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# Diaphragm Neurostimulation Assisted Ventilation in Critically 111 Patients

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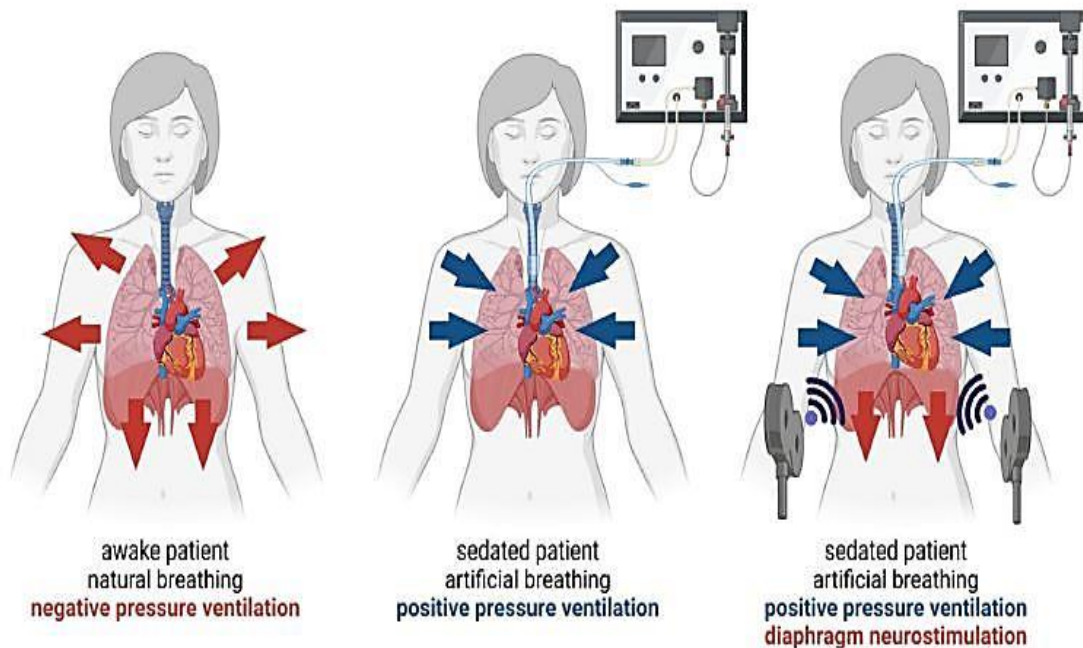
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## Abstract

Diaphragm neurostimulation consists of placing electrodes directly on or in proximity to the phrenic nerve(s) to elicit diaphragmatic contractions. Since its initial description in the 18<sup>th</sup> century, indications have shifted from cardiopulmonary resuscitation to long-term ventilatory support. Recently, the technical development of devices for temporary diaphragm neurostimulation has opened up the possibility of a new era for the management of mechanically ventilated patients. Combining positive pressure ventilation with diaphragm neurostimulation offers a potentially promising new approach to the delivery of mechanical ventilation which may benefit multiple organ systems. Maintaining diaphragm contractions during ventilation may attenuate diaphragm atrophy and accelerate weaning from mechanical ventilation. Preventing atelectasis and preserving lung volume can reduce lung stress and strain and improve homogeneity of ventilation, potentially mitigating ventilator induced lung injury. Furthermore, restoring the thoracoabdominal pressure gradient generated by diaphragm contractions may attenuate the drop in cardiac output induced by positive pressure ventilation. Experimental evidence suggests diaphragm neurostimulation may prevent neuroinflammation associated with mechanical ventilation. This review describes the historical development and evolving approaches to diaphragm neurostimulation during mechanical ventilation and surveys the potential mechanisms of benefit. The review proposes a research agenda and offers perspectives for the future of diaphragm neurostimulation assisted mechanical ventilation for critically ill patients.

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Some of the earliest descriptions of mechanical ventilation used negative pressure ventilation to mimic normal human physiology. Negative pressure ventilation was notably achieved with the first iron lung, called the "spirophore," designed by Alfred Woillez in 1876. This ventilator generated negative pressure using a manually powered bellows (1). Positive pressure ventilation (PPV) was initially described about 150 years earlier by J. Croy d'Etiolles (2), but the era of modern PPV and intensive care rose during the poliomyelitis outbreak in the 1950s when Bjorn Ibsen recommended cyclic insufflations of gas inside the thorax through a tracheostomy tube. The indications for PPV have expanded well beyond the neuromuscular causes of respiratory failure to primarily treat acute respiratory failure. PPV is used to improve gas exchange, decrease the work of breathing, and recruit collapsed alveoli. However, PPV is a double-edged sword, as it has various adverse consequences. First, PPV can cause or exacerbate lung injury by increasing stress and strain within the lung, a phenomenon referred to as ventilator-induced lung injury (VILI) (3). Second, PPV can contribute to critical illness-associated diaphragm weakness, which is partly caused by diaphragm inactivity and atrophy (4). Third, PPV may impair hemodynamics through direct and indirect effects on heart-lung interactions (5). Fourth, recent experimental data raise the possibility that PPV may be associated with neuroinflammation, referred to as ventilator-associated brain injury (6).



**Figure 1.** Principle of diaphragm neurostimulation assisted ventilation.

From a physiological perspective, negative pressure ventilation may mitigate the adverse effects of PPV. Home-customized devices have been tested, but their practical use is challenging in the ICU (7, 8). Diaphragm neurostimulation consists of placing electrodes directly on or near the phrenic nerve, or inside the diaphragm itself in the vicinity of the phrenic nerve termination, with a view to eliciting diaphragmatic contractions. Diaphragm neurostimulation may be beneficial not only because it increases diaphragm activity (and thereby limits diaphragm atrophy) but also because it contributes to ventilation. Therefore, a promising strategy may be to combine PPV with diaphragm neurostimulation (Figure 1), which elicits nonvolitional controlled diaphragm contractions and generates negative swings in pleural pressure in synchrony with positive airway pressure swings.

In this perspective, we first describe the anatomical approaches and technical aspects of diaphragm neurostimulation, present the history and principles, and review the physiological rationale and clinical evidence to date of diaphragm neurostimulation assisted ventilation in adult patients. Finally, we outline current unknowns and a research agenda to further advance the field.

### **Anatomical Approaches and Electrode Placement**

The diaphragm comprises a peripheral muscular portion and a central tendinous portion. It is innervated by two phrenic nerves, which originate from the C3 to C5 cervical nerve roots in the neck and cross the anterior scalene muscles from the lateral to the medial side before entering the thorax. Between the mediastinal pleura and the pericardium, the phrenic nerve passes in front of the pulmonary hilum, descends along the left ventricle or the right a um, and enters into the diaphragm. Diaphragm neurostimulation can be achieved via cervical, thoracic, or abdominal approaches (Figure 2).

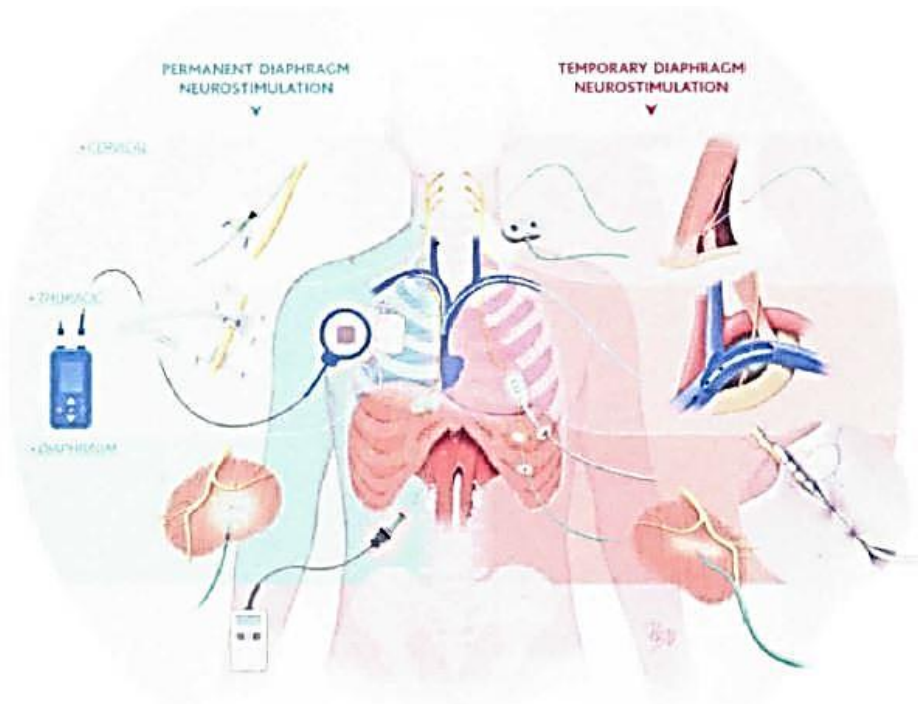
## **Access for Permanent Diaphragm Neurostimulation**

The open cervical approach is characterized by a 4-inch transverse incision, under local anesthesia, followed by the placement of electrodes along the phrenic nerves. An alternative has been described with a percutaneous approach, using a needle to place the electrodes in the fascial plane between the sternocleidomastoid muscle and the anterior scalene muscle (9). The transthoracic approach uses a 5- to 7-cm transverse incision overlying the second costal cartilage and rib, under general anesthesia (10, 11). The mediastinal pleura in front and behind the phrenic nerve are opened to mobilize the phrenic nerve bundle and place the electrode. With the cervical and thoracic approaches, stimulation elicits contraction through electrodes placed in direct contact with the phrenic nerve. Last, the abdominal approach requires the implantation of electrodes in the diaphragm by means of a laparoscopic surgical procedure`

The technique consists of implanting a hook electrode directly within each hemi diaphragm close to the phrenic nerve endings (12). As a result, higher electrical intensity is needed to elicit diaphragm contractions, which can induce pain, because the phrenic nerve is a mixed nerve that carries afferents from the lower par. of the thorax and fi.om the abdomen. Clinically, this presents as referred neck and shoulder pain (13).

## **Access for Temporary Diaphragm Neurostimulation**

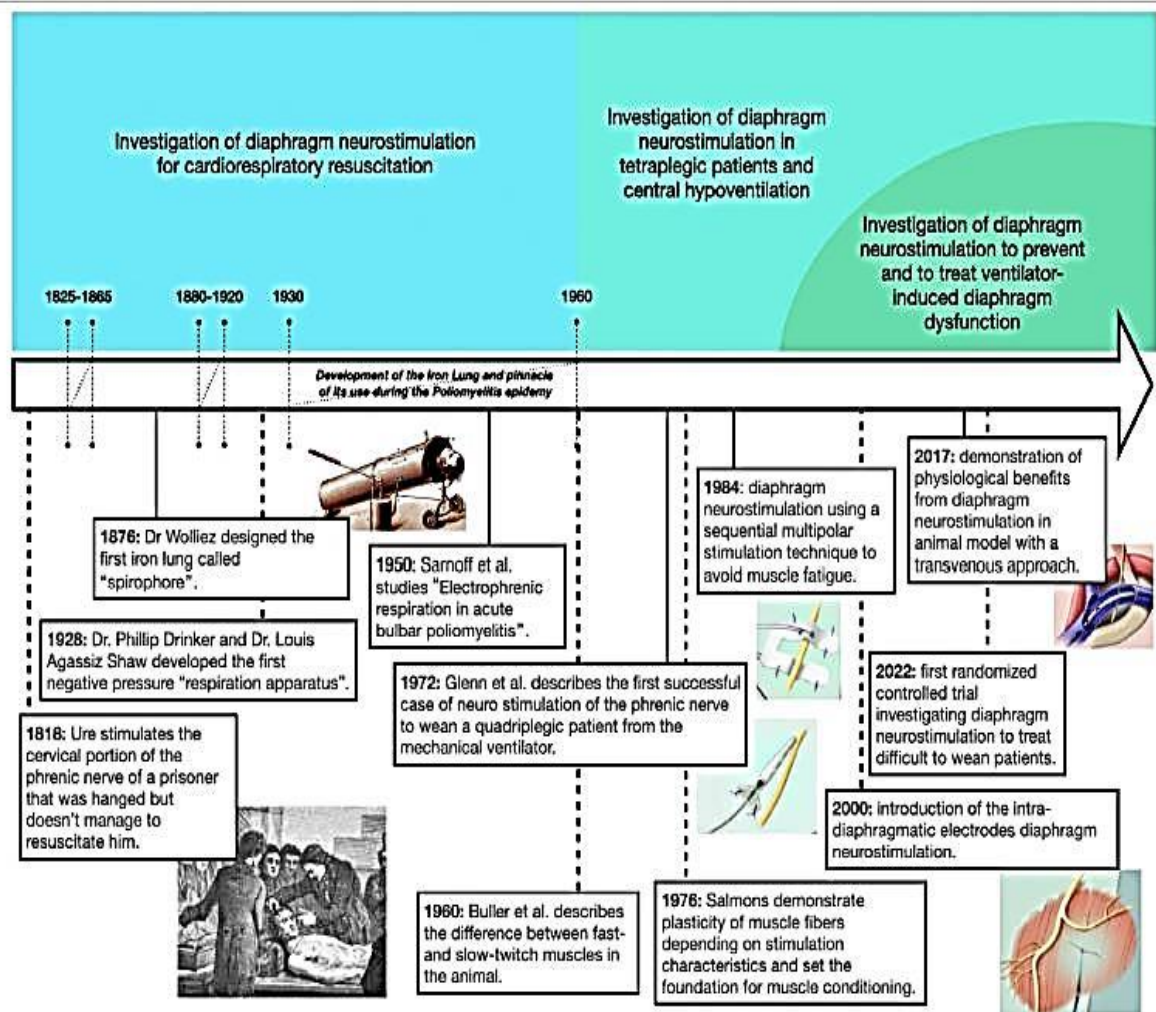
Surgical implantation and removal of electrodes is invasive, carries an operative burden, and is not feasible for critically ill patients. Less-invasive methods are needed to make a strategy of temporary stimulation accessible to these at-risk patients. These methods are based on repetitive cervical magnetic or electrical stimulation (14-16), percutaneous electrical cervical stimulation (9), electrical transvenous approach (17), and electrical stimulation of the free segment of the phrenic nerve (18,19). Similar to epicardial pacing wires, the former approach offers the possibility to insert a removable phrenic electrode intended for temporary use at the end of surgical interventions exposing the phrenic nerve (20, 21). Transvenous phrenic nerve stimulation is, to date, the only nonsurgical technique that has been systematically evaluated in ICU patients. Because of the close proximity of the phrenic nerves to the superior vena cava on the right side and the innominate vein on the left side, a catheter equipped with electrodes can be introduced and used to stimulate one or both phrenic nerves. In 2017, an implantable transvenous phrenic nerve stimulator was approved by the U.S. Food and Drug Administration to treat central sleep apnea (22). More recently, a temporary percutaneous catheter with embedded electrodes was developed (17). It consists of a 9.5 F, single-use central venous catheter with two electrode arrays (proximal and distal arrays stimulate the right and left phrenic nerves, respectively) inserted via the left subclavian or left internal jugular vein. Although the transvenous access facilitates the capture of the phrenic nerves, it remains an invasive procedure that carries the usual risks associated with inserting a central venous catheter or leads into a vessel in a critically ill patient. Recent studies in the ICU have focused on the transvenous access. However, from a theoretical point of view, repetitive percutaneous magnetic cervical stimulation using a collar device may be of clinical interest, although it has not been investigated recently in ICU patients (16).



**Figure 2.** Permanent and temporary approaches of diaphragm neurostimulation (Original illustration, by Pierre Bourcier).

## Historical Context

The first iron lung (a body-enclosing device equipped with a plunger to decrease pressure) was used to treat patients with poliomyelitis. More recently, chamber respirator and microprocessor-based iron lungs have been investigated in acute respiratory distress syndrome (ARDS) and acute exacerbation of chronic obstructive pulmonary disease (7, 8, 23) and showed beneficial effects on oxygenation and ventilatory pattern. However, their use is difficult to generalize; it requires cumbersome and expensive devices and, importantly, high-level expertise. In 1948, Sarnoff and colleagues provided temporary artificial ventilation by the transcutaneous stimulation of a single "phrenic nerve which they called "electro phrenic respiration"(24). In anesthetized cats, monkeys, and rabbits, the investigators successfully achieved normal minute ventilation and gas exchange. Whittenberger and colleagues applied this technique successfully in humans (25). By this time, the objective was to replace iron lung negative pressure ventilation by phrenic stimulation in the context of the poliomyelitis pandemic ( Figure 3). However, because it did not account for the axonal degeneration that followed motor neuron injury, this strategy failed. In the early 1970s, Glenn and colleagues showed that implanted electrodes stimulating the phrenic nerve could allow partial or complete weaning of patients with central respiratory apnea due either to central hypoventilation or to traumatic quadriplegia (20, 21 ). Permanent diaphragm neurostimulation can help wean these patients from the ventilator and has been shown to improve quality of life, restore olfaction (26), and decrease lower respiratory tract infections (27). Last, the correction of central respiratory apnea has been described with a permanently implanted transvenous stimulator (RespiCardia Remede system) (22).



**Figure 3.** Development of diaphragm neurostimulation techniques over time.

## Pathophysiological Rationale and Evidence for Diaphragm Neurostimulation Assisted Ventilation

### Use of Diaphragm Neurostimulation to Prevent and Treat Ventilator-Induced Diaphragm Dysfunction

Critical illness-associated diaphragm weakness refers to the collective effects of all mechanisms of diaphragm injury occurring in critically ill patients (4). Approximately two-thirds of critically ill patients are affected, and they are at substantially higher risk of poor outcomes, including difficult weaning, prolonged mechanical ventilation, and increased mortality (4). Some of this weakness is attributable to diaphragm inactivity during mechanical ventilation, which suggests that maintaining a certain degree of diaphragm contractile activity may prevent the decline in the diaphragm pressure-generating capacity induced by PPV (28, 29).

Achieving diaphragm-protective ventilation with diaphragm neurostimulation assisted ventilation is a promising avenue (30). Animal studies established the biological foundation of phrenic nerve stimulation (to prevent diaphragm dysfunction by showing a reduction in diaphragm atrophy and less damage and fiber disorganization associated with diaphragm

neurostimulation (31, 32). Case reports and cohort studies in ventilator-dependent patients demonstrated that even several years after the injury, permanent diaphragm neurostimulation increases diaphragm thickness and diaphragm pressure generating capacity and allows weaning from mechanical ventilation (33-36). The temporary use of diaphragm neurostimulation has also been successfully reported in a proof-of-concept study in four patients who received lung transplants (37). In a first-in-human study, the transvenous approach with a subclavian catheter fitted with electrodes for electrical stimulation was proved safe and successful to capture the phrenic nerves in 23 patients (17). To date, a single randomized controlled trial comparing transvenous diaphragm neurostimulation to usual care in 112 patients with prolonged weaning from mechanical ventilation has been reported (38). In the intervention arm, patients received 60 stimulations twice a day until successful extubation. There was no difference between groups in terms of the proportion of patients successfully weaned from mechanical ventilation (primary endpoint), but there was a dose-response relationship between the number of stimulations actually delivered and the increase in maximal inspiratory pressure (38). Because the diaphragm was the only inspiratory muscle to be stimulated (other inspiratory muscles were not), the increase in maximal inspiratory pressure is likely to result from an improvement in diaphragm strength. The fact that diaphragm neurostimulation increased maximal inspiratory pressure but not the proportion of weaning success may have several explanations. First, the number of stimulations was limited to 60 twice a day, which could be insufficient to translate the increase in diaphragm strength into clinical outcome, and it is of note that only 79% of the patients in the treatment group received >50% of the target number of stimulations. Second, the rate of weaning success in the control group was higher than anticipated, which may have diluted the effect of the intervention. Last, weaning failure is a multifactorial process, and it is possible that increasing diaphragm strength might not be sufficient to stabilize the respiratory capacity/load balance. A larger randomized controlled trial using the same technology (with the additional option of left internal jugular access) is currently ongoing (NCT 03783884). Apart from the indication of diaphragm neurostimulation as a curative approach during prolonged weaning, the preventive approach at the early phase of the initiation of mechanical ventilation is another promising avenue in critically ill patients. It may allow to provide lung protective ventilation and alleviate VILI (see below) and mitigate the risk of diaphragm atrophy. Of note, in ICU patients, sepsis may contribute to diaphragm dysfunction independent of mechanical ventilation (39). Whether stimulating the diaphragm during sepsis could be harmful is a question that has been raised previously (40), but data are conflicting (41, 42).

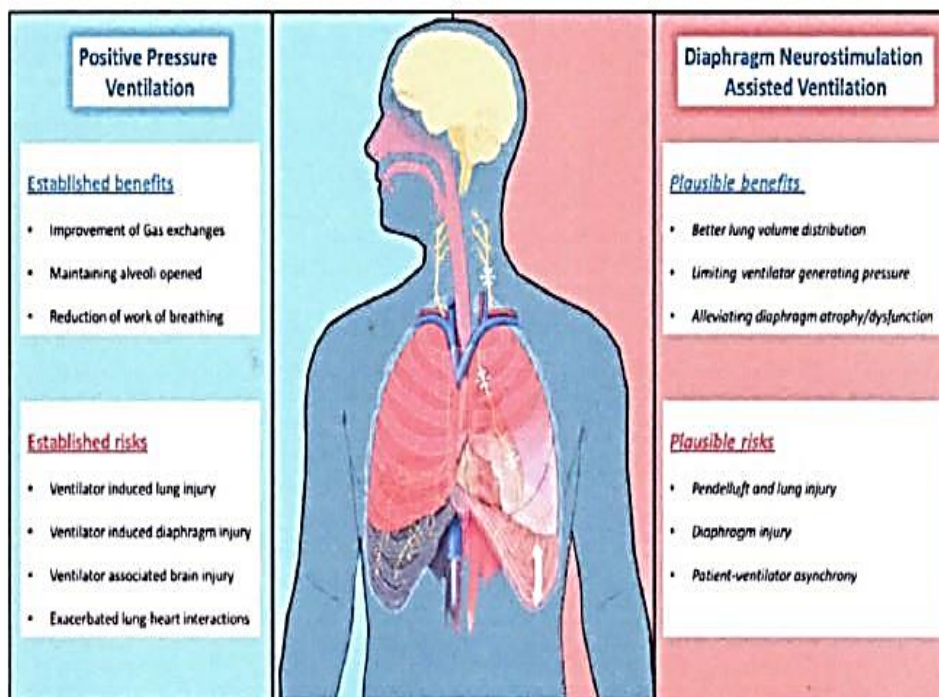
### **Potential of Diaphragm Neurostimulation Assisted Ventilation to Reduce VILI**

Despite improvements in the management of ARDS, mortality remains high. This has been ascribed to multiple factors, notably, the deleterious impact of PPV on the lungs, termed VILI (3). One of the primary causes of VILI is excessive mechanical stress and strain applied to the lungs by the ventilator, with high driving pressures being independently associated with mortality (43). Furthermore, cumulative exposure to higher intensities of mechanical ventilation is harmful, even for short durations (44), highlighting the importance of limiting exposure to high driving pressure as a promising strategy to reduce mortality. Patients with severe ARDS often require deep sedation to suppress respiratory effort for lung-protective ventilation and to avoid patient-ventilator asynchrony, but suppressing diaphragm contractile activity results in progressive dorsal lung atelectasis (45). This decreases the volume of lung available for ventilation and increases mechanical stress and strain. The distribution of the  $V_T$  in patients with ARDS is characterized by inhomogeneity due to consolidation and atelectasis that are notably present in the dependent regions of the lungs (posterior parts of the lungs in



the supine position). PPV may exacerbate lung strain at the interfaces of aerated and nonaerated regions of the lung, which amplifies regional tissue force. Diaphragm neurostimulation assisted ventilation may reduce the lung strain by reopening dorsal consolidations and restoring lung homogeneity in patients with ARDS. In anesthetized patients, lung atelectasis decreased with phrenic nerve stimulation (45, 46). Other studies have demonstrated that controlled mechanical ventilation induces preferential ventilation of nondependent (anterior) lung regions in anesthetized and paralyzed subjects, whereas ventilation driven by diaphragm contractions results in preferential redistribution of volume to posterior lung regions (47). In patients with quadriplegia with normal lungs, diaphragm pacing improved oxygenation and reduced pulmonary dead space compared with PPV (48). Therefore, maintaining diaphragm activity in patients with ARDS may reduce lung stress and strain and prevent VILI, provided that total lung-distending pressures are safely limited (45,49). Promoting spontaneous breathing could theoretically address this conundrum, but the high levels of inspiratory efforts characteristic of acutely ill patients carry the risk of inducing injurious lung-distending pressures that may worsen VILI. In summary, diaphragm activation may be beneficial by recruiting atelectatic alveoli and decreasing global and regional lung stress and strain. Diaphragm neurostimulation may improve lung mechanics while maintaining fine-tuned control of diaphragmatic effort and lung-distending pressure (Figure 4).

In a porcine healthy lung model, Rohrs and colleagues compared oxygenation, lung mechanics, and histology in three groups of animals exposed to 50 hours of PPV in ICU conditions (50). One group was exposed to PPV only (control group, n = 10), and two others were exposed to PPV plus synchronous diaphragm neurostimulation provided through a transvenous approach during volume controlled ventilation. In one group, the diaphragm was stimulated on every second breath (50% group, n = 8), and, in the other, the diaphragm was stimulated with every breath (100% group, n = 7) (50). The authors reported a redistribution of  $V_T$  from ventral to dorsal regions of the lungs, a mitigation of the loss in end-expiratory lung volume, and preserved oxygenation in stimulated animals (50). Moreover, there was a dose-dependent improvement in lung compliance and a reduction in both transpulmonary plateau and driving pressures (50). In a more sophisticated pig model of ARDS induced by oleic acid, the same team reported that animals exposed to PPV plus diaphragm neurostimulation had lower markers of lung strain, reduced loss of endexpiratory lung volume, and less extravascular lung water than animals exposed to PPV only (51). These preliminary findings are very promising and establish a biological and physiological foundation for the potential clinical benefit of diaphragm neurostimulation assisted ventilation in critically ill patients with or at risk of lung injury. However, diaphragm neurostimulation may also potentially provoke asynchronies, which may lead to diaphragm injury and excessive VT. Another potential issue is the risk of pendelluft (52) induced by diaphragm contractions occurring during controlled ventilation. Combining deep sedation with volume-controlled mode might theoretically address this issue, but such a strategy warrants further studies.



**Figure 4.** Established and plausible physiological effects of diaphragm neurostimulation assisted ventilation compared with positive pressure ventilation (Original illustration, by Pierre Bourcier).

### Augmenting thermodynamics by Activating the Respiratory Pump

Transition from negative intrathoracic pressure in spontaneously breathing subjects toward PPV is often associated with hemodynamic impairment (5). By increasing the intrathoracic pressure with positive end-expiratory pressure and cyclic insufflations of  $V_T$ , PPV increases the right atrial pressure, decreases the transmural left ventricular systolic pressure, and reduces the pressure gradients for venous return and left ventricle ejection in cases of preload dependence. Eventually, these mechanisms lead to decreased cardiac output in patients with normal left ventricle function, especially when the vasomotor tone is reduced by the use of sedatives and the presence of sepsis. The detrimental effects of PPV on cardiac output are reversed by fluid administration in the presence of preload dependence, but positive fluid balance is independently associated with poor outcomes (53). The hemodynamic effects of PPV are diametrically opposed to those of diaphragmatic contractions. Other considerations include the potential beneficial effects on right ventricular function. By improving ventilatory homogeneity and reducing pulmonary vascular resistance, diaphragm stimulation may protect the right ventricle and left ventricular end-diastolic volume. Preliminary observations reported that diaphragm contractions induced via a cardiac pacemaker increased cardiac output (54). In a sheep model, phrenic nerve stimulation done produced alveolar ventilation without reducing cardiac output and actually alleviated PPV-induced decrease in cardiac output (55). Theoretically, (voluntary) spontaneous breathing efforts may reduce the drop in cardiac output induced by PPV, but they might be associated with large  $V_{TS}$ , which are harmful in ARDS. Targeting the adequate level of inspiratory effort to achieve bod` lung- and diaphragm-protective ventilation and hemodynamic optimization appears challenging in clinical practice. Therefore, there is a strong physiological rationale for the benefit of diaphragm neurostimulation on hemodynamics.

## **Addressing the Possibility of Brain injury from PPV**

PPV appears to be deeply implicated in the Lung-brain interaction (6, 56). Lungs detect PPV-induced stimuli through their mechanoreceptors and communicate this information to the brain by a variety of mechanisms, most likely involving the autonomic nervous system in general and the vagus nerve in particular (6). This communication can be mediated via a complex web of signaling events involving neural, inflammatory, immunologic, and neuroendocrine pathways. In the specific context of medical ICU patients who have not suffered head trauma or vascular damage, brain injury has no clear definition. Delirium, the most apparent manifestation of brain dysfunction, may be present in 60-80% of mechanically ventilated patients (57). Delirium is independently associated with increased mortality and prolonged duration of PPV in the ICU (58, 59). An experimental study in pigs demonstrated that considerable hippocampal insult can be observed after 50 hours of lung-protective PPV, sedation, and physical immobility and that diaphragm neurostimulation in association with PPV was associated with reduced hippocampal apoptosis and inflammation (60). The underlying mechanisms of this association are still unclear. The beneficial effects of diaphragm neurostimulation on hippocampal inflammation may be mediated by a reduction of the lung inflammatory response and a better sympathetic/parasympathetic balance.

## **Research Agenda and Perspectives**

There may be several indications for diaphragm neurostimulation in mechanically ventilated patients. Although clinical studies to date have mostly focused on rehabilitation of established diaphragm weakness in patients recovering from critical illness, the most interesting potential indication is to prevent the development of diaphragm atrophy and dysfunction while optimizing lung-protective ventilation. Animal data are promising, showing preservation of diaphragm fiber muscle architecture and mitigation of VILI, but studies in mechanically ventilated patients are needed to validate this approach and to evaluate the effects of diaphragm contractions on hemodynamics, lung stress, lung strain, and gas exchange. The optimal approach to delivering and titrating diaphragm neurostimulation (physiological or clinical targets for titration of therapy; intensity, frequency, duration) has yet to be determined.

Further studies will have to evaluate the tolerance and feasibility of continuous diaphragm neurostimulation in critically ill patients. Careful consideration needs to be given to when phrenic pacing should be initiated. On the one hand, if patients are intubated after progressive respiratory failure, then requiring the diaphragm to participate in the work of breathing could conceivably cause harm in cases of excessive spontaneous efforts before intubation. On the other hand, it is well established that diaphragm dysfunction develops rapidly after intubation. Accordingly, it suggests that diaphragm neurostimulation should be initiated as soon as possible after intubation to prevent decline in diaphragm strength. In addition, the effects on the diaphragm myofibers and at the cellular level are not established. Experimental studies are reassuring because histological examination has not revealed diaphragm injury after periods of stimulation over as long as 50 hours (31, 32). Nevertheless, no study investigated the diaphragm function beyond relatively short periods of diaphragm neurostimulation in vivo or in vitro. The use of diaphragm shear wave elastography could be valuable in this purpose (61).

Recent technological developments allow synchronization of the stimulator with the ventilator, which should greatly improve interactions and minimize the risk of patient-ventilator asynchrony. Although it is not yet established, volume control may be the most suitable ventilation mode to guarantee predefined  $V_{TS}$ , avoiding alveolar hypoventilation on one side or high transpulmonary pressure on the other side. To this end, a deep sedation will be necessary to ensure perfect patient~ventilator synchrony.

If continuous diaphragm neurostimulation assisted ventilation proves feasible and safe at the early phase of ARDS, the next step will be to evaluate its potential benefits on lung mechanics and diaphragm function before exploring clinical outcomes. Considering its potential benefits on lung volume distribution, diaphragm neurostimulation acts as a complement or even an alternative to prone positioning.

## Conclusions

In the last 200 years, diaphragm neurostimulation has evolved from being an experimental approach for cardiorespiratory resuscitation toward becoming an established and permanent treatment for patients with high spinal cord injuries or central alveolar hypoventilation who would otherwise remain ventilator dependent. Recent developments involving less-invasive techniques allow diaphragm neurostimulation to be studied as an innovative adjunctive ventilation strategy in critically ill patients. This approach may offer several appreciable advantages at different stages of mechanical ventilation and weaning compared with traditional PPV. Many studies will be needed to evaluate feasibility, optimal dosing, tolerance, physiological effects, and patient-centered outcomes in various ICU populations. Diaphragm neurostimulation assisted ventilation has the potential to transform many aspects of acute ventilatory management in years to come.

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