

# Oxygen Therapy

## When Is Too Much Too Much?

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HERE are approximately 300,000 cardiac surgical procedures annually utilizing cardiopulmonary bypass (CPB) in the United States.<sup>1</sup> The delivery of oxygen has been a cornerstone of anesthesia practice, with titration of oxygen therapy to ensure avoidance of potentially injurious periods of hypoxemia. However, the same attention has not been afforded for levels of relative *hyperoxemia*, mostly due to the assumption that excess oxygen is relatively harmless. Emerging clinical data within a variety of arenas suggest that this assumption may not be true. There appears to be potentially deleterious effects from hyperoxemia, whether it be demonstration of extension of infarct size postmyocardial infarction<sup>2</sup> or worse neurologic outcomes and higher mortality in patients receiving therapeutic hypothermia following return of spontaneous circulation after cardiac arrest.<sup>3</sup> Given these data, there has been rekindled interest in the conceivably detrimental consequences of hyperoxemia in the domain of CPB during cardiac surgery where ischemia–reperfusion injury may lead to an increased susceptibility to formation of reactive oxygen species. In this issue of *ANESTHESIOLOGY*, McGuinness *et al.*<sup>4</sup> investigate the avoidance of hyperoxemia during CPB on postoperative acute kidney injury in cardiac surgery.

McGuinness *et al.* should be commended for undertaking a well-thought-out, pragmatic, prospective randomized study of different levels of oxygenation during CPB in cardiac surgical subjects.<sup>4</sup> Novel in its design, the study compared the effects of standard care with a protocolized intervention of hyperoxemia avoidance on the incidence of postoperative acute kidney injury. The innovative use of inline real-time blood gas monitoring permitted tight and safe fraction of inspired oxygen ( $F_{IO_2}$ ) titration to a narrow range of oxygen tension.



***“[Did the] avoidance of hyperoxemia during [cardiopulmonary bypass affect] postoperative acute kidney injury in cardiac surgery[?]”***

The study did not show a difference in outcome, and given the weight of the data in other patient populations, we must ask ourselves why. First, we should look at the “dose” of the intervention. The protocol for this study resulted in a relatively small difference between the normoxic and the standard care arms during CPB, with an arterial oxygen tension difference of only 80 mmHg. This separation between groups may have been inadequate to demonstrate an effect. It may also not reflect the clinical question, namely, should  $F_{IO_2}$  be arbitrarily set or titrated to effect. Second, in neither group was the partial pressure of oxygen above 200 mmHg during CPB. A lack of consensus regarding the definition of hyperoxemia is currently impeding the study of the phenomena.

Definitions of hyperoxemia in the literature range from 85 to 487 mmHg.<sup>5</sup> Consensus denotes hyperoxemia as being around 300 mmHg, yet there is no set cutoff or definitive standard upon which to base trial design, minimize heterogeneity, or assess clinical practice.<sup>6</sup> Therefore, although a pragmatic trial design, the lack of protocolization of a hyperoxemic arm may have resulted in poor differentiation between groups, thus creating a trial of different grades of normoxia rather than an assessment of hyperoxemic conditions. Furthermore, practice variability exists in the level of oxygen administered routinely, and standard care elsewhere may represent very different oxygen tensions than that in the two trial centers. Interestingly, McGuinness *et al.* found adherence to the protocolized “normoxic” intervention group (target of peripheral oxygen saturations of 92 to 95%) outside of CPB challenging to maintain. Third, it is a substantial challenge to find appropriate biomarker choices that truly reflect kidney injury. Although the “troponin of the

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kidney” is a moving target, the most viable candidates such as neutrophil gelatinase–associated lipocalin, kidney injury molecule-1, or cystatin-C were not examined in this particular study.<sup>7</sup> Despite these limitations, the authors did implement a more sophisticated outcome metric, namely The Kidney Disease: Improving Global Outcome Score.<sup>8</sup>

Hyperoxemia may well have detrimental clinical manifestations in patients undergoing anesthesia with CPB, although admittedly the data are mixed. Increased reactive oxygen species production and inflammation and decreased mitochondrial consumption, microvascular perfusion, and myocardial contractility may all share a role. Nonetheless, the development of a more focused, cohesive translational approach to mechanisms at play will require much work. Whether precise control of oxygenation and maintenance of predefined “normoxia” demonstrate improved clinical outcomes in cardiac surgery remains to be seen. Although intuitive and elegant in its simplicity, the question may well be much more complex. This trial may pose more questions than answers; however, it has opened the door to more dialogue. As the field evolves, the conceivable adoption of more deliberate “normoxic” parameters in a variety of settings has far-reaching implications for our discipline and has the potential to significantly alter clinical practice. Renewed interest in oxygen tensions should come under the ownership of our specialty from a physiologic, interventional, and outcome perspective.

This trial represents an excellent early foray into a ubiquitous and fundamental aspect of our anesthetic practice within cardiac surgery and perhaps beyond. However, the lack of difference seen was not surprising, given the paucity of interventional separation between groups. A more nuanced series of outcome measures and more protocolized adherence to oxygen discrimination would be welcomed next steps in investigation.

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