

Oxygen or Nitrogen: Which Is the Lesser of Two Evils?

To the Editor,

Ever since it was discovered in the 1770s, the risks and benefits of oxygen have been hotly debated (1). The article by Young, “Hyperoxia—A Review of Risk and Benefits,” the author addresses this important question: What is the optimal oxygen management strategy for cardiopulmonary bypass (CPB)? Surprisingly, after 60 years of clinical experience, there is still disagreement on the optimal partial pressure of oxygen during CPB. Perhaps this is because this simple question is complicated by variables such as the common use of iatrogenic anemia and the frequent infusion of gaseous microemboli (GME) during CPB. The author details the risks of high oxygen tension from the standpoint of potential detrimental effects on cardiovascular function, the generation of oxygen free radical species, and the adverse effects to the lungs and other organs during perfusion or on reperfusion. The author also mentions several possible benefits to using hyperoxia, including ischemic preconditioning of the myocardium, favorable effects on the longevity of GME, and a possible safety margin in that tissue stores of oxygen will be greater should oxygenation or blood flow become temporarily disrupted during surgery. He further reviews the evidence related to postoperative surgical site infection, nausea, and vomiting and decides that there is insufficient evidence to suggest hyperoxia confers any benefit in these areas. His conclusion is that hyperoxia is probably harmful and should be avoided unless the risk of GME is thought to be significant: the benefits of hyperoxia then outweighing the risks. Given that iatrogenic anemia is commonly used and it is well established that GME are prevalent during CPB, one could argue that a hyperoxia strategy should be used on all cases, at least at critical times, to enhance tissue oxygenation and attenuate and resolve GME in patients undergoing cardiac surgery.

Membrane oxygenators have been in common use for over two decades. However, during the 30 years prior, bubble oxygenators were the dominant device. The main concern in those days was the excessive hemolysis caused by the bubbles, which resulted in increased renal and coagulation problems. Hyperoxia (95% O₂ + 5% CO₂ or 97% O₂ + 3% CO₂) was a necessity when using a bubbler. No nitrogen could be used during bubble oxygenation because of the very real risk of nitrogen emboli being pumped into the patient. Even after being defoamed by a separate cardiectomy reservoir, the frothy effluent from the ventricular vent and field suckers was diverted to the oxygen bubble column where any nitrogen was quickly off-gassed. GME, composed primarily

of oxygen, exiting the venous reservoir were addressed with the development of purged arterial filters. A reduction of the “sweep (bubble) gas” flow could lower the paO₂ in the blood and bubbles emanating from the oxygenator, but only at the risk of CO₂ retention above acceptable levels. It was not until the advent of the membrane oxygenator that lower FiO₂ values could be used with the reassurance (which we now know is false reassurance) that nitrogenous GME would not be entering the patient.

Cavitation of blood containing normal oxygen and nitrogen levels by mechanical heart valves after implantation generates bubbles that can be detected in the brain using transcranial Doppler ultrasound (2). These bubbles are mainly nitrogenous. Nitrogen is less soluble in water than oxygen. So during excessive turbulence, temperature changes, or pressure changes, nitrogen is the first gas to come out of the solution. (Ask any knowledgeable diver about the physiology of the bends.) We know these bubbles are mainly nitrogen because when the nitrogen in the patient’s blood is off-gassed by breathing 100% oxygen, the cavitated bubbles go away. In one study, the administration of 100% oxygen by facemask reduced the cavitation generation of GME by 98% (3). Oxygen constrains the cavitation process of mechanical heart valves and speeds up the dissolution of gas bubbles generated by cavitation because those residual bubbles are mainly oxygen. By comparison, blood is constantly cavitated into nitrogenous GME to a much greater degree within the CPB pump: from the tips of the venous cannula, the ventricular vent cannula and the field suckers all the way through to the tip of the aortic cannula and beyond. Interventions by the perfusionist and surgeon further contribute to the embolic problem (4). Oxygen or nitrogen bubbles can damage the intimal lining of the capillaries that they enter and the best solution would be to prevent or eliminate GME entirely. However, with the current state-of-the-art technology, this is not practical to do with any consistency. Many perfusion articles over the years have documented these bubbles and have attested to the difficulty of detecting, preventing, and mechanically removing them despite improvements in circuit design (5). The next best thing is to change the nitrogen in GME to oxygen. This dissipates them much more rapidly. However, there are few references to suggest the use of hyperoxia to mitigate the dangers of nitrogenous GME during CPB (6).

Evidence is not fact, although the evidence we choose to believe guides much of what we do. Contradictory evidence is only evidence that the facts are not fully known.

The current article says that there is evidence that hyperoxia does not improve tissue oxygenation. However, there is also contradictory evidence that hyperoxia does lead to improvement in tissue oxygenation, particularly during periods of low hematocrit values (7). Many perfusionists believe the published evidence that blood transfusion and hyperoxia are both bad for the patient. However, there is also evidence that hyperoxia reduces the need for blood transfusion at critical hematocrit levels (8). Once transfused, the patient lives a lifetime with the consequences, but the detrimental effects of hyperoxia are short-lived. When given the choice, which is the lesser of two evils: blood administration or turning up the FiO_2 ? Increasing the paO_2 from 150 mmHg to 500 mmHg increases the oxygen delivery by approximately 10.5 mL/L (the equivalent of approximately 1 g/dL hemoglobin). However, more importantly, during anemic hypoxia, hyperoxia redistributes oxygen to locally hypoxic tissues to create a margin of safety for vital organ oxygenation, further increasing the tolerance to anemia (8).

At times patients may benefit from high vs. normal oxygen levels or high vs. normal CO_2 levels (with rare exceptions, patients never benefit from high nitrogen levels). For example, there is evidence showing that hyperoxia in the form of oxygen-loading and hypercapnia in the form of pH stat gas control before arrest can extend the safe deep hypothermic circulatory arrest time (9–11).

However, the evidence for the use of either high nitrogen levels (normoxia) or hyperoxia in every situation is simply not clinically conclusive not only in extracorporeal support, but in the simple application of oxygen therapy in patients experiencing chest pain from a myocardial infarction (12). Even among cardiac anesthesiologists, there is no clear consensus. Some believe that hyperoxia should be used throughout the entire perioperative period, whereas others disagree with that approach (13).

Oxygen is like any drug: its beneficial effects must be balanced with its adverse effects. No drug is completely without risks. Calcium chloride, often used in the resuscitation of patients with cardiac arrest, is known to have inotropic effects in healthy patients. However, calcium is a major mediator of reperfusion injury as is oxygen. So the administration of calcium or oxygen to patients who are ischemic/hypoxic during CPR is a tradeoff between the hope that their beneficial effects will outweigh their detrimental effects on the ischemic heart and brain (14,15).

The key to the use of normoxia or hyperoxia during CPB as well as extracorporeal membrane oxygenation (ECMO) and extracorporeal cardiopulmonary resuscitation (ECPR) must also be understood in the framework of timing of implementation (during critical periods of GME generation, for example), time of exposure (hours during CPB or weeks during ECMO) and the level of homeostasis; i.e., the magnitude of shock before and during extracorporeal support when patients are at greatest risk of reperfusion injury

or before deep hypothermic circulatory arrest when the risk is minimal (9,16). Extracorporeal support can be used to maintain normal physiology for a few hours like in elective CPB cases or for days or weeks like in ECMO. Alternatively, it can be used to reverse the lethal physiology of patients in extreme shock (or who have actually died and are undergoing CPR) like in emergent ECPR cases. The gas strategies applied in individual cases are based on an educated speculation by individual perfusionists and prejudiced by the evidence that makes the most sense to them, not necessarily on the facts, which may not even be known.

It is well known that 1) without oxygen, living tissues become acidotic and susceptible to reperfusion injury; 2) nitrogen GME can cause capillary flow obstruction, which causes tissue ischemia; and 3) hyperoxia can exacerbate injury to ischemic/hypoxic tissues. The rub is that nitrogen GME commonly come from the CPB pump and changing nitrogen GME to mostly oxygen GME (which are much less dangerous) as they pass through the oxygenator requires the use of hyperoxia. In addition, off-gassing nitrogen GME previously infused into the patient requires the use of hyperoxia for approximately 2 hours depending on the GME load infused (6). Even the exposure to “hyperbaric” hyperoxia has fewer neurologic complications than CPB, in which cerebral air embolism is a likely cause of postcardiotomy stroke (17).

The conclusion of the article states that the use of hyperoxia during CPB is probably harmful unless the risk from GME is thought to be significant. This type of generalization may prevent the prudent perfusionist from using hyperoxia when it is most needed. There are at least three situations when hyperoxia should be seriously considered during CPB: 1) the risk of GME is thought to be significant as a result of poorly designed circuits (perhaps purchased from the low bidder by cost-conscious hospital administrators), the deliberate omission of the arterial filter (to reduce hemodilution), the use of miniaturized circuits, CPB initiation, vacuum-assisted venous drainage, a low venous reservoir level, routine intervention such as drug or fluid administration, a change in blood temperature, surgeons manipulating the cannulae, ventricular vent and field suckers aspirating blood, or a number of other occurrences. During these situations, it is prudent to use hyperoxia; 2) when patients develop a base deficit or lactic acidosis during CPB, it usually indicates suboptimal perfused capillary density. The normal intervention is to increase the blood flow. If that does not halt the acid generation, additional interventions include (usually in this order) the administration of buffer base (which only masks the acidosis rather than stops it), the administration of a blood transfusion to increase the oxygen delivery, and finally increasing the FiO_2 . An elevated FiO_2 does not substantially increase oxygen delivery. Rather, its mechanism is to redistribute oxygen to hypoxic tissues responsible for the acid

generation. Increasing the FiO_2 should be considered first before attempts are made to mask the acidosis or expose the patient to a blood transfusion; and 3) when deep hypothermic circulatory arrest is anticipated, oxygen-loading tissues with hyperoxia to extend the safe arrest time is warranted.

Scientific understanding is constantly evolving. For example, the Newtonian laws of physics can be confirmed by what can be seen, although on the other hand, quantum physics evolved as a contrary set of laws that are just as valid but cannot be confirmed with the senses. In contrast, many perfusionists have failed to evolve beyond their basic Fick laws of normalized arterial oxygen delivery and venous extraction in which increasing the paO_2 and the portion of dissolved O_2 is thought to be of little consequence except to provoke reperfusion injury in susceptible tissues. By not scientifically evolving into the realm of gas exchange at the microvascular level as described by the perspective of the oxygen pressure field theory (OPFT), new opportunities to analyze and address old problems go unrealized (18). OPFT can guide the perfusionist in understanding microvascular gas exchange and take some of the mystery out of using normoxia or hyperoxia, in which increasing the paO_2 and the portion of dissolved O_2 can be of great benefit to prevent tissues from becoming hypoxic and susceptible to reperfusion injury during times of poor perfused capillary density.

The question remains: if contrary evidence shows hyperoxia to be both harmful and beneficial by some indeterminate measure, what choice should the perfusionist make? During CPB, potentially harmful situations frequently occur, some intentionally and some by happenstance (19). In that context and with the common acceptance of lower than normal temperatures, widely disparate pH and pCO_2 controls (alpha vs. pH stat), lower than normal hematocrit values, lower than normal cardiac index values, lower than normal blood pressures, and the great risk of nitrogenous GME infusion, the worry over the implementation of an elevated FiO_2 , especially when circumstances warrant its use, should be the least of our concerns.

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