

# Oxygen: could there be too much of a good thing?

*Robert E Rosenthal, Gary Fiskum*

Supplemental oxygen is provided routinely to virtually all victims of serious injury or illness, often with little attention paid to the consequences of prolonged hyperoxia. Preclinical evidence, however, is mounting which suggests that the simple administration of oxygen can be damaging when given following selected incidences of ischaemia (low flow) and reperfusion.

The ultimate clinical example of ischaemia or reperfusion is cardiac arrest. The authors' laboratory is actively involved in examining the effects of oxygen following resuscitation, in an attempt to define the most appropriate way to ventilate the cardiac arrest survivor.

Advanced cardiac life support (ACLS) protocols teach us that all victims of cardiac arrest should be ventilated with 100% oxygen; no mention is made of how or when to wean the cardiac arrest survivor from supplemental oxygen.

Interestingly, there has never been a clinical study demonstrating the protective effect of high-flow oxygen for the cardiac arrest survivor, yet many patients intubated in the emergency department receive large volumes of supplemental oxygen for prolonged periods, in the absence of clinical hypoxia.

In our own emergency department 23 out of 40 patients intubated in the emergency department were hyperoxic ( $P_{O_2} > 150$  mmHg) on the initial post-resuscitative arterial blood gas (ABG); 16 out of 23 remained hyperoxic when the second arterial blood gas was recorded 0.8–20 hours following the first ABG.

## **HYPEROXIA WORSENS NEUROLOGICAL INJURY FOLLOWING RESUSCITATION FROM EXPERIMENTAL CARDIAC ARREST**

Using a large animal model of cardiac arrest and resuscitation, the authors' laboratories continue to examine the effects of oxygen on the brain following resuscitation from cardiac arrest. Following 10 minutes of cardiac arrest, animals

have been randomized to resuscitation with either 100% oxygen (hyperoxia) or room air (normoxia 21% oxygen). Animals were then ventilated with the same gas for 1 hour following successful resuscitation. At the end of 1 hour, ABGs were used to adjust ventilation to maintain  $pO_2$  in physiological ranges. Interestingly, animals receiving 100% oxygen for just 1 hour had markedly worsened neurological outcome than normoxic animals (Liu et al, 1998). Hyperoxic animals demonstrated increased oxidation of brain lipids (the major component of neuronal membranes), increased neuronal death seen histologically and significantly worse clinical neurological outcome 24 hours following resuscitation. Standard dogma would suggest that provision of supplemental oxygen to the ischaemic brain would improve lactic acidosis. Paradoxically, cortical lactate levels were higher in hyperoxic animals, apparently as a result of oxidative inactivation of a key enzyme (pyruvate dehydrogenase) needed for aerobic metabolism of glucose.

## **IMPLICATIONS FOR HUMAN VICTIMS OF ISCHAEMIA OR REPERFUSION**

It is known, however, that preclinical results do not always correlate with clinical experience in human disease processes. Interestingly, as mentioned above, there has never been a human trial demonstrating a neuroprotective effect for high-flow oxygen following cerebral ischaemia, despite its routine use in clinical practice in the face of growing preclinical evidence that hyperoxia following cardiac arrest is actually damaging.

On the contrary, one human study suggests that there is increased mortality in victims of mild focal cerebral ischaemia (stroke) who received only minimal supplemental oxygen (3 litres via nasal cannulae) for 24 hours following the onset of symptoms (Ronning and Guldvog, 1999). In addition to cardiac arrest and stroke, there are several other clinical scenarios where human experience with hyperoxic resuscitation is now also becoming available, sometimes with conflicting results.

**Professor Robert E Rosenthal** is Professor of Surgery and Anesthesiology, Program in Trauma, Section Chief, Hyperbaric Medicine, The R Adams Cowley Shock Trauma Center, and **Professor Gary Fiskum** is Professor and Vice-Chair, Research, Departments of Anesthesiology, Biochemistry and Molecular Biology, and Pharmacology and Experimental Therapeutics, University of Maryland School of Medicine, Baltimore, MD 21201, USA

Correspondence to:  
Professor RE Rosenthal

## RESUSCITATION OF ASPHYXIATED NEWBORN INFANTS WITH ROOM AIR OR OXYGEN

Birth asphyxia represents a serious problem worldwide, resulting in millions of deaths or serious sequelae annually. The Resuscitation of Asphyxiated Newborn Infants With Room Air or Oxygen (RESAIR) study is an international controlled trial designed to examine the traditional resuscitation of asphyxiated newborns with 100% oxygen (Saugstad et al, 1998, 2003). Asphyxiated newborns from 11 centres in six countries were randomized to resuscitation with either room air or 100% oxygen. The results so far demonstrate that ambient air is as efficient as oxygen for newborn resuscitation. First breath and cry, as well as normal breathing patterns, are established more rapidly with room air resuscitation. Neonatal mortality tended towards lower values in infants resuscitated with ambient air. However, no differences were seen in somatic growth or neurological handicap at 18 or 24 months. The authors conclude that more studies are needed to determine the optimum method of resuscitation.

## RESUSCITATION OF TRAUMA VICTIMS WITH ROOM AIR OR OXYGEN

Haemorrhagic shock and traumatic brain injury each cause significant annual morbidity and mortality. Similar to the conditions previously discussed, virtually all trauma victims receive high-flow oxygen for long periods following initial resuscitation. Preclinical evaluations of optimum ventilatory strategies, however, have been mixed; there is no consensus at present as to the benefit or detriment of inspired oxygen following traumatic injury. Preliminary human trials, however, suggest a potential benefit for supplemental oxygen in victims of severe traumatic brain injury. In one study, for example, high-flow oxygen appears to improve the oxygen supply in post-traumatic ischaemic brain tissue, thus lowering brain lactate, perhaps as a result of a shift from anaerobic to aerobic metabolism (Menzel et al, 1999). Controlled clinical outcome trials will be needed before the implications of these findings can be determined.

## CONCLUSIONS

The studies discussed in this article should serve to heighten the sensitivity of the clinical practitioner to the importance of proper oxygen administration in the setting of critical illness, particularly ischaemia or reperfusion. While there is increasing evidence that high-flow oxygen can be damaging in the presence of experimental global cerebral ischaemia (cardiac

arrest), translation of these results to humans awaits careful clinical evaluation. Clearly not all critical clinical situations are similar; high-flow oxygen may ultimately prove beneficial, for example, in severe traumatic brain injury. Administration of high concentrations of oxygen should not, however, be the 'default' practice for all clinical scenarios, but should most often be reserved for patients with clinical hypoxia. Clinical trials are urgently needed to better define the role of supplemental oxygen in critical illness and injury. **HM**

*Conflict of interest: none*

- Liu Y, Rosenthal RE, Haywood Y, Miljkovic-Lolic M, Vanderhoek JY, Fiskum G (1998) Normoxic ventilation after cardiac arrest reduces oxidation of brain lipids and improves neurological outcome. *Stroke* **29**: 1679–86
- Menzel M, Doppenberg EM, Zauner A, Soukup J, Reinert MM, Bullock R (1999) Increased inspired oxygen concentration as a factor in improved brain tissue oxygenation and tissue lactate levels after severe human head injury. *J Neurosurg* **91**: 1–10
- Ronning OM, Guldvog B (1999) Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. *Stroke* **30**: 2033–7
- Saugstad OD, Rootwelt T, Aalen O (1998) Resuscitation of asphyxiated newborn infants with room air or oxygen: an international controlled trial: the RESAIR 2 study. *Pediatrics* **102**: e1
- Saugstad OD, Ramji S, Irani SF, et al (2003) Resuscitation of newborn infants with 21% or 100% oxygen: follow-up at 18 to 24 months. *Pediatrics* **112**: 296–300

## KEY POINTS

- Supplemental oxygen worsens neurological outcome when administered following experimental cardiac arrest.
- Resuscitation with room air is as effective as resuscitation with supplemental oxygen in the asphyxiated newborn.
- In stroke patients, supplemental oxygen should be reserved for clinical hypoxia.
- Supplemental oxygen may improve aerobic metabolism in the brains of victims of severe traumatic brain injury.
- Clinical trials are needed to better define the proper administration of oxygen to critically-ill patients.

## POINTS OF AGREEMENT

- Tissue perfusion, rather than blood pressure, is the key variable in resuscitation from haemorrhagic shock.
- Maintenance of oxygen-carrying capacity is important in early resuscitation.
- Further studies of resuscitation strategy outcomes are needed.
- Titrate supplemental oxygen to physiologic values. Hyperoxia or hypoxia should be routinely avoided.

## POINTS OF DISAGREEMENT

- Whether deliberate hypotensive resuscitation has been established as a viable strategy in trauma patients.
- Practicality of invasive data (mixed venous oxygen and stroke volume) early in trauma patient resuscitation.