Dyspnoea in COVID-19 recovery beyond the intensive care unit: the potential impact of inspiratory muscle weakness

Bernie Bissett

Faculty of Health, University of Canberra, and University of Canberra Hospital, Canberra, Australia.

Corresponding author: Bernie Bissett (bernie.bissett@canberra.edu.au)

Shareable abstract (@ERSpublications)
Emerging evidence confirms that dyspnoea and inspiratory muscle weakness persist for up to 6 months following mechanical ventilation with #COVID19 pneumonia. Screening for inspiratory muscle weakness should be prioritised, as it may be treatable. https://bit.ly/3CBQXO2

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It is now well-recognised that dyspnoea is a common feature of prolonged recovery from coronavirus disease 2019 (COVID-19). In their living systematic review, capturing the experiences of >10 000 people with "long COVID", Michelen *et al.* [1] report breathlessness in 25% of respondents, rendering it the fifth most common symptom. However, the impact of breathlessness on the disability associated with long COVID is less well understood. A recent study by Hodgson *et al.* [2] revealed that at 6 months following intensive care unit (ICU) discharge, 39% of survivors who had been critically ill with COVID-19 had new-onset disability and 11% could not return to work. The potential contribution of breathlessness to this disability deserves to be more deeply explored, not least because it could be treatable.

Our understanding of dyspnoea in ICU patients has progressed substantially in recent years. In a study of 612 ventilator-dependent patients [3], 34% experienced dyspnoea while in ICU. Even more concerning, at 3 months following ICU discharge, a higher proportion of post-traumatic stress disorder was found in those who had reported dyspnoea in ICU compared to those who had not (29% *versus* 13%). In another study of recently weaned ICU patients who had been ventilator-dependent for ⩾7 days [4], 40% of patients reported dyspnoea at rest and this dyspnoea was strongly correlated with dyspnoea during exercise (r=0.78). Thus, patients who successfully wean from mechanical ventilation have considerable challenges in their recovery, with dyspnoea likely to adversely affect activities of daily life and exercise tolerance. This is true even without the additional complication of COVID-19 pathology.

While dyspnoea is complex and multifactorial [5], inspiratory muscle weakness is one likely contributing factor in patients who have experienced invasive mechanical ventilation. Inspiratory muscle atrophy occurs rapidly in ventilator-dependent patients [6] and reduced inspiratory muscle strength (maximum inspiratory pressure (MIP) <30 cmH_2O) is associated with 1-year mortality [7]. Even following successful ventilator weaning, those who have experienced invasive mechanical ventilation for >7 days typically have residual respiratory muscle weakness (mean MIP 34% predicted values) [4]. It seems reasonable to suspect that this inspiratory muscle weakness could contribute to the sensation of dyspnoea, as atrophied inspiratory muscles struggle to match the work required for spontaneous breathing and daily tasks, let alone additional exercise. Further corroboration of this theory exists in the emerging evidence that targeted high-intensity inspiratory muscle training can improve quality of life [8, 9] and reduce dyspnoea [9] in ICU patients. However, these studies have only measured the impact of inspiratory muscle training for up to 2 weeks following ventilator weaning. Very little is known about the recovery trajectory for inspiratory muscle weakness and dyspnoea beyond the hospital admission for these patients.

The pressure of COVID-19 pneumonia has challenged our health services and taken an enormous toll on millions of people worldwide, but this pandemic has also offered an opportunity to study the evolution of

inspiratory muscle weakness over time in a group of relatively homogeneous ICU survivors. In this issue of *ERJ Open Research*, the longitudinal cohort study by Núñez-Seisdedos *et al.* [10] has achieved precisely this: the authors have comprehensively described the recovery trajectory of 50 survivors of COVID-19 pneumonia up to 6 months following ICU discharge with a specific focus on inspiratory muscle strength and patient-centred outcomes, including dyspnoea and quality of life. The participants in this study appear typical of those mechanically ventilated with COVID-19 [2] (mean age 61 years, mean body mass index 28 $kg \cdot m^{-2}$, median duration of mechanical ventilation 11 days), with 14% having underlying airway disease (COPD or asthma).

In mapping the evolution of inspiratory muscle weakness, this research team included both voluntary measures of strength (MIP) and diaphragmatic ultrasound. Perhaps not surprisingly, they found that both dyspnoea and inspiratory muscle weakness persisted at both 3 and 6 months, with a gradual but incomplete recovery between these two time-points across the cohort. At 3 months, MIP scores remained impaired in 48% and by 6 months, 24% still had MIP scores below predicted values. Notably, none of these participants had evidence of diaphragm dysfunction on ultrasound. There was also no significant correlation between duration of mechanical ventilation and MIP score, suggesting that duration of ventilation may not be a good predictor of those vulnerable to residual inspiratory muscle weakness beyond the ICU.

Meanwhile, dyspnoea (modified Medical Research Council score) was reported by 88% of participants at 3 months and this improved to 76% at 6 months. A deeper analysis revealed that moderate-to-severe dyspnoea reduced from 42% (3 months) to 22% (6 months); however, mild dyspnoea was still reported in 54% of participants at 6 months. It is of note that there was a moderate negative correlation between MIP scores and dyspnoea at both 3 and 6 months ($r = -0.37$), but a strong correlation between MIP and exercise tolerance (6-min walk distance) at both time points ($r=0.65$ and $r=0.62$, respectively). Thus, while not explaining all of the relationships, these results may provide sufficient justification for the use of MIP measurement as a screening tool in such a cohort to identify those at risk of problems with dyspnoea or exercise tolerance following COVID-19 pneumonia.

The results of this single-centre, observational study could potentially underestimate residual issues with dyspnoea and inspiratory muscle weakness in patients mechanically ventilated with COVID-19, as those still undergoing inpatient care or rehabilitation were excluded from the analysis. Moreover, the participants in this study experienced rates of physiotherapy follow-up that would be the envy of many countries in the world, with 34% discharged home with physiotherapy follow-up and 26% benefiting from inpatient rehabilitation. Nonetheless, even with favourable rates of physiotherapy follow-up, it is clear that a significant proportion of survivors of COVID-19 are likely to struggle with inspiratory muscle weakness, dyspnoea and impaired exercise tolerance up to 6 months following their discharge from ICU. These findings align with the levels of disability reported by others at 6 months following ICU discharge [2].

Despite the gloomy picture of these statistics, there is hope that some of these outcomes are modifiable. We already have evidence that high-intensity inspiratory muscle training can reduce dyspnoea in other populations, including those with chronic lung disease [11] and heart failure [12]. In people with COVID-19, one small pilot study [13] used matched controls to study the effect of 2 weeks of daily, high-intensity inspiratory muscle training in 42 people recently weaned from mechanical ventilation. Following 2 weeks of training (two sessions daily at 50% of MIP), those undergoing inspiratory muscle training had significantly lower dyspnoea scores (Dyspnea Severity Index) and higher quality of life scores (EQ-5D) than the control group. This also translated into significantly larger increases in 6-min walk distance relative to the case-matched controls. While lacking randomisation and using a very limited sample size, this study should encourage us to explore the potential benefits of inspiratory muscle training early in the post-weaning period, as it could accelerate dyspnoea recovery.

There may be even more promising news for recovery of inspiratory muscle strength and reduction in dyspnoea for people with long COVID. A randomised trial [14] of 281 people (mean 9 months following acute COVID-19 infection) found that 8 weeks of high-intensity inspiratory muscle training (three sessions per week at 80% of MIP) significantly improved inspiratory muscle strength (MIP), reduced dyspnoea (transitional dyspnoea index) and reduced sedentary time compared to the control group. It would appear that with sufficiently high training stimulus, recovery can be enhanced by inspiratory muscle training, even many months beyond the initial COVID-19 infection.

The results of the cohort study presented by Núñez-Seisdedos *et al.* [10] are the most comprehensive analysis we have to date of the likely challenges our patients face in recovering inspiratory muscle strength

up to 6 months following ICU discharge. As dyspnoea appears somewhat correlated with inspiratory muscle weakness and this weakness is modifiable, these results should be a call to action to clinicians around the world caring for survivors of COVID-19. At the very least, based on the findings of this study, screening of MIP should be standard practice at 3 and 6 months after ICU discharge for survivors of COVID-19 complaining of dyspnoea, and emerging evidence steers us towards exploring the value of inspiratory muscle training in accelerating recovery.

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