RELIAS MEDIA

Vol. 26, Issue 11, February 2019
ReliasMedia.com

Critical Care [ALERT]

Authoritative, evidence-based summaries for the critical care clinician

SPECIAL FEATURE

Liberal Oxygen Therapy in the ICU: Time to Change Practice?

By Trushil Shah, MD, MSc

Assistant Professor of Medicine, University of Texas Southwestern Medical Center, Dallas

Dr. Shah reports he receives grant/research support from Actelion Pharmaceuticals, Liquidia Technologies, and Bayer Pharmaceuticals, and is a consultant for and on the speakers bureau of Gilead Sciences.

The first use of oxygen as a therapy dates to 1885 when it was used to treat pneumonia.[1] Since then, use of oxygen therapy has become one of the most common treatments in hospitalized patients. Hypoxia has been independently associated with mortality across various diseases, and it is common knowledge that treatment of hypoxia is critical for survival. While hypoxia can result in several adverse outcomes and oxygen therapy is warranted to achieve normoxia, data from multiple studies show that a large proportion of patients receive oxygen therapy in the absence of this indication.[2] Be it in an ambulance, ED, medicine floor, or ICU, many patients receiving oxygen therapy do not have documented hypoxemia. At times, oxygen is administered even without a physician prescription.[3,4] Oxygen use has become ubiquitous to medical practice.

More than 25% of all ED patients, as well as most stroke and myocardial infarction patients, receive oxygen therapy.[3,5] An audit of oxygen use in a Brooklyn state hospital revealed only 19% of patients on supplemental oxygen had a clear indication, 53% had no active order for supplementation, and 57% were not on continuous bedside pulse oximetry monitoring despite supplemental oxygen.[6] With such ubiquitous use of oxygen, the medical community and patients assume there is no harm, and perhaps even potential benefit, associated with its use.[7] Current guidelines for using oxygen therapy in medically ill patients are inconsistent and lack consensus on a safe upper limit for oxygenation. Because of the sigmoid nature of the oxygen-hemoglobin dissociation curve, at higher SpO_2 readings, there is an exponential increase in PaO_2.

In contrast, oxygen toxicity has been studied since the 1950s. Many animal studies have revealed different mechanisms of damage.[8-10] Hyperoxia happens when high amounts of reactive oxygen species (ROS) overwhelm natural antioxidant defenses,

Financial Disclosure: *Critical Care Alert*'s Physician Editor Betty Tran, MD, MSc, Nurse Planner Jane Guttendorf, DNP, RN, CRNP, ACNP-BC, CCRN, Peer Reviewer William Thompson, MD, Executive Editor Leslie Coplin, Editor Jonathan Springston, and Editorial Group Manager Terrey L. Hatcher report no financial relationships relevant to this field of study.

Critical Care [ALERT]
Authoritative, evidence-based summaries for the critical care clinician

Critical Care Alert (ISSN 1067-9502) is published monthly by Relias Learning, 111 Corning Road, Suite 250, Cary, NC 27518-9238. Periodicals postage paid at Cary, NC, and additional mailing offices. POSTMASTER: Send address changes to *Critical Care Alert*, Relias Learning, 111 Corning Road, Suite 250, Cary, NC 27518-9238.

GST Registration Number: R128870672.

© 2019 Relias LLC. All rights reserved. No part of this newsletter may be reproduced in any form or incorporated into any information-retrieval system without the written permission of the copyright owner.

This is an educational publication designed to present scientific information and opinion to health professionals to stimulate thought and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual.

SUBSCRIBER INFORMATION
(800) 688-2421
customerservice@reliasmedia.com
ReliasMedia.com

Subscription Prices
United States
Print: 1 year with free *AMA PRA Category 1 Credits™*: $349
Add $19.99 for shipping & handling.
Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits™*: $299

Back issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION
Relias LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Relias LLC designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only credit commensurate with the extent of their participation in the activity.

Relias LLC is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Contact hours [2] will be awarded to participants who meet the criteria for successful completion. California Board of Registered Nursing, Provider CEP#13791.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2 MOC Medical Knowledge points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

This CME activity is intended for critical care physicians and nurses. It is in effect for 36 months from the date of the publication.

leading to cell death and apoptosis. The increase in ROS accelerates the release of endogenous damage-associated molecular pattern molecules that stimulate an inflammatory response, especially in the lungs, and cause vasoconstriction, likely because of reduced nitric oxide levels.[11,12] The lung is a particularly susceptible target; hyperoxia can cause acute lung injury. Hyperoxia-induced acute lung injury (HALI) is associated with alteration in surfactant protein composition, decreased mucociliary clearance, and cellular damage resulting in atelectasis, a reduction in lung compliance, and increased susceptibility to infection.[13] Hyperoxemia-induced vasoconstriction can lead to a reduction in coronary blood flow, decrease cardiac output, and alter microvascular perfusion, too.[11,13] The severity of HALI is directly proportional both to the PaO_2 (particularly above a rate of 450 mmHg or an FiO_2 of 0.6) and exposure time.[14]

Over the last decade, more clinical studies have shown adverse effects of hyperoxia in different patient populations and its association with increased mortality.[15-17] In a meta-analysis, Chu et al synthesized data from 25 randomized, controlled trials comparing a liberal oxygen approach to a conservative approach. They included 16,037 patients with sepsis, critical illness, stroke, trauma, myocardial infarction, cardiac arrest, and emergency surgery. The authors found that liberal oxygen therapy was associated with increased in-hospital mortality, 30-day mortality, and mortality at longest follow-up. The following sections include more details about specific subgroups relevant to ICU practice and a review of the current data on oxygen therapy in these patients.

MYOCARDIAL INFARCTION

Since the early 1900s, it has been routine practice to provide oxygen supplementation to patients with ST-elevation myocardial infarction (STEMI), regardless of their baseline SpO_2.[18] More recently, accumulating evidence suggests that hyperoxia actually may be harmful in myocardial infarction patients. The authors of the AVOID trial compared 8 L oxygen to room air in 441 patients with STEMI without hypoxia. They found an increase in myocardial infarct size in the oxygen therapy group at six months and no benefit.[19] Recently, in the DETO2X-AMI trial, which included 6,629 patients, showed no benefit regarding supplemental oxygen in patients without hypoxemia.[20] Abuzaid et al further confirmed this in a meta-analysis of six randomized, controlled trials.[21] Based on current data, supplemental oxygen should be used only in patients with myocardial infarction with baseline hypoxemia to a goal of SpO_2 between 90% and 95%, remembering that hyperoxia can be harmful.[22]

CARDIAC ARREST

Current guidelines support the usual practice of giving 100% FiO_2 in the setting of cardiac arrest and immediately after achieving return of spontaneous circulation (ROSC).[23] Two retrospective observational studies revealed that hyperoxia (PaO_2 higher than 300 mmHg) during CPR is associated with higher rates of ROSC, lower mortality, and intact neurological survival.[16,24] However, this may not be a function of the administered amount of FiO_2, but could represent better native lung function, superior resuscitation quality, and lower illness severity.[24] In the absence of data to use lower FiO_2 concentrations intra-arrest, it is reasonable to continue to use 100% FiO_2 during CPR.

However, after ROSC is achieved, hyperoxia is associated with a higher risk of mortality.[16] In a recent meta-analysis of observational studies of in-hospital and out-of-hospital cardiac arrests, Patel et al confirmed this association.[16] In a Dutch registry study, Helmerhorst et al showed that PaO_2 values in the first 24 hours after cardiac arrest are related to mortality in a U-shape, where both hypoxia and hyperoxia may be harmful.[25]

SEPTIC SHOCK AND CRITICALLY ILL PATIENTS

In an observational cohort study of 14,441 Dutch ICU patients, Helmerhorst and other colleagues found that severe hyperoxia as defined by $PaO_2 > 200$ mmHg was associated with increased mortality and fewer ventilator-free days.[26] Moreover, they identified a dose-response relationship of hyperoxia with mortality in the first 24 hours and beyond, with more time spent in hyperoxia associated

Table 1. Level of Evidence and Recommended SpO_2 Range in Different Subsets of Critically Ill Patients

Patient Population	Level of Evidence	Recommended SpO_2	Comments
Myocardial infarction	High	90-95%	Hyperoxia increases infarct size
Cardiac arrest	Medium to low	90-95%	100% FiO_2 recommended during resuscitation of cardiac arrest; SpO_2 goal listed to be used after return of spontaneous circulation
Mixed medical ICU patients	High	90-95%	Hyperoxia may increase ICU-acquired weakness and atelectasis
Stroke	High	90-95%	Hyperoxia is not beneficial for either ischemic or hemorrhagic stroke, but its effect on ischemic penumbra is unknown
Postoperative surgical	Low	Unknown	Hyperoxia may decrease surgical site infections but needs to be balanced against other risks of hyperoxia

with increased mortality.[26] A recent meta-analysis of two randomized, controlled trials and seven cohort studies in ICU patients revealed that hyperoxia was associated with increased hospital mortality (hazard ratio, 1.58; 95% confidence interval, 1.26-2.0).[27] In a randomized, controlled trial that included 442 septic shock patients, Asfar et al compared hyperoxia with 100% FiO_2 to normoxia with SpO_2 88-95%. Investigators discovered that the hyperoxia group trended toward an increase in mortality, especially in patients with lactate > 2 mmol/L.[28,29] The hyperoxia group also experienced a significant increase in serious adverse events, mainly driven by a doubling of ICU-acquired weakness and atelectasis.[28]

STROKE

Hypoxemia is associated with worse outcomes in ischemic stroke. Oxygen supplementation may improve outcomes by preventing hypoxemia and secondary brain damage.[30] However, hyperoxia is associated with cerebral vasoconstriction, resulting in decreased cerebral blood flow.[31] In a large multicenter, cohort study that included 2,894 patients, Rincon et al found that in ventilated stroke patients admitted to the ICU, arterial hyperoxia (PaO_2 > 300 mmHg) was associated independently with in-hospital death compared with normoxia or hypoxia.[32] Study limitations included its observational approach, the authors not accounting for ventilator-specific data, and the authors not adhering to common endpoints used in neurological outcomes research.[32]

In a large randomized, controlled trial that included 8,003 patients with acute stroke randomized to continuous low-dose oxygen vs. nocturnal oxygen and control, Roffe et al observed that low-dose oxygen did not improve outcomes of death and disability at three months.[33] A recent study of short burst high-flow oxygen (45 L/min) ended early because of excess mortality in the actively treated group. The authors of an ongoing randomized, controlled trial (PROOF) are assessing the use of high-flow oxygen at 40 L/min to maintain viability of ischemic penumbra to allow for a broader window for thrombolysis.[34] Current guidelines from the American Heart Association suggest using supplemental oxygen in acute ischemic stroke to maintain SpO_2 > 94%.[35]

SURGICAL PATIENTS

Supplemental oxygen has been used in surgical patients intra- and postoperatively to decrease the incidence of surgical wound infections.[36] The oxidative killing of neutrophils depends on PO_2; hence, supplemental oxygen theoretically enhances the bactericidal effects of neutrophils.[37] To date, several randomized, controlled trials have been performed in different surgical patient populations comparing hyperoxia to normoxia, and results have been conflicting.[36] A meta-analysis of these trials has shown a lower incidence of surgical site infections, but the quality of evidence is low, as many of these trials are prone to bias.[36] The authors of a long-term follow-up of the PROXI randomized, controlled trial observed that patients undergoing cancer surgery demonstrated higher mortality rates with high inspired FiO_2 (80% vs. 30%).[38]

TARGET OXYGEN LEVELS

As mounting evidence shows hyperoxia can be harmful, an important question arises: What is a safe level or range of oxygenation in hospitalized and critically ill patients? To make matters more complex, different targets may be indicated for different subsets of patients *(Table 1)*. Guidelines for supplemental oxygen have been inconsistent across countries and even across specialties. Chu et al's meta-analysis of 25 randomized, control trials that

included 16,037 patients revealed that liberal oxygen therapy increased mortality, with one excess death for an average of 71 patients treated with liberal oxygen therapy.[15] Across the trials included in this study, the baseline median SpO_2 in the liberal oxygen arm was 96% (range, 94-99%). When this group was exposed to liberal oxygenation, researchers observed an increase in mortality risk that was dose-dependent on the magnitude of increase in SpO_2. The results of the ICU-ROX randomized, controlled trial may shed more light on this question.[39] However, new evidence and guidelines may not change practice quickly, which will require efforts by physicians, nursing staff, respiratory therapists, and even policymakers.[40] Barriers to appropriate oxygen prescription, monitoring, and administration will need to be identified at individual hospital levels and addressed.[4,40]

SUMMARY

Oxygen is not a harmless "drug." Liberal oxygen therapy is associated with increased harm and mortality across different subpopulations in the ICU. Oxygen supplementation should be reserved only for hypoxic patients (SpO_2 < 90%), with a goal SpO_2 of < 96%.[41] Future studies are needed to establish a specific safe range of oxygenation. ■

REFERENCES

1. Shultz SM, Hartmann PM. George E Holtzapple (1862-1946) and oxygen therapy for lobar pneumonia: The first reported case (1887) and a review of the contemporary literature to 1899. *J Med Biogr* 2005;13:201-206.
2. Albin RJ, et al. Pattern of non-ICU inpatient supplemental oxygen utilization in a university hospital. *Chest* 1992;102:1672-1675.
3. Hale KE, et al. Audit of oxygen use in emergency ambulances and in a hospital emergency department. *Emerg Med J* 2008;25:773-776.
4. O'Driscoll BR. British Thoracic Society Oxygen Guidelines: Another clinical brick in the wall. *Thorax* 2017;72:498-499.
5. Burls A, et al. Oxygen use in acute myocardial infarction: An online survey of health professionals' practice and beliefs. *Emerg Med J* 2010;27:283-286.
6. Nath S, et al. An audit of supplemental oxygen prescribing practices in an inpatient setting and its financial burden. *European Respiratory Journal* 2018;52:PA3160.
7. Kelly CA, et al. A wolf in sheep's clothing? Patients' and healthcare professionals' perceptions of oxygen therapy: An interpretative phenomenological analysis. *Clin Respir J* 2018;12:616-632.
8. Garner WL, et al. The effects of hyperoxia during fulminant sepsis. *Surgery* 1989;105:747-751.
9. Bhandari V, et al. Increased hyperoxia-induced mortality and acute lung injury in IL-13 null mice. *J Immunol* 2007;178:4993-5000.
10. Bhandari V, et al. Hyperoxia causes angiopoietin 2-mediated acute lung injury and necrotic cell death. *Nat Med* 2006;12:1286-1293.
11. Vincent JL, et al. Harmful effects of hyperoxia in postcardiac arrest, sepsis, traumatic brain injury, or stroke: The importance of individualized oxygen therapy in critically ill patients. *Can Respir J* 2017;2017:2834956. doi: 10.1155/2017/2834956.
12. Sjoberg F, Singer M. The medical use of oxygen: A time for critical reappraisal. *J Intern Med* 2013; 274:505-528.
13. Damiani E, et al. Oxygen in the critically ill: Friend or foe? *Curr Opin Anaesthesiol* 2018;31:129-135.
14. Kallet RH, Matthay MA. Hyperoxic acute lung injury. *Respir Care* 2013;58:123-141.
15. Chu DK, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): A systematic review and meta-analysis. *Lancet* 2018;391:1693-1705.
16. Patel JK, et al. Association between intra- and post-arrest hyperoxia on mortality in adults with cardiac arrest: A systematic review and meta-analysis. *Resuscitation* 2018;127:83-88.
17. Stolmeijer R, et al. A systematic review of the effects of hyperoxia in acutely ill patients: Should we aim for less? *Biomed Res Int* 2018; May 14;2018:7841295. doi: 10.1155/2018/7841295. eCollection 2018.
18. Beasley R, et al. Oxygen therapy in myocardial infarction: An historical perspective. *J R Soc Med* 2007;100:130-133.
19. Stub D, et al. Air versus oxygen in ST-segment-elevation myocardial infarction. *Circulation* 2015;131:2143-2150.
20. Hofmann R, et al. Oxygen therapy in suspected acute myocardial infarction. *N Engl J Med* 2017;377:1240-1249.
21. Abuzaid A, et al. Oxygen therapy in patients with acute myocardial infarction: A systemic review and meta-analysis. *Am J Med* 2018;131:693-701.
22. Ibanez B, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. The task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;39:119-177.
23. Field JM, et al. Part 1: Executive summary: 2010 American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010;122:S640-S656.
24. Patel JK, et al. Association of arterial oxygen tension during in-hospital cardiac arrest with return of spontaneous circulation and survival. *J Intensive Care Med* 2018;33:407-414.
25. Helmerhorst HJ, et al. Associations of arterial carbon dioxide and arterial oxygen concentrations with hospital mortality after resuscitation from cardiac arrest. *Crit Care* 2015;19:348.
26. Helmerhorst HJ, et al. Metrics of arterial hyperoxia and associated outcomes in critical care. *Crit Care Med* 2017;45:187-195.
27. You J, et al. Association between arterial hyperoxia and mortality in critically ill patients: A systematic review and meta-analysis. *J Crit Care* 2018;47:260-268.
28. Asfar P, et al. Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): A two-by-two factorial, multicentre, randomised, clinical trial. *Lancet Respir Med* 2017;5:180-190.
29. Demiselle J, et al. Hyperoxia toxicity in septic shock patients according to the Sepsis-3 criteria: A post hoc analysis of the HYPER2S trial. *Ann Intensive Care* 2018;8:90.
30. Rowat AM, et al. Hypoxaemia in acute stroke is frequent and worsens outcome. *Cerebrovasc Dis* 2006;21:166-172.
31. Floyd TF, et al. Independent cerebral vasoconstrictive effects of hyperoxia and accompanying arterial hypocapnia at 1 ATA. *J Appl Physiol* (1985) 2003;95:2453-2461.
32. Rincon F, et al. Association between hyperoxia and mortality after stroke: A multicenter cohort study. *Crit Care Med* 2014;42:387-396.
33. Roffe C, et al. Effect of routine low-dose oxygen supplementation on death and disability in adults with acute

stroke: The stroke oxygen study randomized clinical trial. *JAMA* 2017;318:1125-1135.
34. Poli S, et al. Abstract TMP15: Penumbral Rescue by Normobaric O_2 in Ischemic Stroke With Target Mismatch ProFile (PROOF). *Stroke* 2018;49:ATMP15.
35. Powers WJ, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2018;49:e46-e110.
36. Wetterslev J, et al. The effects of high perioperative inspiratory oxygen fraction for adult surgical patients. *Cochrane Database Syst Rev* 2015; Jun 25;(6):CD008884. doi: 10.1002/14651858.CD008884.pub2.
37. Allen DB, et al. Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms. *Arch Surg* 1997;132:991-996.
38. Meyhoff CS, et al. Increased long-term mortality after a high perioperative inspiratory oxygen fraction during abdominal surgery: Follow-up of a randomized clinical trial. *Anesth Analg* 2012;115:849-854.
39. Young PJ, et al. Intensive care unit randomised trial comparing two approaches to oxygen therapy (ICU-ROX): Results of the pilot phase. *Crit Care Resusc* 2017;19:344-354.
40. O'Driscoll BR, et al. BTS guideline for oxygen use in adults in healthcare and emergency settings. *Thorax* 2017;72:ii1-ii90.
41. Siemieniuk RAC, et al. Oxygen therapy for acutely ill medical patients: A clinical practice guideline. *BMJ* 2018;363: k4169.

ABSTRACT & COMMENTARY

Thiamine for Septic Shock: Is There a Benefit?

By Kathryn Radigan, MD

Attending Physician, Division of Pulmonary and Critical Care, Stroger Hospital of Cook County, Chicago

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

SYNOPSIS: Based on a retrospective review, septic shock patients who were administered thiamine within 24 hours of admission showed improved lactate clearance and reduced 28-day mortality.

SOURCE: Woolum JA, et al. Effect of thiamine administration on lactate clearance and mortality in patients with septic shock. *Crit Care Med* 2018;46:1747-1752.

Often, critically ill patients are thiamine-deficient. Since septic shock is a metabolically demanding state, Woolum et al pursued a retrospective, single-center, matched cohort study to see if critically ill patients with septic shock exposed to thiamine would show improved lactate clearance and better clinical outcomes vs. patients without thiamine supplementation. All adult medical and surgical ICU patients admitted to a tertiary care academic center from 2013-2017 with an International Classification of Diseases, 9th Revision, or an International Classification of Diseases, 10th Revision, septic shock diagnosis code were included. Exclusion criteria included patients younger than 18 years of age or the development of septic shock that was not evident at admission. The primary outcome was whether thiamine administration was associated with faster time to lactate clearance. Secondary outcomes included acute kidney injury, 28-day mortality, mechanical ventilation-free days, vasopressor-free days, and need for renal replacement therapy.

Out of 2,272 patients screened, 1,049 were eligible. Among those who were eligible, 123 thiamine-treated patients were matched with 246 patients who were not treated with thiamine. The authors did not detail the reason for thiamine administration. Patients were matched in a 1:2 (thiamine:control) fashion based on ICU service (medical ICU vs. surgical ICU), peak lactate, presence of liver disease, race, age, sex, Elixhauser comorbidity index, and Sequential Organ Failure Assessment (SOFA) score on ICU admission day. The most common protocol for administration of thiamine within the study was 500 mg every eight hours for three days.

Results from the Fine-Bray survival model revealed that treatment with thiamine was associated with an improved likelihood of lactate clearance (subdistribution hazard ratio [HR], 1.307; 95% confidence interval [CI], 1.002-1.704) and a reduction in 28-day mortality (HR, 0.666; 95% CI, 0.490-0.905). There were no further differences revealed in secondary outcomes. These findings were more pronounced in women. A randomized trial is necessary to further evaluate this intervention for septic shock patients.

■ COMMENTARY

One in every three hospitalized patients who die in that facility is diagnosed with sepsis.[1] For decades, researchers have worked earnestly to discover new interventions and treatments to decrease sepsis-related mortality. More recently, thiamine, an essential vitamin for aerobic metabolism, has gained special attention as a potential avenue to augment the dangerous effects of septic shock.[2,3] Thiamine

acts at critical points in both the Krebs cycle and the pentose-phosphate shuttle. It provides assistance as a key cofactor for pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase in the Krebs cycle and for transketolase as a key enzyme for the pentose phosphate pathway and production in nicotinamide adenine dinucleotide phosphate hydrogen. Without these steps, mitochondrial aerobic metabolism is halted and anaerobic metabolism ensues, leading to refractory acidosis, cardiovascular collapse, and possible death.[4,5] The theoretical benefits of thiamine in septic shock may be even more pronounced in subpopulations of illness as many critically ill patients admitted to the ICU are thiamine-deficient at baseline.[2,5]

One of the first published studies that addressed thiamine in septic shock was a two-center, randomized, double-blind trial. Those authors evaluated the administration of thiamine 200 mg twice daily for seven days in septic shock patients and observed its effect on lactate.[2] Interestingly, patients with liver dysfunction, those who abused alcohol, and those who required thiamine supplementation (the subpopulations at significant risk for thiamine deficiency) were excluded. Although results revealed that thiamine administration did not improve lactate levels in the overall group of patients with septic shock and elevated lactate, the authors observed that lactate levels were lower at 24 hours, with a possible decrease in mortality over time in patients with baseline thiamine deficiency. Despite no significant difference in other secondary outcomes, including proportion and time to shock reversal, SOFA score at 24 hours, mortality rates, and ICU and overall length of stay between the thiamine and placebo groups, it must be recognized that the thiamine dose may not have been adequate because no dose-finding trial was completed prior to the study. Another interesting aspect of this study was that 35% of patients presented with thiamine deficiency at baseline despite the exclusion criteria of liver dysfunction, alcohol abuse, and thiamine supplementation.

To further highlight the potential benefit of thiamine in thiamine-deficient septic shock patients, Holmberg et al published the results of a retrospective cohort trial in 2018. They examined the association between the administration of thiamine vs. no thiamine in septic shock patients with alcohol use disorders.[3] Although thiamine 100 mg was the most commonly prescribed thiamine dose in this retrospective trial (88% of the initial doses and 97% of the total doses), investigators still found that thiamine administration in this patient population was associated with decreased mortality.

Although the study by Woolum et al revealed that thiamine administration within 24 hours of admission in septic shock patients was associated with improved lactate clearance and a reduction in 28-day mortality, there were significant limitations. Unfortunately, the authors did not include a protocol for when and how often to measure repeat lactate. Obviously, this limitation could affect lactate clearance profoundly. This trial also was not randomized, which may lead to substantial confounding. Further, the dose of thiamine was not standardized.

Despite these limitations and considering previous publications, this study is at the very least thought-provoking. Although it is not likely to change current practice significantly, thiamine is relatively safe and inexpensive. These findings highlight the need for future larger randomized studies to further explore the effect of thiamine in septic shock, specifically examining subpopulations after an appropriate dose-response trial. ■

REFERENCES

1. Centers for Disease Control and Prevention. Sepsis. Data & Reports. Available at: https://bit.ly/2FhjlsQ. Accessed Jan. 8, 2019.
2. Donnino MW, et al. Randomized, double-blind, placebo-controlled trial of thiamine as a metabolic resuscitator in septic shock: A pilot study. *Crit Care Med* 2016;44:360-367.
3. Holmberg MJ, et al. Thiamine in septic shock patients with alcohol use disorders: An observational pilot study. *J Crit Care* 2018;43:61-64.
4. Oriot D, et al. Severe lactic acidosis related to acute thiamine deficiency. *JPEN J Parenter Enteral Nutr* 1991;15:105-109.
5. Manzanares W, Hardy G. Thiamine supplementation in the critically ill. *Curr Opin Clin Nutr Metab Care* 2011;14:610-617.

live & on-demand

WEBINARS

✔ Instructor-led Webinars ✔ Live & On-Demand ✔ New Topics Added Weekly

CONTACT US TO LEARN MORE!
Visit us online at ReliasMedia.com/Webinars or call us at (800) 688-2421.

ABSTRACT & COMMENTARY

Early Extubation to Noninvasive Ventilation Does Not Reduce Time to Liberation From All Mechanical Ventilation

By Betty Tran, MD, MSc, Editor

SYNOPSIS: In this multicenter, randomized, open-label trial of patients who failed a spontaneous breathing trial, those who were extubated to noninvasive ventilation did not have a shorter time to liberation from any form of mechanical ventilation compared to those who were randomized to protocolized standard weaning.

SOURCE: Perkins GD, et al. Effect of protocolized weaning with early extubation to noninvasive ventilation vs invasive weaning on time to liberation from mechanical ventilation among patients with respiratory failure. The Breathe Randomized Clinical Trial. *JAMA* 2018;320:1881-1888.

For patients who have passed a spontaneous breathing trial (SBT) but are deemed at high risk for extubation failure (e.g., patients with hypercapnia, chronic obstructive pulmonary disease, congestive heart failure), current guidelines recommend extubation to preventive noninvasive ventilation (NIV). These recommendations are based on evidence that suggests a reduction in ventilator- and ICU-related complications, including improved extubation success and a reduction in ICU length of stay.[1] However, approximately 20-30% of intubated patients will require more than one SBT and up to seven days from the first attempt before extubation; subsequently, they are deemed to be a "difficult weaning group."[2]

Given these findings, Perkins et al hypothesized that extubating patients who were difficult to wean directly to NIV would reduce the time to liberation from mechanical ventilation overall. The authors created a multicenter, randomized, allocation-concealed, controlled, open-label trial that was executed in 41 general adult ICUs in the United Kingdom. Researchers recruited patients between March 2013 and October 2016, with follow-up ending April 2017. The authors randomized 364 adults who received invasive mechanical ventilation through an endotracheal tube for more than 48 hours and who had failed an SBT to receive a NIV weaning protocol (n = 182) or an invasive ventilation weaning protocol (n = 182). The NIV group underwent extubation directly to NIV via face mask with initially equivalent pressure support settings that were provided via invasive ventilation. The treating physician assessed patients every two hours for distress or fatigue. The treating physician increased the inspiratory positive airway pressure to achieve patient comfort and a respiratory rate less than 30/minute. In the absence of clinical issues, patients were trialed off the mask or was put on a lower level of positive airway pressure (reduction by 2 cm H_2O). In the invasive mechanical ventilation group, the patient also was assessed every two hours and their pressure support settings were adjusted down by 2 cm H_2O in the absence of distress or fatigue or up if no reversible causes could be corrected and they were showing signs of distress or fatigue.

This cycle continued until patients could pass an SBT to be extubated or underwent tracheostomy. The primary outcome was time from randomization to successful liberation from ventilation, defined as the time point when the patient was alive and free of both invasive and noninvasive ventilator support for more than 48 hours. There were multiple secondary outcomes, including duration of invasive ventilation, total ventilator days, proportion of patients receiving antibiotics, rate of reintubation, and mortality at 30, 90, and 180 days, although the study was not adequately powered to detect differences in any of these.

The primary outcome of time from randomization to liberation from ventilation was not significantly different in the NIV group — 4.3 days (95% confidence interval [CI], 2.63-4.48) vs. 4.5 days (95% CI, 3.46-7.25), compared with the invasive group (adjusted hazard ratio, 1.1; 95% CI, 0.86-1.34). Patients in the NIV group received less invasive ventilation (median 1 day vs. 4 days; incidence rate ratio, 0.6; 95% CI, 0.47-0.87). There were no significant differences in rates of reintubation, tracheostomy, survival, or adverse events between the two groups.

■ COMMENTARY

Traditionally, an SBT with inspiratory pressure augmentation (5-8 cm H_2O) is recommended as the best test to gauge whether a patient is "ready" to come off the ventilator.[1] Interestingly, the results of this trial suggest that despite the results of our best test (i.e., an SBT), patients can be extubated and supported without the need for an endotracheal tube. Although this method was not superior in terms of shortening the time on positive pressure ventilation overall, it was not associated with any significant differences in

PHYSICIAN EDITOR
Betty Tran, MD, MSc
Assistant Professor of Medicine
Pulmonary and Critical Care Medicine
Rush University Medical Center
Chicago

PEER REVIEWER
William Thompson, MD
Associate Professor of Medicine
University of Washington, Seattle

NURSE PLANNER
Jane Guttendorf, DNP, RN, CRNP, ACNPBC, CCRN
Assistant Professor, Acute & Tertiary Care,
University of Pittsburgh, School of Nursing

EDITORIAL ADVISORY BOARD
Kay Ball, PhD, RN, CNOR, FAAN
Professor of Nursing, Otterbein University,
Westerville, OH

Cody J. Benthin, MD
Staff Physician
Pulmonary and Critical Care Medicine
Northwest Permanente
Portland, OR

Elaine Chen, MD
Assistant Professor, Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Section of Palliative Medicine,
Rush University Medical Center,
Chicago

James E. McFeely, MD
Medical Director, Critical Care Units, Alta Bates Summit Medical Center, Berkeley, CA

Samuel Nadler, MD, PhD
Critical Care, Pulmonary Medicine
The Polyclinic Madison Center, Seattle
Clinical Instructor
University of Washington, Seattle

Alexander Niven, MD
Senior Associate Consultant
Division of Pulmonary/Critical Care Medicine
Mayo Clinic
Rochester, MN

Kathryn Radigan, MD, MSc
Attending Physician, Division of Pulmonary and Critical Care
Stroger Hospital of Cook County,
Chicago

Trushil Shah, MD, MS
Assistant Professor of Medicine
University of Texas Southwestern

EDITOR EMERITUS
David J. Pierson, MD
Professor Emeritus
Pulmonary and Critical Care Medicine
University of Washington, Seattle

EDITOR
Jonathan Springston

EXECUTIVE EDITOR
Leslie Coplin

EDITORIAL GROUP MANAGER
Terrey L. Hatcher

SENIOR ACCREDITATIONS OFFICER
Lee Landenberger

terms of reintubation, tracheostomy, or survival rates (with the caveat that these were all secondary outcomes that the study was underpowered to evaluate). It is possible that extubation to NIV does not shorten the time to liberation from mechanical ventilation, as patients will come off ventilator support when they are truly "ready."

A few limitations in this trial need to be noted. First, most of the enrolled patients mainly came from three centers that recruited an average of 1.3 patients/month (compared to 1.5 patients per year in the remaining hospitals). This likely limits generalizability in terms of patient population enrolled and physician expertise and patterns of decision-making overall. Second, the authors of the editorial accompanying this study[3] noted that the standard weaning protocol group received quite intensive support and intervention, perhaps more than typical usual care, which resulted in a median duration of ventilator support that was much shorter than anticipated (2.9 days vs. the originally projected 6.4 days). This led to a reduction in the projected sample size to encourage enrollment. Therefore, a lack of a treatment effect in the NIV group could have happened because the control group received more aggressive, better-than-standard care. Finally, minimal details are available on how the NIV group fared while on ventilator support and how/why they were not able to be liberated sooner. It is possible that subsets of patients in this group could have benefited from early extubation to NIV, but this benefit was diluted by a more heterogeneous treatment effect as a whole.

The results of this trial suggest that difficult-to-wean patients potentially could be extubated to NIV despite failing an SBT, although this pathway has not been shown to be superior in terms of time to liberation from all mechanical support. The risk/benefit ratio with either invasive and noninvasive ventilation will need to be evaluated carefully in each case. Further investigation in terms of how NIV is provided in specific patient groups in such situations is warranted before it can be recommended as a viable alternative to continuing invasive support until a patient successfully passes an SBT. ■

REFERENCES

1. Ouellette DR, et al. Liberation from mechanical ventilation in critically ill adults: An official American College of Chest Physicians/American Thoracic Society clinical practice guideline: Inspiratory pressure augmentation during spontaneous breathing trials, protocols minimizing sedation, and noninvasive ventilation immediately after extubation. *Chest* 2017;151:166-180.
2. Peñuelas O, et al. Characteristics and outcomes of ventilated patients according to time to liberation from mechanical ventilation. *Am J Respir Crit Care Med* 2011;184:430-437.
3. Munshi L, Ferguson ND. Weaning from mechanical ventilation. What should be done when a patient's spontaneous breathing trial fails? *JAMA* 2018;320:1865-1867.

CME/CE QUESTIONS

1. **In most studies of ICU patients, hyperoxia is harmful beyond an oxygen saturation of:**
   a. 100%.
   b. 96%.
   c. 92%.
   d. 90%.

2. **In the study by Woolum et al, administration of thiamine within 24 hours of admission in patients presenting with septic shock was associated with:**
   a. lactate clearance.
   b. reduction in 14-day mortality.
   c. longer ICU lengths of stay.
   d. None of the above

3. **Which is true regarding noninvasive ventilation (NIV) in difficult-to-wean patients in the Breathe Randomized Clinical Trial?**
   a. NIV does not reduce time to liberation from any mechanical ventilation.
   b. NIV can reduce rates of reintubation.
   c. NIV is associated with improved survival.
   d. Increased NIV duration resulted in an increase in adverse events, including facial trauma.

Interested in reprints or posting an article to your company's site? There are numerous opportunities for you to leverage editorial recognition for the benefit of your brand. Call us at (800) 688-2421 or email us at reprints@reliasmedia.com.

Discounts are available for group subscriptions, multiple copies, site licenses, or electronic distribution. For pricing information, please contact our Group Account Managers at groups@reliasmedia.com or (866) 213-0844.

To reproduce any part of Relias Media newsletters for educational purposes, please contact The Copyright Clearance Center for permission at info@copyright.com or (978) 750-8400.