

Commentary

Dear vasopressin, where is your place in septic shock?

Martin W Duenser¹ and Walter R Hasibeder²

¹Resident, Division of General and Surgical Intensive Care Medicine, Department of Anesthesiology and Critical Care Medicine, The Medical University of Innsbruck, Austria

²Head, Department of Anesthesiology and Critical Care Medicine, Krankenhaus der Barmherzigen Schwestern, Ried im Innkreis, Austria

Corresponding author: Martin W Duenser, csab3987@uibk.ac.at

Published online: 15 November 2004

This article is online at <http://ccforum.com/content/9/2/134>

© 2004 BioMed Central Ltd

Critical Care 2005, **9**:134-135 (DOI 10.1186/cc2996)

See review, page 212 [<http://ccforum.com/content/9/2/212>]

Abstract

Cardiovascular failure is one of the central therapeutic problems in patients with severe infection. Although norepinephrine is a potent and, in most cases, highly effective vasopressor agent, very high dosages leading to significant side effects can be necessary to stabilize advanced shock. As a supplementary vasopressor, arginine vasopressin can reverse hemodynamic failure and significantly decrease norepinephrine dosages. Whether the promising possibility of 'bridging' advanced septic shock when the benefit/risk ratio of catecholamine therapy leaves a clinically tolerable range may improve quantitative and qualitative patient outcome can only be determined by a large, prospective, randomized study.

Cardiovascular failure is one of the central therapeutic problems in patients with severe infection. Current recommendations for the treatment of septic shock include volume therapy, and the use of dobutamine and dopamine or norepinephrine [1]. Although particularly norepinephrine is a potent and, in most cases, highly effective vasopressor agent, it cannot stabilize cardiovascular function in some patients with severe hemodynamic failure and sepsis-mediated vascular hyposensitivity to endogenous and exogenous catecholamines [2]. By further increasing norepinephrine dosages ($>0.5-1 \mu\text{g}/\text{kg}/\text{min}$) to guarantee adequate perfusion pressure at these stages of shock, intensivists often enter a vicious circle when significant adrenergic side effects occur that may further deteriorate shock and contribute to an adverse outcome (tachyarrhythmias, myocardial ischemia, decreased cardiac output, increased tissue oxygen consumption, pulmonary hypertension, etc.) [3]. In a minor, but for the critical care clinician most challenging, portion of patients with catecholamine-resistant septic shock, therefore, mortality approaches 80–100%. Correspondingly, more than one-half of the patients succumbing to sepsis die from advanced cardiovascular failure in which conventional

catecholamine vasopressor therapy has reached its therapeutic limits.

Landry and colleagues first reported the successful stabilization of catecholamine-resistant septic shock by infusion of arginine vasopressin (AVP) [4]. In response to this interesting finding, numerous smaller clinical studies have examined the hemodynamic response to AVP infusion in advanced septic shock. As concisely summarized in the review article by Delmas and colleagues [5], most studies reported the reversal of hypotension after the initiation of AVP therapy even in the late stages of cardiovascular failure. Simultaneously, supplementary AVP infusion allowed for a significant reduction in catecholamine support. High adrenergic vasopressor dosages could therefore be decreased into ranges with a tolerable benefit/risk ratio, where significantly less cardiovascular complications occurred when compared with high-dose norepinephrine infusion alone [6]. Moreover, further positive effects of additional AVP infusion on renal and endocrinologic function have been reported in patients with septic shock [7–9].

After cardiovascular function has stabilized and norepinephrine support could be withdrawn to dosages $<0.2-0.3 \mu\text{g}/\text{kg}/\text{min}$, AVP was slowly withdrawn in most studies. Administered as a supplementary vasopressor agent, AVP seems to be capable of bridging the phase of advanced cardiovascular failure and prevent that a vicious circle of high-dose catecholamine therapy develops. The pivotal issue of clinical research on the use of AVP in septic shock must therefore not be the question 'Can AVP replace norepinephrine therapy?', but be the question 'Can the supplementary infusion of AVP in addition to norepinephrine improve the quantitative and qualitative outcome of advanced septic shock?'

Although, as described in this review [5], the cardiovascular response to AVP infusion in septic shock has been well reported, the mechanisms of action of AVP remain much less clear. Since low AVP plasma concentrations have been found in septic shock patients, AVP infusion was first proposed to represent hormone replacement therapy rather than vasopressor therapy [10,11]. Delmas and colleagues are right to ask how robust such a concept of AVP replacement in advanced cardiovascular failure is. A recent study demonstrated that plasma AVP levels were almost always increased in the initial phase of septic shock, and decreased thereafter. Accordingly, the relative AVP deficiency and consequently the suggested indication for AVP hormone replacement was found only in one-third of late septic shock patients [12]. Additionally, the increase in arterial pressure during AVP infusion occurs independently of plasma AVP concentrations [9,13]. AVP therapy at dosages from 0.01 to 0.1 U/min increases plasma concentrations to 100–250 pg/ml [9,14], which is 50-fold to 100-fold higher than the AVP levels reported in patients with cardiogenic shock and septic shock states still responding to conventional therapy [15]. Therefore, institution of AVP infusion in advanced septic shock should not be guided by endocrinologic, but by hemodynamic indications!

Whether the promising possibility of 'bridging' advanced septic shock when the benefit/risk ratio of catecholamine therapy leaves a tolerable clinical range may also improve quantitative and qualitative patient outcome can only be determined by a large, prospective, randomized study. Such a study will finally also answer the question of whether positive effects of AVP on macrocirculatory parameters are outweighed by possible adverse side effects on the microcirculation system, the hepatosplanchnic system or the coagulation system. A prospective multicenter study is currently underway in North America and Australia, with the first results expected in late 2006. While no data of supplementary AVP infusion in advanced septic shock on patient outcome exist, the infusion of AVP in addition to catecholamine vasopressor agents in order to reduce high, potentially toxic adrenergic vasopressor dosages can only be recommended as a last-resort therapy [1].

Delmas and colleagues must be congratulated on their precise and clinically relevant review article, which excellently describes the physiological background of AVP. Moreover, it supplies the critical care clinician with a reasonable overview of the studies so far published on the use of AVP in septic shock [5].

Competing interests

The author(s) declare that they have no competing interests.

References

- Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, *et al.*: **Surviving Sepsis Campaign Management Guidelines Committee: surviving sepsis campaign guidelines for management of severe sepsis and septic shock.** *Crit Care Med* 2004, **32**:858-873.
- Parillo JE: **Pathogenetic mechanisms of septic shock.** *N Engl J Med* 1993, **328**:1471-1477.
- Dünser M, Wenzel V, Mayr AJ, Hasibeder WR: **Arginine vasopressin in vasodilatory shock: a new therapy approach?** *Anaesthesist* 2002, **51**:650-659.
- Landry DW, Levin HR, Gallant EM, Seo S, D'Alessandro D, Oz MZ, Oliver JA: **Vasopressin pressor hypersensitivity in vasodilatory septic shock.** *Crit Care Med* 1997, **25**:1279-1282.
- Delmas A, Leone M, Rousseau S, Albanese J, Martin C: **Vasopressin and terlipressin in septic shock patients.** *Crit Care* 2005, **9**:212-222.
- Dünser M, Mayr AJ, Ulmer H, Knotzer H, Sumann G, Pajk W, Friesenecker B, Hasibeder WR: **Arginine vasopressin in advanced vasodilatory shock. A randomized, prospective, controlled study.** *Circulation* 2003, **107**:2313-2319.
- 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**:1416-1421.
- Patel BM, Chittock DR, Russell JA, Walley KR: **Beneficial effects of short-term vasopressin infusion during severe septic shock.** *Anesthesiology* 2002, **96**:576-582.
- Dünser MW, Hasibeder WR, Wenzel V, Schwarz S, Ulmer H, Knotzer H, Pajk W, Friesenecker BE, Mayr AJ: **Endocrinologic response to vasopressin infusion in advanced vasodilatory shock.** *Crit Care Med* 2004, **32**:1266-1271.
- Oliver JA, Landry DW: **Patient with a sudden drop in blood pressure.** *Crit Care Med* 2003, **31**:326-327.
- Robin JK, Oliver JA, Landry DW: **Vasopressin deficiency in the syndrome of irreversible shock.** *J Trauma* 2003, **54**:149-154.
- Sharshar T, Blanchard A, Paillard M, Raphael JC, Gajdos P, Annane D: **Circulating vasopressin levels in septic shock.** *Crit Care Med* 2003, **31**:1752-1758.
- Argenziano M, Choudhri AF, Oz MC, Rose EA, Smith CR, Landry DW: **A prospective, randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement.** *Circulation* 1997, **96**:286-290.
- Tsuneyoshi I, Yamada H, Kakiyama Y, Nakamura M, Nakano Y, Boyle WA 3rd: **Hemodynamic and metabolic effects of low dose vasopressin infusion in vasodilatory septic shock.** *Crit Care Med* 2001, **29**:487-493.
- Landry DW, Levin HR, Gallant EM, Ashton RC Jr, Seo S, D'Alessandro D, Oz MC, Oliver JA: **Vasopressin deficiency contributes to the vasodilatation of septic shock.** *Circulation* 1997, **95**:1122-1125.