Commentary

Vasopressin in vasodilatory shock: hemodynamic stabilization at the cost of the liver and the kidney?

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Abstract

Infusing arginine vasopressin (AVP) in advanced vasodilatory shock is usually accompanied by a decrease in cardiac index and systemic oxygen transport. Whether or not such a vasoconstriction impedes regional blood flow and thus visceral organ function, even when low AVP is used, is still a matter of debate. Krejci and colleagues now report, in this issue of *Critical Care*, that infusing 'low-dose' AVP during early, short-term, normotensive and normodynamic fecal peritonitis-induced porcine septicemia markedly reduced both renal and portal blood flow, and consequently total hepatic blood flow, whereas hepatic arterial flow was not affected. This macrocirculatory response was concomitant with reduced kidney microcirculatory perfusion, whereas liver microcirculation remained unchanged. From these findings the authors conclude that the use of AVP to treat hypotension should be cautioned against in patients with septic shock. Undoubtedly, given its powerful vasoconstrictor properties, which are not accompanied by positive inotropic qualities (in contrast with most of the equally potent standard care 'competitors', namely catecholamines), the safety of AVP is still a matter of concern. Nevertheless, the findings reported by Krejci and colleagues need to be discussed in the context of the model design, the timing and dosing of AVP as well as the complex interaction between visceral organ perfusion and function.

In this issue of *Critical Care*, Krejci and colleagues report that infusing 0.06 IU kg^{-1} h^{-1} arginine vasopressin (AVP) during porcine fecal peritonitis reduced renal, portal and, consequently, total hepatic blood flow, whereas hepatic arterial flow was not affected [1]. This macrocirculatory response was concomitant with reduced kidney microcirculatory perfusion, whereas liver microcirculation remained unchanged. From these findings the authors concluded that the use of AVP to treat hypotension should be cautioned against in patients with septic shock.

How does the study by Krejci and colleagues compare with the existing literature? The observed redistribution of hepato-splanchnic macrocirculatory blood flow can most probably be explained by the maintenance of the hepatic arterial buffer response. A similar finding was reported by Asfar and colleagues during long-term hyperdynamic porcine endotoxemia, when the AVP analog terlipressin was incrementally adjusted to maintain blood pressure at pre-endotoxin levels [2]. Interestingly, in the study by Krejci and colleagues the microcirculation did not invariably parallel the macrocirculatory flow: whereas liver microcirculatory perfusion remained unchanged despite reduced total liver blood flow, capillary blood flow in the pancreas and kidney was impaired. This observation is complementary to the authors' report on gastrointestinal microcirculation [3]: whereas the AVP-induced fall in superior mesenteric flow was associated with reduced capillary perfusion of the upper gastrointestinal tract, no difference was observed in the colon. Consequently, within the limits imposed by the use of a single laser Doppler flowmetry probe on the liver and kidney, precluding the assessment of any intra-organ redistribution in blood flow and/or heterogeneity in capillary perfusion, infusing AVP caused a widespread reduction of visceral organ microcirculatory perfusion, which moreover could not be predicted by the upstream macrocirculatory effect.

How can the authors' present findings be explained? In other words, why do they markedly differ from other studies on low-dose infusion with vasopressin [4] or terlipressin [2] reporting unaffected hepato-splanchnic macrocirculatory and microcirculatory perfusion and improved energy balance and tissue integrity in large animal models? In this context, the experimental design and the AVP infusion rate must be taken

AVP = arginine vasopressin; VASST = Vasopressin in Septic Shock Trial.

into account: the authors' model itself is normodynamic; that is, it is characterized by a virtually unchanged cardiac output. It therefore differs from the hyperdynamic circulation commonly seen in patients with septic shock. Furthermore, its duration is limited to 6 hours, so that mediator pathways that would result in pronounced vasodilation and, subsequently, increased organ blood flow (for example excess nitric oxide release resulting from activation of the inducible isoform of nitric oxide synthase) probably did not assume major importance. Finally, as the authors themselves acknowledge, although labelled 'low dose', the infusion rate used was about double the rate that was considered 'safe' by others [5,6] and that was used in the Vasopressin in Septic Shock Trial (VASST).

What are the conclusions about the clinical use of AVP? To answer this question, the consequences of AVP-induced vasoconstriction for tissue energy balance assume crucial importance. Unfortunately, the authors do not provide any data on regional metabolism, such as regional venous lactate/pyruvate ratios, tissue microdialysis or tonometric partial pressure of CO_2. There are conflicting data in the literature. During long-term, resuscitated ovine peritonitis Sun and colleagues showed that combining vasopressin and norepinephrine was associated with the least metabolic impairment and tissue damage when compared with that caused by norepinephrine or vasopressin alone [4]. Asfar and colleagues reported marked hyperlactatemia during low-dose infusion of terlipressin in a long-term resuscitated porcine endotoxic shock model [2], but interestingly, this hyperlactatemia did not originate from the hepato-splachnic system and was even associated with attenuated regional venous metabolic acidosis. It is noteworthy that most of the studies reporting improved organ function and/or tissue energy balance during low-dose infusion of AVP actually compared this approach with the clinical standard vasopressor treatment, namely norepinephrine infusion. The study by Krejci and colleagues therefore raises the question of whether AVP compares favorably with catecholamines. In a complementary investigation the same group compared the regional macrocirculatory and microcirculatory effects of epinephrine, norepinephrine and phenylephrine. In a similar manner to the effects of AVP in the present investigation, norepinephrine and epinephrine reduced both superior mesenteric artery flow and capillary perfusion in the small bowel and pancreas [7].

Taking these results together, what do we learn from the authors' experiments? Despite the encouraging preliminary report on VASST showing an improved 28 and 90 days' survival in patients with less severe septic shock (Congress of the European Society of Intensive Care Medicine, Barcelona, 2006), any safety issue that could limit the clinical use of AVP is a matter of utmost concern. Given its powerful vasoconstrictor properties, which are not accompanied by positive inotropic qualities shown by its comparably potent standard care 'competitors', namely the catecholamines norepinephrine and epinephrine, infusing AVP decreases cardiac index, which is in turn accompanied by regional vasoconstriction – albeit to a varied degree [6] – in virtually all vascular beds. Krejci and colleagues confirm that the unrestricted use of even 'low-dose' AVP may result in 'overconstriction', in particular in the hepato-splanchnic region and the kidney. Furthermore, the authors' study clearly demonstrates that only combining the investigation of macrocirculatory and microcirculatory perfusion together with tissue energy balance and organ function will allow one to define the patients likely to benefit from low-dose infusion with AVP. In this context, the design of the model, namely whether hemodynamics are characterized by a hypodynamic or normodynamic circulatory state [6,8-14] versus a hyperdynamic circulatory state [2,4,15], will assume crucial importance.

Competing interests

The authors declare that they have no competing interests.

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