The Effect of Vasopressin on Gastric Perfusion in Catecholamine-Dependent Patients in Septic Shock*

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Objective: To study the effect of continuous infusion of vasopressin on the splanchnic circulation in patients with severe septic shock.

Design: Prospective clinical study.

Setting: ICU in a teaching hospital.

Patients: Eleven consecutive patients with documented septic shock who remained hypotensive despite norepinephrine infusion at a rate ≥ 0.2 μg/kg/min.

Interventions: Insertion of a gastric tonometry catheter, and continuous infusion of vasopressin 0.04 U/min during 4 h.

Measurements and main results: Difference between gastric and arterial CO₂ partial pressure (P[g-a]CO₂ gap), mean arterial pressure, and cardiac index were recorded at baseline and after 15 min, 30 min, 60 min, 120 min, and 240 min.

Results: The median P[g-a]CO₂ gap increased from 5 mm Hg at baseline to 19 mm Hg after 4 h (p = 0.022). Mean arterial pressure increased from 61 ± 13 mm Hg at baseline to 68 ± 9 mm Hg after 4 h (p = 0.055). No significant changes in cardiac index were noted.

Conclusions: In norepinephrine-dependent patients in septic shock, continuous infusion of low-dose vasopressin results in a significant increase of the P[g-a]CO₂ gap compatible with GI hypoperfusion.

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Key words: catecholamines; GI tonometry; intensive care; prospective study; sepsis; septic shock; splanchnic circulation; vasopressin

Abbreviations: APACHE = acute physiology and chronic health evaluation; P[g-a]CO₂ gap = difference between gastric and arterial CO₂ partial pressure; SOFA = sequential organ failure assessment

Septic shock is often characterized by profound vasodilation that requires treatment with catecholamines. Norepinephrine-resistant hypotension associated with septic shock has a high mortality rate.

Patients with septic shock, compared to other forms of shock, have low levels of circulating endogenous vasopressin.1–3 This may be related to depletion of vasopressin stores in the neurohypophysis.4 In experimental septic shock, release of vasopressin is inhibited by central nitric oxide production arising from the inducible nitric oxide synthase pathway.5 Other experimental data indicate that sepsis also causes cytokine-mediated downregulation of vasopressin V(1A) receptors.6

Vasopressin is a potent vasoconstrictor in patients with septic shock. Vasopressin increases BP, improves some measures of renal function, and decreases catecholamine requirements.7–10 Terlipressin, a long-acting vasopressin analog, also restores BP in patients with catecholamine-resistant septic shock.11

Despite its favorable effect on global hemodynamics in patients with septic shock, few clinically relevant data are available on the effect of vasopressin on the splanchnic circulation.12 In patients with bleeding esophageal varices, vasopressin leads to vasoconstriction of the splanchnic circulation and may stop the bleeding.13

The aim of our study was to investigate the effect of vasopressin infusion on the splanchnic circulation.
in patients with septic shock. We hypothesized that vasopressin, being a potent vasoconstrictive agent, decreases GI blood flow and therefore may be potentially harmful.

**Patients and Methods**

**Patients**

The study was approved by the medical ethical committee of the Jeroen Bosch Hospital. Informed consent was obtained from the nearest relative. Thirteen consecutive patients with documented septic shock were screened for inclusion in the study. Septic shock was defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. All patients were resuscitated with fluid until no further improvement of cardiac output was obtained, and received dobutamine based on the judgment of the treating physician. All patients received a continuous infusion of low-dose hydrocortisone. Norepinephrine was added in case of persistent hypotension. Patients were included when they met the criteria for septic shock and had mean arterial pressures ≥ 70 mm Hg despite norepinephrine infusion at a rate ≥ 0.2 μg/kg/min.

Exclusion criteria were age < 18 years, pregnancy, and myocardial ischemia or infarction < 6 months prior to the study.

**Interventions**

A gastric tonometry catheter (Tonometrics-catheter, TONO-16F; Datex-Ohmeda Division; Helsinki, Finland) was inserted in the stomach. Calibration was performed according to the guidelines of the manufacturer. Enteral feeding was discontinued, and all patients received omeprazole, 40 mg IV, 1 h before the first measurements. After data collection at baseline, patients received vasopressin, 0.04 U/min, by continuous central venous infusion for 4 h. Catecholamine doses were not changed during the study period unless mean arterial pressure dropped below 50 mm Hg despite fluid resuscitation. Vasopressin was continued after 4 h in case of persistent hypotension, based on the judgment of the treating physician.

**Measurements**

We recorded demographic data as well as the severity of illness using APACHE (acute physiology and chronic health evaluation) II (first 24 h of admission to the ICU) and sequential organ failure assessment (SOFA) scores (24 h prior to inclusion in the study). Partial pressure of CO₂ in the stomach was measured by automated air tonometry using an equilibration time of 10 min. Paco₂ was measured simultaneously with a blood gas analyzer (Bayer; Mejdrecht, the Netherlands), and the difference between gastric and arterial CO₂ partial pressure (P[g-a]CO₂ gap) was calculated. BP and cardiac index were also recorded. Plasma levels of vasopressin were measured with a radioimmunoassay kit (Wizard gamma counter; Nichols; Wallac, Finland). All measurements were performed at baseline and after 15 min, 30 min, 60 min, 120 min, and 240 min. Data on hospital mortality were collected after completion of the study.

**Statistical and Data Analysis**

Data are presented as mean ± 1 SD or as median (25 to 75th percentile) depending on their distribution. Changes over time were analyzed by analysis of variance. All statistics were done using SPSS version 10.0 (SPSS; Chicago, IL).

**Results**

**Patient Characteristics**

Thirteen consecutive patients were eligible for inclusion in the study. In two patients, it was not possible to measure partial pressure of CO₂ in the stomach due to technical problems. The demographic and clinical characteristics of the patients are shown in Table 1. Septic shock was caused by pneumonia in five patients, abdominal sepsis in five patients, and urosepsis and aspiration pneumonia in one patient. All patients received mechanical ventilation. Mean APACHE II score was 26.6 ± 8.7, and mean SOFA score was 10.8 ± 1.8. Hospital mortality was 82% (9 of 11 patients died).

**Measurements**

The P[g-a]CO₂ gap at baseline and following vasopressin infusion is shown in Figure 1, top. The median P[g-a]CO₂ gap increased from 5 mm Hg at
baseline to 19 mm Hg after 4 h; this increase was statistically significant (p = 0.022). Vasopressin infusion resulted in an increase in mean arterial pressure from 61 ± 13 mm Hg at baseline to 68 ± 9 mm Hg after 4 h (p = 0.055; Fig 1, middle) without a significant decrease in cardiac index (p = 0.978). Plasma vasopressin levels increased from 17 pg/mL at baseline to 230 pg/mL after 4 h of infusion (p < 0.001; Fig 1, bottom). There was a strong correlation between median plasma levels of vasopressin and the median P(g-a)CO₂ gap (r² = 0.98) [Fig 2].

**DISCUSSION**

In this study, we investigated the effect of low-dose vasopressin infusion on gastric perfusion in patients in septic shock who remained hypotensive despite high-dose norepinephrine infusion. Infusion of vasopressin increased plasma levels of vasopressin to values that were > 10 times higher than those reported during comparable degrees of hypotension from other causes such as cardiogenic shock.³ This resulted in an increase in BP that was not accompanied by a reduction in cardiac output, compatible with an impairment of the baroreflex in patients with septic shock. These findings are consistent with those previously reported by others.³,⁹

We found that vasopressin infusion leads to an immediate and important increase in P(g-a)CO₂ gap in a dose-dependent fashion. This P(g-a)CO₂ gap is a reliable measure of GI hypoperfusion. In animal experiments, increased levels of circulating vasopressin in different states of shock have been shown to contribute to redistribution of blood from the peripheral to the cerebral circulation.¹⁵ Although low concentrations of vasopressin have been shown to have vasodilatory effects in selected organs,² the results of the only placebo-controlled trial¹⁶ that has been conducted with vasopressin in patients with septic shock show that vasopressin treatment results in peripheral vasoconstriction. Our study shows that vasopressin probably also leads to vasoconstriction of the splanchnic vasculature. This finding is consistent with studies¹⁷ in human gastroepiploic arteries that demonstrate a concentration-dependent vasoconstriction effect starting at levels that are lower than those obtained in our study. An increase in gastric PCO₂ indicating splanchnic vasoconstriction has also been shown in patients who received ornipressin (a vasopressin agonist specific for the V1 receptor) to reverse the hypotension associated with combined general/epidural anesthesia.¹⁸ In animal experiments, endogenous release of vasopressin during endotoxin administration has been associated with gastric, duodenal, and jejunal microcirculatory and mucosal injury.¹⁹ Several studies²⁰–²⁶ have demonstrated that GI hypoperfusion, reflected by a low gastric intramucosal pH, is a good predictor of poor outcome. Gut intramucosal hypoxia is thought to be important both as an indicator of inadequate resuscitation and as a mechanism by which multiorgan failure may occur; however, resuscitation based on the results of gastric tonometry has failed to show improvement in outcome.²⁷
Other vasoconstrictive agents used in septic shock do not share the apparent detrimental effect of vasopressin on the GI perfusion. In one study, for example, both epinephrine and the combination of norepinephrine and dobutamine in septic shock patients increased gastric mucosal perfusion. GI hypoperfusion can be reversed by infusion of prostacyclin. In our study, all patients acquired gastric hypoperfusion despite standard use of low-dose vasodilating agents.

There are several limitations to this study: the number of patients studied is small, but an increase in the P(g-a)CO₂ gap was seen in 10 of 11 patients. Furthermore, the patients included in this study were severely ill, which makes generalization to all patients with septic shock difficult. Although hospital mortality was unusually high, the study design permits no further speculations to be made on this observation.

Because all patients received high-dose norepinephrine infusion as well as vasopressin, interaction between these two vasoconstrictive agents cannot be ruled out. Several studies indicate that subconstricting doses of vasopressin are able to potentiate the constricting effects of catecholamines. In a recent study, low-dose terlipressin without administration of other catecholamines increased ileal microcirculation in fluid-challenged endotoxic rats. It is possible, therefore, that the effect of vasopressin observed in our patients reflects the potentiating effect of vasopressin to infused and endogenous catecholamines.

Finally, the vasopressin dose administered to the patients may have been too high. We showed that higher levels of vasopressin led to more profound gastric hypoperfusion in a dose-dependent fashion. Landry et al showed in six patients with septic shock that administration of vasopressin at a lower infusion rate of 0.01 U/min resulted in plasma concentrations expected for the level of hypotension (approximately 30 pg/mL), with an increase of systolic arterial pressure from 83 to 115 mm Hg.

In this prospective study, infusion of low-dose vasopressin in patients with severe septic shock resulted in a rapid increase in P(g-a)CO₂ gap compatible with GI hypoperfusion. In our view, vasopressin treatment of patients with septic shock should be limited to controlled clinical trials until its effect on clinical outcome such as organ failure and mortality has been clarified.

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REFERENCES