



SYSTEMATIC REVIEW

Outcomes in critically ill patients after diaphragmatic stimulation on ventilator-induced diaphragmatic dysfunction: a systematic review

Alessandro PANELLI¹, Julius J. GRUNOW¹, Michael A. VERFUß¹,
Hermann G. BARTELS¹, Zarina BRASS², Stefan J. SCHALLER^{1,3*}

¹Department of Anesthesiology and Intensive Care Medicine (CCM/CVK), Charité – Universitätsmedizin, Berlin, Germany; ²School of Medicine, University of Nottingham, Nottingham, UK; ³School of Medicine, Department of Anesthesiology and Intensive Care, Klinikum rechts der Isar Hospital, School of Medicine and Health, Technical University of Munich, Munich, Germany

*Corresponding author: Stefan J. Schaller, School of Medicine, Department of Anesthesiology and Intensive Care Medicine (CCM/CVK), Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany. E-mail: stefan.schaller@charite.de

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ABSTRACT

INTRODUCTION: Mechanical ventilation (MV) is a lifesaving procedure for critically ill patients. Diaphragm activation and stimulation may counteract side effects, such as ventilator-induced diaphragm dysfunction (VIDD). The effects of stimulation on diaphragm atrophy and patient outcomes are reported in this systematic review.

EVIDENCE ACQUISITION: Studies investigating diaphragmatic stimulation *versus* standard of care in critically ill patients and evaluating clinical outcomes were extracted from a Medline database last on January 23, 2023, after registration in Prospero (CRD42021259353). Selected studies included the investigation of diaphragmatic stimulation *versus* standard of care in critically ill patients, an evaluation of the clinical outcomes. These included muscle atrophy, VIDD, weaning failure, mortality, quality of life, ventilation time, diaphragmatic function, length of stay in the Intensive Care Unit (ICU), and length of hospital stay. All articles were independently evaluated by two reviewers according to their abstract and title and, secondly, a full texts evaluation by two independent reviewers was performed. To resolve diverging evaluations, a third reviewer was consulted to reach a final decision. Data were extracted by the reviewers following the Oxford 2011 levels of evidence guidelines and summarized accordingly.

EVIDENCE SYNTHESIS: Seven studies were extracted and descriptively synthesized, since a meta-analysis was not feasible. Patients undergoing diaphragm stimulation had moderate evidence of higher maximal inspiratory pressure (MIP), less atrophy, less mitochondrial respiratory dysfunction, less oxidative stress, less molecular atrophy, shorter MV time, shorter ICU length of stay, longer survival, and better SF-36 scores than control.

CONCLUSIONS: Evidence of the molecular and histological benefits of diaphragmatic stimulation is limited. The results indicate positive clinical effects of diaphragm activation with a moderate level of evidence for MIP and a low level of evidence for other outcomes. Diaphragm activation could be a therapeutic solution to avoid diaphragm atrophy, accelerate weaning, shorten MV time, and counteract VIDD; however, better-powered studies are needed to increase the level of evidence.

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KEY WORDS: Critical care; Phrenic nerve; Respiration, artificial; Ventilators, mechanical.

Introduction

Mechanical ventilation (MV) is a life-saving intervention for critically ill patients while simultaneously carrying a significant burden regarding its side effects. One side effect is ICU acquired weakness (ICUAW) and ventilator-induced diaphragm dysfunction (VIDD), defined as a reduction in the diaphragm force-generating capacity;¹ the latter can overlap with ICUAW or be uncorrelated to it.² VIDD is a very prevalent condition present in mechanically ventilated patients; 80% of ICU patients develop one or more forms of neuromuscular dysfunction,³ one of which is the diaphragm weakness associated to critical illness.⁴ VIDD occurs early, within 18-69 hours of inactivity and mechanical ventilation³ and leads to weaning failure in more than 50% of patients with confirmed diaphragm dysfunction,³ prolonged stay in the Intensive Care Unit (ICU),⁵ and increased ICU mortality.⁴ The main clinical consequence of VIDD is a weaning failure from the ventilator;³ difficult weaning occurs in about 30% of patients mechanically ventilated for more than 3 days. Ventilator weaning failure results in extended hospital stays and increased patient morbidity and mortality.⁶

The pathophysiology of VIDD is multifaceted; the atrophy molecular pathway activated by higher oxidative stress was identified as the main pathophysiological mechanism leading to diaphragm muscle tissue disarrangement and diaphragm thickness reduction.⁷⁻⁹ The bioenergetic machinery is also compromised; Martin *et al.* compared the left and right hemidiaphragm, while one side was inactive, and the other was activated by electric stimulation.¹⁰ The inactive hemidiaphragm showed reduced mitochondrial biomass and intrinsic respiratory chain dysfunction within 48-72 hours after diaphragm paralysis during MV in humans.¹¹

VIDD diagnosis and quantification of diaphragm dysfunction have not been standardized. Diagnostic tools for VIDD include lung function testing ultrasound (US) diaphragm assessment to measure diaphragm thickness and thickening fraction according to the most recent ERC guidelines.¹² US imaging is an easily available diagnostic tool to assess two classes of parameters: 1) static parameters – the assessment of diaphragm thickness at the end of inspiration (Tdi insp) or expiration (Tdi exp);^{9, 13} and 2) dynamic parameters – the assessment of diaphragm thickness fraction ($\Delta Tdi\%$) and diaphragm excursion (DE).¹⁴

Currently, there is no therapeutic protocol for VIDD treatment. The aim of the present review was to determine the outcomes of diaphragm muscle stimulation in preventing VIDD and improving outcomes in critically ill patients.

Peripheral muscle stimulation prevents muscle atrophy in critically ill patients without evidence of improved muscle strength;¹⁵ similar evidence regarding diaphragm atrophy and its function has not been assessed. In parallel to peripheral muscles, we hypothesize that the muscle activation consequent to diaphragm stimulation could decelerate the progression of diaphragm atrophy.

The present report aimed to answer the following research questions systematically:

- Does diaphragmatic stimulation of the diaphragm prevent muscle atrophy (diaphragm thickness or reduction of thickness loss) or VIDD (clinical outcomes of diaphragm weakness) in critically ill patients ventilated by active muscle contraction?
- Do diaphragmatic stimulation of the diaphragm improve outcomes in critically ill patients?

Evidence acquisition

Study registration

This systematic review is fully compliant with the PRISMA¹⁶ (preferred reporting items for systematic reviews and meta-analyses) guidelines and the systematic review has been prospectively registered in an international database of prospectively registered systematic reviews Prospero (CRD42021259353) on June 28, 2021. The review protocol was applied as intended without the need for amendments.

Eligibility criteria

Only systematic reviews with or without meta-analyses, randomized controlled trials, observational studies, and case reports with a substantial number of cases published in English or German were reviewed.

Population

Critically ill adults (≥ 18 years old) were the population of interest.

Intervention

The reviewed intervention was any type of diaphragmatic stimulation leading to involuntary contraction either directly or *via* the phrenic nerve, independent of modality (electrically, magnetically, or both).

Comparator

Standard of care and no stimulation (or sham stimulation) were accepted comparators.

Outcomes

Clinical outcomes included muscle atrophy, VIDD (clinical outcomes of diaphragm weakness), weaning failure (reintubation or NIV rescue after extubation), mortality, quality of life (Barthel Index, activities of daily living, SF-36 score), ventilation time, diaphragmatic function, ICU length of stay, and hospital length of stay.

Information sources

We used the Medline database for the systematic literature search and performed the search on June 28, 2021. A search update was performed on January 31, 2023. References were further screened for relevant studies, which were included if they met selection criteria.

Search strategy

The previously listed databases were searched for publications according to the keywords and Medical Subject Headings (MeSH) connected with Boolean logic operators¹⁷ defined to cover the relevant PICO questions. The search terms used are presented in the Supplementary Digital Material 1 (Supplementary Text File 1).

Selection process

The identified articles were evaluated in a two-step process using a web-based tool (Rayyan, <https://rayyan.ai>) that allowed blinded collaboration, and each article was assessed by two reviewers.¹⁸ In the first step, all articles were independently evaluated by two reviewers according to their abstract and title. Duplicates were removed at this stage.

In the second step, the full texts of all identified articles were retrieved and evaluated by two independent reviewers to determine their eligibility for inclusion. To resolve diverging evaluations, a third reviewer was consulted to reach a final decision.

Data extraction

Data regarding study design, population characteristics, specifications of the intervention, and relevant outcome parameters, as listed under outcomes, were extracted by the reviewers using the Oxford 2011 Levels of Evidence table.

Level of evidence

The evidence grade for the studies included in the systematic review was assessed according to the Oxford 2011

Levels of Evidence developed by the Oxford Centre for Evidence-Based Medicine (CEBM <https://www.cebm.net>, University of Oxford, Oxford, UK).¹⁹

Risk of bias assessment

Risk of bias assessment was performed according to the Cochrane methods using three different collaboration tools available on Cochrane's website (<https://methods.cochrane.org>):

- ROBINS-I tool, for non-randomized studies;²⁰
- ROB 2 tool, for randomized clinical trials;²¹
- ROBIS tool, for systematic reviews and meta-analyses.²²

Three reviewers assessed bias for eligible studies. In the case of incongruence, a further reviewer verified or corrected the bias assessment.

Data synthesis

The extracted data were descriptively synthesized. However, a prospective meta-analysis was not planned.

Evidence synthesis

The initial literature search identified 6533 articles. Five hundred six unique titles and abstracts were selected as potentially relevant. Figure 1 depicts the search and evaluation process. Seven articles were included in the systematic review: questions 1 and 2, respectively, yielded three and four articles out of seven extracted. Results are summarized Supplementary Digital Material 2 (Supplementary Table I), while the risk of bias is presented in Figure 2.^{10, 20-29} A metanalysis, however, was not feasible.

Classification of diaphragm stimulation techniques

The included studies were performed using different kinds of diaphragm stimulation or activation. These techniques can be classified as invasive and non-invasive.

The invasive diaphragm stimulation techniques are transcutaneous electrical diaphragmatic stimulation^{23, 30} and percutaneous electrical phrenic nerve stimulation (PEPNS),²⁴ where a needle or stimulation device is inserted close to the phrenic nerves; invasive phrenic nerve pacing, by which the phrenic nerves can be stimulated directly by surgical access to the nerves;^{10, 25, 26} temporary transvenous phrenic nerve stimulation, by which both phrenic nerves can be stimulated through a central venous line equipped with two electrodes.²⁷

Among the non-invasive techniques, the only study

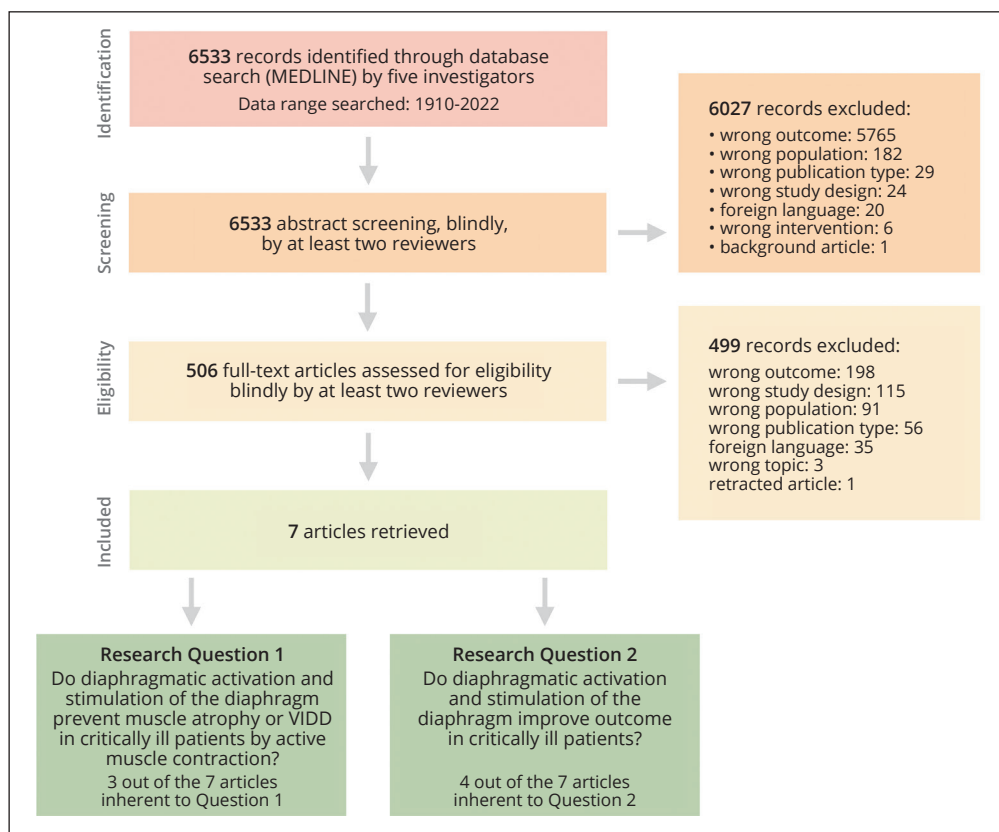


Figure 1.—Selection process for scientific literature.

that fulfilled the inclusion criteria was performed with diaphragm external neuromuscular electrical stimulation (NMES), by which a diaphragm contraction is achieved through a thoracic belt equipped with external electrodes.²⁸

Worth noting, even though not fulfilling the inclusion criteria for the present systematic review, was the study using non-invasive magnetic phrenic nerve stimulation, performed with butterfly-shaped transcranial magnetic stimulation (TMS) coils, however too cumbersome to achieve usability in the critical care setting.³¹

Preventing muscle atrophy or VIDD by diaphragmatic stimulation

Two case-control series studies analyzed biopsies from an electrically stimulated hemidiaphragm. They compared them with biopsies of the contralateral inactive hemidiaphragm, using high-resolution respirometry and western blotting, respectively.^{10, 26} Both studies showed positive outcomes of diaphragm stimulation:

- significantly less mitochondrial respiratory dysfunction

was observed in the stimulated hemidiaphragm (better state III and IV respiratory rates, both $P < 0.05$);

- the oxidative stress and lipid peroxidation levels (4-HNE) were significantly lower in the stimulated hemidiaphragm ($P < 0.05$);
- autophagy biomarker levels (Beclin-1 and LC3II/I) were significantly higher (indicating less oxidative stress and atrophy) in the stimulated hemidiaphragm ($P < 0.05$);
- the antioxidant enzyme activities of CuZnSOD and MnSOD (superoxide dismutase) were not statistically different between the stimulated and non-stimulated hemidiaphragm.

A prospective control double-center study compared PEPNS with control (standard of care) using an ultrasound diaphragm assessment of thickness. Both phrenic nerves were identified using ultrasound to steer the percutaneous stimulation. Patients in the intervention group experienced an increase in diaphragm thickness at 48 h (baseline: 1.98 ± 0.52 mm; at 48 h: 2.20 ± 0.45 mm; $P = 0.001$), while a diaphragm thickness reduction occurred in the control patients (baseline: 2.00 ± 0.33 mm; at 48 h: 1.72 ± 0.2 mm; $P < 0.001$). The average diaphragm thickness was 15%

	Duarte <i>et al.</i> (2021)	Leite <i>et al.</i> (2018)	Martin <i>et al.</i> (2014)	Mankowski <i>et al.</i> (2016)	Romero <i>et al.</i> (2012)	Dres <i>et al.</i> (2022)	Soták <i>et al.</i> (2021)
Selection	⚡	✅	✅	✅	✅	✅	⚡
Intervention	✅	✅	⚡	⚡	✅	⚡	✅
Deviation	✅	✅	✅	✅	n/a	✅	n/a
Missing data	✅	✅	✅	✅	✅	✅	✅
Outcome	✅	⚡	✅	❌	⚡	✅	✅
Report	✅	✅	✅	✅	n/a	✅	n/a
Confounding	❌	⚡	⚡	❌	❌	⚡	⚡
Performance	n/a	n/a	n/a	n/a	✅	n/a	✅
Overall	✅	⚡	⚡	✅	⚡	✅	✅

Figure 2.—Risk of bias, “traffic light” plot. Low, medium and high risk of bias are depicted in gray (green in the online version), light gray (yellow in the online version) and dark gray (red in the online version), respectively.^{10, 23-28} Bias assessment was performed according to Cochrane’s guidelines,²⁹ using ROBINS-I tool (for non-randomized studies),²⁰ ROB 2 tool (for randomized clinical trials)²¹ and ROBIS tool (for systematic reviews and meta-analyses).²²

thicker in the intervention group and 12% thinner in the control group; this difference was statistically significant (P<0.001).²⁴

Improving outcome by diaphragmatic stimulation

A prospective randomized pilot study by Leite *et al.* compared three different therapeutic protocols in 67 critically ill ICU patients.²⁸

- diaphragm group – one daily session of electrical diaphragm stimulation, in addition to one standard daily physical therapy;
- quadriceps group – one daily session of electrical quadriceps stimulation, in addition to one standard daily physical therapy;
- the control group underwent two sessions of daily physical therapy, including gross motor therapy and respiratory therapy.

Diaphragm stimulation and quadriceps stimulation had similar outcomes with better maximum inspiratory pres-

sure (MIP) than the control group (P<0.001), which was identified by comparing the last MIP measurement at ICU discharge with the first MIP measurement at MV start. The Rapid Shallow Breathing Index showed no statistical differences between the two intervention groups. Surprisingly, MV duration was shorter in the control group (15.8±5.75 h) than in both intervention groups (diaphragm stimulation: 27.5±12.16 h, quadriceps stimulation: 23.3±10.61 h; P<0.001).








In a retrospective case series performed on mechanically ventilated spinal cord injury patients, Duarte *et al.* tested the difference in MV time and ICU length of stay of transcutaneous electrical diaphragm stimulation against a standard weaning protocol.²³ The intervention group had a significantly shorter MV time (1.77 times shorter) and ICU length of stay (2.54 times shorter) than the control group; however, P values were not published for this study. The authors implicitly assumed that, as known in the scientific literature, spinal cord injury patients develop diaphragm muscle atrophy if the corresponding nerves no longer stimulate the muscle.²³

Romero *et al.* assessed outcomes after phrenic nerve stimulation compared to standard mechanical ventilation in patients with respiratory failure and spinal cord injury (SCI). Survival length, defined as time (days) between SCI and death or end of the study, was higher in the stimulated group (OR=0.98; 95% CI: 0.97-0.99; P=0.04) and better social functioning measured with the SF-36 questionnaire for quality of life (phrenic nerve stimulation group 7.67±1.8 vs. MV group 5.67±1.17; P<0.001) in comparison with the MV group.²⁵

Temporary transvenous diaphragm neurostimulation was used by Dres *et al.* to achieve diaphragmatic stimulation and contraction.²⁷ Using an invasive transvenous device, the researchers were able to perform phrenic nerve stimulation in the intervention group and compare the results with those of controls, who received a standard weaning protocol. No differences in MV duration or incidence of death were found between the groups. However, the intervention group had a higher MIP at day 8 in comparison with the control (+10.9 cmH₂O vs. +3.8 cmH₂O, absolute difference 7 [95% CI: 1; 14] cmH₂O, P=0.029) as well as on day 15 (+11.9 cmH₂O vs. +4.5 cmH₂O, absolute difference 7 [95% CI: 1; 14] cmH₂O, P=0.024).²⁷

Inclusion criteria, exclusion criteria, type of study, Oxford Evidence Grades, type of intervention, type of control and measurements are presented in Supplementary Table I. Results and characteristics of the included study population are summarized in Table I.^{10, 23-28} The risk of bias is shown in Figure 2.^{10, 20-29}

TABLE I.—Results summary of seven articles identified for the systematic review.

Evidence Grade	Study	Results	Bias
Evidence Grade 3	Duarte <i>et al.</i> ²³	Retrospective case series MV time 1.77 times shorter for TEDS in comparison with SWP alone. ICU stay 2.54 times shorter for TEDS in comparison with SWP alone.	
Evidence Grade 2	Leite <i>et al.</i> ²⁸	Prospective randomized pilot study Diaphragm electrical stimulation (DG) did not produce better results than quadriceps stimulation (QG). Maximum inspiratory pressure (MIP) higher for both DG and QG, in comparison with CG. Difference for all muscle strength indexes (Rapid Shallow Breathing Index and MRC) between DG and QG not significant. QG had shorter ICU stay and better Barthel index than both DG and CG. Duration of mechanical ventilation (MV) shorter for CG in comparison with both DG and QG (CG: 15.8±5.75 hours, DG: 27.5±12.16 hours, QG: 23.3±10.61 hours; P=0.0001). DG and QG had no significant difference in MV duration.	
Evidence Grade 4	Martin <i>et al.</i> ¹⁰	Case control series study Diaphragm pacing produces positive mitochondrial effects: the stimulated hemidiaphragm has better mitochondrial State III and IV (respiratory rates) than the control, which suffers higher grade of mitochondrial respiratory rate dysfunction.	
Evidence Grade 3	Mankowski <i>et al.</i> ²⁶	Case control series study 4-HNE (marker of lipid peroxidation levels and oxidative stress) lower in the stimulated hemidiaphragm. Antioxidant enzyme activities of CuZnSOD and MnSOD were not different between the hemidiaphragms. Macroautophagy biomarker levels of Beclin-1 and the LC3II/I ratio were significantly higher in the stimulated side.	
Evidence Grade 3	Romero <i>et al.</i> ²⁵	Retrospective study of non-randomized, prospectively collected data Phrenic nerve stimulation group had higher probability of survival than MV group (OR=0.98; 95% CI: 0.97-0.99; P=0.04). Phrenic nerve stimulation group had better social functioning (SF-36) than MV group (PNP group 7.67±1.8 vs. MV group 5.67±1.17; P=0.0002).	
Evidence Grade 2	Dres <i>et al.</i> ²⁷	Multicenter, open label, randomized, controlled study No significant difference in MV time and incidence of death between the two groups. Significant difference in MIP changes from baseline to last measurement: +16.6 cmH ₂ O (intervention) and +4.8 cmH ₂ O (control); P=0.001, 95% CI: 11.8 [5;19] cmH ₂ O. Significant change in MIP over time differed significantly between groups by day 8: +10.9 cmH ₂ O (intervention) and +3.8 cmH ₂ O (control); P=0.029, 95% CI: 7 [1;14] cmH ₂ O. Adjusting for baseline differences in MIP and BMI, significant change in MIP reached at day 15: +11.9 cmH ₂ O (intervention) and +4.5 cmH ₂ O (control); P=0.024, 95% CI: 7 [1;14] cmH ₂ O.	
Evidence Grade 3	Soták <i>et al.</i> ²⁴	Prospective, interventional, controlled, double-center study PEPNS group (4 patients in PSV, 8 patients in ACV and/or PSV) experienced an increase in diaphragm thickness at 48 h (baseline: 1.98±0.52 mm; 48 h: 2.20±0.45 mm; P=0.001). Control group (9 patients in ACV, 1 patient in PSV) experienced a decrease in diaphragm thickness at 48h of MV (baseline: 2.00±0.33 mm; 48 h: 1.72±0.2 mm; P<0.001). An overall increase shown (right and left together) in diaphragm thickness in the PEPNS group after 48 hours. This increase was statistically significant (P=0.0003). By 48 hours MV, the diaphragm thickness was on average almost 15% thicker than at baseline in the PEPNS group and 12% thinner than at baseline in the control group (P=0.0002).	

Discussion

Diaphragm stimulation might be an option to prevent or treat VIDD; nevertheless, evidence of the positive or negative outcomes of diaphragm stimulation on diaphragm muscle atrophy and critically ill patient outcomes has never been assessed by any systematic review.

The crosstalk between the oxidative pathways and atrophy pathways is the key molecular actor for VIDD.³²⁻³⁴ Hints of the positive impact of stimulation on diaphragm atrophy chain reactions at a molecular level, resulting in less oxidative stress and less atrophy, has been shown.^{10, 26} The causative role of mitochondrial dysfunction and oxidative stress in the pathophysiology of VIDD is, however, controversial, as van der Berg *et al.* suggested that treatment aimed at mitochondria may not be beneficial for critically ill patients since mitochondrial function in the diaphragm was preserved and oxidative stress levels were not increased, even in severely ill patients.³⁵ Important key biomarkers for muscle atrophy as Titin³⁶ or diaphragm-specific atrophy mRNA markers^{37, 38} were not assessed in the included studies. Hints of less oxidative stress have been demonstrated, suggesting a positive effect in counteracting VIDD. Nevertheless, a broader spectrum of molecular tests is needed to confirm these results.

Diaphragm atrophy can easily be assessed by ultrasound in the ICU setting to predict weaning outcomes.³⁹ Patients without diaphragm atrophy have a higher rate of liberation from MV,⁴⁰ shorter ICU length of stay⁴¹ and shorter MV time in the ICU setting.^{7, 9, 13, 42-44} Diaphragm ultrasound can assess diaphragm thickness, a known predictor of MV time. These findings reinforce the results of Soták *et al.*: diaphragm stimulation by phrenic stimulation maintains or increases diaphragm thickness, avoiding or decelerating diaphragm atrophy.²⁴ No indication of a difference in MV time between intervention and control is available and the study power and optimal population were not calculated; moreover, considering that the patients were enrolled several days after intubation could be a source of confounding, the pathological mechanisms which initiate VIDD are triggered within 72 h after the start of MV.^{7, 8, 11} The results are promising, nevertheless, some limitations and confounding were found: indicators of a positive effect of diaphragm stimulation on diaphragm thickness have been shown but insufficient to assess effects on key outcomes as MV time.

We found the best available evidence of diaphragmatic stimulation for MIP. In a prospective randomized pilot study by Leite *et al.*, patients who received diaphragm

stimulation had higher MIP than control patients.²⁸ These findings were reinforced by assessing MIP using temporary transvenous diaphragmatic neurostimulation in difficult-to-wean patients.²⁷ Higher MIP as an index of “readiness to wean” was established in reviews⁴⁵ and prospective studies⁴⁶ nevertheless, some remarks should be made regarding these results. First, MIP and diaphragm thickness combined are better predictors for successful weaning than MIP alone.⁴⁷ Secondly, although improved muscle strength is an important variable when considering “readiness to wean,”⁴⁸ MIP is an ancillary clinical parameter, while MV time is an important outcome for critically ill patients;⁴⁹ in the included studies shorter MV time after diaphragm stimulation was not found, nevertheless no population adjustment was performed and the studies are likely underpowered. Third, the control group in the first study²⁸ received an intensive PT protocol (two sessions per day) and the intervention group received one session of PT per day; two sessions of physical therapy are considered standard care in some clinics, and control patients should receive the kind of physical therapy normally used *in loco*; muscle or diaphragm stimulation is not meant to substitute for physical therapy; on the contrary, it should be used as a prophylactic therapy to avoid diaphragm atrophy and VIDD. Fourth, many authors have suggested the importance of P0.1 and occlusion pressure, as shown in a recent systematic review and meta-analysis.⁵⁰ P0.1 and occlusion pressure were never measured after diaphragm stimulation; on the contrary, occlusion was performed with bilateral magnetic phrenic stimulation to diagnose VIDD in critically ill patients.⁵¹ These two, however, measure diaphragm drive and effort: P0.1 and occlusion pressure cannot assess muscle function. Since diaphragm stimulation is intended as muscle function enhancement, no change in P0.1 and occlusion pressure (*i.e.*, diaphragm drive and effort) should be expected. While MIP is a good assessment for muscle function, P0.1 and occlusion pressure are not expected to be good parameters to assess the outcome after diaphragm stimulation: no studies to confirm this were performed.

The interesting finding concerning MIP after diaphragm stimulation adds information about the possible therapeutic outcomes in critically ill patients. These results must fit in a wider context since many pathological determinants can influence MV time, and the level of evidence is insufficient to postulate general assumptions concerning positive effects on VIDD.

No scientific literature on long-term survival after diaphragm stimulation in the critical ill was found; similarly aimed randomized controlled studies have never been

performed. However, survival was assessed in two studies; the first assessed 30-day survival stating that no difference between diaphragm stimulation and control was identified.²⁷ Romero *et al.* showed positive outcomes after phrenic nerve stimulation, longer survival rates, and better SF-36 scores in comparison with the standard of care.²⁵ The population considered is only limited to patients with cervical spine injury. The low level of evidence concerning survival after diaphragm activation does not allow any certain assumption on the general ICU population.

The techniques used are heterogeneous and space between highly invasive electric pacing to non-invasive techniques. Phrenic nerve stimulation with invasive techniques is feasible, nevertheless presents risks comparable to the mechanical, infectious, or thrombotic side effects of a central venous line.⁵² Safety could be increased with magnetic stimulators of the phrenic nerve, which have only been used for diagnostic purposes.^{53, 54}

Limitations of the study

We limited our search to English and German literature. Due to the focus on the critically ill population, we may have missed other important factors not commonly evaluated in studies of critically ill patients yet, like residual autonomy (*e.g.*, better management of the voice like timbre, length of sentences, or autonomy in dialogue). Furthermore, we prospectively decided not to perform a meta-analysis because we assumed that the heterogeneity would be too high. The assumption was confirmed during the execution of the systematic review, and a statistician was involved in the attempt of performing a statistical analysis that could summarize the results of the seven studies included; according to the expert opinion, no statistical analysis was scientifically meaningful in the given circumstances.

Conclusions

In summary, there is some evidence available regarding the molecular benefits and prevention of diaphragmatic atrophy by diaphragmatic stimulation. Hints and indicators of positive outcomes like higher MIP and longer survival are available in the scientific literature. Preventive approaches to VIDD have not been extensively studied, and the few available publications are not adequately powered and insufficient to confirm a clinical benefit. Invasive procedures to achieve diaphragmatic stimulation in critically ill patients present limitations and risks, and further experimental efforts are needed to assess these issues.

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Conflicts of interest

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Authors' contributions

Alessandro Panelli has given substantial contributions to data acquisition, analysis, interpretation and investigation, manuscript writing and revision, Julius J. Grunow, Michael A. Verfuß, Hermann G. Bartels and Zarina Brass to data collection, analysis and investigation, and manuscript revision, Stefan J. Schaller to study design, data collection, analysis, interpretation and investigation, and manuscript revision. All authors read and approved the final version of the manuscript.

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Supplementary data

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