Editorial

Too much of a good thing…, blow me! is it oxygen ?

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From the time Joseph Priestley discovered oxygen in 1774[1] and called it *dephlogisticated air*, this gas, which is known to be the very essence of life, has remained a bit of an enigma. Perhaps, nothing in medicine is more steeped in myth than oxygen. From its initial success in treating pulmonary tuberculosis to its failure in treating cholera, oxygen has fallen in and out of style.

It is well established that oxygen is absolutely essential for survival of all forms of life. It takes part in many vital functions in the human body and lack of oxygen is equivalent to cell death and ultimately the death of the individual. It is just another good thing which is required in abundance for sheer continued existence of the human species.

From a general treatment perspective, it has been a long held belief that loads of oxygen could be constructively engaged as a useful tool in our day-to-day therapeutic armamentarium. High concentrations of oxygen were used in the treatment of neonatal resuscitation, many lung diseases, artificial ventilation, cardiopulmonary bypass surgery, cardiac decompensation, states of shock etc., just to name a few. The theory was that if one could get as much oxygen as possible into a patient, he or she could only derive benefits from the manoeuvre. The premise was that one could never get too much of a good thing. It is not an uncommon sight, especially in the paediatric wards of our country, to see many patients receiving higher concentrations of oxygen on a daily basis.

Yet, it is only quite recently, a full 175 years after its original discovery, that it has been revealed that an excess of oxygen could be harmful. The fact that high concentrations of oxygen could damage the newborns was first discovered in the fifties[2]. The saga of retinopathy of prematurity is well known today and globally it has become a very important cause of troublesome and persistent visual problems in children. However, this was thought to be just a one-off thing and not many people really looked for other possible adverse effects of inspired high concentrations of oxygen.

This premise has seen drastic changes over the last couple of decades. Exposure to high oxygen concentrations causes direct oxidative cell damage through increased production of reactive oxygen species[3]. Hyperoxic damage to cells is being investigated with vigour and many unexpected findings are coming to light. The first of these is the discovery that the lung itself, the first portal of entry for inspired gases, is vulnerable to oxidative stress. *In vivo* oxygen induced lung injury is well characterised in rodents and has been used as a valuable model of human respiratory distress syndrome. The injury is a bimodal process resulting from direct oxygen toxicity as well as from the accumulation of inflammatory mediators within the lung. Both apoptosis and necrosis have been described in alveolar cells, mainly epithelial and endothelial cells, during hyperoxia. A pivotal role seems to be played by mitochondria[3]. Hyperoxia causes lung injury and reduces lung compliance. This is indicative of deficiencies in surfactant and tends to elicit a vigorous immune response leading to further damage. This is corroborated by certain animal experiments which show a protective effect of Cyclosporin A against oxidative lung injury[4]. These finding have obvious implications for prevention and treatment of patients undergoing prolonged oxygen therapy and possibly other lung injuries as well. It has also been shown that hyperoxia in conjunction with nitric oxide therapy result in increased cellular dysfunction and apoptotic cell death of Type II pneumocytes in a dose-dependent manner[5]. This may have significant clinical implications in the use of nitric oxide in combination with oxygen in pre-term infants.

Traditionally very high concentrations of oxygen were used during neonatal resuscitation. The idea was to get as much oxygen as possible into the tissues of the newborn in trouble. We started using oxygen for resuscitation because it seemed like a good idea. Now we use it because we have always used it. It was however shown that asphyxiated newborn infants can be resuscitated with room air as efficiently as with pure oxygen[6]. In fact, time to first breath and first cry was significantly shorter in room air versus oxygen-resuscitated infants. Resuscitation with 100% oxygen may depress ventilation and

therefore delay the first breath. In addition, neonates resuscitated with 100% oxygen exhibit biochemical findings reflecting prolonged oxidative stress even after 4 weeks of postnatal life but such manifestations do not appear in those resuscitated with room air[7]. The real question is whether in this age of evidence-based medicine, should we continue to use this historical, yet unsupported, therapy until it is proved to be harmful or should we step back and recognize that supplemental oxygen is a medicine with potentially significant side effects that should be used only when there is an indication? Until we accept that the only reason we so strongly cling to supplemental oxygen as a therapy in resuscitation is because we were taught simplistically that "oxygen is good," with the implication that "more must be better", we are doomed to perpetuate the myth[8]. For term and near-term infants, we can reasonably conclude that air should be used initially, with oxygen as backup if initial resuscitation fails. The effect of intermediate concentrations of oxygen at resuscitation needs to be investigated. Future trials should include and stratify its use in pre-term infants[9].

In cardiology, it has been the conventional practice to administer oxygen in high concentrations. However, data mainly from animal studies suggest that free radical injury may promote myocardial decompensation. In humans, a progressive increase in free radical injury and encroachment on antioxidant reserves have been demonstrated with evolution of heart failure[10]. Oxidative stress may be an important determinant of prognosis. One may justifiably postulate that uncontrolled high concentration oxygen therapy may indeed be counter-productive in this scenario.

Even in very special situations like surgery under cardiopulmonary bypass, the use of high oxygen concentrations is now contested. Hyperoxic cardiopulmonary bypass during cardiac operations in adults results in oxidative myocardial damage related to oxygen-derived free radicals and nitric oxide. These adverse effects can be markedly limited by reduced oxygen tension management during the procedure. The concept of normoxic cardiopulmonary bypass may be applied to surgical advantage during cardiac operations[11]. Laboratory studies have shown that myocardial reperfusion injury is exacerbated by free radicals when pure oxygen is used during cardiopulmonary bypass. In further animal experiments, normoxic perfusion does not increase the risk of microembolic brain injury so long as a membrane oxygenator with an artificial filter is used[12].

It is perhaps interesting that even in apparently unrelated conditions, there is evidence of detrimental effects of oxidative stress. A case in point is type I diabetes mellitus in children and adolescents. Persistent hyperglycaemia has been reported to cause increased production of oxygen free radicals through auto-oxidation and non-enzymatic glycation. A cross-sectional study in young diabetic patients has shown that systemic oxidative stress is present in early onset type I diabetes mellitus and is increased by early adulthood[13].

The beneficial use of supplemental oxygen therapies to increase arterial blood oxygen levels and reduce tissue hypoxia is offset by the knowledge that it injures and kills cells, resulting in increased morbidity and mortality. Although many studies have focused on understanding how hyperoxia kills cells, recent findings reveal that it also inhibits proliferation through activation of cell cycle checkpoints rather than through overt cytotoxicity. Cell cycle checkpoints are thought to be protective because they allow additional time for injured cells to repair damaged DNA and other essential molecules. During recovery in room air, the lung undergoes a burst of proliferation to replace injured and dead cells. Failure to terminate this proliferation has been associated with fibrosis. These observations suggest that growth-suppressive signals, which inhibit proliferation of injured cells and terminate proliferation when tissue repair has been completed, may play an important role in the pulmonary response to hyperoxia. Because DNA replication is coupled with DNA repair, activation of cell cycle checkpoints during hyperoxia may be a mechanism by which cells protect themselves from oxidant genotoxic stress[14].

It makes one wonder whether our over-enthusiastic and uncontrolled administration of high concentrations of oxygen may be similar to venturing into unchartered waters. It is likely that the known untoward effects are perhaps only the tip of the iceberg. There is probably a lot more than what meets the eye in this time-honoured ploy of oxygen therapy. The author has been going round his unit taking children off unnecessary oxygen for a considerable length of time. Current evidence seems to vindicate this practice unreservedly.

References

1. The king of serendipity. Available from, http://home.nycap.rr.com/useless/priestly/priestly.html

2. Varughese S, Jain S, Gupta N, Singh S, Tyagi V, Puliyel JM. Magnitude of the problem of retinopathy of prematurity. Experience in a large maternal unit with a medium sized level-3 nursery. *Ind J Ophthalmology* 2001; **49**:187-8

3. Pagano A, Barazzone-Argiroffo C. Alveolar cell death in hyperoxia-induced lung injury. *Ann New York Acad Sci* 2003; **1010**:405-16.

4. Mathew E, Pun R, Simonich M, Iwamoto H, Dedman J. Cyclosporin A protects lung function from hyperoxic damage. *Am J Physiol Lung Cepp Mol Physiol* 1999; **276**:L786-95.

5. Bhandari V, Johnson L, Smith-Kirwin S, Vigliotta G, Funanage V, Chander A. Hyperoxia and Nitric Oxide reduce surfactant components and increase apoptosis in adult and fetal rat Type II pneumocytes. *Lung* 2002; **180**:301-17.

6. Saugstad OD, Rootwelt T, Aalen O. Resuscitation of asphyxiated newborn infants with room air or oxygen: An international controlled trial: The Resair Study. *Pediatrics* 1998; **102**: el-7.

7. Vento M, Asensi M, Sastre J, Garcia-Sala F, Pallardo FV, Vina J. Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. *Pediatrics* 2001; **107**:642-7.

8. Lefkowitz W. Oxygen and resuscitation: Beyond the myth. *Pediatrics* 2002; **109**:517-9.

9. Davis P, Tan A, O'Donnell C, Schulze A. Resuscitation of newborn infants with 100% oxygen or air : A systematic review and meta-analysis. *The Lancet* 2004; **364**:1329-33.

10. Keith M, Geranmayegan A, Sole MJ, Kurian R, Robinson A, Omran AS, Jeejeebhoy KN. Increased oxidative stress in patients with congestive heart failure. *J Am Coll Cardiol* 1998; **31**:1352-56.

11. Ihnken K, Winkler A, Schlensak C, Sarai K, Neidhart G, Unkelbach U, Mulsch A, Sewell A. Normoxic cardiopulmonary bypass reduces oxidative myocardial damage and nitric oxide during cardiac operations in the adult. *J Thoracic Cardiovasc Surgery* 1998; **116**:327-31.

12. Nollert G, Nagashima M, Bucerius J, Shin'oka T, Lidov HGW, du Plessis A, Jonas RA. Oxygenation strategy and neurologic damage after deep hypothermic circulatory arrest. II. Hypoxic versus free radical injury. *J Thoracic Cardiovasc Surgery* 1999; **117**:1172-9.

13. Dominguez C, Ruiz E, Gussinye M, Carrascosa A. Oxidative stress at onset and in early stages of type I diabetes in children and adolescents. *Diabetes Care* 1998; **21**:1736-42.

14. Michael A. O'Reilly MA. DNA damage and cell cycle checkpoints in hyperoxic lung injury: braking to facilitate repair. *Am J Physiol Lung Cell Mol Physiol* 2001:**281**:L291-305.

B J C Perera
Joint Editor