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Diaphragm Dysfunction as a Contributor to Breathlessness after COVID-19 Infection

There will be few readers of this journal who have not had some exposure to patients with coronavirus disease (COVID-19), although the acute pandemic has now been brought under control by vaccination and attenuation in virus severity. Nevertheless, because of the number of patients infected, there are now millions worldwide experiencing post-COVID symptoms. The post-COVID syndrome is a symptom complex that persists at least 3 months after the initial infection and comprises a wide range of symptoms, of which dyspnea is present in 30% of patients (1). In some cases, investigation will identify a cause for dyspnea, but in others, it remains unexplained, which prompts the question whether diaphragm weakness could be an explanation.

Regmi and colleagues were drawn to this hypothesis partly as a result of initial investigations in 10 patients, which they have already reported (2) and which are included again in the current study. However, other data also make this a plausible hypothesis, including the direct identification of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 4 of 26 patients in whom postmortem diaphragm biopsies were available and, more importantly, a specific pattern of fibrosis (and corresponding gene expression) compared with patients who succumbed to non–COVID-related acute lung injury (3). Of course, the phenomenon of ventilator-induced diaphragm dysfunction is not new (4), and disentangling this effect from a specific effect of COVID-19 is difficult. Supportive data include the observation of thinning of the diaphragm in patients with COVID-19 not ventilated for their illness (5); these patients, of course, should have exhibited increased work of breathing protecting them from diaphragm atrophy. Respiratory muscle weakness can also occur as a result of nerve dysfunction, and phrenic nerve mononeuritis has been reported as a complication of COVID-19 (6). Interestingly, in the original description of neuralgic amyotrophy by Parsonage and

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Turner (7), published before the advent of clinical virology, the cause was attributed to a mild fever, which was probably viral, in 11 of 136 patients.

Investigating diaphragm dysfunction is difficult, and an important strength of the study by Regmi and colleagues in this issue of the *Journal* (pp. 1012–1021) is that the investigators, who are one of the most experienced groups in this field globally, used state-of-the-art techniques (8). Essentially, most commonly used measurements, for example, mouth or nasal pressures, rely on the patient making a maximal voluntary effort, which is difficult even in highly motivated individuals. The alternative is to use a nerve stimulation technique in which the measured variable is independent of patient effort (9). In the present study, Regmi and colleagues magnetically stimulated the phrenic nerves bilaterally, placing the stimulator coil over the cervical spine at the point where the cervical nerve roots forming the phrenic nerves exit. Measurements were made at end-expiratory lung volume (FRC), which the investigators were able to confirm by inspection of the esophageal pressure trace measured directly from an esophageal balloon, and appropriate care was taken to minimize the effects of prior contractile activity (termed potentiation). They also used the technique of twitch interpolation to assess the degree to which patients could activate their diaphragm. The principle here is that a stimulus is delivered while the patient makes what they regard as a maximal effort. If it is a truly maximal effort, no additional effect of phrenic nerve stimulation is observed, whereas if, say, 75% of the nerve fibers are activated, the twitch produced by phrenic nerve stimulation is reduced by 75%. A similar approach was used to assess expiratory muscle strength by placing the stimulator coil at the 10th thoracic intervertebral space.

Regmi and colleagues studied a group of COVID survivors for a mean of 15 months after their illness who had required ventilation and a second group who had been admitted to the hospital but had required oxygen therapy alone. The control group was age-matched control subjects without illness studied prepandemic; the paper would have been strengthened, of course, had they also studied patients with mild or asymptomatic disease and also if they had studied patients with acute lung injury due to non-COVID causes. They found that both groups of patients had reduced diaphragm strength (measured as twitch transdiaphragmatic pressure), expiratory muscle strength (measured as Twitch T10 gastric pressure [Tw T10 Pga]), and contractility (measured as diaphragm thickening ratio), but the weakness was not different between the ventilated group and those who required oxygen alone. This latter observation argues to some extent in favor of a virus-specific, as opposed to a disease severity–specific, etiology. In addition, when the entire patient group was stratified by breathlessness severity measured using the Medical Research Council (MRC) dyspnea scale, those with severe dyspnea had the most profound diaphragm weakness; data from the twitch interpolation part of the study suggest that this is due to a primary problem of peripheral nerve and/or muscle rather than a central activation problem.

So where does this leave the clinician? Older readers will recall Campbell and Howell's aphorism that "a respiratory physiologist offering a unitary explanation for breathlessness should arouse the same suspicions as a tattooed archbishop offering a free ticket to heaven" (10), and even the authors' own data show (Figure 3 in Reference 8) that some of the patients experiencing severe dyspnea have normal diaphragm strength. Nevertheless, this study adds to an emerging body of evidence that phrenic nerve and/or diaphragm dysfunction is a contributor in some patients. This is helpful because although there is no proven way of restoring diaphragm or phrenic nerve function, the experience from neuralgic amyotrophy is that function usually returns over a 2- to 5-year time frame (11), which patients and their physicians may find reassuring. Moreover, this observation provides both a rationale and pilot data for designing and conducting trials of inspiratory muscle training in patients with post-COVID syndrome. ■

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