

EDITORIAL



Rethinking High-Flow Oxygen in Acute Hypoxemic Respiratory Failure

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Acute hypoxemic respiratory failure remains one of the most common conditions encountered in the intensive care unit (ICU).¹ During the past decade, high-flow nasal oxygen has moved from physiological curiosity to frontline therapy.² Early enthusiasm followed the publication of the results of the 2015 FLORALI trial,³ which showed improved survival with high-flow nasal oxygen. Subsequent studies, however, showed less consistent signals, particularly regarding survival.^{2,4}

In parallel, clinical practice shifted toward routine use of high-flow oxygen in patients with hypoxemic respiratory failure, often ahead of definitive evidence regarding its effect on hard outcomes.⁵ Against this backdrop, the results of the SOHO trial,⁶ now published in the *Journal*, provide important clarity by testing a simple and pragmatic question: does high-flow oxygen improve 28-day mortality, as compared with standard-oxygen therapy, in patients with acute hypoxemic respiratory failure?

In this large, multicenter trial involving patients with acute hypoxemic respiratory failure, Frat and colleagues found that the use of high-flow oxygen did not result in lower 28-day mortality than standard-oxygen therapy. However, intubation within 28 days appeared to occur less frequently in the high-flow-oxygen group than in the standard-oxygen group (42.4% vs. 48.4%). The median time until intubation appeared to be similar in the two groups, which suggests that the lower intubation rate in the high-flow-oxygen group was not simply caused by delayed decision making but rather reflected a sustained reduction in the percentage of patients who had undergone invasive ventilation. Secondary analyses

suggested early improvements in respiratory rate and dyspnea with high-flow oxygen, a finding that was consistent with its physiological effects on work of breathing and dead-space washout.⁷ Together, these findings suggest that the use of high-flow oxygen can meaningfully alter the course of respiratory support, even without affecting survival.

Some aspects of the trial warrant reflection, although not disproportionate emphasis. As in most respiratory-support trials, the trial was unblinded, and intubation retains an element of clinical judgment, despite the adoption of pre-specified criteria. The trial was powered to detect a relatively large mortality difference, and the lower-than-expected event rate limited the ability to rule out smaller but potentially meaningful effects. Nevertheless, the confidence intervals effectively ruled out a large mortality benefit. Even so, the absence of a mortality effect should not be interpreted as an absence of clinical value. In critical care, the causal pathway between a noninvasive-oxygenation strategy and 28-day survival is long and complex. Between the initiation of high-flow oxygen and a mortality end point lie multiple potential interventions, complications, and competing risks. Expecting a substantial mortality reduction from an oxygen-delivery interface may set an unrealistic benchmark for success.

The results of the SOHO trial invite a broader discussion about outcome selection in critical care trials. Mortality remains the standard end point, yet not all interventions are biologically positioned to influence this outcome directly.⁸ The use of high-flow oxygen primarily reduces inspiratory effort, improves comfort, and optimizes

oxygenation.⁷ These mechanisms plausibly reduce the need for intubation, which is a proximal and mechanistically coherent outcome, rather than altering downstream mortality driven by disease severity, multiorgan dysfunction, coinfections, or coexisting disease. Such a reduction in intubation is consistent with previous evidence, including large network meta-analyses suggesting that the use of high-flow oxygen lowered the need for invasive ventilation, as compared with standard-oxygen therapy.² Moreover, the recent RENOVATE trial showed that the performance of high-flow oxygen was similar to that of noninvasive ventilation across several phenotypes of acute respiratory failure.⁴ Viewed collectively, these data consolidate the use of high-flow oxygen as a foundational method within noninvasive respiratory support.

Clinically, the implications are tangible. The avoidance of intubation is not a trivial goal. Invasive ventilation carries risks of ventilator-associated pneumonia, sedation-related complications, diaphragmatic dysfunction, and prolonged ICU stay.⁹ Even when mortality is unaffected, reducing exposure to invasive ventilation may improve the patient's experience, preserve functional outcomes, and reduce health care costs.⁹ The similar median time to intubation between the two groups in the SOHO trial is particularly reassuring: the use of high-flow oxygen did not appear to prolong unsuccessful trials of noninvasive support, a concern that has shadowed the widespread adoption of this method.¹⁰ Instead, the use of high-flow oxygen seems to selectively prevent intubation in a subset of patients without deferring inevitable escalation in others.

Thus, where do the results of the SOHO trial leave the field? Essentially, the trial recalibrates expectations. The use of high-flow oxygen should not be viewed as a mortality-reducing therapy in unselected patients with hypoxemic respiratory failure. Rather, it is a strategy that may meaningfully influence the pathway of respiratory support. For clinicians, this factor reinforces the rationale for early use of high-flow oxygen in appropriate patients while maintaining vigilance for clinical deterioration. For researchers, it underscores the importance of aligning primary

outcomes with plausible mechanisms of action and considering composite or hierarchical end points that better capture patient-centered benefit. As critical care continues to refine its methodologic standards, the results of this trial stand as a reminder that improving care does not always mean extending life but sometimes means altering the journey through critical illness in ways that matter deeply to patients and systems alike.

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