Commentary

Vasopressin in vasodilatory shock: is the heart in danger?

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Abstract

In patients with hyperdynamic hemodynamics, infusing arginine vasopressin (AVP) in advanced vasodilatory shock is usually accompanied by a decrease in cardiac output and in visceral organ blood flow. Depending on the infusion rate, this vasoconstriction also reduces coronary blood flow despite an increased coronary perfusion pressure. In a porcine model of transitory myocardial ischemia-induced left ventricular dysfunction, Müller and colleagues now report that the AVP-related coronary vasoconstriction may impede diastolic relaxation while systolic contraction remains unaffected. Although any AVP-induced myocardial ischemia undoubtedly is a crucial safety issue, these findings need to be discussed in the context of the model design, the dosing of AVP as well as the complex direct, afterload-independent and systemic, vasoconstriction-related effects on the heart.

In the previous issue of *Critical Care* Müller and colleagues reported that arginine vasopressin (AVP) (either 0.005 U/kg/min or titrated to a mean arterial pressure of 90 mmHg) after porcine myocardial ischemia reduced the cardiac output and the brain, coronary and kidney blood flow [1]. The fall in blood flow was compensated for by a marked increase in oxygen extraction. In particular, while left heart systolic contraction was not affected, AVP impaired diastolic relaxation and ventricular compliance. Neither the ischemic period nor the subsequent AVP infusion influenced the plasma troponin T level. The authors conclude that using AVP should be cautioned during cardiac surgery and AVP should be withheld in ischemic heart failure.

How does Müller and colleagues' study compare with the existing literature? The observed cerebral and renal vasoconstriction confirms findings by Malay and colleagues: incremental AVP – similar to the pure α-agonist phenylephrine – dose-dependently reduced organ blood flow [2]. Müller and colleagues unfortunately did not measure portal venous flow, but it is tempting to speculate that the increased hepatic arterial flow reflects a well-maintained hepatic arterial buffer response, which at least partially compensated for the most likely reduced portal venous flow. In fact, low doses of the AVP analogue terlipressin during long-term, hyperdynamic porcine endotoxemia restored this otherwise impaired physiologic adaptation [3].

The myocardial effects reported by Müller and colleagues deserve particular attention: in good agreement with their results, ample literature is available that the dose-dependent vasoconstrictor properties of AVP are also present in the coronary circulation [4-8]. Nevertheless, direct afterload-independent (that is, unrelated to systemic vasoconstriction) myocardial effects of AVP are a matter for debate: both positive inotrope properties [6,9] and negative inotrope properties [4,8,10,11] have been reported in isolated heart, papillary muscle or cardiomyocyte preparations. Furthermore, it remains unsettled whether any negative inotrope effect is mainly caused by the reduced coronary perfusion [7], because cardiac efficiency (that is, the product of left ventricular pressure times the heart rate normalized for myocardial oxygen consumption) was well maintained under constant flow conditions [12]. The present data do not allow one to conclude whether the impaired diastolic relaxation is afterload dependent or is a genuine myocardial effect: unfortunately, the authors did not perform experiments using other pure vasoconstrictors, – for example, pure α-adrenoceptor agonists or K_{ATP} channel blockers devoid of cardiac

AVP = arginine vasopressin.

and mitochondrial effects, titrated to the same systemic hemodynamic endpoints.

What do we learn from Müller and colleagues' findings? In this context, the experimental design must be taken into account. The model *per se* is hypodynamic (that is, characterized by hypotension and a simultaneous fall in cardiac output resulting from ischemic heart failure), and thus differs from the hyperdynamic, vasodilatory circulation in patients usually treated with AVP [13]. In addition, the current rationale of AVP use comprises a supplemental infusion, targeted to restore vasopressin levels to those comparable with other causes of hypotension, and presents AVP simultaneously with catecholamines rather than using AVP alone [13]. In fact, we found during long-term, resuscitated hyperdynamic porcine fecal peritonitis that combining noradrenaline with AVP to maintain baseline blood pressure did not affect the heart rate-independent parameters of left ventricular systolic and diastolic function, and that the combination coincided with significantly lower plasma troponin I levels than treatment with noradrenaline alone (Hauser B, Giudici R, Simon F, Nguyen CD, Radermacher P, Calzia E, unpublished data).

Furthermore, although Müller and colleagues used the lowest infusion rate necessary to restore blood pressure, it was still substantially higher than that considered safe by others [2,13] and used in the Vasopressin in Septic Shock Trial [14]. It is noteworthy that this low dose of AVP was associated with, if any, beneficial effects on parameters of myocardial function and/or injury: in a retrospective, uncontrolled study, Dünser and colleagues observed a time-dependent fall of troponin I levels in patients treated for catecholamine-resistant vasodilatory shock after cardiotomy [15]; and in a prospective, randomized, controlled study investigating a mixed intensive care unit population, the same group found a markedly reduced incidence of new-onset tachyarrhythmias in patients treated with AVP and noradrenaline compared with those patients receiving noradrenaline alone [16].

What can we conclude on the clinical use of AVP? The rate of adverse events in the Vasopressin in Septic Shock Trial was similar in the two populations with and without vasopressin infusion, but patients with underlying heart disease were not enrolled [14]. Any safety issue potentially limiting the clinical use of AVP therefore remains a matter of concern. Given its vasoconstrictor properties, which are not accompanied by positive inotropic qualities such as in the case of comparably potent standard care competitors (that is, the catecholamines noradrenaline and adrenaline), AVP may depress cardiac function as a result of impaired coronary blood flow despite increased coronary artery perfusion pressure. Consequently, as Müller and colleagues conclude, and despite encouraging case reports [17], the use of AVP should be cautioned during cardiogenic shock resulting from congestive heart failure and/or myocardial ischemia.

It is noteworthy that despite only short-term symptomatic improvement and the neutral long-term results of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study using tolvaptan, AVP receptor blockade is still under investigation in patients with congestive heart failure [18]. A recent comment in *Critical Care* is therefore more valid than ever: 'Vasopressin in vasodilatory shock: ensure organ blood flow, and take care of the heart!' [19].

Competing interests

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