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COMMENTARY

Vasopressors in shock: too early to move away from catecholamines?

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Adrenergic and non-adrenergic vasopressor agents can be used to correct hypotension in shock states. For a similar increase in arterial pressure, these agents may be associated with different haemodynamic, metabolic, endocrinological or immunological effects. But how relevant are these differences? Do these affect the outcome of patients with shock? Large-scale randomized trials comparing the effects of different vasopressor agents are scarce. Data on potential alternatives, and especially vasopressin, are even more scarce. Over-interpretation of the data, and especially of data obtained in subgroups, is common. Analysis of subgroups may be useful to address mechanisms and to raise hypotheses. However, subgroup analysis is often biased by confounding factors, especially when subgroup categorization is defined by response to therapy and not by intrinsic patient or disease characteristics. In this issue of the *British Journal of Pharmacology*, Bracht and colleagues present their interpretation of data from trials comparing vasopressin with noradrenaline in patients with septic shock. Here, we present an alternative interpretation.

LINKED ARTICLES
This article is a commentary on Bangash *et al.*, pp. 2015–2033 and Bracht *et al.*, pp. 2009–2011 of this issue. To view Bangash *et al.* visit http://dx.doi.org/10.1111/j.1476-5381.2011.01588.x and to view Bracht *et al.* visit http://dx.doi.org/10.1111/j.1476-5381.2011.01776.x

Commentary

Shock, whatever its cause, is characterized by hypotension and signs of tissue hypoperfusion, which contribute to the development of organ dysfunction. Both severity and duration of hypotension are associated with a poor outcome (Varpula *et al.*, 2005; Dunser *et al.*, 2009). Experimental data suggest that correction of hypotension is associated with prolonged survival time (Sun *et al.*, 2003). However, experimental trials investigate only the short-term impact of shock and its therapy, while unwanted effects of vasopressor agents may have delayed effects on outcome. Several agents can be used to correct hypotension or to increase cardiac output, but physicians face an important question: what agent should be used? In this issue, Bangash *et al.* (2012) provide an extensive overview of the pharmacological profile of various adrenergic and non-adrenergic agents that can be used for this purpose. The different agents not only have slightly different haemodynamic effects (including on systemic haemodynamics but also on regional circulations and microcirculation) but also different metabolic or immunological effects. The true question raised by this excellent review is whether differences in pharmacological profile may be associated with, or may even contribute to, differences in outcome. Only large-scale randomized trials can provide relevant information on the clinical relevance of these differences, but such trials are still relatively scarce.

Several moderate to large-scale randomized trials compared the effects on outcome of different vasopressor agents. Although these provide important information, one should be cautious about over-interpreting these data. Trials should be evaluated on their primary outcome for which these are powered. Adrenaline and noradrenaline were compared in two randomized trials, but both trials were relatively small in size (610 patients in total) and did not reach sufficient power to draw definitive conclusions on the superiority of one agent over the other. Dopamine and noradrenaline were compared in two trials. In the largest trial including 1679 patients, no significant difference for the risk of death was observed in the entire population (odds ratios with dopamine 1.17; 95% confidence interval, 0.97–1.42; $P = 0.10$). However, dopamine was associated with increased incidence of arrhythmic events. In addition, the risk of death in patients with cardiogenic shock increased with dopamine. In a smaller trial (252

patients), 28 day mortality was 50% with dopamine compared with 43% for noradrenaline (P = 0.282). In a meta-analysis including 2043 patients with any type of shock, the aggregated risk of death was significantly lower for patients receiving noradrenaline compared with patients randomized to dopamine [relative risk (RR): 0.91 (0.83–0.99), P = 0.028] (Vasu *et al.*, 2011). Similarly, in 1408 patients with septic shock, the aggregated risk of death was also higher with dopamine compared to noradrenaline [RR: 1.10 (1.01–1.20), P = 0.035] (De Backer *et al.*, 2012). Hence, the choice of the adrenergic agent may indeed affect outcome.

Adrenergic agents have important drawbacks, but should non-adrenergic vasopressor agents be preferred? Obviously, alternative options are not always better. Administration of a non selective nitric oxide synthase inhibitor, L-NMMA, was associated with an increased risk of death (Lopez *et al.*, 2004). As demonstrated by the VASST trial, vasopressin may be a better candidate (Russell *et al.*, 2008), but do the available data really support replacement of adrenergic agents by vasopressin? This was the core of the accompanying commentary by Bracht *et al.* (2012), but it deserves some further comments.

The data provided by Bracht *et al.* (2012) to support the concept of 'decatecholaminization' are interesting but require detailed scrutiny. First, trials indeed relate cumulative adrenergic load to outcome. For example, patients who fail to respond to dopamine and require addition of a second vasopressor agent have a higher mortality than those responding to dopamine (Levy *et al.*, 2005; De Backer *et al.*, 2010). Statistical association does not mean that these agents are responsible for the increased mortality. These comparisons are indeed biased, as high doses of agents are required due to a higher severity of shock. Second, randomized studies comparing the effects on outcome of adrenergic agents (and noradrenaline in particular) to vasopressin as the first vasopressor agent are still lacking. Third, in terms of weaning from noradrenaline, the data from the VASST trial (Russell *et al.*, 2008) do not explain the difference in mortality. In the low severity group, the difference in outcome (–9%) largely outweighs the difference in rate of full weaning from noradrenaline (+3%). Similarly, in the more severe group, mortality failed to decrease, while the proportion of patients weaned from noradrenaline similarly increased (+2%). Hence, the almost similar increase in the number of patients totally weaned from noradrenaline in both subgroups cannot account for differences in outcome. Fourth, if an agent has deleterious effects, decreasing its dose, even if not resulting in full weaning, would, *per se*, lead to an improvement. In the VASST trial, weaning from a low dose of noradrenaline in the less severe group was beneficial, while decreasing higher doses of noradrenaline in the more severe group did not lead in an improved outcome. Fifth, if 'decatecholaminization' was important, one would expect that the earlier the introduction of vasopressin, and hence the shorter the exposure to adrenergic agents, the better the effect. The VASST investigators failed to observe any difference in the effects of vasopressin in patients treated within 12 h of shock onset or later, with a P-value for interaction at 0.28. Sixth, Bracht *et al.* (2012) stated 'more patients died while still on noradrenaline in the noradrenaline group (20%) than in the AVP group (9%). This comment is not relevant to "decatecholaminization', as these patients died anyway, whether or not they were exposed to noradrenaline. If anything, one may consider that increasing 'decatecholaminization' rate from 80% to 91% did not affect the final outcome, as all these patients ultimately died.

Finally, the analysis showing that vasopressin may behave differently in subgroups of patients depending on their baseline renal function (Gordon *et al.*, 2010) is attractive but should also be cautiously interpreted. Indeed, vasopressin seemingly affected the evolution of renal function in a subgroup of 106 patients (53 randomized to vasopressin) but not in the remaining 672 patients. In this subgroup of patient, vasopressin was also associated with a marked reduction in risk of death, even though most of these were in more severe shock (which is apparently in contradiction with predefined subgroup analysis according to shock severity). Given the multiplicity of comparisons, these results may either be due to chance or confounding factors (no stratification for this criteria: eight very small subgroups) or, even worse, can be real but compensated by a deleterious effect in other groups as there was no beneficial effect for the entire population. So, at best, this subgroup analysis is hypothesis generating.

At this stage, all we can say from the excellent VASST trial is that, in an adequately powered trial, there was no significant improvement in outcome with vasopressin, compared with noradrenaline. In the predefined subgroup of less severe shock, for which randomization was stratified, low-dose vasopressin resulted in an improved outcome. Although attractive, it is difficult to state that vasopressin should be used in less severe patients. First, the doses of adrenergic agents change over time, and some patients may have moved from less severe to more severe group (and *vice versa*) during the pre-randomization period, making group definitions quite loose. Second, how can this criterion be used at bedside? If a patient is treated with 20 $\mu g \cdot min^{-1}$of noradrenaline for more than 12 h after the onset of shock, but this dose is progressively decreased in the following hours, should vasopressin then be initiated? Third, noradrenaline doses are usually expressed as $\mu g\ kg^{-1} \cdot min^{-1}$ not as $\mu g \cdot min^{-1}$ (the latter were the units used for stratification in the VASST trial), and this makes comparisons and applicability of the results even more difficult. According to subgroup categorization, vasopressin should be considered as beneficial in a 50 kg patient receiving noradrenaline at a dose of 10 $\mu g\ min^{-1}$ but not in a 100 kg patient receiving noradrenaline at dose of 20 $\mu g\ min^{-1}$, even though both patients receive exactly the same dose of 0.2 $\mu g\ kg^{-1} \cdot min^{-1}$ of noradrenaline. Finally, from a purely statistical perspective, the test for interaction was negative, suggesting that the more and less severe groups of patients did not behave differently. We cannot agree more with the final sentence of the VASST investigators 'We did not find a significant reduction in mortality rates with vasopressin' (Russell *et al.*, 2008). Further trials should evaluate the effects of vasopressor agents in shock and, in particular, vasopressin and noradrenaline.

References

Bangash M, Kong ML, Pearse R (2012). Use of inotropes and vasopressor agents in critically ill patients. Br J Pharmacol 165: 2015–2033.

Bracht H, Calzia E, Georgieff M, Singer J, Radermacher P, Russell J (2012). Inotropes and vasopressors: more than haemodynamics! Br J Pharmacol 165: 2009–2011.

De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C *et al*. (2010). Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 362: 779–789.

De Backer D, Aldecoa C, Njimi H, Vincent J-L (2012). Dopamine versus norepinephrine in the treatment of septic shock: a meta analysis. Crit Care Med 40: 725–730.

Dunser MW, Takala J, Ulmer H, Mayr VD, Luckner G, Jochberger S *et al*. (2009). Arterial blood pressure during early sepsis and outcome. Intensive Care Med 35: 1225–1233.

Gordon AC, Russell JA, Walley KR, Singer J, Ayers D, Storms MM *et al*. (2010). The effects of vasopressin on acute kidney injury in septic shock. Intensive Care Med 36: 83–91.

Levy B, Dusang B, Annane D, Gibot S, Bollaert PE (2005). Cardiovascular response to dopamine and early prediction of outcome. A prospective multicenter study. Crit Care Med 33: 2172–2177.

Lopez A, Lorente JA, Steingrub J, Bakker J, McLuckie A, Willatts S *et al*. (2004). Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. Crit Care Med 32: 21–30.

Russell JA, Walley KR, Singer J, Gordon AC, Hebert PC, Cooper DJ *et al*. (2008). Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 358: 877–887.

Sun Q, Tu Z, Lobo S, Dimopoulos G, Nagy N, Rogiers P *et al*. (2003). Optimal adrenergic support in septic shock due to peritonitis. Anesthesiology 98: 888–896.

Varpula M, Tallgren M, Saukkonen K, Voipio-Pulkki LM, Pettila V (2005). Hemodynamic variables related to outcome in septic shock. Intensive Care Med 31: 1066–1071.

Vasu TS, Cavallazzi R, Hirani A, Kaplan G, Leiby B, Marik PE (2011). Norepinephrine or dopamine for septic shock: a systematic review of randomized clinical trials. J Intensive Care Med. DOI: 10.1177/0885066610396312.