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SPECIAL ISSUE INSIGHT

Phrenic nerve stimulation to protect the diaphragm, lung, and brain during mechanical ventilation

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Phrenic nerve stimulation (PNS) to elicit diaphragm contraction was first described over 200 years ago in the management of a case of neonatal asphyxia [1]. Since then the technique has developed significantly with established therapeutic indications for patients with high cervical cord injury or central sleep apnoea syndromes. Temporary PNS may offer potential physiological benefits for multiple organ systems and may prevent or treat diaphragm weakness in critically ill patients (Fig. 1). PNS can be delivered by multiple routes including direct surgical implantation of electrodes[2], or via transvenous[3], percutaneous[4] or transcutaneous[5] routes.

Diaphragm function

Ventilator-induced diaphragm dysfunction (VIDD) is common in intensive care patients and is independently associated with weaning failure and mortality [6]. Disuse atrophy is one of the major contributors to VIDD and temporary PNS may mitigate diaphragm atrophy and weakness or be used to promote diaphragm rehabilitation and recovery in this context. Experimental studies over the last decade have shown that intermittent stimulation of the phrenic nerves can mitigate the rate of diaphragm atrophy [7] and prevent diaphragm weakness [8]. In one pre-clinical study, continuous PNS, titrated to reduce ventilator pressure-time product by 20–30%, prevented diaphragm atrophy during 60 h of mechanical ventilation when compared to ventilated non-stimulated controls [9].

In patients, Ahn et al. presented a series of 4 patients undergoing open cardiothoracic surgery, where intermittent unilateral PNS applied intraoperatively by means of an external cardiac pacemaker prevented diaphragm weakness [2]. Compared to the muscle fibres obtained from the non-stimulated hemidiaphragm, fibres from the stimulated hemidiaphragm exhibited a 30% increase in specific force. In a separate study, PNS was shown to ameliorate mitochondrial dysfunction (a key mediator of VIDD) compared to non-stimulated controls [10]. In the intensive care unit, the recently published RESCUE 2 multi-centre open-label randomized clinical trial ($n=112$) focused on patients that had established difficulty in weaning from mechanical ventilation and applied PNS using a transvenous technique by 4–6 sets of 10 stimulations, delivered 2–3 times per day (for a maximum of 120 stimulations per day) in the intervention arm [3]. PNS increased maximal inspiratory pressure compared to standard care (by 17 cmH_2O vs 5 cmH_2O, respectively, $p=0.001$), suggesting that the technique can meaningfully enhance diaphragm function. A larger clinical trial, RESCUE3 (clinicaltrials.gov NCT03783884) is currently underway to establish whether PNS can improve patient-centred outcomes in difficult-to-wean patients. The feasibility and efficacy of continuous on-demand PNS to prevent diaphragm atrophy and dysfunction have not yet been evaluated in humans [9].

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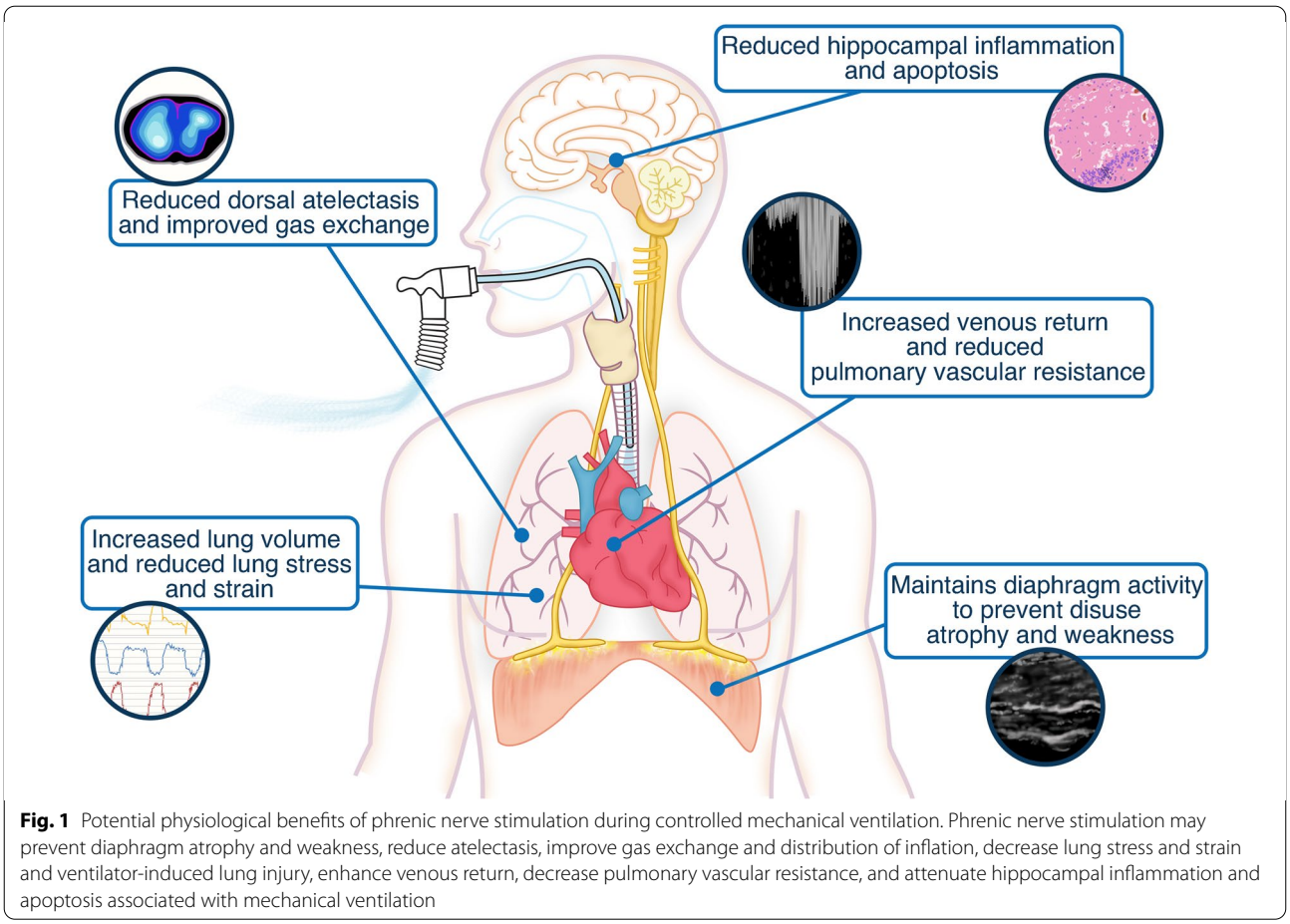

Fig. 1 Potential physiological benefits of phrenic nerve stimulation during controlled mechanical ventilation. Phrenic nerve stimulation may prevent diaphragm atrophy and weakness, reduce atelectasis, improve gas exchange and distribution of inflation, decrease lung stress and strain and ventilator-induced lung injury, enhance venous return, decrease pulmonary vascular resistance, and attenuate hippocampal inflammation and apoptosis associated with mechanical ventilation

Respiratory mechanics

Positive pressure ventilation results in a non-physiological distribution of tidal ventilation with a predilection for non-dependent lung regions. In the absence of diaphragmatic contractions, posterior lung regions become atelectatic and anterior lung regions are relatively overdistended. In the 1990s, Hedenstierna and colleagues studied the effects of percutaneous right-sided PNS in 12 patients under general anesthesia [4]. They found that isovolumetric PNS (stimulus delivered at end-expiration with an occluded endotracheal tube) reduced the atelectatic area on serial computed tomography (CT) imaging. When the airway was open, tidal ventilation by positive pressure ventilation combined with PNS reduced the atelectatic area in comparison to positive pressure ventilation alone. More recently Rohrs et al. [11] varied the stimulation duty cycle and demonstrated a dose-dependent increase in dorsal ventilation from PNS with improved alveolar homogeneity, reduced atelectasis, and improved oxygenation. Taken together, these observations suggest that by preventing atelectasis, PNS might reduce lung stress and strain during mechanical ventilation and ameliorate ventilator-induced lung injury.

Cardiovascular function

PNS increases venous return and attenuates the reduction in cardiac output associated with positive pressure ventilation in preload-dependent conditions [12]. PNS-mediated effects on lung function might in theory improve pulmonary vascular resistance and protect against right ventricular dysfunction, though this remains to be studied.

Neurological function

Even with judicious sedative use and fastidious lung-protective ventilation, mechanical ventilation may independently lead to hippocampal inflammation, apoptosis, and impaired cognitive function [13]. Proposed mechanisms have included inflammatory (systemic) and neural (pulmonary vagal afferent signalling) pathways. In a recent porcine model submitted to 50 h of sedation with lung-protective ventilation and variations in stimulation duty cycle (nil, alternate breaths, every breath), PNS was associated with a dose-dependent reduction in hippocampal apoptosis and inflammation [14]. Lung histology and systemic inflammatory biomarkers were similar across groups, suggesting

that the effect of PNS on brain injury during mechanical ventilation may be mediated by mechanisms other than lung injury or systemic inflammation. The precise mechanism and clinical significance of this observed effect, however, remains unclear.

Risks, limitations, and uncertainties

Despite the potential multisystem benefits of PNS, there are still many unknowns. First, the patient population that is most likely to benefit from PNS has not yet been established. Second, the optimal dosing (output and duty cycle) of stimulation is uncertain. Stimulation output should target sufficient levels of diaphragmatic force generation to prevent disuse atrophy while avoiding excessively forceful contractions that might cause diaphragm myotrauma or lung injury. Third, it is likely important to ensure that stimulation is synchronized to the patient and the ventilator. Muscle stimulation during the expiratory phase could cause eccentric diaphragm loading and injury and breath-stacking dyssynchrony. Fourth, there may be conditions where PNS and diaphragmatic contractions are harmful rather than beneficial: PNS could contribute to diaphragm injury in the case of established diaphragmatic fatigue and injury or systemic inflammation leading to sarcolemmal hyperfragility [15]. Also, by increasing diaphragmatic oxygen consumption and generating negative pleural pressure swings, PNS might exacerbate cardiovascular shock or acute systolic heart failure. Furthermore it may be necessary to defer PNS in patients with severe hypoxemia requiring neuromuscular blockade.

Temporary PNS in mechanically ventilated patients offers a promising approach to mitigating the harmful effects of mechanical ventilation on the diaphragm, lung, cardiovascular system, and brain. Future research will focus on establishing the feasibility and physiological efficacy of various PNS techniques in critically ill patients and clarifying the patient populations who may benefit, the optimal parameters to target for dosing, the ideal timing of initiation, and ultimately the impact on patient-centred outcomes.

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Declarations

Conflict of interest
MD and ECG are members of the Lungpacer Clinical Advisory Board. MD received honorarium from Lungpacer Inc. MD has signed research contracts with Bioserenity SA and Lungpacer Inc.

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