Efficacy of Phrenic Nerve Stimulation in Improving Diaphragm Contraction in Ventilator-Induced Diaphragm Dysfunction

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Abstract:

➢ ***Background and Need:***
Mechanical ventilator (MV) is a life-saving technology that assist or restores breathing. Prolonged mechanical ventilator has its own side effects, like promoting ventilator induced diaphragm dysfunction, diaphragmatic atrophy and even weaning difficulty. Stimulation of the phrenic nerve can play an important role in diaphragm contraction which can have a potential to prevent and treat diaphragm atrophy. This article aims to give an overview of phrenic nerve stimulation to improve diaphragm contraction in ventilator induced diaphragm dysfunction.

➢ ***Methods:***
788 articles were retrieved from databases viz. PubMed, Science Direct and Google Scholar. Considering the inclusion and exclusion criteria, five studies were found eligible for this review that consisted of interventional and cohort studies.

➢ ***Results:***
Two randomised controlled trials found significant improvement in diaphragm contraction that led to the weaning of the patient from the ventilator. Alternately, one clinical study two nonrandomised trials and one prospective cohort study showed lower the twitch pressure and thickness fraction can lead to failure.

➢ ***Conclusion:***
Phrenic nerve stimulation can be a promising avenue for the treatment of ventilator induced diaphragm dysfunction and diaphragm atrophy by improving the diaphragm contraction, which causes liberation from the mechanical ventilator.

Keywords: *Muscle Atrophy, Muscle Paresis, Lung Injuries, Ventilator Induced, VIDD, Ventilator-Induced Lung Injury.*

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I. INTRODUCTION

Mechanical ventilation (MV) is a critical life-support intervention widely used in intensive care units (ICUs). Despite its life-saving benefits, prolonged MV is associated with several adverse outcomes, including ventilatorassociated pneumonia, lung injury, increased healthcare costs, and the development of ventilator-induced diaphragm dysfunction (VIDD). Studies have reported that VIDD can occur in nearly 50–53% of mechanically ventilated patients within the first 24 hours of intubation, while an additional proportion may develop the condition during their ICU stay. Furthermore, the use of endotracheal intubation and MV has significantly increased over recent years, highlighting the growing clinical importance of complications related to prolonged ventilatory support. [1–6,12,13]

Ventilator-induced diaphragm dysfunction refers to a reduction in the diaphragm's force-generating capacity that specifically occurs due to prolonged mechanical ventilation, diaphragm inactivity, and muscle unloading. Controlled mechanical ventilation (CMV), particularly when prolonged, can lead to diaphragmatic fiber atrophy, inspiratory muscle weakness, and impaired contractile function. Human studies have demonstrated that complete diaphragm inactivity during invasive MV rapidly produces profound diaphragmatic weakness. Histological evidence has shown atrophy of both slow-twitch and fast-twitch diaphragm muscle fibers, accompanied by oxidative stress and proteolysis. [1,2,4–6]

Diaphragmatic dysfunction is a broad term encompassing diaphragmatic eventration, weakness, and paralysis. Eventration refers to permanent elevation of part or all of the hemidiaphragm due to thinning, while diaphragmatic weakness indicates partial loss of the muscle's ability to generate sufficient ventilatory pressure. Paralysis represents a complete loss of diaphragmatic function. Depending on the underlying etiology, diaphragmatic dysfunction may be unilateral or bilateral, temporary or permanent.[1–3,5–7] VIDD has been associated with prolonged ventilator dependence, difficulty in weaning, higher rates of nosocomial pneumonia, and increased in-hospital mortality.[1–5] Phrenic nerve stimulation (PNS), also known as phrenic pacing, has emerged as a promising minimally invasive intervention for preventing or reducing diaphragmatic dysfunction in mechanically ventilated patients. Traditionally, phrenic pacing has been used to provide ventilatory support in patients with bilateral diaphragmatic paralysis and intact phrenic nerves, particularly in individuals with high cervical spinal cord injuries or central hypoventilation syndromes.[3,6,14,16] More recently, advances in laparoscopic motor point mapping and intramuscular diaphragmatic stimulation techniques have demonstrated encouraging outcomes in reducing diaphragm atrophy and improving respiratory muscle strength in critically ill patients.[4–6]

Compared to conventional interventions, phrenic nerve stimulation may offer a feasible and effective therapeutic strategy for preserving diaphragmatic function in patients receiving prolonged mechanical ventilation. Therefore, this review aims to comprehensively evaluate the role of phrenic nerve stimulation in the management and prevention of ventilator-induced diaphragm dysfunction among mechanically ventilated patients.

II. METHODOLOGY

➤ *Search Strategy*

Databases used for this review were PubMed, Science Direct and Google Scholar. The following keywords were used: "muscle atrophy", "muscle paresis", "Lung Injuries", "ventilator induced", "VIDD", "ventilator-induced lung injury", "phrenic nerve stimulation", "PNS"

➤ *Study Selection*

Studies were considered for inclusion if they met the following criteria: (a) articles in English language (b) articles that include phrenic nerve stimulation and/or focused on phrenic nerve stimulation (c) articles published from 2014-2024 and (d) studies done on human subjects. Studies were considered for exclusion if they met the following criteria: (a) articles whose full text was not available (b) articles published before 2014 (c) articles that used phrenic nerve stimulation for conditions other than diaphragm contraction.

➤ *Examined Variables*

The variables examined in the study were: (a) Diaphragm contraction, (b) Diaphragm thickness, (c) Diaphragm excursion/mobility, (d) Inspiratory muscle strength, (e) Weaning outcome from mechanical ventilation, (f) Duration of ventilator support and (g) Respiratory parameters.

➤ *Search of Literature*

The literature search through the database showed 788 articles, out of which 468 duplicates were ruled out. After initial screening, 299 were excluded and 21 papers remained for abstract review. A total of 16 articles that did not meet the remaining inclusion criteria were excluded, after which only 5 studies that met all the inclusion criteria were considered for further review. (Figure 1).

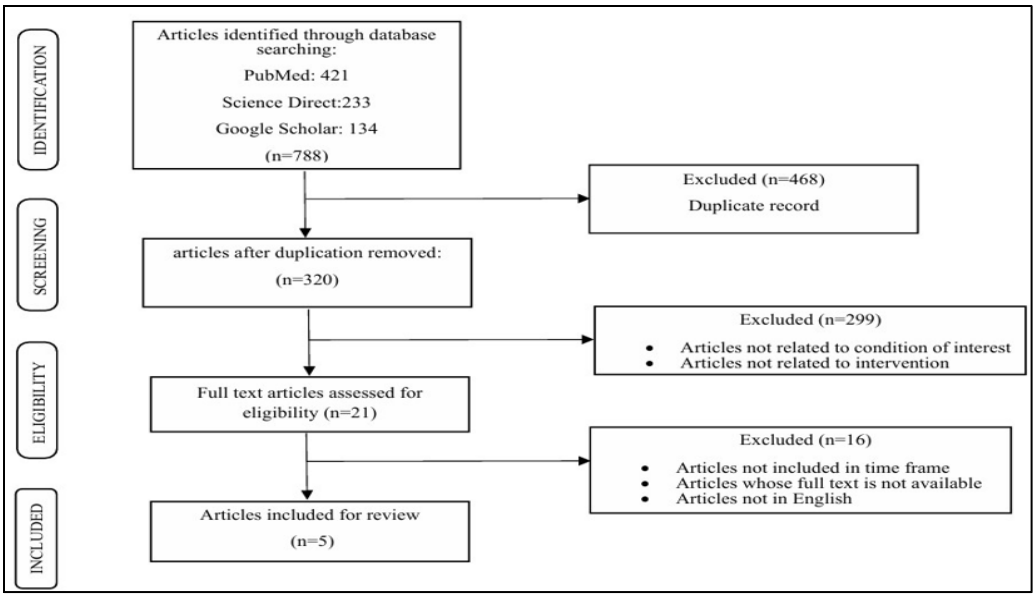

Fig 1 The Prisma Flow Diagram, Illustrating Each Step in the Process to Identify the Final Selection of Studies to be Reviewed.

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III. RESULTS

➢ *Sample*

The study samples consisted of adults who were on ventilator support.

➢ *Methodological Quality of Trials*

In accordance with the selection and rejection criteria, only 5 studies were finally accepted for the present study (Figure 1). Since the study done by Dres et al.[14] and Soták et al.[2] adopted the design of a randomised controlled trial (Level 2), the PEDro scale was used to assess the quality of these trials, which was 7/10 and 7/10 respectively. The studies conducted by Keogh Conor et al.[12] and Ataya et al.[13] were a non-randomised clinical trial whereas the study by Dres et al.[4] adopted the design of a prospective cohort study (Level 3).

➢ *Interventions*

The intensity and type of PNS differed in the studies. Keogh Conor et al.[12]. demonstrated pulsed current was applied with a pulse duration ranging from 10 µs to 400 µs, an amplitude of 1 mA to 150 mA, and frequencies between 1 Hz and 30 Hz, with the stimulation continued until maximal diaphragmatic response was elicited. Dres et al.[14] demonstrated diaphragm neurostimulation was delivered using a multielectrode stimulating central venous catheter for bilateral phrenic nerve stimulation, consisting of either 4 sets of 10 stimulations or 6 sets of 10 stimulations, administered 2–3 times daily for a total of 120 stimulations per day. All interventions were given for an average of 2 to 3 times a day (Table 1).

Table 1 Brief Description of Included Studies

No	Author & Year	Sample size	Intervention/Device	Duration, Frequency, Intensity of Intervention	Dependent variables	Evaluation/ reassessment	Results
1	Keogh Conor et al.[12] (2022)	N=10 (5 males, 5 females)	custom stimulation that delivered a constant monophasic current	Pulsed current- 10 µs to 400 µs Amplitude -1mA to 150mA Frequencies - 1Hz to 30Hz Duration-until diaphragm elicited maximal response	Diaphragm contraction and function	Post intervention	Intervention showed significant diaphragm contraction improving ventilation outcomes.
2	Dres et al.[14] (2022)	N=127 Group A = 57 (intervention) Modified Group A = 43 Group B = 55 (controlled)	diaphragm neurostimulation using a multielectrode stimulating central venous catheter (bilateral phrenic stimulation)	4 set * 10 stimulations Or 6 sets * 10 stimulations 2-3 times a day of 120 stimulations	Diaphragm thickness Successful weaning	After 30 days on being on the mechanical ventilator	Group A Showed increased the maximal inspiratory pressure, resulting in the reversal of the diaphragm dysfunction than group B
3	Soták et al.[2] (2021)	N=22 Group A = 12 (intervention) Group B = 10 (controlled)	Percutaneous Electrical Phrenic Nerve Stimulation (PEPNS) system	Six times of 2 hours of electrical stimulation during patients' inspiration to keep the work of breathing within 0.2–2 joules/L over 48 hours	Diaphragm thickness	Before treatment and after treatment that was 48 hours Post treatment after been extubated Post intervention after treatment	Group A showed statistically significant improvement in diaphragm thickeness than Group B
4	Ataya et al.[13] (2020)	N=19	Phrenic Nerve Stimulator (PNS) with proximal and distal electrode	3 sessions of 4sets*10 diaphragmatic stimulations Every 3hours	Diaphragm strength		Intervention showed improvement in maximal inspiratory pressure and better

							diaphragmatic contraction.
5	Dres et al.[4] (2016)	N=48	Phrenic nerve stimulator	Maximum intensity till diaphragm showed contraction	Diaphragm thickness		Intervention showed lower the twitch pressure and thickness fraction can lead to the failure in spontaneous breath tests.
N: Sample Size; PNS: Phrenic nerve stimulator; PEPNS: Percutaneous Electrical Phrenic Nerve Stimulation							

IV. DISCUSSION

Ventilator-induced diaphragm dysfunction (VIDD) is a common complication observed in mechanically ventilated patients, characterized by diaphragmatic weakness, muscle atrophy, and reduced contractile function. Prolonged mechanical ventilation decreases normal diaphragmatic activity, leading to impaired respiratory muscle performance and difficulty in ventilator weaning. The present review aimed to evaluate the effectiveness of phrenic nerve stimulation (PNS) in improving diaphragm contraction in patients with VIDD.

A total of five studies were analysed in this review, including two randomized controlled trials, two clinical studies, and one prospective cohort study. Among these, four studies demonstrated positive outcomes following phrenic nerve stimulation, while one study reported limited or negative effects. Overall, the findings suggest that phrenic nerve stimulation may be an effective intervention for improving diaphragmatic function and facilitating ventilator weaning in critically ill patients.

One of the major outcome measures used across the included studies was standardized diaphragm ultrasound assessment. Ultrasound is considered a reliable and non-invasive method for evaluating diaphragm thickness, excursion, and contractility. Improvements in diaphragm thickness and contraction following phrenic nerve stimulation were consistently observed in most studies, indicating enhanced diaphragmatic muscle activity. Increased diaphragm thickness may reflect reduced muscle atrophy and improved muscle recruitment during respiration.

The study conducted by Conor Keogh highlighted that phrenic nerve stimulation improved diaphragm contraction and function, thereby contributing to better ventilatory outcomes. The study utilized diaphragm ultrasound to objectively assess changes in diaphragm thickness and contractility. The findings support the physiological basis of phrenic nerve stimulation, where electrical stimulation of the phrenic nerve activates diaphragmatic muscle fibers, producing contractions similar to spontaneous breathing activity. Repeated stimulation may help maintain diaphragmatic strength, prevent disuse atrophy, and improve respiratory muscle endurance in mechanically ventilated patients.

Furthermore, improved diaphragm contraction may contribute to successful ventilator liberation and reduced duration of mechanical ventilation. By enhancing respiratory muscle performance, phrenic nerve stimulation may reduce dependence on ventilatory support and improve overall patient outcomes. These findings are clinically important, as delayed weaning from mechanical ventilation is associated with increased ICU stay, higher healthcare costs, and greater morbidity.

However, one included study reported a negative or nonsignificant outcome, which may be attributed to differences in stimulation protocols, patient selection, severity of illness, duration of ventilation, or timing of intervention. Variability in sample size and methodology among the included studies may also influence the overall findings. Therefore, although the majority of evidence supports the beneficial role of phrenic nerve stimulation, further large-scale randomized controlled trials are necessary to establish standardized treatment protocols and determine long-term effectiveness. In conclusion, the findings of this review indicate that phrenic nerve stimulation has the potential to improve diaphragm contraction, preserve diaphragm thickness, and facilitate ventilator weaning in patients with ventilator-induced diaphragm dysfunction. The use of diaphragm ultrasound as an assessment tool further supports the objective evaluation of diaphragmatic improvements. Nevertheless, additional high-quality research is required to strengthen the evidence regarding its clinical application and effectiveness in critical care settings.

V. CONCLUSION

The effectiveness of phrenic nerve stimulation (PNS) in ventilator-induced diaphragm dysfunction (VIDD) for improving diaphragmatic contraction has been evaluated both subjectively and objectively across the studies included in this review. Various assessment methods, including standardized diaphragmatic ultrasound measurements, were utilized by the respective authors to determine treatment outcomes. Comparison of pre- and post-intervention findings demonstrated significant improvements in diaphragmatic contraction, muscle thickness, and overall diaphragm function.

Improved diaphragmatic performance was further reflected in enhanced patient outcomes, particularly through successful weaning from mechanical ventilation. These findings strongly support the role of phrenic nerve stimulation as an effective intervention for improving diaphragm contraction and functional recovery in patients with ventilator-induced diaphragm dysfunction.

➢ *Declaration of Conflicting Interests*

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