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Diaphragm-Protective Mechanical Ventilation to Improve Outcomes in ICU Patients?

The respiratory muscle pump drives alveolar ventilation. The diaphragm, a thin (2–3 mm in healthy adults) dome-shaped muscle, is an essential component of the respiratory muscle pump. In critically ill patients, ventilatory demands may exceed the capacity of the respiratory muscle pump, and in this case mechanical ventilation is used to unload the respiratory muscles to prevent the development of muscle fatigue and injury. However, in the past decade, several studies have provided evidence that respiratory muscle weakness may develop in ICU patients on ventilator support (1–4). In fact, diaphragm dysfunction is highly prevalent. For instance, Dres and colleagues (5) demonstrated that at the time of the first spontaneous breathing trial in patients who had undergone mechanical ventilation, 63% of the patients had developed diaphragm dysfunction, which has recently been termed “critical illness-associated diaphragm weakness” (6).

In this issue of the *Journal*, Goligher and colleagues (pp. 204–213) present their findings from a large prospective cohort study in invasively ventilated ICU patients (7). This study was designed to examine whether changes in the thickness of the diaphragm, as assessed by ultrasound, were associated with adverse outcomes, including prolonged ventilator dependence, reintubation, and death. At least two thickness measurements were obtained in 191 ventilated patients. A rather complex statistical plan was used, but the main message of the study can be summarized as follows: diaphragm muscle thickness decreased by $\geq 10\%$ in 41% of patients by median day 4, and this was associated with a lower probability of ventilator liberation, prolonged ICU admission, and respiratory complications (including reintubation and tracheostomy) compared with patients with a $< 10\%$ change in diaphragm thickness. Remarkably, in 24% of the patients, diaphragm thickness increased by $\geq 10\%$ in the first week of ventilation, and this was also associated with prolonged ventilation. The authors also demonstrated that the change in diaphragm thickness varied with diaphragm effort as assessed by muscle-thickening fraction or diaphragm electrical activity: low effort was associated with reduced thickness and high effort was associated with increased thickness.

This study is very important for a number of reasons that should be emphasized. First, this is the first prospective study with a large

number of patients to report a relationship between changes in diaphragm muscle thickness and clinical outcomes. Second, this study demonstrates a relationship between changes in diaphragm thickness and diaphragm effort. The development of diaphragm atrophy under conditions of disuse or low effort is rather intuitive and was previously demonstrated by analyses of diaphragm muscle biopsies from ventilated, brain-dead patients (1, 2). The pathophysiology and histological substrate for increased diaphragm thickness during mechanical ventilation are less intuitive, but the fact that increased diaphragm thickness resulted in a lower cumulative incidence of ventilation liberation suggests that the increased thickness is not just a reflection of diaphragm hypertrophy (i.e., increased contractile tissue in the muscle fibers). An alternative hypothesis is that increased diaphragm thickness results from diaphragm injury. The authors propose that the high breathing effort induced diaphragm muscle fiber injury, resulting in an inflammatory response and fiber swelling. This is an intriguing proposition, and is supported by a previous study in humans that showed excessive diaphragm fiber injury after acute inspiratory muscle loading (8), and another study that demonstrated elevated numbers of inflammatory cells in diaphragm fibers of critically ill patients (3). In the latter study, increased expression of inflammatory cells was also present in the diaphragm of nonseptic patients, suggesting that this does not reflect systemic inflammation but rather a local inflammatory response, possibly elicited by diaphragm injury. Further evaluation of these findings, however, does not show a positive correlation between the number of neutrophilic granulocytes and macrophages in the diaphragm and the cross-sectional area of fibers in those specimens ($n = 14$; unpublished observations). The absence of such a correlation does not seem to support the proposition that increased local inflammation causes fiber swelling. Furthermore, it remains to be established that fiber swelling occurs, as previous analyses of diaphragm fiber cross-sectional areas in critically ill patients did not provide evidence in support of swelling (3, 9). Whether diaphragm injury in critically ill patients causes interstitial fluid accumulation (i.e., swelling of the space in between muscle fibers) and thus provides an alternative explanation for increased diaphragm thickness remains to be determined and warrants further investigations.

Taken together, these studies demonstrate that diaphragm structure and function are very sensitive to high and low loading conditions, both of which have been observed in ICU patients (2, 10) and may occur at different time points during the ICU stay

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Figure 1. In patients with a critical illness, the respiratory muscle pump may exert a level of effort beyond its physiological limits for hours or even days. Before ICU admission, patients with impending respiratory failure may exhibit very high respiratory muscle effort. After endotracheal intubation and institution of controlled mechanical ventilation, the respiratory muscles are at risk for disuse atrophy. In subsequent days, both high and low breathing efforts may occur, particularly if the activity of the diaphragm is not monitored. This may result in functional and structural modifications of the diaphragm muscle, especially in a hostile environment due to hypercapnia, hypoxemia, and inflammation.

(Figure 1). Goligher and colleagues (7) now convincingly demonstrate that this has an important impact on patient outcomes. Based on these data, it seems reasonable to conclude that prevention of disuse and high breathing effort for prolonged periods of time is the cornerstone of diaphragm-protective mechanical ventilation. It may be possible to target physiological loading of the diaphragm by adjusting the level of inspiratory ventilator support and/or dose of sedatives. However, this requires monitoring of the respiratory muscle effort. Several techniques are feasible in critically ill patients, including monitoring of esophageal pressure, diaphragm electromyography, and ultrasound (11, 12). The relevant question is, which level of activity can be considered diaphragm protective? A pragmatic approach would be to aim for values reported for healthy subjects (e.g., when using the esophageal balloon, a muscle pressure of 5–10 cm H₂O [13] or diaphragm electrical activity of 8% of maximum value [14]). The data from Goligher and colleagues (7) indicate that an inspiratory thickening fraction of ~40% prevents changes in diaphragm thickness.

Obviously, more studies are required to identify the optimal range of diaphragm effort in critically ill patients under different clinical conditions, and, more importantly, to confirm that a treatment algorithm that uses diaphragm monitoring can improve outcomes. But let us not forget that even with regard to arterial blood pressure, we are still debating optimal targets for specific patient

populations (15), despite the fact that intra-arterial catheters have been used for decades. Goligher and colleagues provide important evidence that both high and low levels of breathing effort are associated with adverse outcomes, and therefore, in addition to lung-protective ventilation, we now may incorporate diaphragm-protective ventilation into our clinical protocols. Undoubtedly, future studies will provide better guidance and even personalized target values. For now, let not better be the enemy of good. ■

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Breathing Easier: A Well-tolerated Corrector for F508del

Fundamentally, cystic fibrosis (CF) is caused by numerous mutations that alter transcription or translation in the cell, resulting in reduced or dysfunctional CF transmembrane conductance regulator (CFTR) protein. The CF research and clinical communities have been energized by the emergence of new therapies that, while not curative, work to correct this primary impairment in CFTR function. Ivacaftor has been shown to potentiate ion transport in people with the gating mutation G551D, resulting in durable clinical improvement (1–5). Based on clinical and *in vitro* study results, the Food and Drug Administration–approved indication for ivacaftor has expanded to include over 30 mutations, representing approximately 10% of the CF population in the United States (6–9).

Although CFTR has many distinct mutations, the single mutation F508del is recognized as the most important target for CFTR-enhancing therapy. This mutation is present in 90% of U.S. patients with CF, nearly half of whom are homozygous (10). F508del affects multiple steps in gene translation and protein function, and it appears that combinations of CFTR modulator compounds will be needed to significantly increase CFTR ion transport. Genetic therapies that are both mutation-specific and -agnostic are also being investigated as alternative or complementary therapeutic approaches, but their clinical efficacy remains to be proved (11).

Lumacaftor is a corrector compound that improves intracellular protein processing and trafficking, and, when combined with the potentiator ivacaftor, can improve CFTR function in people homozygous for F508del (12, 13). In clinical trials, this was associated

with significant, albeit modest, clinical improvement. Unfortunately, the use of lumacaftor is complicated by potential interactions between drugs, including hormonal contraceptives, certain antimicrobials, and the partner drug ivacaftor (14). Lumacaftor can cause pulmonary symptoms that many find intolerable (15). These symptoms often resolve over the first few weeks but can unfavorably shift the benefit-to-risk balance, limiting its use (10).

In this issue of the *Journal*, Donaldson and colleagues (pp. 214–224) report the first results of a CF clinical trial testing tezacaftor as monotherapy and combined with ivacaftor in individuals homozygous for F508del (16). The authors also report the effects of adding tezacaftor to ivacaftor in individuals compound heterozygous for F508del and G551D. Tezacaftor is a corrector compound that targets F508del and possibly other mutations. The collective findings of this complex study, which included 14 alternative treatment groups, are encouraging. In this phase 2 trial, the investigators found that tezacaftor demonstrated excellent safety and tolerability when administered alone or in combination with ivacaftor. The individual treatment groups were relatively small, but collectively the results indicate that tezacaftor is free of the side effects (e.g., chest tightness) that complicate lumacaftor use. Similarly, the pharmacokinetic results show that tezacaftor and ivacaftor do not alter the metabolism of each other, and tezacaftor does not appear to affect CYP3A4 activity, reducing the potential for drug interactions. The early efficacy measurements show that tezacaftor/ivacaftor may provide improvements similar to those reported in pivotal phase 3 studies testing lumacaftor/ivacaftor (13). Additionally, tezacaftor or other corrector molecules may further improve CFTR function when added to existing ivacaftor therapy in people with F508del/G551D mutations. Although the present study was not designed to