepsis, the  $PCO_2$ -gap was not correlated with global measures of hepato-splanchnic oxygenation, including hepato-splanchnic blood flow, the suprahepatic venous blood oxygen saturation, and the mesenteric venoarterial  $PCO_2$  gradient.<sup>17</sup> However, Kavarana *et al.* demonstrated that gastric hypercarbia was associated with adverse postoperative morbidity.<sup>32</sup>

Although we found that vasopressin infusion was associated with impaired gastric mucosal perfusion, the possible effect of these alterations on outcome is yet to be determined. Indeed, a large multicenter randomized controlled study reported that low-dose vasopressin was not associated with reduced mortality rates compared with norepinephrine among patients with septic shock.<sup>33</sup> The authors demonstrated a potential benefit of vasopressin in patients with low to moderate norepinephrine dosage.<sup>33</sup> A subsequent subgroup analysis showed improved outcome in septic patients who were treated with a combination of vasopressin and corticosteroids.<sup>34</sup> However, in this study,<sup>33</sup> vasopressin was administered at a lower dose than that used in our study.

Our study has some limitations. First, the sample size is small, which increases the likelihood of type II error. Our study should, therefore, be considered as a pilot study, and additional studies with adequately powered sample sizes are needed to confirm our observation. Second, vasopressin was

administered for only 4 h. We cannot elaborate, therefore, on whether the effects of vasopressin infusion on gastric mucosal microvascular alterations may persist if used for longer periods. Third, our results cannot be extrapolated to lower dosages of vasopressin. Fourth, different sedation regimens were used, which may have had different effects on our study parameters. Nevertheless, the choice of sedating agents was left to the discretion of the attending physician to avoid inappropriate prolongation of mechanical ventilation due to the use of agents with relatively long half-lives. However, the dosage of sedation was kept constant during all measurements and the alterations in gastric mucosal perfusion occurred in patients who received midazolam and those who received propofol.

## Conclusion

Vasopressin at a dosage of  $0.04 \text{ IU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  may impair gastric mucosal perfusion with minimal global and regional hemodynamic effects. The routine use of vasopressin in patients with severe sepsis may, therefore, be associated with potential risks.

The authors thank Mrs. Ilona Witte and Mrs. Astrid Trinks (Technicians, Department of Anesthesiology and Intensive Care, Friedrich Schiller University, Jena, Germany) for medical-technical assistance.

## References

- Martin GS, Mannino DM, Eaton S, Moss M: The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; 348:1546–54
- Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–10
- Engel C, Brunkhorst FM, Bone HG, Brunkhorst R, Gerlach H, Grond S, Gruendling M, Huhle G, Jaschinski U, John S, Mayer K, Oppert M, Olthoff D, Quintel M, Ragaller M, Rossaint R, Stuber F, Weiler N, Welte T, Bogatsch H, Hartog C, Loeffler M, Reinhart K: Epidemiology of sepsis in Germany: Results from a national prospective multicenter study. *Intensive Care Med* 2007; 33:606–18
- De Backer D, Creteur J, Dubois MJ, Sakr Y, Koch M, Verdant C, Vincent JL: The effects of dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects. *Crit Care Med* 2006; 34:403–8
- Landry DW, Levin HR, Gallant EM, Seo S, D'Alessandro D, Oz MC, Oliver JA: Vasopressin pressor hypersensitivity in vasodilatory septic shock. *Crit Care Med* 1997; 25:1279–82
- Morales DL, Gregg D, Helman DN, Williams MR, Naka Y, Landry DW, Oz MC: Arginine vasopressin in the treatment of 50 patients with postcardiotomy vasodilatory shock. *Ann Thorac Surg* 2000; 69:102–6
- Dünser MW, Mayr AJ, Ulmer H, Ritsch N, Knotzer H, Pajk W, Luckner G, Mutz NJ, Hasibeder WR: The effects of vasopressin on systemic hemodynamics in catecholamine-resistant septic and postcardiotomy shock: A retrospective analysis. *Anesth Analg* 2001; 93:7–13
- Holmes CL, Walley KR, Chittock DR, Lehman T, Russell JA: The effects of vasopressin on hemodynamics and renal function in severe septic shock: A case series. *Intensive Care Med* 2001; 27:1416–21
- Tsuneyoshi I, Yamada H, Kakihana Y, Nakamura M, Nakano Y, Boyle WA 3rd: Hemodynamic and metabolic effects of

- low-dose vasopressin infusions in vasodilatory septic shock. *Crit Care Med* 2001;29:487-93
10. Landry DW, Oliver JA: The pathogenesis of vasodilatory shock. *N Engl J Med* 2001; 345:588-95
  11. Goulis J, Burroughs AK: Role of vasoactive drugs in the treatment of bleeding oesophageal varices. *Digestion* 1999; 60 Suppl 3:25-34
  12. Zhou Y, Qiao L, Wu J, Hu H, Xu C: Comparison of the efficacy of octreotide, vasopressin, and omeprazole in the control of acute bleeding in patients with portal hypertensive gastropathy: A controlled study. *J Gastroenterol Hepatol* 2002; 17:973-9
  13. Klinzing S, Simon M, Reinhart K, Bredle DL, Meier-Hellmann A: High-dose vasopressin is not superior to norepinephrine in septic shock. *Crit Care Med* 2003; 31:2646-50
  14. Sharshar T, Blanchard A, Paillard M, Raphael JC, Gajdos P, Annane D: Circulating vasopressin levels in septic shock. *Crit Care Med* 2003; 31:1752-8
  15. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992;20:864-74
  16. Reinhart K, Brunkhorst FM, Bone HG, Bardutzky J, Dempfle CE, Forst H, Gastmeier P, Gerlach H, Grundling M, John S, Kern W, Kreymann G, Kruger W, Kujath P, Marggraf G, Martin J, Mayer K, Meier-Hellmann A, Oppert M, Putensen C, Quintel M, Ragaller M, Rossaint R, Seifert H, Spies C, Stuber F, Weiler N, Weimann A, Werdan K, Welte T: Prevention, diagnosis, therapy and follow-up care of sepsis: 1st revision of S-2k guidelines of the German Sepsis Society (Deutsche Sepsis-Gesellschaft e.V. (DSG)) and the German Interdisciplinary Association of Intensive Care and Emergency Medicine (Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI)). *Ger Med Sci* 2010; Jun 28;8:Doc14
  17. Creteur J, De Backer D, Vincent JL: Does gastric tonometry monitor splanchnic perfusion? *Crit Care Med* 1999; 27:2480-4
  18. Uusaro A, Ruokonen E, Takala J: Estimation of splanchnic blood flow by the Fick principle in man and problems in the use of indocyanine green. *Cardiovasc Res* 1995; 30:106-12
  19. Voelckel WG, Lindner KH, Wenzel V, Bonatti J, Hangler H, Frimmel C, Künszberg E, Lingnau W: Effects of vasopressin and epinephrine on splanchnic blood flow and renal function during and after cardiopulmonary resuscitation in pigs. *Crit Care Med* 2000; 28:1083-8
  20. Takala J: Determinants of splanchnic blood flow. *Br J Anaesth* 1996; 77:50-8
  21. Nygren A, Thorén A, Ricksten SE: Vasopressin decreases intestinal mucosal perfusion: A clinical study on cardiac surgery patients in vasodilatory shock. *Acta Anaesthesiol Scand* 2009; 53:581-8
  22. Westphal M, Freise H, Kehrel BE, Bone HG, Van Aken H, Sielenkämper AW: Arginine vasopressin compromises gut mucosal microcirculation in septic rats. *Crit Care Med* 2004; 32:194-200
  23. Dünser MW, Mayr AJ, Ulmer H, Knotzer H, Sumann G, Pajk W, Friesenecker B, Hasibeder WR: Arginine vasopressin in advanced vasodilatory shock: A prospective, randomized, controlled study. *Circulation* 2003; 107:2313-9
  24. Patel BM, Chittock DR, Russell JA, Walley KR: Beneficial effects of short-term vasopressin infusion during severe septic shock. *ANESTHESIOLOGY* 2002; 96:576-82
  25. van Haren FM, Rozendaal FW, van der Hoeven JG: The effect of vasopressin on gastric perfusion in catecholamine-dependent patients in septic shock. *Chest* 2003; 124:2256-60
  26. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL: Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med* 2002; 166:98-104
  27. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL: Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med* 2004; 32:1825-31
  28. Sakr Y, Gath V, Oishi J, Klinzing S, Simon TP, Reinhart K, Marx G: Characterization of buccal microvascular response in patients with septic shock. *Eur J Anaesthesiol* 2010; 27: 388-94
  29. Uusaro A, Ruokonen E, Takala J: Gastric mucosal pH does not reflect changes in splanchnic blood flow after cardiac surgery. *Br J Anaesth* 1995; 74:149-54
  30. Gomersall CD, Joynt GM, Freebairn RC, Hung V, Buckley TA, Oh TE: Resuscitation of critically ill patients based on the results of gastric tonometry: A prospective, randomized, controlled trial. *Crit Care Med* 2000; 28:607-14
  31. Lang CH, Bagby GJ, Ferguson JL, Spitzer JJ: Cardiac output and redistribution of organ blood flow in hypermetabolic sepsis. *Am J Physiol* 1984; 246:R331-37
  32. Kavarana MN, Frumento RJ, Hirsch AL, Oz MC, Lee DC, Bennett-Guerrero E: Gastric hypercarbia and adverse outcome after cardiac surgery. *Intensive Care Med* 2003; 29:742-8
  33. Russell JA, Walley KR, Singer J, Gordon AC, Hébert PC, Cooper DJ, Holmes CL, Mehta S, Granton JT, Storms MM, Cook DJ, Presneill JJ, Ayers D, VASST Investigators: Vasopressin *versus* norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877-87
  34. Russell JA, Walley KR, Gordon AC, Cooper DJ, Hébert PC, Singer J, Holmes CL, Mehta S, Granton JT, Storms MM, Cook DJ, Presneill JJ, Dieter Ayers for the Vasopressin and Septic Shock Trial Investigators: Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock. *Crit Care Med* 2009; 37:811-8