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LETTER

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Septic shock, noradrenaline requirements and alpha-2 agonists: Fishing in the right pond?

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Bellomo et al. [1] confirm the clinical [2–4] data showing a reduction in noradrenaline (NA) requirements in the setting of septic shock following administration of an alpha-2 agonist, dexmedetomidine.

The intensivist is unaware that the retrospective analysis has thoroughly changed the design of the study from "sedation vs. outcome" to "sympathetic de-activation vs. circulation" (i.e., upregulation of alpha-1 receptors vs. NA requirements). Furthermore, the design is not optimal. SPICE III [5] compared early dexmedetomidine ("dex") versus usual sedation ($-2 < \text{RASS} < +1$) [5]. Bellomo achieved RASS ~ −4, in both groups (results [1]): The dex group received also propofol (95% of the patients), midazolam (43%) and *higher* doses of opioids (Table S1 [1]). Thus, any effect of dex is *drowned* as a consequence of adding usual sedation to dex. Nevertheless, in the dex group, (a) the overall NA requirement ("NA equivalent") is lowered by 25%, nonsignificantly, but of daily clinical relevance for the intensivist; (b) The NA requirement necessary to achieve a target pressure lowered, as a function of dose (i.e., compatible with a dose-dependent sympathetic de-activation). NA requirements should be readdressed in the dexmedetomidine-*only* patients versus the usual sedation-*only* patients, throughout the whole SPICE III [5] database.

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Authors' response

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We thank Dargent and colleagues for the comments about our study on the hemodynamic changes seen in patients with septic shock treated with dexmedetomidine as primary sedating agent versus usual care [1]. We agree that the retrospective nature of the study creates problems because the original study was a sedation trial with mortality as the outcome, while the retrospective investigation of the hemodynamic effects of dexmedetomidine was a post hoc physiological assessment in patients who were mostly deeply sedated at the time of investigation (median RASS of −3) and receiving propofol in most cases, fentanyl in the majority and midazolam in close to half of cases. In such a setting, the effect of dexmedetomidine is markedly attenuated by the impact of these drugs. Thus, we agree that it is all the more remarkable that, in the dexmedetomidine group, the overall norepinephrine (noradrenaline) requirements were lower and that the dose required to achieve target mean arterial pressure was also decreased. Finally, we agree that comparing patients on dexmedetomidine only versus patients receiving usual care would be ideal. Unfortunately, we were unable to identify such a cohort of patients. Nonetheless, within the limitations of the design and the population studied, we think that our findings are consistent with a substantial body of experimental data supporting the view that, in the septic, vasodilated state,

dexmedetomidine (and central alpha-2 agonists) infusion does not exacerbate hypotension or increase vasopressor requirements but, in fact, appears to do the opposite [6–9].

Abbreviations
APACHE: Acute Physiology and Chronic Health Evaluation; NA: Noradrenaline; RASS: Richmond agitation-sedation scale.

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AD, LQ, and JPQ, contributed to the writing. All authors read and approved the final manuscript.

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LQ received honoraria and unrestricted research grants from Boehringer-Ingelheim, France, UCB Pharma, Belgium, and Abbott International, Il, USA [1986–1996], and holds US patent 8 846 606 B2, September 30, 2014 (method and drug composition for treating septic shock hypotension).

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