Avoidance of Hyperoxemia during Cardiopulmonary Bypass: Why Does Pathophysiology Not Always Translate into Clinical Outcome?

To the Editor:

The safety of hyperoxemia during cardiopulmonary bypass (CPB) has long been debated, with some evidence suggesting it induces vasoconstriction that may reduce organ (*e.g.*, myocardial, kidney) perfusion.[1] Even though the mechanism of this purported hyperoxic vasoconstriction is only partially understood, the production of reactive oxygen species (ROS) seems to play a pivotal role. Nevertheless, despite the excessive production of ROS enhancing ischemia/reperfusion (IR) injury, recent studies[2,3] have thus far failed to demonstrate any relationship between avoidance of hyperoxemia during CPB and clinical outcomes. So why do apparently obvious pathologic mechanisms fail to translate into clinical outcome?

The answer, in part, may be in the nuances of the study design. For example, in the recent study published by McGuinness *et al.*,[3] the "avoidance of hyperoxemia" was studied as an "intervention" to reduce CPB-related IR and its consequence on the incidence of postoperative acute kidney injury (AKI). If IR is a central mechanism in the pathophysiology of CPB-related AKI, and oxygen is a substrate for the production of IR injury mediators (*i.e.*, ROS), then it makes sense that higher levels of oxygen during the "reperfusion" could raise ROS levels and thus increase the incidence of AKI. However, critical to the duality of the IR process is that "ischemia" must actually be followed by a period of "reperfusion," and the reperfusion milieu itself must contain sufficient oxygen substrates for the increased production of injurious ROS.

It is important to consider, however, that oxygen levels *per se* can have vastly different effects on each of the intertwined IR processes of "ischemia" and "reperfusion." For example, low oxygen levels (perhaps as low as the relatively "normoxemic" levels in the study's intervention group) might actually aggravate the occurrence of the CPB-related ischemia. One can equally argue that the "hyperoxemic" levels in the study's control group could theoretically reduce the ischemic injury occurring during CPB (just as increasing Pa_{O_2} and other maneuvers[4] have been used to improve cerebral oximetry measurements) and thus reduce the chances of any subsequent injury induced during the post-CPB reperfusion period.

Simply put, if there is little or no ischemia in the first place (*i.e.*, in the hyperoxemia group which was originally hypothesized to be injurious), there is actually no basis for IR injury and the amount of oxygen that the patient receives during reperfusion becomes irrelevant. Alternatively, if significant ischemia *per se* actually does occur during CPB, then the higher oxygen levels in the control group might actually aggravate the IR injury, but only if those oxygen levels are present during the actual reperfusion phase (*i.e.*, in the post-CPB period). Of note, the study (partly due to its pragmatic nature) did not have any between-group differences in the post-CPB oxygen levels, and thus the milieu for reperfusion injury was, at best, equal between the groups, and potentially worse in the intervention group because of its lower Pa_{O_2} levels during the preceding actual ischemia-inducing CPB phase of the study.

Therefore, the investigators may have significantly disadvantaged themselves by designing a study wherein the conditions for injury were counterproductively increased by the intervention (which was originally hypothesized to be protective) and reduced in the controls (that had originally been presumed to be more prone to injury).

Despite these shortcomings, the study by McGuiness *et al.*[3] has raised the awareness of the value in studying the potentially therapeutic (or alternatively, injurious—depending on one's perspective) "intervention" of hyperoxemia avoidance. In the end, however, their results (particularly as they pertain to AKI) were somewhat of a wash and, unfortunately, we're no closer to understanding what the optimal oxygen management strategy is during CPB.

Competing Interests

The authors declare no competing interests.

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This letter was sent to the author of the original article referenced above, who declined to respond.—Evan D. Kharasch, M.D., Ph.D., Editor-in-Chief.

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