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SPECIAL FEATURE

Dyspnea and Asynchrony During Mechanical Ventilation

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Mr. Kallet reports no financial relationships relevant to this field of study.

A Uruguayan military interrogator made a matter-of-fact statement while discussing "el submarino" ("water-boarding") during that country's state of siege in the early 1970s: "There is something more terrifying than pain, and that is the inability to breathe."[1] Particularly unsettling is the fact that practitioners of torture clearly appreciate what often eludes us: Breathing is the primal sensation of postnatal life, the disturbance of which produces the most profound sense of dread.

Compared to pain management, dyspnea and breathlessness in the ICU receive scant attention, as little prospective research informs clinicians and clinical management guidelines are nonexistent.[2] Most research on dyspnea and breathlessness occurs outside the ICU in normal subjects or patients with chronic lung disease. Understandably, self-reporting of symptoms is crucial to advancing knowledge. In critical care literature, however, dyspnea has been inferred largely from the results of studies on patient-ventilator asynchrony and work of breathing (WOB). The few studies that have addressed dyspnea during mechanical ventilation (MV) report moderate to severe dyspnea is common (47-62% incidence) and often linked to anxiety.[3-6] Moreover, clinicians systematically underestimate the intensity of dyspnea patients experience.[4]

Dyspnea and breathlessness are distinct phenomena that capture nuanced, overlapping sensations associated with breathing discomfort. Dyspnea and pain are similar in that both sensations possess qualitatively distinct features with varying intensity and cause suffering. In fact, neuroimaging confirms the same primitive brain structures as pain process dyspnea and activate areas associated with emotions.[5,6] What are the basic theories regarding the nature of breathing perception and dyspnea and its likely relationship to WOB and asynchrony during MV?

When used as a specific descriptor, dyspnea refers to

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difficulty in the mechanical act of breathing, or what originally was referred to as length-tension inappropriateness.[9] A more comprehensive term (efferent-reafferent dissociation) acknowledges that a complex array of receptors are involved in generating these sensations.[10] In essence, dyspnea occurs when an imbalance (or a phase-lag) develops between proprioceptive information regarding tension development in the chest muscles with corresponding proprioceptive signals associated with the magnitude (and/or speed) of displacement of the chest and lungs. When this reaches sufficient intensity, one becomes consciously aware of his or her respiratory drive. Breathlessness, on the other hand, is an unpleasant urge to breathe that can occur regardless of encumbered breathing. It is believed to be the conscious perception of intense neural discharge from the brain stem. Additionally, researchers believe acute hypercapnia, acidosis, hypoxemia, and possibly intense stimulation of irritant receptors in the lung parenchyma clinically trigger the event.

Emotional distress perpetuates and magnifies dyspnea and breathlessness. Factors such as situation, knowledge, and control influence emotional distress. Whereas a healthy person identifies the source of breathlessness and arrests the symptom (i.e., stop exercising or holding breath), patients suffering from cardiopulmonary disease often cannot control their symptoms and may not be able to identify its source, which provokes anxiety. Yet another perplexing aspect of dyspnea is psychogenic hyperventilation syndrome associated with panic disorders.[11] Breathlessness and hyperventilation resulting in respiratory alkalosis often accompany anxiety. This, in turn, amplifies breathlessness, further provoking anxiety and increasing the intensity of hyperventilation. This vicious cycle is worse in those whose baseline WOB is elevated due to cardiopulmonary or neuromuscular disease. In patients requiring MV, dyspnea was most strongly associated with anxiety, or was found to coexist with it.[3,6] Furthermore, the presence of pain magnifies dyspnea when WOB is abnormal.[12] Although the likelihood of identifying patients in the ICU with a documented history of psychogenic hyperventilation disorder is nil, clinicians should suspect it whenever respiratory distress appears enigmatic and disproportionate to the intensity of stimulation (e.g., weaning intolerance despite normal chest mechanics, gas exchange, and low minute ventilation requirements).

In large measure, critically ill patients require MV because pathologic increases in resistance, elastance, and minute ventilation place an unsustainable workload on respiratory muscles. Given the dearth of clinical evidence, clinicians infer the relationship between dyspnea and MV from laboratory studies using respiratory muscle loading either to induce acute fatigue or measure the perceived intensity of inspiratory effort. Not surprisingly, these studies have reported similar results. When inspiratory muscle pressure exceeds ~60% of maximum, acute fatigue eventually develops and occurs more quickly as the duration of inspiratory muscle contraction increases.[13,14] Likewise, the perception of effort is linearly related to the fraction of inspiratory muscle pressure/maximal pressure. Dyspnea was rated as "very severe" when inspiratory effort reached 60% of maximum and again was magnified as duration of muscular contraction increased.[15]

DYSPNEA AND LIMITATIONS OF MV

Dyspnea occurring during MV modifies primarily due to three ventilator settings that interact with spontaneous breathing efforts: tidal volume, or V_T, (which approximates global inspiratory muscle shortening); peak inspiratory flow rate and flow pattern (which reflects the velocity of muscular contraction); and trigger sensitivity (which represents threshold loading, the phase-lag between the onset of muscular contraction, and onset of gas flow). Seminal research from the 1980s focused practices on adjusting ventilator flow to meet patient demand and minimizing trigger-related work.[16,17] With the advent of lung-protective ventilation (LPV), other studies demonstrated that restricting V_T increased WOB by imposing resistive work or limiting the power output of the ventilator.[18] Moreover, restricting V_T below demand interacts with hypercapnia to magnify dyspnea and is particularly

relevant when LPV requires permissive hypercapnia.[19]

There is also a latency period for load detection that is different depending on the nature of inspiratory work (i.e., resistive and threshold loads are detected earlier than elastic loads that are V_T-dependent).[20] The prolonged detection latency for elastic loading explains a unique form of asynchrony ("reverse triggering") observed during LPV.[18,21] In addition, positive end-expiratory pressure (PEEP), at least in the short term, appears to reduce respiratory drive as evidenced by a decreased respiratory rate that may ameliorate breathlessness in those with moderate to severe acute respiratory distress syndrome; the effect is strongest in those with decreased lung compliance. [22] This suggests PEEP modifies the Hering-Breuer deflation reflex associated with acute volume loss.

Ventilator adjustments often cannot fully alleviate dyspnea. Decreased lung compliance increases threshold loading by blunting negative pressure transmission across edematous lung tissue. Threshold loads are magnified as respiratory drive increases (i.e., greater pressure drop/unit time delay) and also by the presence of intrinsic PEEP. Even mild threshold loads (-2.5 cm H_2O) provoke dyspnea and cause hyperpnea.[23] Severe acidosis can potentiate asynchrony during LPV because hyperpnea is the compensatory response. The amino alcohol buffer, tromethamine, is a direct respiratory depressant and alleviates severe dyspnea, which at higher doses may be partly due to its ability to directly lower $PaCO_2$.[24]

What makes the treatment of dyspnea and breathlessness in the ICU perplexing is that adjusting ventilator settings and sedation to minimize symptoms increases morbidity and mortality risks. Alleviating dyspnea ultimately requires substantial off-loading of the respiratory muscles or chemically suppressing respiratory drive. The former strategy often requires a supranormal V_T; dyspnea largely drove the practice of using large V_T in the 1970s.[25] Likewise, high levels of sedation causes delirium, which may exacerbate patient-ventilator asynchrony, and is associated with poorer outcomes. Patient-ventilator asynchrony has been associated with increased mortality risk.[26] Whether this merely signifies the presence of more severe disease or plays a contributory role remains unknown.

A BALANCED, PRAGMATIC APPROACH TO TREATING DYSPNEA

Balancing these competing problems is vexing but perhaps not hopeless, even if a completely satisfying solution is unrealistic. First, early in the course of severe disease/trauma associated with a hyper-proinflammatory state, give LPV precedence. Treat dyspnea and severe asynchrony with sedation and paralysis. However, excessive sedation stymies the accurate assessment of pain and other potential sources of discomfort that often are the etiologies of apparent anxiety. Prioritizing appropriate pain management may reduce dyspnea and excessive WOB/asynchrony and may result in lower levels of sedation. Thus, treatment of dyspnea becomes a balancing act of harm reduction, in which one must consider multiple variables and options.

During recovery from acute respiratory failure as the proinflammatory state subsides, judicious V_T liberalization is often required to promote comfort as clinicians reduce sedation. This should prompt an assessment of weaning readiness. Also, do not overlook minimizing unnecessary ventilatory workloads. High airway resistance associated with prolonged MV often is related to biofilm build-up that can be removed with endotracheal tube cleaners. Patients with large positive fluid balances should undergo aggressive diuresis once hemodynamically stable to reduce elastic workloads and facilitate weaning. These small gestures may have an additive effect that might substantially reduce WOB and if not fully alleviate dyspnea, at least reduce it to discomfort that the patient can tolerate. ■

REFERENCES

1. Danner M. Abu Ghraib: The hidden story. *The New York Review of Books*. Oct. 7, 2004. http://bit.ly/1RUOEaM.
2. Schmidt M, et al. Unrecognized suffering in the ICU: Addressing dyspnea in mechanically ventilated patients. *Intensive Care Med* 2014;40:1-10.
3. Schmidt M, et al. Dyspnea in mechanically ventilated critically ill patients. *Crit Care Med* 2011;39:2059-2065.
4. Haugdahl HS, et al. Underestimation of patient breathlessness by nurses and physicians during a spontaneous breathing trial. *Am J Respir Crit Care Med* 2015;192:1440-1448.
5. Powers J, Bennett SJ. Measurement of dyspnea in patients treated with mechanical ventilation. *Am J Crit Care* 1999;8:254-261.
6. Knebal AR, et al. Comparison of breathing comfort during weaning with two ventilatory modes. *Am J Respir Crit Care Med* 1994;149:14-18.
7. Evans KC, et al. BOLD fMRI identifies limbic, paralimbic, and cerebellar activation during air hunger. *J Neurophysiol* 2002;88:1500-1511.
8. Von Leupoldt A, et al. Dyspnea and pain share emotion-related brain network. *NeuroImage* 2009;48:200-206.
9. Campbell EJM, Howell JBL. The sensation of breathlessness. *Brit Med Bull* 1963;19:36-40.
10. Schwartzstein RM, Parker MJ. *Respiratory physiology. A clinical approach*. Lippencott Williams & Wilkins, Philadelphia 2006. 169-179.
11. Gardner WN. The pathophysiology of hyperventilation syndrome. *Chest* 1996;109:516-534.
12. Nishino T, et al. Experimental pain augments experimental dyspnea but not vice versa in human volunteers. *Anesthesiology* 1999;91:1633-1638.
13. Roussos C, et al. Fatigue of inspiratory muscles and their synergic behavior. *J Appl Physiol* 1979;46:897-904.

14. Bellemare F, Grassino A. Effect of pressure and timing of contraction on human diaphragm fatigue. *J Appl Physiol* 1982;53:1190-1195.
15. Bradley D, et al. The relationship of inspiratory effort sensation to fatiguing patterns of the diaphragm. *Am Rev Respir Dis* 1986;134:1119-1124.
16. Marini JJ, et al. The inspiratory workload of patient-initiated mechanical ventilation. *Am Rev Respir Dis* 1986;134:902-909.
17. Katz JA, et al. Inspiratory work and airway pressure with continuous positive airway pressure delivery systems. *Chest* 1985;88:519-526.
18. Kallet RH, et al. Work of breathing during lung-protective ventilation in patients with acute lung injury and acute respiratory distress syndrome: A comparison between volume and pressure-regulated breathing modes. *Respir Care* 2005;50:1623-1631.
19. Chonan T, et al. Effects of changes in level and pattern of breathing on the sensation of dyspnea. *J Appl Physiol* 1990;69:1290-1295.
20. Burdon JGW, et al. Detection latency of added loads to breathing. *Clin Sci* 1982;63:11-15.
21. Akoumianaki E, et al. Mechanical ventilation-induced reverse-triggered breaths: A frequently unrecognized form of neuromechanical coupling. *Chest* 2013;143:927-938.
22. Haberthur C, Guttmann J. Short-term effects of positive end-expiratory pressure on breathing pattern: An interventional study in adult intensive care patients. *Crit Care* 2005;R407.
23. Yan S, Bates JHT. Breathing responses to small inspiratory threshold loads in humans. *J Appl Physiol* 1999;86:874-880.
24. Nishino T, et al. THAM improves an experimentally induced severe dyspnea. *J Pain Symptom Mange* 2009;37:212-219.
25. Pontoppidan H, et al. Acute respiratory failure in the adult (third of three parts). *N Engl J Med* 1972;287:799-806.
26. Blanch L, et al. Asynchronies during mechanical ventilation are associated with mortality. *Intensive Care Med* 2015;414:633-641.

ABSTRACT & COMMENTARY

What is the Best Rate Control Agent for Patients with Sepsis and Atrial Fibrillation?

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Dr. Nadler reports no financial relationships relevant to this field of study.

SYNOPSIS: Beta-blockers may be associated with better outcomes in patients with sepsis and atrial fibrillation.

SOURCE: Walkey AJ, et al. Practice patterns and outcomes for treatments for atrial fibrillation during sepsis: A propensity-matched cohort study. *Chest* 2016;149:74-83.

Both sepsis and atrial fibrillation (AF) are common conditions in the ICU, and the presence of both together is not a rare occurrence. Common approaches to the management of AF include rate control agents and cardioversion. However, in the context of sepsis, cardioversion is often unsuccessful, and rate control is the most appropriate goal. The choice of rate control agent can be complicated. Beta-blockers (BBs) and calcium channel blockers (CCBs) may cause hypotension in a patient already with shock due to sepsis. Amiodarone can be pro-arrhythmic and has many drug interactions. Digoxin may be less effective in sepsis due to high catecholamine levels, and its use may be problematic with variable renal function.

This study evaluated the practice patterns of treating AF and sepsis and compared outcomes to better inform the choice of rate control agents. A cohort of 113,511 adult patients was identified from an advanced database of patients in non-federal hospitals in the United States admitted with sepsis with AF. Of these, 39,711 (35%) received a single intravenous therapy for AF. The most common prescription was for a CCB (36%), followed by a BB (28%), digoxin (20%), and amiodarone (16%). Compared with BBs, CCBs were less likely to be prescribed in the Northeast, in teaching hospitals, and by surgeons. Digoxin was more likely to be prescribed in older patients and those with pre-existing comorbidities, such as heart failure, valvular heart disease, cirrhosis, cancer, chronic obstructive pulmonary disease, or shock. Patients with septic shock with new-onset AF, heart failure, cancer, or acute organ failure more commonly used amiodarone. Pulmonary and critical care physicians more likely prescribed it. Using propensity-score matching, relative rates of mortality were determined for each agent. Compared with all other agents, patients receiving BBs had the lowest mortality (relative risk [RR], 0.92; 95% confidence interval [CI], 0.86-0.97) vs CCB (RR, 0.79; 95% CI, 0.75-0.84) vs digoxin (RR, 0.65; 95% CI, 0.61-0.69) vs amiodarone.

■ COMMENTARY

This study's strength is its examination of a large cohort of patients in the United States admitted with sepsis complicated by AF. It uncovered significant

variability in practice patterns that differ due to patient factors but also geographic location, teaching status, and physician specialty. Compared with BBs, patients in the Midwest had a multivariate-adjusted RR of 2.8 (95% CI, 2.07-3.77) times more likely to receive amiodarone. Patients in the South had an increased RR of 1.96-fold (95% CI, 1.64-2.33) in terms of receiving CCBs. Surgeons were least likely to prescribe agents other than BBs (RR of 0.39 for CCBs, RR of 0.50 for digoxin, and RR of 0.68 for amiodarone), while cardiologists and pulmonary/critical care physicians were associated with increased amiodarone use (RR of 1.38 and 1.36, respectively). Other patient-specific factors, including comorbidities, acute organ failure, mechanical ventilation, and site of infection, had associated RRs ranging from 0.72-1.45. Interestingly, no significant variability in prescribing patterns was attributable to race or age. About 10% of the variability was unexplained. Thus, there was no clear "standard of care."

More striking were the data regarding mortality and choice of rate control agent. However, closer examination of these findings raises questions. This study design used propensity matching to eliminate known confounding variables. Important variables will continue to confound this analysis. For example, surgeon prescriptions were associated with decreased likelihood of CCB, amiodarone, and digoxin use. Patients in surgical ICUs are quite different from those in cardiovascular units or medical ICUs. While amiodarone use was associated with the worst outcomes, it was also used more in patients with acute respiratory failure (RR = 1.4), acute circulatory failure (RR = 1.37), acute renal failure (RR = 1.2), and acute liver failure (RR = 1.37). These patients clearly have a higher acuity and therefore have a higher likelihood of death, regardless of rate control agent choice. The authors appropriately cautioned that these findings should be considered "hypothesis-generating" and support the need for randomized, controlled trials.

This article reveals significant practice variations in the treatment of concomitant sepsis and AF, both due to patient and non-patient factors. No clear "gold standard" exists. Researchers must conduct further randomized, controlled trials to evaluate which rate control agents yield the best patient outcomes. ■

ABSTRACT & COMMENTARY

Does Acetaminophen Help Febrile Patients with Infection?

By Elaine Chen, MD

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Dr. Chen reports no financial relationships relevant to this field of study.

SYNOPSIS: Scheduled intravenous acetaminophen lowers temperature but does not affect ICU-free days, mortality, length of stay, or adverse events in patients with sepsis.

SOURCE: Young P, et al. Acetaminophen for fever in critically ill patients with suspected infection. *N Engl J Med* 2015;373:2215-2224.

Fevers are common in critically ill patients with suspected infection. Elevated temperatures can create additional physiologic stress on critically ill patients but can also enhance immune cell function, inhibit pathogen growth, and increase the activity of antimicrobial drugs. A study of external cooling of mechanically ventilated patients with septic shock showed decreased vasopressor requirements and decreased early mortality.[1] Acetaminophen is commonly administered to lower the temperature of febrile, critically ill patients but has not been well studied for clinical benefit. Young et al hypothesized that the early administration of intravenous acetaminophen in febrile patients with probable infection would result in fewer ICU-free days compared to placebo.

The study was a prospective, blinded, parallel-group, randomized, controlled trial in Australia and New Zealand. Subjects included adults with a temperature > 38° C receiving antimicrobial therapy; patients with acute brain disorders and liver dysfunction were excluded. Patients were assigned to scheduled intravenous infusion of either 1 g of acetaminophen or placebo every 6 hours for 28 days or until cessation criteria were met. The primary outcome was ICU-free days from randomization to day 28. Secondary outcomes included all-cause mortality at days 28 and 90, survival time, ICU and hospital length of stay, hospital-free days, and ventilator-free days, among others. Researchers also collected physiologic and laboratory outcome variables.

An intention-to-treat population of 690 was obtained, with 346 subjects assigned to acetaminophen

and 344 assigned to placebo. Median doses of study drug were 8 in the acetaminophen group and 9 in the placebo group. Most common reasons for discontinuation of study drug were discharge from ICU and resolution of fever. Physiologically, the group receiving acetaminophen had significantly lower daily peak and average body temperatures, and a significantly increased number had sustained resolution of fever. There were no statistically significant differences in ICU-free days at day 28 (primary outcome), mortality at 28 and 90 days, ICU length of stay, or hospital length of stay.

Acetaminophen was associated with a shorter median ICU length of stay than placebo among survivors but a longer median ICU length of stay among non-survivors. Both groups had similar rates of liver dysfunction. Overall, this study showed that the early administration of acetaminophen did not affect clinical outcomes. Acetaminophen lowered body temperature and did not cause significantly more adverse events. Similar to prior studies, acetaminophen works as an antipyretic, and cooling to normothermia may delay death.[1-3]

■ COMMENTARY

While outcomes in critically ill patients with infection continue to improve due to evidence-based changes in care, mortality due to sepsis remains high. Clinicians administer acetaminophen commonly to febrile patients without contraindications to lower temperature. First, a few questions. Does one order acetaminophen in this patient population? If so, what are the goals? Is it to decrease the temperature? This, as the study demonstrated, will happen. Is one hoping to decrease physiologic concerns, such as shivering and metabolic demand? This study does not address this. Does one think there would be morbidity or mortality benefit or simply symptomatic improvement?

In this study, researchers administered 4 g acetaminophen intravenously daily. This is in contrast to usual clinical practice of as-needed enteral acetaminophen with a dose limit of 3 g daily in patients with normal liver function. From this study, it seems higher-dose acetaminophen does not cause harm.

Researchers did not perform subjective assessments. If a drug causes no harm and no significant clinical benefit, use can be justified for improving patient comfort. In patients who are febrile but sedated, such sedation use ensures patient comfort. In awake patients, fevers can cause significant discomfort.

That acetaminophen administration may result in a longer ICU stay in non-survivors and shorter ICU stay in survivors has no clear clinical implication at this point. In non-survivors, for whom death seems to be delayed, is there any way to predict this group and avoid acetaminophen use in them? If hospital death is inevitable, then delaying death increases hospital costs and prolongs suffering of patients, family, and staff.

Is there a difference between medically mediated cooling and external cooling? In two prior studies, one using paracetamol administration and one using external cooling, there was a decrease in early mortality but overall mortality did not change, reflecting a delay of death similar to this study.[1,4]

Will this change my practice? Probably not. I will continue to use acetaminophen in highly febrile patients without hepatic dysfunction. If a patient is intubated and sedated, but febrile to 104° F, I will try to decrease the temperature, even though I only may be treating myself. ■

REFERENCES

1. Schortgen F, et al. Fever control using external cooling in septic shock: A randomized controlled trial. *Am J Respir Crit Care Med* 2012;185:1088-1095.
2. Greenberg RS, et al. Acetaminophen has limited antipyretic activity in critically ill patients. *J Crit Care* 2010;25:363.e1-363.e7.
3. Dippel DWJ, et al. Timing of the effect of acetaminophen on body temperature in patients with acute ischemic stroke. *Neurology* 2003;61:677-679.
4. Suzuki S, et al. Paracetamol therapy and outcome of critically ill patients: A multicenter retrospective observational study. *Crit Care* 2015;19:162-171.

ABSTRACT & COMMENTARY

Apneic Oxygenation During Intubation for Respiratory Failure

By Richard Kallet, MS, RRT, FAARC, FCCM

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Mr. Kallet reports no financial relationships relevant to this field of study.

SYNOPSIS: Use of apneic oxygenation with a high-flow nasal cannula during endotracheal intubation for acute respiratory failure is no better at preventing arterial oxygen desaturation than usual care using pre-oxygenation.

SOURCE: Semler MW, et al. Randomized trial of apneic oxygenation during endotracheal intubation of the critically ill. *Am J Respir Crit Care Med* 2016;193:273-280.

In this prospective trial, 150 medical ICU patients were randomized to receive oxygen therapy with a high-flow nasal cannula (HFNC) at 15 L/min during endotracheal intubation or usual care (no supplemental oxygen during laryngoscopy). All other decisions regarding endotracheal intubation (e.g., pre-oxygenation strategy, patient positioning, etc.) were based on clinician discretion. Primary exclusion criteria were emergency intubations that prevented randomization (i.e., cardiac or respiratory arrest) or need for fiberoptic/video-assisted endotracheal intubation. The primary endpoint was lowest pulse oximetry saturation (SpO_2) between induction and 2 minutes following successful intubation. Secondary outcomes were any incidence of hypoxemia (SpO_2 < 90%), severe hypoxemia (< 80%), and any decrement in SpO_2 > 3% from the start of induction. Baseline demographics and patient characteristics were not different between groups. Most patients (66%) had sepsis and 57% were intubated for hypoxemia and/or hypercapnia. The median number of intubation attempts was 1, with an initial success rate of 67% in each group. Endotracheal intubation duration was not different between the groups (2.2 vs 2.5 minutes for HFNC and usual care, respectively).

All patients received singular or multiple forms of pre-oxygenation. For the HFNC and usual care treatment arms, the median SpO_2 prior to induction was 99% and 98%. There was no statistically significant difference between HFNC and usual care with regard to median lowest SpO_2 (92% vs 90%, respectively), incidence of hypoxemia (44.7% vs 47.2%, respectively), incidence of severe hypoxemia (16% vs 25%, respectively) or incidence of an SpO_2 decrement > 3% (54% vs 56%, respectively). Moreover, even when controlling for risk factors associated with hypoxemia (e.g., high body mass index, higher oxygen requirements or lower SpO_2 prior to intubation, difficult or prolonged intubation), use of HFNC still provided no benefit compared to usual care.

■ COMMENTARY

This is the second prospective, randomized, controlled trial demonstrating that use of HFNC during endotracheal intubation for acute respiratory failure in the ICU setting does not offer any benefit compared to pre-oxygenation alone. Vourc'h et al recently compared HFNC at 60 L/min during endotracheal intubation to pre-oxygenation using a face mask at 15 L/min in patients whose acute respiratory failure was primarily due to pneumonia and acute respiratory distress syndrome (ARDS).[1] In that study, pre-oxygenation was protocolized using each assigned technique for 4 minutes prior to induction. The median SpO_2 for the HFNC and face mask treatment arms was 92% vs 89%, respectively (P = 0.2). For the 25% of study patients whose pre-oxygenation period was extended beyond 4 minutes, SpO_2 was 89% vs 91%, respectively (P = 0.8).

Apneic oxygenation occurs because mass flow of oxygen from the upper airway toward the alveoli is sustained via continuous oxygen uptake by the blood with the simultaneous, rapid loss of a carbon dioxide diffusion gradient into the alveoli. This lowers intra-alveolar pressure, creating an intrapulmonary pressure gradient (estimated to reach -20 cm H_2O) favoring mass flow.[2]

With appropriate pre-oxygenation, healthy, supine individuals have a functional residual capacity (FRC) of ~1.9-2.3 L that, together with a fully saturated blood volume, yields a total body oxygen reservoir of ~2.8-3.2 L. With normal oxygen consumption during apnea (250 mL/min), it would take approximately 11-13 minutes to reach complete depletion. In contrast, patients with acute respiratory failure are at higher risk for hypoxemia because of increased oxygen consumption, decreased FRC, and severe pulmonary oxygenation dysfunction. The mean FRC in these patients is ~1.8 L and ~0.5 L in severe ARDS. The effect of these factors was apparent in both ICU studies, as the incidence of severe hypoxemia (SpO_2 < 80%) during intubation was 16-25% and 22-26%.[2]

A study examining intubation time in more than 600 patients in both controlled (general anesthesia) and pre-hospital settings found the median time for non-difficult airways was < 1 minute (89% of all intubations).[3] In the minority of difficult airway cases, the median intubation time was 2.5-8.3 minutes. In two ICU trials (n = 269), the median intubation duration was 1-2.5 minutes, and in one trial, the reported incidence of difficult intubation was 4%.[2]

These studies imply that pulmonary oxygenation dysfunction, endotracheal intubation duration, and adequate pre-oxygenation are the most important determinants of procedural hypoxemia. Therefore, to guarantee that FRC contains 100% O_2, patients should be pre-oxygenated for approximately 4 minutes using a tight seal, form-fitting mask connected to a device with sufficient oxygen flow (2-3 times/minute ventilation or > 15 L/min) and a large reser-

voir bag (e.g., 1 L modified Jackson-Rees circuit). Apneic oxygenation with HFNC during intubation is likely to be beneficial only when confronted with a difficult airway, particularly in someone with low FRC (e.g., severe ARDS, morbid obesity). ■

REFERENCES

1. Vourc'h M, et al. High-flow nasal cannula oxygen during endotracheal intubation in hypoxemic patients: A randomized controlled clinical trial. *Intensive Care Med* 2015;41:1538-1548.
2. Fruman MJ, et al. Apneic oxygenation in man. *Anesthesiology* 1959;20:789-798.
3. Adnet F, et al. The intubation difficulty scale. *Anesthesiology* 1997;87:1290-1297.

CME/CE QUESTIONS

1. All the following statements are true regarding mechanical ventilation and respiratory muscle function *except*:
a. Tidal volume reflects global inspiratory muscle shortening.
b. Triggering the ventilator causes threshold loading of the muscles.
c. PEEP increases respiratory drive via the Hering-Breuer reflex.
d. Inspiratory flow reflects the velocity of muscle shortening.
e. Restricting tidal volume while inducing hypercapnia magnifies dyspnea.

2. In patients with atrial fibrillation and sepsis, the most common rate control agent prescribed was:
a. amiodarone.
b. calcium channel blockers.
c. digoxin.
d. beta-blockers.
e. None of the above

3. Which of the following statements is true regarding the use of acetaminophen in critically ill patients?
a. Febrile patients with baseline normal liver function had no increased risk of elevated liver enzymes when receiving 4 g of daily intravenous acetaminophen compared with placebo.
b. Receiving intravenous acetaminophen for 8 continuous days decreased the incidence of fever in critically ill patients with infection.
c. While overall mortality did not change, survivors who received acetaminophen had a longer ICU length of stay compared with placebo.
d. Decreasing temperatures led to decreased rates of ventilator-associated events.
e. Acetaminophen use delays death; thus, its use should be avoided in patients with infection.

4. All the following statements are true regarding apneic oxygenation and endotracheal intubation *except*:
a. In the studies reviewed, the median time for successful intubation in patients without a difficult airway was < 3 minutes.
b. In the studies reviewed, the proportion of patients with a difficult airway was 25%.
c. In the studies reviewed, among difficult airway cases, the median intubation time was 2.5-8.3 minutes.
d. Patients with acute respiratory failure are at a much higher risk for hypoxemia because of increased oxygen consumption, decreased functional residual capacity, and severe pulmonary oxygenation dysfunction.
e. In both ICU studies of apneic oxygenation, among the treatment arms, the incidence of severe hypoxemia (SpO_2 < 80%) during intubation was 16-25% and 22-26%.

We Need Your Help!

The *Critical Care Alert* editors are planning topics for 2016 issues and would like your feedback on topics recently covered. Please help us by answering three questions at the following link: https://www.surveymonkey.com/r/CRCSurvey2016. Thank you for your help!