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SPECIAL FEATURE

How Should the Respiratory Muscles be Managed During Critical Illness?

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

Mechanical ventilation (MV) increases the cost and duration of critical care by an average of 240% and 170%, respectively.[1] Although the average duration of MV in critically ill patients is approximately 6 days, it occurs with a wide dispersion.[2] Approximately 40% of time spent on MV is devoted to weaning,[3] and a sizable minority of patients (perhaps 25%) are considered difficult to wean.[4] This implies that respiratory muscle dysfunction is a significant factor. Despite intense research on respiratory muscle physiology and patient-ventilator interfacing, this knowledge has not been integrated into a comprehensive approach toward managing the respiratory muscles in critical illness. This special feature describes the complex array of issues complicating such an endeavor.

EFFECTS OF MECHANICAL VENTILATION ON THE RESPIRATORY MUSCLES

The art and science of MV are inextricably bound to its own history. In a 25-year span beginning in the late 1960s, several technological advancements occurred, including patient-triggered ("assisted") volume ventilation, intermittent mandatory ventilation, pressure control/pressure support ventilation, airway pressure-release ventilation, and dual mode control. Yet, introduction of these purported advancements invariably preceded both clinical and laboratory studies assessing their impact on respiratory muscle function. Also, the general success of critical care in rescuing catastrophically ill/injured patients often resulted in pronounced respiratory muscle weakness as a sequela. Theories developed in the early 1970s to explain this phenomenon (along with

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its implications for MV strategies) occurred under a "veil of ignorance."

Research on respiratory muscle physiology did not begin in earnest until the mid 1970s. And studies of the impact of MV on respiratory muscle function began only in the mid-1980s with the seminal work of Marini[5] and others. From these studies, several crucial facts have emerged: 1) the respiratory muscles continue to perform considerable work during assisted mechanical breaths; 2) the off-switch for patient effort during assisted MV is based on a neural-targeted tidal volume approximating the patient's spontaneous tidal volume;[6] 3) ventilators actually *impose* resistive, elastic, and threshold loads *in addition to* intrinsic loads caused by disease; and 4) settings for trigger sensitivity, inspiratory flow rate, flow pattern, and tidal volume significantly impact both the magnitude of imposed work as well as modifying the intrinsic workload.

Recent evidence has introduced several more vexing problems. Generous tidal volumes off-load the respiratory muscles and ameliorate dyspnea, but have a profound negative impact on morbidity and mortality. High doses of sedatives effectively suppress tidal volume demand and promote synchrony, but are associated with delirium, prolonged MV, and other sequelae. Likewise, prolonged use of neuromuscular blocking agents also can cause profound respiratory muscle weakness. Yet, restricting tidal volume below patient demand increases work of breathing.[7]

Allowing *sustained* high-level work can cause acute inflammation and structural damage to the respiratory muscles,[8] as well as fatigue. Similarly, *complete* respiratory muscle inactivity causes inflammation and muscle damage that also results in weakness.[9] Moreover, patients with sepsis and organ dysfunction have pronounced respiratory muscle weakness at the onset of MV.[10] This finding is consistent with preclinical evidence that the diaphragm appears particularly vulnerable to inflammation and structural damage from severe gram-negative bacterial infections.[11,12] Paradoxically, passive MV may protect the respiratory muscles during sepsis.[13] Thus, from the standpoint of both physics and pathophysiology, there are important but contradictory goals of care during MV. These require a careful balancing of competing issues at different time points in the course of critical illness and are discussed below.

VENTILATOR-INDUCED DIAPHRAGMATIC DYSFUNCTION

Like all skeletal muscles, the respiratory muscles are prone to disuse atrophy, which develops within days of *controlled* ventilation. However, disuse atrophy requires prolonged, passive MV and seemingly has little relevance when patient-triggered ("assisted") MV is used.[14] Studies of assisted MV consistently demonstrate that patient work of breathing is elevated above normal limits. Therefore, minimizing the risk of disuse atrophy requires that sedation and mandatory ventilator frequencies be titrated to achieve consistent patient triggering. Passive ventilation should be restricted to situations characterized by some combination of pronounced gas exchange dysfunction, profound abnormalities in chest mechanics, hemodynamic instability, severe intracranial hypertension, or ensuring the stability of large surgical wounds.

FATIGUE, WEAKNESS, AND USE ATROPHY

Muscle fatigue is the inability to generate a targeted force because of activity under loaded conditions and is reversible by rest, whereas weakness is the inability to develop a targeted force in a rested muscle. Acute fatigue occurs when inspiratory muscle pressures reach 50-70% of maximum capability. The time to actual fatigue onset in normal muscles is not immediate but decreases based on both the degree of loading and the inspiratory time percentage ("duty-cycle"). During critical illness, the duty cycle often reaches 50% when the muscles are stressed.[15] In addition, weakened muscles are more susceptible to fatigue precisely because of their diminished force-producing capacity.

In general, fatigue is categorized into high- or low-frequency forms according to the muscle fibers most affected. Type 2 fibers have enhanced power output but are readily susceptible to fatigue (high frequency), whereas Type 1 fibers have high endurance but limited power-generating capacity (low frequency). High-frequency fatigue occurs first during weaning failure, when the Type 2 fibers deplete their energy stores and begin to fail as pressure generators. This typically coincides with overt signs of distress, so that quickly unloading the muscles often results in functional recovery within a matter of hours. However, prolonged exposure to fatiguing loads likely induces tension-related muscle injury[8] and complete recovery may require between 24-48 hours of rest.[16] Moreover, preclinical evidence now suggests that, like other skeletal muscle, even brief periods (e.g., 1.5 hours) of high fatigue-inducing loads are associated with secondary diaphragmatic injury detected several days later.[17] Although the damage appears limited in scope, this raises the possibility that chronically exposing the respiratory muscles to excessive workloads might perpetuate muscle damage and prolong ventilator dependence in some patients.

REST VS EXERCISE

That the respiratory muscles must reach at least 50% of their maximal force capacity during tidal breathing to induce fatigue contradicts the notion that work of breathing must be normalized or minimized during MV. Given this physiologic reserve, and in the absence of fatigue, malnutrition, or hemodynamic/gas exchange instability, the majority of patients can likely tolerate sustained increases in work of breathing of at least twice normal (e.g., ~1 joule/L) without difficulty. The likely exception is when acute respiratory failure occurs under conditions of either prolonged respiratory distress prior to instituting MV (e.g., COPD exacerbation) or severe gram-negative infection. These patients may require careful reintroduction of respiratory muscle activity after a reasonable period of complete rest (e.g., 24 hours). However, the rate and magnitude by which respiratory muscle work is reintroduced should be tested empirically. In other words, this process should not be assumed problematic until patients "declare" themselves so. In contrast, many patients with acute respiratory failure have normal respiratory muscle function, and likely have MV initiated prior to the development of low frequency fatigue and muscle damage. These patients should be managed initially with assisted ventilation and quickly challenged with a spontaneous breathing trial once the underlying cause of respiratory failure has subsided.

In this regard, spontaneous breathing trials are concordant with the principles of muscle training, and should be used (at least initially) in all patients. Discrete periods of intense activity stimulate muscle growth and strength.[18] However, to be effective, strenuous activity must be interspersed with periods of *relative* rest. In patients requiring prolonged weaning, pressure support levels should be titrated toward usual weaning parameters for tidal volume (e.g., ≥ 5 mL/kg) and respiratory frequency (25-35 breaths/minute) to ensure that the respiratory muscles are sufficiently challenged. When pain, discomfort, or anxiety have been ruled out, overt distress and pronounced accessory muscle use likely indicate the onset of high-frequency fatigue. Therefore, these signs should be used to discontinue discrete weaning trials and provide at least several hours of rest. Although patient work of breathing cannot be measured without esophageal manometry, it can be reasonably inferred by evaluating changes in the breathing pattern, accessory muscle use, vital signs, and ventilator waveform graphics in response to changes in the level of MV support.

THE CARDIOPULMONARY IMPACT OF STRENUOUS INSPIRATORY EFFORTS

In the presence of either altered pulmonary capillary permeability or hypervolemia, the repetitive generation of large negative intrathoracic pressure increases the transcapillary hydrostatic pressure and promotes pulmonary edema.[19] In addition, cardiac afterload is increased, which may have a significant negative impact on patients with depressed myocardial contractility. Finally, when respiratory muscle work is highly elevated, expiration becomes active. This, in part, is a compensatory response to increased resting diaphragmatic length and enhances inspiratory muscle performance. Under conditions of alveolar instability (e.g., ARDS), active expiration promotes de-recruitment and thus counteracts the effects of PEEP. Thus, pronounced patient-ventilator asynchrony and labored breathing in severe respiratory failure are clear justifications for rapid institution of passive ventilation until the patient can be stabilized.

In summary, respiratory muscle dysfunction is common in critical illness but has multiple causes, not all of which are fully understood or whose treatment approach has been clearly demonstrated. One of the primary goals of mechanical ventilation is to assume all or some of the work of breathing. Unfortunately, achieving this end often is at odds with other equally important goals, such as the prevention of ventilator-induced lung injury and avoiding the use of both paralytics and high amounts of sedatives that also can increase the duration of MV. A comprehensive strategy for managing respiratory muscle function requires the clear delineation of when competing goals take precedence over one another. When the respiratory muscles should be rested or stressed should be based on the best clinical and preclinical evidence available, in concert with the particular circumstances of individual patients and how they respond empirically to adjustments in MV. ■

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ABSTRACT & COMMENTARY

A Worldwide Assessment of Procedure-Related Pain Intensity and Distress in ICU Patients

By Linda L. Chlan, RN, PhD, FAAN

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Dr. Chlan reports that she receives grant/research support from Hospira.

SYNOPSIS: Results from a large, multinational study indicate that ICU patients worldwide experience moderately intense pain, most commonly from chest tube removal, wound drain removal, and arterial line insertion.

SOURCE: Puntillo KA, et al. Determinants of procedural pain intensity in the Intensive Care Unit: The Europain Study. *Am J Respir Crit Care Med* 2014;189:39-47.

Attention to pain management for intensive care unit (ICU) patients remains a priority for critical care clinicians. The pain intensity and distress associated with common ICU procedures, such as positioning, has not been evaluated since 2001 with the Thunder II project.[1] As pointed out by the authors, pain management has come a long way since the Thunder II report was published, with clinical practice guidelines for managing ICU pain, agitation, and delirium much more prominent.[2] Further, pain intensity from ICU patients around the world has not been previously reported. Thus, a large group of investigators, led by U.S. pain expert Dr. Kathleen Puntillo, conducted a prospective, cross-sectional, multinational designed study to assess the characteristics and determinants of pain associated with 12 common ICU procedures. Participating investigators and ICUs were recruited through the European Society of Intensive and Critical Care Medicine, and included those who had previously participated in international studies.

A predefined list of common ICU procedures such as positioning, device and line insertion and removal, wound care, mobilization, endotracheal suctioning, and respiratory exercises was used to guide the pain intensity and pain distress ratings, based on a 0 = no pain or no distress to 10 = worst pain or severe distress numeric rating scale. Patients were also observed during the procedures. Patients were enrolled from the participating ICUs for one or two procedures performed on the same day, or over 2 consecutive days. Patients were eligible if they were ≥ 18 years, met the institutional review board requirements, and were to experience at least one of the 12 study procedures during their stay. Patients' pain was assessed prior to and immediately after the selected procedures.

Overall, 28 countries participated with a total of 192 ICUs worldwide. A majority of the participating hospitals were university or university-affiliated centers (66%) and public facilities (82%). ICUs were classified as medical/surgical (60%), medical (12%), surgical (8%), trauma (7%), other (8%), or cardiac (5%). A total of 4812 procedures experienced by 3851 patients were included in the analysis. Median patient age was 62 years with median Sequential Organ Failure Assessment and Richmond Agitation-Sedation Scale (RASS) scores of 3 and 0, respectively. Across the list of specified ICU procedures, the most common was positioning and the least common was wound drain removal. When considering all of the pre-procedure pain assessments, patients reported mild pain intensity, but they experienced a significant increase in pain intensity during a procedure. The most painful procedures were chest tube removal, wound drain removal, and arterial line insertion. Factors that contributed to higher pain intensity ratings included the specific procedure, high pre-procedure pain intensity and distress ratings, higher intensity of "worst" pain on the evaluation day, whether opioids were administered for the specific procedure, and procedures not being performed by a nurse.

■ COMMENTARY

Pain intensity and distress emanating from common ICU procedures is a worldwide phenomenon, regardless of country or culture. As reported by Puntillo and colleagues, patients evaluated their pain intensity as moderate, and this pain was associated with a variety of common procedures that ICU patients experience daily. While clinicians may aim to "do no harm," these necessary procedures do cause pain and distress in ICU patients.

The findings from this paper should be a reminder to all ICU clinicians that patients experience pain very individually, and that a majority of ICU patients can evaluate their pain intensity and distress using a simple numeric rating scale. Pain assessment evaluations should be standard practice in all ICUs, regardless of a patient's RASS score! Further, while ICU clinicians may think that short-duration procedures such as chest tube removal may not "bother" patients, the findings from this large study remind us that despite a common ICU procedure not being lengthy, it can be extremely painful and distressing for patients.

ICU clinicians should strive to work collaboratively with patients to assess pain and premedicate patients with the appropriate medication for the specific pain associated with common procedures (e.g., topical anesthetic or intravenous opioid). Remember, ICU patients frequently recall painful experiences while in the ICU that can be psychologically detrimental. ICU clinicians around the world should strive to implement best practices for pain assessment and pain management in their ICUs to ensure this common ICU symptom is not distressful for patients. ■

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ABSTRACT & COMMENTARY

Futile Care in the ICU: Prevalence, Risk Factors, Costs

By Betty Tran, MD, MS

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

SYNOPSIS: This prospective, single-center study reported that critical care perceived to be futile is common, is associated with certain patient factors, and can be quite costly.

SOURCE: Huynh TN, et al. The frequency and cost of treatment perceived to be futile in critical care. *JAMA Intern Med* 2013;173:1887-1894.

As members of the critical care team, we have doubtless cared for patients whom we knew had no hope of recovery. The treatments provided to these patients may be described by some as "futile," although there is no uniform definition of that term, which is inherently controversial from medical, ethical, and legal perspectives. Huynh and colleagues sought to quantify the prevalence and cost of treatment perceived to be futile in the ICU in a single center.

A questionnaire was devised based on responses from a focus group of physicians from surgery, anesthesia, cardiology, and pulmonary/critical care exploring reasons that treatment may be considered futile, and subsequently administered to attending critical care physicians in five ICUs located in an academic health care system. For each ICU patient under the physician's care on a given day, the physician was asked whether the patient was receiving, probably receiving, or not receiving futile treatment and, if applicable, the reason treatment was futile: burdens grossly outweigh benefits, patient would never survive outside the ICU, patient is permanently unconscious, treatment cannot achieve patient's goals, or death is imminent. Patient and physician demographic and clinical data were collected as well as daily charges from which costs were estimated.

Over a 3-month period, 6916 assessments were performed on 1136 patients, of whom 98 (8.6%) were perceived to receive probably futile treatment and 123 (11%) were perceived to have received futile treatment. Assessments of futile treatment accounted for 6.7% of all assessments. Overall, physicians cited multiple reasons why a patient was receiving futile treatment. The most common reason was because the burdens outweighed the benefits (58%), followed by treatment could never reach the patient's goals (51%), death was imminent (37%), the patient would never survive outside the ICU (36%), and the patient was permanently unconscious (30%). Patients who were perceived as receiving probably futile treatment or futile treatment were older, more likely to be male, had higher Medicare Severity Diagnosis-Related Group (MS-DRG) weights, had longer lengths of stay, and were more likely to be admitted from a skilled nursing or long-term acute care facility. No physician descriptor was a significant predictor of the perception of futile treatment, although patients in the MICU were significantly more likely to be perceived as receiving futile treatment than in the cardiac or cardiothoracic care units. The average cost for 1 day of treatment in the ICU that was perceived to be futile was $4004. For the 123 patients who were perceived to be receiving futile treatment, hospital costs for the days considered futile amounted to $2.6 million.

COMMENTARY

Given significant advances in critical care medicine in prolonging life, this study highlights concerning perceptions among critical care physicians at the front lines of providing such treatments. The reasons treatment is perceived to be "futile" in the study are not surprising, and from personal experience, are often verbalized among the treating medical team members when discussing the patient on rounds or stated in the medical chart. What should happen afterward, however, is a discussion, or more realistically, multiple discussions with and an assessment of the views of the patient or surrogate decision maker. In certain instances where this alone is not enough, input from a third party (e.g., second physician opinion, hospital ethics committee, transfer of the patient to a different institution) may be needed to help resolve conflicts. Although it is unclear whether any of this occurred in the present study and may be outside its intended scope, the complexity of this topic highlights limitations regarding how this study was presented and potential difficulties in how its findings could be interpreted or applied.

The authors sought to describe the prevalence of ICU treatment perceived to be "futile," but given the lack of standard criteria, the prevalence reported is solely subjective and based on the opinion of a single physician on any given day. The authors rightfully acknowledge that it is unclear if other physicians would agree if asked or whether patients or their families would agree, which seems unlikely. Furthermore, in an editorial accompanying the article, Truog and White point out that the use of the term "futile" is problematic as ICU interventions are often never technically "futile" (i.e., incapable of producing any useful result).[1] More often, there is a discrepancy between the values of the patient or surrogate decision maker of "doing everything" to prolong life and the judgment of medical providers that certain interventions come at high cost with little overall benefit.[1] To make matters even more complex, there may be differences in opinion even among physicians as to what interventions are acceptable at the end of life.

Finally, the authors quote a significant cost of providing ICU treatment that is considered "futile" on the order of $2.6 million as 3.5% of the total hospital costs for the total number of patients included in the study. As they also acknowledge, however, this number is deceptive in that there are no data to support the implication that limiting ICU treatments considered "futile" would result in significant cost savings. As argued by Luce and Rubenfeld,[2] not only are we unable to predict successfully which critically ill patients will be the most expensive or will die shortly after arrival in the ICU, but denying ICU treatments to these patients will unlikely result in significant cost savings because the vast majority of ICU costs are fixed. In summary, the perception of inappropriate medical treatment among critical care physicians is an important issue with significant clinical and ethical considerations, but defining the true prevalence and cost implications of such care is much more complex than what is presented here. ■

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CME/CNE Questions

1. Which of the following statements is *false* with respect to patient-ventilator interactions during assisted mechanical ventilation?

a. The off-switch for patient effort is their spontaneous tidal volume demand.
b. The ventilator can impose or add work to the respiratory muscles.
c. Trigger sensitivity and tidal volume settings are important determinants of patient work.
d. Patient effort ceases with the onset of a mechanical breath.
e. Peak inspiratory flow rate and flow pattern are important determinants of patient work.

2. Which of the following statements is *false* with respect to respiratory muscle function?

a. Disuse muscle atrophy and weakness occur within days of controlled ventilation.
b. Fatigue occurs when the respiratory muscles exceed 50% of maximum pressure capacity during tidal breathing.
c. Sustained high-tension work above the fatigue threshold causes respiratory muscle inflammation.
d. Many patients have evidence of respiratory muscle weakness at the initiation of mechanical ventilation.
e. Severe gram-negative infections have no impact on respiratory muscle function.

3. Which of the following procedures was identified by patients as producing the most intense pain?

a. Turning in bed
b. Marching in place at the bed side
c. Chest tube removal
d. Daily weighing
e. All of the above

4. Which of the following statements is correct concerning the characteristics of the patients in the study of procedural pain in the ICU?

a. A majority of the patients were too sedated to provide pain assessment responses
b. A majority of the patients in the study were receiving mechanical ventilatory support.
c. A majority of the patients rated their baseline pain intensity as severe.
d. A majority of patients had their pain intensity increase with common ICU procedures.
e. All of the above

5. In the study by Huynh et al, approximately what percentage of patients over a 3-month period were perceived by their physicians to be receiving "futile" ICU treatment?

a. 1%
b. 5%
c. 11%
d. 28%
e. 62%

6. What was the most common reason patients were perceived to be receiving "futile" treatment?

a. Death was imminent
b. Burdens of treatment outweigh benefits
c. The patient had an incurable disease
d. The patient was comatose
e. Treatment was actively causing harm

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.