

Managing Intraoperative Blood Pressure with Norepinephrine

Effects on Perfusion and Oxygenation of the Intestinal Tract

THE perioperative period is complicated by low blood pressures, redistribution of fluid compartments, and possible steal phenomena as the result of perfusion prioritization reflexes, which all may compromise tissue perfusion and oxygen delivery. In this month's issue of *ANESTHESIOLOGY*, Hildebrand *et al.*¹ provide an interesting study on perioperative use of norepinephrine and its effects on tissue oxygenation and perfusion during mild hypotension, which is relatively frequently experienced in daily practice. The researchers report safe use of low- to mid-range doses of norepinephrine to preserve hemodynamic stability, which helps to maintain sufficient oxygen delivery to splanchnic organs during the perioperative period.¹

In this well-designed and executed large animal study, investigators simulated an abdominal surgery setting that involved both solid organ and small- and large-bowel handling for approximately 4 h. After the induction of anesthesia, they used a restrictive fluid regimen throughout the study period in all animals. In the treatment group, they kept the mean arterial pressure (MAP) at 65 and 75 mmHg (each for 2 h) by using norepinephrine; in the control group, they did not treat with medications and allowed blood pressure decreases. Investigators need to be acknowledged for using state-of-the-art measurement techniques to monitor global, splanchnic, and renal perfusion and oxygenation. In addition, the presentation of data in tissue oxygen delivery format brings a new perspective to the perfusion and oxygenation field.

To begin, the restrictive fluid approach may be examined to determine whether it should be the preferred choice in abdominal surgery. The amount and type of fluids seriously contribute to tissue oxygenation and perfusion. Liberal use of crystalloids improves tissue oxygenation.² However, this does not necessarily mean that it improves perioperative outcomes.³ Sometimes, it may even worsen them.^{4,5} Colloids are known to improve perioperative tissue oxygenation, similar to crystalloids^{6,7}; however, both the extent and duration of this effect are greater. On the other hand, acute hypervolemia, caused by colloids, may alter the structure of endothelial glycocalyx and increase the fluid shift to the interstitial space.⁸ This effect brings a mechanistic controversy to the liberal use of colloids as replacement fluids. Overall, neither type of fluid can be recommended in extensive quantities for optimization of tissue oxygen delivery.

Is perioperative oxygenation an important parameter that requires consideration for adjustment? The key role of tissue oxygenation in healing wounds was established by Hunt *et al.*⁹

Tissue oxygenation's strong diagnostic role in surgical wound infections was reported in a landmark trial by Hopf *et al.*¹⁰ more than a decade ago. Delivery of oxygen to tissues is being altered by various factors in the perioperative period, such as fraction of inspired oxygen,¹¹ cardiac output, tissue injury itself, injury response systems (*e.g.*, coagulation and inflammation), vasoconstriction resulting from hypothermia and the sympathetic response, intravascular volume status, carbon dioxide partial pressures,¹² and pain.¹³ Higher tissue oxygen improves collagen formation around the wound after major abdominal surgery. In addition, oxygen has an important role in the elimination of bacteria by oxidative killing function through increasing superoxide radical in leukocytes.¹⁴ In summary, perioperative oxygenation requires attention.

In the study of Hildebrand *et al.*,¹ the control group's MAP stayed at approximately 58 to 60 mmHg, which produced a 5- to 17-mmHg difference in MAP from the treatment group; this much blood pressure optimization was accomplished by norepinephrine. However, literature on the effects of vasopressors on splanchnic tissue oxygenation is too limited to guide perioperative management. In the care of intubated and sedated postoperative cardiac surgery patients, phenylephrine resulted in more pronounced splanchnic vasoconstriction compared with norepinephrine; however, neither of them altered gastrointestinal mucosal perfusion.¹⁵ Several years ago, Hildebrand *et al.*¹⁶ reported the effects of dopamine, dobutamine, and dopexamine during a sepsis model in a short-interval, crossover, large-animal study. Although cardiac output was increased by all three vasopressors (mostly by dobutamine), superior mesenteric artery blood flow was improved only by some (mostly by dopamine); however, microcirculatory blood flow was not altered by any of them. Dopamine's positive role on splanchnic perfusion was also highlighted by Priebe *et al.*¹⁷ In a human septic shock outcome trial, Annane *et al.*¹⁸ compared epinephrine with norepinephrine plus dobutamine to optimize MAP at 70 mmHg; they did not report any difference in mortality, duration of vasopressor needs, or duration of hospitalization. It is easy to expand this list of vasopressor trials, especially for sepsis, but the real question is whether we can draw any conclusions to affect outcomes. How and when do the vasopressors alter tissue perfusion and oxygenation? We do not know enough to produce detailed peri-

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operative guidelines, and the little known has limited effect on the surgical patient.

The trial of Hildebrand *et al.*¹ did not result in any statistically significant difference in global or organ-specific oxygenation and perfusion using norepinephrine. Although the threshold parameters of perioperative hypotension are not well-defined, whether the blood pressure difference or hypotension insult in the trial of Hildebrand *et al.* was sufficient enough to expect a difference can be discussed. This will shed light on the management of perioperative hypotension. The following are my conclusions from their study. (1) Mild hypotension during a restrictive fluid regimen may possibly be treated with low- to mid-range doses of norepinephrine without causing any serious compromise in splanchnic perfusion and oxygenation. (2) A threshold low concentration of splanchnic tissue oxygenation may occur at an MAP lower than 60 mmHg. As Boerma and Ince¹⁹ suggested in their article, in which they reviewed the role of vasoactive agents in the resuscitation of microvascular perfusion and oxygenation in critically ill patients, there may be no beneficial effect on microcirculatory perfusion at an MAP higher than 65 mmHg.

In conclusion, the delivery of oxygen to tissues may be compromised because of various perioperative factors using a restrictive fluid regimen. A low MAP may eventually decrease tissue perfusion pressures. To prevent detrimental effects of compromised tissue perfusion and oxygenation, blood pressure needs to be managed. Hildebrand *et al.*¹ showed that mild perioperative hypotension could be managed by low to moderate doses of norepinephrine without any major concerns regarding splanchnic organ perfusion and oxygenation.

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