The reoxygenation injury: Is it clinically important?

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Repair of cyanotic congenital heart defects necessitating cardiopulmonary bypass (CPB) is becoming more frequent in infants and neonates. Despite apparently successful surgical correction, postoperative myocardial and pulmonary dysfunction continues to be a major contributor to morbidity and mortality and is more severe than after repair of acquired defects in adults with normoxic conditions.¹⁻³ The neonatal heart also has a reduced response to inotropic agents compared with the adult heart.^{1,2} Thus, preservation of myocardial function in neonates during cardiac operations assumes even greater importance, because a perioperative insult is less well tolerated and more difficult to treat.

Congenital malformations of the heart frequently lead to physiologic abnormalities ("stress") that are quite different from those seen in the adult, and so the concerns during CPB are not necessarily the same. The most common preoperative stress in adults is ischemia, secondary to coronary artery disease, and the major concern is avoidance of a "regional" myocardial reperfusion injury with the reintroduction of blood.⁴ In contrast, the most common preoperative stress in pediatric patients is hypoxia (cyanosis).^{1,2} The major concern, therefore, is whether a reoxygenation injury (similar to a reperfusion injury) occurs with the abrupt reintroduction of oxygen. The occurrence of such an injury could be even more detrimental, as it would result in "global" damage, since hypoxia affects the entire body, not just the heart.

Acute hypoxia and acidosis may occur as a consequence of many congenital heart defects and can result in depletion of glycogen, adenosine triphosphate, and Krebs cycle intermediates, leading to myocardial dysfunction.^{2,5,6} Significant acute hypoxia forces the myocardium to rely on anaerobic metabolism, and when acidosis is present, this further heightens these deleterious effects. Chronic hypoxia leads to cyanosis, a condition frequently encountered in infants and children undergoing cardiac operations. Despite compensatory mechanisms, substrate depletion and metabolic derangements are more common in cyanotic hearts than in normoxic hearts.^{1-3,5,6} Moreover, cyanosis depletes the myocardium of endogenous antioxidants, and a growing body of experimental and clinical evidence indicates that this may make the cyanotic immature heart more susceptible to an oxygen-mediated injury when molecular oxygen is restored.⁷⁻¹⁰

The reversal of hypoxemia occurs with initiation of extracorporeal circulation and *precedes* the surgical ischemia used for operative repair in children with cyanotic disease. The conventional method of starting CPB in infants and children with hypoxemia is to abruptly raise oxygen tension (P_{O_2}) to approximately 400 to 500 mm Hg. Does this sudden reintroduction of oxygen causes a significant "unintended injury" and, if so, can it be prevented? Such an injury might explain why the cyanotic heart is more vulnerable and less tolerant to subsequent surgical ischemia than the normoxic heart.^{1-3,5,6}

Corno and colleagues,¹¹ as well as others, have documented experimentally that a reoxygenation injury does occur after an acute hypoxic insult.⁷⁻⁹ Our studies support this work.^{3,10,12} We subjected neonatal piglets to 60 minutes of acute ventilator hypoxia (fraction of inspired oxygen [F_{IO_2}] 8%-10%) and then abruptly reoxygenated them by increasing the ventilator F_{IO_2} to 100%, or we placed them on CPB at an F_{IO_2} of 100%, simulating the usual clinical practice. Abrupt reoxygenation by either method caused an oxygen-derived free radical-mediated injury, resulting in a reduction in cardiac output, depressed myocardial function, elevated

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pulmonary vascular resistance, and a reduction in the arterial/alveolar ratio. This injury was independent of the method of reoxygenation; thus, it is related to the sudden reintroduction of oxygen and not the effects of CPB. Conversely, maintaining normoxemia (Po_2 80-100 mm Hg) rather than hyperoxemia during the initiation of CPB and then gradually increasing oxygen levels substantially reduced oxidant damage and decreased the extent of myocardial dysfunction. These benefits coincided with the Po_2 -dependent nature of the reoxygenation injury, because free radical production and myocardial injury after reoxygenation of isolated heart preparations are proportionate to Po_2 .^{13,14} In clinical practice, hyperoxemic CPB is performed routinely but is likely never needed, because a Po_2 of 400 to 500 mm Hg confers only a negligible increase in oxygen content compared with a Po_2 of 100 to 150 mm Hg. In both instances the oxygen saturation is essentially 100%. Moreover, a CPB Po_2 of more than 180 mm Hg has been associated with impairment of peripheral perfusion.¹⁵ The avoidance of hyperoxemia during reoxygenation in cyanotic infants to reduce injury may be comparable, in a sense, with controlling the initial reperfusate after ischemia to avoid a reperfusion injury.⁴

Leukocytes may also be active mediators of the reoxygenation injury. Activated white cells have been shown to play a major role in the generation of oxygen-derived free radicals after ischemia, and it seems logical that they should contribute to the reoxygenation injury, since both ischemia and hypoxia subject tissue to low oxygen levels.^{3,12,16} Leukocyte depletion is a readily available method that allows the surgeon to safely minimize the harmful effects of neutrophils, without risking side effects of pharmacologic interventions aimed at altering leukocyte function or preventing the free radical injury through the use of exogenous oxygen radical scavengers. The effect of leukocyte removal was tested in neonatal piglets after the same acute (60 minutes) hypoxic stress. By use of leukocyte-depleting filters, the detrimental effects of sudden reoxygenation were prevented to an even greater extent than with gradual reoxygenation (normoxic strategy), with a marked reduction in oxygen-derived free radical formation, preservation of left ventricular contractility and diastolic compliance, maintenance of pulmonary alveolar capillary gas exchange (arterial/alveolar ratio), and only a slight rise in pulmonary vascular resistance.^{3,10,12} In fact, the change in pulmonary vascular resistance was even less than in nonhypoxic animals subjected to CPB, suggesting that leukocyte filtration should be used in all pediatric operations where postoperative pulmonary hypertension could be problematic. Several experimental and clinical studies support this implication and have documented a reduction in pulmonary injury with leukocyte filtration even in noncyanotic infants.^{17,18}

Despite these findings, many surgeons still doubt the

existence and the clinical significance of suddenly restoring oxygen to the hypoxic heart. They point out that the majority of studies that have documented this injury have used an acute hypoxic injury, which, in contrast to chronic hypoxia in the infant, may not allow sufficient time for compensatory adaptation to develop. This adaptation, they argue, may allow the chronically hypoxic patient to avoid an injury with the reintroduction of oxygen. As such, they believe that this is an unimportant injury, artificially created in the laboratory, and of little clinical significance. The argument of acute versus chronic is perennial. However, in this case I believe the argument is tenuous at best, because postreoxygenation changes seen after acute experimental hypoxemia parallel those reported in cyanotic patients who undergo reoxygenation during CPB.^{7,8} Moreover, we have now confirmed the findings of our acute experimental studies in cyanotic infants using the same biochemical tests.^{3,10,12}

In this issue of the *Journal*, Corno and his associates¹¹ attempt to address the major issue in this continuing debate by comparing the results of reoxygenation after acute and chronic (2 weeks) hypoxia. To accomplish this goal, they developed a new chronic hypoxic animal model that closely mimics the clinical setting. The model is quite ingenious, as it avoids the problems of previous chronic models that subjected animals to brief periods of normoxia during feeding and cleaning of their cages. These repeated episodes of reoxygenation do not usually occur in the clinical setting and may significantly alter (ie, condition) the response of the hypoxic heart to reoxygenation; in the same way, repeated episodes of ischemia and reperfusion make the ischemic heart more tolerant to subsequent ischemic insults.

Although their model is quite innovative and allowed the animals to undergo chronic hypoxia, the experiment did not exactly mimic the clinical setting, as rats were 5 weeks old before hypoxia. In contrast, most hypoxic patients are hypoxic either immediately after birth or within the first few days of life. However, as pointed out by Corno's group, this is not always true, because some patients (ie, those with tetralogy of Fallot) may not become hypoxic for weeks to months. It is possible that cellular changes (adaptations) may be different if chronic hypoxia is preceded by a prolonged period of normoxia. Nevertheless, this study still has two important lessons. First, despite any cellular adaptations that may develop with chronic hypoxia, an oxygen-mediated injury (reoxygenation injury) still occurs with the abrupt reintroduction of oxygen. Second, the injury after chronic hypoxia is greater than after acute hypoxia. Moreover, despite the 5-week delay in initiating chronic hypoxia, the results are identical to our findings in hypoxic patients, where we demonstrated greater oxygen-derived free radical production in cyanotic (chronic hypoxic) infants compared with acutely hypoxic animals.^{3,10,12} The most probable explanation for these results is that chronically hypoxic ani-

mals (or patients) often become ischemic during periods of increased stress (tachycardia) or exercise.^{19,20} This subjects them to both a hypoxic and an ischemic stress. In contrast, acute experimental hypoxia usually results in no ischemia.¹² It is therefore not surprising that a combination of hypoxia and ischemia results in a more severe injury with reperfusion.

On the basis of this extensive experimental and clinical infrastructure, we now routinely use a normoxic CPB strategy combined with leukocyte depletion in all hypoxic (cyanotic), hypertrophied, or high-risk normoxic patients. The CPB circuit is primed and initiated at a P_{O_2} of 80 to 100 mm Hg (normoxic strategy), and the F_{IO_2} is increased slowly to 30% to 50% as needed over the next 10 to 20 minutes to maintain a P_{O_2} of 100 to 150 mm Hg. We resort to higher oxygen levels (F_{IO_2} 100%) only if we require a period of low flow or deep hypothermic circulatory arrest, as Nollert and associates²¹ have shown that under these conditions an increased oxygen content is important for neurologic protection. A leukocyte-depleting filter is placed in the arterial line for the entire procedure, and if a blood prime is used, it is always washed and leukocyte depleted.

To assess the clinical efficacy of this approach, we retrospectively examined all patients undergoing a Norwood procedure at our institution between July 1, 1996, and March 31, 2000. There were 72 patients, 41 with a diagnosis of hypoplastic left heart syndrome (HLHS) and 31 with a variant (HLHV) of HLHS. The overall survival was 78% (76% HLHS, 81% HLHV). More important, there was complete preservation of myocardial function in the patients with HLHS, both initially, as assessed by echocardiogram (shortening fraction preoperatively $37\% \pm 10\%$ vs postoperatively $35\% \pm 11\%$), and several months later, when evaluated by angiogram (ejection fraction $57\% \pm 7\%$) before the Glenn procedure. In contrast, the surgical survival in the 38 patients undergoing a Norwood procedure in the 2 years before institution of this strategy was only 53%, and postoperative low output syndrome was a significant problem. I acknowledge that other changes might have accounted for these findings, but I believe these results, as well as the extensive experimental infrastructure, support the safety and efficacy of this approach.

In summary, although the study by Corno and colleagues¹¹ does much to further our knowledge, because of the age of the animals at the time of hypoxia, some may still argue that it does not definitively prove that this injury is clinically important. However, it adds another "piece to the puzzle" and leaves less room for those who still cling to the belief that the reoxygenation injury is simply a mirage, and clinically unimportant. Therefore, perhaps the question should be why risk any damage, no matter what the severity, when it is easy to minimize the reoxygenation injury by

using a CPB strategy of normoxia and white blood cell filtration.

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