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Arterial carbon dioxide tension after cardiac arrest: Too little, too much, or just right?*

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Evidence is accumulating that goal-directed post-resuscitation patient care should include targeting oxygenation and ventilation for outcome optimization. Emphasis was initially placed on the oxygenation strategy, as experimental studies demonstrated detrimental effects of hyperoxia post-cardiac arrest.¹ Similarly, adults resuscitated from cardiac arrest with hyperoxia ($\text{PaO}_2 > 300$ mm Hg) on initial ABG had worse outcomes than those with hypoxia or normoxia.²

More recently, the optimal ventilatory strategy was reexamined, along with the effects of carbon dioxide on cardiac and neurological function after ischemia. International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science recognizes that routine hyperventilation after resuscitation should be avoided to prevent cerebral ischemia due to decreased cerebral blood flow that occurs with hypocapnia.³ Important knowledge gaps were realized, however, in how hypo- and hypercapnia relate to neurological outcome in patients resuscitated from cardiac arrest.

In this issue of *Resuscitation*, Schneider et al.⁴ performed a large retrospective observational study to assess the association of early post-resuscitation PaCO_2 values with outcomes in adults with cardiac arrest. The study included 16,542 patients enrolled at 125 participating intensive care units in Australia and New Zealand between 2000 and 2011. Patients were classified into three groups based on PaCO_2 obtained in the first 24 h after cardiac arrest: hypocapnia ($\text{PaCO}_2 < 35$ mm Hg), normocapnia (PaCO_2 of 35–45 mm Hg), and hypercapnia ($\text{PaCO}_2 > 45$ mm Hg). Nearly all values were obtained within the first 4 h post-arrest in a nested subset.

The authors found that patients in the hypocapnia group had worse outcomes vs. the other groups in terms of mortality and discharge home in a multivariate analysis. Hypercapnic patients had a similar mortality rate as normocapnic patients but had a higher chance of being discharged home vs. the normocapnia group.

Similar to these results, children with hypocapnia following cardiac arrest had worse outcomes vs. children with normocapnia.⁵ These results are also supported by experimental

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Conflict of interest

None.

studies suggesting that hypocapnia, induced either by hyperventilation or by ventilation with a reduced percentage of carbon dioxide, worsened neurological outcome after focal or global ischemia. Additionally, in models of focal and global hypoxic-ischemic brain injury, hypocapnia resulted in increased lesion volumes, decreased cerebral blood flow, lower cerebral glucose and ATP, and increased lactate levels.⁶ These studies suggest that the deleterious effects of hypocapnia in ischemic tissue might be due either effects of acidosis on the activity of glycolytic enzymes, effects of hypocapnia on cerebral blood flow, or systemic effects of hypocapnia.⁷

Furthermore, detrimental cardiovascular effects have been noted in hypocarbic patients. Hyperventilation-induced hypocapnia, notably a common phenomena during and post cardiopulmonary resuscitation, can lead to decrease in coronary blood flow and cardiac output. Recent studies in swine suggest that hyperventilation during CPR produced increased intrathoracic pressure, decreased coronary perfusion, and decreased survival after cardiac arrest. These effects were secondary to the mechanical effects of hyperventilation and independent of hypocapnia, as evidenced by the persistence of worse outcomes in pigs receiving hyperventilation and supplemented with inhaled carbon dioxide after cardiac arrest.^{8,9} Additionally, hypothermia, which can increase the solubility of carbon dioxide in blood, can potentially contribute to hypocarbia and cerebral vasoconstriction.¹⁰

Alternatively, mild or moderate hypercapnia had neuroprotective effects in animal models of cerebral ischemia. In a model of hypoxic ischemic encephalopathy in spontaneously breathing neonatal rats, mild hypercapnia decreased lesion volume.⁶ Extreme hypercapnia, on the other hand, worsened lesion volume vs. mild hypocapnia and normocapnia.¹¹ In these studies, cerebral blood flow was preserved during mild hypercapnia, and was decreased during severe hypercapnia.¹² The protective effect of mild hypercapnia was attributed to inhibition of apoptosis, evidenced by increased hippocampal caspase-3 activity and TUNEL-positive cells in the severe hypercapnia group vs. mild hypercapnia group, and protection against cerebral edema, as evidenced by increased expression of aquaporin-4 in the severe vs. mild hypercapnia group. In a pediatric study, early hypercapnia (within 24 h after resuscitation) was found to be associated with increased mortality, however no PaCO₂ threshold was reported, hypercapnia after 24 h post-arrest was not associated with poor outcome.⁵

The cerebral vasoconstrictor effect of hypocapnia and vasodilator effect of hypercapnia, present in the non-injured brain, may be altered after ischemia. Preservation of carbon dioxide reactivity is likely brain region- and insult-duration dependent after ischemia. After global ischemia in rodents, carbon dioxide reactivity to hypercapnia was preserved in the cerebellum and was abolished in the cortical areas and hippocampus.¹³ In two studies of comatose patients resuscitated from cardiac arrest, reactivity to carbon dioxide was preserved, evidenced by decreased cerebral blood flow and jugular bulb oxygen saturation with hypocapnia.^{14,15} However, few animal studies suggested either unresponsiveness or attenuation of reactivity of the microcirculation to changes in PaCO₂ induced by either hypo- or hyperventilation after ischemia.^{16–19} Reactivity of the arterioles in the cortical microvasculature was variable after focal ischemia and this was postulated to be secondary

to ischemic damage to the vessel wall.²⁰ It is reasonable to hypothesize that there is regional variability and insult-duration variability to carbon dioxide in patients post-arrest.

There are several limitations, acknowledged by the authors. One representative PaCO₂ value obtained during the first 24 h was selected for correlation with outcome. Although this value was obtained early post-arrest, PaCO₂ values obtained strictly during the early period of the post-cardiac arrest syndrome²¹ when critical cerebral blood flow disturbances occur, might have a stronger significance. Additionally, these results demonstrate an association of PaCO₂ values with outcomes in adults with cardiac arrest, not causation.

Nevertheless, Schneider et al. provide important evidence that can be easily translated into clinical care to potentially optimize patient outcomes. These data suggest that clinicians should be monitoring arterial blood gas early post-arrest in order to avoid hypocarbia and instead target normocarbia early (first 24 h) after resuscitation from cardiac arrest.

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