



Editorial

# Ventilator-induced Diaphragmatic Dysfunction in Patients with Traumatic Brain Injury

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Moderate to severe traumatic brain injury (TBI) represents one of the most important causes of death and disability. Although morbidity and mortality in these patients are principally due to their primary pathology, non-neurological complications, including respiratory dysfunction, are frequent contributors. Therefore, all TBI patients with moderate and severe brain damage are managed with invasive mechanical ventilation. Notwithstanding the fact that mechanical ventilation to support respiration is a life-saving intervention in critically ill patients, weaning becomes progressively more difficult with the increasing duration of ventilation. Ventilator-induced diaphragmatic dysfunction (VIDD) is believed to be one of the major contributors to the weaning difficulties in intensive care unit (ICU) patients. It significantly influences the duration of mechanical ventilation, weaning failure, morbidity, and mortality. The combination of prolonged mechanical ventilation and the effects of extended immobility in the ICU causes significant changes to muscle fibers, reducing both respiratory and peripheral muscle strength.<sup>1</sup> Administration of muscle relaxants and/or steroids in mechanically ventilated patients further exaggerates the VIDD. The prevalence of diaphragm dysfunction has been reported to be twofold higher than the prevalence of ICU-acquired weakness.<sup>2</sup> Although VIDD has received considerable attention in critically ill patients in general ICU, it has not attracted sufficient diligence in the moderate to severe TBI patient population despite their requirement for prolonged mechanical ventilation.<sup>3</sup>

The diaphragm thickness decreases rapidly during the initial several days of mechanical ventilation in 40% of patients, and lower levels of inspiratory effort and higher levels of ventilatory support predict this decrease. Diaphragmatic thickness has been shown to reduce by 6 to 7.5% per day in mechanically ventilated patients.<sup>4</sup> The diaphragm thickness negatively correlates with the ICU length of stay and positively correlates with the before/after rehabilitation functional scores and the change in functional independence measure scores.<sup>5</sup> Diaphragmatic weakness and dysfunction decrease

inspiratory pressure, resulting in difficult weaning.<sup>6</sup> Patients with VIDD are significantly more likely to experience new-onset sepsis and ventilator-associated pneumonia, are more likely to have extubation failure, and require a more prolonged duration of mechanical ventilation.<sup>7</sup> Ultrasound imaging of the diaphragm is a reliable and reproducible tool for diagnosing neuromuscular diaphragm dysfunction.

Several studies have demonstrated that maintaining spontaneous respiration during mechanical ventilation can reduce VIDD. Under forced breathing, the increased inspiratory effort minimizes the incidence of diaphragmatic dysfunction to 11.5%, emphasizing that prolonged mechanical ventilation impairs diaphragmatic function independent of underlying lung disease.<sup>8</sup>

In brain-dead organ donors, a combination of 18 to 69 hours of complete diaphragm inactivity and mechanical ventilation resulted in marked atrophy of myofibers, which is consistent with increased diaphragmatic proteolysis. The diaphragm biopsy of these brain-dead donors showed marked atrophy of both slow- and fast-twitch fibers.<sup>9</sup> Increased activity of the ubiquitin-proteasome pathway, marked decreases in myosin heavy chains (MyHCs), and atrophic AKT-FOXO signaling play important roles in eliciting the myofiber atrophy and decreases in diaphragm force generation associated with prolonged human diaphragm disuse.<sup>10</sup> Mechanical ventilation also increases oxidative stress in the diaphragm, causing decreased protein synthesis and increased activity of proteolytic pathways, further accelerating the atrophy process.<sup>11</sup> Other comorbidities and metabolic stressors could negatively affect patients with VIDD as well.<sup>12</sup>

There is a need for alternative therapeutic strategies for preventing VIDD, including antioxidants and inotropic agents such as theophylline, digoxin, levosimendan, angiotensin receptor blockers, and phrenic nerve pacing.<sup>13,14</sup> Amino acid intake during the first 24 hours of stay in the ICU may represent a significant, modifiable risk factor for VIDD; it may have a direct causal effect on mortality.<sup>7</sup>

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In this issue of the journal, Das et al<sup>15</sup> have published their observations on diaphragmatic function (VIDD and diaphragmatic thickness) in mechanically ventilated adult patients with moderate to severe TBI. While the study deserves appreciation, it has raised some pertinent issues. Contrary to the available literature on VIDD in general ICUs, the authors could not establish any significant correlation between VIDD and length of hospital stay. Is it due to the underlying pathology (TBI vs. non-TBI) having a role in the variable progression of VIDD and, thereby, length of hospital stay? The lack of a control group comprising TBI patients not subjected to mechanical ventilation or patients undergoing mechanical ventilation for reasons other than TBI limits the ability to isolate the specific contribution of mechanical ventilation to observed diaphragmatic changes. A relatively modest sample size of 40 patients, while providing initial insights, may lack statistical robustness. The study focuses on the initial week of ICU admission without extending the observation period to capture the peak of VIDD, which literature suggests occurs between the first and second weeks of mechanical ventilation. A more extended follow-up period would provide a more comprehensive understanding of the temporal progression of diaphragmatic dysfunction. Enrolling a larger sample size of moderate to severe TBI patients is essential to addressing this issue. Another area of research could be on automatic and spontaneous breathing-synchronized phrenic nerve stimulation (invasive and noninvasive) in combination with invasive or noninvasive ventilatory support forms.<sup>16</sup> Future studies should also focus on nutrition and various modes of invasive mechanical ventilation vis-a-vis their impact on VIDD. It should also be studied whether gender has dissimilar courses of VIDD, given their distinct hormonal profiles.

#### Conflict of Interest

None declared.

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