BACKGROUND

The most common support of organ function routinely administered in intensive care units (ICUs) is mechanical ventilation (MV), which carries significant adverse effects. In recent years, an area of interest for intensivists has been ventilator-induced diaphragmatic dysfunction (VIDD). This complex process plays a major role in prolonged weaning which occurs in almost half of mechanically ventilated patients. As the time spent on MV increases morbidity, mortality, and healthcare costs increase proportionally.

It is well known that like any other muscle in the body, the diaphragm atrophies when not in active use.

Abstract

Background: Prolonged mechanical ventilation caused by ventilator-induced diaphragm dysfunction (VIDD) is a serious problem in critically ill patients. Identification of patients who will have difficulty weaning from ventilation along with attempts to reduce total time on mechanical ventilation is some of the aims of intensive care medicine.

Observations: This article briefly summarizes current options for temporary phrenic nerve stimulation therapy in an effort to keep the diaphragm active as direct prevention and treatment of ventilator-associated diaphragmatic dysfunction in patients on mechanical ventilation. The results of feasibility studies using different approaches are promising but so far, the clinical relevance is low. One important question is which tool would reliably identify early signs of diaphragmatic dysfunction and also be useful in guiding therapy. The authors present a brief overview of the current options considering the advantages and disadvantages of the available examination modalities. Despite the fact that current data point out some limitations of ultrasound examination, we believe that it still has a unique position in the bedside examination of critically ill patients on mechanical ventilation.

Conclusion: Temporary phrenic nerve stimulation, regardless of the specific approach used, has the potential to directly treat or reverse VIDD, and ultrasound examination plays an important role in the comprehensive care of critically ill patients.

Keywords: diaphragm, phrenic nerve stimulation, ultrasonography, VIDD
The thickness of the diaphragm progressively decreases during the use of assist-control ventilation modes and, conversely, increases during pressure support ventilation (PSV). Therefore, ventilation strategy in ICUs is to keep the patient minimally sedated and preferentially use PSV mode, where all breaths are initiated by the patient's spontaneous respiratory activity. However, deep sedation cannot always be avoided and the patient may, therefore, be forced to spend many hours or even days on fully controlled ventilation with all its adverse effects. Various temporary stimulation methods are being studied in an attempt to keep the diaphragm active even when the patient is under deep sedation.

2 | TEMPORARY PHRENIC NERVE STIMULATION METHODS

Three approaches in the published research are particularly promising in the fight against VIDD. The first is electrical stimulation using electrodes inserted percutaneously near the phrenic nerves in the cervical region. Although the PEPNS (Percutaneous Electrical Phrenic Nerve Stimulation) study was performed on a small sample of 12 stimulated patients, the results confirmed the feasibility of using this method in the human population. The authors demonstrated safe insertion of the stimulation electrodes using ultrasound guidance, excellent synchronization of stimulation with the patient's respiratory effort (regardless of the chosen ventilation mode) and good tolerance of stimulation without the need for deep sedation. Moreover, 48-h stimulation carried out in six 2-h sessions resulted in an increase in diaphragm thickness of 15%. A prospective, controlled, randomized clinical trial to analyze the effect of neurostimulation of the diaphragm on weaning outcomes is currently being prepared.

The second approach studied is non-invasive electrical stimulation of the phrenic nerves applied, again, in the neck area. Keogh et al. demonstrated that non-invasive capture of the phrenic nerve is feasible using surface electrodes without the application of pressure and characterized the stimulation parameters required to achieve therapeutic diaphragm contractions. The non-invasiveness and the ease of electrode application are the main advantages of this approach. However, the study has so far only been conducted on healthy volunteers. The potential clinical validity of non-invasive phrenic nerve stimulation for maintaining diaphragm activity requires a clinical study of the efficacy of this approach in the intensive care environment.

The last promising, minimally invasive method of temporary phrenic nerve stimulation is the transvenous approach. In the RESCUE 1 study, the authors demonstrated the feasibility and safety of their novel device Lungpacer IntraVenous Electrode Catheter, a 9.5F, single-use, central venous catheter placed in the left subclavian vein, designed to bilaterally stimulate the phrenic nerves to induce diaphragmatic contraction. The follow-up multicenter, open-label, randomized, controlled study RESCUE 2 aimed to evaluate the effects of temporary transvenous diaphragm neurostimulation on weaning outcomes and maximal inspiratory pressure. The study enrolled 112 patients, with 43 of the 57 patients in the treatment group being successfully bilaterally stimulated. Although the authors demonstrated a significant increase in maximal inspiratory pressure, suggesting reversal of the course of diaphragm dysfunction, stimulation did not lead to an increase in the proportion of patients successfully weaned from MV. The authors offer several explanations for this limitation. One was the wide heterogeneity of the studied population of critically ill patients, as well as of the various centres where the study was conducted. The calculation of optimal statistical power was forgone to ensure reasonable feasibility leading to an underpowered study. Furthermore, only 79% of patients in the treatment group received more than 50% of the target number of stimulations, which probably contributed to the lack of a significant difference between groups. The authors chose maximal inspiratory pressure (MIP) as one of the primary parameters, in spite of the fact that there is evidence that peak MIP is not specific enough to be clinically useful as a predictor of weaning outcomes. It might be more appropriate to use sustained maximum inspiratory pressure (SMIP) instead of MIP. Finally, the inclusion of standardized weaning protocols in centers where they did not previously exist certainly led to improved outcomes for patients in the control group.

The current evidence regarding methods of temporary stimulation of the phrenic nerves could be summarized as follows: electrodes can be successfully inserted or applied to the skin to stimulate the phrenic nerves. The success of induction of diaphragmatic contractions in response to stimulation of the phrenic nerves is high. As it is possible to reliably synchronize electrical stimulation with MV, even when initiating supported breath by the patient's respiratory effort, stimulation is well tolerated and does not lead to the need for deep sedation. It has been verified that neurostimulation, whether applied transcutaneously or transvenously, has no serious side effects and is safe. And finally, it has been shown that stimulation of the diaphragm leads to a significant increase not only in ventilation parameters such as MIP, but also in ultrasound-measured parameters of diaphragm thickness and thickening fraction.
3 | EVALUATION OF DIAPHRAGMATIC DYSFUNCTION IN CRITICALLY ILL PATIENTS

3.1 | Common assessments in patients with diaphragm dysfunction

Considering the high incidence of VIDD in patients on MV and the knowledge of the effect of unnecessarily excessive ventilatory support on the development of diaphragmatic dysfunction, it is essential to have a monitoring tool to dynamically adjust the adequate level of ventilatory support. Another indication is the detection of possible asynchronies between the patient and the ventilation mode. Finally, monitoring of diaphragm function would be useful to predict success or failure of weaning trials and to titrate ventilatory assistance in case of already prolonged weaning.

Several approaches can be used to evaluate diaphragm function at the bedside. The reference method used to diagnose diaphragm dysfunction is measuring pressure-generating capacity. The capacity of the diaphragm to generate pressure, which increases abdominal pressure and decreases thoracic pressure resulting in transdiaphragmatic pressure (Pdi). However, determining the maximum Pdi requires full patient cooperation, which is difficult to achieve in critically ill patients. A reasonable alternative in sedated patients is the detection of Pdi in response to supramaximal bilateral phrenic nerve magnetic stimulation (Pdi, Tw). To measure transdiaphragmatic pressure, it is necessary to use esophageal and gastric balloons. Alternatively, changes in tracheal pressure during magnetic stimulation (Ptr, stim) can be used.

Another bedside method is the measurement of diaphragm electrical activity (EAdi). This can be achieved either by using a dedicated esophageal catheter with multi-array electrodes or by using surface electromyography. The advantage is the non-invasiveness and the possibility of continuous EAdi recording. However, the EAdi values themselves are difficult to interpret due to wide inter-patient variability. The use of EAdi monitoring in conjunction with the breathing pattern allows the calculation of several other interesting parameters such as the neuromechanical efficiency ratio (ΔPdi/ΔEAdi) to estimate inspiratory effort or the neuroventilatory efficiency index (VT/EAdi) to predict the success of the spontaneous breathing trial.

The routine use of ultrasound by intensivists offers a unique opportunity for bedside assessment of diaphragm function using this method. This technique is now very attractive because it is non-invasive, the equipment is readily available in most ICUs and the examination is technically easier to perform than the previous methods mentioned. There are generally two parameters used: determination of diaphragm excursion and measurement (with calculation) of diaphragm thickening. Low-frequency curvilinear or phased-array probes (1–5 MHz), using the liver and spleen as an acoustic window in B-mode and M-mode are used for obtaining diaphragm excursion. The range of diaphragm movement toward or away from the transducer during breathing is measured. Normal values reported in adults are between 0.9 and 9 cm when measured from resting expiratory position to deep inspiration. Diaphragm thickness is measured using a linear probe (10–15 MHz) in B-mode at the zone of apposition between the eighth or ninth intercostal space on both sides in the midaxillary line. The diaphragm is identified as a three-layer structure comprised of two hyperechoic lines representing the pleural and peritoneal membranes and a middle hypoechoic layer representing the diaphragm muscle itself. Measurement is obtained at the end of expiration during relaxation of the diaphragm prior to the initiation of the next breath. For increased accuracy, it is appropriate to measure several values in the course of the diaphragm and during several separate breaths. Finally, thickening fraction is calculated in the same zone of apposition. Thickening fraction = thickness at end inspiration – thickness at end expiration.

3.2 | Barriers of current assessments

The gold standard in the diagnosis of diaphragmatic dysfunction in critically ill patients in the ICU is the measurement of the transdiaphragmatic twitch pressure (PdiTw) generated in response to bilateral phrenic nerve magnetic stimulation. However, this diagnostic method requires special equipment and operator experience and is thus only available in specialized centres.

Measurement of diaphragm electrical activity would be more appropriate for many clinics from this perspective. However, as already mentioned, EAdi values alone are difficult to interpret due to wide inter-patient variability and there are only limited data of normal values. The same is applicable to the neuromechanical efficiency ratio, in addition to poor repeatability requiring repeated measurements during brief period of airway occlusion to find the lowest variability to more accurately estimate the patient’s inspiratory effort.

The initial enthusiasm for the use of ultrasound in monitoring diaphragm function and its applicability as a predictor of successful weaning has been attenuated by studies where generally poor correlation between these parameters and parameters such as pressure-generated capacity or weaning outcomes where observed. This is due to several of its limitations. In particular, image
acquisition and analysis is operator-dependent and requires training. Particularly, it depends on the timing of the examination - ideally during a spontaneous breathing trial or during fully controlled diaphragm activation achieved in a sedated patient by exogenous electrical or magnetic stimulation. The poor correlation of diaphragmatic atrophy with pressure-generating capacity suggests that atrophy alone is only one of several markers of diaphragm dysfunction. The limitation of the usefulness of that atrophy alone is only one of several markers of diaphragmatic atrophy with pressure-generating capacity suggests that atrophy alone is only one of several markers of diaphragm dysfunction.25 The poor correlation of diaphragmatic atrophy with pressure-generating capacity suggests that atrophy alone is only one of several markers of diaphragm dysfunction.25 The poor correlation of diaphragmatic atrophy with pressure-generating capacity suggests that atrophy alone is only one of several markers of diaphragm dysfunction.25

The limitation of the usefulness of the diaphragmatic thickening fraction is explained by the difference between measuring a one-dimensional parameter and the actual three-dimensional movement of the diaphragm muscle.15

4 | USEFULNESS OF ULTRASOUND EXAMINATION IN CONJUNCTION WITH TEMPORARY PHRENIC STIMULATION

Although neurostimulation of the diaphragm has been shown to have a positive effect on both diaphragm thickness and ventilation parameters, no clinically significant effect of stimulation in shortening weaning time from MV has yet been achieved. Some of the probable reasons for the failure of the RESCUE 2 trial have been mentioned above. However, several other questions remain unanswered. It is necessary to define the target group of patients to determine who would benefit most from temporary phrenic nerve stimulation. It is also not clear when it is appropriate to start stimulation therapy, whether from the beginning of the initiation of MV, or only after initial weaning attempts fail and long-term MV is expected. Furthermore, the ideal intensity of stimulation is not precisely known, both for individual sessions and for the intervals between stimulations, including the total duration of therapy. Finally, it is not known which parameters (ventilation or ultrasound) are most indicative as targets for clinical outcomes and which should be monitored as a standard.

If muscle weakness is found in a mechanically ventilated patient, first, causes such as electrolyte imbalance, endocrine disorders such as hypothyroidism, profound malnutrition, severe renal failure, unnecessary use of muscle relaxants, and use of corticosteroids should be diagnosed. Nevertheless, the most common causes of respiratory muscle weakness in critically ill patients remains infection-induced along with ventilator-induced diaphragmatic dysfunction. Thus, the approach to the patient is always comprehensive in order to treat the infection and at the same time take steps to prevent VIDD, including minimal use of sedative drugs and gradually reducing the level of ventilatory support. If the need for deep sedation cannot be avoided or the infection is not fully under control, active rehabilitation of the diaphragm by electrical stimulation could be considered. The use of ultrasound parameters such as diaphragm thickness together with the calculation of the thickening fraction at the initiation of MV to establish a baseline and target subsequent pacing to these values could be beneficial but would need to be clinically validated.

Nevertheless, ultrasound examination still has an indispensable role in the complex therapy of critically ill patients requiring MV. The daily use of lung and pleural ultrasonography in conjunction with other critical care modalities allows the intensivist to rapidly diagnose and manage the treatment of a wide range of disease processes that are associated with VIDD and are involved in prolonged weaning time. Ultrasound has a unique role in the detection of pneumothorax, with a pooled sensitivity of 78.6% (95% CI 68.1–98.1) and specificity of 98.4% (95% CI 97.3–99.5), superior to chest radiography with pooled sensitivity of 39.8% (95% CI 29.4–50.3) and specificity of 99.3% (95% CI 98.4–100). Furthermore, given the high incidence of pleural effusions seen in critically ill patients, which can be associated with prolonged time on MV, ultrasound again has an important role. It can be used not only to determine the presence of pleural fluid, but also to estimate its volume or to predict the characteristics of the fluid and ultimately to safely guide its evacuation. The risks of ultrasound-guided drainage of pleural effusions in patients on positive pressure ventilation are low. In conjunction with other modalities such as bedside echocardiography and imaging of the deep venous system, ultrasound examination can help to rule out pulmonary embolism. Ultrasound features of lung consolidation may help to identify the cause and could guide adequate treatment. If the air bronchogram is absent or static in the consolidated lung, air passage is prevented in the corresponding airway and de-obstructive bronchoscopy is indicated. However, if a dynamic air bronchogram is detected, pneumonia is the more likely etiology of the consolidation and, therefore, microbiological sampling and initiation of antibiotic therapy should be initiated. In the case of pneumonia and using color Doppler ultrasonography, the consolidation has a typical appearance. Lung ultrasonography may also be useful in monitoring the development of respiratory infection. To assess these changes, a scoring system based on lung tissue aeration assessment—Lung ultrasonography score was proposed to allow pseudo-quantification of regional loss of aeration. Differentiation between acute cardiogenic pulmonary edema (ACPE) and acute respiratory distress syndrome (ARDS) is difficult in clinical
practice. Different pathophysiology in patients with ARDS and ACPE leads to a different pleuropulmonary ultrasound pattern allowing the use of ultrasound as a unique bedside imaging modality. Another interesting indication for the use of chest ultrasound is during lung recruitment maneuver with optimization of PEEP settings. Thus, it can provide information when regional ventilation is impaired in the case excessive PEEP levels where lung sliding is impaired or severely reduced and reappears when the level of PEEP is subsequently reduced. As already mentioned, in conjunction with echocardiography, chest ultrasound may help in determining the cause of weaning failure.

5 CONCLUSION

Ventilator-induced diaphragm dysfunction is a serious problem in intensive care medicine. There is currently no established strategy to directly treat or reverse VIDD. Rather, a combination of interventions is used in an attempt to mitigate its effects. Temporary stimulation of phrenic nerves is currently a highly researched approach to directly combat VIDD. The results of recent studies on this topic are very promising, but their clinical relevance is still low and further clinical studies are needed. A fundamental question is how to identify patients who will have difficulty weaning off MV and would benefit most from active diaphragm rehabilitation using neurostimulation. The most recent research in lung ultrasound examination doubts its role in the diagnosis of diaphragmatic dysfunction and in the prediction of failure or success of weaning from MV. The authors believe that in terms of a comprehensive approach to the critically ill patient, ultrasound examination still has an indispensable role, especially in identifying potentially treatable causes associated with prolonged weaning time.

AUTHOR CONTRIBUTIONS
Michal Soták prepared and drafted the manuscript; Karel Roubík revised and edited the manuscript critically for important intellectual consent; and Tomáš Tyll supervised, revised, and edited the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST
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