CRITICAL CARE

COMMENTARY

Inotropes in goal-directed therapy: Do we need 'goals'?

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See related research by Jhanji *et al.*, http://ccforum.com/content/14/4/R151

Abstract

There is substantial evidence to demonstrate the benefits of goal-directed hemodynamic optimization using fluid loading or inotropic support or both to improve outcome during major surgery. However, until now, only limited pathophysiological data have been available to explain this benefit. The maintenance of adequate tissue perfusion and global oxygen delivery is an essential goal for therapy. In an interesting study, Jhanji and colleagues provided additional data that emphasize the roles of optimization of intravascular fluid status and low doses of inotropes to improve microvascular blood flow and tissue oxygenation. This commentary aims to highlight some issues raised by this important study and provides additional elements to further position these results.

Adequate hemodynamic management using well-defined perioperative goal-directed therapy (GDT) is a cornerstone of tissue perfusion and oxygenation that can improve outcome. The aim of GDT is to prevent tissue oxygen debt and energy crisis by maintaining adequate tissue perfusion and oxygenation in relation to increased metabolic demand during major surgery.

In an elegant study in the previous issue of *Critical Care*, Jhanji and colleagues [1] highlighted the important pathophysiological mechanisms involved behind the benefit of GDT. The authors showed that stroke volume-targeted colloid administration coupled with a fixed infusion rate of dopexamine improved oxygen delivery (DO_2), central venous oxygen saturation ($ScvO_2$), microvascular blood flow, and tissue oxygenation and that fluid therapy alone led to additional modest improvements. These data echo previous findings that optimizing DO_2 improves outcome [2-5] and that microvascular flow abnormalities could be a key point in determining postoperative complications following high-risk surgery [6]. These results were consistent with those of Lobo and colleagues [5], who compared the use of fluids and dobutamine and fluids alone in high-risk surgical patients. The use of fluids and dobutamine to achieve a DO_2 goal (of greater than 600 mL/min per m^2) determined better postoperative outcomes than fluids alone did.

The study of Jhanji and colleagues, however, raises several important questions that might deserve future clinical trials. First, we have to ask whether the hemodynamic optimization should be performed postoperatively or, more logically, once the surgical trauma is induced. In the three study groups, it is clear that baseline postoperative inflammatory markers were largely elevated, rendering the hemodynamic optimization less able to reduce complications that appear to be present at a very high rate regardless of the intervention protocol (between 58% and 69% of the patients). Indeed, several pieces of evidence suggest that the timing of therapeutic intervention during GDT could be a critical issue [7], and most studies predominantly performed GDT starting intraoperatively [8]. Second, one may question the use of a fixed low infusion rate of dopexamine (0.5 μg/kg per minute) without targeting any specific goals for cardiac output or DO_2. Although the use of a low dose of dopexamine demonstrated benefits in terms of survival and reduction in hospital stay in a previous small-scale study [9], this was not observed here by Jhanji and colleagues [1] in this randomized trial on a larger scale. In the latter context, it seems important to emphasize that the serum lactate concentration and the base deficit remained a bit higher (though not significantly so) during the first 4 hours of treatment in the fixed-dose dopexamine treatment group. Therefore, two important complementary questions remain: Do we need, as for fluids, an individualized approach to deliver inotrope during GDT? What should be the goal to address the

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adequacy of inotrope infusion? From an 'energy debt' perspective, it is certainly much more important to consider the DO_2-to-O_2 consumption (VO_2) relationship than to indicate a specific value of DO_2 as a goal [10]. To this end, Donati and colleagues [7] demonstrated improved outcome in patients treated with individualized GDT using fluids and dobutamine titrated to maintain O_2 extraction (ERO_2, the ratio of VO_2 to DO_2) at less than 27% (corresponding approximately to an $ScvO_2$ of greater than 73%). An increase in VO_2 without a corresponding increase in DO_2, or a decrease in DO_2 and no change in O_2 requirements, results in an increase in ERO_2, rendering $ScvO_2$ an interesting contributor to patient monitoring. In critical illness, however, the ability of tissue to increase ERO_2 might be impaired, and 'normalized $ScvO_2$' would lose its ability to guide fluid or inotrope therapy [11,12]. This constitutes the third important remaining issue raised by this study: Should we systematically integrate other markers of cellular energy adequacy (besides $ScvO_2$) such as serum lactate [12,13], base deficit, or tissue hypercarbia [14]? In any case, these markers deserve further investigations in GDT-based protocols, as has been done in critical illness such as severe sepsis [12,15], before being considered eligible tools for high-risk surgery.

In total, we believe it would be more rational to apply GDT according to individual patients' targets based on their specific physiological profile, whether it pertains to fluid loading or dopexamine titration. It is obvious that the use of inotropes should be cautious in patients with high risk of ischemic cardiovascular events, in which beta stimulation may be harmful. In a previous study of 122 high-risk patients (81% with an American Society of Anesthesiologists score of at least 3), Pearse and colleagues [16] reported a 13% rate of adverse events (tachycardia and myocardial ischemia) using mean doses of dopexamine of 0.75 μg/kg per minute (interquartile range of 0.5 to 1.0 μg/kg per minute) whereas 24% of patients did not achieve the DO_2 goal despite receiving the maximum therapy allowed. Inotrope titration should integrate the relationship of O_2 needs to the O_2 costs to be delivered. Finally, we feel that GDT must be applied at the time of injury (that is, intraoperatively) and not after inflammation has already started. Such an approach, applied in further clinical trials, might provide us with responses to our yet unanswered questions.

Abbreviations

DO_2, oxygen delivery; ERO_2, oxygen extraction; GDT, goal-directed therapy; $ScvO_2$, central venous oxygen saturation; VO_2, oxygen consumption.

Competing interests

The authors declare that they have no competing interests.

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