Commentary

Vasopressin and ischaemic heart disease: more than coronary vasoconstriction?

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See related research by Indrambarya *et al*., http://ccforum.com/content/13/3/R98

Abstract

During advanced vasodilatory shock, arginine vasopressin (AVP) is increasingly used to restore blood pressure and thus to reduce catecholamine requirements. The AVP-related rise in mean arterial pressure is due to systemic vasoconstriction, which, depending on the infusion rate, may also reduce coronary blood flow despite an increased coronary perfusion pressure. In a murine model of myocardial ischaemia, Indrambarya and colleagues now report that a 3-day infusion of AVP decreased the left ventricular ejection fraction, ultimately resulting in increased mortality, and thus compared unfavourably with a standard treatment using dobutamine. The AVP-related impairment myocardial dysfunction did not result from the increased left ventricular afterload but from a direct effect on cardiac contractility. Consequently, the authors conclude that the use of AVP should be cautioned in patients with underlying cardiac disease.

In the previous issue of *Critical Care*, Indrambarya and colleagues compared a 72-hour infusion of arginine vasopressin (AVP) (infusion rate equivalent to 0.04 IU/min in a 70 kg human being), dobutamine (8.33 μg/kg/min) and vehicle in mice that had undergone myocardial ischaemia induced by a 1-hour ligation of the left anterior descending coronary artery [1]. While AVP did not affect heart function in sham control mice, echocardiography demonstrated a more pronounced fall in the left ventricular ejection fraction at day 1 after coronary ischaemia than in the vehicle-treated and dobutamine-treated animals, which had not resumed at day 3. Since the heart rate, blood pressure and end-diastolic volume remained unaffected, the decreased ejection fraction was affiliated with a reduced stroke volume. This difference in contractility coincided with a marked depression of the cardiac oxytocin receptor expression and, ultimately, a nearly doubled mortality at day 7.

How does Indrambarya and colleagues' study compare with the existing literature? Müller and colleagues reported recently in this journal that AVP dose-dependently reduced coronary blood flow in swine after transient myocardial ischaemia, which coincided with impaired left heart diastolic relaxation [2]. While other authors also highlighted its coronary vasoconstrictor properties [3-6], AVP more efficiently increased coronary blood flow in swine after closed-chest cardiopulmonary resuscitation than adrenaline [7] and attenuated the otherwise progressive rise in troponin I blood levels during porcine faecal peritonitis-induced hypotension treated with noradrenaline [8]. Moreover, infusing AVP was devoid of adverse effects on the heart in patients after cardiac surgery [9,10] and with cardiogenic shock [11,12]. Finally, supplementing an ongoing noradrenaline infusion in patients with vasodilatory shock was associated with a sixfold reduction of new-onset tachyarrhythmias when infused to supplement [13].

Direct (that is, afterload-independent) myocardial effects unrelated to coronary vasoconstriction of AVP are also controversially discussed: positive inotrope properties [5] and negative inotrope properties [3,4,6] have been reported. Obviously, any coronary hypoperfusion assumes particular importance in this context: 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 [14]. Unfortunately, the recent multicentre Vasopressin in Septic Shock Trial is inconclusive on this issue: cardiac arrhythmia and myocardial ischaemia events were identical in the two study groups receiving vasopressin or the standard noradrenaline treatment, but patients with cardiogenic shock, patents with congestive heart failure of New York Health Association class

AVP = arginine vasopressin; K_{ATP} = ATP-dependent potassium.

III or class IV, and patents with unstable coronary syndrome were explicitly excluded [15].

Can we reconcile these contradictory observations? Clearly, the model studied by Indrambarya and colleagues markedly differs from the previous studies: while the latter studies focused on short-term AVP infusion during vasodilatory shock with or without a cardiogenic component, the former investigated the effects of AVP over several days after myocardial ischaemia without overt circulatory shock [1]. In fact, none of the experimental groups presented with a major drop in mean blood pressure, and deterioration of behaviour, grooming, or activity level was not observed at all. Consequently, the adequacy of the model might be a matter for debate. Nevertheless, it must be emphasized that the AVP effects were unrelated to any modification of cardiac loading parameters and were completely absent in sham-operated animals. Indrambarya and colleagues therefore elegantly demonstrate that cardiac ischaemia and subsequent reperfusion injury may specifically contribute to the deleterious side effects of AVP. This observation is in good agreement with previous authors reporting that increased circulating vasopressin levels predispose to persistent pronounced myocardial ischaemia [16], most probably as a result of an attenuated modulatory role of nitric oxide and the release of vasonconstrictor prostanoids [17].

Interestingly, although cardiac function was nearly identical in the three experimental groups at day 3 after myocardial ischaemia, mortality was significantly higher in the AVP-treated mice. The authors speculate that this observation mirrors sudden cardiac arrhythmia events, which are referred to an increased membrane excitability that results from a vasopressin-related blockade of cardiomyocyte ATP-dependent potassium (K_{ATP}) channels. Clearly, infusing vasopressin has been reported to induce arrhythmia (for example, torsade de pointes) even without evidence of myocardial ischaemia [18,19]. In addition, the deleterious consequences of K_{ATP} channel blockade during myocardial ischaemia are well established [20]. Nevertheless, it remains open whether K_{ATP} channel blockade is the underlying mechanism of a vasopressin-related cardiac arrhythmia: K_{ATP} channel blockers (for example, glibenclamide) can prevent cardiac arrhythmia associated with myocardial ischaemia, and compounds selective for sarcolemmal K_{ATP} channels represent a new class of ischaemia-selective anti-arrhythmic drugs [21].

What can we conclude from the study by Indrambarya and colleagues? Safety issues on the clinical use of AVP remain a matter of concern. Given its vasoconstrictor properties, which are not accompanied by positive inotropic qualities such as in the case of its 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. Indrambarya and colleagues now show that cardiac ischaemia may specifically contribute to (or even enhance?) the deleterious side effects of AVP independently of its afterload effects. Consequently, the authors caution the use of AVP in patients with underlying cardiac failure – in particular, ischaemic heart disease – thus further emphasizing a previous commentary in this journal: 'Vasopressin in vasodilatory shock: ensure organ blood flow, but take care of the heart!' [22].

Competing interests

PA and PR have received a research grant from the Ferring Research Institute Inc., San Diego, CA, USA and consultant fees from Ferring Pharmaceutical A/S, København, Denmark, for help with designing preclinical experiments – companies that are involved in the development of selective vasopressin agonists for therapeutic purposes.

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