

Expiratory Muscles, Neglected No More

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In this issue of *ANESTHESIOLOGY*, Shi *et al.*¹ report on the reproducibility of expiratory muscle thickness measured with ultrasound imaging in 30 patients ventilated in the intensive care unit (ICU). They also assess changes in expiratory muscle thickness during the first week of mechanical ventilation in 77 ICU patients. They conclude that ultrasound thickness measurements are reproducible, and that thickness decreases in 2 of 10 patients and increases in 1 of 10 patients during the first week of mechanical ventilation.

Should we concern ourselves with expiratory muscle thickness? Yes, for several reasons. Forceful contractions of the expiratory muscles are necessary to achieve dynamic airway compression, an essential element in effective cough.² Expiratory muscle recruitment improves diaphragmatic neuromechanical coupling during loaded breathing,³ including during a failed weaning trial.⁴ Indirect measurements of expiratory muscle weakness have been associated with need for reinstitution of mechanical ventilation after initial extubation.⁵

Two crucial aspects of any transducer, including ultrasound transducers, are validity, or how well the measurement represents the measured variable, and reliability, or consistency of the measuring test. Shi *et al.*¹ assume that ultrasound imaging is a valid tool to measure expiratory muscle thickness. Is this assumption acceptable? Likely so, considering that with a similar technique, Wait *et al.*⁶ reported a close correlation between diaphragmatic thickness measured in cadavers using ultrasound imaging and thickness measured with a ruler. As for reliability, Shi *et al.*¹ compared interrater reproducibility⁷ of measurements obtained by two investigators at the same anatomical location about 5 min apart and intrarater repeatability⁷ obtained by each investigator. The interrater intraclass correlation coefficient was high (0.994). The 95% limits of agreement ranged from -13.1 to 6.8%. Similarly, the intrarater intraclass



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correlation coefficient for the two investigators was also high (0.991 and 0.998), and the corresponding limits of agreement ranged from -11.4 to 13.8%.

Based on the limits of agreement in the reproducibility arm of the study and sensitivity analysis, the investigators used a 15% and 20% change in thickness as thresholds to identify changes in thickness “likely to be attributable to biologic processes such as atrophy and hypertrophy, as opposed to measurement variance [alone].”¹ Using these two thresholds, 17 to 22% patients experienced a decrease in expiratory muscle thickness during the first week of mechanical ventilation. These figures are about half the purported

prevalence of diaphragmatic atrophy in ventilated patients.⁸

That the diaphragm is more susceptible to atrophy than other skeletal muscles is not surprising. For example, after less than 3 days of controlled mechanical ventilation and immobilization, the cross-sectional area of diaphragm fibers decreases more than half while that of pectoralis major muscle fibers does not.⁹ At a functional level, in a rat model of long-term mechanical ventilation in ICU conditions, Corpeno *et al.*¹⁰ reported a decrease in specific force before development of atrophy. The decrease in force was associated with posttranslational modifications of myosin. Salah *et al.*¹¹ reversed these post-translational modifications and almost completely restored the diaphragm’s specific force at day 10 of mechanical ventilation in rats treated with BGP-15, a heat shock protein 72 co-inducer. In contrast, at days 8 to 10 of mechanical ventilation, BGP-15 has no effect on the soleus muscle, in which severe loss of function starts later, and it parallels myosin loss.¹² These observations suggest that different pathways are implicated in the development of diaphragmatic and peripheral muscle dysfunction in critically ill patients.¹³ They also raise the possibility that distinct interventions may be required to address these different muscle groups.

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In the group of patients who experienced a decrease in muscle thickness, Shi *et al.*¹ recorded an 11.5% decrease in expiratory muscle thickness within 24 h of study enrollment. This decrease is more than double that observed in limb muscles of critically ill ventilated patients.¹⁴ If such differences are confirmed in future studies, we must conclude that it is inaccurate to expect the same response to critical illness from different muscle groups such as lower limb and expiratory muscles even if those muscles have similar fiber-type distribution (Type I fiber predominance)¹⁵ and share some functional role (posture and balance).^{16,17}

Except for longer hospital length of stay, changes in expiratory muscle thickness were not associated with worse clinical outcomes including duration of mechanical ventilation and mortality. Several mechanisms may explain these results. First, the study by Shi *et al.*¹ was not powered to assess clinical outcomes. Indeed, the investigators themselves caution against overinterpretation of their explorative outcome data. Second, changes in expiratory muscle thickness—and conceivably worse muscle function—do not affect respiratory physiology. This is difficult to reconcile with the important role of the expiratory muscles when patients are faced with increased respiratory loads,⁴ unless thickness measured with ultrasound imaging alone does not accurately reflect function.¹⁰ The latter possibility is supported by two observations. In ventilated patients, changes in limb muscle thickness underestimate loss of muscle dimension as measured by muscle fiber cross-sectional area and by the protein-to-DNA ratio.¹⁴ In a pilot study,¹⁸ functional electrical stimulation of the abdominal wall muscles reduced duration of mechanical ventilation and ICU length of stay despite leading to no differences in abdominal muscle thickness.

Finally, the proposed threshold(s) to classify patients as having a decrease (or increase) in muscle thickness are *distribution-based* and not *anchor-based*.¹⁹ That a biologic variable, such as muscle thickness, changes more than the variability of the measuring technique used for its quantification does not mean that crossing that threshold *ipso facto* leads to functional impairment. It also does not mean that that impairment (if present) necessarily translates into a clinically significant deficit. For example, overall respiratory muscle strength has to be less than half of normal to cause hypercapnia (in some patients).²⁰ Maximal expiratory pressure has to be less than one third to one half of normal for a cough to be ineffective.² Distribution-based thresholds imply that the distribution recorded within a limited time frame reflects the distribution over longer periods of time. To limit the influence of day-to-day variance, Shi *et al.*¹ categorized patients by obtaining a regression line using the available thickness measurements for each patient. Whether this strategy is sufficient to limit measurement variance is unclear considering that the investigators reported in a similar study that ultrasound imaging was marred by “large intra- and inter-participant variability” and that 27.3% of ultrasound sessions recorded during the experiment had

to be excluded due to interrater disagreements.¹⁸ It is also unclear whether the large intra- and interparticipant variabilities in the previous study were due to fluid overload, edema, and high intra-abdominal pressures. These factors could lead to changes in muscle architecture unrelated to atrophy.

In conclusion, with their elegant investigation, Shi *et al.*¹ make a strong case for the use of ultrasound imaging to assess expiratory muscle thickness in ventilated patients. Challenges remain. Does mechanical ventilation independently contribute to changes in expiratory muscle thickness? Are these changes mechanistically linked to worse muscle function and respiratory outcomes, or are they an indirect marker of disease severity? Can strategies designed to limit changes in expiratory muscle thickness or to restore thickness impact patients’ outcomes?

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Competing Interests

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