Can We Finally Take the "$\dot{V}_E$" Out of THRIVE?

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The term "apneic oxygenation" and research on it in humans originated in the 1950s.[1] Interest in the topic likely arose from problems with airway management in the early days of anesthesia practice, the recent introduction of arterial blood gas analysis, and an increasingly academic bent to anesthesiology. From the 1960s to 1980s, researchers studying apneic subjects reported the use of passive insufflation of oxygen to prevent arterial desaturation, as well as reporting that an initial nonlinear rise of arterial carbon dioxide was followed by a linear rise thereafter.[2,3] During the last 2 decades, humidified high-flow nasal cannula devices have transitioned from specialized use in neonatal intensive care units to widespread use in critically-ill adults, as the devices provide more effective noninvasive oxygenation and some degree of ventilatory support with less discomfort to the patient than other options.[4,5] Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE), was coined by Patel *et al.* as the application of high-flow nasal cannula to apneic oxygenation during difficult airway management with "continuous positive airway pressure and gaseous exchange through flow-dependent dead space flushing."[6] While use of a high-flow nasal cannula during apnea provides effective oxygenation in children and adults, studies of carbon dioxide clearance have produced mixed findings and call into question the ventilatory exchange ($\dot{V}_E$) of THRIVE.[4–7] A recent editorial called for randomized trials to address the limited data on carbon dioxide clearance during high-flow apneic oxygenation.[8]

"[There are] limited data on carbon dioxide clearance during high-flow apneic oxygenation."

In this issue of Anesthesiology, Riva *et al.* shares a response to the call: a single-center, five-armed, randomized, controlled noninferiority trial of the use of high-flow nasal cannulas in apneic oxygenation.[9] They randomized healthy adult patients undergoing elective surgical procedures requiring general anesthesia to five groups of 25 participants each with a wide range of rates and varying routes of oxygen delivery: minimal-flow *via* endotracheal tube; low-, medium- and high-flow nasal oxygen with continuous jaw thrust; and a control group consisting of high-flow nasal oxygen with continuous video laryngoscopy.[9] After preoxygenation and standardized induction of anesthesia with target-controlled infusions of propofol and remifentanil and neuromuscular blockade with rocuronium, oxygen was delivered according to randomized assignment. The authors visually confirmed upper airway patency throughout the experiment using a nasopharyngeal flexible scope at the start, at 7 min, and at 14 min of the apnea period. An oropharyngeal tube was inserted if the airway was obstructed; if the airway remained obstructed, the study intervention was terminated. Serial arterial blood gas measurements were performed every 2 min during a 15-min period of apnea or until predefined safety endpoints occurred. The primary outcome was the linear rate of mean increase of arterial carbon dioxide during the 15-min apnea period computed from linear regressions. All four experimental groups met the predetermined noninferiority criteria of 0.3 mmHg/min with mean increases in arterial carbon dioxide of 2 mmHg/min, while mean absolute arterial carbon dioxide increases over time ranged from 30 to 33 mmHg across the five groups. Because there was no significant difference between the high-, medium-, low-, and minimal-flow study groups, the authors concluded that high-flow nasal oxygenation did not supply a ventilatory effect.[9]

Studies of high-flow nasal oxygenation and transcutaneous carbon dioxide measurements in anesthetized, apneic children have reported similar findings. A randomized controlled trial using two different high-flow rates of nasal

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This editorial accompanies the article on p. 82. This editorial has an audio podcast.

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apneic oxygenation in healthy anesthetized children did not show a ventilatory effect.[7] A randomized trial comparing high-flow nasal cannula oxygen to control in healthy children determined that high-flow nasal oxygenation prolonged the safe apnea time, yet had no effect on carbon dioxide clearance.[10]

Riva *et al.* took their study several steps further: only carbon dioxide measurements from arterial samplings were used in the model calculations; four experimental groups and one control group were included with a wide range of oxygen flow rates; and granular data across the five groups are displayed along with extensive sensitivity analyses in graphical and tabular formats. The authors' interpretation of their results, along with refuting earlier studies' claims of ventilatory exchange in THRIVE, are attributed to sole use of end-tidal carbon dioxide concentration sampling and use of historical controls from much earlier studies.[6,9]

While the focus of the study by Riva *et al.* was carbon dioxide clearance, the oxygenation findings are noteworthy. A patent airway and preoxygenation to an end-tidal oxygen concentration greater than 90% are remarkably effective in a healthy adult: only 6 of 125 patients (5%) met the oxygen desaturation termination criterion during the 15-min period of apnea. The rates of oxygen desaturation were similar in all five groups, with Spo_2 decreasing to less than 92% in not only the minimal-, low-, and medium-flow groups, but also in the high-flow (control) group! Having a patent airway through which oxygen can be insufflated would seem to be especially important. As noted in the study by Riva *et al.*, despite the demonstrated lack of a ventilatory component, high-flow nasal oxygenation in combination with a patent airway is an effective means of providing apneic oxygenation in the operating room during preoxygenation, induction of anesthesia, intubation, and awake flexible optic intubation, as well as for other purposes.[9]

What implications might the study by Riva *et al.* have in the context of high-flow nasal oxygenation in the intensive care unit? A joint panel of experts from the European Society of Intensive Care Medicine conducted systematic reviews of the literature to synthesize an evidence-based clinical practice guideline that was released in November 2020.[11] This guideline made a strong recommendation for high-flow nasal oxygenation in patients with hypoxemic respiratory failure and made no recommendation for patients during intubation.[11] When compared to conventional oxygen therapy and noninvasive positive pressure ventilation, use of a high-flow nasal cannula during intubation had no effect on the incidence of hypoxemia during intubation (defined as Spo_2 less than 80%), 28-day mortality, serious complications, or length of stay in the intensive care unit.[11] The study by Riva *et al.* adds additional evidence that supports the panel's finding that high-flow nasal cannula use had no effect on arterial carbon dioxide measured after intubation when compared to conventional oxygen therapy or noninvasive positive pressure ventilation.[9,11]

Despite the recent flurry of interest in the literature, there is minimal use of high-flow nasal cannula therapy in the operating room, likely because it requires respiratory therapy support to set up and in most perioperative settings, it entails added cost with unproven benefits. However, the COVID-19 pandemic has markedly increased the exposure of anesthesiologists to high-flow nasal cannulas given their new clinical responsibilities in intensive care units.[12,13] Anesthesiologists translating their newfound experience to the operating room can use the study from Riva *et al.*, along with practice guidelines, for valuable context as to when and when not to employ high-flow nasal cannula therapy.

Riva *et al.* should be commended for rising to the challenge of conducting a randomized trial to address this controversy. Their study and the studies of high-flow nasal oxygen in children suggest we can finally take the "$\dot{V}e$" (which is generally equated with carbon dioxide clearance) out of THRIVE.[7,9,10] The main limitation of the study is its generalizability—with its single-center design and extensive exclusion criteria, how applicable is it to the more general (*i.e.*, less healthy) adult surgical population that we commonly encounter? On the other hand, how feasible is a prospective, randomized, controlled, five-armed, multicenter study that may result in as many as 15 min of apnea in higher-risk patients (*e.g.*, those with known coronary heart disease or body mass index greater than 35 kg/m^2)? A Herculean and more risky endeavor of that nature seems highly unlikely. Meanwhile, Riva *et al.* have provided elegant study design and analysis for other researchers to emulate when responding to the call for more data on carbon dioxide clearance during high-flow nasal apneic oxygenation.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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