Commentary

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Less oxygen for cardiac arrest patients is better

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Abstract

There is no doubt that oxygen is necessary to sustain life. We have been using oxygen since the late 19th century with its use taken for granted. However, administering oxygen above atmospheric concentration should be prescribed as a medication accounting for potential adverse effects. Exposure to high dose of supplemental oxygen has been associated with pulmonary and cardiac toxicity. Moreover, an increase in oxygen radicals was found to be involved in cell death after cerebral ischemia. Cardiac arrest, both in and out of hospital, is a major cause of death worldwide. Brain injury, myocardial dysfunction and multi-organ failure comprise post cardiac arrest syndrome and reactive oxygen species play a central role in initiating and exacerbating the damage. Studies in animal models of cardiac arrest have found that the administration of 100% oxygen following return of spontaneous circulation (ROSC) may cause neurological harm in comparison to low-dose oxygen. Hyperoxia (PaO2>300 mmHg) is not uncommon among patients after ROSC however, since oxygen therapy is considered integral during resuscitation and post resuscitation care there are no large randomized controlled trials in humans. The existing data from retrospective studies demonstrates correlation between hyperoxia after ROSC and increased in-hospital mortality as well as poor neurological outcome. Hence, we should regard oxygen therapy carefully and use the lowest fraction of inspired oxygen to ensure adequate arterial saturation while avoiding hyperoxia and hypoxia.

Key words: Cardiac arrest, hyperoxia, in-hospital mortality, oxygen.

It is well known that oxygen is necessary to sustain life. The first usage of continuous oxygen administration to treat acute illness was reported in the late 19th century by Dr. Albert Blodgett and we have been using oxygen ever since. (1) Supplemental oxygen is a vital part of every aspect of patient care and its use has become taken for granted. However, administering oxygen above atmospheric concentration is equivalent to the administration of medications and it should be prescribed accordingly taking into account potential adverse effects. (2)

Exposure to high dose of supplemental oxygen has been associated with pulmonary toxicity, reduction in coronary blood flow, increase in lipid peroxidation in the brain as well as an increase in reactive oxygen radicals, which were found to be involved in cell death after cerebral ischemia. (3-8) Facilitation of seizure activity and induction of cerebral vasoconstriction were also found to be induced by hyperoxia. (9,10)

Cardiac arrest, both in and out of hospital, is a major cause of death worldwide. (11,12) Patients who regain spontaneous circulation may suffer morbidity and mortality related to post cardiac arrest syndrome triggered by the ischemia-reperfusion injury. Brain injury, myocardial dysfunction and multi-organ failure comprise post cardiac arrest syndrome and reactive oxygen species play a central role in initiating and exacerbating the damage. (13,14)

Several studies conducted in various animal models of cardiac arrest have examined the effect of high dose oxygen during the peri-resuscitation period. A recent meta-analysis by Pilcher and colleagues included 95 animals that were treated with either 100% oxygen or a lower fraction for 60 minutes after return of spontaneous circulation (ROSC). (15) The administration of 100% oxygen after ROSC resulted in a significantly worse neurological deficit score than lower oxygen concentrations with no statistical evidence of heterogeneity

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despite the different animals included in the analysis. Histological evidence of greater neurological cell damage was also present in animals that were treated with 100% oxygen. The authors concluded that in animal models of cardiac arrest, administration of 100% oxygen following ROSC may bring about neurological harm in comparison to low-dose oxygen.

The incidence of hyperoxia defined as PaO2>300 mmHg among patients after ROSC is considerable and range from 6% to 41%. (16) Since oxygen therapy is widespread and considered integral during resuscitation and post resuscitation care, there are no large randomized controlled trials in humans. Kuisma and colleagues randomized patients with ROSC after out-of-hospital cardiac arrest to be ventilated with either 30% or 100% oxygen for the first hour of post resuscitation care with maintenance of saturation at or above 95%. (17) Patients who received 30% oxygen faired as good as patients who received 100% oxygen. Exposure to 100% oxygen was associated with increased levels of neuron specific enolase (NSE) at 24h after ROSC in patient not treated with hypothermia in comparison to similar patients who received 30% oxygen. Although the authors conclude that the significance of increased NSE level in these patients is unknown, it is still a finding that points towards greater neurological cell damage. More importantly, the administration of a lower concentration of oxygen was not associated with hypoxemia and was safe and feasible.

The majority of data on the effects of hyperoxia is derived from retrospective observational studies. In their multicenter cohort study, the investigators for the emergency medicine shock research network used the project IMPACT registry to examine whether exposure to hyperoxia after ROSC from cardiac arrest was associated with poor neurological outcome. (18) Out of 6326 patients included in the analysis, 18% were exposed to hyperoxia with PaO2≥300 mmHg. After controlling for various confounders, hyperoxia was independently associated with an odds ratio of 1.8 (95% CI, 1.5-2.2) for in hospital mortality. Moreover, among patients who survived to hospital discharge hyperoxia was associated with a lower proportion of functionally independent discharge in comparison to normoxic patients. Subsequent analysis of 4500 patients from the same cohort revealed a dose-dependent association between supranormal PaO2 and the risk of in-hospital mortality with a 24% increase in mortality risk for every 100 mmHg increase in PaO2. (19) Janz and colleagues performed a retrospective analysis of a single center prospective cohort of 170 patients treated with hypothermia after cardiac arrest. (20) In this cohort, higher levels of the maximum measured arterial oxygen tension were associated with increased in hospital mortality and lower CPC score at hospital discharge. It is worth to note that the investigators included the presence of bystander CPR, initial rhythm and time to ROSC in the multivariate analysis. Lee et al., investigated a similar cohort of patient treated with hypothermia after cardiac arrest and found a V-shaped relationship between mean PaO2 and poor neurological outcome with the lowest probability of poor neurological outcome at around 130 mmHg. However, PaO2 had no association with in hospital mortality. (21)

In the study of oxygen in critical care (SOCC) the researchers retrospectively analyzed 12,806 patients admitted after cardiac arrest and registered in the ANZICS-APD database. The investigators found no association between hyperoxia and in-hospital mortality. (22) Similar findings were also reported in a cohort of patients who suffered out-of-hospital cardiac arrest secondary to ventricular tachycardia as well as in patients after in and out of hospital resuscitation. (23,24) However two recent meta-analysis studies aimed to explore the effect of hyperoxia on the outcomes post ROSC patients included data from above mentioned publications and both concluded that hyperoxia might be correlated with increased in-hospital mortality of post cardiac arrest patients. (25,26)

Recent analysis of the Pittsburgh post cardiac arrest service database demonstrated that hyperoxia (PaO2>300 mmhg) was independently associated with decreased survival to hospital discharge with an odds ratio of 0.83 per hour exposure to hyperoxia. (27) Furthermore, higher levels of FiO2 during the first 24h after ROSC were also associated with decreased survival and worse neurological outcome. (28) A study focused on patients who suffered in-hospital cardiac arrest and sustained ROSC for at least 20 min, indicated that there was an optimal range of first measured PaO2 between 70-240 mmHg that was associated with favorable neurological outcome. (29) This range of PaO2 corresponds with the clinical guidelines published by the American Heart Association (AHA) to titer inspired oxygen to the lowest level required to achieve an arterial oxygen saturation of ≥94%, so as to avoid potential oxygen toxicity. (30) During the resuscitation phase the American Heart Association also recommends that a lone rescuer during the first minutes of a witnessed cardiac arrest scenario should not interrupt chest compressions for rescue breaths. The reasoning for this recommen-

dation stems from the principle that in low blood-flow states such as CPR, oxygen delivery is limited by blood flow rather than by oxygen content. (31)

In conclusion, it is not trivial to avoid the administration of oxygen. Oxygen is our parachute and withholding oxygen from critically ill patients may be perceived as attempting sky-diving without a parachute. However oxygen is not free from adverse effects. The data published in the last decade should prompt us to regard oxygen therapy carefully and to use the lowest fraction of inspired oxygen to ensure adequate arterial saturation while avoiding hyperoxia.

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