Arginine Vasopressin in Vasodilatory Shock
To the Editor:
Dünser et al\(^1\) concluded that the combined infusion of vasopressin and norepinephrine is superior to infusion of norepinephrine alone in the treatment of shock resistant to catecholamine. We believe that this study is flawed and do not support such a conclusion. First of all, the design included two interventions in parallel, one of arginine vasopressin (and its control group in the other arm, without such treatment) and the other with two different doses of norepinephrine. They concluded that the combination group required a lower dose of norepinephrine, which was a consequence of the experimental protocol. The major shortcoming of this study, however, is an evident mistake in the statistical interpretation of their main results. The authors concluded that patients treated with the combination had improved cardiac performance, an effect that did not occur at all. Table 2 of the article shows that the cardiac index (CI) was different between groups among all experiments, a finding that resulted in the \( P \) value of 0.001 presented in the table (significant group effect). In fact, the CI was different between groups at the time of the beginning of the infusion, and it remained different for 48 hours. In the ANOVA for multiple measurements and factors, the treatment effect is tested by the time-group interaction, with its corresponding \( F \) and \( P \) values and not by the group or time effect in isolation. It is clear that there is no time-group interaction in the case of CI and probably not also in the evaluation of mean arterial pressure. On the basis of such findings, the authors stated that norepinephrine is cardiotoxic. Their conclusion is not supported by the reference cited,\(^2\) which does not address the potential deleterious effect of norepinephrine in vasodilatory shock. It addresses instead the role of the sympathetic nervous system in the genesis of ventricular arrhythmia.

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Response
We thank Drs Fuchs and Filho for their comments concerning our work. Unfortunately, they seem to have misunderstood or misinterpreted our findings.
First, in both study groups, norepinephrine (NE) infusion was titrated to keep mean arterial pressure >70 mm Hg. Patients in the study arm received an additional arginine vasopressin (AVP) infusion at a fixed dosage (4 U/h), which remained unchanged during the study. The finding that AVP patients required significantly less NE is thus not a flaw of the study protocol but results from strong vasopressor effects of AVP. If AVP did not significantly increase mean arterial pressure (as in normotensive patients\(^1\)), NE requirements would not have been different between groups. Therefore, although a significant difference in NE requirements was anticipated from results of previous studies,\(^2\) this finding more likely reflects strong vasopressor effects of AVP in vasodilatory shock than a bias of the study protocol.

Second, the statistical considerations of Drs Fuchs and Filho are interesting, but, as cited in the statistical analysis section of the article, repeated measurements were not analyzed using ANOVA, but with a mixed-effects model to account for death-related dropouts.\(^3\) Further, although suspected by Drs Fuchs and Filho, there were no significant differences between groups in cardiac index at baseline (\( P = 0.138 \)). Nonetheless, they are right that there is an absolute difference of 0.6 L/min per m\(^2\). When we added this baseline difference as a covariate into the main analysis, there was still a significant group effect between AVP and NE patients (\( P = 0.03; \ F = 4.85 \)). In our view, it is preferable to evaluate differences between groups in such an analysis by testing for group effects adjusted for baseline differences than by using time-group interactions.

Third, the manuscript suggests that cardiotoxicity of NE seems to be dose dependent. In this study, hemodynamic data, a significantly higher rate of new-onset tachyarrhythmias in NE patients (8.3 versus 54.3%), and the fact that 3 of 24 NE patients suffered from new myocardial infarction or ischemia support such an effect of high NE dosages.

Fourth, regarding the reference of Dr Podrid and colleagues,\(^4\) it is true that it does not address the potential cardiotoxic effects of NE in vasodilatory shock, which was never intended and was not stated in the manuscript. The reference was cited because an increased adrenergic stress may trigger tachyarrhythmias, especially in patients with impaired left ventricular function.

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