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COMMENTARY

Inotropes and vasopressors: more than haemodynamics!

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Circulatory shock is characterized by arterial hypotension requiring fluid resuscitation combined with inotropes and/or vasopressors to correct the otherwise life-threatening impairment of oxygen supply to peripheral tissues. Catecholamines represent the current therapeutic choice, but this standard is only based on empirical clinical experience. Although there is evidence that some catecholamines may be better than others, it is a matter of debate which one may be the most effective and/or the safest for the different situations. In their review in this issue of the *British Journal of Pharmacology*, Bangash *et al.* provide an overview of the pharmacology as well as the available clinical data on the therapeutic use of endogenous catecholamines, their synthetic derivatives and a range of other agents (vasopressin and its analogues, PDE inhibitors and levosimendan). The authors point out that, despite well-established receptor pharmacology, the clinical effects of these treatments are poorly understood. Hence, further investigations are essential to determine which catecholamine, or, in a broader sense, which alternative vasopressor and/or inotrope is the most appropriate for a particular clinical condition.

LINKED ARTICLES

This article is a commentary on Bangash *et al.*, pp. 2015–2033 of this issue and is commented on by De Backer and Scolletta, pp. 2012–2014 of this issue. To view Bangash *et al.* visit http://dx.doi.org/10.1111/j.1476-5381.2011.01588.x and to view De Backer and Scolletta visit http://dx.doi.org/10.1111/j.1476-5381.2011.01746.x

In the present issue of the *British Journal of Pharmacology*, Bangash *et al.* (2012) review the pharmacology as well as the available clinical data on the therapeutic use of various inotropes and vasopressor agents used for the haemodynamic management of (septic) shock. By definition, circulatory shock is characterized by arterial hypotension that necessitates immediate intervention to maintain the balance of tissue oxygen supply and demand. In practice, the longer and the more frequent periods of hypotension are present in a patient, the less likely is survival (Dünser *et al.*, 2009b), and early aggressive resuscitation is associated with improved outcome (Rivers *et al.*, 2001). Besides fluid administration to increase the circulating blood volume, in most cases, vasoactive drugs are required to restore an adequate perfusion pressure, and up to now, catecholamines represent the current therapeutic choice. According to their pharmacological profile, catecholamines are traditionally used for their predominant inotropic, vasodilating or constrictor effects. However, most of the substances currently available for clinical use share properties of each category in variable amounts. In addition, clinicians should not forget two fundamental aspects of catecholamine action. First, because of the ubiquitous presence of adrenoceptors, endogenous catecholamines. as well as their synthetic derivatives, have pronounced effects on virtually all tissues (many of which were described several years ago), in particular on the immune system (van der Poll *et al.*, 1996; Flierl *et al.*, 2008), on energy metabolism (Cori and Cori, 1928; Bearn *et al.*, 1951) and on gastrointestinal motility (McDougal and West, 1954). Second, the adrenoceptor density and responsiveness to catecholamines are markedly altered by both the underlying disease and the ongoing catecholamine treatment (Silverman *et al.*, 1993; Pichot *et al.*, 2010). Bangash *et al.* (2012) have to be commended that they not only describe the various endogenous catecholamines and their synthetic derivatives but also thoroughly discuss possible alternatives, such as vasopressin and its analogues, PDE inhibitors and levosimendan. For sake of conciseness, the authors do not discuss other drugs, which have also been

investigated to treat arterial hypotension associated with circulatory shock, such as inhibitors of ATP-dependent K^+-channels (glibenclamide; Singer *et al.*, 2005; Warrillow *et al.*, 2006) of NOS (N^{ω}-monomethyl-L-arginine; Bakker *et al.*, 2004; López *et al.*, 2004)and of cGMP (methylene blue; Kirov *et al.*, 2001; Juffermans *et al.*, 2010), but this self-limitation is more than justified given the paucity of the clinical data available for these treatments, as well as the fairly equivocal results of these approaches in larger trials.

What conclusions can intensive care physicians and pharmacologists draw from this review? Clearly, '*not all catecholamines are created equal*' (Carpati *et al.*, 1997), and consequently, some catecholamines (noradrenaline) can be superior to others (dopamine, adrenaline), at least under specific conditions such as cardiogenic (De Backer *et al.*, 2010) or septic (De Backer *et al.*, 2003) shock. However, regardless of the drug class and, hence, by no means exclusively catecholamines, all inotropes and vasopressors have a plethora of properties beyond those contributing to haemodynamic stabilization. Toxic effects can therefore result from the haemodynamic effects *per se* (as highlighted by the authors), for example, from regional ischemia due to vascular 'overconstriction' and/or the use of unusually high doses to achieve physiological goals but also from increased oxidative stress (Rump and Klaus, 1994), interaction with cellular energy metabolism (Koo *et al.*, 2000; Lünemann *et al.*, 2001; Heringlake *et al.*, 2007; Simon *et al.*, 2009) and/or modulation of the inflammatory response (van der Poll *et al.*, 1996; Loick *et al.*, 1997; Russell and Walley, 2010). Bangash *et al.* take into account all these aspects in a well-balanced way, but one crucial problem necessarily remains unsolved: the present standard use of catecholamines for the treatment of circulatory shock is only based on empirical clinical experience, and therefore, it is not known if an alternative practice might result in improved outcome (Singer, 2007). In other words, could '*de-catecholaminization*' (Singer and Matthay, 2011) to reduce iatrogenic stress (Brame and Singer, 2010) be the target of research, rather than finding the 'best' catecholamine? In fact, two results from the Randomized, Controlled Trial of Vasopressin vs. Norepinephrine in Septic Shock (VASST) trial (Russell *et al.*, 2008) might allow the generation of a new hypothesis, from this notion of seeking a 'non-catecholamine' treatment for circulatory shock. Firstly, the overall result did not show any benefit for the vasopressin-treated patients; however, in contrast to the underlying hypothesis that the more severe patients might benefit from this approach, the subgroup of patients with only moderate noradrenaline requirements, that is, those in whom weaning off the catecholamine support was more frequent (% of patients weaned off noradrenaline in the four subgroups of the VASST trial: 'vasopressin, less severe': 79%; 'noradrenaline, less severe': 76%; 'vasopressin; more severe: 67%; 'noradrenaline, more severe': 69%), presented with significantly improved survival. In addition, more patients died while still on noradrenaline in the noradrenaline group (20%) than in the AVP group (9%). Secondly, vasopressin reduced the progression to renal failure and the need for extracorporeal renal support at least in one out of the five patient subgroups, after *post hoc* stratification according to the RIFLE criteria, namely those 'at risk of kidney injury' (i.e. patients with an increase by a factor of 1.5–2.0) (Gordon *et al.*, 2010). In addition, other authors have demonstrated a direct relationship between mortality and the vasopressor load (Dünser *et al.*, 2009a), that is the weighted mean infusion rate of the catecholamines (adrenaline, noradrenaline, dopamine) and phenylephrine (Russell *et al.*, 2008).

In conclusion, the review by Bangash *et al.* (2012) provides a well executed, state-of-the-art, survey of the current knowledge and clinical practice of vasopressors and inotropes for the haemodynamic management of circulatory shock. Additional studies are now warranted to answer the question, which type of agent is the most appropriate for which aetiology of shock? Most likely, only experimental studies *in vivo* that fulfil the criteria of a clinically relevant model (Wagner *et al.*, 2011) will be able to provide an answer than can be transferred to clinical practice.

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