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Editorial

The elusive goal carbon dioxide target after cardiac arrest

Despite the use of mechanical ventilation in the majority of comatose post-cardiac arrest patients admitted to the hospital after return of spontaneous circulation (ROSC), considerable doubt remains regarding how to target their ventilation. If one defines the normal physiologic carbon dioxide range as 35–45 mm Hg (4.7–6.0 kPa), exposure to hypocapnia and hypercapnia in the post-resuscitation phase exceeds 90%.[1,2] The 2015 consensus guidelines[3,4] recommend a normal (35–45 mm Hg) $PaCO_2$ target, though on the basis of very limited data. A number of prior observational studies have examined the association between arterial carbon dioxide tension ($PaCO_2$) with outcome and generally report a bimodal or "U-shaped" curve[5–7] where optimal $PaCO_2$ lays around normal values. A closer look at these studies reveals the increase in mortality which is universally noted with lower than normal $PaCO_2$ is not reciprocated on the higher extreme. Here a suggestion of a benefit due to hypercapnia may be found.[7–10]

The attention to $PaCO_2$ goal is largely driven by its impact on cerebral blood flow (CBF) which may influence neurologic outcome after ROSC. Hyperventilation and hypocapnia reduce CBF whereas hypercapnia increases it.[11] Blood pressure autoregulation appears to be lost or right-shifted in most patients after ROSC,[12] whereas the response of CBF to $PaCO_2$ is preserved[13] providing an important route to prevent hypoperfusion early after ROSC.

This seemingly simple issue, where to target $PaCO_2$, is rendered more complex when one considers the potential confounders. How one achieves any goal $PaCO_2$ is dependent on the respiratory rate and tidal volumes (i.e minute ventilation). Prescribed minute ventilation poorly corresponds to $PaCO_2$.[14] In addition, most cardiac arrest patients have metabolic (lactic) acidosis following global ischemia,[15] such that hypocapnia could be considered physiologic respiratory compensation normalizing the pH, whereas hypercapnia will further lower pH. Yet few prior studies have incorporated pH into models examining the association between $PaCO_2$ and outcomes. Within these studies, one found no impact of pH[14] whereas another noted hypercapnia to be associated with poor outcome only when uncompensated[16] but excluded patients with metabolic acidosis.

The definitive answer to the optimal $PaCO_2$ target will be best answered by a randomized controlled trial (RCT). Two such studies are ongoing (TAME: NCT03114033 and COMACARE: NCT02698917) targeting different $PaCO_2$ ranges (50–55 and 43–45 mm Hg in the higher $PaCO_2$ group, respectively). In the interim, the well done study of Kilgannon et al. in this month's issue of Resuscitation[17] provides some important insights. The authors are the first to collect blood gas data prospectively adhering to a strict protocol for obtaining data at 1 and 6 h after ROSC providing high resolution sampling in the early post-ROSC period. This is distinct from prior reports which were retrospective[5,9,10,14,18,19] and bundled blood gas values from various times into blocks (e.g. first 6 h). The authors simultaneously collected data on important ventilator parameters such as prescribed, though not necessarily delivered, minute ventilation, plateau and driving pressures, alveolar dead space, FiO_2 and PEEP. Their analysis also accounted for important confounders such as hyperoxia, comorbidities such as chronic obstructive pulmonary disease, blood pressure and Sequential Organ Failure Assessment (SOFA) scores which impact CBF and/or outcome. $PaCO_2$ and pH were analyzed as continuous variable preventing loss of granularity and permitting us to examine the impact of each upon one another and outcomes.

Perhaps for all these reasons, the authors arrive at a very different result than prior reports or current guideline recommendations.[3,4] While the relationship between $PaCO_2$ and outcome remains U-shaped in Kilgannon's et al. report,[17] the center of the resultant U, which represents the $PaCO_2$ associated with best outcome, is considerably right shifted to 68 mm Hg (and pH 7.19). Worse outcomes are associated with both higher and lower $PaCO_2$ values. In the presence of metabolic acidosis, defined as base deficit exceeding −6 on one or more measures within the first 6 h, the optimal shifts leftward to a more modest hypercapnia ($PaCO_2 = 51$ mm Hg). Nonetheless, this means adding a respiratory acidosis to a metabolic acidosis which is virtually certain to be present in the first 6 h after ROSC.[15] Many intensivists will find this strategy to be uncomfortable as we all have a bias to prefer "normal" physiologic values. Yet "normal" is impossible in the early post-ROSC phase if one wants to increase CBF using higher, or even normal, $PaCO_2$.

These results provide biological plausibility for the ongoing TAME and COMACARE trials which targets mild hypercapnia ($PaCO_2 = 50$–55 mm Hg) as a therapeutic intervention to increase CBF contrary to the current guidelines.[3,4] In a pilot RCT which was preparatory to TAME, this target $PaCO_2$ range resulted in a lower neuron specific enolase level.[8] By providing us continuous data on the association between $PaCO_2$, pH and outcome, Kilgannon's et al. report[17] provides intensivists who often are dealing with simultaneous metabolic acidosis and hypercarbia some data to set boundaries on the degree of hypercapnia and acidosis which can be safely tolerated ($PaCO_2 > 51$ mm Hg or pH < 7.20). This is novel and clinically very important.

The authors have done a good job discussing limitations of their work, several of which are inherent to the observational nature of the study. The authors selected discharge neurologic outcome as their primary measure, which is limiting compared to longer term outcomes (e.g. 30 and 90 days) particularly in the healthcare systems where financial pressures often steer patients to skilled nursing or long-term acute care before their final neurological outcome is manifested. Nonetheless, this is a meaningful patient centered outcome. The study included in-hospital and out-of-hospital cardiac arrests patients which although increasing heterogeneity also improves generalizability of the results for the intensivist caring for both populations. It remains for an RCT to determine whether the associations noted with $PaCO_2$ reflect causality and are whether modification of $PaCO_2$ by changing ventilator settings will improve outcomes. Based on these results and prior reports, there is certainly equipoise to compare normocapnia to hypercapnia in the ongoing RCTs. Until these are reported, intensivists must avoid hypocapnia and may even consider tolerating or actively targeting higher than normal $PaCO_2$ in comatose post-arrest patients in whom persistent cerebral hypoperfusion is a concern as long as it does not result in severe metabolic acidosis ($pH < 7.20$).

REFERENCES

1. Ebner F, Harmon MBA, Aneman A, et al. Carbon dioxide dynamics in relation to neurological outcome in resuscitated out-of-hospital cardiac arrest patients: an exploratory Target Temperature Management Trial substudy. Crit Care 2018;22:196.
2. Falkenbach P, Kamarainen A, Makela A, et al. Incidence of iatrogenic dyscarbia during mild therapeutic hypothermia after successful resuscitation from out-of-hospital cardiac arrest. Resuscitation 2009;80:990–3.
3. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines for post-resuscitation care 2015: section 5 of the European Resuscitation Council guidelines for resuscitation 2015. Resuscitation 2015;95:202–22.
4. Callaway CW, Donnino MW, Fink EL, et al. Part 8: post-cardiac arrest care 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132:S465–82.
5. Lee BK, Jeung KW, Lee HY, et al. Association between mean arterial blood gas tension and outcome in cardiac arrest patients treated with therapeutic hypothermia. Am J Emerg Med 2014;32:55–60.
6. McKenzie N, Williams TA, Tohira H, Ho KM, Finn J. A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest. Resuscitation 2017;111:116–26.
7. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, Abu-Hanna A, de Keizer NF, de Jonge E. Associations of arterial carbon dioxide and arterial oxygen concentrations with hospital mortality after resuscitation from cardiac arrest. Crit Care 2015;19:348.
8. Eastwood GM, Schneider AG, Suzuki S, et al. Targeted therapeutic mild hypercapnia after cardiac arrest: a phase II multi-centre randomised controlled trial (the CCC trial). Resuscitation 2016;104:83–90.
9. Schneider AG, Eastwood GM, Bellomo R, et al. Arterial carbon dioxide tension and outcome in patients admitted to the intensive care unit after cardiac arrest. Resuscitation 2013;84:927–34.
10. Vaahersalo J, Bendel S, Reinikainen M, et al. Arterial blood gas tensions after resuscitation from out-of-Hospital cardiac arrest: associations with long-Term neurologic outcome. Crit Care Med 2014;42:1463–70, doi:http://dx.doi.org/10.1097/CCM.0000000000000228.
11. Raichle ME, Plum F. Hyperventilation and cerebral blood flow. Stroke 1972;3:566–75.
12. Sundgreen C, Larsen FS, Herzog TM, Knudsen GM, Boesgaard S, Aldershvile J. Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. Stroke 2001;32:128–32.
13. Buunk G, van der Hoeven JG, Meinders AE. Cerebrovascular reactivity in comatose patients resuscitated from a cardiac arrest. Stroke 1997;28:1569–73.
14. Tolins ML, Henning DJ, Gaieski DF, Grossestreuer AV, Jaworski A, Johnson NJ. Initial arterial carbon dioxide tension is associated with neurological outcome after resuscitation from cardiac arrest. Resuscitation 2017;114:53–8.
15. Donnino MW, Andersen LW, Giberson T, et al. Initial lactate and lactate change in post–cardiac arrest: a multicenter validation study. Crit Care Med 2014;42:1804–11, doi:http://dx.doi.org/10.1097/CCM.0000000000000332.
16. Tiruvoipati R, Pilcher D, Botha J, Buscher H, Simister R, Bailey M. Association of hypercapnia and hypercapnic acidosis with clinical outcomes in mechanically ventilated patients with cerebral injury. JAMA Neurol 2018;75:818–26.
17. Kilgannon JH, Hunter BR, Puskarich MA, et al. Partial pressure of arterial carbon dioxide after resuscitation from cardiac arrest and neurological outcome: a prospective multi-center protocol-directed cohort study. Resuscitation 2019;135:212–20.
18. Wang HE, Prince DK, Drennan IR, et al. Post-resuscitation arterial oxygen and carbon dioxide and outcomes after out-of-hospital cardiac arrest. Resuscitation 2017;120:113–8.
19. Roberts BW, Kilgannon JH, Hunter BR, et al. Association between early hyperoxia exposure after resuscitation from cardiac arrest and neurological disability: a prospective multi-center protocol-directed cohort study. Circulation 2018;137:2114–24.

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