Commentary

Skin microcirculation and vasopressin infusion: a laser Doppler study

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See related research by Luckner *et al*. in this issue [http://ccforum.com/content/10/2/R40]

Abstract

Use of arginine vasopressin in the management of refractory vasodilatory shock has been associated with development of ischaemic skin lesions. Because of the increasing popularity of arginine vasopressin, it is important to evaluate its effects on microcirculatory blood flow. Such studies are crucial if we are to appreciate the microcirculatory consequences of our various resuscitation strategies. However, methodological issues must always be considered because they can significantly influence interpretation of the results. Some aspects of use of laser Doppler to evaluate the microcirculation are reviewed within the context of recent findings presented by Luckner and coworkers in this issue of *Critical Care*.

Introduction

Arginine vasopressin (AVP) is increasingly used in the management of refractory vasodilatory shock. Indeed, it was recently incorporated into the recommendations (grade IIB) proposed by the American Heart Association for treatment of refractory septic shock [1] and the guidelines of the Surviving Sepsis Campaign (grade E) [2]. However, although the global haemodynamic effects of AVP are relatively well described, its effects on the microcirculation are still largely unknown.

In this issue of *Critical Care*, Luckner and coworkers [3] present an original study in which they evaluated skin microvascular blood flow, using laser Doppler fluxmetry, before and after AVP infusion in patients with refractory septic shock. They report that AVP infusion did not impair forearm skin perfusion compared with norepinephrine alone. The authors intended to explore further the results of two of their previous studies: a retrospective analysis [4], in which they reported a 30.2% rate of ischaemic skin lesions with AVP infusion; and a prospective controlled trial [5] that found no difference in the incidence of such lesions between a group of patients treated with AVP plus norepinephrine and patients treated with norepinephrine alone. Of note, it is difficult to draw conclusions regarding the safety of AVP administration on the basis of the latter study because the dose of norepinephrine received by the patients in the AVP/norepinephrine group was half that in the other group.

As mentioned by the authors, their results presented in this issue are in striking contrast to those of several published physiological experiments on the topic. Indeed, animal and human studies [6-9] have revealed significant dose-dependant impairment in skin blood flow with AVP. Indeed, the skin microvasculature is considered to be a vascular bed that is rather sensitive to AVP [10]. Accordingly, the results of the study presented by Luckner and coworkers are somewhat unexpected, and some methodological issues might account for the discrepancies.

Technical issues: laser Doppler fluxmetry

It is important to note the technical limitations of laser Doppler. Laser Doppler fluxmetry only provides an estimate of the average blood flow in a given volume of tissue; this volume can vary according to its intrinsic refractive properties. Multiple individual and environmental factors, including haemoglobin level and temperature, can also influence the results of laser Doppler fluxmetry [11]. Moreover, laser Doppler fluxmetry does not take into account the type of microvessels under study, their morphology, the direction of flow and, more importantly, the heterogeneity of perfusion; the latter is a key component in the study of microcirculation, especially in sepsis. More specifically, the biological zero, which can represent up to 80% of the total laser Doppler fluxmetry signal, can be modified during ischaemia/reperfusion procedures because it is influenced by vasodilatation [12]. Therefore, various authors

AVP = arginine vasopressin.

have suggested that the biological zero should always be taken into account when red blood cell flux is measured in the skin using laser Doppler fluxmetry [12]. Finally, measurement of differential perfusion is impeded by the rather small signal and oscillatory pattern of basal cutaneous microcirculation [13]. In addition, it is worth noting that vasomotion patterns are highly dependant on probe location relative to the tissue of interest [14]. This could explain, to some extent, the considerable difference reported in baseline vasomotion between groups. These technical issues account for the substantial short-term variability in laser Doppler fluxmetry measurements [15]. Hence, it is apparent that relatively large observed changes or large sample sizes are needed to detect statistically significant differences between groups.

Statistical issues: power calculation and variance

The power of a study is a measure of its ability to detect a statistical difference when it truly exists; it is particularly important to bear this in mind when interpreting studies that return negative findings. The calculated power of the study reported by Luckner and coworkers is approximately 40%, considering the observed difference in primary outcome (area under the curve of the laser Doppler fluxmetry signal) between the two groups. This means that there is a 60% chance that a true difference will remained undetected. With only three additional patients in each group (assuming the same difference in variance between groups) the study would identify a significant difference in microvascular blood flow perfusion and lead to the conclusion that AVP has, in fact, a considerable deleterious impact on skin microcirculation. Finally, the important variance in AVP response (8.56 in the AVP group versus 3.25 in the norepinephrine group; data provided by Luckner and coworkers) suggests that AVP had rather heterogeneous effects from patient to patient and that other factors (e.g. interindividual variability in sensitivity to AVP stimulation, endogenous AVP level, relative adrenal insufficiency, among others) could have played a role.

Conclusion

Luckner and colleagues [3] are to be commended for their pioneering work on the microcirculatory effects of AVP. Such studies are essential if we are to understand better the microcirculatory consequences of our resuscitation strategies. However, this work should be duplicated, and we should exercise caution interpreting these results as reassurance that AVP is devoid of adverse microcirculatory side effects. Further work examining different microcirculatory beds and using different measurement tools to assess microcirculation will improve our knowledge of the role of AVP in resuscitation.

Competing interests

The authors declare that they have no competing interests.

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