Ribeiro and Restelatto *Critical Care* (2016) 20:289
DOI 10.1186/s13054-016-1465-4

Critical Care

LETTER Open Access

Increased mortality with the use of adrenaline in shock: the evidence is still limited

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See related research by Tarvasmäki et al. http://ccforum.biomedcentral.com/articles/10.1186/s13054-016-1387-1

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, Odds ratio; RR, Relative risk

We have read with great interest, but also with some concern, the paper by Tarvasmäki et al., recently published in *Critical Care* [1]. In this observational study, adrenaline was independently associated with mortality in cardiogenic shock (CS). The data presented are the odds ratio (OR) of a multivariable propensity score-adjusted analysis, where patients that used adrenaline had an adjusted OR of 3.0 (95 % confidence interval 1.3–7.2) for 90-day mortality in comparison with patients who had not received adrenaline.

The main concern with the article is precisely the choice of the OR as its measure of effect. The misleading use of OR as an approximation of the relative risk (RR) when the outcome of interest is very frequent (which is certainly the case in this study, where the mortality incidence was around 40 %) is a long recognized problem and alternative methods for analysis, such as the Poisson regression with robust variance, have been suggested as appropriate approaches to estimate the RR for more than a decade [2]. Since the authors did not present the RR, one could use a suggested well-known formula [3] to estimate the RR from a given OR and outcome incidence: $RR = OR/(1 - Incidence + (Incidence \times OR))$. Applying this equation, the RR for 90-day mortality would be 1.67 (1.16–2.07).

Although this number still shows a statistically significant increase in mortality, one must remember that this information comes from an observational study. The GRADE working group proposal for rating the quality of evidence for interventions ranks the conclusions from observational studies as low quality evidence [4]. This quality of evidence can be rated up if a large magnitude of effect is present. However, the suggestion in the GRADE guidelines is that this rating up should be done when the RR as at least equal to 2, which was not the case in this study [5]. In conclusion, the evidence

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suggesting an increased mortality risk associated with adrenaline use in CS is low quality (at best, since one could rate it down to very low quality if we consider that there is imprecision in the estimate) and, therefore, an adequately designed and powered clinical trial is imperative to provide a reliable answer to this question.

Authors' response to "Increased mortality with the use of adrenaline in shock: the evidence is still limited"

Tuukka Tarvasmäki, Reijo Sund, Johan Lassus, Alexandre Mebazaa and Veli-Pekka Harjola

We thank Ribeiro and Restelatto for their comments on our article about assessing the concurrent use of vasoactive medications in cardiogenic shock [1]. They raise two potential issues regarding our main finding, the association between adrenaline use and 90-day mortality: the use of the odds ratio (OR) instead of relative risk (RR) and that the evidence is from an observational study. While we agree that the OR might not always accurately describe the RR, logistic regression analysis is a gold standard statistical technique for binary responses, so it was an obvious choice also in our study. Moreover, after conversion from ORs, both the univariate and adjusted multivariable RR for adrenaline use were over 2 (2.3 and 2.2, respectively).

As we were curious about the association between adrenaline use and increased mortality, we performed and reported further analyses using additional propensity score adjustments in the subgroup of vasopressor-treated patients as described in our article. The effect size diminished a bit but remained statistically significant (OR 3.0, 95 % confidence interval 1.3–7.2, $p = 0.01$). We also reported analyses using propensity score matching, Kaplan–Meier curves and log-rank tests, as well as an adjusted Cox regression model and the association was statistically significant regardless of the analysis technique. As suggested by Ribeiro and Restelatto, we performed an additional analysis using Poisson regression with robust variance: for adrenaline use in a multivariable model with propensity score adjustment within the subgroup of vasopressor-treated patients, the RR for 90-day mortality was 1.5 (95 % confidence interval 1.1–2.1, $p = 0.017$), i.e., still a statistically significant association.

So, the main finding is supported by several sensitivity analyses and we can be confident that there is a clearly statistically significant association between adrenaline use and 90-day mortality in our data. Albeit being a result from an observational study, we argue that this is still a clinically significant finding, especially considering the very high frequency of (poor) outcome also emphasized by Ribeiro and Restelatto. This warrants attention because it raises justified questions about the safety of this treatment. And we fully agree, as we conclude in our article, that there is a need for randomized controlled trial to confirm this detected association.

Authors' contributions
Both authors wrote the manuscript and conducted the data re-analysis. Both authors read and approved the final manuscript.

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Dr. Ribeiro is professor of epidemiology in the Federal University of Rio Grande do Sul. Dr. Restelatto is an intensive care specialist in Hospital de Clínicas de Porto Alegre.

Competing interests
The authors declare that they have no competing interests regarding this manuscript.

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Published online: 20 September 2016

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