Transvenous Phrenic Nerve Stimulation: A Novel Therapy Gathering Pace

Weaning from mechanical ventilation or, more correctly, the process of liberating patients from the ventilator is estimated to account for up to 40% of the total duration of ventilation and is one of the best-studied aspects of ventilatory practice (1). Most patients fall into the category of simple weaning (i.e., liberation following a first attempt), whereas a variable number (10–35%) take several days to be separated (difficult weaning), and finally approximately 10% of patients require more than 1 week to separate from the ventilator, so-called prolonged weaning, a state that is associated with increased mortality (2, 3).

Critical illness–associated diaphragm weakness is a common problem in the ICU, occurring in 63–80% of patients at the time of weaning from mechanical ventilation, and is a significant contributor to difficult and prolonged weaning (4). The cause of this weakness is often multifactorial (5), but one important driver is the degree of spontaneous respiratory effort made by the patient, which is in turn influenced by the degree of mechanical ventilatory support; both too much effort (undersupport) and too little effort (oversupport) can be harmful. Diaphragm dysfunction is independently associated with worse clinical outcomes (2, 3, 6), and methods to mitigate or reverse this are the subject of important ongoing research.

To this end, in this issue of the *Journal*, Dres and colleagues (pp. 1169–1178) present the results of a multicenter open-label randomized clinical trial of temporary transvenous diaphragm neurostimulation (TTDN) (7). They randomized 112 patients for whom two spontaneous breathing trials had failed after at least 4 days of invasive mechanical ventilation to standard care ($n = 55$) or TTDN ($n = 57$), 43 of whom actually were able to receive the intervention: the modified intention-to-treat (mITT) population. The primary outcome of successful weaning by Day 30 was achieved by 82% in the mITT treatment group versus 74% in the control group (absolute difference, 7%; 95% confidence interval, −10% to 25%; $P = 0.59$). However, there was some physiological promise, with change in maximal inspiratory pressure (MIP) being significantly greater in the TTDN group with an improvement of 16.6 cm H_2O versus 4.8 cm H_2O in the usual care arm. The authors should be congratulated on the use of novel technology to tackle an important and common clinical problem.

"Inspiratory muscle training" (IMT) is a general term to describe rehabilitation that aims to increase strength and fatigue resistance of the diaphragm and other inspiratory muscles. This is typically achieved by targeting either resistive loading (proportionally increasing the pressure required to generate a given flow) or threshold loading (increasing minimum inspiratory pressure required for flow to be initiated). Pooled effects of these strategies have shown improvements in MIP by approximately 6 cm H_2O when compared with control subjects (8), roughly half the improvement seen with phrenic nerve stimulation in the present trial (12 cm H_2O). We must not forget, however, that the most common and simplest form of IMT occurs in the form of titration of ventilator settings, including reducing ventilatory support, or in performing spontaneous breathing trials. Thus, the approach to titration of ventilatory support may be particularly important in the control arm (the only potential form of muscle load training these patients receive); unfortunately, in this trial, the interpretation of the results is obfuscated by the lack of information available about the ventilatory support provided in both groups during weaning once enrolled.

Respiratory drive is often increased in critical illness but may be suppressed by factors such as sedative and opioid administration as well as alkalemia (including overventilation), hyperoxemia, and brainstem pathologies (9). Neuromechanical uncoupling, in which an increase in respiratory drive does not translate to an increase in contractile force, can be seen with diaphragm weakness and would not be expected to be overcome by nerve electrostimulation techniques in patients whose respiratory drive is already elevated. The population selected for this trial was mostly alert and calm (Richmond Agitation–Sedation Scale score, 0) and under minimal sedation, which may have contributed to a slower than anticipated recruitment rate. It is important to note that only 112 patients were randomized from 20 centers over 28 months of enrollment—clearly a very select population. Alert and cooperative patients may allow more reliable assessment of MIP, but excluding patients with lower drive may have reduced the magnitude of the observed effect. We might hypothesize that patients with low respiratory drive benefit more from TTDN, but this trial does not address this question.

With any treatment, dosing is important. Here, both the size and the number of stimulations should be considered. The chosen regimen of 120 stimulations per day divided over two or three sessions is similar to other IMT regimens. One may question exactly how feasible this technique was, because almost one-fourth of patients (14 of 57) randomized to the TTDN were unable to undergo the treatment (7 because of failure to place the catheter and 7 because of inability to achieve capture). Some of these treatment delivery issues might be addressed by subsequent device advancements, such as enabling positioning via the left internal jugular (in addition to the left subclavian vein) and augmented electrode coverage to improve chances of phrenic nerve capture (10). Once set up and functional, stimulations may be straightforward to deliver; however, training is required, and only 79% of the mITT population received >50% of the scheduled number of stimulations. Those who received a higher number of stimulations (>62.5% of target) had greater increases in MIP, which may suggest that the treatment effect could have been increased with greater protocol compliance or number of stimulations. A recent porcine model study showed that prolonged and continuous TTDN (alternate breaths over 2.5 d) prevented diaphragm atrophy (11). The ideal time to start, the best form in which to deliver, and the optimal duration to continue this therapy are still unknown.

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Another consideration in dosing this TTDN is the achieved physiological effect. Although this trial protocol used a standard predetermined target electrical output from the pacing device for all patients, the degree of phrenic nerve stimulation, and thereby the potential to increase force of diaphragm contraction, also depends on the relative stimulation threshold. This is impacted by the distance between the selected electrode and the nerve, in addition to the resistance posed by the tissues, both of which may vary significantly between individuals. Comparing and standardizing dosing is therefore difficult based on TTDN settings alone without assessment of the effect on individual patient mechanics.

In summary, diaphragm dysfunction is a common and clinically important problem in need of a solution. TTDN appears safe and largely feasible and has shown a physiological signal of benefit in this latest study. Despite this, there is further work to be done to establish the optimal treatment dosing, timing of initiation, and target population. We look forward to following further developments in this field. ■

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How Differential Are the Effects of Smoking Cannabis versus Tobacco on Lung Function?

Cannabis use has increased in recent years with the decriminalization of its production and medicinal or recreational use. Because of the similarity in smoke contents between cannabis and tobacco (1), there is a nagging concern that smoking cannabis might have deleterious effects on lung function, similar to the well-known consequences of tobacco smoking. However, the relatively sparse literature involving systematic examinations of the impact of cannabis use on lung function suggests little independent effect of cannabis on FEV_1 (2–9) and an actual increase in FVC and other measures of lung volume (7–9). These results are in contrast to the clearly detrimental effect of tobacco on FEV_1 with little or no effect on FVC in otherwise healthy

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