Commentary

Vasopressin in vasodilatory shock: ensure organ blood flow, but take care of the heart!

Martin W Dünser[1] and Walter R Hasibeder[2]

[1]Department of Intensive Care Medicine, Inselspital Bern, Murtenstrasse, 3010 Bern, Switzerland
[2]Department of Anesthesiology and Critical Care Medicine, Krankenhaus der Barmherzigen Schwestern, Ried im Innkreis, Austria

Corresponding author: Martin W Dünser, Martin.Duenser@uibk.ac.at

Published: 22 November 2006
This article is online at http://ccforum.com/content/10/6/172

Critical Care 2006, **10:**172 (doi:10.1186/cc5089)

See related research by Ertmer *et al*., http://ccforum.com/content/10/5/R144

Abstract

Supplementary arginine vasopressin infusion in advanced vasodilatory shock may be accompanied by a decrease in cardiac index and systemic oxygen transport capacity in approximately 40% of patients. While a reduction of cardiac output most frequently occurs in patients with hyperdynamic circulation, it is less often observed in patients with low cardiac index. Infusion of inotropes, such as dobutamine, may be an effective strategy to restore systemic blood flow. However, when administering inotropic drugs, systemic blood flow should be increased to adequately meet systemic demands (assessed by central or mixed venous oxygen saturation) without putting an excessive beta-adrenergic stress on the heart. Overcorrection of cardiac index to hyperdynamic values with inotropes places myocardial oxygen supply at significant risk.

In a previous issue of *Critical Care*, Ertmer and colleagues [1] present an experimental study in which they examine the effects of dobutamine when given together with arginine vasopressin (AVP) in endotoxemic sheep. AVP is an increasingly used supplementary vasopressor in advanced vasodilatory shock states where standard treatment cannot stabilize cardiovascular function with an acceptable benefit:risk ratio. Due to its strong vasoconstrictive and lack of beta-mimetic effects it was repeatedly shown to stabilize hemodynamic function and result in beneficial cardiovascular changes [2]. Preliminary results of a recently accomplished multicenter trial including patients with septic shock suggest a significant survival benefit at 28 and 90 days with a supplementary AVP infusion when given to patients with moderate cardiovascular failure (Congress of the European Society of Intensive Care Medicine, Barcelona, September 24-27, 2006).

A potentially deleterious decrease in cardiac index (CI) during AVP infusion was reported soon after the first results on the use of AVP in septic shock had been published [3]. Whereas animal experiments (mostly applying AVP as a single vasopressor) homogeneously reported a decrease in CI and systemic oxygen transport capacity (DO_2I), clinical observations (applying AVP as a supplementary vasopressor) showed heterogeneous responses, with most studies reporting neutral or even beneficial effects of AVP on cardiac performance [2,4]. A recent analysis demonstrated a decrease in CI during AVP infusion in 41% of vasodilatory shock patients. High CI before AVP was the single independent risk factor for a subsequent fall of CI. While patients with hyperdynamic circulation exhibited a decrease in CI to normodynamic values, patients with hypodynamic circulation experienced a slight improvement of CI. Stroke volume index increased irrespective of the circulatory state, with the most pronounced increase in patients with hypodynamic circulation [5].

In their present study, Ertmer and colleagues [1] evaluate whether dobutamine can reverse an AVP-induced decrease in CI and DO_2I. The highly experienced working group used an ovine endotoxinemic model, in which AVP has been shown to depress CI and DO_2I [6,7]. The authors' conclusions are fully supported by the results of their experiment and prove that dobutamine is indeed a useful agent to reverse an AVP-associated depression in CI and DO_2I in this animal model.

When taking the results of this experimental study into clinical practice, important limitations need to be considered. As stated by the authors themselves, their protocol did not analyze end organ perfusion and can, therefore, not prove if the decrease in CI and DO_2I resulted in organ hypoperfusion. Moreover, AVP was applied as a single vasopressor at dosages twice as high as recommended in clinical practice (0.04 IU/minute in 35 kg sheep versus 0.04 IU/minute in

AVP = arginine vasopressin; CI = cardiac index; DO_2I = systemic oxygen transport capacity; SVRI = systemic vascular resistance index.

70 kg patients). A small prospective study infusing high AVP dosages has shown a highly different hemodynamic response to AVP [8] than observed with standard recommended dosages. Accordingly, the systemic vascular resistance index (SVRI) during AVP infusion in this experimental study reached supranormal values (approximately 2,000 dynes × m^2 × cm^{-5}) when compared to baseline values. This unphysiological increase in SVRI could well explain a baroreceptor-mediated (although possibly attenuated in endotoxemia [9]) decrease in CI. The fact that in clinical practice SVRI is, at maximum, increased to subnormal values by vasopressors, might be one reason for the AVP-induced depression in CI in this experiment.

Nonetheless, this study underlines important points of hemodynamic management in vasodilatory shock: Systemic blood flow must be ensured to guarantee adequate organ perfusion as reflected by central venous oxygen saturation >70% [10] or mixed venous oxygen saturation >65% [11]. As shown by the authors, inotropes such as dobutamine are a good choice to reverse low systemic blood flow if preload optimization cannot adequately increase CI. What must never be forgotten when infusing inotropic agents and assessing adequate organ perfusion is that, in critical illness, beta-adrenergic stimulation has virtually no positive, but merely adverse effects on the heart itself (exponential elevation of oxygen demand due to increases in heart rate or triggering of tachyarrhythmias, induction of myocardial stunning at high dosages [12]). Recent data revealed that cardiac pathologies made up almost 50% of the causes of death in patients with advanced vasodilatory shock [5]. Considering the heart as the obviously most vulnerable link of the cardiovascular chain, it must be one of our goals to relieve the heart as much as possible, while 'enforcing' as much systemic blood flow as necessary for peripheral organs. A demand-based strategy relying on central/mixed venous oxygen saturation is a very useful tool to achieve this critical balance [10].

A putative mechanism by which supplementary AVP infusion may exert beneficial effects is the significant reduction of high, potentially toxic catecholamine dosages [13]. When reviewing the results of Ertmer and colleagues, dobutamine did not only restore hyperdynamic circulation, but also reversed potentially beneficial effects of AVP on myocardial oxygen balance. As shown in Figure 1 of the paper, the dobutamine-induced increase in CI was accompanied by an increase in heart rate from approximately 85 to 135 beats/minute. As cited by Ertmer and collleagues, a recent study has shown an alarmingly high incidence of major cardiac events (49%) in high risk cardiac patients with tachycardia (>95 beats/minutes for >12 hours) [14]. Finding the delicate balance between pharmacological stress on the heart and adequate organ perfusion is difficult but crucial to guarantee optimal patient outcome in vasodilatory and septic shock.

Competing interests

The authors declare that they have no competing interests.

References

1. Ertmer C, Morelli A, Bone HG, Stubbe HD, Schepers R, Van Aken H, Lange M, Borking K, Lucke M, Traber DL, Westphal M: **Dobutamine reverses the vasopressin-associated impairment in cardiac index and systemic oxygen supply in ovine endotoxemia.** *Crit Care* 2006, **10:**R144.
2. Mutlu GM, Factor P: **Role of vasopressin in the management of septic shock.** *Intensive Care Med* 2004, **30:**1276-1291.
3. Holmes CL, Walley KR, Chittock DR, Lehman T, Russell JA: **The effects of vasopressin on hemodynamics in severe septic shock: a case series.** *Intensive Care Med* 2001, **27:**1416-1421.
4. Treschan TA, Peters J: **The vasopressin system – physiology and clinical strategies.** *Anesthesiology* 2006, **105:**599-612.
5. Luckner G, Dünser MW, Jochberger S, Mayr VD, Wenzel V, Ulmer H, Schmid S, Knotzer H, Pajk W, Hasibeder W, *et al.*: **Arginine vasopressin in 316 patients with advanced vasodilatory shock.** *Crit Care Med* 2005, **33:**2659-2666.
6. Westphal M, Stubbe H, Sielenkämper AW, Ball C, Van Aken H, Borgulya R, Bone HG: **Effects of titrated arginine vasopressin on hemodynamic variables and oxygen transport in healthy and endotoxemic sheep.** *Crit Care Med* 2003, **31:**1502-1508.
7. 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.
8. Klinzing S, Simon M, Reinhard K, Bredle DL, Meier-Hellmann A: **High-dose vasopressin is not superior to norepinephrine in septic shock.** *Crit Care Med* 2003, **31:**2646-2650.
9. Schmidt HB, Werdan K, Müller-Werdan U: **Autonomic dysfunction in the ICU patient.** *Curr Opin Crit Care* 2001, **7:**314-322.
10. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M; Early Goal Directed Therapy Collaborative Group: **Early goal-directed therapy in the treatment of severe sepsis and septic shock.** *N Engl J Med* 2001, **345:**1368-1377.
11. Heiselman D, Jones J, Cannon L: **Continuous monitoring of mixed venous oxygen saturation in septic shock.** *J Clin Monit* 1986, **2:**237-245.
12. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, Wu KC, Rade JJ, Bivalacqua TJ, Champion HC: **Neurohumoral features of myocardial stunning due to sudden emotional stress.** *N Engl J Med* 2005, **352:**539-548.
13. Dünser MW, Hasibeder WR: **Dear vasopressin, where is your place in septic shock?** *Crit Care* 2005, **9:**134-135.
14. Sander O, Welters ID, Foex P, Sear JW: **Impact of prolonged elevated heart rate on incidence of major cardiac events in critically ill patients with a high risk of cardiac complications.** *Crit Care Med* 2005, **33:**81-88.