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SPECIAL FEATURE

Ventilator Withdrawal in Anticipation of Death: An Intersection of Critical Care and Palliative Care

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

Following initiation of mechanical ventilation for respiratory failure, most patients are successfully weaned, but some develop ventilator dependence. These patients or their families may opt for long-term ventilator support or withdrawal of the ventilator with the understanding that death will likely ensue. Here we address ventilator-dependent patients who otherwise have functioning vital organs. What options are available, what questions need to be answered, and how should we proceed?

Ventilator withdrawal is multidisciplinary, with a complex and evolving history involving ethics, law, and culture.[1,2] Healthcare providers in critical care settings should be able to counsel their patients about the risks, benefits, and options regarding mechanical ventilation in both the short term and the long term. Patients and families may face ethical and psychological barriers, and clinicians should be prepared to discuss these concepts. Once a decision has been made to withdraw the ventilator, the clinician must be able to manage symptoms, which may include dyspnea and anxiety, during the peri-withdrawal time period.[3,4]

EPIDEMIOLOGY

Withdrawal of life support in the intensive care setting is increasing in frequency. More than half a million deaths a year, or 20-25% of all deaths in the United States, occur in ICUs.[5] Serial review of ICU deaths in San Francisco found that from the 1980s to the 1990s, the percentage of ICU deaths that occurred following withdrawal or withholding of life support increased from approximately 50% to approximately 90%.[6,7] The factor most strongly associated with withdrawal

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of mechanical ventilation are the physician's perception of patient's preferences about use of life support.[8] This emphasizes the importance of asking patients, especially those with serious or life-limiting illness, to consider what kind of quality of life is acceptable when they are stable in the outpatient setting.

PROGNOSIS

When deciding whether to withdraw ventilator support, families often want an estimate as to how long the patient is likely to survive following removal. Uncertainty is the rule, but having a rough prognostic estimate can be useful. A predicted survival time of ≤ 60 minutes following withdrawal has been used to help families and clinicians prepare for palliative symptom management, family grieving, and allocation of ICU beds. Post-withdrawal survival has been described in several studies, with median survival of approximately 1 hour, and interquartile ranges of minutes to a few hours.[9-13] Patients surviving more than a week have also been described, so counseling should include the discussion of potential transfer out of the ICU, especially for patients expected to survive beyond the first hour.

There is no standard tool for prediction of survival, but intensivist prediction of death within 60 minutes seems to be the prevailing clinical standard.[12] Tools such as the United Network for Organ Sharing Criteria, developed to assist in prediction of time to death in the setting of organ donation after cardiac death, have been validated but not universally applied.[13] Clinical parameters, such as lower pH, lower Glasgow Coma Scale, lower spontaneous respiratory rate, lower systolic blood pressure, higher positive end-expiratory pressure (PEEP), and higher fraction of inspired oxygen (FiO_2), have been shown to correlate well with death within 60 minutes, with a greater number of positive parameters increasing the predictive value (*see Table 1*).[11,12] Other clinical concerns, such as respiratory mechanics, muscular weakness, neurologic status, and extent of multi-organ dysfunction, can contribute to predictions of survival time.[14] Providing accurate predictions remains a challenge.

Alternatives to withdrawal of the ventilator should be discussed in detail during counseling. With a stable surgical airway, a ventilator-dependent patient can be kept alive for months, even years. Some patients may gradually wean from the ventilator support over weeks or months, while others may never be liberated, depending on the nature of the underlying condition. Autonomy and independence can vary, and definitive prognosis may take months to determine.[15,16]

ETHICAL AND PSYCHOLOGICAL CONCERNS

Withdrawal of life support with expected death has significant ethical, legal, moral, and psychological facets for clinicians, patients, and families. Some may feel a sense of moral obligation to try all available therapies, regardless of potential benefit.[2] Patients have the right to refuse or withhold any treatments or therapies at any time. The benefit, or lack thereof, of a potential therapy may not be known prior to a therapeutic trial. If the therapy does not demonstrate significant benefit after a therapeutic trial, withdrawal allows the irreversible underlying disease to take its natural course; the intention is to acknowledge the limits of medicine and not to hasten death. Thus, withholding and withdrawing a life-sustaining therapy such as a ventilator are considered ethically equivalent.[4]

Psychologically, however, withdrawal may feel more burdensome than withholding due to the active nature of removing treatment. This psychological barrier is important to consider in grieving family members who may suffer from guilt at "killing" their loved one. In such instances, the gradual withdrawal of other life-sustaining therapies over a period of hours to days prior to ventilator withdrawal has been associated with improved satisfaction. Ventilators are frequently the last therapy discontinued prior to death.[17]

When families are considering ventilator withdrawal they may show signs of resistance, conflict, disagreement, anger, and grief. Cultural, religious, personal, or social issues may affect caregivers' perceptions and attitudes.[18] It is important to provide a multidisciplinary approach to support, including chaplains and other psychosocial support staff, allow time and space for reflection, answer questions honestly, and offer empathy and assurance.[19,20]

Table 1. Clinical Parameters Suggesting Prognosis of <1 Hour Following Ventilator Withdrawal[11,12,13]

- pH ≤ 7.32
- Glasgow coma scale ≤ 3
- Spontaneous respiratory rate ≤ 10
- Systolic blood pressure ≤ 84 mm Hg
- PEEP > 10 cm H_2O
- Peak Inspiratory Pressure > 35 cm H_2O
- FiO_2 > 70%
- Vasopressor use
- No analgesia

After the ventilator is withdrawn, the goal is to allow the disease to take its natural course, to neither hasten nor prolong death. When observing the patient's discomfort, requests may come from family or bedside caregivers to shorten the duration of suffering. Medical methods for hastening death could include increasing doses of sedatives beyond what is symptomatically indicated or administration of lethal medication that has no symptomatic benefit. These options are legally and ethically unacceptable in the United States.[1] The patient's suffering should not be discounted, and every effort must be made by clinicians to ensure the patient's comfort.[2,4,21]

Conversely, clinicians or families may express a fear of hastening death. The doctrine of double effect provides the ethical rationale and moral imperative to treat symptoms with sedating medications, even when they may have the foreseen (but unintended) consequence of hastening death.[4,21] A number of studies have evaluated the effect of opioids and benzodiazepines on timing of death and found no definitive correlation between dose and timing of death. Indeed, some studies have shown that patients receiving higher doses may actually have longer survival, with the theory being that relieving dyspnea and anxiety may decrease oxygen demand.[22-24] Overall, general principles of critical care and palliative care should be followed when administering analgesia and sedation surrounding ventilator withdrawal.

Withdrawing a ventilator in a patient who is awake, aware, and cognizant that removal of the ventilator will result in their death is also psychologically and ethically challenging. While the ultimate prognosis may be similar to the patient who is unaware, it may feel like suicide. However, legal precedents and ethicists have deemed that if the quality of life is unacceptable to the patient, removing a ventilator from an awake patient is ethically equivalent to removing a ventilator from a patient who is unaware. One benefit is that the provider can be confident of the patient's actual wishes. However, one must ensure durability of the patient's desire and an absence of reversible reasons for desire to hasten death, such as clinical depression, concerns of being a burden to family, or uncontrolled pain.[25,26]

Table 2. Process of Ventilator Withdrawal[4,20]

- Counsel family
- Explain process and unpredictable time course
- Encourage family to pursue rituals, spiritual support
- Enter and confirm DNR/DNI order
- Document findings, discussion, goals in the record
- Turn off monitors
- Remove restraints
- Symptom control (*see Table 3*)
- Titrate down FiO_2 and put on a nasal cannula, if desired
- If on assist control, change to pressure support
- Down-titrate pressure support 5-10 cm H_2O while maintaining RR < 30 by up-titrating opioids
- Silence ventilator
- If intubated, deflate cuff, remove ETT with towel underneath
- If tracheostomy, remove ventilator and leave trach intact
- Suction excess secretions
- Turn off ventilator

In a patient who is unable to communicate, a legal decision maker must be used to decide the plan of care. This may be a power of attorney previously designated by the patient or a surrogate decision maker chosen based on a legal hierarchy. A power of attorney or surrogate is obligated to choose what they think the patient would have wanted, even if it conflicts with what they themselves would want. This speaks to the importance of a patient making their wishes known ahead of time.

SYMPTOM MANAGEMENT AND PRACTICAL ISSUES

The process of ventilator withdrawal should be stepwise and systematic in order to decrease unnecessary distress among all involved (*see Table 2*).[4,20] Prior to withdrawal of the ventilator, communication should be thorough and well-documented. A "Do Not Resuscitate" order should be confirmed. Alarms and monitors should be turned off, allowing visitors to focus on the patient without distracting noises.

While withdrawal of life-sustaining therapies, such as vasopressors or intravenous fluids, should cause no immediate discomfort, withdrawal of mechanical ventilation may be accompanied by dyspnea and anxiety. Symptom management during this time must be aggressive, and drug titration may need to be frequent. Clinicians have a broad array of medications from which to select for symptom management in this time period (*see Table 3*). First-line therapy for management of dyspnea and pain is usually an intravenous opioid, such as fentanyl, morphine, or hydromorphone. First-line therapy for management of anxiety is usually an intravenous benzodiazepine, such as midazolam or lorazepam. Both opioids and benzodiazepines can be administered as a bolus dose or as a continuous infusion.[9] Patients may require higher doses of opioids or

Table 3. Symptom Management After Ventilator Withdrawal[4,28]

Symptom	Medication Class	Medication	Route of Administration
Dyspnea and Pain	Opiods	Morphine Hydromorphone Fentanyl	IV infusion or bolus IV infusion or bolus IV infusion or bolus
Anxiety	Benzodiazepines	Midazolam Lorazepam	IV infusion or bolus IV infusion or bolus
Oropharyngeal secretions	Anticholinergics	Scopolamine Atropine Glycopyrrolate	Transdermal Sublingual (eye drops, off-label) IV infusion or bolus
Agitation	Neuroleptics	Haloperidol	IV bolus
Paralysis	Neuromuscular blockers	NOT INDICATED	NOT INDICATED
Uncontrolled symptoms	General anesthesia Deep sedation Barbiturates	RARE USE Propofol Pentobarbital Phenobarbital	IV infusion IV infusion IV bolus

benzodiazepines than used in routine critical care settings to adequately manage dyspnea and anxiety during ventilator withdrawal; the doses should be titrated to symptoms without a set ceiling.[27] Deep sedation, such as with propofol, is sometimes used, usually in patients who are already receiving the medication or in those who are anticipated to have a high degree of tolerance to opioids or benzodiazepines. Barbiturates have been cited in older literature but they used less frequently today.[4,28]

Neuromuscular blockade (i.e., paralysis) is sometimes used to decrease ventilator dyssynchrony in patients on mechanical ventilation. Patients appear comfortable as the facial muscles are relaxed and all breathing is triggered by the ventilator. Neuromuscular blockers provide no additional comfort to the patient and should not be initiated as a comfort measure prior to ventilator withdrawal. Additionally, if a ventilator is withdrawn on a paralyzed patient, there will be immediate death as there will be no spontaneous breaths. If paralytics are being previously administered, a provider should ensure they are discontinued with enough time for the patient to initiate their own breaths prior to ventilator withdrawal.[29]

Two distinct weaning methods for withdrawal of mechanical ventilation have previously been described: gradual terminal weans and immediate terminal extubations.[30] Current guidelines advocate for a hybrid, with a rapid wean over no more than an hour or so to allow for aggressive titration of medications to adequately control dyspnea and anxiety but not to allow for prolongation of death.[4,31] When ventilator support and symptom control are such that symptoms are not expected to escalate upon removal of support, mechanical ventilation is discontinued by extubation or disconnection of the ventilator from the tracheostomy.

After removal of the endotracheal tube, saliva and secretions may pool in the posterior oropharynx and tracheobronchial tree, leading to rattling sounds with inspiration and expiration. This phenomenon, sometimes called the "death rattle," tends to occur in the terminal phase in patients who are too weak or obtunded to adequately expectorate. It can be frequent, reported in up to 90% of patients at the end of life. Although the death rattle is thought not to be extremely distressing to the patient, caregivers may experience distress that their loved one is choking. Temporary postural drainage can be used to decrease the volume of secretions, and anticholinergic medications can also be used to decrease formation of secretions.[32] Further titration of medications may be required following removal of ventilator support, and if patients survive beyond the initial few hours, arrangements may be made for transfer out of the ICU.

CONCLUSION

Patients can end up on life support, even in unexpected circumstances. Ventilator withdrawal with expected death is a complex process, now considered an ethically and morally acceptable practice. Familiarity and literature on this topic are increasing. Life expectancy following withdrawal varies from minutes up to weeks. Critical care providers should be comfortable with counseling families before ventilator withdrawal and the process and symptom management surrounding ventilator withdrawal. ■

REFERENCES

1. Luce JM, Alpers A. Legal aspects of withholding and withdrawing life support from critically ill patients in the United States and providing palliative care to them. *Am J Respir Crit Care Med* 2000;162:2029-2032.
2. Reynolds S, et al. Withdrawing life-sustaining treatment: Ethical considerations. *Surg Clin North Am* 2007;87:919-936.

3. Rubenfeld G. Principles and practice of withdrawing life-sustaining treatments. *Crit Care Clin* 2004;20:435-451.
4. Truog RD, et al. Recommendations for end-of-life care in the intensive care unit: A consensus statement by the American Academy of Critical Care Medicine. *Crit Care Med* 2008;36:953-963.
5. Angus DC, et al. Use of intensive care at the end of life in the United States: An epidemiologic study. *Crit Care Med* 2004;32:638-643.
6. Smedira NG, et al. Withholding and withdrawal of life support from the critically ill. *N Eng J Med* 1990;322:309-315.
7. Prendergast TJ, Luce JM. Increasing incidence of withholding and withdrawal of life support from the critically ill. *Am J Respir Crit Care Med* 1997;155:15-20.
8. Cook D, et al. Withdrawal of mechanical ventilation in anticipation of death in the intensive care unit. *N Eng J Med* 2003;349;1123-1132.
9. O'Mahony S, et al. Ventilator withdrawal: Procedures and outcomes. Report of a collaboration between a critical care division and a palliative care service. *J Pain Symptom Manage* 2003;26:954-961.
10. Cooke CR, et al. Predictors of time to death after terminal withdrawal of mechanical ventilation in the ICU. *Chest* 2010;138:289-297.
11. Huynh TH, et al. Factors associated with palliative withdrawal of mechanical ventilation and time to death after withdrawal. *J Palliat Med* 2013;16:1368-1374.
12. Brieva J, et al. Prediction of death in less than 60 minutes following withdrawal of cardiorespiratory support in ICUs. *Crit Care Med* 2013;41:2677-2687.
13. DeVita MA, et al. Donors after cardiac death: Validation of identification criteria (DVIC) study for predictors of rapid death. *Am J Transplant* 2008;8:432-441.
14. Wind T, et al. Prediction of time of death after withdrawal of life-sustaining treatment in potential donors after cardiac death. *Crit Care Med* 2012;40:766-769.
15. Nelson JE, et al. Chronic critical illness. *Am J Respir Crit Care Med* 2010;182:446-454.
16. Ankrom M, et al. Elective discontinuation of life-sustaining mechanical ventilation on a chronic ventilator unit. *J Am Geriatr Soc* 2001;49:1549-1554.
17. Gerstel E, et al. Duration of withdrawal of life support in the intensive care unit and association with family satisfaction. *Am J Respir Crit Care Med* 2008;178:798-804.
18. Cook D, et al. Understanding and changing attitudes toward withdrawal and withholding of life support in the intensive care unit. *Crit Care Med* 2006;24(Suppl.):S317-S323.
19. Prendergast TJ, Puntillo KA. Withdrawal of life support: Intensive caring at the end of life. *JAMA* 2002;288:2732:2732-2740.
20. Curtis JR, Vincent JL. Ethics and end-of-life care for adults in the intensive care unit. *Lancet* 2010;376:1347-1353.
21. Truog RD, et al. Should patients receive general anesthesia prior to extubation at the end of life? *Crit Care Med* 2012;40:631-633.
22. Bakker J, et al. Why opioids and sedatives may prolong life rather than hasten death after ventilator withdrawal in critically ill patients. *Am J Hosp Pall Med* 2008;25:152-154.
23. Edwards MJ. Opioids and benzodiazepines appear paradoxically to delay inevitable death after ventilator withdrawal. *J Palliat Care* 2005;21:299-302.
24. Chan JD, et al. Narcotic and benzodiazepine use after withdrawal of life support: Association with time to death? *Chest* 2004;126:286-293.
25. Edwards MJ, Tolle SW. Disconnecting a ventilator at the request of a patient who knows he will then die: The doctor's anguish. *Ann Int Med* 1992;177:254-256.
26. Billings JA. Terminal extubation of the alert patient. *J Pall Med* 2011;14:800-801.
27. Billings JA. Humane terminal extubation reconsidered: The role for preemptive analgesia and sedation. *Crit Care Med* 2012;40:625-630.
28. Von Gunten CF, Weissman MD. Symptom control for ventilator withdrawal in the dying patient, 2nd edition. Fast Facts and Concepts. July 2005;34. Available at: www.capc.org/fast-facts/34-symptom-control-ventilator-withdrawal-dying-patient/.
29. Truog RD, et al. Pharmacologic paralysis and withdrawal of mechanical ventilation at the end of life. *N Engl J Med* 2000;342:508-511.
30. Truog RD, et al. Recommendations for end-of-life care in the intensive care unit: The ethics committee of the Society of Critical Care Medicine. *Crit Care Med* 2001;29:2332-2348.
31. Campbell ML. Patient responses during rapid terminal weaning from mechanical ventilation: A prospective study. *Crit Care Med* 1999;27:73-77.
32. Wildiers H, Menten J. Death rattle: Prevalence, prevention, and treatment. *J Pain Symptom Manage* 2002;23:310-317.

ABSTRACT & COMMENTARY

Optimal Duration of Anticoagulation for Unprovoked Pulmonary Embolism

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

SYNOPSIS: Treatment for 24 months with oral anticoagulation for unprovoked, first-time pulmonary embolism was superior to treatment for 6 months only.

SOURCE: Couturaud F, et al. Six months vs extended oral anticoagulation after a first episode of pulmonary embolism: The PADIS-PE randomized clinical trial. *JAMA* 2015;314:31-40.

Long-term treatment of pulmonary embolism (PE) with oral anticoagulant therapy is the standard of care, but the duration of therapy has not been well established. Based largely on a single, non-blinded study, the American College of Chest Physicians (ACCP) recommended that an unprovoked PE be treated with at least 3 months of oral anticoagulant therapy (Evidence: Grade 1B) with an extended course of treatment if the bleeding risk is low to moderate (Evidence: Grade 2B); similarly, the European Society of Cardiology recently recommended at least 3 months of therapy (Evidence: Class I, Level A) with extended therapy in patients with low bleeding risk (Evidence: Class IIa, Level B).[1,2]

The PADIS-PE study is a randomized, double-blind trial of adult patients with a first episode of unprovoked PE that seeks to better define the appropriate duration of therapy. In this study, 371 patients with radiographically confirmed PE who had already completed 6 months of therapy with a vitamin K antagonist were randomized to an additional 18 months of therapy or placebo. Unprovoked PE was defined by the absence of any reversible risk factor within 3 months of the PE, such as surgery, trauma, and bed rest, for more than 72 hours and the absence of active cancer within the last 2 years. Patients were excluded if they had previously experienced a deep vein thrombosis (DVT) or PE, had an independent indication for anticoagulation, had bleeding during the initial 6 months of therapy, had known thrombophilia, increased bleeding risk, platelets < 100,000, were expecting major surgery in the upcoming 18 months, or had a life expectancy of < 18 months. The primary outcome was a composite of recurrent venous thromboembolism or major bleeding within the 18-month trial period. This outcome was reassessed 24 months after the treatment period was completed.

During the 18-month trial period, treatment with warfarin reduced the primary endpoint significantly (HR, 0.22; CI, 0.01-1.20; $P = 0.001$.). This effect was due to a reduction in the rate of recurrent venous thromboembolism in the treatment group compared with the placebo group (1.7% vs 13.5%, HR 0.15, $P < 0.001$), while there was a non-significant increase in bleeding in the warfarin group (2.2% vs 0.5%, HR 3.96, $P = 0.22$). Overall, there was no difference in mortality during this period between the two groups (1.1% vs 1.1%, HR 1.32, $P = 0.78$). In the subsequent 24-month period, while not anticoagulated, the effects of prior treatment were largely lost. The overall rate of recurrent thromboembolism was similar in the former treatment and placebo groups (17.9% vs 22.1%, HR 0.69, $P = 0.14$), as was the bleeding risk (3.5% vs 3%, HR 1.12, $P = 0.85$). Mortality was similar in the two groups (9.1% vs 3.6%; HR 1.51; $P = 0.45$).

■ COMMENTARY

Previous professional guidelines have recommended "extended" courses of anticoagulation, but the optimal duration of therapy was ill-defined. The PADIS-PE study provides strong evidence that 24 months of vitamin K antagonism is superior to 6 months for the treatment of first-time, unprovoked PE. At the end of the 24-month therapeutic trial, patients were further monitored off therapy (median 41 months total). Interestingly during this period, the overall rates of recurrence of PE in the warfarin and placebo groups became statistically similar, as the warfarin group had 25 additional events while the placebo group experienced only 14 additional episodes of venous thromboembolism. This implies that the underlying cause of the PE, while unknown, had not resolved. This is further supported by the observation in this and other studies that the form of recurrence was similar to the index event. Additionally, the rate of recurrence was almost twice as high in the group that stopped therapy compared with the placebo group, implying that a rebound effect may increase the risk of clot after discontinuation of therapy. Therapy well beyond 24 months, even lifelong, might be beneficial.

As described above, recommendations regarding treatment of PE also vary based on the likelihood of bleeding complications. This study included patients with low, moderate, and high risks of bleeding based on ACCP scoring. These factors include advanced age, previous bleeding, cancer, renal failure, liver failure, diabetes, previous stroke, poor anticoagulant control, frequent falls, and alcohol abuse. This study included 45.7% and 40.7% of patients at high risk (more than two risk factors) in the warfarin and placebo groups, respectively. Unfortunately, no subgroup analysis was performed, but a benefit was demonstrated despite inclusion of this proportion of high-risk patients.

The questions remain: What is the optimal length of treatment, and is there a way to prospectively determine who would benefit from extended anticoagulation? The PROLONG study stratified patients with unprovoked DVT after at least 3 months of treatment based on D-dimer levels and compared rates of recurrence in individuals with normal levels to individuals with elevated levels with or without extended treatment.[3] Remarkably, the lowest level of recurrence was in patients with elevated D-dimer levels who then received extended treatment. The HR for recurrence in patients with elevated D-dimer levels without vs with treatment was 5.36 ($P = 0.007$). As in the PADIS-PE trial, extended anticoagulation was clearly beneficial. Elevated D-dimer levels indicated elevated risk for recurrence and benefit of extended anticoagulation, but normal D-dimer levels did not preclude patients from benefiting from extended anticoagulation. Future development of biomarkers may assist in determining benefit of extended anticoagulation,

but current studies suggest that lifelong anticoagulation after unprovoked PE is beneficial. ■

REFERENCES

1. Kearon C, et al. Antithrombotic therapy for VTE disease: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(suppl);e419s-494s.
2. Konstantinides SV, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology. *Eur Heart J* 2014;35:3033-3080.
3. Palareti G, et al. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med* 2006:355:1780-1789.

ABSTRACT & COMMENTARY

Using Critical Care Ultrasonography to Diagnose the Etiology of Acute Respiratory Failure

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

SYNOPSIS: This single-center study suggests that thoracic ultrasound and limited echocardiography may be useful to help differentiate the causes of acute hypoxic respiratory failure in the ICU.

SOURCE: Sekiguchi H, et al. Critical care ultrasonography differentiates ARDS, pulmonary edema, and other causes in the early course of acute hypoxic respiratory failure. *Chest* 2015 May 21[Epub ahead of print].

Acute hypoxic respiratory failure is common in the ICU, yet determining the etiology can be challenging. Thoracic ultrasound (US) and limited echocardiography (echo) are increasingly being used in the ICU. This prospective study evaluated the effectiveness of thoracic US and limited echo in determining the etiology of acute hypoxic respiratory failure.

This was a single-center study performed at an academic teaching hospital. Adults with acute hypoxic respiratory failure (defined as arterial partial pressure of oxygen to fraction of inspired oxygen ratio [PaO_2/FiO_2] < 300) were eligible (241 screened and 134 enrolled). Thoracic US and limited echo were performed within 6 hours of the diagnosis of acute respiratory failure. The exam was limited to 10 minutes. Thoracic US included five lung zones bilaterally (second and fourth intercostal spaces at the midclavicular and midaxillary lines and at the diaphragmatic arch). Limited echo included the subcostal 4-chamber, parasternal long- and short-axis, and apical 4-chamber views. Images were saved for later interpretation by board-certified radiologists and cardiologists blinded to the clinical data. Medical records were reviewed by two investigators blinded to the US and echo findings. Acute hypoxic respiratory failure was classified by these reviewers into one of three groups: 1) miscellaneous causes (unilateral pneumonia, pulmonary embolism, chronic obstructive pulmonary disease [COPD], mucous plugging), 2) cardiogenic pulmonary edema (CPE), or 3) acute respiratory distress syndrome (ARDS). After chart review, 25% were diagnosed with miscellaneous causes, 44% with CPE, and 31% with ARDS. The authors then used complex statistical modeling to associate imaging findings and cut-points that could predict these diagnoses. Based on these findings, an algorithm was suggested.

The first step is to evaluate for B-lines with thoracic ultrasound. B-lines, or lung comets, are hyperechoic or isoechoic vertical lines arising from the pleural line and spreading down to the edge of the screen. B-lines have previously been found to be associated with extravascular lung water.[1] B-lines in less than three lung zones suggested a miscellaneous cause, whereas B-lines in three or more lung zones suggested either ARDS or CPE. The presence of a left pleural effusion > 20 mm moderately or severely decreased left ventricular function, and a large minimal inferior vena cava diameter (> 23 mm) suggested CPE over ARDS.

■ COMMENTARY

Ultrasound is a test with distinct advantages. It uses no radiation, results are immediately available at the bedside, and testing can be repeated as the clinical situation changes. Sekiguchi et al add to the growing literature supporting US in the ICU, but this study should be considered more as a proof of concept study than definitive evidence. The authors recorded many

different US measurements in an attempt to identify markers that could predict certain diagnoses. The use of so many measures increases the probability of type 1 error (finding an association when it truly does not exist). Furthermore, other questions need to be answered before US can be recommended as a useful tool in the evaluation of acute hypoxic respiratory failure. Is US better than other tests commonly used, such as chest x-ray or basic natriuretic peptide? For clinicians already using these studies, as well as the history and physical exam, will US add appreciable information beyond what is already used? Will US potentially be better than clinical gestalt?

Perhaps the biggest disadvantage to critical care US is the technical skills required to both obtain and interpret images. In this study, it was not clear if the images were obtained by intensivists or certified ultrasonographers. Images were interpreted by board-certified cardiologists and radiologists. In this proof of concept study, it made sense to use experts to obtain and review images. However, this limits the generalizability of the study. Future studies should see if intensivists at the bedside can demonstrate the same results. Critical care US is in its infancy but promises to be a valuable new tool. Too frequently, new tools are adopted in the ICU before being critically evaluated. Studies such as this are welcome evaluations. Over time, they will help us understand how and when US can best be used. ■

REFERENCE

1. Enghard P, et al. Simplified lung ultrasound protocol shows excellent prediction of extravascular lung water in ventilated intensive care patients. *Crit Care* 2015;19:36.

CME/CNE QUESTIONS

1. **The doctrine of double effect provides the ethical rationale for which of the following?**
   a. Initiation of neuromuscular blockade prior to ventilator withdrawal to ensure a relaxed facial expression
   b. Increasing the dose of morphine in a patient who shows signs of pain despite concerns that the higher dose may suppress the respiratory rate
   c. Decreasing the dose of morphine in a patient who is moaning with pain because the respiratory rate of 8 indicates respiratory suppression
   d. Increasing the dose of lorazepam in a patient who appears comfortable in order to shorten the duration of suffering
   e. Withdrawing a ventilator in a patient who is awake and expresses understanding that withdrawal will lead to death

2. **In the PADIS-PE study, what was the effect of 24 months of anticoagulation vs 6 months?**
   a. Increased risks of both bleeding and recurrent PE
   b. Decreased risks of both bleeding the recurrent PE
   c. Decreased risk of recurrent PE without statistically increased bleeding risk
   d. Decreased overall mortality
   e. Patients were treated with warfarin for longer than 24 months

3. **In thoracic ultrasound, B-lines:**
   a. are suggestive of pleural empyema.
   b. are hyperechoic or isoechoic vertical lines arising from the pleural line and spreading. down to the edge of the screen.
   c. are not associated with extravascular lung water.
   d. are horizontal lines that are parallel and equidistant to the chest wall.
   e. are suggestive of pneumothorax.

CME/CNE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- identify the particular clinical, legal, or scientific issues related to critical care;
- describe how those issues affect physicians, nurses, health care workers, hospitals, or the health care industry; and
- cite solutions to the problems associated with those issues.

[IN FUTURE ISSUES]

High-flow oxygen in acute respiratory failure