

# Lung- and Respiratory Muscle-Protective Mechanical Ventilation

From Physiology to Clinical Applications

**Heder Jonathan de Vries**

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ISBN/EAN: 978-94-6361-993-6  
doi: 10.5463/thesis.615  
Cover design by: Heder de Vries with DALL-E 3 from OpenAI  
Layout and printing: Optima Grafische Communicatie

The work described in this thesis was performed at the Department of Intensive Care Medicine, AmsterdamUMC location VUmc, Amsterdam, while part of the Amsterdam Cardiovascular Sciences research institute.

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VRIJE UNIVERSITEIT

# **Lung- and Respiratory Muscle-Protective Mechanical Ventilation**

From Physiology to Clinical Applications

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan  
de Vrije Universiteit Amsterdam,  
op gezag van de rector magnificus  
prof.dr. J.J.G. Geurts,  
in het openbaar te verdedigen  
ten overstaan van de promotiecommissie  
van de Faculteit der Geneeskunde  
op vrijdag 14 juni 2024 om 13.45 uur  
in een bijeenkomst van de universiteit,  
De Boelelaan 1105

door

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## **General introduction and outlines of the thesis**



## GENERAL INTRODUCTION AND OUTLINES OF THE THESIS

### The respiratory system, a source of endless inspiration

The respiratory system drives respiration: moving oxygen-rich air from the atmosphere into the bloodstream, and removing carbon-dioxide via the opposite route.<sup>1</sup> The importance of this act is reflected in its etymology: re-spiritus, “to (repeatedly) bring back the spirit (into the body)”.<sup>2</sup>

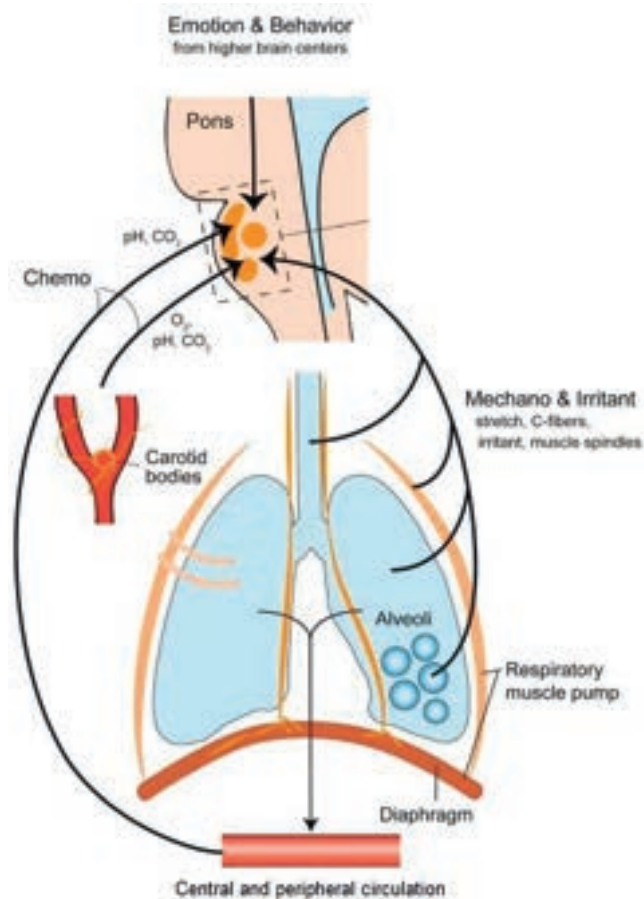
The respiratory system consists of several parts that work together to ensure respiration matches the metabolic demands of the body (**Figure 1**). Several sensors are distributed throughout the body, both central and peripheral, that continuously monitor whether ventilation is matched with metabolic demands. Chemoreceptors in the carotid bodies and aortic arch sense the partial oxygen and carbon-dioxide pressures in the circulation. A rising level of carbon-dioxide, caused for instance by exercise or fever, prompts an increase in respiratory minute volume. Irritant receptors are positioned mostly in the airways, and are sensitive to potentially injurious molecules and particles in inhaled air. Mechanoreceptors are found in the lung tissue and chest wall, and respond to stretching of the lungs and chest wall. The respiratory control center integrates information from these peripheral sensors with emotional and behavioral stimuli from the brain cortex to generate a rhythmic pattern of activity.<sup>3</sup> These signals are transmitted through various nerves to drive the respiratory muscle pump.<sup>4</sup>

The respiratory muscle pump generates the pressure gradients that move air into and out of the lungs. The respiratory muscle pump consists of the diaphragm, the accessory inspiratory muscles (including the external intercostal muscles, the sternocleidomastoid, the scalenus, and to a lesser extent the pectoralis minor and major, the latissimus dorsi and the parasternalis), and the expiratory muscles (including the internal intercostal muscles, the rectus abdominis, the transverse abdominis and the internal and external oblique muscles).<sup>5</sup>

A strict order exists in which these muscles are recruited during progressive inspiratory loads. The diaphragm is the main muscle of inspiration, responsible for generating over 70% of minute volume during relaxed, tidal breathing.<sup>6</sup> This is an extraordinary achievement considering its size. The diaphragm is a thin, dome-shaped muscle that separates the thorax from the abdomen. The diaphragm is only 1.5-2.5mm thick, but it can generate pressures over 150 cmH<sub>2</sub>O per breath.<sup>7</sup> Contraction of the diaphragm moves the diaphragm dome caudally, increasing the size of the thorax. This reduces the pressure in the pleural cavity, generating a pressure gradient between the alveoli and the pleura, causing the alveoli to expand. As soon as alveolar pressure is lower than atmospheric

pressure, air from outside the lungs will flow towards the lower pressure. The elastic energy stored in lungs and chest wall during inspiration drives expiration at rest.<sup>8</sup>

When respiratory demands increase, the accessory muscles are recruited to share the workload with the diaphragm.<sup>9</sup> These muscles are all connected to the thorax, and can further increase the size of the thorax when they contract, further lowering pleural pressure, thus leading to larger pressure gradients to drive inspiration. The expiratory muscles work quite differently, as their contractions increase pleural pressure either directly or by first increasing abdominal pressure and shifting the diaphragm upwards,



**Figure 1. Overview of the respiratory system.** The respiratory control centers (yellow areas) are positioned in the brainstem, and are responsible for generating the neural signals that drive the respiratory muscle pump (only the diaphragm is shown for clarity). Information from several types of sensors (chemo, mechano and irritant) is integrated with information from the cortex, which leads to a recruitment pattern of the respiratory muscles. The goal of the respiratory system is to generate a minute volume that matches metabolic demand. *Adapted from de Vries et al., Crit Care 2020.*

which in turn increases the pressure gradient leading to expiratory flow. At rest, the expiratory muscles are mostly used for airway clearance and posture, but they can be recruited during high respiratory demands to further increase expiratory minute volume.<sup>5</sup>

Finally, the lungs are an essential component of the respiratory system, as they are responsible for exchanging oxygen from the inhaled air with carbon-dioxide from the blood.<sup>1</sup>

As a whole, the respiratory system will perform the task of matching minute volume to metabolic demands diligently and without stop from the moment of birth until the literal final breath. In the time that you will spend reading this introduction (approximately 15 minutes), you will take 200-300 breaths, move approximately 100 liters of air and saturate 80 liters of blood. Perhaps you will cough once or twice, and sigh and yawn, too – but hopefully not because of this introduction!

### **Assessing respiratory drive and breathing effort**

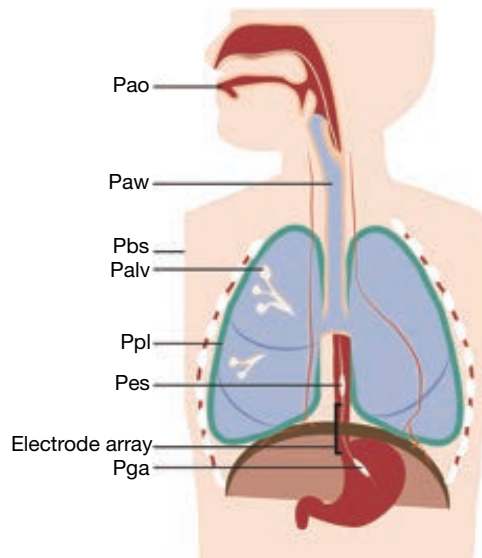
Several techniques have been developed to quantify respiratory drive and the force output of the different muscle groups of the respiratory system. The technique that influenced research and clinical care the most is esophageal manometry. First advocated by Buytendijk in his thesis in 1949,<sup>10</sup> esophageal manometry relies on a catheter inserted into the esophagus to measure esophageal pressure (Pes). Pes is considered to represent pleural pressure due to close anatomical relation of the pleural cavity and the esophagus, and because the esophageal has little to no wall tension (**Figure 2**). The catheter has small holes at the end to allow for better pressure transmission. These holes are covered with an inflatable balloon to prevent occlusion (hence the name ‘balloon catheters’).

As discussed above, the respiratory muscles drive ventilation by generating a negative intrapleural pressure. The tidal swings in pleural pressure, and by extent the swings in esophageal pressure, are therefore a global assessment on the force output of the respiratory muscles. The respiratory muscles must simultaneously overcome the pressure generated by the inwards tendency of the chest wall to collapse (Pcw). A more precise measurement of the force output of the respiratory muscles (Pmus) can therefore be obtained by correcting for chest wall pressure ( $P_{mus} = P_{cw} - P_{es}$ ).

An additional balloon catheter can be placed in the stomach to measure gastric pressure (Pga). When gastric pressure is available, a clinician can assess the exact pressure generated by the diaphragm alone, excluding the pressure generated by the accessory

inspiratory muscles, by calculating transdiaphragmatic pressure ( $P_{di}$ , calculated as  $P_{ga} - P_{es}$ ).<sup>11,12</sup>

The intensity of respiratory drive cannot be measured directly. Nevertheless, catheters have been developed that can assess the intensity of the neural signal sent to the diaphragm. These catheters employ a small array of electrodes, which are positioned at the transition between the esophagus and the stomach, to continuously record the electromyography of the crural part of the diaphragm. Integration of these myography signals with dedicated software provides an estimate of the electrical activity of the diaphragm (Edi).<sup>13-15</sup>



**Figure 2: Assessment of respiratory drive and respiratory muscle force output.** A small catheter (white line in the figure) is inserted via the nose into the esophagus. This catheter has an esophageal balloon, positioned at the lower third of the esophagus to measure esophageal pressure ( $P_{es}$ ), and a gastric balloon, positioned in the stomach, to measure gastric pressure ( $P_{ga}$ ). Also shown is an array of electrodes positioned between the esophageal and gastric balloon the record the electromyogram of the diaphragm (Edi). Adapted from de Vries et al, *Assessing breathing effort in mechanical ventilation*, *Annals of Translational Medicine* 2018.

## Respiratory failure and mechanical ventilation

The respiratory system is highly adaptive, as it can increase minute ventilation twenty-fold during strenuous exercise.<sup>1</sup> Nevertheless, the respiratory system might become overwhelmed in extraordinary situations, such as severe pneumonia and asthmatic attacks, or can be suppressed due to intoxications or neurotrauma. Failure of the respiratory system is often fatal without rapid intervention.

Mechanical ventilation is a life-saving intervention in respiratory failure.<sup>16</sup> Mechanical ventilation can replace or support the inspiratory muscles by generating a positive pressure at the airway opening, creating a pressure gradient between the airway opening and the alveoli, causing air to move into the lungs. Note that the pressure gradient between the airway opening and alveoli is now caused by a higher (positive) pressure at the airway opening, as opposed to lowering alveolar pressure by expanding the size of the thorax, hence the name 'positive pressure ventilation'. The elastic energy stored in the lungs and chest wall during inspiration will drive expiration during mechanical ventilation. Additionally, positive end-expiratory pressure (PEEP) can be applied continuously to the airway to reopen closed lung areas (recruitment), which improves oxygenation and ventilation.

Several modes of mechanical ventilation can be applied, depending on the type and severity of the patients underlying condition. A controlled mode of ventilation is applied if the patient has no own respiratory drive, e.g., during deep sedation or after neurological trauma, or when the patient cannot use their respiratory muscles at all, e.g., due to extreme muscle weakness or after poisoning with neurotoxins. In these cases, clinicians setting the ventilator essentially take over the function of the chemoreceptors and respiratory control centers by frequently sampling a patient's arterial blood, and by setting the frequency and intensity of pressure (or volume) delivered by the ventilator.

A partially-supported mode of ventilation can be used if a patient still has some respiratory drive and muscle effort, but is not able to generate sufficient minute volumes. For example, patients with severe exacerbations of chronic obstructive airway diseases have very high flow resistance in the airways, requiring high breathing effort. This might lead to respiratory muscle fatigue and inadequate minute ventilation. A supported mode of ventilation can increase a patient's minute volume in such cases. In partially supported modes, the patient initiates an inspiration by generating a negative interpleural pressure leading to flow in the airways and ventilator circuit, which is detected by the ventilator. The ventilator, in turn, provides positive pressure to the airways to support the inspiratory effort of the patient, effectively unloading the patient.<sup>17,18</sup>

More recently, dedicated catheters have been developed that measure the neural activation of the diaphragm with electromyography as discussed above. These catheters can be used to steer a mechanical ventilator. With this mode of ventilation, called neurally-adjusted ventilatory assist (NAVA), it is easier for the patient to trigger the ventilator. Additionally, this mode delivers tidal volumes proportional to the respiratory drive in each breath.<sup>19</sup>

## **Lung-protective ventilation**

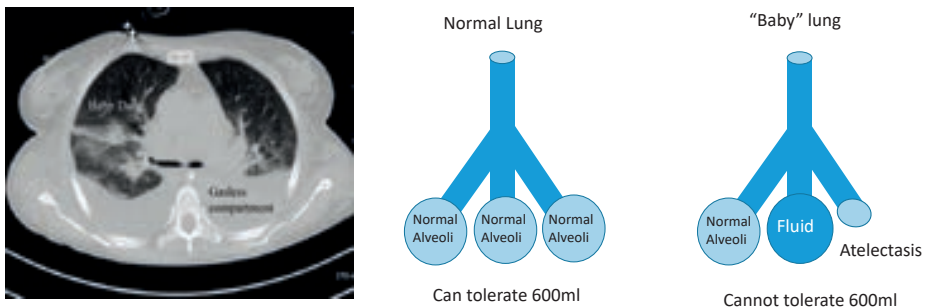
Mechanical ventilation, however, is not without risk. It had already been theorized in 1744 that mechanical ventilation could overwhelm the protective reflexes that prevent a patient from taking injuriously large breaths.<sup>20</sup> Pneumothorax was indeed a common complication after the widespread adoption of invasive positive pressure mechanical ventilation in the 1950s.<sup>21</sup> The lungs of critically ill patients are susceptible to injury by the mechanical ventilator due to various mechanisms.<sup>22</sup>

First, a loss of aerated lung tissue can lead to more stress applied to the remaining alveoli. A large proportion of critically ill patients have primary diseases at admission to the intensive care, such as a pneumonia, leading to build-up of inflammatory cells, debris and fluid in the alveoli, causing a loss of aeration. Other critically ill patients can have an overwhelming systemic inflammatory response to an infection in another part of the body, for instance due to pancreatitis, leading to increased vascular permeability and fluid leakages into the lung tissue (lung edema). Both primary lung diseases and systemic inflammatory responses can therefore lead to a critical state in which oxygenation and ventilation are severely impaired, which is the hallmark of the acute respiratory distress syndrome (ARDS). Parts of the lung might collapse completely in ARDS patients, resulting in collapse of lung tissue. The lungs of certain critically ill patients therefore have less lung tissue available for gas exchange, which was termed the 'baby lung'.<sup>23</sup> It is not difficult to imagine that applying tidal volumes that are normal to healthy adults to such baby lungs can overstretch the alveoli that remain available for gas exchange.

Second, the distribution of lung edema in critically ill patients further increases their risk for lung injury due to mechanical ventilation. Lung edema is often distributed very unevenly in the critically ill; areas of complete lung collapse can border areas with hyperinflation. The interfaces between closed and open alveoli in critically ill lungs act as local stress raisers, doubling the sheer stresses at these places, further increasing the risk of lung injury.<sup>24</sup>

Third, critically ill patients can have a tremendously high respiratory drive because of overwhelming feedback from the chemoreceptors, mechanoreceptors and irritant receptors discussed above caused by acidemia and pulmonary inflammation. Elevated respiratory drive causes the respiratory muscles to generate large negative pressure swings in the thorax. These negative pressure swings impose large stresses on the lung tissue and can increase vascular leakage, potentially causing even more lung damage in a phenomenon termed patient self-inflicted lung injury.<sup>25</sup>

The ARDSnet-trial was a landmark trial in mechanical ventilation that was designed to limit lung stresses.<sup>26</sup> Data from this trial showed that application of lower tidal volumes (6 ml/kg vs 12 ml/kg) lead to a 9% absolute reduction intensive care unit (ICU) mortality (25% relative reduction), prompting immediate implementation of ‘lung-protective’ ventilation. Later studies found that assessment of the driving pressure, essentially normalizing tidal volume to the compliance of the patients’ individual lungs, allowed for even better titration of mechanical ventilation settings.<sup>27</sup> Additional parameters for lungs stress are being validated, such as the mechanical power, which combines the applied pressure, volume and frequency.<sup>28</sup>



**Figure 3: The baby lung.** CT-scan image showing the concept of the “baby lung”. On the left a transversal computed tomography image showing reduced lung volume due to atelectasis. In the middle and left, a schematic is shown explaining why the baby lung is subject to more stress for the same applied volume.

*Adapted from Gattinoni et al, Intensive Care Medicine, 2016*

### Critical illness-associated diaphragm weakness and weaning from mechanical ventilation

Limiting lung stress during mechanical ventilation improved patient outcomes, but it did not solve all problems associated with mechanical ventilation. Accumulating evidence suggests that mechanical ventilation rapidly affects the structure and function of the diaphragm, leading to diaphragm weakness.<sup>29</sup>

Like any skeletal muscle, the diaphragm becomes weak when it is not used, so-called disuse atrophy. This phenomenon was first observed in infants on mechanical ventilation<sup>30</sup> and was confirmed in adults two decades later when Levine described reductions in fiber cross-area of diaphragm biopsies taken from mechanically-ventilated brain dead organ donors.<sup>31</sup> Further research showed that the involuntary strength of the diaphragm also decreases rapidly in ICU patients, losing more than 40% of their strength in the first week of ventilation.<sup>32</sup> Diaphragm biopsies from critically ill patients by our group confirm widespread atrophy of diaphragm fibers.<sup>33,34</sup> Presence of sepsis, neuromuscular

blocking agents and steroids can further increase susceptibility of the diaphragm to develop weakness.<sup>35</sup>

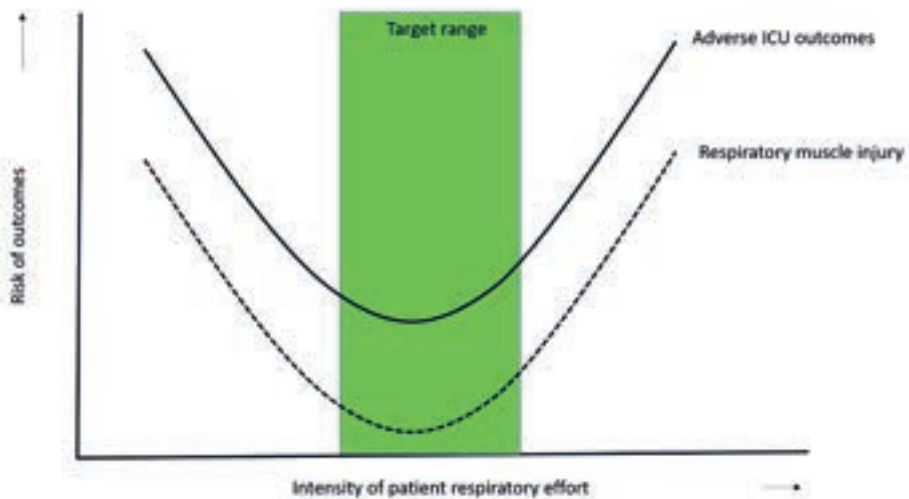
Diaphragm weakness is problematic, as it is associated to difficulties in weaning from the mechanical ventilation and poor clinical outcome.<sup>36-38</sup> Most patient can be liberated from mechanical ventilation as soon as the primary reason for respiratory failure has resolved, e.g., after the pneumonia has been treated with antibiotics for a few days and lung infiltrates have resolved. Up to a quarter of patients experience difficulties in weaning from mechanical ventilation, however.<sup>39</sup> In these patients, the primary reason for respiratory failure has been resolved, but nevertheless the patient fails to generate adequate minute volume without assistance from the ventilator. Almost half of all time spend on mechanical ventilation is due to difficulties in weaning.<sup>40</sup> More than half of all patients that are difficult to wean from mechanical ventilation have severe diaphragm weakness.<sup>41</sup>

Avoiding diaphragm inactivity can limit the development of disuse atrophy. As discussed above, several modes of mechanical ventilation were developed in which the patient and ventilator work simultaneously to limit development of diaphragm atrophy and reduce time spend on weaning. The effectiveness of these modes in limiting diaphragm weakness has been confirmed in interventional animal studies<sup>42</sup> and trials in critically ill patients.<sup>43,44</sup>

Finding a balance between no diaphragm activity and too much activity is challenging. As discussed above, elevated respiratory drive resulting in high patient effort can be detrimental to the lungs. It has been theorized that high patient effort is also harmful to the diaphragm itself (load-induced injury), although evidence is currently scarce.<sup>35</sup> Some of the diaphragm biopsies taken from critically ill patients demonstrated fiber disruption and infiltration of inflammatory cells, a pattern that consistent with overexertion or myotrauma, not with disuse and atrophy.<sup>33</sup> Indeed, an observational trial in critically ill patients demonstrated that patients with high diaphragm effort have an increase in diaphragm thickness (possibly due to edema caused by inflammation), and have worse ICU outcomes. Patients with diaphragm effort in the same range as healthy subjects maintain their diaphragm thickness and have better ICU outcomes than patients with effort below this range or above this range.<sup>43,45,46</sup> This led to the hypothesis that a 'diaphragm-protective' range for breathing effort exists, that prevents the development of disuse atrophy and-load induced injury (**Figure 3**).

## A new concept: lung- and diaphragm protective ventilation

These observations led to a new concept: the lung- and diaphragm-protective approach to mechanical ventilation.<sup>47-49</sup> This approach aims to limit the stresses posed on the lungs while maintaining a physiological level of breathing effort. The hypothesis is that a moderate intensity of breathing effort prevents disuse atrophy, and limits the chance of developing load-induced injury. Simultaneously, lung stress has to be as low as possible to limit the risk of developing lung injury. The ultimate goal is to improve patient outcomes by reducing lung stress and diaphragm injury.

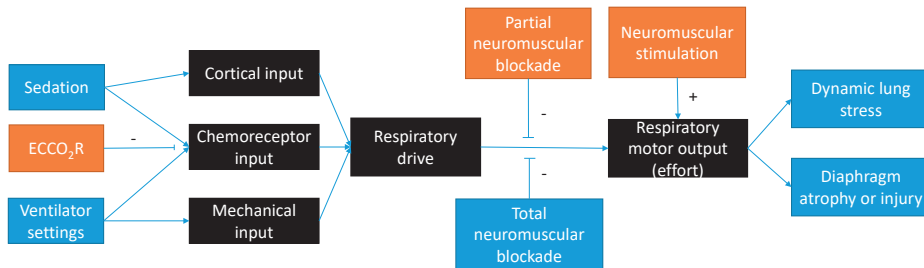


**Figure 4: Proposed relation between respiratory effort and adverse outcomes.** It is assumed that every patient has an optimal range of breathing effort to prevent disuse atrophy and effort-induced myotrauma and lung injury. Having a lower or a higher intensity of respiratory effort increases the chance for muscle injury and adverse outcomes. Adapted from Zhou et al. *Respiratory Monitoring in Mechanical Ventilation*, *Thoracic Key J* 2022

Several therapeutic options are available to a clinician when patient breathing effort is absent or excessively high (**Figure 5**). These interventions can act directly or indirectly on the intensity of the signals generated in the respiratory centers (respiratory drive), or by influencing the force output of the respiratory muscles. First, the level of sedation can be increased to dampen the output of the respiratory centers, lowering (or abolishing) respiratory muscle output. Second, the level of support provided by the ventilator can be adjusted. Increasing ventilator support tends to lower respiratory drive by increasing minute volume, lowering carbon-dioxide levels and providing negative feedback via mechanoreceptors in the chest wall.<sup>50</sup> Positive expiratory pressure can be applied to

recruit lung tissue, increasing the efficiency of gas exchange and thus lowering respiratory drive. Neuromuscular blockers can be applied to completely abolish patient effort when the above-mentioned interventions are ineffective.<sup>51</sup>

Several experimental techniques exist to influence respiratory motor output, but these require more research. First, extracorporeal carbon-dioxide removal can be used to lower carbon-dioxide levels and thus reduce respiratory drive,<sup>52,53</sup> but increases risk of bleeding and coagulation.<sup>54</sup> Another experimental technique is partial neuromuscular blockade, in which lower doses of neuromuscular blocking agents are titrated to a desired range of patient breathing effort.<sup>55</sup> Last, stimulation of the respiratory muscles with electrodes to prevent disuse atrophy has been used in animal studies<sup>56</sup> and pilot trials in patients.<sup>57</sup> All these experimental techniques require further assessment before they can be implemented in clinical care.



**Figure 5: Therapeutic options to influence respiratory drive and effort.** Techniques that are currently applied in clinical practice are shown in blue, experimental techniques are shown in orange. *Adapted from Goligher et al., Intensive Care Medicine 2020*

## Aims and outlines of the thesis

This thesis focuses on limiting the detrimental effect of mechanical ventilation on the lungs and the respiratory muscles of critically ill patients. The general aim was to develop and assess techniques to monitor and control lung stress and respiratory muscle effort in clinical practice, and to improve understanding of respiratory physiology in the critically ill.

Part one of this thesis focusses on monitoring and controlling lung stress and diaphragm effort in critically ill patients. The general hypothesis of this part of thesis was that respiratory drive and respiratory muscle effort can be measured and controlled in critically ill patients by understanding respiratory physiology.

In **chapter two**, we discuss how breathing effort is controlled by the brainstem in healthy subjects and critically ill patients. Additionally, we discuss the arsenal of options

available to the clinician to influence the respiratory control centers and thus respiratory muscle effort. In **chapter three**, we describe how the force output of the respiratory muscles can be assessed in critically ill patients on mechanical ventilation. We also highlight the benefits and limitations of all the currently-available techniques to assess breathing effort in the critically ill, and provide target ranges for optimal breathing effort based on available literature. In **chapter four**, we describe the pathophysiology of an unexpected interaction between the mechanical ventilator, a patient's respiratory control center and a patient's respiratory muscles. This case illustrates that advanced monitoring of respiratory drive and muscle effort is vital to understand the interplay between a patient and the mechanical ventilator.

In **chapter five**, we describe a randomized-controlled trial in critically ill patients. We hypothesized that lung- and diaphragm-protective ventilation could be obtained in the majority of patients by titrating the inspiratory support level provided by the ventilator. We used state-of-the-art monitoring tools and a bedside algorithm to obtain diaphragm effort within ranges observed in healthy adults at rest. Prior to this study, it was unknown how often patients had lung stress and diaphragm effort outside of the proposed safe ranges. It was also unknown whether continuous monitoring of lung stress and patient effort was feasible in clinical practice, and whether titration of inspiratory support was effective in titrating patient effort. The primary outcome was the time that the diaphragm operates within predefined diaphragm-protective ranges. Our data show that many patients in the control group have very low or excessive high diaphragm effort during partially supported ventilation. Second, the data shows that titration of diaphragm effort by adjusting ventilator support is feasible and highly effective, improving the time that the diaphragm has effort in the target range from 35% to 81%. Importantly, we demonstrate that titration of diaphragm effort has little effect on lung stress in the vast majority of critically ill patients.

However, the technique that we used to monitor diaphragm effort and lung stress, esophageal and gastric manometry, is not available in most ICUs. Therefore, we performed an additional analysis on the data obtained in the clinical trial in **chapter six**. The aim of this analysis was to assess whether bedside measurements can estimate lung stress and diaphragm effort. Our hypothesis was that the drop in airway pressure during the first 100ms of a breath ( $P_{0.1}$ ) and the total drop in airway pressure during an occluded inspiration ( $P_{occ}$ ) would correlate strongly with lung stress and patient effort. These parameters had been assessed separately in earlier studies, but it was unknown how well they correlated with  $P_{di}$  and whether either of the measurements outperformed the other. The primary outcomes were the correlations of  $P_{occ}$  and  $P_{0.1}$  with lung stress and diaphragm effort, and their diagnostic performance in detecting

extremes of lung stress and diaphragm effort. We found that both P0.1 and Pocc correlate with lung stress and diaphragm effort, but that the limits-of-agreement are too wide to replace esophageal manometry. Nevertheless, our data shows that Pocc can accurately detect patients with extremes of lung stress and diaphragm in ~90% of cases, outperforming P0.1. This is interesting, as these patients are most at-risk of developing lung injury and diaphragm weakness, and could benefit the most from interventions to lower lung stress and diaphragm effort.

Part two of this thesis focusses on the expiratory muscles, the often-neglected part of the respiratory muscle pump, and on the expiratory phase of respiration. The general aim of this part of the thesis was to evaluate how critically ill patients use their expiratory muscles, and whether the function of the expiratory muscles change during their ICU admission. The general hypothesis was that the expiratory muscles should not be ignored when considering a new approach to ventilation aimed at protecting the respiratory muscle pump. We describe the (patho)physiology of expiratory muscle recruitment in critically ill patients in the **preamble**.

In **chapter seven**, we describe an observational study in critically ill patients focusing on the expiratory muscles. Prior to this study, it was unknown whether the expiratory muscles develop atrophy during intensive care admission. We hypothesized that the expiratory muscles would also develop atrophy, and that this would be related to diaphragm atrophy. We measured the thickness of the diaphragm and expiratory muscles with ultrasound every other day during the first week of ICU admission. Our data show that the expiratory muscles do develop atrophy, albeit in a minority of patients. Furthermore, we show that diaphragm atrophy and expiratory muscle atrophy are not correlated, suggesting that diaphragm and expiratory muscle atrophy are entirely different entities.

We continue to assess both the diaphragm and expiratory muscles in **chapter eight**. In this secondary analysis of two trials, we aimed to assess whether the diaphragm remains active during expiration in critically ill patients, and whether this leads to eccentric contractions of the diaphragm (or 'active lengthening'). Earlier studies in pigs had shown that the diaphragm can remain active during expiration, but whether this occurred in human adults was unknown. We show the diaphragm remains active during expiration in the majority of healthy subjects and critically ill patients. We also show that expiratory diaphragm activity leads to active lengthening, a type of muscle contraction that has been theorized to contribute to diaphragm weakness.

Finally, we combine all our findings with current evidence and conclusions in the **synthesis**, and provide future recommendations.

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# **Part I**

**Monitoring and protecting  
the diaphragm and lungs**

2

# **Physiology of the Respiratory Drive in ICU Patients: Implications for Diagnosis and Treatment**

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*Critical Care. 2020 Mar 24;24(1):104*

*Author contributions: HdV and AJ contributed equally to this work. All authors were involved in the conception and design of the manuscript. All authors critically revised the manuscript and gave final approval of the submitted version.*

## **ABSTRACT**

The aim of this paper is to discuss the physiology of the respiratory drive, techniques to monitor drive and modulate drive, as far as relevant for ICU patients. Respiratory drive is the intensity of the output of the respiratory centers, and determines the effort to breathe. A combination of chemical, mechanical, behavioral and emotional factors contributes to respiratory drive. The most important receptors that provide feedback to the respiratory centers are central chemoreceptors sensitive to changes in pH in the cerebrospinal fluid. Both high and low respiratory drive can be present in critically ill patients under mechanical ventilation. High or low respiratory drive may worsen, or even result in lung injury and diaphragm injury. Several techniques are available to monitor respiratory drive in critically ill patients, including clinical evaluation, diaphragm electromyography, the airway occlusion pressure ( $P_{0.1}$ ), and transdiaphragmatic pressure. Monitoring and modulating respiratory drive might limit the clinical impact of high or low respiratory drive on the lungs and diaphragm. Potential strategies to modulate respiratory drive towards physiological levels include adaptation of ventilator inspiratory support, medication (i.e., opioids, sedatives), and extracorporeal  $CO_2$  removal. The impact of modulating respiratory drive on the patient's outcome requires further evaluation.

## INTRODUCTION

The primary goal of the respiratory system is gas exchange, especially the uptake of oxygen and elimination of carbon dioxide. The latter plays an important role in maintaining acid-base homeostasis. This requires tight control of ventilation by the respiratory centers in the brain stem. The respiratory drive is the intensity of the output of the respiratory centers, and determines the mechanical output of the respiratory muscles (also known as breathing effort).<sup>1,2</sup>

Detrimental respiratory drive is an important contributor to inadequate mechanical output of the respiratory muscles, and might thus contribute to the onset, the duration, and the recovery from acute respiratory failure. Studies in mechanically ventilated patients have demonstrated detrimental effects of both high and low breathing effort, including patient self-inflicted lung injury (P-SILI), critical illness-associated diaphragm weakness, hemodynamic compromise and poor patient-ventilator interaction.<sup>3,4</sup> Strategies that prevent the detrimental effects of both high and low respiratory drive might therefore improve patient outcome.<sup>5</sup>

Such strategies require a thorough understanding of the physiology of respiratory drive. The aim of the current paper is to discuss the (patho)physiology of the respiratory drive, as far as relevant to critically ill ventilated patients. We discuss the clinical consequences of high and low respiratory drive, and evaluate techniques that can be used to assess respiratory drive at the bedside. Last, we propose optimal ranges for respiratory drive and breathing effort, and discuss interventions that can be used to modulate the patient's respiratory drive.

### Definition of respiratory drive

The term “respiratory drive” is frequently used, but is rarely precisely defined. It is important to stress that the activity of the respiratory centers cannot be measured directly, and therefore the physiological consequences are used to quantify respiratory drive. Most authors define respiratory drive as the *intensity* of the output of the respiratory centers,<sup>3</sup> using the amplitude of a physiological signal as a measure for *intensity*. Alternatively, we consider the respiratory centers to act as oscillatory neuronal networks that generate rhythmic, wave-like signals. The intensity of such a signal depends on several components, including the amplitude and frequency of the signal. Accordingly, we propose a more precise, but clinical useful definition of respiratory drive: the time integral of respiratory muscle activity. As such, a high respiratory drive might mean that the output of the respiratory centers has a higher amplitude, a higher frequency, or both.

The respiratory drive directly determines breathing effort when neuromuscular transmission and respiratory muscle function are intact. We define breathing effort as the mechanical output of the respiratory muscles, including both the magnitude and the frequency of respiratory muscle contraction.<sup>1</sup>

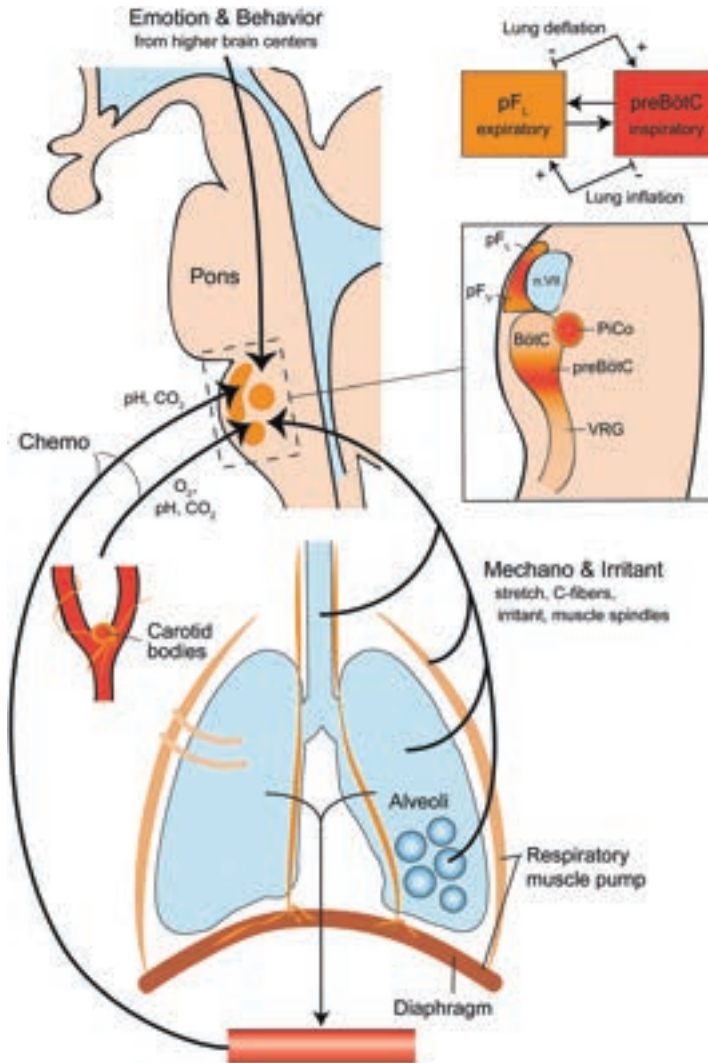
## WHAT DETERMINES THE RESPIRATORY DRIVE?

### Neuroanatomy and Physiology of the Respiratory Control Centers

The respiratory drive originates from clusters of interneurons (respiratory centers) located in the brainstem (**Figure 1**).<sup>2</sup> These centers receive continuous information from sources sensitive to chemical, mechanical, behavioral and emotional stimuli. The respiratory centers integrate this information and generate a neural signal. The amplitude of this signal determines the mechanical output of the respiratory muscles (and thus tidal volume). The frequency and timing of the neural pattern relates to the breathing frequency and the duration of the different phases of the breathing cycle. Three phases can be distinguished in the human breathing cycle: inspiration, post-inspiration and expiration (**Figure 2**). Each phase is predominately controlled by a specific respiratory center (**Figure 1**).<sup>2</sup>

#### *Inspiration*

Inspiration is an active process that requires neural activation and subsequent contraction (and energy expenditure) of the inspiratory muscles. The preBötzinger complex, a group of interneurons positioned between the ventral respiratory group and the Bötzing complex in the brainstem (**Figure 1**), is the main control center of inspiration.<sup>2</sup> The output of the preBötzinger complex rises gradually during inspiration, and rapidly declines when expiration commences. Axons of the preBötzinger complex project to premotor and motor neurons that drive the inspiratory muscles and the muscles of the upper airways. The preBötzinger complex has multiple connections to the other respiratory centers, which is thought to ensure a smooth transition between the different breathing phases and to prevent concomitant activation of opposing muscle groups.<sup>6</sup>



**Figure 1: Schematic representation of the anatomy and physiology of respiratory drive.** The respiratory centers are located in the medulla and the pons and consist of groups of interneurons that receive information from sources sensitive to chemical, mechanical, behavioral and emotional stimuli. Important central chemoreceptors are located near the ventral parafacial nucleus ( $pF_V$ ) and are sensitive to direct changes in pH of the cerebral spinal fluid. Peripheral chemoreceptors in the carotid bodies are the primary site sensitive to changes in  $PaO_2$ , and moderately sensitive to changes in pH and  $PaCO_2$ . Mechano and irritant receptors are located in the chest wall, airway, lungs, and respiratory muscles. Emotional and behavioral feedback originate in the cerebral cortex and hypothalamus. The preBötzing complex (pre-BötC) is the main control center of inspiration, located between the ventral respiratory group (VRG) and the Bötzing complex (BötC). The post-inspiratory complex (PiCo) is located near the Bötzing complex. The lateral parafacial nucleus ( $pF_L$ ) controls expiratory activity and has continuous interaction with the preBötzing complex, to prevent inefficient concomitant activation of inspiratory and expiratory muscle groups: lung inflation depresses inspiratory activity and enhances expiratory activity, which ultimately results in lung deflation. Lung deflation has the opposite effect on these centers.

### **Post-inspiration**

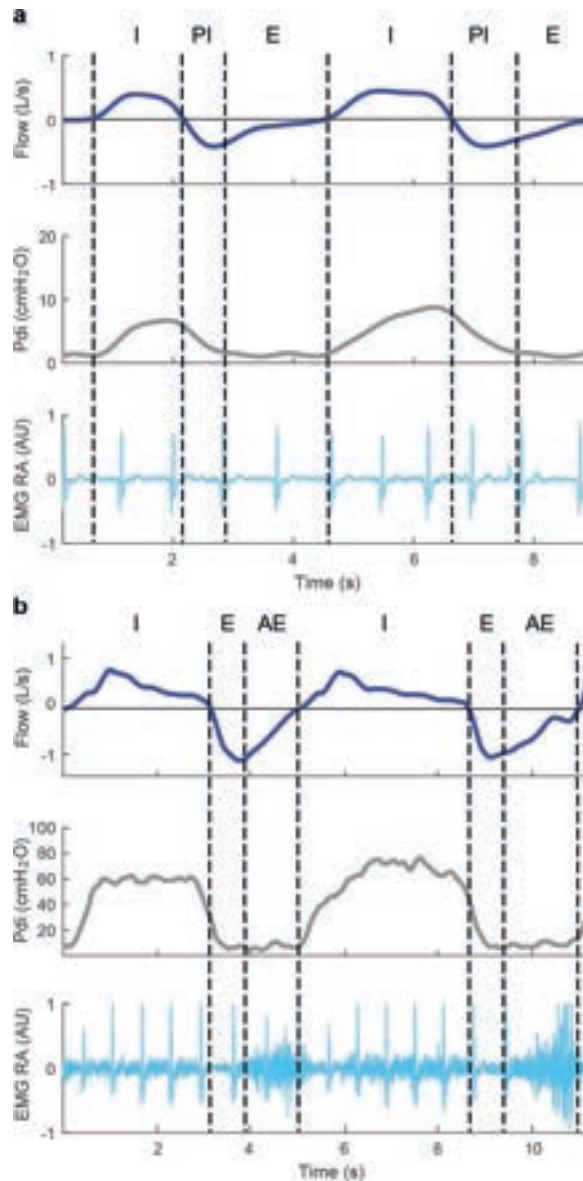
The aptly named post-inspiratory complex controls the transitional phase between inspiration and expiration by *reducing* expiratory flow. This is achieved by gradually lowering the excitation (and thus contraction) of the inspiratory muscles, which leads to *active lengthening* (i.e., eccentric contractions) of the diaphragm.<sup>2,7</sup> Additionally, the post-inspiratory center controls the upper airway muscles. Contraction of the upper airway muscles increases expiratory flow resistance, effectively reducing expiratory flow. Post-inspiratory activity increases the time before the respiratory system reaches end-expiratory lung volume. This can lead to a more laminar expiratory flow and might prevent alveolar collapse, while also increasing the duration of gas exchange in the alveoli.<sup>2</sup> Post-inspiration is a common part of the breathing cycle in healthy subjects at rest, but disappears rapidly when respiratory demands rise to favor faster expiration (**Figure 2**).<sup>8</sup>

The importance of the post-inspiratory phase in mechanically ventilated patients remains unclear, as the onset and duration of inspiratory and expiratory flow depend predominantly on the interplay between ventilator settings (e.g. cycle criteria, breathing frequency, ventilator mode) and the respiratory mechanics of the patient. Additionally, the endotracheal tube bypasses the actions of the upper airway muscles. Experimental data in piglets suggest that post-inspiratory activity of the diaphragm prevents atelectasis and possibly cyclic alveolar recruitment,<sup>9</sup> although studies in patients weaning from the ventilator did not find clear evidence for post-inspiratory activity.<sup>10</sup> Clearly, this field requires further research.

### **Expiration**

Expiration is generally a passive event during tidal breathing. The elastic recoil pressure of the lungs and chest wall will drive expiratory flow until the lung and chest wall recoil pressures are in equilibrium at functional residual capacity, or at the level of positive end-expiratory pressure (PEEP) in mechanically ventilated patients. In passive conditions, expiratory flow depends solely on the time-constant (i.e., the product of compliance and resistance) of the respiratory system. The expiratory muscles are recruited with high metabolic demands, low inspiratory muscle capacity, increased end-expiratory lung volume and/or increased expiratory resistance.<sup>11</sup>

The lateral parafacial nucleus controls the expiratory phase of breathing. An increased respiratory drive leads to late-expiratory bursts, and consequent recruitment of the expiratory muscles (extensively reviewed in Reference 11). Several inhibitory connections exist between the inspiratory preBötzinger complex and the expiratory lateral parafacial nucleus, which prevent concomitant activation of inspiratory and expiratory muscle groups (**Figure 1**).<sup>2,6</sup>



**Figure 2: Breathing phases.** Flow, transdiaphragmatic pressure (Pdi), and electromyography of the rectus abdominal muscle (EMG RA, in arbitrary units; note that this signal is disturbed with ECG artifacts) during tidal breathing at rest (Figure2A) and during high resistive loading (Figure2B) in one healthy subject. Vertical dashed lines mark the onset of the different breathing phases. Inspiration (I) is characterized by a steady rise in Pdi and positive flow, and is present during both tidal breathing and high loading. The gradual decrease in Pdi during expiratory flow in (Figure2A) is consistent with post-inspiration (PI). Notice that the rate of decline in Pdi during high loading (Figure2B) is much more rapid during high loading. During tidal breathing (Figure2A) expiration (E) is characterized by the absence of Pdi and EMG RA activity, and occurs after post-inspiration. High loading (Figure2B) leads to active expiration (AE), which can be recognized by the increase in EMG RA activity. Also, active expiration directly follows the inspiratory phase.

## **Feedback to the respiratory control centers**

### ***Central chemoreceptors***

The most important chemoreceptors in the central nervous system are positioned on the ventral surface of the medulla and near the ventral parafacial nucleus (also referred to as the retrotrapezoid nucleus). These receptors are sensitive to the hydrogen proton concentration ( $[H^+]$ ) of the cerebrospinal fluid, commonly known as pH.<sup>12</sup> Because  $CO_2$  can rapidly diffuse across the blood-brain barrier, changes in  $PaCO_2$  quickly affect the pH of the cerebral spinal fluid. A set-point exists in the control centers that keeps pH (and  $PaCO_2$ ) within a relatively tight range. A slight rise in  $PaCO_2$  above this set-point provides a powerful stimulus to breathe; a change in  $PaCO_2$  of 5 mmHg can already double minute ventilation in healthy subjects. When  $PaCO_2$  falls only a few mmHg below the set-point, the respiratory drive lowers gradually and can abruptly disappear causing apnea, especially during sleep.<sup>13</sup> In contrast, metabolic changes in pH are sensed less rapidly because it takes several hours before the electrolyte composition of the cerebral spinal fluid is affected by changes in metabolic acid-base conditions.

### ***Peripheral chemoreceptors***

The carotid bodies are positioned close to the carotid bifurcation and are the primary sites sensitive to  $PO_2$ ,  $PCO_2$  and pH of the arterial blood. The aortic bodies contribute to the respiratory drive in infants, but their importance in adults is probably minor.<sup>14</sup> The output of the carotid bodies in healthy subjects remains relatively stable over a wide range of  $PaO_2$  values; their output rises gradually below a  $PaO_2$  of 80 mmHg and then rises steeply when  $PaO_2$  falls below 60 mmHg.<sup>15</sup> Their contribution to respiratory drive in healthy subjects is therefore probably modest. However, concomitant hypercapnia and acidosis has a synergistic effect on the response of the carotid bodies, meaning their output is increased by more than the sum of their individual parts. This makes the carotid bodies in theory more relevant in ventilated patients in which hypoxemia, hypercapnia and acidosis are more common.

### ***Thoracic receptors***

Several receptors have been identified in the chest wall, lungs, respiratory muscles and airways that provide sensory feedback to the respiratory centers on mechanical and chemical conditions. Slowly adapting stretch receptors and muscle spindles are located in the chest wall, respiratory muscles, upper airways and terminal bronchioles, and provide information on stretch and volume of the respiratory system, through vagal fibers.<sup>2</sup> These receptors are well-known for their contribution to the Hering-Breuer reflexes, which terminate inspiration and facilitate expiration at high tidal volumes (**Figure 1**). Irritant receptors line the epithelium of the proximal airways, and are sensitive to irritant

gases and local inflammation. These sensors promote mucus production, coughing and expiration. C-fibers are found inside the lung tissue, and might be activated by local congestion causing dyspnea, rapid breathing and coughing.<sup>16</sup>

The relative contribution of these receptors to the respiratory drive of critically ill patients is uncertain. Feedback from these sensors might explain the hyperventilation observed in pulmonary fibrosis, pulmonary edema, interstitial lung disease, and pulmonary embolisms, which persist even in the absence of hypoxemia or hypercapnia. Further research into the contribution of these sensors during mechanical ventilation is warranted.

### ***Cortical and emotional feedback***

Stimuli based on emotional and behavioral feedback, originating in the cerebral cortex and hypothalamus, modulate the respiratory drive. Pain, agitation, delirium and fear are common in mechanically ventilated patients and can increase respiratory drive.<sup>17</sup> The role of the cortex and hypothalamus in respiratory drive of critically ill patients has rarely been studied, and requires more attention before recommendations can be made.

There is some evidence that the cerebral cortex has an inhibitory influence on breathing. Damage to the cortex might dampen this inhibitory effect, which could explain the hyperventilation sometimes observed in patients with severe neuro-trauma.<sup>18</sup>

## **WHAT IS THE EFFECT OF NON-PHYSIOLOGICAL RESPIRATORY DRIVE ON MY PATIENTS?**

### **Consequences of excessive respiratory drive**

#### ***Patient self-inflicted lung injury***

Excessive respiratory drive could promote lung injury through several mechanisms. In the absence of (severe) respiratory muscle weakness, high respiratory drive leads to vigorous inspiratory efforts, resulting in injurious lung distending pressures. Recent experimental studies demonstrate that this may worsen lung injury, especially when the underlying injury is more severe.<sup>19,20</sup> Particularly in patients with acute respiratory failure, large inspiratory efforts could result in global and regional over-distention of alveoli and cyclic recruitment of collapsed lung areas, due to an inhomogeneous and transient transmission of stress and strain (so-called P-SILI).<sup>3,21</sup> Large efforts may cause “pendelluft”: air redistributes from nondependent to dependent lung regions, even before the start of mechanical insufflation, and hence, without a change in tidal volume.<sup>20</sup>

Excessive respiratory drive may overwhelm lung-protective reflexes (e.g. Hering-Breuer inflation-inhibition reflex), which in turn leads to high tidal volumes and promotes further lung injury and inflammation.<sup>3</sup> In addition, large inspiratory efforts could result in negative pressure pulmonary edema, especially in patients with lung injury and/or capillary leaks.<sup>21</sup> As such, a high respiratory drive is potentially harmful in spontaneously breathing mechanically ventilated patients with lung injury. Applying and maintaining a lung-protective ventilation strategy (i.e., low tidal volumes and low plateau pressures) is challenging in these patients, and may often lead to development of patient-ventilator dyssynchronies such as double-triggering and breath stacking; again, leading to high tidal volumes and increased lung stress. Furthermore, maintaining low plateau pressures and low tidal volumes does not guarantee lung protective ventilation in patients with high respiratory drive.

### ***Diaphragm load-induced injury***

In non-ventilated patients excessive inspiratory loading can result in diaphragm fatigue and injury as demonstrated by sarcomere disruption in diaphragm biopsies.<sup>5</sup> Whether this occurs in critically ill ventilated patients is less clear, although we have reported evidence for diaphragm injury including sarcomere disruption.<sup>22</sup> The concept of load-induced diaphragm injury may explain recent ultrasound findings demonstrating increased diaphragm thickness during the course of mechanical ventilation in patients with high inspiratory efforts.<sup>23</sup> In addition to high breathing effort, patient-ventilator dyssynchronies, especially eccentric (lengthening) contractions may promote load-induced diaphragm injury.<sup>24</sup> Whether eccentric contractions are sufficiently severe and frequent to contribute to diaphragm injury in ICU patients is yet unknown.

### ***Weaning and extubation failure***

During ventilator weaning, high ventilatory demands with high respiratory drive increase dyspnea, which is associated with anxiety and impacts weaning outcome.<sup>25</sup> “Air hunger” is probably the most distressing form of dyspnea sensation, which occurs in particular when inspiratory flow rate is set insufficiency (“flow starvation”), or when tidal volumes are decreased under mechanical ventilation while the PaCO<sub>2</sub> level is held constant.<sup>25</sup> In patients with decreased respiratory muscle strength and excessive respiratory drive, the muscle’s ability to respond to neural demands is insufficient; dyspnea is then characteristically experienced as a form of excessive breathing effort. Activation of accessory respiratory muscles was found strongly related to the intensity of dyspnea,<sup>26</sup> and can lead to weaning and/or extubation failure.<sup>10</sup> In addition, dyspnea impacts ICU outcome, and may contribute to ICU-related post-traumatic stress disorders.

## Consequences of low respiratory drive

In ventilated patients, a low respiratory drive due to excessive ventilator assistance and/or sedation, is a critical contributor to diaphragm weakness. The effects of diaphragm inactivity have been demonstrated both *in vivo* and *in vitro* in the form of myofibrillar atrophy and contractile force reduction.<sup>22,27</sup> Diaphragm weakness is associated with prolonged ventilator weaning and increased risks of ICU readmission, hospital readmission, and mortality.<sup>28</sup> In addition, low respiratory drive can lead to patient-ventilator dyssynchronies, such as ineffective efforts, central apneas, auto-triggering, and reverse triggering.<sup>29</sup> Excessive ventilator assistance may result in dynamic hyperinflation, particularly in patients with obstructive airway diseases. Dynamic hyperinflation reduces respiratory drive and promotes ineffective efforts (i.e., a patient's effort becomes insufficient to overcome intrinsic PEEP). Although asynchronies have been associated with worse outcome, whether this is a causal relationship requires further investigation.

## HOW CAN WE ASSESS RESPIRATORY DRIVE?

As the respiratory centers' output cannot be measured directly, several indirect measurements have been described to assess respiratory drive. It follows that the more proximal these parameters are to the respiratory centers in the respiratory feedback loop, the better they reflect respiratory drive. This includes, from proximal to distal: diaphragm electromyography, mechanical output of the respiratory muscles and clinical evaluation.

### ***Clinical signs and breathing frequency***

Clinical signs such as dyspnea and activation of accessory respiratory muscles strongly support the presence of high respiratory drive, but do not allow for quantification. Although respiratory drive comprises a frequency component, respiratory rate alone is a rather insensitive parameter for the assessment of respiratory drive; respiratory rate varies within and between subjects, depends on respiratory mechanics, and can be influenced by several factors independent of the status of respiratory drive, such as opioids,<sup>30</sup> or the level of pressure support ventilation. We therefore reckon to evaluate more sensitive parameters of respiratory drive.

### ***Diaphragm electrical activity***

Diaphragm electrical activity (EAdi) reflects the strength of the electrical field produced by the diaphragm and, hence, the relative change in discharge of motor neurons over time. Provided that the neuromuscular transmission and muscle fiber membrane excitability are intact, EAdi is a valid measure of phrenic nerve output and thus the most precise es-

timation of respiratory drive.<sup>7,31</sup> Real-time recording of the EAdi signal is readily available on a specific type of ICU ventilator (Maquet; Servo-I/U). The EAdi signal is acquired using a dedicated nasogastric (feeding) catheter with nine ring-shaped electrodes positioned at the level of the diaphragm.<sup>31</sup> Computer algorithms within the ventilator software continuously select the electrode pair that is closest to the diaphragm, and correct for disturbances such as motion artifacts, esophageal peristalsis and interference from the electrocardiogram or other nearby muscles. EAdi reflects crural diaphragm activity and is representative of activity from the costal parts of the diaphragm (and thus, the whole diaphragm). In addition, the EAdi signal remains reliable at different lung volumes and was found to correlate well to transdiaphragmatic pressure (Pdi) in healthy individuals and ICU patients.<sup>32,33</sup> As respiratory drive comprises both an amplitude and duration component, we reason that the inspiratory EAdi integral may better reflect respiratory drive than EAdi amplitude alone.

### Reference values

Normal values for EAdi are yet unknown, but it is proposed that an amplitude of at least 5  $\mu\text{V}$  per breath in ICU patients is likely sufficient to prevent development of diaphragmatic disuse atrophy.<sup>1</sup>

### Limitations

As EAdi amplitude varies considerably between individuals and normal values are unknown, recordings are mainly used to evaluate changes in respiratory drive in the same patient. EAdi activity during tidal breathing is often standardized to respiratory muscle pressure (i.e., neuromechanical efficiency index)<sup>34</sup> or to that observed during a maximum inspiratory contraction (i.e.,  $\text{EAdi}_{\% \text{max}}$ ).<sup>7</sup> Although the latter was shown to correlate to the intensity of breathlessness in non-ventilated COPD patients,<sup>35</sup> maximum inspiratory maneuvers are generally not feasible to perform in ICU patients. In addition, recruitment of accessory respiratory muscles is not reflected in the EAdi signal. Finally, suboptimal filtering of the raw electromyography signal may affect validity to quantify drive with EAdi.<sup>34</sup>

### ***Airway occlusion pressure at 100ms***

The airway occlusion pressure at 100 msec ( $P_{0.1}$ ) is a readily-accessible and non-invasive measurement that reflects output of the respiratory centers. The  $P_{0.1}$  is the static pressure generated by all inspiratory muscles against an *occluded* airway at 0.1 sec after the onset of inspiration. The  $P_{0.1}$  has been described over 40 years ago as an indirect measurement of drive that increases proportionally to an increase in inspiratory  $\text{CO}_2$  and directly depends on its neural stimulus (i.e., diaphragm electromyography or phrenic nerve activity).<sup>36</sup> Advantages of  $P_{0.1}$  are that short and unexpected occlusions

are performed at irregular intervals such that there is no unconscious reaction (normal reaction time is  $> 0.15$  sec).<sup>36</sup> Secondly, the maneuver itself is relatively independent of respiratory mechanics, for the following reasons: 1)  $P_{0.1}$  starts from end-expiratory lung volume, meaning that the drop in airway pressure is independent of the recoil pressures of the lung or chest wall; 2) since there is no flow during the maneuver,  $P_{0.1}$  is not affected by flow resistance; 3) lung volume during an occlusion does not change (with the exception of a small change due to gas decompression), which makes it unlikely that vagal volume-related reflexes or force-velocity relations of the respiratory muscles influence the measured pressure.<sup>7,36</sup> In addition, the maneuver remains reliable in patients with respiratory muscle weakness,<sup>37</sup> and in patients with various levels of intrinsic PEEP and dynamic hyperinflation.<sup>38</sup> Although the latter patient category shows an important delay between the onset of inspiratory activity at the alveolar level (estimated by esophageal pressure ( $P_{es}$ )) and the drop in airway pressure during an end-expiratory occlusion, Conti et al. proved good correlation and clinically acceptable agreement between  $P_{0.1}$  measured at the mouth and the drop in  $P_{es}$  at the first 0.1 sec of the inspiratory effort ( $r=0.92$ , bias  $0.3 \pm 0.5$  cmH<sub>2</sub>O).<sup>38</sup> The  $P_{0.1}$  can therefore be considered as a valuable index for estimation of respiratory drive.

#### Reference values

During tidal breathing in healthy subjects,  $P_{0.1}$  varies between 0.5 and 1.5 cmH<sub>2</sub>O with an intra-subject breath-to-breath variability of 50%. Due to this variation, it is recommended to use an average of three or four  $P_{0.1}$  measures for a reliable estimation of respiratory drive. In stable, non-intubated patients with COPD,  $P_{0.1}$  values between 2.4 and 5 cmH<sub>2</sub>O have been reported,<sup>7</sup> and from 3 to 6 cmH<sub>2</sub>O in ARDS patients under mechanical ventilation.<sup>39</sup> An optimal upper threshold for  $P_{0.1}$  was found to be 3.5 cmH<sub>2</sub>O in mechanically ventilated patients; a  $P_{0.1}$  above this level is associated with increased respiratory muscle effort (i.e., esophageal pressure-time product (PTP) above 200 cmH<sub>2</sub>O·s/min).<sup>40</sup>

#### Limitations

Although the  $P_{0.1}$  is readily available on most modern mechanical ventilators, each ventilator type has a different algorithm to calculate  $P_{0.1}$ ; some require manual activation of the maneuver, others continuously display an estimated value based on the ventilator trigger phase (i.e., the measured pressure drop before the ventilator is triggered, extrapolated to 0.1 sec), whether or not averaged over a few consecutive breaths. Considering that the trigger phase is often shorter than 0.05 sec,  $P_{0.1}$  is likely to underestimate true respiratory drive, especially in patients with high drive.<sup>39</sup> The accuracy of the different calculation methods remains to be investigated.

In addition, extra caution is required when interpreting the  $P_{0.1}$  in patients with expiratory muscle activity; since recruitment of expiratory muscles results in an end-expiratory lung volume that may fall below functional residual capacity, the initial drop in  $P_{0.1}$  during the next inspiration may not reflect inspiratory muscle activity solely, but comprises the relaxation of the expiratory muscles and recoil of the chest wall as well.<sup>7</sup>

### ***Inspiratory effort***

Respiratory drive may also be inferred from inspiratory effort measured with esophageal and gastric pressure sensors. The derivative of Pdi ( $dP_{di}/dt$ ) reflects respiratory drive only if both the neural transmission and diaphragm muscle function are intact. As such, high  $dP_{di}/dt$  values reflect high respiratory drive. In healthy subjects,  $dP_{di}/dt$  values of 5 cmH<sub>2</sub>O/s are observed during quiet breathing.<sup>4</sup>  $dP_{di}/dt$  is often normalized to the maximum Pdi, but maximum inspiratory maneuvers are rarely feasible in ventilated ICU patients. A limitation of using Pdi-derived parameters is that Pdi is specific to the diaphragm and therefore does not include accessory inspiratory muscles, which are often recruited when respiratory drive is high. Calculating the pressure developed by all inspiratory muscles ( $P_{mus}$ ) may overcome this.  $P_{mus}$  is defined as the difference between  $P_{es}$  (i.e., surrogate of pleural pressure) and the estimated pressure gradient over the chest wall. Other measurements of inspiratory effort are the work of breathing (WOB), and the PTP, which have been shown to correlate closely with  $P_{0.1}$ .<sup>41,42</sup> However, all above measurements require esophageal manometry, a technique that demands expertise in positioning of the esophageal catheter and interpretation of waveforms, making it less suitable for daily clinical practice. Another major limitation is the risk of underestimating respiratory drive in patients with respiratory muscle weakness; despite a high neural drive, inspiratory effort might be low.

A non-invasive estimate of inspiratory effort can be derived with diaphragm ultrasound. Diaphragm thickening during inspiration (i.e., thickening fraction) has shown a fair correlation with the diaphragmatic PTP.<sup>43</sup> However, diaphragm ultrasound does not account for recruitment of accessory inspiratory and expiratory muscles, and the determinants of diaphragm thickening fraction require further investigation. Nonetheless, diaphragm ultrasound is readily available at the bedside, relatively low cost, and non-invasive, and may therefore be a potential promising technique for the evaluation of respiratory drive.

## STRATEGIES TO MODULATE RESPIRATORY DRIVE

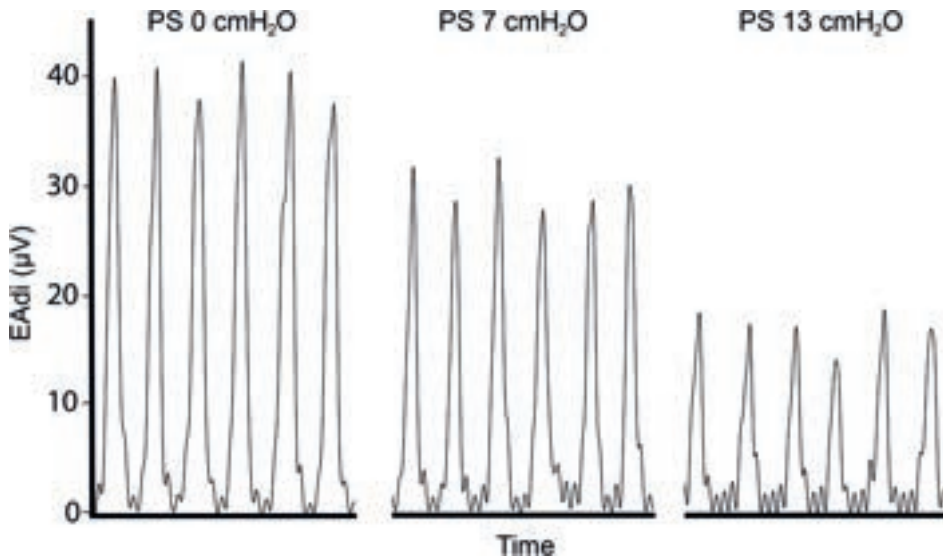
Targeting physiological levels of respiratory drive or breathing effort may limit the impact of inadequate respiratory drive on the lungs, diaphragm, dyspnea sensation, and such patients' outcome. However, optimal targets and upper safe limits for respiratory drive and inspiratory effort may vary among patients, depending on factors such as the severity and type of lung injury (i.e., inhomogeneity of lung injury), the patient's maximum diaphragm strength, and the presence and degree of systemic inflammation.<sup>3,19</sup> In this section we discuss the role of ventilator support, medication, and extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R) as potential clinical strategies for modulation of respiratory drive.

### Modulation of ventilator support

Mechanical ventilation provides a unique opportunity to modulate respiratory drive by changing the level of inspiratory assist and PEEP. Ventilator settings directly influence PaO<sub>2</sub>, PaCO<sub>2</sub>, and mechanical deformation of the lungs and thorax, which are the main determinants of respiratory drive. Titrating the level of inspiratory support to obtain adequate respiratory drive and breathing effort might thus be an effective method to prevent the negative consequences of both high and low breathing effort on the lungs and diaphragm,<sup>44</sup> although more research is required to determine optimal targets and the impact of such strategy on patient outcomes.

Several studies have evaluated the effect of different ventilator support levels on respiratory drive during partially supported mechanical ventilation.<sup>45,46</sup> Increasing inspiratory support reduces respiratory drive, most evidently seen as reduction in EAdi amplitude (**Figure 3**) or the force exerted by the respiratory muscles per breath. With high inspiratory assistance the patient's respiratory effort may even decrease to virtually zero. The respiratory rate seems much less affected by modulation of ventilatory support.<sup>4</sup>

If changing inspiratory support level has little to no influence on the patients' respiratory drive, a clinician should consider whether the elevated respiratory drive originates from irritant receptors in the thorax, agitation, pain or intracerebral pathologies, and treat accordingly.



**Figure 3. Influence of inspiratory support levels on electrical activity of the diaphragm.** Example of a representative patient showing a decrease in electrical activity of the diaphragm (EAdi, in micro voltage) in response to increasing levels of inspiratory pressure support (PS).

## Medication

Drugs can affect the respiratory centers directly, or act by modulating the afferent signals that contribute to respiratory drive.<sup>2</sup> Opioids such as remifentanyl act on the  $\mu$ -receptors in the PreBötzing complex. Remifentanyl was shown to reduce the respiratory rate, while having little effect on the amplitude of the respiratory drive.<sup>30</sup> The effect of propofol and benzodiazepines is likely mediated by GABA-receptors, which are widely distributed in the central nervous system. In contrast to opioids, these drugs reduce the amplitude of the respiratory drive while having little effect on respiratory rate.<sup>47</sup>

Neuromuscular blocking agents (NMBA) block the signal transmission at the neuromuscular junction. These agents do not control drive per se, but can be used to reduce the mechanical output of the respiratory muscles. High dosage of NMBA completely prevent breathing effort, which might prevent from the effects of detrimentally high breathing effort, but could also contribute to diaphragm atrophy.<sup>5</sup> A strategy using low dosage of NMBA might allow for effective unloading the respiratory muscles without causing muscle inactivity. Short-term administration of low dosage of NMBA was demonstrated to be feasible in ventilated patients.<sup>48</sup> The feasibility and safety of prolonged (24h) partial neuromuscular blockade and the effects of this strategy on respiratory drive and diaphragm function is currently under investigation (NCT03646266).

**Extracorporeal CO<sub>2</sub> removal**

ECCO<sub>2</sub>R (also known as low-flow extracorporeal membrane oxygenation), can be applied to facilitate lung-protective ventilation in patients with hypoxemic failure and respiratory acidosis due to low tidal volumes.<sup>49</sup> ECCO<sub>2</sub>R has been shown to reduce respiratory drive (EAdi and Pmus) in patients with ARDS and in patients with acute exacerbation of COPD.<sup>49,50</sup> The feasibility, safety and effectiveness of awake ECCO<sub>2</sub>R in patients with acute respiratory failure in order to limit excessive respiratory drive need further investigation. An ECCO<sub>2</sub>R strategy is probably more complex in this group, as the control of drive may be partly independent of PaCO<sub>2</sub> (e.g. if the Hering-Breuer reflex is overwhelmed), and other organ dysfunctions and sepsis may complicate the clinical picture.<sup>49,50</sup>

**CONCLUSION**

Respiratory drive is the intensity of the respiratory centers' output, and determines the effort of the respiratory muscles. A combination of chemical, mechanical, behavioral and emotional factors contributes to respiratory drive. Both high and low respiratory drive in patients under mechanical ventilation may worsen or even cause lung injury and diaphragm injury, and should thus be prevented. Several techniques and interventions are available to monitor and modulate respiratory drive in critically ill patients. The impact of preventing detrimental respiratory drive requires further evaluation, but might be crucial to improve ICU outcomes.

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3

# **Assessing Breathing Effort in Mechanical Ventilation: Physiology and Clinical Implications**

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*Ann Transl Med.* 2018 Oct;6(19):387

*Author contributions: Conception by HdV and LH. Writing, critically revisions and final approval of the manuscript by all authors.*

## **ABSTRACT**

Recent studies have shown both beneficial and detrimental effects of patient breathing effort in mechanical ventilation. Quantification of breathing effort may allow the clinician to titrate ventilator support to physiological levels of respiratory muscle activity. In this review we will describe the physiological background and methodological issues of the most frequently used methods to quantify breathing effort, including esophageal pressure measurements, the work of breathing, the pressure-time product, electromyography and ultrasound. We will also discuss the level of breathing effort that may be considered optimal during mechanical ventilation at different stages of critical illness.

## INTRODUCTION

In the past decade, multiple important studies have underlined that maintaining patient breathing effort during mechanical ventilation is a double-edged sword.<sup>1-5</sup> Positive effects of patient breathing effort may include improved recruitment of basal lung fields and facilitated oxygenation.<sup>5,6</sup> Furthermore, preserving patient breathing effort might protect against the development of diaphragm atrophy and contractile dysfunction resulting from disuse.<sup>2</sup> On the other hand, patients with high respiratory drive can generate pressures that are incompatible with lung-protective ventilation, a phenomenon termed patient self-inflicted lung injury (P-SILI).<sup>7</sup> Additionally, studies in the early course of the acute respiratory distress syndrome (ARDS) have demonstrated that continuous infusion of the neuromuscular blocker cisatracurium improves survival, possibly by abolishing breathing effort.<sup>4</sup> Striking a balance between the beneficial and detrimental effects of breathing effort is one of the contemporary challenges in mechanical ventilation management.<sup>8</sup> It has been proposed that ventilator assist should be titrated to the individual patient's disease state, based on the respiratory drive, pressure output of the respiratory muscles, and lung mechanics.<sup>5,8-10</sup>

However, it is difficult to assess activity of the respiratory muscle pump during mechanical ventilation without specific diagnostic techniques.<sup>11</sup> The “gold standard” parameters are the work of breathing (WOB) and the pressure-time product (PTP), which are based on pressure measurements.<sup>12</sup> These measurements can be difficult to obtain and interpret. As such, the PTP and WOB are rarely used in clinical care and are mostly considered to be a research tool.<sup>13</sup> Recently, diaphragm electromyography<sup>9</sup> and ultrasound<sup>14</sup> have become increasingly popular to assess breathing effort in research and clinical care. The aim of this review is to describe the physiological basis of breathing effort assessment. We will discuss how esophageal pressure (Pes), gastric pressure (Pga), PTP, WOB, ultrasound and electromyography can be used to quantify breathing effort during mechanical ventilation, and highlight the technical issues related to these measurements. Furthermore, we will discuss which levels of breathing effort may be considered desirable during mechanical ventilation at different stages of critical illness.

## PHYSIOLOGY

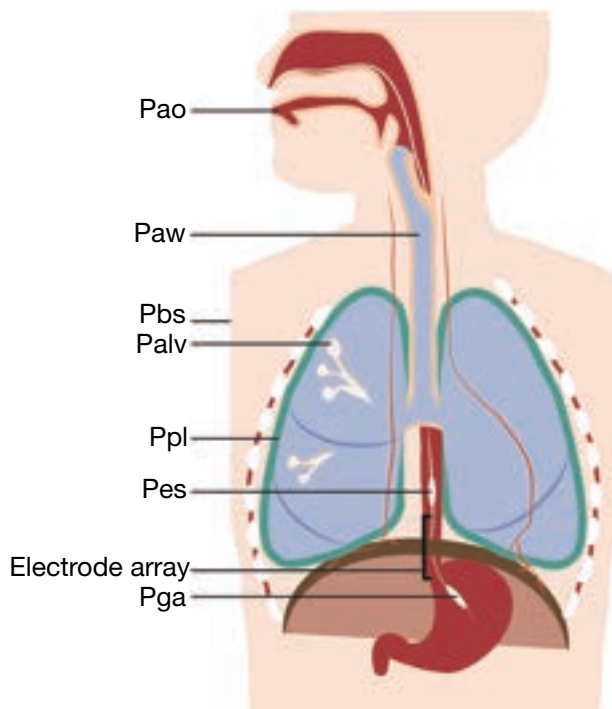
### ***Definition of breathing effort***

Although the term breathing effort feels intuitive, there is no clear definition, and many authors and textbooks define it differently. In this review we have defined breathing

effort as any energy-consuming activity of the respiratory muscles aimed at driving respiration.

### Function of the respiratory muscle pump

The respiratory muscle pump comprises multiple skeletal muscles that act in a coordinated fashion to maintain alveolar ventilation under different metabolic demands. Breathing effort is tightly controlled to match the respiratory demands of the body. An imbalance between breathing effort and the respiratory demands of the body will result in respiratory failure. Mechanical ventilation is life-saving in respiratory failure by taking over the patient's WOB, restoring the balance between respiratory load and capacity. During partially-supported ventilation, the WOB is shared by the patient and the ventilator. To assess the patient's relative contribution to ventilation, it is useful to separate the inspiratory and expiratory muscle pump. See **Figure 1** and **Table 1** for a schematic representation of the respiratory system, muscle pressures and pressure gradients.



**Figure 1.** Schematic representation of the respiratory muscle pump.

*Note the single catheter equipped with an esophageal pressure balloon, gastric pressure balloon and an electrode array in between the two balloons. Orange lines represent the phrenic nerves. For calculations of the pressure gradients refer to the text. Definition of abbreviations: Pao = airway opening pressure, Paw = Airway pressure, Palv = alveolar pressure, Pel(L) = elastic recoil pressure of the lungs (alternatively written as transalveolar pressure), Ppl = pleural pressure, Pbs = pressure at body surface, Prs = pressure over the respiratory system, Pga = gastric pressure, Pab = abdominal pressure, Pdi = transdiaphragmatic pressure, Pes = esophageal pressure*

**Table 1:** Pressure gradients of the respiratory system

Gradient name	Abbreviation	Formula	Clinical assessment
Transpulmonary pressure	$P_L$	$Pao - Ppl$	$Paw - Pes$
Transalveolar pressure / Elastic recoil pressure of the lung	$Pel(L)$	$Palv - Ppl$	$Paw \text{ (zero flow)} - Pes$
Transdiaphragmatic pressure	$Pdi$	$Pabd - Ppl$	$Pga - Pes$
Pressure gradient over the chest wall	$Pcw$	$Ppl - Pbs$	$Pes \text{ (as } Pbs \text{ is conventionally 0)}$
Pressure gradient over the respiratory system	$Prs$	$Pao - Pbs$	$Paw \text{ (as } Pbs \text{ is conventionally 0)}$

**Table 1 legend:** Definition of abbreviations: *Pabd*, abdominal pressure; *Pao*, Pressure at airway opening; *Palv*, Alveolar pressure; *Pbs*, Pressure at body surface; *Ppl*, Pleural pressure; *Pel(L)*, elastic recoil pressure of the lung

### Inspiratory muscle pump

Inspiration is mainly driven by the diaphragm in healthy individuals during tidal breathing.<sup>15</sup> The diaphragm is a thin ( $\pm 2.0$  mm) dome-shaped muscle that forms the boundary between the thorax and the abdomen.<sup>16</sup> The muscle fibers are conventionally divided into two main components: the crural portion inserts into the first three lumbar vertebrae, and the costal portion projects onto the rib cage and xiphoid process. The muscle fibers of the costal diaphragm that directly appose to the lower rib cage constitute the “zone of apposition”.<sup>16-18</sup> In simplified form, the diaphragm acts like a piston in a barrel. Shortening of the muscle fibers in the zone of apposition descends the dome of the diaphragm, increasing the size of the thoracic cavity and compressing the abdominal cavity. Consequently, intrapleural pressure ( $Ppl$ ) falls and abdominal pressure ( $Pab$ ) rises, creating a pressure gradient called the transdiaphragmatic pressure ( $Pdi$ ):<sup>19,20</sup>

$$Pdi \text{ (cmH}_2\text{O)} = Pab \text{ (cmH}_2\text{O)} - Ppl \text{ (cmH}_2\text{O)} \quad (1)$$

The drop in pleural pressure will generate a pressure gradient over the lungs, the transpulmonary pressure ( $P_L$ ), which can be calculated by subtracting  $Ppl$  from the airway opening pressure ( $Pao$ ):

$$P_L \text{ (cmH}_2\text{O)} = Pao \text{ (cmH}_2\text{O)} - Ppl \text{ (cmH}_2\text{O)} \quad (2)$$

The cyclic rises and falls in  $P_L$  ultimately drive alveolar ventilation.

Clinically,  $Ppl$  and  $Pab$  are often estimated by  $Pes$  and  $Pga$ . The assessment of  $Ppl$  and  $Pab$  requires placement of esophageal and/or gastric balloons (**Figure 1**), which may

be perceived as too invasive for some patients. Today, balloon catheters are available that can be used for gastric feeding as well; thus, assessing Pes and/or Pga is not more invasive than routine clinical care.<sup>13</sup> It is important to note that the balloon catheters provide an estimation of pleural pressure, but the actual pressure in the pleural space differs from region to region due to gravity and differences in spatial respiratory mechanics.<sup>21</sup> Nevertheless, Pes measurements provide a useful estimation of the mean pleural pressure at the dependent lung regions.<sup>21,22</sup> The advantages, limitations and technical aspects of Pes and Pga measurements in critically ill patients have been discussed in two excellent review articles.<sup>23,24</sup>

Additional muscle groups are recruited when the respiratory load is elevated. The most important accessory inspiratory muscles are the sternocleidomastoid, parasternal, scalene and rib cage muscles.<sup>25</sup> Like the diaphragm, contraction of the accessory inspiratory muscles expands the thorax and lowers Ppl, promoting a rise in  $P_L$  and subsequent lung inflation. Contraction of accessory inspiratory muscles does not generate a pressure gradient between the abdominal and thoracic compartment if the diaphragm is relaxed.<sup>12</sup> At any time, Ppl depends on the pressure generated by all the respiratory muscles (Pmus) and the pressure gradient over the chest wall (Pcw):

$$Ppl \text{ (cmH}_2\text{O)} = Pmus \text{ (cmH}_2\text{O)} + Pcw \text{ (cmH}_2\text{O)} \quad (3)$$

Accordingly,

$$Pmus \text{ (cmH}_2\text{O)} = Ppl \text{ (cmH}_2\text{O)} - Pcw \text{ (cmH}_2\text{O)} \quad (4)$$

Pmus provides a global assessment of all inspiratory muscles, while Pdi is specific to the diaphragm.<sup>12,26</sup> Pcw is often calculated by dividing the inspired volume by the theoretical compliance of the chest wall (Ccw), estimated as 4% of vital capacity. Accordingly, a (predicted) vital capacity of 4000 mL will reveal an estimated Ccw of 160 mL/cmH<sub>2</sub>O.<sup>12</sup> Reference values for Ccw are between 150 and 200 mL/cmH<sub>2</sub>O.<sup>12</sup> However, these values were obtained in healthy subjects and might not be accurate in critical illness. The actual Ccw of a patient can be determined by constructing a pressure-volume curve for Pes during passive inflation; Pmus is zero during passive inflation and muscle paralysis, meaning that the observed Pes is completely determined by Pcw (see *Equation 3*).<sup>26</sup>

### **Expiratory muscle pump**

Expiration is a passive process during quiet breathing.<sup>19,26,27</sup> When the inspiratory muscles relax, the elastic energy build up in the structures of the respiratory system drives lung deflation. The expiratory muscles are recruited to assist in expiration when

the load imposed on the inspiratory muscles is elevated.<sup>28</sup> Additionally, the expiratory muscles are recruited when passive expiration is hampered by reduced elasticity of the lungs (e.g., emphysema) or elevated expiratory resistance (e.g., exacerbation of chronic obstructive pulmonary disease (COPD)).<sup>29</sup> The abdominal wall muscles are the principal muscles of expiration. The internal interosseous intercostal and the triangularis sterni muscles are accessory expiratory muscles.<sup>25</sup> Contraction of the abdominal wall muscles compresses the abdominal compartment, increasing  $P_{ab}$ . If the diaphragm is relaxed, the increased  $P_{ab}$  will be transmitted to the thorax and will increase  $P_{pl}$ , facilitating lung deflation. Contraction of the accessory expiratory muscles directly increases  $P_{pl}$  by compressing the thorax. Notably, the expiratory muscles can also facilitate inspiration. By contracting during the expiratory phase, lung volume is reduced below functional residual capacity and the diaphragm is shifted cephalad to a more optimal position.<sup>30,31</sup> When the expiratory muscles relax during the subsequent inspiration, the diaphragm will descend and  $P_{pl}$  will fall, facilitating lung inflation.<sup>30</sup> During high respiratory loads, the expiratory muscles might generate more pressure than the diaphragm.<sup>32</sup> Therefore, assessment of breathing effort at high loads should also take the expiratory muscles into account.

## Quantifying Breathing Effort

### ***Physical examination and graphical inspection of ventilator waveforms***

Physicians may rely on physical examination to assess breathing effort in clinical practice. For instance, recruitment of accessory muscles is a sign of increased respiratory workload.<sup>32</sup> Inward movement of the abdomen during inspiration (abdominal paradox) means that the accessory muscles exert more force than the diaphragm, which is often interpreted as a sign of impending diaphragm fatigue.<sup>33</sup> Most patients develop a breathing pattern characterized by low tidal volumes and high respiratory frequency during prolonged fatiguing loads.<sup>34</sup> However, these breathing patterns suggest an increased workload and impending fatigue, but do not allow quantitative assessment of breathing effort.<sup>35</sup> The pressure and flow waveforms displayed on the ventilator are also inadequate in assessing breathing effort during partially-supported ventilation, as they cannot distinguish between patient breathing effort and the work of the ventilator.<sup>11</sup>

### ***Pressure-based quantification of breathing effort***

Because the respiratory muscles exert their function by generating pressure, breathing effort can be assessed by analysis of these pressures. The requirements and reference values of pressure-based assessment of breathing effort are summarized in **Table 2**.

**Table 2.** Parameters, reference values and comments of pressure-based assessment of breathing effort.

Technique	Parameters	Reference values	Comments
Pressure amplitudes	Pes, Pga, Pdi	Pdi and pes: absolute differences of 5-10 cmH <sub>2</sub> O per breath in healthy subjects at rest(10,20,41,104)	Suitable for bedside evaluation without the need for dedicated software.
Work of breathing (WOB)	Pes, volume. Further analysis: Ccw, E <sub>L</sub> ,dyn.	2.4-4J/min(105,106) and 0.35-0.7 J/L(12,105) in healthy subjects at rest.	Advanced breathing effort assessment. Can be divided into elastic, resistive and PEEP components. Viable during high minute ventilation and flow. Not sensitive to isometric contractions.
Pressure-time product (PTP)	Pes, Pga, Pdi. Further analysis: Ccw, C <sub>L</sub> ,dyn	50-150 cmH <sub>2</sub> O*s/min in healthy subjects at rest. (23,89,107)	Advanced breathing effort assessment. Can be divided into elastic, resistive and PEEP components. Sensitive to isovolumetric contractions.
Tension-time index (TTI)	Pes, Pga, Pdi, Pimax, Ti/Ttot	0.03 in healthy subjects at rest.(108) TTIdi up to 0.15-0.18 can be continued indefinitely. (109)	Useful to predict whether the observed effort is sustainable. Corrects for reduced muscle efficiency. Pimax can be difficult to obtain in ICU patients.

**Table 2 legend.** Definition of abbreviations: Pdi = transdiaphragmatic pressure; Pes = oesophageal pressure; Pga = gastric pressure; Pimax = maximal inspiratory pressure; Ccw = compliance of the chest wall; C<sub>L</sub>,dyn = dynamic lung compliance; PEEP= positive end-expiratory pressure; ICU = intensive care unit; Ti = Inspiratory time, Ttot = cycle time.

### Pressure amplitudes

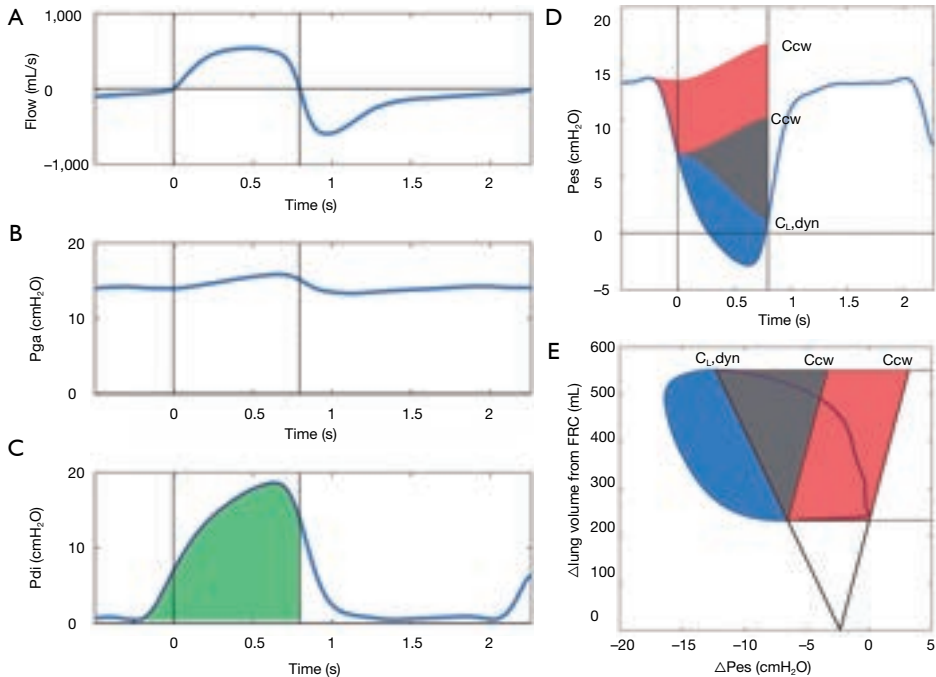
If an esophageal and a gastric balloon are present, the amplitude of tidal swings in Pes, Pdi and Pga can be studied during partially supported ventilation by using the following calculation:

$$\Delta P (\text{cmH}_2\text{O}) = P_{\text{expiration}} (\text{cmH}_2\text{O}) - P_{\text{inspiration}} (\text{cmH}_2\text{O}) \quad (5)$$

The formula can be used with Pes, Pga and Pdi to obtain their respective amplitude during inspiration and expiration. If the patient's respiratory muscles are active, Pes will fall and Pga and Pdi will rise during inspiration (**Figure 2**). A rise in Pga during expiration is a sign of expiratory muscle recruitment.

Pressure amplitude assessment is relatively straightforward and can be performed real-time at the bedside, making it especially useful to observe trends within a patient. However, there are several limitations to assessment of breathing effort based on Pes and Pga swings solely. Amplitude of pressure swings neglects the duration and frequency of muscle contractions. Additionally, Pes swings are usually not corrected for the recoil

pressure of the chest wall and intrinsic positive end-expiratory pressure (PEEPi), which can result in both underestimation and overestimation of Pmus. Consequently, pressure swings show a rather poor correlation to energy expenditure.<sup>35</sup> More in-depth analysis of breathing effort may be warranted in selected critically ill patients.



**Figure 2.** Pressure-based assessment of breathing effort during the inspiratory phase.

Dashed lines represent moments of zero flow. Panel A: Flow waveform. Panel B: Gastric pressure (Pga) tracings. Panel C: Transdiaphragmatic pressure (Pdi), calculated as Pga - Pes. Green hatched area is the pressure-time-product (PTP) of the diaphragm during inspiration. Notice the presence of Pdi before onset of inspiratory flow, a sign of internal PEEP. Panel D: Esophageal pressure (Pes) tracings. The compliance of the chest wall (Ccw), estimated at 4% of VC, has been superimposed on Pes at the onset of the fall in Pes and at onset of inspiratory flow generation (first vertical line line), together with the dynamic lung compliance (C<sub>d,dyn</sub>). The colored area comprises the total PTP of respiratory muscle pressure (Pmus). The red area is the PTP attributed to intrinsic PEEP (PEEPi), the gray area represents elastic PTP and the blue area represents resistive PTP. Panel E: Pressure-volume curve of Pes and lung volume. The Ccw and C<sub>d,dyn</sub> intersect at FRC. The red area represent WOB to PEEPi, the gray area represents elastic WOB and the blue area represent resistive WOB.

### Pressure-time product (PTP)

A more sophisticated parameter to quantify breathing effort is the PTP. The PTP is calculated as the time integral of the Pmus:<sup>12</sup>

$$PTP = P \text{ (cmH}_2\text{O)} \times t \text{ (s)} = \int P dt \text{ (cmH}_2\text{O}\cdot\text{s)} \quad (6)$$

PTP is commonly reported over a 1-minute interval. The PTP of the respiratory muscle pressure (PTP<sub>mus</sub>) can be constructed if P<sub>es</sub> measurements are available as an assessment of global respiratory muscle activity (**Figure 2D**). If P<sub>ga</sub> is also available, the PTP of the diaphragm pressure (PTP<sub>di</sub>) can be constructed as a specific measurement of diaphragm effort (**Figure 2C**). Because the PTP is sensitive to the frequency and duration of contractions, it correlates well with energy expenditure during a broad range of inspiratory loadings.<sup>44</sup> The PTP is insensitive to changes in volume, meaning that it is also valid when effort does not result in volume generation, such as during isometric contractions. This is especially relevant in ICU patients with PEEP<sub>i</sub> and poor interaction with the ventilator, that exhibit ineffective efforts.<sup>45</sup> The PTP of the esophageal pressure (PTP<sub>es</sub>) can be divided into parts to overcome elastic, resistive and threshold (i.e., PEEP<sub>i</sub>) forces (**Figure 2D**). This subdivision may be of clinical interest in patients who are difficult to wean off the ventilator, or to monitor effects of ventilator management and pharmacological interventions. The technical aspects of measuring the PTP have been covered recently.<sup>23,24</sup> It is also possible to construct a PTP of the expiratory muscles (PTP<sub>ex</sub>),<sup>46</sup> but this technique is seldom used and reference values are not available. More research is required before overall recommendations on PTP<sub>ex</sub> can be made.

There are limitations to the PTP. First, volume and flow are not considered, even though contractions at higher flows and volumes are less efficient and thus require more effort. This has been demonstrated in studies where equal PTPs were generated at different flows and volumes. This resulted in widely different levels of the oxygen cost of breathing at equal PTPs.<sup>44,47</sup> Furthermore, calculation of PTP<sub>mus</sub> requires measurement of C<sub>cw</sub>, which is cumbersome in patient on partially-supported ventilation as it requires passive inflation and muscle paralysis.<sup>12</sup> Despite these limitations, the PTP is very useful as it is linearly related to activity and energy expenditure of the respiratory muscle pump during relatively constant ventilation. This was demonstrated in conditions of flow below 1 L/s and duty cycles between 0.3 and 0.6, which is applicable to most ICU patients.<sup>36,44,48</sup>

#### Tension-time index (TTI)

Another method to assess breathing effort is the TTI, which relates the average inspiratory pressure (P<sub>i,mean</sub>) to the maximal inspiratory pressure (P<sub>i,max</sub>) that a patient can generate:

$$TTI = (P_{i,mean}/P_{i,max}) \times (T_i/T_{tot}) \quad (7)$$

in which P<sub>i,mean</sub> can be either P<sub>di,mean</sub> or P<sub>mus,mean</sub>, and T<sub>i</sub>/T<sub>tot</sub> is the relative duration of inspiration to a full breath cycle. For example, generating a P<sub>di,mean</sub> equal to 30% of P<sub>i,max</sub> at a duty cycle of 0.5 would yield a diaphragmatic TTI (TTI<sub>di</sub>) of 0.15.

Some ventilators can calculate  $P_{i,\text{mean}}$  over a time period of a few breaths. Additionally, it is possible to obtain the  $P_{i,\text{mean}}$  by dividing the inspiratory PTP by the sampling period.<sup>12</sup> The advantage of TTI over other indices is that the TTI partially corrects for reductions in muscle efficiency and weakness by relating the observed pressures to the maximal pressures. The TTI correlates well with oxygen consumption of the respiratory muscle pump.<sup>43,44</sup> The TTI is also correlated with the time that a certain load can be upheld by the diaphragm. In healthy individuals a TTIdi below 0.15–0.18 can be sustained indefinitely, while higher values will eventually lead to fatigue and task failure.<sup>43,49</sup>

There are some technical and theoretical limitations of the TTI. Technically, it is difficult to obtain reliable  $P_{i,\text{max}}$  measurements in critically ill patients as it requires maximal voluntary efforts which is hindered by sedation and motivation.<sup>12</sup> Furthermore, the TTI does not take volume and flow into account. This was illustrated in two studies where the maximal sustained TTIdi ranged from 0.11 to 0.22 and the maximal sustained TTI of the respiratory muscles ranged from 0.16 to 0.32 within the same subject, depending on flow, volume and duty cycles.<sup>50,51</sup> Despite these limitations, the TTI is a clinically useful parameter, especially to assess whether a load imposed on the patient's respiratory muscle pump is sustained.

### Work of breathing (WOB)

The classic method to assess breathing effort is the WOB. Work is done when a force moves its point of application over a distance. In case of the respiratory system work is done when a pressure changes the volume of the system:<sup>26</sup>

$$WOB = P \text{ (cmH}_2\text{O)} \times V \text{ (L)} = \int P dV \text{ (J)} \quad (8)$$

WOB is often reported as work per liter (J/L), obtained by dividing the work per breathing cycle by the tidal volume. Increased work per liter means that more pressure is required to generate an equal volume. This can be caused by several factors, such as reduced lung compliance or the presence of PEEPi.<sup>52</sup> Detailed analysis of the WOB is possible using the Campbell diagram to divide work into resistive, elastic and PEEPi components (**Figure 2E**).<sup>23,26,52</sup> Furthermore, WOB of the expiratory muscles can be assessed by attributing any observed  $P_{\text{es}}$  exceeding the Ccw curve to expiratory muscle activity. Additionally, work per breathing cycle can be multiplied by the respiratory rate (in breaths per minute) to obtain the power of breathing, or work rate.<sup>12</sup> This is an interesting parameter from a physiological point of view, as it combines time and volume dimensions. Work rate correlates closely to oxygen consumption of the respiratory muscles in a wide range of flows, volumes and duty cycles.<sup>44,47</sup> It has been proposed that the work rate, or mechani-

cal power, is a unifying factor that might predict development of ventilator-induced lung injury (VILI).<sup>53,54</sup>

There are limitations to WOB. First, as work is only performed when a volume is displaced, the WOB is insensitive to isometric contractions. Second, duration and frequency of contractions are also not considered. For example, the same breath might generate the same tidal volume at the same  $P_{es}$ , but could take twice as long. Work would not be different between these two breaths, even though the longer breath will consume substantially more energy.

### **Other methods to quantify breathing effort**

Other techniques to quantify breathing effort that do not depend on direct assessment of pressure have been developed, including the electrical activity of the diaphragm (EAdi) and ultrasound. See **Tables 3 and 4** for details, including reference values on these techniques.

**Table 3:** Parameters, reference values, and comments of electromyographic assessment of breathing effort.

Technique	Parameters	Reference values	Comments
Electrical activity of the diaphragm (EAdi)	EAdi during inspiration and expiration	Amplitude of 5-20 $\mu\text{V}$ per breath in ICU patients (expert opinion)	Parameter of respiratory drive. Allows assessment of patient-ventilator interaction.
Neuromuscular efficiency index (NME)	EAdi, $P_{es}$ , $P_{ga}$ .	0.5-2 $\text{cmH}_2\text{O}/\mu\text{V}$ in ICU patients (expert opinion)	Parameter of muscle efficiency.
Patient-ventilator breath contribution (PVBC)	Eadi and $V_t$ during assisted and unassisted breath.	Unavailable	Not yet validated in larger ICU cohorts.
Surface electromyography	Surface electrodes	Unavailable	Non-invasive, but hampered by cross-talk of adjacent muscles and movement artifacts.

**Table 3 legend.** Definition of abbreviations: EAdi = electrical activity of the diaphragm; EMG= electromyography;  $P_{es}$  = oesophageal pressure;  $P_{ga}$  = gastric pressure; NME = neuromuscular efficiency index; PVBC = patient ventilator breath contribution;  $V_t$  = tidal volume;

### Respiratory muscle electromyography

Neural control of breathing effort is tightly matched to the respiratory demands of the body. As such, both surface electrodes and electrodes placed on a nasogastric tube have

been used to acquire electromyography signals of the respiratory muscles in order to assess breathing effort in research and clinical care.

Surface electrodes have been used to measure activity of the diaphragm, accessory respiratory muscles and expiratory muscles. Although noninvasive, the quality of the recordings can be heavily impaired by cross-talk of adjacent muscles and other factors such as fat, edema and movement artifacts.<sup>60,61</sup> Furthermore, there are no standardized procedures for placement and analysis of the surface electrode signals and no reliable reference values are available. Therefore, further study is required before this technique can be used to quantify breathing effort in clinical care.

The EAdi signal circumvents some of the technical difficulties of surface electromyography. EAdi can be monitored real-time using a dedicated nasogastric tube with wired electrodes positioned at the level of the crural diaphragm (**Figure 1**).<sup>62</sup> This catheter was originally designed to control the ventilator in a specific ventilation mode (neurally adjusted ventilatory assist, NAVA), but recent reports indicate that EAdi recordings are also useful to monitor breathing effort and patient-ventilator interaction.<sup>63-65</sup> Measurement of EAdi does generally not require additional invasive procedures as most ventilated ICU patients are instrumented with a feeding tube for regular care. The electrodes acquire the spatial and temporal summation of action potentials from the motor units in the crural diaphragm. There is a close correlation between electrical activity from the crural and costal parts of the diaphragm [66]. Furthermore, the EAdi signal is independent of changes in lung volume.<sup>67</sup> EAdi correlates well to Pdi in healthy individuals and ICU patients.<sup>67</sup> Thus, EAdi appears to be a reliable estimate of global diaphragm muscle activity in ICU patients.<sup>68-70</sup>

Electrical activity is not synonymous with muscle contraction and force generation. The coupling between electrical activity and pressure is expressed as the neuromuscular efficiency (NME) index:

$$NME (cmH_2O/\mu V) = Pdi (cmH_2O) / EAdi (\mu V) \quad (9)$$

The NME can be used to calculate pressure from EAdi when assuming constant coupling over time. NME obtained during expiratory holds and multiplied by the observed EAdi appeared to be a reliable estimation of Pmus under different conditions of ventilator assistance.<sup>9</sup> Another index derived from the EAdi is the patient-ventilator breath contribution (PVBC) index. The PVBC estimates the patient's relative contribution to tidal volume generation during NAVA by comparing EAdi peaks with tidal volume in assisted

and non-assisted breaths.<sup>71</sup> The PVBC reliably predicted the fraction of breathing effort generated by the patient in a small group of ARDS patients.<sup>72</sup>

Although promising, there are still limitations of EAdi-derived parameters to assess breathing effort: EAdi-derived parameters are not necessarily a direct measure of breathing effort, but are more closely related to neural drive. In addition, EAdi is insensitive to recruitment of accessory muscles, making it less suited to assess breathing effort at high workloads. Furthermore, reference values for EAdi-derived parameters are not yet known. NME and PVBC indices need to be further evaluated in larger ICU populations before both indices can be widely implemented in daily clinical practice.

### Ultrasound

Ultrasound has gained in popularity as a diagnostic tool in clinical management and research in the ICU.<sup>14</sup> The role of ultrasound to evaluate respiratory muscle function and effort have been discussed in recent articles.<sup>65,73</sup> Components of the respiratory muscle pump, including the diaphragm, abdominal wall muscles and accessory muscles, are positioned relatively superficial and are readily accessible for ultrasound. Changes in the absolute thickness of the respiratory muscles over time within a patient can be used to recognize the development of atrophy.<sup>2,74,75</sup> The thickening fraction of the diaphragm (TFdi) in the zone of apposition during inspiration can be used as a measure of contractile activity.<sup>76,77</sup> This requires measurement of diaphragm thickness (Tdi) at end-expiration (Tdi,ee) and end-inspiration (Tdi,ei).<sup>73</sup>

$$TFdi = (Tdi,ei - Tdi,ee) / Tdi,ee \times 100\% \quad (10)$$

TFdi has shown fair correlation to the Pdi<sup>78</sup>, PTPdi and PTPes<sup>76,77</sup> in some studies, but was not significantly correlated to Pdi in another study.<sup>55</sup>

Movement of the diaphragm dome during inspiration has also been used to evaluate diaphragm function and reference values are available (**Table 4**). To study diaphragm movement, the ultrasound probe is placed at the subcostal position, using the liver as a window on the right side and the spleen on the left side. In contrast to the TFdi, assessment of diaphragm movement should only be conducted in patients disconnected from the ventilator, as ventilator assistance will result in caudal movement of the diaphragm, even in a patient on neuromuscular blockers. As such, there is a poor correlation between diaphragm excursion and TFdi, PTPes and PTPdi during partially supported ventilation.<sup>77</sup>

Advantages of ultrasound include the noninvasive nature, low costs, steep learning curve and straightforward calculations which allows bedside evaluation of breathing effort.<sup>73</sup> However, several technical and methodological limitations apply to ultrasound assessment of breathing effort. Because the diaphragm is very thin, small errors in measurement can result in large overestimation and underestimation of thickness and thickening fraction.<sup>73</sup> Additionally, the left hemidiaphragm is harder to visualize than the right side.<sup>78</sup> Furthermore, TFdi is insensitive to duration and frequency of contractions and does not account for recruitment of accessory and expiratory muscles.<sup>59</sup> Despite these limitations, ultrasound is a very promising technique in clinical care, especially as a bedside evaluation tool.

**Table 4:** Parameters, reference values and comments of ultrasound assessment of breathing effort.

Technique	Parameter	Reference values	Comments
Diaphragm Thickness (Tdi)	Diaphragm thickness at end-expiration.	1.5-2.4 mm(68,110) at end-expiration.	Non-invasive and useful to assess development of atrophy. Not a measurement of effort per se. Left hemidiaphragm may be difficult to visualize.
Thickening fraction (TFdi)	$TFdi = (Tdi_{ei} - Tdi_{ee}) / Tdi_{ee}$	24-53% during quiet breathing,(111) up to 157% during vigorous effort.	Does not allow for direct quantification of muscle pressures.
Caudal Displacement	M-mode during tidal breathing.	1.6-1.8 cm during quiet breathing, up to 7.5 cm during deep breathing(69)	Cannot distinguish patient work from ventilator work during partially supported ventilation

**Table 4 legend:** Definition of abbreviations: US = ultrasound; Tdi (ee/ei)=Diaphragm thickness (at end-expiration / end-inspiration); TFdi = Thickening fraction of the diaphragm;

## CLINICAL IMPLICATIONS

Although assessment of breathing effort has been applied in physiological research and clinical studies for decades, the optimal range of breathing effort in critically ill patients remains to be established. Trials that compare different levels of effort have not been published so far. Therefore, we are dependent on physiological principles and reasoning to guide lung-protective and diaphragm-protective ventilation.<sup>79</sup>

### Insufficient breathing effort

Studies in the past decade have promoted the idea that insufficient breathing effort leads to atrophy and weakness of the diaphragm, a process termed ventilator-induced

diaphragm dysfunction (VIDD).<sup>80,81</sup> For instance, significant diaphragm atrophy has been observed after complete inactivity of the diaphragm for 18 to 69 hours in brain-dead organ donors.<sup>1</sup> Subsequent studies demonstrated that diaphragm atrophy also occurs during partially-supported ventilation,<sup>82-85</sup> and that the extent of atrophy is related to the level of assistance provided by the ventilator.<sup>2</sup> Recently, development of diaphragm atrophy has been associated with prolonged ICU admission and an increased risk of complications,<sup>86</sup> further supporting the idea of ventilator over-assistance and VIDD.

Additional factors can play a role in the development of muscle weakness and atrophy in ICU patients including inflammation<sup>87</sup>, myotoxic drugs<sup>88</sup>, nutritional deficiency and catabolic state.<sup>89</sup> The term critical illness-associated diaphragm weakness (CIADW) is now preferred over VIDD to describe respiratory muscle weakness in critically ill patients.<sup>90</sup> Remarkably, clinical studies have shown that neuromuscular blockers administered in the first 48 hours of moderate to severe ARDS improves outcome without the development of clinically relevant muscle weakness.<sup>4,91-93</sup> Recently, it was observed that patients on assist-control ventilation regularly exhibited contractions of the diaphragm, a type of asynchrony called reversed triggering.<sup>94</sup> This mechanism prevents complete inactivity of the diaphragm, and possibly hampers the development of disuse atrophy during controlled ventilation. Indeed, short daily sessions of low-frequency pacing prevents development of disuse atrophy in peripheral skeletal muscles of ICU patients.<sup>95,96</sup> In a case study on a single patient receiving controlled ventilation for eight months, pacing one hemidiaphragm for 30 minutes a day prevented the development of disuse atrophy.<sup>97</sup> Although further study is warranted, it is possible that levels below resting breathing effort can prevent development of disuse atrophy.<sup>40</sup>

### **Excessive breathing effort**

Prevention of excessive breathing effort by unloading the respiratory muscles is a cornerstone of mechanical ventilation. Excessive effort can be detrimental to lung mechanics and the function of the respiratory muscle pump.

### **Detrimental effects on the lungs**

Vigorous efforts can generate substantial negative pleural pressures [98], potentially leading to injurious  $P_L$  in ventilated patients.<sup>7,99-101</sup> As such, it is advised to keep the peak  $P_L$  below 25 cmH<sub>2</sub>O and tidal amplitude swings below 12 cmH<sub>2</sub>O based on the physiological principles of stress and strain.<sup>23,102</sup> Furthermore, vigorous patient effort could result in poor synchrony with the ventilator and impairs oxygenation and comfort,<sup>103</sup> warranting sedation and paralysis.<sup>91</sup> Reduced Ppl can cause intrapulmonary air shifts from nondependent to dependent regions (pendelluft), potentially leading to injurious alveolar overdistention and rupture.<sup>3</sup> Additionally, the reduced Ppl brought on by vigor-

ous patient effort increases the vascular transmural pressure and can lead to elevated lung perfusion and development of alveolar edema.<sup>22,23</sup> Increased activity of the expiratory muscles could result in elevated Ppl during expiration. If the Ppl is higher than alveolar pressure (Palv) the alveoli have a tendency to collapse, promoting atelectasis and possibly cyclic recruitment of alveoli (atelectrauma).<sup>94,104</sup> It is possible that the beneficial effects of muscle relaxants during the early course of ARDS can be attributed to the prevention of excessive muscle effort, although effort was not measured in these studies.<sup>4,92,93</sup>

### ***Detrimental effects on the respiratory muscles***

Excessive breathing effort could incite eccentric contractions of antagonizing muscle groups, for example concomitant activation of the diaphragm and abdominal muscles. Eccentric contractions were found to cause sarcolemmal disruption and inflammation on a microscopic level in animal models.<sup>105,106</sup> Furthermore, sarcolemmal disruption has been observed in animal models of mechanical ventilation after high breathing effort<sup>107-109</sup> and in patients with COPD.<sup>110</sup> Infiltration of inflammatory cells has been observed in diaphragm fibers obtained from ventilated ICU patients.<sup>83</sup> Additionally, patients exhibiting high efforts as assessed by diaphragm ultrasound showed increased Tdi,ee over time, which could be a sign of muscle inflammation and/or injury.<sup>2</sup> However, both studies were observational, so whether vigorous breathing effort leads to sarcolemmal damage in critically ill patients, and at which levels of effort this occurs, warrants further study.

### **Appropriate effort during different stages of illness**

Based on the aforementioned considerations we recommend monitoring of breathing effort in selected mechanically ventilated patients.<sup>65,111</sup> During the very early course of critical illness respiratory drive can be excessive, leading to injurious respiratory muscle contractions and damaging P<sub>L</sub>, especially in ARDS.<sup>98</sup> In this early phase, high effort occurs in a “muscle hostile environment” characterized by systemic and local inflammation. It is reasonable to prioritize unloading of the respiratory muscles to prevent lung injury and diaphragm dysfunction under these conditions.<sup>7,79</sup> Employing a partially-supported mode to regain patient breathing activity is advisable after the initial phase of critical illness, although strenuous efforts should still be prevented.<sup>79,101</sup> This strategy has the potential to allow simultaneous lung-protective and diaphragm-protective ventilation.

## **CONCLUSIONS**

Both ventilator over-assistance and under-assistance may have adverse effects on respiratory muscle function. As outlined in this review, the desired level of respiratory muscle effort depends on patient characteristics, in particular the phase of critical illness and mechanical output of the respiratory muscles. Quantification of breathing effort requires specific monitoring techniques and calculations. This is a developing field, and new studies will help us to better define optimal levels of respiratory muscle activity in ICU patients. The fact that we do not have clinical studies to demonstrate that monitoring of respiratory muscle function improves outcome should not be used as a reason to withhold such techniques in selected patients. Future clinical trials will provide data if guiding ventilator management on breathing effort improves outcome of critically ill patients.

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### Chapter 3

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4

# **Respiratory Entrainment and Reverse Triggering in a Mechanically Ventilated Patient**

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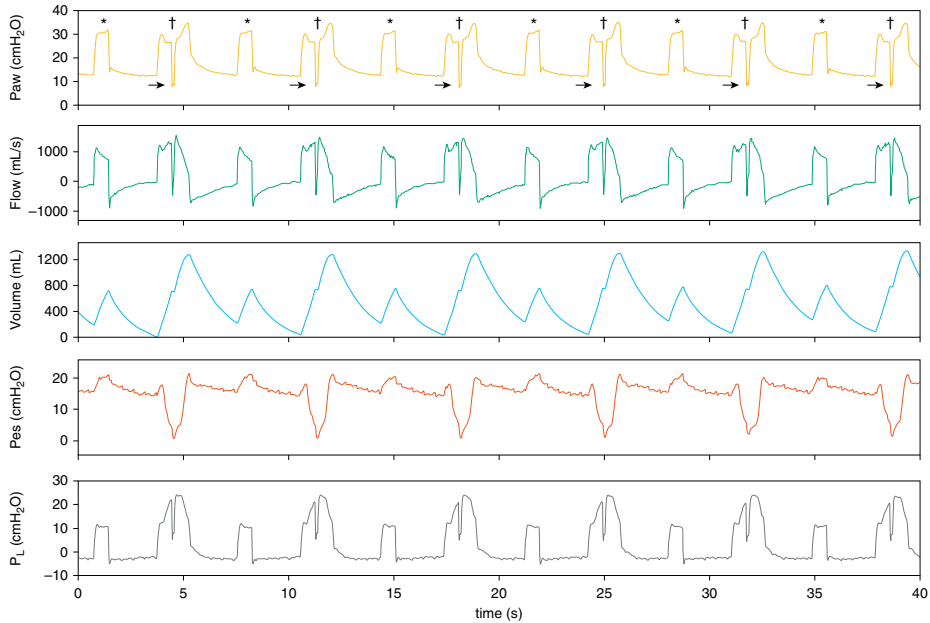
*Ann Am Thorac Soc.* 2019 Apr; 16(4):499-505

*Author contributions: Conception and design by HdV and LH. HdV and AJ conducted the experiments and measurements. All authors had significant intellectual contribution to the manuscript. All authors read and approved the final version of the manuscript.*



## THE CLINICAL CHALLENGE

A 35-year-old man with no relevant past medical history was admitted to a community hospital with dyspnea, cough productive of purulent mucus, and fever. A chest radiograph showed bilateral basal consolidations, and he was diagnosed with community-acquired pneumonia. The patient did not improve with ceftriaxone and developed severe bronchospasm after bronchoalveolar lavage, leading to hypercapnic respiratory failure, and consequently, endotracheal intubation. Computed tomographic imaging of the chest revealed a tree-in-bud configuration without ground-glass opacifications, consolidations, pleural effusions, or signs of pulmonary embolism. Despite treatment with prednisolone and bronchodilators, the patient required increasing ventilatory support, and his peak airway pressure eventually reached 46 cmH<sub>2</sub>O (in pressure control mode) with 18 cmH<sub>2</sub>O of positive end-expiratory pressure. The patient was transferred to our hospital four days after intubation for possible extracorporeal CO<sub>2</sub> removal or extracorporeal membrane oxygenation. An esophageal balloon was inserted to evaluate pulmonary mechanics (**Table 1**), which revealed that the high airway pressure was mostly used to overcome resistance in the conducting airways. The true lung-distending pressure was within lung-protective range; as such, we continued ventilation with high inspiratory support levels. After results of cultures of blood and bronchial fluid were found to be negative, the patient was treated with 1.0 g of methylprednisolone daily for three days for idiopathic interstitial lung disease. His condition improved steadily over the next seven days; his ratio of arterial oxygen pressure to fraction of inspired oxygen increased from 97 to 218 mmHg, and his arterial carbon dioxide pressure (PaCO<sub>2</sub>) decreased from 72 to 49 mmHg. On the patient's eight day at our center, we observed a remarkable pattern of pressure and flow on the ventilator screen (**Figure 1**), which we initially interpreted as "fighting the ventilator". Increasing doses of sedatives did not abolish the pattern. The patient-ventilator interaction was subsequently identified and managed with esophageal pressure measurements and knowledge of respiratory physiology.



**Figure 1.** Airway pressure (Paw), flow, volume, esophageal pressure (Pes), and transpulmonary pressure (P<sub>L</sub>) in 12 consecutive breaths. P<sub>L</sub> is calculated as Paw - Pes. Asterisks mark passive mandatory ventilator insufflations, as can be deduced from the rise in Pes during inspiration. The hash signs mark breaths that start as a passive insufflation but are rapidly followed by patient effort, as can be concluded from the drop in Pes. The decreases in Pes lower the Paw and trigger the ventilator before complete exhalation of the previous breath (arrows), leading to breath stacking with high tidal volumes (1.3 Liters). These breaths with patient effort are likely reverse triggered. That is, the mandatory insufflations elicit a neural response leading to patient effort. There is a 2:1 ratio of mandatory to reverse-triggered breaths, which is consistent with respiratory entrainment.

**Table 1.** Initial respiratory parameters and ventilator settings

Parameter	Value
Ventilator settings	
Mode	Pressure control
Inspiratory pressure support (cmH <sub>2</sub> O)	36
Positive end-expiratory pressure set (cmH <sub>2</sub> O)	12
Respiratory rate set (min <sup>-1</sup> )	30
Fraction of inspired oxygen	0.6
Respiratory mechanics	
Tidal volume (ml)	502
Tidal volume (ml/kg predicted body weight)	5.7
Peak airway pressure (cmH <sub>2</sub> O)	43
Plateau pressure (cmH <sub>2</sub> O)	23
Total positive end-expiratory pressure (cmH <sub>2</sub> O)	13
Esophageal pressure at inspiratory occlusion (cmH <sub>2</sub> O)	14
Esophageal pressure at expiratory occlusion (cmH <sub>2</sub> O)	10
Compliance of the respiratory system (ml/cmH <sub>2</sub> O)	50
Lung compliance (ml/cmH <sub>2</sub> O)	83
Chest wall compliance (ml/cmH <sub>2</sub> O)	125
Inspiratory airway resistance (cmH <sub>2</sub> O/L/s)	22
Inspiratory transpulmonary pressure (cmH <sub>2</sub> O)	9
Expiratory transpulmonary pressure (cmH <sub>2</sub> O)	3
Arterial blood gas analysis	
pH	7.26
PaCO <sub>2</sub> (mmHg)	77
PaO <sub>2</sub> (mmHg)	67
HCO <sub>3</sub> <sup>-</sup> (mmol/L)	32.7

**Table 1 legend.** Abbreviations: HCO<sub>3</sub><sup>-</sup>, bicarbonate; PaCO<sub>2</sub>, arterial carbon dioxide pressure; PaO<sub>2</sub>, arterial oxygen pressure. The parameters of the respiratory mechanics were obtained during static conditions in volume control mode with constant flow rates. Plateau airway pressure was measured during an inspiratory hold. Total positive end-expiratory pressure was measured on the airway pressure curve during a prolonged expiratory hold. Inspiratory airway resistance was calculated by dividing the difference between peak airway pressure and plateau airway pressure by the end-inspiratory flow. Inspiratory and expiratory transpulmonary pressures were calculated by subtracting esophageal pressure from airway pressure during an end-inspiratory hold and an end-expiratory hold, respectively. Ideal body weight was calculated using the length of this patient (195 cm) and the Devine formula.

**Table 2.** Differences between respiratory mechanics in mandatory (passive) insufflations and reverse-triggered breaths with breath stacking

Parameter	Mandatory breaths	Breath-stacked breaths	Lung-protective range
Volume (ml)	620	1413	530–710 <sup>*</sup>
Volume (ml/kg predicted body weight)	7	16	6–8
Transpulmonary pressure (cmH <sub>2</sub> O)	9	23	<20
Plateau airway pressure (cmH <sub>2</sub> O)	30	36	<30
Driving pressure (cmH <sub>2</sub> O)	10	28 <sup>#</sup>	<15

**Table 2 legend.** <sup>\*</sup>Safe limit was calculated using the height of this patient (195 cm) and the Devine formula, assuming 6–8 ml/kg predicted body weight to be lung protective. Transpulmonary pressure was obtained by subtracting esophageal pressure from airway pressure during an end-inspiratory hold. Driving pressure was obtained by subtracting the airway pressure during an expiratory hold from the airway pressure during an inspiratory hold. <sup>#</sup>Estimated by dividing the tidal volume by the compliance of the respiratory system.

## CLINICAL SOLUTION

Respiratory entrainment produces involuntary inspiratory effort. As such, increasing the dose of sedatives is not expected to stop or prevent reverse triggering, and might even facilitate its occurrence. Because the first response to a patient “fighting the ventilator” is often to increase sedation, it is essential to recognize this form of patient-ventilator interaction. In fact, reducing sedation and changing respiratory rate, inspiratory pressure, and applied volume can disrupt entrainment and prevent reverse triggering. Unfortunately, these measures were ineffective in our patient. Therefore, the neuromuscular blocker rocuronium was administered to abolish respiratory muscle output and prevent reverse-triggered efforts with breath stacking.

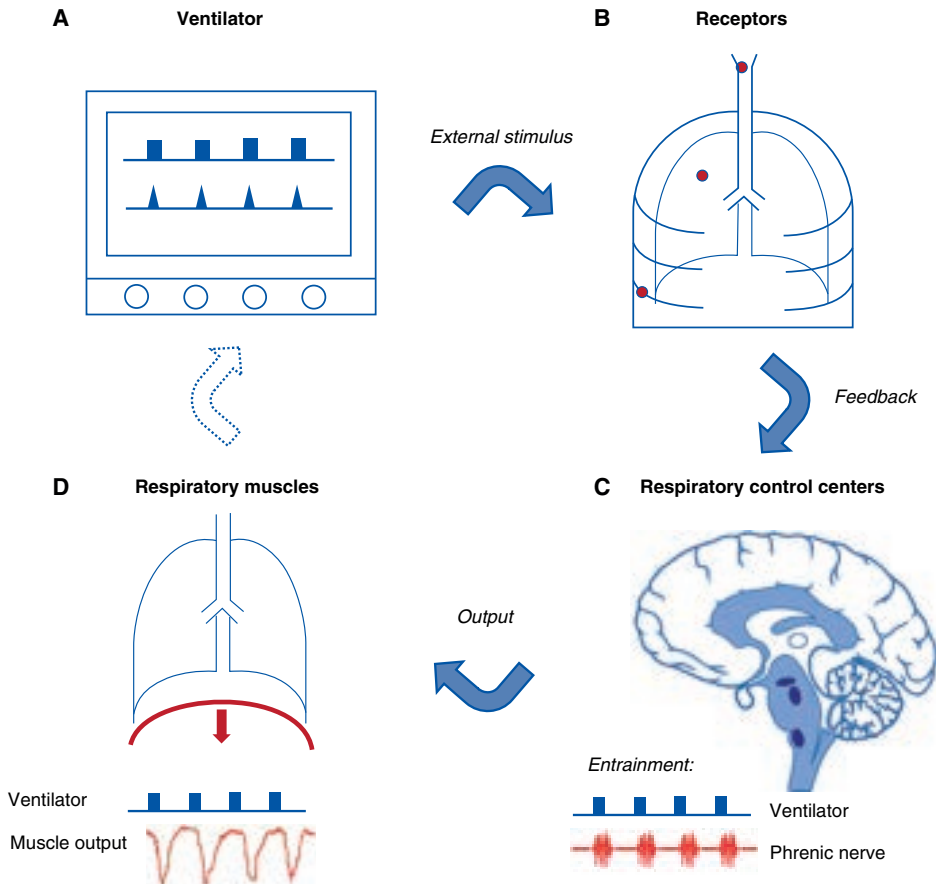
## THE SCIENCE BEHIND THE SOLUTION

### The definition and origin of reverse triggering

“Reverse triggering” is a new term for a distinct type of patient-ventilator interaction. It is a consequence of respiratory entrainment, a physiological phenomenon that was described as early as the 19<sup>th</sup> century. Entrainment refers to the resetting of an oscillator’s period and phase to match an external stimulus. Respiratory entrainment exists when the rhythm imposed by the ventilator is matched by the patient’s respiratory center.

Respiratory entrainment can be induced in wakeful, sleeping, and anesthetized human subjects on mechanical ventilation, both in health and in disease. Entrainment most often occurs when tidal volumes and respiratory rates are close to a subject’s own

respiratory rate and tidal volume (i.e., as observed during wakefulness). The leading theory is that the flow and pressure applied by the ventilator activate stretch receptors in the upper airways, lungs, and chest wall. Feedback by these receptors causes the respiratory control center to match the phase and frequency of the external stimulus, producing a repetitive respiratory pattern (**Figure 2**).



**Figure 2.** Feedback loop leading to entrainment and reverse triggering. Starting upper left: the ventilator applies pressure and volume in a fixed and repetitive pattern. This acts as the external stimulus, leading to the activation of different receptors (in red) in the airways, lung tissue, and chest wall. These receptors provide neural feedback to the respiratory control center through vagal (and possibly other) fibers. The respiratory control centers in the brain stem (dark green) try to match the pattern generated by the ventilator. In this figure, a 1:1 entrainment ratio is generated (every mandatory insufflation is followed by phrenic nerve activity). The respiratory muscles contract according to this phrenic nerve activity output. This results in the drop in pleural (and esophageal) pressure. The timing, duration, and magnitude of the inspiratory muscle effort show little variation. The dotted arrow that goes back to the ventilator illustrates that the reverse-triggered effort may trigger the ventilator, leading to breath stacking.

The term “reverse triggering” refers to the abnormal relationship between the ventilator and the patient. The external stimulus, in this case the mandatory breath applied by the ventilator, elicits a reflexive neural response from the patient. The ventilator seemingly “triggers” the patient. The resulting neural and muscular activity is “reverse-triggered” effort. A 1:1 ratio of mechanical to reverse-triggered breaths is most common, but other ratios, such as 2:1, 3:1, and 1:2 have been described as well. Our patient presented a 2:1 ratio (one muscular effort for every two machine insufflations) for most of the 30-minute recording period.

The evolutionary benefit of the “reverse-triggering” reflex is unknown. Reacting to an external stimulus could merely be a feature common to other pattern-generating centers in the brain, such as the resetting of the circadian rhythm to the sunrise and sunset.

### Recognizing reverse triggering

Clinically, it is important to differentiate reverse triggering from “spontaneous” (patient-initiated) effort because pathophysiology and treatment strategies differ. There are two distinguishing characteristics of reverse-triggered breaths, and both are related to respiratory entrainment.

First, reverse-triggered breaths occur in a stable and repetitive pattern. It has been proposed that at least 5–10 breaths with a fixed mechanical/patient effort ratio (1:1, 1:2, or 2:1) must be present. Second, reverse-triggered breaths differ minimally in the timing, duration, and magnitude of inspiratory effort, which can be measured and quantified by either diaphragmatic electromyography or esophageal pressure measurements (**Figure 3**). The duration of inspiratory effort equals the time between the drop in esophageal pressure and its return to baseline. The timing of inspiratory effort is quantified by the time difference (or phase delay) between the onset of the mandatory insufflation and the onset of subsequent patient effort. This is often expressed as the phase angle:

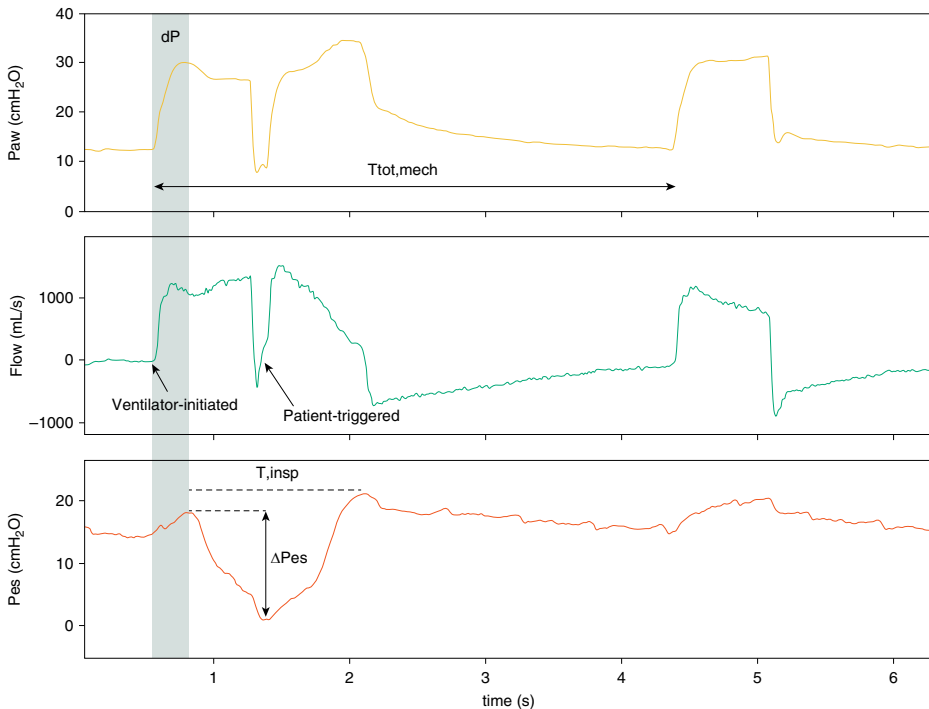
$$\text{Phase angle } (^{\circ}) = \frac{[(\text{inspiratory effort onset time} - \text{ventilator onset time}) / \text{ventilator cycle duration}] \times 360^{\circ}}{\quad} \quad (1)$$

where ventilator cycle duration is the time difference between the onset of two mandatory insufflations. A phase angle of 0 degrees would mean perfect synchronization between neural and mechanical effort; a phase angle of 180 degrees would mean patient effort commences exactly halfway between the onset of two mandatory insufflations. The magnitude of inspiratory effort can be quantified by subtracting the nadir esophageal pressure during the breath from the baseline esophageal pressure. The degree of

variation of the phase angles, inspiratory duration, and magnitude of inspiratory effort can then be quantified by calculating the coefficient of variation for each parameter:

$$\text{Coefficient of variation (\%)} = (\text{standard deviation} / \text{mean}) \times 100\% \quad (2)$$

We consider a coefficient of variation less than 15% to be consistent with respiratory entrainment, although there is no consensus in the literature. Spontaneous patient effort is more likely to vary in magnitude and timing and generally does not occur in a fixed pattern.



**Figure 3.** Airway pressure (Paw), flow, and esophageal pressure (Pes) tracings for the measurements and calculation of phase angle, inspiratory duration, and magnitude of inspiratory effort. Total ventilator cycle duration is the time (in ms) between the onset of two mandatory mechanical insufflations. Patient inspiratory time (Ti) is the time (in ms) between the drop in Pes until its return to baseline. The phase delay (dP; light blue area) is the time (in ms) between the onset of mandatory mechanical insufflation and the onset of patient effort (rapid drop in Pes). The phase angle is obtained by dividing the phase delay by ventilator cycle duration, multiplying by 360 degrees. The magnitude of inspiratory effort ( $\Delta P_{\text{es}}$ , in cmH<sub>2</sub>O) is calculated as the difference between the Pes at the onset of its rapid decline and its nadir.

The response to a prolonged expiratory hold can also help to distinguish between respiratory entrainment with reverse triggering and spontaneous patient effort. A 20-second expiratory hold suppresses the external stimulus that sustains respiratory entrainment and should prevent reverse triggering (**Figure 4**). Spontaneous patient effort is likely to continue during the expiratory hold and often becomes more vigorous.

Our patient demonstrated a 2:1 ratio of mechanical to reverse-triggered breaths. The phase angle, inspiratory activity duration, and magnitude of inspiratory effort demonstrated minimal variance, and patient effort ceased during a prolonged expiratory hold (**Figure 4**). We concluded that this pattern was a typical example of respiratory entrainment with reverse triggering. This diagnosis would have been difficult to confirm without esophageal pressure measurements because the phase angle, inspiratory time, and magnitude of inspiratory effort cannot be measured reliably on the airway pressure curve.

## **Consequences of reverse triggering**

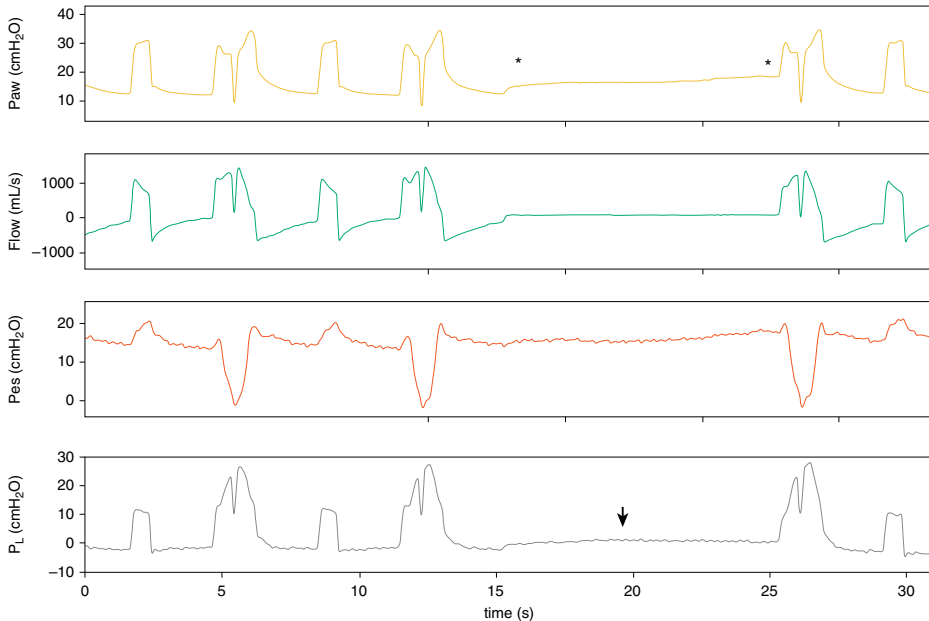
### ***Potentially harmful effects on the lungs***

The transpulmonary pressure is a clinical estimate of stress applied to the lungs:

$$\text{Transpulmonary pressure} = \text{airway opening pressure} - \text{pleural pressure} \quad (3)$$

Esophageal pressure is often used to approximate pleural pressure in the clinical setting. Both high ventilator assistance (increased airway opening pressure) and elevated patient effort (lower pleural pressure) will increase the transpulmonary pressure and thus result in more lung stress. The negative intrathoracic pressures that accompany reverse-triggered breaths can also predispose to alveolar edema by increasing the transmural vascular pressure. In addition, strong inspiratory effort can cause a shift in the intrapulmonary air left over at end expiration, an effect known as “pendelluft” that increases lung stress on relatively healthy regions of lung tissue.

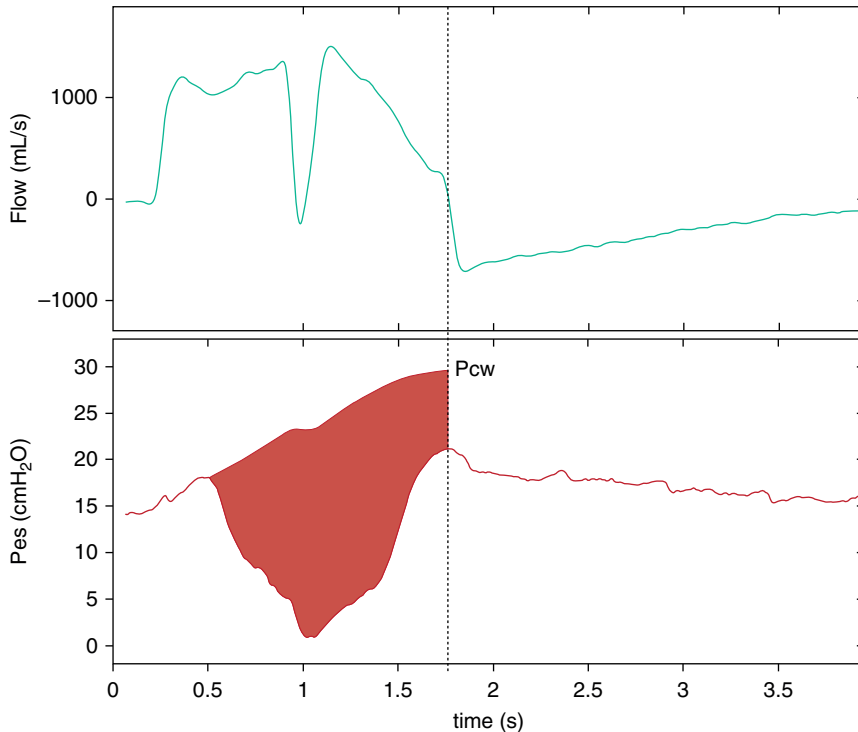
Reverse triggering may also result in breath stacking if the timing and magnitude of patient effort are sufficient to trigger the ventilator. Breath stacking can elevate transpulmonary pressures and increase tidal volumes to levels incompatible with lung-protective ventilation (**Table 2**), as illustrated in this case.



**Figure 4.** Elimination of reverse-triggered breaths during an end-expiratory hold: airway pressure (Paw), flow, esophageal pressure (Pes), and transpulmonary pressure ( $P_L$ ; calculated as  $Paw - Pes$ ) during six breaths and an expiratory hold. The first four breaths show signs of respiratory entrainment: a 2:1 pattern of mandatory to reverse-triggered breaths, with the magnitude and duration of inspiratory effort very similar for both breaths. An end-expiratory occlusion was performed, which abolished respiratory muscle activity for more than 12 seconds. The arrow on the Pes curve marks the moment that inspiratory effort was expected if patient effort would have been generated spontaneously. After the expiratory hold, another mandatory insufflation was administered by the ventilator; patient effort immediately followed. This is suggestive of reverse triggering because the patient effort seems to depend on the external stimulus provided by the mandatory ventilator insufflation.

### ***Potentially harmful effects on the respiratory muscles***

On one hand, excessive respiratory muscle activity can damage the respiratory muscle fibers and thus contribute to respiratory muscle dysfunction and prolonged weaning. In addition, diaphragmatic contractions can become eccentric if reverse triggering occurs during expiration. Eccentric contractions are more injurious to muscle fibers than concentric contractions, although this has not been proven in the setting of reverse triggering. On the other hand, maintaining some respiratory muscle effort during mechanical ventilation (in this case due to reverse triggering) may protect against disuse atrophy of the inspiratory muscles. In our patient, the pressure-time product of the respiratory muscles due to reverse triggering was 172  $\text{cmH}_2\text{O}\cdot\text{s}/\text{min}$  (**Figure 5**), which is close to a physiological level of effort. However, we reasoned that in this case the potential harm to the lungs outweighed this potential benefit.



**Figure 5.** Advanced analysis of breathing effort: flow and esophageal pressure (Pes) during one breath with reverse triggering. The vertical dotted line crosses the flow curve at 0 L/s. The green area represents the pressure-time product of the respiratory muscles, calculated by integrating the area between the chest wall pressure (Pcw) curve and the Pes curve during inspiration. The Pcw curve was obtained by dividing the inhaled volume by the chest wall compliance (125 cmH<sub>2</sub>O/ml; obtained during static measurements). The pressure-time product for this breath was 19.1 cmH<sub>2</sub>O·s. At nine reverse-triggered breaths per minute, the pressure-time product due to reverse triggering was 172 cmH<sub>2</sub>O·s/min.

### ***Potentially harmful effects on homeostasis and hemodynamics***

The reverse-triggered patient effort might contribute significantly to CO<sub>2</sub> production and oxygen demand, which could warrant a higher minute volume or result in an elevated PaCO<sub>2</sub>. The negative intrathoracic pressure can also increase the preload of the right ventricle and elevate the afterload of the left ventricle; both could contribute to cardiac failure.

### **Preventing and treating reverse triggering**

Because reverse triggering originates from respiratory entrainment, interrupting or modifying the entrainment pattern can prevent or limit reverse triggering. Because entrainment is more likely to occur during sedation, it is unwise to increase sedatives as a treatment. One might be tempted to reduce the trigger sensitivity of the ventilator.

Although this can effectively prevent breath stacking, it does not abolish the potentially injurious muscular effort or the harmful effects of negative intrathoracic pressure.

Instead, the entrainment between the ventilator and the patient can be disrupted by changing the tidal volume (or pressure) and the mandatory respiratory rate. In general, entrainment is more likely to occur during longer mechanical insufflations with lower flow rates and higher volumes. Reducing tidal volume can therefore break entrainment. In addition, increasing the mandatory respiratory rate can completely abolish a patient's neural effort and disrupt respiratory entrainment. Lowering the mandatory respiratory rate might cause patient effort to commence before mechanical inflation, thereby effectively breaking entrainment. As a final option, a neuromuscular blocker can be administered to abort the mechanical consequences of reverse triggering.

## **CONCLUSIONS**

Mechanical ventilation may entrain a patient's respiratory rhythm, especially during deep sedation, and lead to reverse triggering with potentially detrimental effects on the lungs, respiratory muscles, and hemodynamics. Recognizing this patient-ventilator interaction can help to prevent its potentially injurious consequences.

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5

# Lung- and Diaphragm-protective Ventilation by Titrating Inspiratory Support to Diaphragm Effort: a Randomized Clinical Trial

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*Crit Care Med.* 2022 Feb 4;50(1):192-203

*Author contributions: HV, AJ, AM, CO and LH designed the study. HV, AJ, HG and YZ conducted study measurements. HV, HG and PV conducted statistical analyses. HV and LH drafted the manuscript. AJ, HG, JD, AG, CO, MS, PT, AM, and LH critically revised the manuscript. All authors have read and accepted the final version of the manuscript.*

*The supplements to this article are available open source from the Publisher's website at <https://links.lww.com/CCM/G924>*

## ABSTRACT

**Objective:** Lung- and diaphragm-protective ventilation is a novel concept that aims to limit the detrimental effects of mechanical ventilation on the diaphragm while remaining within limits of lung-protective ventilation. The premise is that low breathing effort under mechanical ventilation causes diaphragm atrophy, while excessive breathing effort induces diaphragm and lung injury. In a proof-of-concept study, we aimed to assess whether titration of inspiratory support based on diaphragm effort increases the time that patients have effort in a pre-defined “diaphragm-protective” range, without compromising lung-protective ventilation.

**Methods** Randomized clinical trial in mixed medical-surgical ICU in a tertiary academic hospital in the Netherlands. Patients (n=40) with respiratory failure ventilated in a partially-supported mode. In the intervention group, inspiratory support was titrated hourly to obtain transdiaphragmatic pressure swings in the predefined “diaphragm-protective” range (3 to 12 cmH<sub>2</sub>O). The control group received standard-of-care.

**Measurements and main results:** Transdiaphragmatic pressure, transpulmonary pressure, and tidal volume were monitored continuously for 24 hours in both groups. In the intervention group, more breaths were within “diaphragm-protective” range compared with the control group (median 81%, interquartile range [64-86%] versus 35% [16-60%], respectively, p<0.001). Dynamic transpulmonary pressures (20.5±7.1 cmH<sub>2</sub>O vs 18.5±7.0 cmH<sub>2</sub>O, p = 0.321) and tidal volumes (7.56 ±1.47 ml/kg vs 7.54 ±1.22 ml/kg, p = 0.961) were not different in the intervention and control group, respectively.

**Conclusions:** Titration of inspiratory support based on patient breathing effort greatly increased the time that patients had diaphragm effort in the predefined “diaphragm-protective” range without compromising tidal volumes and transpulmonary pressures. This study provides a strong rationale for further studies powered on patient-centered outcomes.

## INTRODUCTION

New approaches are needed to limit the adverse effects of invasive mechanical ventilation on the diaphragm of critically ill patients, as diaphragm weakness in these patients is common and has been associated with poor clinical outcomes.<sup>1,2</sup> The level of diaphragm effort has been proposed to play a role in the development of critical illness-associated diaphragm weakness:<sup>3</sup> inactivity of the diaphragm causes disuse atrophy and diaphragm weakness,<sup>4-6</sup> while excessive diaphragm effort has been implicated to contribute to diaphragm injury in observational<sup>7</sup> and preclinical studies.<sup>8-10</sup> Prospective clinical trials are required to confirm this hypothesis.<sup>11</sup>

Additionally, excessive diaphragm effort might worsen lung injury by increasing stress and strain imposed on the lung (self-inflicted lung injury),<sup>12,13</sup> and by the hemodynamic consequences of large intrathoracic pressure swings.<sup>14-16</sup> Preventing low and excessive diaphragm effort by titrating inspiratory support might thus limit the complications associated with mechanical ventilation on the diaphragm and lungs.<sup>7,13,17</sup>

Lung- and diaphragm-protective mechanical ventilation is a novel concept to managing patients on mechanical ventilation, aimed at achieving physiological diaphragm effort while remaining within limits of lung-protective ventilation.<sup>18,19</sup> While incorporating diaphragm effort into management of ventilated patients has gained attention in the past years, the feasibility of this concept and its compatibility with lung-protective ventilation strategies has not been investigated.

We performed a randomized clinical trial to establish the feasibility of a lung- and diaphragm-protective ventilation approach in invasively ventilated, critically ill patients. We hypothesized that titrating inspiratory support to diaphragm effort would increase the time that patients have effort in a predefined “diaphragm-protective” range, without compromising lung-protective ventilation.

## MATERIALS AND METHODS

### Study Design

We performed a randomized clinical trial in a mixed medical-surgical ICU of an academic hospital in the Netherlands. The trial was registered at [clinicaltrials.gov](https://clinicaltrials.gov) (NCT03527797). The study protocol was approved by the institutional review board (NL62486.029.17). The patient or their legal representatives provided written informed consent. The study

was performed in accordance with the 2008 Declaration of Helsinki and its later amendments. No commercial support was received for this project.

## Patients

Adult patients were eligible if they were intubated and mechanically-ventilated in a partially supported mode, and if the attending physician expected invasive ventilation would be required for at least 24–48 hours at the time of screening. Exclusion criteria were: past medical history of neuromuscular disorders (including diaphragm paralysis); contraindications for placement of a nasogastric catheter; active air leak in the pleural space; or abnormal anatomy of the esophagus or stomach.

## Randomization And Masking

Enrolment, randomization and clinical data collection were handled in an online system (Castor EDC, Castor, the Netherlands). Patients were allocated to the control or intervention group in a 1:1 ratio using variable block randomization with blocks of size 4, 6, or 8. Patients and their families were blinded to group allocation. Blinding was not possible for the investigators and the clinical team given the study design. Patients excluded before randomization were replaced.

## Procedures

Flow, airway opening pressure (Pao), esophageal pressure (Pes), gastric pressure (Pga), transdiaphragmatic pressure (Pdi, calculated as  $Pga - Pes$ ) and dynamic transpulmonary pressure (PL<sub>dyn</sub>, calculated as  $Pao - Pes$ )<sup>14</sup> were recorded continuously during the 24-hour study period and stored for later analyses (**Figure 1**).

The first hour of measurements in both groups (T=0h) was conducted before adjusting the inspiratory support to serve as baseline.

Patients in the control group received standard clinical care following local protocols for lung-protective ventilation and sedation (**online supplement**) from T= 0h to T=24h. In the intervention group, ventilator support was adjusted from T=1h to T=24h based on diaphragm effort according to the algorithm presented in **Figure 2** (“*diaphragm-protective ventilation*”). A study investigator (HdV, LH or AJ) measured the mean Pdi in the first two minutes of every hour in real time using the data capture software (Acknowledge, BIOPAC, USA). The steps of the algorithm were repeated until the mean Pdi was between 3 and 12 cmH<sub>2</sub>O, or if a predefined limit for lung-protective ventilation was crossed. The lower limit (3 cmH<sub>2</sub>O) for diaphragm effort was selected because we could reliably differentiate pressure swings of 3 cmH<sub>2</sub>O from cardiac oscillations, and very low diaphragm effort was found to prevent disuse atrophy in animal models<sup>20</sup> and preliminary clinical

studies.<sup>21,22</sup> The upper limit (12 cmH<sub>2</sub>O) was based on the upper range of tidal swings in esophageal pressure in healthy subjects.<sup>14,23</sup> This range is in agreement with the opinion of a group of international experts published recently.<sup>18,19</sup> The investigators only adjusted the inspiratory support; other ventilator settings (including PEEP, FiO<sub>2</sub>, cycle criteria, trigger settings) and all other aspects of care (including drugs) were managed by the clinical team according to local protocols. Study data were not available to the clinical team. Blood samples (5-10ml) were drawn from the indwelling arterial catheter at T=0h, T=12h and T=24h.

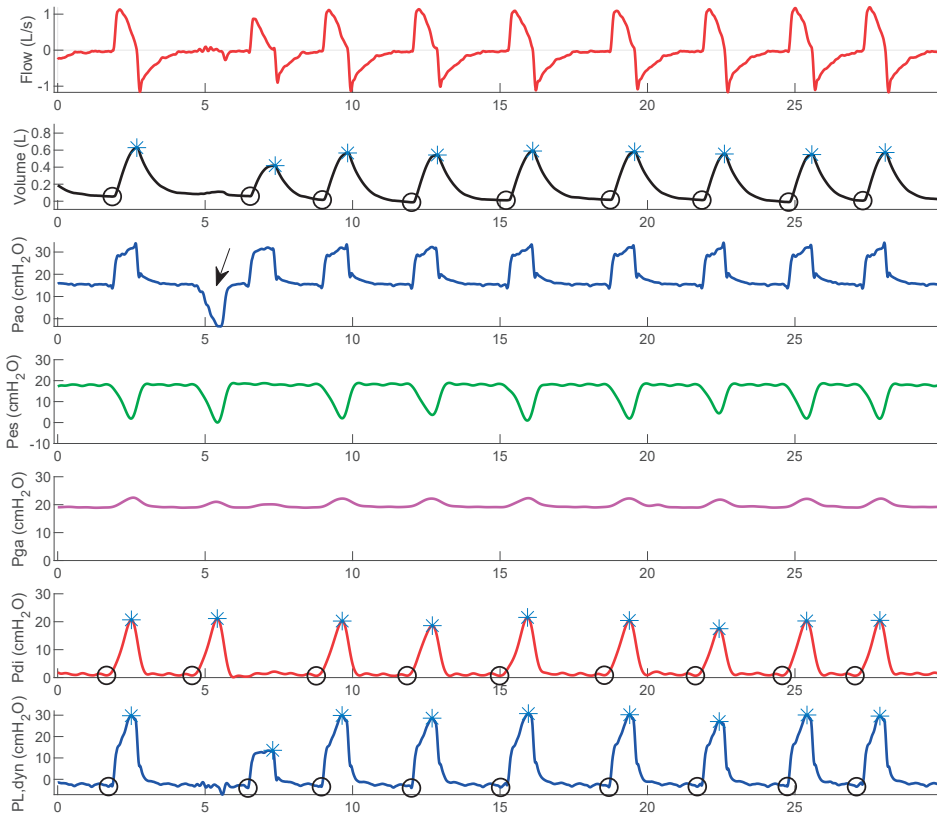
## Outcomes

The primary outcome was the proportion of breaths in the “diaphragm-protective” range per patient, calculated as [number of breaths with Pdi swings between 3 and 12 cmH<sub>2</sub>O] / [all recorded breaths] \* 100%. Secondary outcome parameters included the tidal volume normalized to predicted bodyweight (ml/kg PBW), and the dynamic and driving transpulmonary pressures measured in every breath in the 24-hour study period (**Figure 1**).

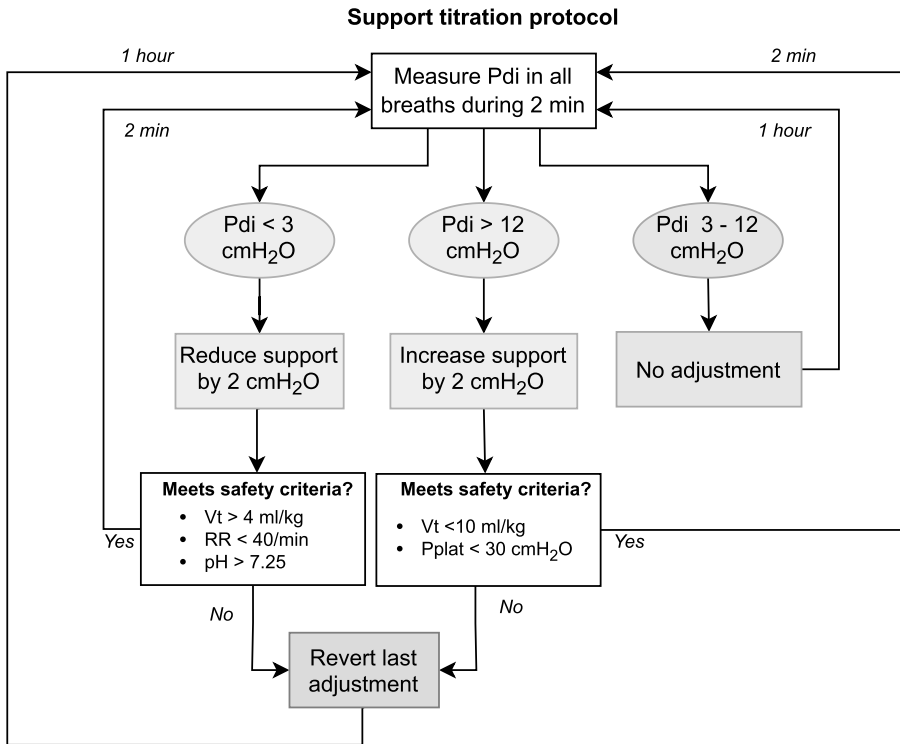
Additional measures of lung-protective ventilation, including the pressure-time product of the diaphragm and the concentrations of protein biomarkers for endothelial function, lung injury and systemic inflammation are described in the online supplement.

## Statistical Analysis

A convenience sample of 40 patients (20 per group) was recruited, because the distribution of respiratory effort during a 24-hour period was not well-characterized in the target population, and because no previous study had titrated diaphragm effort to this specific range. All statistical analyses were performed on the intention-to-treat population, consisting of all randomized patients that had completed at least one hour of measurements. Baseline characteristics were summarized as mean ± standard deviation, median [interquartile range] or frequency (percentages) as appropriate. Aggregated outcome data were compared between groups using the Wilcoxon rank-sum test or Student T-test, as appropriate. For the nonparametric variables, the effect size is reported as the difference in medians with bootstrapped 95% confidence intervals. Normality was assessed with normal-probability plots. When required, a suitable transformation was used to achieve normality. A two-tailed significance level of 5% was used for all statistical analysis. All the statistical analyses were performed in R version 4.0.1 (R Foundation for Statistical Programming, Vienna, Austria). Additional details on the statistical analyses are available in the online resources.



**Figure 1. Analysis of the physiological signals.** Flow, volume, airway opening pressure (Pao), esophageal pressure (Pes), gastric pressure (Pga), transdiaphragmatic pressure (Pdi) and transpulmonary pressure (PL,dyn) during the first 30 seconds of an hour of recordings. An end-expiratory occlusion was administered at the arrow to confirm adequate positioning and filling of the catheter. The asterisks mark the maximal volume, Pdi and P<sub>L</sub> identified by the script in each breath, while the circles mark the minimal values. The delta in each breath was calculated as maximum – minimum (dynamic pressures).



**Figure 2: Titration algorithm.** Pdi = transdiaphragmatic pressure, Vt = tidal volume, RR = respiratory rate, Pplat = plateau airway pressure. An increase in tidal volume greater than 2ml/kg PBW compared to a subject’s own baseline was also considered a breach of lung-protective ventilation.

## RESULTS

In total, 451 patients on partially-supported ventilation were assessed between April 25<sup>th</sup>, 2018 and July 16<sup>th</sup>, 2020 (**Figure E1**). The trial was stopped because the intended number of participants was included. The intention-to-treat analysis included 39 patients (19 intervention, 20 control). Patient characteristics are summarized in **Table 1** and **Table E1**. The two groups were similar at baseline. Expected hospital mortality based on the APACHE IV-score was 45%. 35 patients (90%) met criteria for ARDS according to the Berlin definition.<sup>24</sup>

**Table 1.** Baseline characteristics

Parameter	Overall (n = 39)	Control (n = 20)	Intervention (n = 19)
<b>Biometrics</b>			
Age, yr	65 (14)	66 (14)	65 (13)
Gender = male, n (%)	26 (68%)	13 (65%)	13 (68%)
BMI, kg/m <sup>2</sup>	27 [26, 29]	28 [26, 30]	26 [25, 28]
<b>Risk scores</b>			
SAPS II	50 (12)	51 (13)	49 (11)
SOFA score at enrolment	9 [8, 11]	9 [8, 10]	10 [9, 12]
APACHE IV	85 (28)	84 (30)	87 (26)
<b>Mechanical ventilation</b>			
<i>Ventilation prior to study, days</i>	8 [4, 15]	8 [4, 15]	9 [5, 16]
Controlled ventilation	3 [1, 5]	3 [1, 4]	3 [1, 8]
Partially-supported ventilation	4 [2, 10]	4 [2, 10]	3 [2, 9]
PEEP, cmH <sub>2</sub> O	10 [8, 12]	10 [8, 12]	10 [8, 10]
Pressure above PEEP, cmH <sub>2</sub> O	9.5 (4.8)	8.5 (4.7)	10.7 (4.8)
FiO <sub>2</sub>	0.45 [0.40, 0.50]	0.45 [0.40, 0.50]	0.45 [0.40, 0.50]
<b>Gas exchange</b>			
pH	7.42 (0.08)	7.42 (0.08)	7.42 (0.07)
PaO <sub>2</sub> , mmHg	79.5 (13.5)	78.8 (15.0)	79.5 (12.8)
PaCO <sub>2</sub> , mmHg	45.0 (9.0)	44.2 (8.2)	45.0 (10.5)
PaO <sub>2</sub> /FiO <sub>2</sub> -ratio, mmHg	190 (54)	185 (50)	198 (60)
Ventilatory ratio	2.1 (0.6)	2.1 (0.6)	2.1 (0.6)
<b>Respiratory mechanics</b>			
Compliance of respiratory system, ml/cmH <sub>2</sub> O	36 (14)	33 [23,41]	35 [26,47]
Lung compliance, ml/cmH <sub>2</sub> O	48 (28)	45 [29,64]	48 [33, 71]
Chest wall compliance, ml/cmH <sub>2</sub> O	150 (57)	143 (58)	159 (56)
Intrinsic PEEP, cmH <sub>2</sub> O	2.6 (2.2)	2.3 (1.7)	2.9 (2.7)
<b>Neurological</b>			
RASS at enrolment	-1 [-3, 0]	-1 [-2, 0]	-2 [-3, 0]

**Table 1 legend.** Definition of abbreviations: PC = Pressure Controlled ventilation, PS = Pressure Support ventilation, APACHE = Acute Physiology and Chronic Health Evaluation, SAPS = Simplified Acute Physiology Score, SOFA = Sequential Organ Failure Assessment, RASS = Richmond Agitation and Sedation Score.

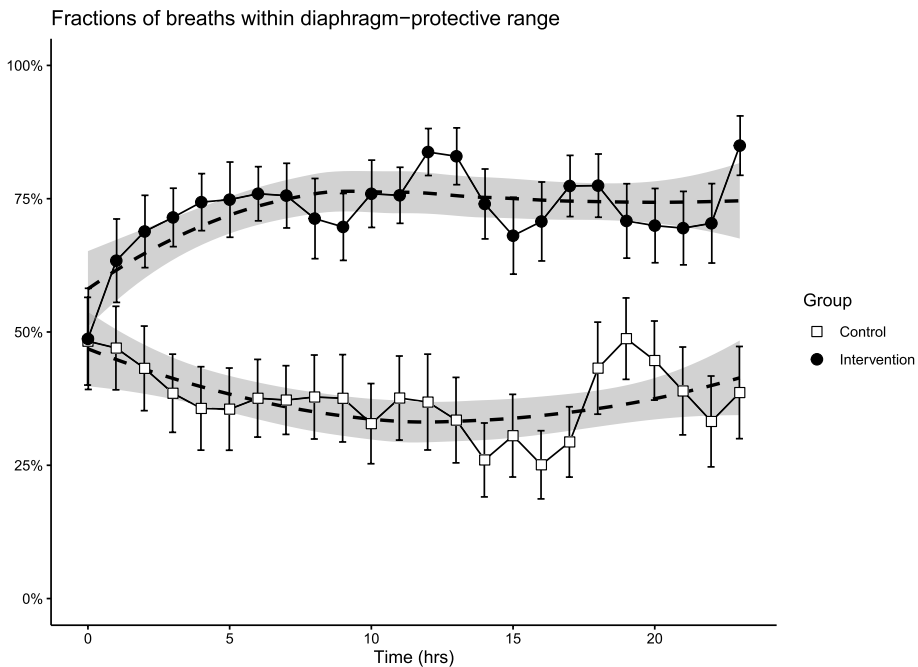
### Inspiratory support adjustments

Inspiratory support was adjusted a median of 2 [IQR 1-2] times per subject in the control group (by the clinical team) and median 8 [IQR 4-11] times per subject in the intervention group (by the investigators according to the titration algorithm) in the 24-hour study period ( $p < 0.001$ , **Figure E2**). Most of the adjustments in the intervention group (52%) were required in the first 4 hours of the study period (**Figure E3**), and most subjects received a net increase in support (median 3 cmH<sub>2</sub>O, IQR 2-6 cmH<sub>2</sub>O). Median difference in dynamic transpulmonary pressure was equal in both groups, with two notable outliers in the intervention group (**Figure E2**).

### Diaphragm effort

More than one million breaths were analyzed for the primary and secondary outcome parameters (mean 28,894 ± 9,796 breaths per subject). 72 hours (7.7% of the total) had missing data. At baseline, 7% of breaths had effort below and 37% of breaths had effort above the target range (**Figure E4**).

The evolution of diaphragm effort from T=0h to T=24h is shown in **Figure 3**. Proportions of breaths within the target range of diaphragm effort, summarized over the total study period, were higher for patients in the intervention group compared with patients in the control group (median 81% [64-86%] versus 35% [16 – 59%], respectively, difference in median 46%, 95% CI: 24 – 64%,  $p < 0.001$ ). The longitudinal course differed significantly between the groups ( $p < 0.001$ ). Post-hoc subgroup analyses showed that the inspiratory support titration was equally effective in patients with a compliance below and above the median (35 ml/cmH<sub>2</sub>O), and in patients included within 7 days after onset of ventilation or later (**Table E2**). Distribution of breaths below and above the target range for diaphragm effort, pressure-time product of the diaphragm, and patient-level data on diaphragm effort are available in the online supplement (**Figures E5, E6 and E7**).



**Figure 3. Diaphragm effort over time.** Proportion of breaths in diaphragm-protective range, defined as 3-12 cmH<sub>2</sub>O per breath, in each group. Dots represent the mean; bars represent the standard error of the mean; asterisks represent the hours with a significant difference between the groups in the post-hoc analysis. Shaded area represents the 95% confidence interval obtained with Loess-regression.

### Markers for lung injury

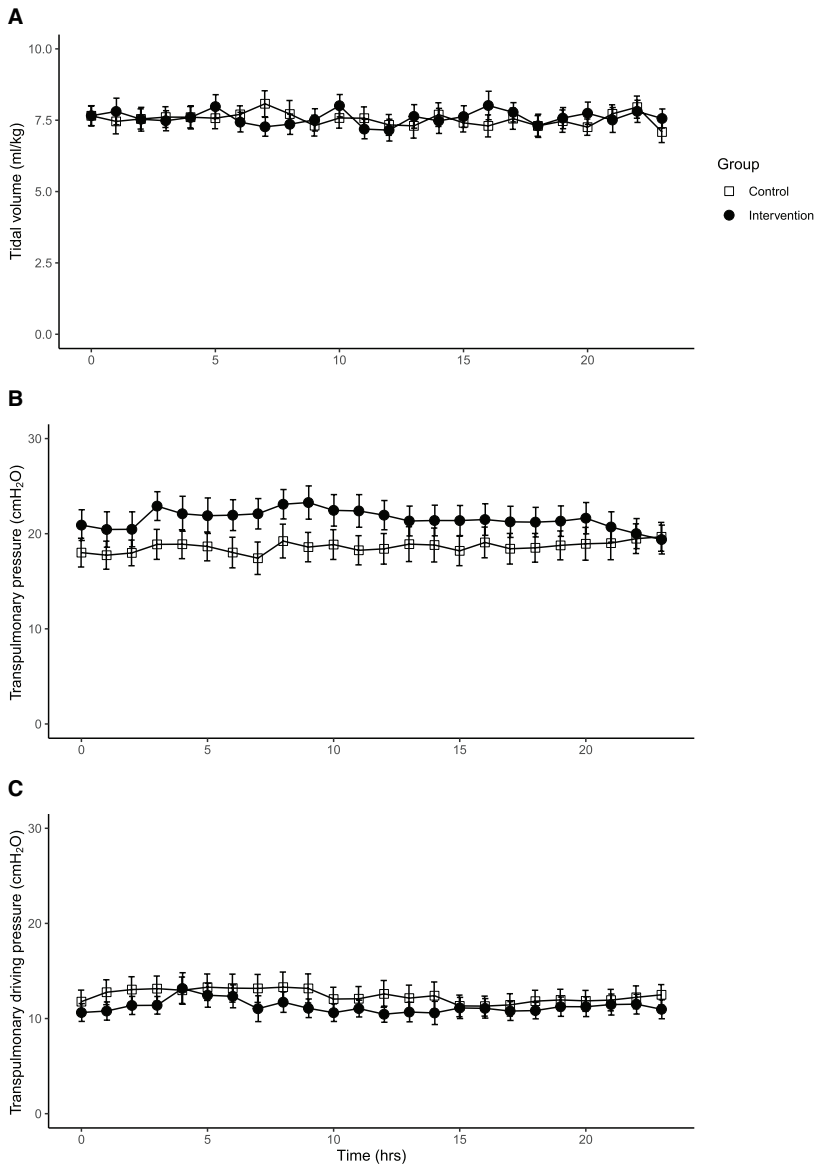
Tidal volumes were similar in the intervention and control groups ( $7.56 \pm 1.47$  vs  $7.54 \pm 1.22$  ml/kg PBW,  $p = 0.959$ , **Figure 4A**). The proportion of breaths in lung-protective range, defined as [number of breaths with tidal volumes  $< 8$  ml/kg] / [all breaths], was found to be similar in the intervention and control groups (median 96% [54-99%] vs 83% [35-86%], respectively,  $p = 0.255$ , **Figure E8**) in a post-hoc analysis. The cut-off ( $< 8$  ml/kg) was based on a recent expert statement.<sup>18</sup>

The dynamic transpulmonary pressures, the sum of pressures used to overcome air-flow resistance and elastance of the lungs, were similar in the intervention and control groups ( $20.5 \pm 7.1$  vs  $18.5 \pm 7.0$  H<sub>2</sub>O cmH<sub>2</sub>O, respectively,  $p = 0.373$ , **Figure 4B**). The transpulmonary *driving* pressure, the pressure used to overcome the elastance of the lungs, was measured in 28 subjects and calculated in 11 subjects in a post-hoc analysis (supplements). The transpulmonary driving pressures were similar in the intervention and control groups ( $11.2 \pm 5.6$  vs  $12.4 \pm 4.4$  cmH<sub>2</sub>O, respectively,  $p = 0.295$ ) (**Figure 4C**).

The doses of sedatives, pH, PaCO<sub>2</sub> and PaO<sub>2</sub> did not differ between the groups (**Table E3**). Longitudinal course of 12 protein biomarkers of lung endothelial cell function, lung injury and systemic inflammation, did not differ between the groups for any of the tested biomarkers (**Table E4**). Longitudinal course of minute volume was not different in both groups (**Figure E9**).

### **Patient outcomes and adverse events**

Weaning outcome and mortality were similar in both groups (**Table E5**). One subject developed subcutaneous emphysema 10 hours after study titration commenced. Subcutaneous emphysema did not lead to cardiovascular or ventilatory complications and resolved without a chest tube. Severity of the event was categorized as mild. More information is available in the online supplement (**Fig E10**).



**Figure 4: Tidal volume (a), dynamic transpulmonary pressures (b) and transpulmonary driving pressures (c) over time.** Dots represent the mean; bars represent the standard error of the mean. None of the hours differed significantly between both groups in the post-hoc analysis.

## DISCUSSION

This is the first study to investigate the feasibility and efficacy of a bedside titration algorithm to obtain diaphragm-effort in a predefined “diaphragm-protective” range in a heterogeneous group of invasively ventilated critically ill patients, while maintaining tidal volume and transpulmonary pressures in ranges considered as lung-protective. We found that titration of ventilator support guided by transdiaphragmatic pressure resulted in higher proportions of breaths in the pre-defined “diaphragm-protective range” compared with standard of care (81% versus 35%, respectively). This approach did not compromise key characteristics of lung-protective ventilation, including tidal volumes, transpulmonary pressures, and biomarkers for lung injury.

### Diaphragm effort, diaphragm weakness and ICU outcomes

The evidence for disuse atrophy caused by ventilator over-assist in critically ill patients is convincing.<sup>25, 26</sup> However, load-induced diaphragm injury is an attractive concept, but is not yet supported by strong evidence. Animal studies have demonstrated that loaded breathing during mechanical ventilation can induce diaphragm injury, but the load imposed was generally very high.<sup>9, 27, 28</sup> Also, it has been demonstrated that high inspiratory loading is associated with diaphragm sarcomeric disruption,<sup>8</sup> indicating that the diaphragm is susceptible to load-induced injury. Interestingly, we have reported sarcomeric injury in the diaphragm of ventilated ICU patients.<sup>6, 29</sup> Finally, high diaphragm contractile activity assessed indirectly with ultrasound, was associated with increases in diaphragm thickness in an observational study.<sup>1, 7</sup> Whether the increased diaphragm thickness reflects muscle injury remains to be investigated. For more extensive discussion we refer to recent papers.<sup>3, 11</sup> Second, the relationship between diaphragm weakness and ICU outcomes, including difficult weaning and ICU mortality, has been observed to various degrees in observational studies,<sup>2, 30-36</sup> but whether diaphragm weakness is a causal contributor to poor ICU outcomes or a merely a marker for disease severity remains to be established.<sup>37</sup> A causal relationship seems plausible, as the diaphragm is the main muscle of inspiration and improving diaphragm strength led to improved weaning outcome in selected patients.<sup>38</sup> A recent mediation analysis of observational data has strengthened the hypothesis that inappropriate diaphragm effort contributes to poor clinical outcomes.<sup>11</sup> Nevertheless, large interventional trials that target optimization of diaphragm effort are required to assess the whether inappropriate diaphragm effort leads to diaphragm “myotrauma” and poor outcomes, and this current study might aid in designing such trials.

## Effectiveness of the titration algorithm

At baseline, 49% of the subjects (19/39) had insufficient or excessive diaphragm effort according to our predefined limits (**Fig E3**). This high incidence of excessive diaphragm effort matches an observational study in patients on partially supported mechanical ventilation.<sup>39</sup> Other cohorts have found more patients with low respiratory effort.<sup>7</sup> The lower proportion of patients with ventilator over-assistance in our study may be explained by our local clinical protocol that promotes reducing inspiratory support as much as tolerated by the patient. The titration algorithm effectively prevented both insufficient and excessive diaphragm effort in the intervention group; 10% (2/19) of the subjects in the intervention group had diaphragm effort outside the predefined range in the total study period versus 60% (12/20) in the control group (**Fig E5**). Notably, this reduction in excessive diaphragm effort was achieved without changing the level of sedation.

The tidal volumes in both groups of our trial closely match the tidal volumes reported for partially-supported ventilation in LUNG-SAFE cohort<sup>40</sup> and those observed during partially-supported breathing in patients without ARDS,<sup>41</sup> demonstrating that the titration-algorithm did not compromise lung-protective ventilation. This is further supported by the observation that biomarkers for lung injury and systemic inflammation did not differ significantly between the control and intervention group during the course of the study.

Application of the titration algorithm did not lead to lower diaphragm effort at all in two subjects in the intervention group, and instead led to tidal volumes incompatible with lung-protective ventilation. Interestingly, both subjects had a pH >7.48, suggesting that their respiratory drive did not originate from pH and PaCO<sub>2</sub>. Their elevated drive might have originated from mechano- and irritant-receptors in the alveoli and chest wall, or pain and agitation. Instead of increasing support, these patients might require sedatives, analgesics or partial neuromuscular blockade to achieve lung- and diaphragm protective ventilation.<sup>42</sup>

## Strengths and limitations

### Strengths

This is the first randomized clinical trial to investigate the feasibility of a lung- and diaphragm-protective ventilation approach in ventilated critically ill patients. The target range for diaphragm effort that we selected is in agreement with the opinion of a group of international experts published recently.<sup>18,19</sup> Additionally, we used the reference standard to measure diaphragm effort<sup>43</sup> and employed a detailed analysis of every single

breath in the 24-hour study period. Although the study was single blinded, the clinical team did not have access to results from esophageal pressure monitoring. We used a simple algorithm to titrate inspiratory ventilator support to achieve respiratory effort within physiological limits without modifying sedation levels, because higher sedation levels are associated with delirium and prolonged mechanical ventilation.<sup>44</sup>

### **Limitations**

This study has several limitations. First, this study was not designed to detect a meaningful impact of “diaphragm-protective” ventilation on diaphragm function, markers for lung injury or patient outcomes, but instead focused on the feasibility of such an approach and its compatibility with lung-protective ventilation. The relatively small number of subjects allowed us to collect in-depth physiological data, but restricted the analysis to physiological parameters. Future studies will have to assess whether this approach indeed reduces the development of diaphragm weakness and improves ICU outcomes.

Second, the precise range of diaphragm effort to prevent both disuse atrophy and load-induced injury remains to be established. Especially, the upper limit for safe diaphragm effort is subject of discussion and probably depends on several factors including patient characteristics, such as maximal diaphragm strength<sup>45</sup> and the phase of critical illness.<sup>34</sup>

Third, the study population was heterogeneous. Patients varied considerably in the duration of mechanical ventilation before study inclusion and in their respiratory system compliance. Nevertheless, additional analyses revealed that the titration algorithm was equally effective in patients with a compliance below and above 35 cmH<sub>2</sub>O, and in patients included in the first week of ventilation or thereafter (**Table E2**). Future studies may start inspiratory support titration as soon as a patient exhibits respiratory effort, as in the early phase of critical illness the diaphragm may be more susceptible to injury.<sup>3,5</sup> Additionally, the total duration of ventilation and the reintubation rate was high in our cohort because we selected patients in which prolonged mechanical ventilation was expected. However, it can be argued that this is the population in which protection of the diaphragm can have most impact.

Fourth, the study protocol requires esophageal and gastric pressure monitoring, which limits generalizability. Recent reports evaluated readily-available metrics of respiratory effort based on airway pressure, the P0.1. and end-expiratory occlusion pressure.<sup>39, 46</sup> If further research has validated these indirect measurements of respiratory muscle effort, and when the optimal range of effort is better defined, they may be useful to screen for patients who can benefit from invasive measurement techniques.<sup>47</sup>

Fifth, additional ventilator settings such as the cycle-off criterion, trigger sensitivity,  $\text{FiO}_2$  and PEEP could have been incorporated in the algorithm as these parameters influence diaphragm effort. However, the role of these settings in lung-injury and diaphragm dysfunction is currently less established.<sup>3,11</sup>

## **CONCLUSION**

We found that titration of inspiratory support guided by transdiaphragmatic pressure increases the time that patients have diaphragm effort in a predefined 'diaphragm-protective' range without compromising lung-protective ventilation. Larger trials are required to establish the clinical impact of titrating diaphragm effort on patient-centered outcomes.

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6

# Performance of Noninvasive Airway Occlusion Maneuvers to Assess Lung Stress and Diaphragm Effort in Mechanically Ventilated Critically Ill Patients

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*Anesthesiology*. 2023 Mar 1;138(3):274-288.

*Author contributions: HV, AJ, AM, LH, LL and HQ designed the original trails and conducted the study measurements. HV, HG, PT, AJ and LH designed the current manuscript. HV and HG conducted statistical analyses. HV, PT, HG and LH drafted the manuscript. AJ, HG, AG, PT, AM, LL, HQ, YZ and LH critically revised the manuscript. All authors have read and accepted final version of the manuscript.*

*The supplements to this article are available open source from the publisher's website at <http://links.lww.com/ALN/C989>*

## ABSTRACT

**Background:** Monitoring and controlling lung stress and diaphragm effort has been hypothesized to limit lung injury and diaphragm injury. The occluded inspiratory airway pressure (Pocc) and the airway occlusion pressure at 100ms (P0.1) have been used as non-invasive methods to assess lung stress and respiratory muscle effort, but comparative performance of these measures and their correlation to diaphragm effort is unknown. We hypothesized that Pocc and P0.1 correlate to diaphragm effort and lung stress, and would have strong discriminative performance in identifying extremes of lung stress and diaphragm effort.

**Methods:** Secondary analysis of two studies. Transdiaphragmatic pressure ( $\Delta P_{di}$ ) and transpulmonary pressure ( $\Delta P_L$ ) were obtained with double-balloon nasogastric catheters in critically ill patients ( $n = 38$ ). Pocc and P0.1 were measured every 1-3 hours. Correlations between Pocc and P0.1 with  $\Delta P_L$  and  $\Delta P_{di}$  were computed from patients from the first cohort. Accuracy of Pocc and P0.1 to identify patients with extremes of lung stress ( $\Delta P_L > 20 \text{cmH}_2\text{O}$ ) and diaphragm effort ( $\Delta P_{di} < 3 \text{cmH}_2\text{O}$  and  $> 12 \text{cmH}_2\text{O}$ ) in the preceding hour was assessed with area under receiver-operator characteristic curves (AUROC). Cut-offs were validated in patients from the second cohort ( $n = 13$ ).

**Results:** Pocc and P0.1 correlate with  $\Delta P_L$  ( $r^2 = 0.62$  and  $0.51$ , respectively) and  $\Delta P_{di}$  ( $r^2 = 0.53$  and  $0.22$ , respectively). AUROC to detect high lung stress is  $0.90$  ( $0.86-0.94$ ) for Pocc and  $0.88$  ( $0.84-0.92$ ) for P0.1. AUROC to detect low diaphragm effort is  $0.97$  ( $0.87-1.00$ ) for Pocc and  $0.93$  ( $0.81-0.99$ ) for P0.1. AUROC to detect high diaphragm effort is  $0.86$  ( $0.81-0.91$ ) for Pocc and  $0.73$  ( $0.66-0.79$ ) for P0.1. Performance was similar in the external dataset.

**Conclusions:** Pocc and P0.1 correlate with lung stress and diaphragm effort in the preceding hour. Diagnostic performance of Pocc and P0.1 to detect extremes in these parameters is reasonable to excellent. Pocc is more accurate in detecting high diaphragm effort.

## INTRODUCTION

Implementation of lung-protective ventilation with low tidal volumes has improved outcomes of critically ill patients,<sup>1,2</sup> likely by limiting lung stress and strain caused by excessive regional volume expansion and distending (driving) pressures of the alveoli.<sup>3,4</sup> It has been proposed that monitoring and controlling diaphragm effort in addition to lung stress may further benefit ventilated patients.<sup>5,6</sup> The rationale is that absence of diaphragm effort during mechanical ventilation rapidly leads to disuse atrophy and weakness,<sup>7,8</sup> which can be ameliorated by keeping the diaphragm active.<sup>9,10</sup> Preventing high effort may limit diaphragm injury and fatigue<sup>11</sup> and reduce sources of lung stress such as lung edema and pendelluft.<sup>12,13</sup>

The reference methods to assess lung stress and diaphragm effort are esophageal and gastric manometry to calculate the transpulmonary pressure ( $P_L$ ) and transdiaphragmatic pressure (Pdi),<sup>14-16</sup> which is seldom used in clinical practice due to invasiveness and complexity.<sup>1</sup> Two measurements based on airway occlusion maneuvers have recently been evaluated as proposed non-invasive estimates for lung stress and respiratory muscle effort. The occluded inspiratory airway pressure (Pocc), also known as the 'expiratory occlusion pressure', is the drop in airway pressure during an inspiration against an occluded airway. Pocc correlates with total respiratory muscle pressure (Pmus) and lung stress, albeit with wide limits of agreement.<sup>17,18</sup> The drop in airway pressure in the first 100ms of an occluded inspiration (P0.1) has recently been compared with respiratory effort as well.<sup>19</sup> Despite the moderate correlations, the parameters were proposed to be useful in identifying patients with extremes of respiratory muscle effort.

However, several questions remain regarding the validity of Pocc and P0.1. First, the relation of Pocc and P0.1 to diaphragm effort is unknown. Second, performance of P0.1 to detect potentially injurious lung stress has not been reported. Third, the correlation of Pocc and P0.1 with mechanical power, an advanced parameter for lung stress, is unknown. Finally, the performance of Pocc and P0.1 have not been compared to each other in the same cohorts.

Therefore, our aim was to validate and compare Pocc and P0.1 as measurements for lung stress and diaphragm effort in invasively ventilated critically ill patients. We hypothesized that Pocc and P0.1 correlate with lung stress and diaphragm effort, and that both parameters would have good diagnostic performance in identifying patients with extremes of lung stress and diaphragm effort.

## MATERIALS AND METHODS

### Study Design

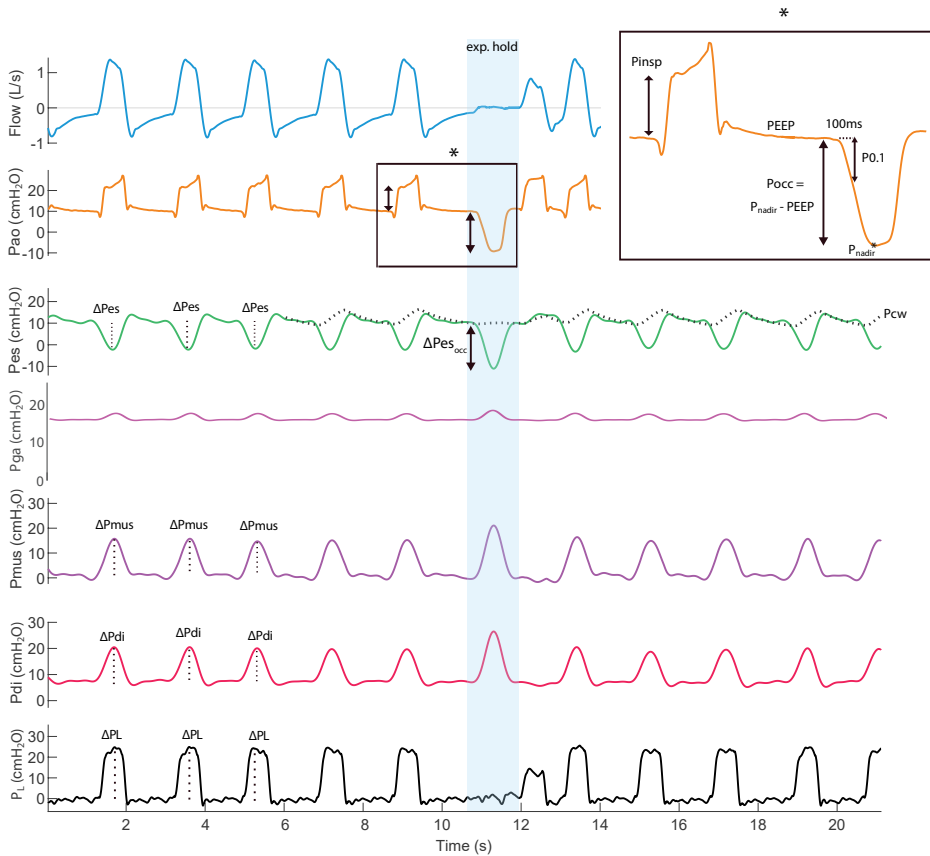
This diagnostic study is a secondary analysis on data from two clinical trials: a randomized-controlled trial conducted in The Netherlands (NCT 03527797)<sup>20</sup> and a physiological trial conducted in China (NCT 01663480).<sup>21</sup> This analysis was not registered *a priori*. The manuscript is reported according to the STARD guidelines.<sup>22</sup>

### Patients

The primary cohort was recruited at the mixed medical-surgical ICU of a tertiary university hospital (Amsterdam UMC, location VUmc, Amsterdam, the Netherlands), and consisted of patients ( $n = 39$ ) with acute respiratory failure ventilated with a spontaneous mode of mechanical ventilation (either pressure support or neurally-adjusted ventilatory assist, NAVA) with an expected duration of ventilation of at least 48 hours.<sup>20</sup> The external validation cohort was recruited at another academic hospital (South East University, Nanjing, China) and consisted of patients ( $n = 13$ ) ventilated in NAVA-mode at different NAVA-levels.<sup>21</sup> Both cohorts were convenience samples.

### Procedures

In the primary cohort flow, volume (time-integral of flow), airway opening pressure (Pao), esophageal pressure (Pes), gastric pressure (Pga), Pdi (Pga – Pes) and  $P_L$  (Pao – Pes) were recorded continuously for 24 hours with a flow sensor and a double-balloon nasogastric catheter (Nutrivent, Sidam, Italy) connected to a dedicated signal acquisition system (MP160, BIOPAC Systems Inc, USA) as described previously.<sup>23</sup> Airway occlusions lasting 2-3 seconds were performed at baseline and were repeated every 1-3 hours (**Figure 1**) to assess correct positioning and filling of the esophageal balloons and to calculate Pocc and P0.1. End-inspiratory occlusions lasting 2-3 seconds were performed at baseline and were repeated every 4-6 hours to calculate the elastance of the chest wall and lungs in semi-static conditions. Patients in the external validation cohort had a nasogastric catheter (NeuroVent Research, Toronto, Canada) to record Pes, Pga, Pdi,  $P_L$  and the electrical activity of the diaphragm (Edi). The patients received multiple expiratory occlusions at baseline, after which the NAVA-level (i.e., cmH<sub>2</sub>O of inspiratory support above PEEP per  $\mu V$  of Edi) was increased gradually to induce a wide range of diaphragm effort in the subjects. Airway occlusion maneuvers lasting 2-3 seconds were repeated at each NAVA-level.<sup>21</sup> All recordings with airway occlusion maneuvers with a  $\Delta P_{ao}/\Delta P_{es}$ -ratio below 0.8 or above 1.2 were discarded because the Pes-based measurements were deemed unreliable due to inadequate balloon filling or positioning.<sup>14,24</sup> In this manuscript, the term ‘diaphragm effort’ refers to diaphragm pressure output (Pdi), and respiratory drive to the intensity of respiratory center output to the diaphragm.



**Figure 1 legend:** Line graphs showing flow, airway pressure (Paw), esophageal pressure (Pes) with superimposed chest wall recoil pressure (Pcw), gastric pressure (Pga), total respiratory muscle pressure (Pmus, calculated as Pcw - Pes), transdiaphragmatic pressure (Pdi, calculated as Pga - Pes) and transpulmonary pressure ( $P_L$ , calculated as Paw - Pes) over time.  $\Delta P_{mus}$ ,  $\Delta P_{di}$  and  $\Delta P_L$  were calculated as the maximal absolute difference in the respective pressure tracings per breath (dotted vertical lines). An expiratory occlusion was administered in the shaded area. The inset shows a zoomed-in portion of airway pressure during the expiratory occlusion and the preceding breath: Pocc was calculated as the total drop in airway pressure during the occlusion, while the airway occlusion pressure at 100ms (P0.1) was calculated as the drop in the first 100ms of the occlusion. The inspiratory support provided by the ventilator (Pinsp) was measured as the plateau airway pressure shortly after inspiratory triggering and pressurization by the ventilator.

## Signal analyses

Signal analyses for the current study were performed with a custom software (Matlab 2021a, MathWorks, USA) as described previously,<sup>20</sup> and are shown in **Figure 1** and **Figure E1**. Comprehensive description of the signal analysis including calculation of mechanical power is available in the **online supplements**. In this study, we have adopted the term ‘occluded inspiratory airway pressure’ for Pocc instead of ‘expiratory occlusion pressure’ to reflect that the measurement is obtained during inspiration.

## Statistical Analysis

Descriptive statistics are expressed as mean  $\pm$  standard deviation, median [interquartile range] or count (percentages), as appropriate. The reference parameters were averaged per hour before each occlusion in each subject. Normality of distributions was assessed visually on normal-probability plots. Log-transformations were used to transform distributions to normal if required. Sample size calculations were not performed. Biological variability of  $\Delta P_{di}$ ,  $\Delta P_{mus}$  and the ratio of  $\Delta P_{di}/\Delta P_{mus}$  was estimated by calculating the coefficient of variation (standard deviation / mean) of the respective parameters in each hour of the recordings, averaged for each subject.

The steps shown in **Figure 2** were taken consecutively to assess the diagnostic accuracy of Pocc and P0.1 to assess lung stress and diaphragm effort. First, the conversion factors to estimate  $\Delta P_L$ , transpulmonary mechanical power ( $MP_L$ ) and  $\Delta P_{di}$  from Pocc and P0.1 were obtained with internal bootstrap procedures as described previously in the primary cohort.<sup>17</sup> The bootstrap procedure randomly selected half of the patients in each loop, after which repeated-measures mixed models were used to obtain the optimal coefficient to convert Pocc and P0.1 into the reference parameters ( $\Delta P_L$ ,  $MP_L$  or  $\Delta P_{di}$ ). The mean coefficient factor after 1000 loops was selected as the final conversion factor for each respective measure, the confidence interval is reported to show variability of this factor in the different loops of the bootstrap.

Next, correlations between the observed and predicted lung stress and diaphragm effort (based on Pocc and P0.1) were calculated using the obtained conversion factors, and were compared with the reference-standards with the methods of Bland and Altman in the primary cohort.<sup>25</sup> Within-subject limits of agreement were calculated with repeated-measure mixed models as described previously.<sup>17</sup> The within-subject explained variance ( $r^2$ ) was calculated with the methods described by Nakagawa.<sup>26</sup> Correlations with  $r^2$  below 0.30 were defined as poor, 0.31 to 0.50 as moderate, 0.51 to 0.80 as fair, 0.81 to 0.90 as strong, and above 0.90 as very strong.

Additionally, the discriminative power of Pocc and P0.1 to detect extremes of lung stress and diaphragm effort were calculated using standard formulas and by constructing the receiver-operator characteristic (ROC)-curves in the primary and external cohort.<sup>27</sup> The limits for high lung stress were set at  $\Delta P_L > 20$  cmH<sub>2</sub>O<sup>5,14</sup> and  $MP_L > 12$  J/min<sup>28</sup> based on recent consensus statements. The limits for low and high diaphragm effort were set at  $< 3$  cmH<sub>2</sub>O and  $> 12$  cmH<sub>2</sub>O, respectively, also based on consensus statements.<sup>5,6,20</sup> Because no interventional studies have shown that these limits are not injurious in critically ill patients as of yet, additional limits for potentially-injurious lung stress and diaphragm effort were analyzed as well (**Table E1**). Areas under the ROC-curves (AUROC) between

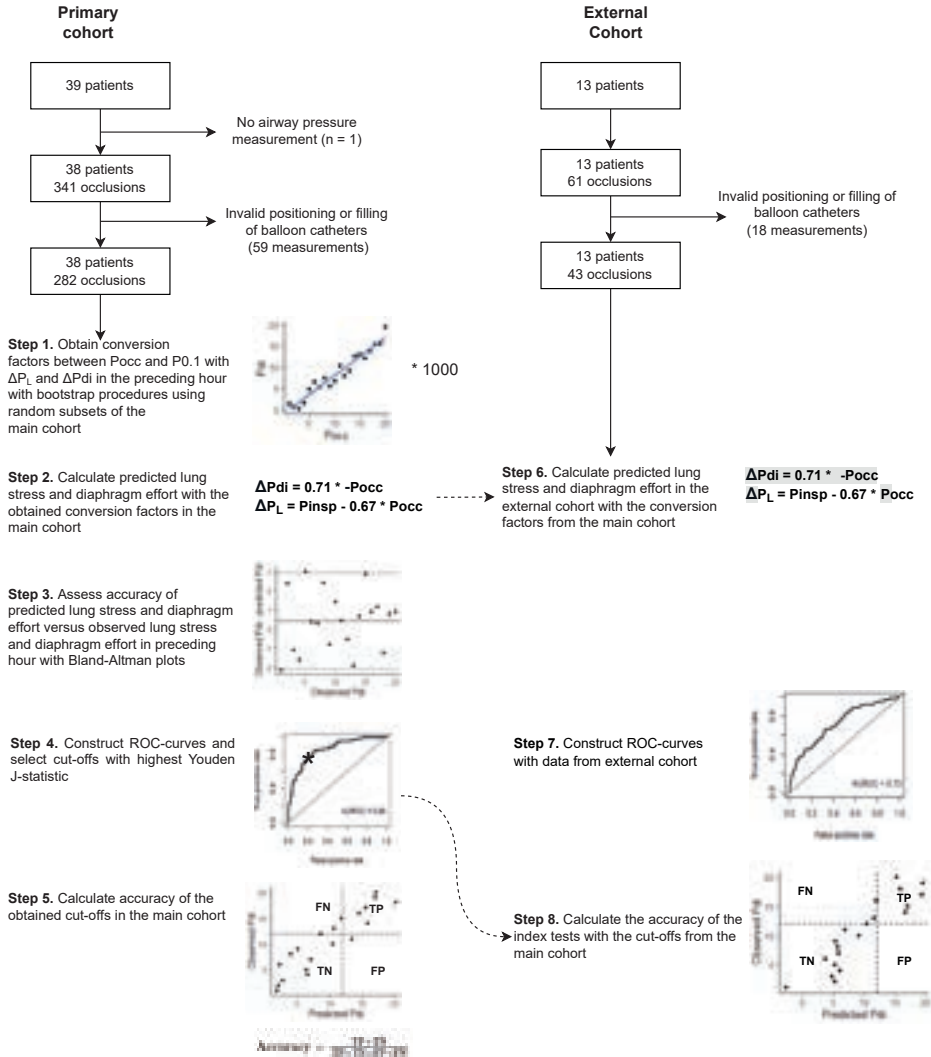
0.5-0.7 were defined as poor, 0.7-0.8 as acceptable, 0.8-0.9 as excellent and >0.9 as outstanding discrimination.<sup>29</sup> The cut-offs with the highest Youden *J*-statistic (sensitivity + specificity -1) were selected from the ROC curves.<sup>30</sup> The confidence interval of the AUROCs was constructed with the standard error of the Wilcoxon statistic as described previously.<sup>31</sup>

Next, the overall diagnostic accuracy of Pocc and P0.1 to identify patients with extremes in lung stress and diaphragm effort was calculated as the proportion of cases that were correctly identified by these cut-offs (i.e., (true positives + true negatives) / all cases) in the primary cohort and in the external validation cohort. Accuracy of different tests was compared with the “N-1” Chi-squared test.<sup>32</sup>

A two-tailed significance level of 5% was used for all statistical analyses. All the statistical analyses were performed in R version 4.0.1 (R Foundation for Statistical Programming, Vienna, Austria). Additional details are available in the **Online Supplement and Figure E2**.

## RESULTS

Patient characteristics are summarized in **Table 1**, patient flow is shown in **Figure 2**. In total, 840.817 breaths obtained in 38 patients during a 24-hour period were analyzed from the primary cohort, including 341 occluded inspiration maneuvers from which 282 met the criteria for adequate filling and positioning of the esophageal and gastric balloon which were used for further analysis. Number of recordings with low and high lung stress and diaphragm effort are shown in **Table 2**. The average hourly within-subject coefficients of variation of  $\Delta P_{es}$ ,  $\Delta P_{di}$  and  $\Delta P_{mus}$  were  $32 \pm 5\%$ ,  $33 \pm 6\%$  and  $25 \pm 4\%$ , respectively. The average ratio between  $\Delta P_{di}$  and  $\Delta P_{mus}$  was  $0.93 \pm 0.15$ , with a within-subject breath-by-breath coefficient of variation of  $48 \pm 12\%$ .



**Figure 2 legend:** Diagram of study flow. Occlusion measurements were excluded from analysis if the drop in esophageal pressure during the occlusion differed more than 20% from the drop in airway pressure because the reference parameters in the preceding hour were deemed unreliable in this case (invalid Baydur maneuver). Data in the inset graphs are simulated for illustrative purposes. The conversion factors and cut-offs found in the primary cohort were used in the external cohort to assess external validity.

**Table 1:** Baseline Characteristics

Patient characteristic	Primary cohort (n = 38)	External cohort (n = 13)
Age, years	65 ± 14	60 [ 57, 73]
Sex = female, n (%)	13 (33)	10 (83)
Cause of respiratory failure, n (%)		
Pulmonary ARDS	21 (54)	10 (77)
COPD exacerbation	0	1 (8)
Non-pulmonary ARDS	14 (36)	0
Cardiogenic shock	3 (7)	2 (15)
Intracranial disease	1 (3)	0
APACHE IV score	85 ± 28	-
Pao <sub>2</sub> /Fio <sub>2</sub> -ratio at baseline, mmHg	190 ± 54	-
Ventilator settings		
Pressure support, n (%)	37 (95)	0 (0)
NAVA, n (%)	2 (5)	13 (100)
PEEP, cmH <sub>2</sub> O	10 [ 8, 12]	7 ± 2
Inspiratory support, cmH <sub>2</sub> O	10 ± 5	12 [ 10, 17]
RASS score	-1 [-3, 0]	-
Respiratory mechanics		
Tidal volume, ml / kg PBW	7.5 ± 1.8	6.7 ± 1.8
ΔP <sub>L<sub>2</sub></sub> , cmH <sub>2</sub> O	21 [16, 25]	17 [10, 21]
Breathing effort		
Respiratory rate, breaths/min	25 ± 7	23 ± 7
ΔP <sub>di</sub> , cmH <sub>2</sub> O/breath	11 ± 5	7 [ 5 - 10]
PTP <sub>di</sub> , cmH <sub>2</sub> O*s/min	155 [114, 224]	136 [75, 180]
ΔP <sub>mus</sub> , cmH <sub>2</sub> O/breath	12 ± 4	8 [ 4, 10]
PTP <sub>mus</sub> , cmH <sub>2</sub> O*s/min	205 ± 51	186 [102, 214]
ΔP <sub>occ</sub> , cmH <sub>2</sub> O	15 [12, 19]	11 [6, 15]
P0.1, cmH <sub>2</sub> O	2.4 [1.7, 3.5]	1.7 [1.2, 2.4]

**Table 1 legend:** Parameters are reported as mean ± standard deviation when distribution is normal, and with median [interquartile range] for non-parametric distributions. Risk scores, oxygenation and sedation scores were not available in the external cohort. PBW, predicted bodyweight; NAVA, neurally-adjusted ventilatory assist; RASS, Richmond Agitation and Sedation Scale; PL<sub>dyn</sub>, dynamic transpulmonary pressure; P<sub>di</sub>, transdiaphragmatic pressure; PTP<sub>di</sub>, transdiaphragmatic pressure-time product; P<sub>mus</sub>, total respiratory muscle pressure during inspiration; PTP<sub>mus</sub>, total respiratory muscle pressure-time product during inspiration; P<sub>occ</sub>, airway occlusion pressure; P0.1, airway occlusion pressure at 100ms.

**Table 2:** Diagnostic Performance

Parameter	# Observations	Predictor	AUROC	Cut-off	Acc	Sens	Spec	PPV	NPV
Insufficient effort, $\Delta P_{di} < 3$ cmH <sub>2</sub> O	9 observations (3%) in 4 patients	$\Delta P_{es}$	0.97	4 cmH <sub>2</sub> O	93%	98%	88%	48%	99%
		$\Delta P_{occ}$	0.97	7 cmH <sub>2</sub> O	92%	84%	95%	31%	99%
		P0.1	0.93	1.3 cmH <sub>2</sub> O	89%	83%	89%	17%	99%
Excessive effort, $\Delta P_{di} > 12$ cmH <sub>2</sub> O	88 (31%) observations in 27 patients	$\Delta P_{es}$	0.91	10 cmH <sub>2</sub> O	86%	89%	85%	71%	92%
		$\Delta P_{occ}$	0.86	15 cmH <sub>2</sub> O	80%	80%	76%	63%	83%
		P0.1	0.73	2.9 cmH <sub>2</sub> O	71%	57%	72%	58%	72%
Excessive lung stress, $\Delta P_{i} > 20$ cmH <sub>2</sub> O	155 (55%) observations in 31 patients	P <sub>insp</sub> + $\Delta P_{occ}$	0.90	22 cmH <sub>2</sub> O	85%	90%	77%	86%	83%
		P <sub>insp</sub> + P0.1	0.88	21 cmH <sub>2</sub> O	81%	89%	74%	73%	89%
		P <sub>insp</sub> + $\Delta P_{occ}$	0.89	12 J/min	84%	63%	92%	89%	56%
Excessive power, $MP_{i} > 12$ J/min	199 (71%) observations in 32 patients	P <sub>insp</sub> + P0.1	0.72	13 J/min	73%	69%	69%	87%	42%

**Table 2 legend:**  $P_{di}$  = transdiaphragmatic pressure;  $P_{mus}$  = inspiratory muscle pressure,  $P_{i}$  = transpulmonary pressure, calculated as  $P_{ao} - P_{es}$ ; AUROC = area under the receiver-operator characteristic curve, PPV = positive predictive value, NPV = negative predictive value.

## Relation between reference standards

### ***Relation Between Esophageal Pressure, Total Respiratory Muscle Pressure and Transdiaphragmatic Pressure in the Same Breath***

$\Delta P_{mus}$  and  $\Delta P_{di}$  of individual breaths were strongly correlated ( $\Delta P_{di} = 0.85 * \Delta P_{mus}$ ,  $r^2=0.87$ ,  $p<0.001$ , **Figure E3**). Converting  $\Delta P_{mus}$  into  $\Delta P_{di}$  with this formula resulted in a bias of  $<0.1\text{cmH}_2\text{O}$  and 95% limits-of-agreement from  $-4.5$  to  $4.3\text{cmH}_2\text{O}$ .  $\Delta P_{es}$  and  $\Delta P_{di}$  of individual breaths were very strongly correlated ( $\Delta P_{di} = 1.08 * \Delta P_{es}$ ,  $r^2=0.92$ ,  $p<0.001$ , **Figure E3**). Converting  $\Delta P_{es}$  into  $\Delta P_{di}$  with this formula resulted in a bias of  $1.1\text{cmH}_2\text{O}$  with 95% limits-of-agreement from  $-1.9$  to  $3.8\text{cmH}_2\text{O}$ .

### ***Relation between esophageal and transdiaphragmatic pressure in the preceding hour***

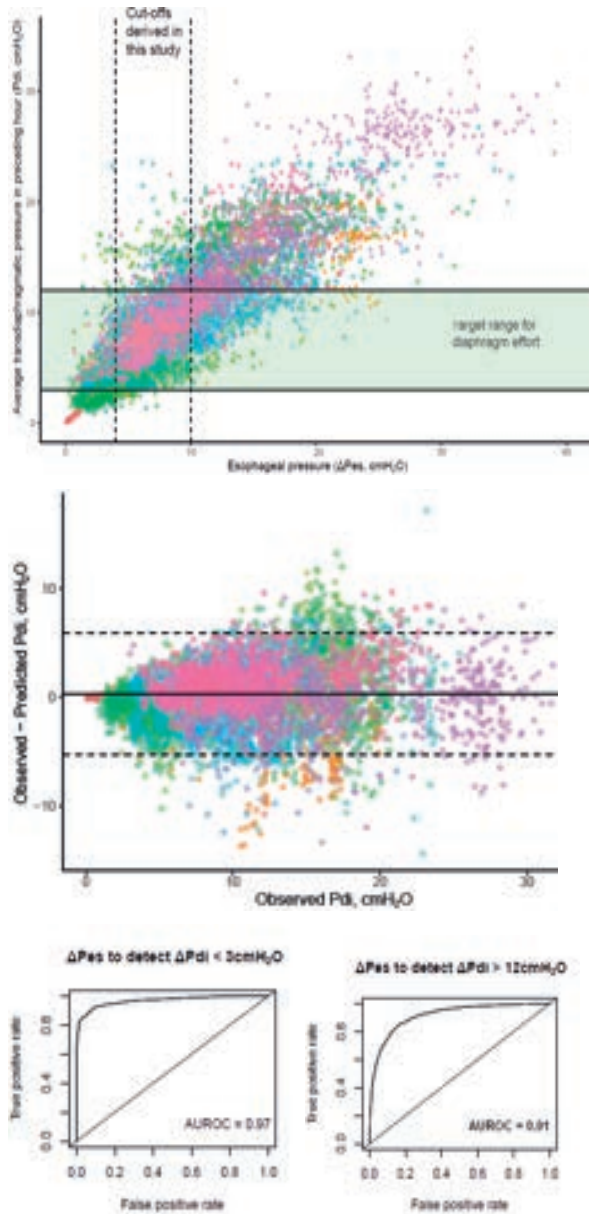
$\Delta P_{es}$  correlated fairly with diaphragm effort ( $\Delta P_{di}$ ) in the preceding hour (average  $\Delta P_{di}=1.04 * \Delta P_{es}$ ,  $r^2 = 0.79$ ,  $p<0.001$ , **Figure 3**). Converting  $\Delta P_{es}$  into  $\Delta P_{di}$  with this formula, bias was  $0.4\text{cmH}_2\text{O}$  and 95% limits-of-agreement ranged from  $-3.5$  to  $+3.7\text{cmH}_2\text{O}$ . Averaging 3 consecutive  $\Delta P_{es}$ -measurements improved the correlation slightly ( $r^2=0.84$ ,  $p<0.001$ , **Figure E4**). Diagnostic metrics to identify patients with extremes in lung stress and diaphragm effort are shown in **Table 2**. Diagnostic metrics for additional parameters and cut-offs are reported in **Table E1**.

## Relation and diagnostic performance of non-invasive measurements for lung stress and diaphragm effort

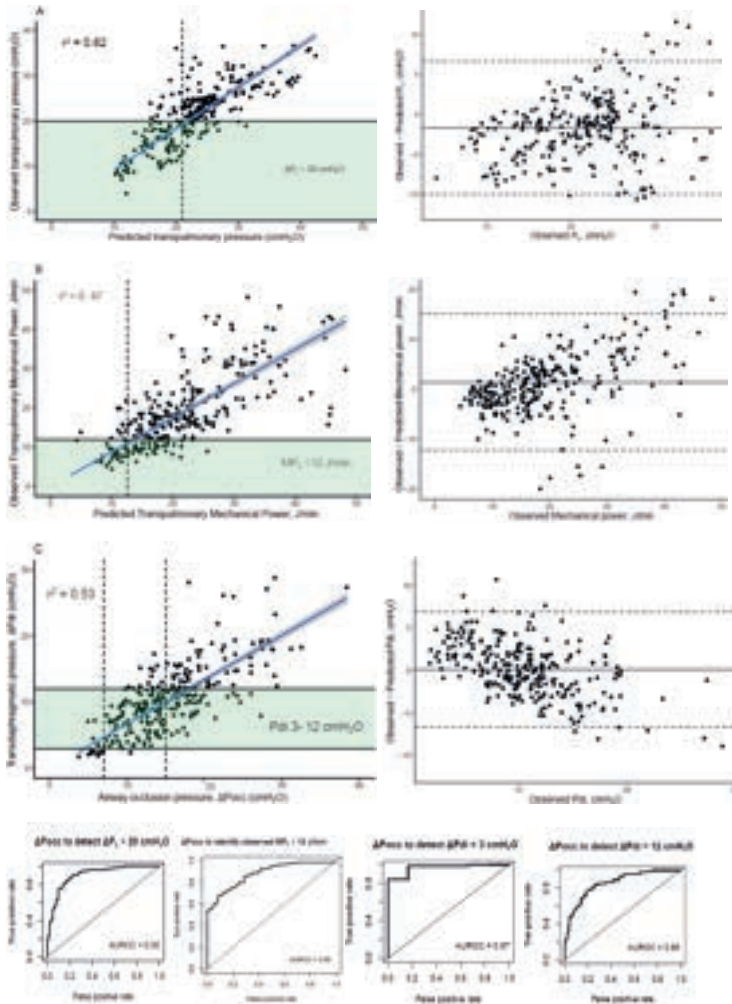
### ***Relation between the airway occlusion pressure and lung stress in the preceding hour***

The mean conversion factor to predict  $\Delta P_L$  with  $P_{occ}$  was  $0.67$  ( $0.64 - 0.71$ ). The predicted lung stress ( $\Delta P_L = P_{insp} - 0.67 * P_{occ}$ ) correlated fairly well with the observed lung stress in the preceding hour ( $r^2=0.62$ ,  $p<0.001$ , **Figure 4**). Bias was  $-1.6\text{cmH}_2\text{O}$ , 95% limits-of-agreement ranged from  $-10.0$  to  $+6.6\text{cmH}_2\text{O}$ .

The conversion factor to predict  $MP_L$  with  $P_{occ}$  was on average  $0.93$  ( $0.90 - 0.95$ ). The predicted mechanical power (predicted  $MP_L = 0.5 * (P_{insp} - 0.93 * P_{occ}) * Vt * RR * 0.098$ , with  $Vt$  in liters) correlated moderately well with the observed mechanical power ( $r^2=0.47$ ,  $p<0.001$ , **Figure 4**); bias was  $0.4\text{J}/\text{min}$ , 95% limits-of-agreement ranged from  $-6.4$  to  $7.6\text{J}/\text{min}$ .



**Figure 3 legend: Top**) Correlation between random esophageal pressure ( $\Delta P_{es}$ )-measurements and diaphragm effort (average transdiaphragmatic pressure,  $\Delta P_{di}$ ) in the preceding hour. Each dot is a measurement ( $n = 7729$ ), each color represents one subject ( $n = 38$ ). Green shaded area shows the target range for diaphragm effort ( $\Delta P_{di}$  3-12 cmH<sub>2</sub>O). Dashed lines cross the x-axis at the obtained cut-offs (4 and 10 cmH<sub>2</sub>O) for detecting  $\Delta P_{di} < 3$  cmH<sub>2</sub>O and  $> 12$  cmH<sub>2</sub>O, respectively. In total, 522/7729 (6.7%) of the recordings had a  $\Delta P_{di} < 3$  cmH<sub>2</sub>O and 2749/7729 (35.7%) had a  $\Delta P_{di} > 12$  cmH<sub>2</sub>O. **Right**) Bland-Altman plot of predicted  $\Delta P_{di}$  based on  $\Delta P_{es}$  versus observed  $\Delta P_{di}$ . Solid horizontal line shows bias, dashed lines show 95% limits-of-agreement. **Bottom**) Receiver-operator characteristic (ROC)-curves of using a random  $\Delta P_{es}$ -measurement to detect average  $\Delta P_{di} < 3$  cmH<sub>2</sub>O (left) and  $> 12$  cmH<sub>2</sub>O (right).



**Figure 4 legend.** Occluded inspiratory airway pressure ( $\Delta P_{occ}$ ) to assess lung stress and diaphragm effort. Green shaded areas show the proposed safe limits for lung stress and diaphragm effort. Note that  $P_{occ}$  is presented as a positive number for this plot to preserve a positive correlation, while it is measured as a negative number. **A)** Left: Correlation between the predicted lung stress ( $\Delta P_L$  based on  $P_{occ}$ ) and the observed lung stress in the preceding hour. Each dot is a measurement ( $n = 282$ ). Dashed line shows the selected cut-off for predicted  $\Delta P_L$  at 22 cmH<sub>2</sub>O. Right: Bland-Altman plot of predicted  $\Delta P_L$  based on  $P_{occ}$  versus observed  $\Delta P_L$ . Solid horizontal line shows bias, dashed lines show 95% limits-of-agreement. **B)** Left: Correlation between predicted transpulmonary mechanical power ( $MP_L$ ) and observed  $MP_L$  in the preceding hour. Each dot is a measurement ( $n = 282$ ). Dashed line shows the selected cut-off (predicted  $MP_L$  of 12J/min). Right: Bland-Altman plot of predicted  $MP_L$  based on  $P_{occ}$  versus observed  $MP_L$ . Solid horizontal line shows bias, dashed lines show 95% limits-of-agreement. **C)** Left: Correlation between  $P_{occ}$  and the average transdiaphragmatic pressure ( $\Delta P_{di}$ ) in the preceding hour. Each dot is a measurement ( $n = 282$ ). Dashed lines show the selected cut-offs for  $P_{occ}$  (-7 and -15 cmH<sub>2</sub>O). Right: Bland-Altman plot showing the predicted diaphragm effort ( $P_{di}$  based on  $\Delta P_{occ}$ ) versus observed diaphragm effort. Solid horizontal line shows bias, dashed lines show 95% limits-of-agreement. **Bottom:** ROC-curves of using  $P_{occ}$  to identify patients with potentially injurious diaphragm effort and lung stress.

### ***Relation between the airway occlusion pressure and transdiaphragmatic pressure in the preceding hour***

The conversion factor to predict  $\Delta P_{di}$  with Pocc was on average 0.71 (0.65 - 0.76). The predicted diaphragm effort ( $\Delta P_{di} = 0.71 \cdot P_{occ}$ ) correlated fairly well with observed diaphragm effort ( $r^2=0.53$ ,  $p < 0.001$ , **Figure 4**). Bias was 1.2cmH<sub>2</sub>O and 95% limits-of-agreement from -6.4 to +7.6cmH<sub>2</sub>O. Cut-offs and diagnostic metrics are shown in **Table 2**.

### ***Relation between P0.1 and lung stress in the preceding hour***

The conversion factor to predict  $\Delta P_L$  with P0.1 was on average 3.3 (2.4 - 4.1). The predicted lung stress ( $\Delta P_L = 3.3 \cdot P_{0.1} + P_{insp}$ ) correlated fairly well with the observed lung stress in the preceding hour ( $r^2=0.51$ ,  $p < 0.001$ , **Figure 5**). Bias was -0.6cmH<sub>2</sub>O; 95% limits-of-agreement ranged from -10.2 to +10.1cmH<sub>2</sub>O.

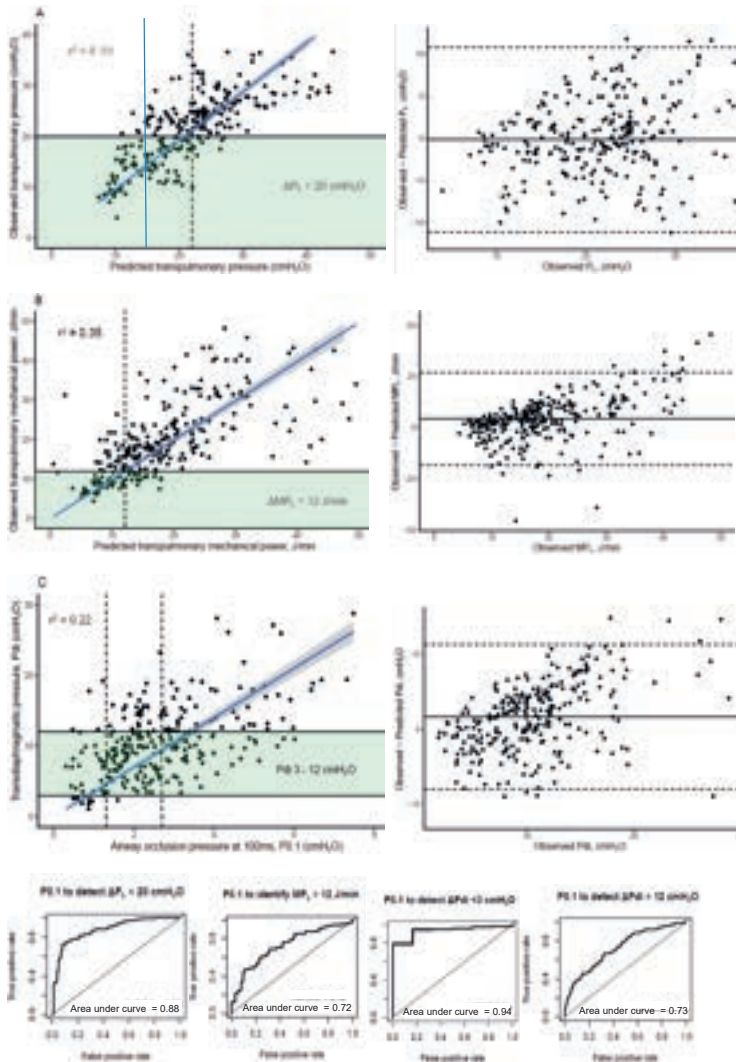
The conversion factor to predict  $MP_L$  with P0.1 was on average 4.7 (4.2 - 5.3). The predicted mechanical power (predicted  $MP_L = 0.5 \cdot (P_{insp} + 4.7 \cdot P_{0.1}) \cdot RR \cdot V_t \cdot 0.098$ , with  $V_t$  in liters) correlated moderately with the observed mechanical power ( $r^2=0.35$ ,  $p < 0.001$ , **Figure 5**). Bias was 1.4J/min, 95% limits-of-agreement ranged from -6.7 to 8.2J/min.

### ***Relation between P0.1 and transdiaphragmatic pressure in the preceding hour***

The conversion factor to predict  $\Delta P_{di}$  with P0.1 was on average 3.5 (2.0 - 4.9). The predicted diaphragm effort ( $\Delta P_{di}=3.5 \cdot P_{0.1}$ ) correlated poorly with observed diaphragm effort ( $r^2=0.22$ ,  $p < 0.001$ , **Figure 5**). Bias was -0.6cmH<sub>2</sub>O; 95% limits-of-agreement ranged from -7.3 to 6.2cmH<sub>2</sub>O. Cut-offs and diagnostic metrics are shown in **Table 2**.

## **External validation**

In total, 14,651 breaths obtained in 13 patients were analyzed in the external validation cohort. The recordings included sixty-one expiratory occlusions, of which 43 had a Pocc/ $\Delta P_{es_{occ}}$ -ratio between 0.8 and 1.2 which were used for further analysis (**Figure 2**). Correlations are shown in **Figure E5** and **Figure E6**. Lung stress was high in 7/43 (16%) of the recordings. Diaphragm effort was low in 4/43 (10%) and high in 3/43 (7%) of the recordings. Accuracy of Pocc and P0.1 to identify patients with extremes in lung stress and diaphragm effort was not significantly different in the external cohort compared with the primary cohort (**Figure E5 and E6**).



**Figure 5 legend:** Airway occlusion pressure at 100ms (P0.1) to assess lung stress and diaphragm effort. Green shaded areas show the proposed safe limits for lung stress and diaphragm effort. **A)** Left: Correlation between the predicted transpulmonary pressure ( $\Delta P_L$ ) based on P0.1 and the observed lung stress ( $\Delta P_L$ ) in the preceding hour. Each dot is a measurement ( $n = 282$ ). Dashed line shows the selected cut-offs (21  $\text{cmH}_2\text{O}$ ). Right: Bland-Altman plot of predicted lung stress ( $\Delta P_L$  based on P0.1) versus observed lung stress. Solid horizontal line shows bias, dashed lines show 95% limits-of-agreement. **B)** Left: Correlation between predicted transpulmonary mechanical power ( $MP_L$ ) and observed  $MP_L$  in the preceding hour. Dashed line shows the selected cut-off (predicted  $MP_L$  of 12J/min). Each dot is a measurement ( $n = 282$ ). Right: Bland-Altman plot of predicted lung stress ( $\Delta P_L$  based on P0.1) versus observed lung stress. Solid horizontal line shows bias, dashed lines show 95% limits-of-agreement. **C)** Left: Correlation between  $\Delta P_{occ}$  and the average transdiaphragmatic pressure ( $\Delta P_{di}$ ) in the preceding hour. Each dot is a measurement ( $n = 282$ ). Dashed lines show the selected cut-offs (7 and 15  $\text{cmH}_2\text{O}$ ). Right: Bland-Altman plot of predicted diaphragm effort ( $\Delta P_{di}$  based on P0.1) versus observed diaphragm effort. Solid horizontal line shows bias, dashed lines show 95% limits-of-agreement. **Bottom:** ROC-curves of using P0.1 to identify patients with potentially injurious diaphragm effort and lung stress.

## DISCUSSION

In the current study we tested the validity of noninvasive airway occlusion maneuvers to quantify lung stress and diaphragm effort in ventilated critically ill patients. Our findings can be summarized as follows: First, Pocc and P0.1 cannot be used to calculate the exact values of diaphragm effort and lung stress in the preceding hour, due to wide limits of agreement between occlusions pressures and the reference standard (esophageal pressure). Second, if the goal is to obtain lung stress and diaphragm effort in purported safe ranges,<sup>5,6</sup> Pocc and P0.1 have good to excellent diagnostic performance in identifying extremes of lung stress and diaphragm effort. Third, Pocc is at least as reliable as P0.1 in all instances, but outperforms P0.1 in detecting patients with high diaphragm effort.

The predicted lung stress based on Pocc and P0.1 correlate with  $\Delta P_L$  in the preceding hour ( $r^2=0.62$  and  $0.51$ , respectively), albeit with wide limits of agreement ranging from 5 to 10 cmH<sub>2</sub>O in either direction (**Figure 4 and 5**). Likewise, Pocc and P0.1 correlate with  $\Delta P_{di}$  ( $r^2=0.53$  and  $0.22$ , respectively) with equally wide limits of agreement. The limits of agreement are likely wide because of variations in breathing effort within subjects over time, and because a single breath is extrapolated to diaphragm effort and/or lung stress over a longer period of time. Pocc and P0.1 can therefore not replace esophageal pressure when precise values are required such as in physiological studies.

The AUROCs of Pocc and P0.1 to identify patients with extremes in lung stress and diaphragm effort are high (**Table 2**). The predicted lung stress and diaphragm effort show considerable heteroscedasticity ('fanning out') when compared with observed  $\Delta P_L$  and  $\Delta P_{di}$  (**Figure 4 and 5**), meaning that errors are lower at low lung stress and diaphragm effort, and greater at higher levels. This provides an explanation for the discrepancy between the wide limits of agreement and the high accuracy; most of the errors are made at higher levels of lung stress and diaphragm effort, where differences of 5 cmH<sub>2</sub>O might be less important than at lower levels (e.g., a  $\Delta P_L$  of either 30 or 35 cmH<sub>2</sub>O are both far beyond proposed safe values so precision is less important at this level).

Pocc has higher discriminative power than P0.1 in detecting patients with high P<sub>di</sub> in our cohort (AUROC 0.86 vs 0.73, respectively), which might be explained by several factors. First, P0.1 is based on a shorter measurement interval and thus suffers more from high-frequency noise such as cardiac artefacts. Second, factors that cause a time-delay in the transmission of pressures between the patient and measurement setup might have more effect on dynamic measurements such as P0.1. Third, properties of the respiratory system and control center might influence the convexity of airway pressure curves, distorting the relation between P0.1 and P<sub>mus</sub> in the same breath.<sup>33</sup>

Our data shows that Pocc together with tidal volume and respiratory rate may be used to estimate mechanical power ( $MP_L$ ), which correlates moderately well to observed  $MP_L$  ( $r^2=0.47$ ) as shown in **Figure 4**. AUROCs to detect high mechanical power are acceptable to excellent (**Table 2**).<sup>34</sup> Mechanical power has been theorized to better reflect the risk of lung injury than pressure alone in animal studies<sup>28</sup> and retrospective cohorts of ICU patients.<sup>35</sup> However, the superiority of mechanical power to predict lung injury requires further validation in prospective clinical studies.

### Clinical implications

Lung- and diaphragm-protective mechanical ventilation is an emerging concept for ventilatory management in critically ill patients. The hypothesis is that monitoring and controlling breathing effort and lung stress in critically ill patients could have several benefits: limiting lung stress might hamper development of lung injury, while targeting moderate diaphragm effort has been theorized to protect against disuse atrophy while limiting the probability of developing load-induced diaphragm injury.<sup>5,6</sup> The evidence that absence of diaphragm effort leads to atrophy and weakness is compelling,<sup>7,8</sup> and maintaining some diaphragm effort reduces diaphragm atrophy in animal studies.<sup>9,10</sup> Evidence that high diaphragm effort leads to injury is currently based on small sets of experimental human and animal data.<sup>36-38</sup> Apart from potentially preventing diaphragm injury, limiting excessive diaphragm effort might improve patient comfort by reducing dyspnea,<sup>39</sup> and is proposed to reduce regional lung stress by limiting pendelluft.<sup>12</sup> The proposed pathophysiology of diaphragm protective ventilation, including current knowledge gaps, has been covered in-depth recently.<sup>5,40</sup>

State of the art monitoring of lung stress and diaphragm effort requires esophageal (and gastric) pressure measurement, which is not routine performed in clinical practice.<sup>1</sup> Our data show that the Pocc and P0.1 cannot replace esophageal and gastric manometry when precise values are desired. At best, Pocc and P0.1 give an indication of a range of the true lung stress and diaphragm effort. This range can allow a clinician to identify patients that are most likely to benefit from advanced respiratory monitoring: a patient with a predicted Pdi of 20 cmH<sub>2</sub>O based on Pocc has an actual  $\Delta P_{di}$  between 13 and 27 cmH<sub>2</sub>O with 95% certainty, and could thus benefit from additional monitoring. Additionally, a clinician can use Pocc and P0.1 to estimate whether lung stress and diaphragm effort are likely within proposed safe limits when esophageal manometry is not available by using the cut-offs provided in **Table 2**: 86% of patients with an estimated  $\Delta P_L < 22$  cmH<sub>2</sub>O are expected to have actual lung stress in the proposed safe range ( $< 20$  cmH<sub>2</sub>O), and 89% of patients with a Pocc between -7 and -15 cmH<sub>2</sub>O will have diaphragm effort in the proposed safe range (Pdi 3-12 cmH<sub>2</sub>O). An example of a bedside monitoring protocol based on Pocc and these cut-offs is presented in **Figure E7**, but prospective

studies are required to assess whether using this protocol results in more lung stress and effort in purported safe ranges.

### **Validity of transdiaphragmatic pressure and the proposed cut-offs**

Pdi, the pressure output of the diaphragm, is the current reference standard to assess diaphragm effort.<sup>6,14–16,23</sup> Several factors influence a patient's capacity to generate pressure, such as diaphragm weakness prior to ICU admission<sup>41</sup> and changes in diaphragm geometry due to lung collapse and PEEP.<sup>42</sup> Consequently, a certain Pdi may require more myofiber recruitment in critically ill patients compared with healthy subjects. Thus, the precise "safe Pdi interval" may be patient specific. Furthermore, diaphragm weakness was found to associate strongly to ICU outcomes such as weaning failure in several studies,<sup>41,43,44</sup> but the correlation was absent in others.<sup>45,46</sup> Prospective trials are thus required to assess whether diaphragm effort during mechanical ventilation is indeed causally related to ICU outcomes, and not merely a confounder for disease severity.<sup>47,48</sup> Additionally further research must assess the optimal cut-offs to prevent lung and diaphragm injury, as the current cut-offs are based only on consensus.

### **Comparison to other studies**

The conversion factor to predict lung stress from Pocc in our cohort (0.67) closely matches the conversion factor reported in an earlier study (0.66),<sup>17</sup> suggesting that this factor is generalizable to external populations. Likewise, the conversion factor to predict  $\Delta P_{mus}$  with Pocc found in our cohort (0.73, **Figure E8**) was very close to value reported previously (0.75).<sup>17</sup> The high accuracy of P0.1 to identify patients with purported insufficient respiratory muscle effort is in agreement with recent studies.<sup>19,49</sup> Accurately detecting insufficient effort is a novel observation for Pocc, as an earlier study lacked recordings with low effort.<sup>17</sup>

### **Strengths and Limitations**

This study has several strengths. We included a heterogeneous group of patients with acute respiratory failure, displaying a wide range of lung stress and diaphragm effort. In contrast to previous studies, we used the reference methods to assess lung stress and diaphragm effort, recorded patients for prolonged periods of time (24 hours), included more patients (38 versus 16) and conducted much more occlusion measurements (282 versus 52). We also confirmed the robustness of Pocc and P0.1 in an external cohort. Earlier studies validated the Pocc and P0.1 with Pmus, which reflects total pressure generation resulting from activation of the diaphragm, accessory muscles and relaxation of the expiratory muscles.<sup>17,18,50</sup> Pdi may be more linked to studies on diaphragm injury during mechanical ventilation which have demonstrated an association (but not necessarily causation<sup>47</sup>) between *diaphragm* function and clinical outcome.<sup>41,43</sup> Whether

monitoring Pdi leads to better outcomes than monitoring Pmus requires further study. Last, we have estimated the potential magnitude of measurement errors in our study, and found that these likely do not influence our conclusions (**Supplements**).

Several limitations should be acknowledged. First, the optimal ranges for lung stress and diaphragm effort to prevent both lung injury and diaphragm weakness are unknown and were based on expert consensus. Second, although we used data from two independent centers, performance of Pocc and P0.1 needs to be evaluated in larger cohorts from multiple international centers. Third, earlier reports averaged three consecutive P0.1 measurements to improve reliability.<sup>19</sup> We could not conduct the same analysis as single occlusions were performed in our protocol. We have, however, estimated to which degree averaging multiple consecutive  $\Delta P_{es}$  measurements would improve correlations and diagnostic accuracy with  $\Delta P_{di}$  (**Figure 3 and E4**), and found the benefit to be relatively minor: averaging 3 measurements improved  $r^2$  from 0.79 to 0.84, but had little effect on diagnostic performance. Fourth, we used the same external validation cohort as an earlier report validating Pocc.<sup>17</sup> This external cohort had few recordings with low diaphragm effort, underlining the importance of further validation in larger cohorts. Fifth, the external validation cohort ventilated patients exclusively in NAVA, which is a proportional mode of ventilation, while the primary cohort used mostly pressure support. This likely had little effect on the validity of the Pocc and P0.1, however, as single airway occlusions were found not to affect respiratory drive<sup>17</sup> and the correlations and diagnostic performance were not different in primary cohort and the external cohort (**Figure E5 and E6**). Finally, 20-30% of all recordings in the main cohort and external data set had to be discarded due to our strict quality control for adequate calibration of the Pes-balloons.

## CONCLUSION

This study shows that Pocc and P0.1 cannot predict exact values for lung stress and diaphragm effort in ventilated critically ill patients. Both maneuvers can reliably identify patients with purported low diaphragm effort and high lung stress in the preceding hour. Pocc is more accurate than P0.1 in identifying patients with high diaphragm effort.

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# **Part II**

**The expiratory muscles, the neglected part  
of the respiratory muscle pump**

P

# **Expiratory Muscle Dysfunction in Critically Ill Patients: Towards Improved Understanding**

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*Adapted from Intensive Care Med. 2019 Aug;45(8):1061-1071*

*Author contributions: Conception by ZS and LH. ZS, AJ and HV drafted the first version. ZS, AJ and HV conducted measurements and made the figures. All authors had important intellectual contributions to the manuscript. All authors read and approved the final version of the manuscript.*



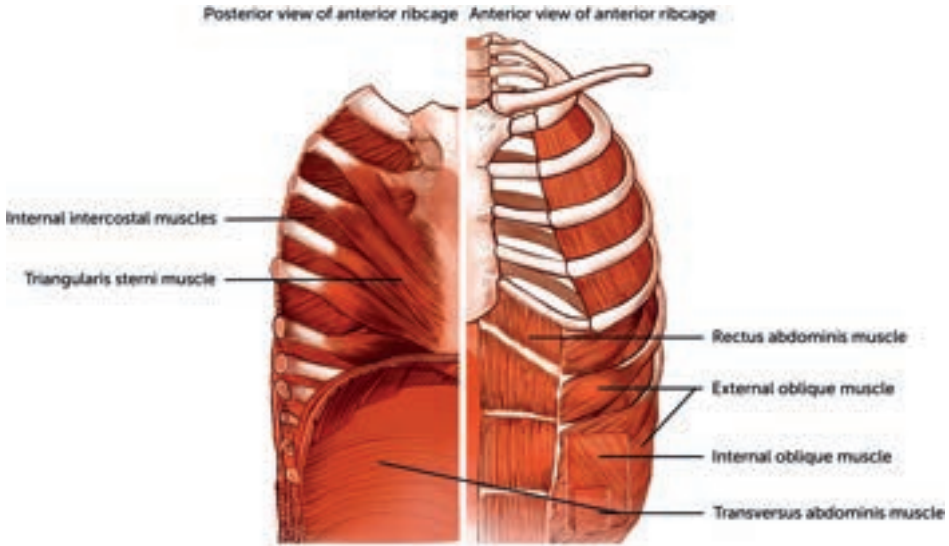
## INTRODUCTION

The respiratory muscle pump drives alveolar ventilation and is therefore of vital importance. The diaphragm, rib cage muscles and abdominal wall muscles are the most important components of the respiratory muscle pump.<sup>1</sup> Recruitment of each muscle depends on the (relative) load imposed on the respiratory system, lung volume, and the phase of the respiratory cycle. An acute imbalance between respiratory muscle load and capacity will result in respiratory failure and, ultimately, the need for mechanical ventilation. Many studies and reviews have focused on diaphragm structure and function in patients with acute respiratory failure, including critically ill patients.<sup>2-11</sup> However, the role of the expiratory muscles in the physiology of breathing in acute respiratory failure is largely neglected in the literature. This is surprising, given the important role of these muscles in respiration, especially in patients with impending respiratory failure.

The aim of the current paper is to discuss the role of the expiratory muscles in respiration, in particular in critically ill patients in whom respiratory muscle weakness develops rapidly, and may thus have a large clinical impact. We will also describe techniques used to evaluate expiratory muscle function in intensive care unit (ICU) patients. We will not focus in detail on the role of the expiratory muscles in coughing or maintaining body position.

## PHYSIOLOGY OF EXPIRATORY MUSCLE RECRUITMENT

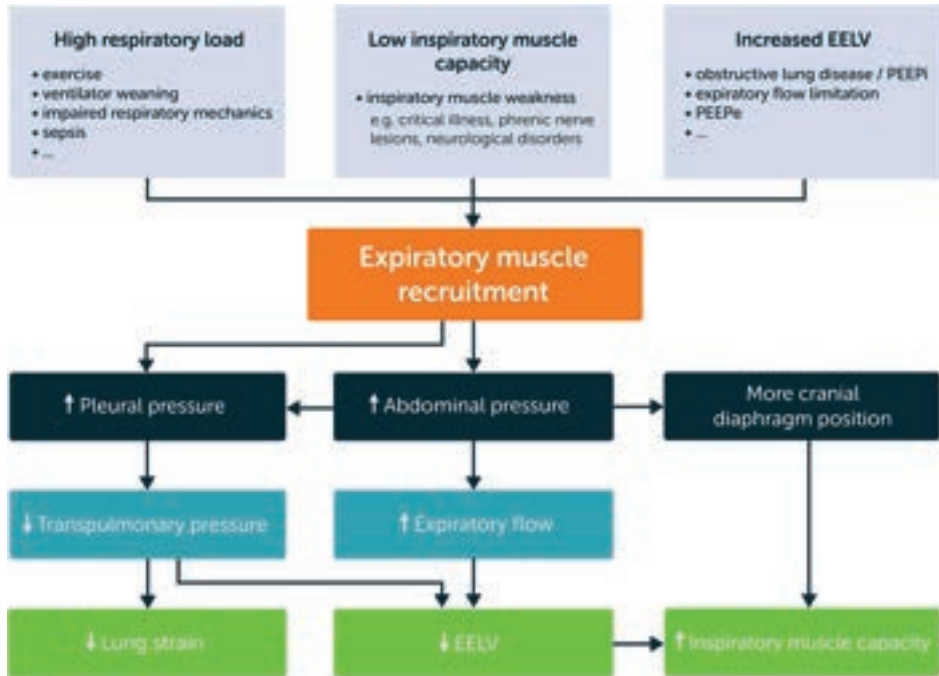
The expiratory muscles include those of the abdominal wall (transversus abdominis muscle, internal oblique muscle, external oblique muscle, and rectus abdominis muscle) and some of the rib cage ones (e.g., the internal intercostal muscles and the triangularis sterni muscle, **Figure 1**).<sup>1,12-16</sup> During tidal breathing, the expiratory muscles are largely inactive, although the transversus abdominis muscle may occasionally show some activity during quiet breathing.<sup>16</sup> Also, in the upright position, the abdominal wall muscles exhibit tonic activity to counteract the gravitational forces acting on the abdominal contents and thus to maintain the diaphragm at optimal length for pressure generation.<sup>17-19</sup>



**Figure 1. The expiratory muscles of the respiratory muscle pump.** The respiratory muscle pump is a complex organ that involves a large number of muscles that contribute to inspiration or expiration. This figure schematically demonstrates the expiratory muscles. With the exception of the diaphragm, other inspiratory muscles are not shown.

**Figure 2** shows the physiology of expiratory muscle recruitment. Activation of the expiratory muscles during breathing occurs when the (relative) load imposed on the inspiratory muscles increases. High absolute respiratory loading may occur under different conditions, such as exercise, low respiratory system compliance, and intrinsic positive end-expiratory pressure (PEEPi). Low inspiratory muscle capacity (high relative load on the inspiratory muscles) is common in ICU patients due to ICU-acquired respiratory muscle weakness.<sup>20</sup> In the presence of an imbalance between inspiratory muscle load and capacity, the abdominal wall muscles are recruited during expiration in a fixed hierarchy:<sup>21-24</sup> initially the transversus abdominis muscle, followed by the internal oblique muscle and the external oblique muscle, and finally the rectus abdominis muscle.<sup>16,17,25</sup> Activation of the abdominal wall muscles increases abdominal pressure in the expiratory phase. As the diaphragm is relaxed during (most of the) expiratory phase, this increased abdominal pressure is transmitted to the pleural space, consequently reducing the expiratory transpulmonary pressure, which helps to deflate the lung (less pulmonary hyperinflation/lung strain). Furthermore, increased abdominal pressure enhances inspiratory muscle capacity via at least two mechanisms. First, increased abdominal pressure moves the diaphragm at end expiration to a more cranial position, which results in a more optimal length for tension generation.<sup>26,27</sup> Second, when the end-expiratory lung volume falls below functional residual capacity (FRC), elastic energy is stored in the respiratory system. This stored energy facilitates the next inspiration (i.e.,

allows a more rapid and greater development of negative pleural pressure).<sup>28,29</sup> In fact, during strenuous inspiratory loading, up to 28% of tidal volume is generated below FRC, which can be attributed to expiratory muscle contraction.<sup>21</sup>



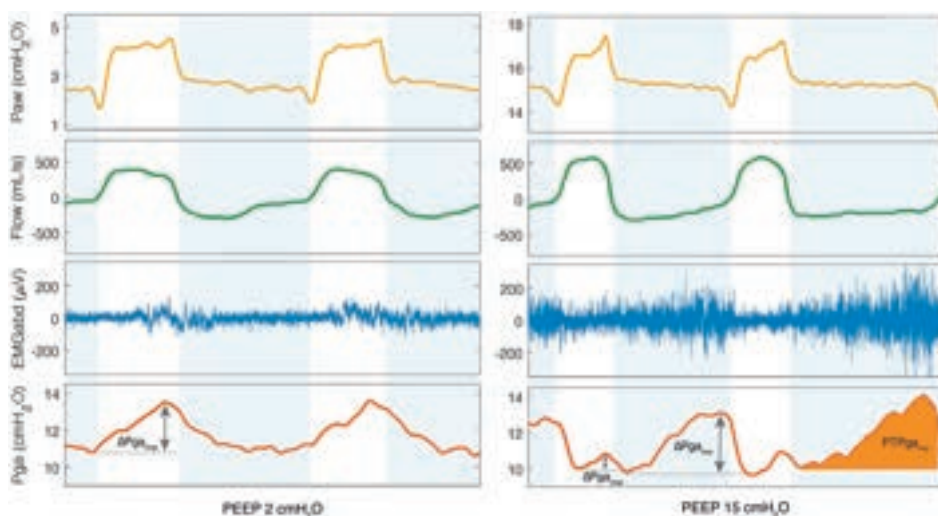
**Figure 2. Physiology of expiratory muscle recruitment.** Schematic illustration of the causes and consequences of expiratory muscle recruitment under physiological (healthy) conditions. All the consequences of expiratory muscle recruitment occur during expiration, except for the increased inspiratory muscle capacity (which occurs during the subsequent inspiration). See main text for explanation. Abbreviations: EELV, end-expiratory lung volume; PEEPi, intrinsic positive end-expiratory pressure; PEEPe, external positive end-expiratory pressure.

It should be recognized that isolated contraction of the abdominal expiratory muscles causing an increase in abdominal pressure and pleural pressure would result in chest wall distortion, in particular expansion of the lower rib cage. This would likely increase the elastic inspiratory work of breathing and flatten the diaphragm. To limit distortion of the lower rib cage during active expiration, the internal intercostal muscles are recruited to stabilize the rib cage.<sup>1</sup>

In addition to an imbalance between inspiratory muscle load and capacity, an increased end-expiratory lung volume, as in application of positive end-expiratory pressure (PEEP), may also recruit the abdominal wall muscles (**Figures 2 and 3**).<sup>30</sup> For example, in patients with normal respiratory system compliance (i.e., 80 ml/cmH<sub>2</sub>O), application

of 10 cmH<sub>2</sub>O of PEEP would, theoretically, increase end-expiratory lung volume by 800 ml (in the absence of airway closure). However, a physiological feedback mechanism involving vagal pathways or proprioceptive influences limits the increase in end-expiratory lung volume by activation of the abdominal wall muscles during expiration, and thus protects against high lung strain.<sup>31,32</sup>

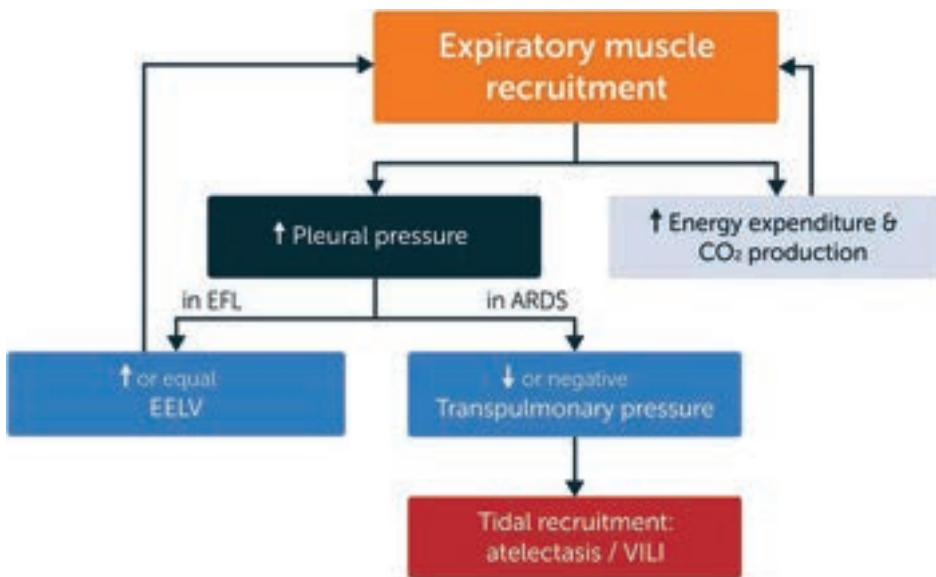
Another fundamental role of the expiratory muscles is to develop effective cough pressure to facilitate airway clearance.<sup>33</sup> Contraction of the expiratory muscles against a closed airway may increase the intrathoracic pressure to as high as 300 mmHg within 0.2 seconds. Once the glottis is open, a very high expiratory flow (up to 720 L/min) can be generated.<sup>33,34</sup> Expiratory muscle weakness reduces cough strength and peak flow velocity, predisposing patients to pneumonia and atelectasis.<sup>33,35,36</sup>



**Figure 3. Activation of the abdominal muscles during high PEEP.** Tracings of airway pressure (Paw), flow, EMG of the abdominal muscles (EMGabd) and gastric pressure (Pga) obtained from a healthy subject during noninvasive ventilation with PEEP levels of 2 cmH<sub>2</sub>O (a) and 15 cmH<sub>2</sub>O (b). White column: inspiration; light blue column: expiration. At 2 cmH<sub>2</sub>O of PEEP there is no evidence of activation of the abdominal wall muscles (no EMGabd activity during expiration and no rise in Pga during expiration); however, at 15 cmH<sub>2</sub>O of PEEP, the abdominal muscles are recruited during the expiratory phase, as shown by the presence of EMGabd activity during expiration and the rise in Pga during expiration. In the Pga tracing obtained during PEEP 15 cmH<sub>2</sub>O, calculation of parameters to estimate expiratory muscle activity are shown: increase in gastric pressure during expiration ( $\Delta P_{ga,exp}$ ); and the gastric pressure-time product during expiration ( $PTP_{ga,exp}$ ) represented by the dark blue area. Abbreviations: EMGabd, electromyography of abdominal wall muscles; Paw, airway pressure; PEEP, positive end-expiratory pressure; Pga, gastric pressure;  $PTP_{ga,exp}$ , gastric pressure-time product during expiration.

## UNDESIRABLE EFFECTS OF EXPIRATORY MUSCLE RECRUITMENT

Recruitment of the expiratory muscles during expiration may have undesirable effects in critically ill patients (**Figure 4**). First, in patients with the acute respiratory distress syndrome (ARDS) or atelectasis, increased pleural pressure during expiration resulting from expiratory muscle recruitment may result in negative transpulmonary pressure during expiration, leading to cyclic alveolar collapse or airway closure and thereby facilitating small airway and alveolar injury.<sup>37-40</sup> Consistent with this reasoning, a recent study in ARDS patients demonstrated a higher expiratory transpulmonary pressure in patients receiving neuromuscular blockers compared with control patients ( $1.4 \pm 2.7$  cmH<sub>2</sub>O versus  $-1.8 \pm 3.5$  cmH<sub>2</sub>O, respectively,  $p = 0.02$ ).<sup>41</sup> Interestingly, neuromuscular blockers also abolish expiratory activity of the diaphragm (if present),<sup>42</sup> which is expected to decrease expiratory transpulmonary pressure. However, the pressure generated by the diaphragm in the expiratory phase is relatively low compared with that generated by the expiratory muscles. Therefore, the effects of neuromuscular blockers on expiratory transpulmonary pressure largely depend on the relaxation of the expiratory muscles.

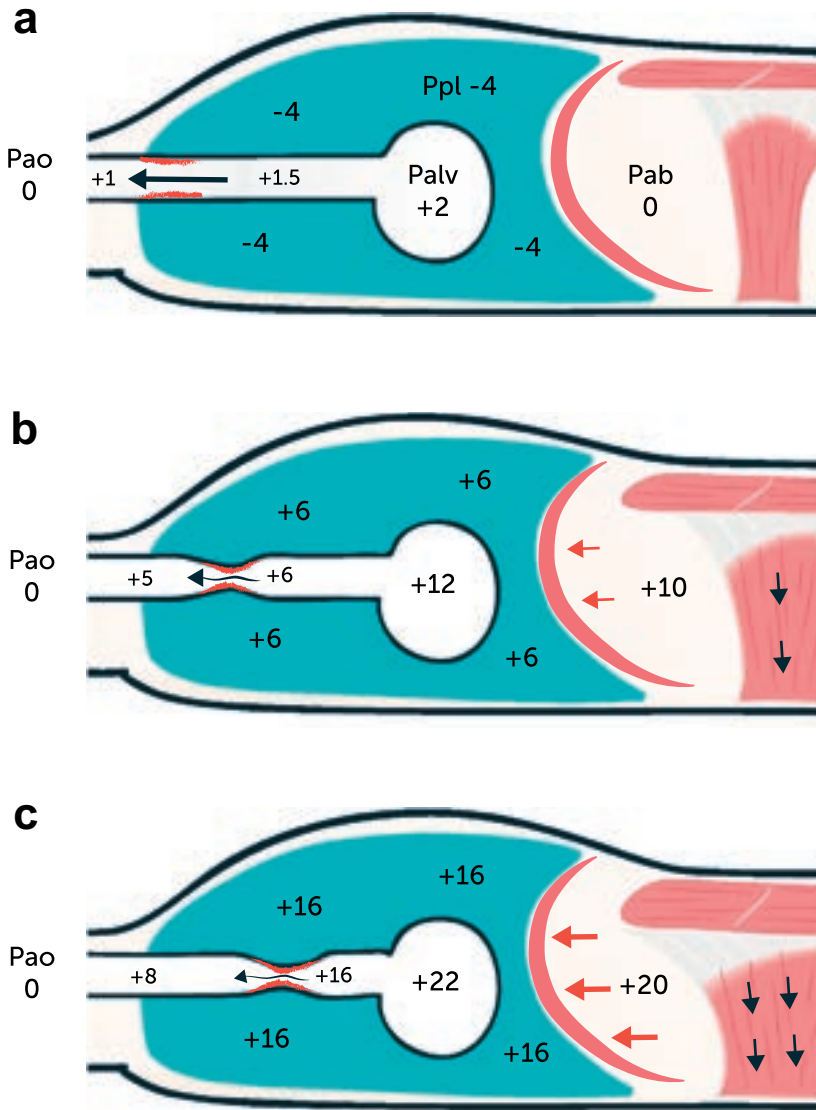


**Figure 4. Pathophysiology of expiratory muscle recruitment.** Schematic illustration of the pathophysiological consequences of expiratory muscle recruitment in critically ill patients. The depicted relationships are mostly hypothetical due to the low number of studies on expiratory muscle function in ICU patients. The elevated pleural pressure caused by expiratory muscle recruitment might lead to dynamic airway collapse, especially in patients who already have expiratory flow limitation (EFL). This leads to an equal or increased end-expiratory lung volume (EELV). On the other hand, elevated pleural pressure might lead to negative expiratory transpulmonary pressures, especially in diseases with an increased lung elastance such as in the acute respiratory distress syndrome (ARDS). In turn, this leads to atelectasis and tidal recruitment, potentially causing or worsening ventilator-induced lung injury (VILI).

Second, expiratory flow limitation is a condition in which expiratory flow cannot be increased, despite an increase in expiratory driving pressure (pressure difference between the alveoli and mouth during expiration).<sup>43</sup> Typically, this occurs in patients with emphysema, but it may also occur during tidal breathing in patients with expiratory muscle activity. The exact mechanism is unclear, but it has been proposed that dynamic airway compression plays an important role (**Figure 5**).<sup>44</sup> Elevated pleural pressure during active expiration decreases the airway transluminal pressure, which subsequently may compress the collapsible part of the airway. Total airway collapse is prevented as increased pleural pressure is also transmitted to the alveoli/airways (for an extensive discussion see also reference 43). Expiratory airway compression may result in elevated end-expiratory lung volume and PEEPi,<sup>43</sup> especially in patients with chronic obstructive pulmonary diseases (COPD) and in patients failing ventilator weaning.<sup>24,45</sup>

Third, in patients weaning from mechanical ventilation, expiratory muscle recruitment is expected when an imbalance exists between the respiratory load and inspiratory muscle capacity. Indeed, activation of the expiratory muscles has been demonstrated during ventilator weaning, especially in patients failing a weaning trial.<sup>22-24</sup> We recently found that expiratory muscle effort progressively increased throughout the trial in such patients.<sup>24</sup> The neuromuscular efficiency of the diaphragm was lower in weaning failure patients compared with weaning success patients, which challenges the concept that expiratory muscle activation improves diaphragm contractile efficiency,<sup>24</sup> although this requires further evaluation. Nevertheless, recruitment of the expiratory muscles during a weaning trial appears to be a strong marker of weaning failure.

Technically, expiratory muscle activity interferes with the assessment of PEEPi. PEEPi can be measured using different techniques. In patients with expiratory muscle activity, an end-expiratory occlusion will be highly influenced and exaggerated by the contraction of the expiratory muscles.<sup>46</sup> Similarly, the relaxation of the expiratory muscles at the beginning of the effort explains part of the initial drop in esophageal pressure, which is not entirely explained by so-called dynamic PEEPi. Either the drop in gastric pressure (Pga) at the beginning of the inspiratory effort or the rise in Pga during expiration must be subtracted from the esophageal pressure drop in order to measure a reliable PEEPi.<sup>47</sup>



**Figure 5. Schematic and simplified illustration of the role of expiratory muscle recruitment in the development of expiratory flow limitation (EFL).** (a-c) With activation of the expiratory muscles, the abdominal pressure increases, also increasing pleural pressure during expiration. This decreases the transmural pressure resulting in partial airway collapse and therefore EFL. With higher expiratory muscle pressure, the flow-limiting site, or choking point, moves towards the alveoli. Note that gravitational forces are not considered in this illustration. Abbreviations: Pab, abdominal pressure; Palv, alveolar pressure; Pao, airway opening pressure; Ppl, pleural pressure

## EXPIRATORY MUSCLE STRENGTH IN CRITICALLY ILL PATIENTS

Several studies have demonstrated the development of expiratory muscle weakness in critically ill patients.<sup>48-62</sup> Most studies used the maximum expiratory pressure (MEP) as a marker of expiratory muscle strength.<sup>48-57</sup> Despite the heterogeneity of the studies in terms of populations and measurement techniques, the MEP was lower than the reference values<sup>63</sup> in all studies that obtained MEP at the time of ventilator weaning.<sup>48-55,64</sup> Patients failing extubation exhibit a lower MEP (mean decrease varying from 9 to 31 cmH<sub>2</sub>O) compared with extubation success patients.<sup>48-55,64</sup> This indicates that expiratory muscle weakness is a potential predictor of weaning outcome. How expiratory muscle weakness affects weaning and extubation outcome is largely unknown. Potential explanations include inadequate secretion clearance and insufficient cough capacity resulting in atelectasis, reduced contractile efficiency of the diaphragm, or inadequate reduction of PEEPi.

Remarkably, no studies have investigated the association between diaphragm weakness and expiratory muscle weakness.

### Risk factors for expiratory muscle weakness in critically ill patients

Risk factors for the development of ICU-acquired weakness of the peripheral muscles and the diaphragm have been discussed recently.<sup>2,4,57,65</sup> Whether these risk factors also have an impact on the expiratory muscles is largely unknown. We briefly discuss risk factors that may contribute to the development of expiratory muscle weakness.

#### **Sepsis**

Sepsis and systematic inflammation have been linked to the development of muscle weakness, including weakness of the expiratory muscles.<sup>2,61,65</sup> Sepsis induces a severe and persistent increase in protein catabolism, resulting in muscle wasting and muscle weakness.<sup>59,60</sup> Compared with non-septic surgical patients, the rectus abdominis muscle from surgical patients with sepsis showed significantly lower *in vitro* contractility.<sup>59</sup> In addition, the reduced MEP ( $\leq 30$  cmH<sub>2</sub>O) found at the time patients regained normal consciousness showed an independent association with septic shock.<sup>57</sup>

#### **Mechanical ventilation**

Mechanical ventilation plays an important role in the development of diaphragmatic dysfunction in critically ill patients.<sup>2,9,10,66</sup> Potential mechanisms include disuse atrophy due to ventilator over-assist, or load-induced injury as a result of ventilator under-assist. The impact of mechanical ventilation on the expiratory muscles has not been systematically investigated. However, as mentioned earlier, ventilator settings including PEEP

and the level of inspiratory assist may have an impact on the activity of the expiratory muscles (**Figure 3**),<sup>46,67</sup> although the ultimate impact of mechanical ventilation on expiratory muscle strength is largely unknown and should be further investigated.

### **Other risk factors**

Co-morbidities, such as COPD and myopathies, or complications such as intra-abdominal hypertension, may put patients at increased risk of ICU-associated expiratory muscle weakness.<sup>68,69</sup> Drugs such as sedatives, neuromuscular blockers and corticosteroids have been shown to affect peripheral muscle function and diaphragm muscle function in ICU patients.<sup>2,65,70</sup> The effects of these drugs on expiratory muscle function have not been systematically studied.

### **Strategies to maintain or improve expiratory muscle strength**

Strategies that aim to improve diaphragm function<sup>71,72</sup> may also benefit the expiratory muscles, although clinical studies are lacking. The feasibility of neuromuscular electrical stimulation to reduce expiratory muscle atrophy in ICU patients is under investigation (Clinicaltrials.gov: NCT03453944).

## **QUANTIFICATION OF EXPIRATORY MUSCLE EFFORT IN CRITICALLY ILL PATIENTS**

While visual inspection of the trunk and palpation of the abdominal wall may reveal activation of the expiratory muscles, they do not allow quantification of effort. In this section, we summarize the main clinical techniques that can be used to quantify expiratory muscle effort in ICU patients.

### **Gastric pressure**

Activation of the abdominal wall muscles increases abdominal pressure. Changes in Pga during expiration reflect changes in abdominal pressure and can thus be used to quantify expiratory muscle effort.<sup>22,24,39,63,73</sup> Pga is measured using an air-filled balloon catheter inserted into the stomach. Bladder pressure has also been proposed as a means of quantifying intra-abdominal pressure,<sup>74,75</sup> and showed an acceptable correlation with Pga in the supine position (bias, 0.5 mmHg; precision, 3.7 mmHg (limits of agreement, -6.8 to 7.5 mmHg)).<sup>74</sup> To quantify the effort of expiratory muscles, Pga amplitude and the pressure-time product (PTP) of Pga during expiration can be calculated (**Figure 3**).

### ***Amplitude of gastric pressure***

Both the rise in Pga over the course of expiration<sup>46</sup> and the drop in Pga at the onset of the next inspiration<sup>76</sup> have been used to quantify the activity of the expiratory muscles. However, only the expiratory increase in Pga showed a good correlation with the electromyographic amplitude of the transverse abdominis muscle (correlation coefficient ranging from 0.70 to 0.95).<sup>77</sup>

### ***Pressure-time product***

The PTP of the expiratory muscles has been quantified using the area enclosed by the esophageal pressure curve and the static chest wall recoil pressure curve during expiration.<sup>78</sup> The PTP accounts for the energy expenditure during both the isometric and dynamic phases of expiration (independent of volume displacement). However, expiratory esophageal pressure only represents the pressure generated by the abdominal wall muscles when the diaphragm is completely relaxed.<sup>39,79</sup> As diaphragm activity has been demonstrated during expiration,<sup>42,67</sup> abdominal wall muscle effort cannot be reliably quantified using the expiratory esophageal PTP alone. Therefore, it is recommended to use the expiratory Pga in order to calculate the PTP of the expiratory muscles.<sup>80-83</sup> The gastric PTP (PTP<sub>ga,exp</sub>) can be obtained from the area under the expiratory Pga curve, in which the baseline is defined as the resting end-expiratory Pga from the preceding breath (**Figure 3**).<sup>24,80,81</sup>

### ***Work of breathing***

Traditionally, the Campbell diagram is used to quantify the inspiratory work of breathing, but it allows estimation of the expiratory work as well.<sup>84</sup> The area of the esophageal pressure-volume loop at the right side of the chest wall relaxation curve represents expiratory muscle effort.<sup>85,86</sup> By definition, work is performed only when there is volume displacement (work = pressure × volume). However, as explained above, during dynamic airway collapse, part of the pressure generated by the expiratory muscles does not result in lung volume displacement, and therefore the Campbell diagram underestimates the total effort of the expiratory muscles.<sup>44,87</sup> Under these circumstances, the PTP may better reflect expiratory muscle effort.

## **Volitional tests of expiratory muscle strength**

### ***Maximal expiratory pressure***

The MEP is the most widely used measure of expiratory muscle strength.<sup>63</sup> Standard procedures for non-intubated subjects have been established. For intubated patients, the MEP can be measured using a unidirectional valve that allows inspiration but prevents expiration.<sup>48,51,88</sup> Some investigators coached subjects to perform an expiratory effort

against an occluded airway for 25 to 30 seconds, and then recorded the most positive pressure developed.<sup>48,51,88</sup> Calculating the ratio of maximum inspiratory pressure to MEP is a simple way to assess the relative impairment of the inspiratory muscles versus the expiratory muscles.<sup>89</sup> As MEP measurement requires a voluntary patient effort, this might not be feasible in a proportion of ICU patients. As an alternative to MEP, cough pressure can be assessed to quantify expiratory muscle strength.<sup>33,63,73</sup>

### **Cough test**

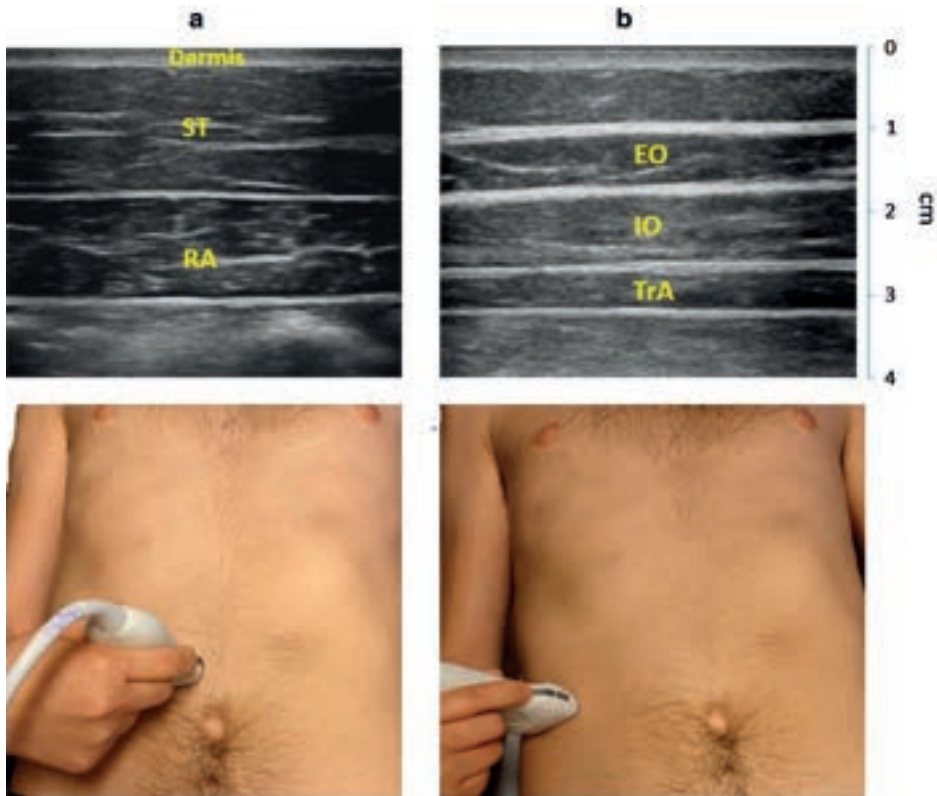
The cough test is a relatively easy to perform, complementary test for the diagnosis of expiratory muscle weakness. Both cough pressure measured via air-filled balloons in the stomach or esophagus, and cough peak expiratory flow measured at the opening of an endotracheal tube or using the ventilator flow sensor,<sup>90</sup> are feasible in ICU patients. In patients unable to cooperate, a cough may be induced either by instilling physiological saline [35] or by advancing a suctioning catheter through the patient's tube.<sup>36</sup>

### **Abdominal wall muscle ultrasound**

Ultrasound has become a popular tool for quantifying changes in the thickness and activity of the diaphragm in ICU patients,<sup>3,91,92</sup> but few studies have used this technique to evaluate the expiratory muscles. Abdominal ultrasound allows direct visualization of the three layers of the abdominal wall muscles and the rectus abdominis muscle (**Figure 6**).<sup>93-96</sup> In our experience, the abdominal wall muscles are easy to visualize using ultrasound, and measurements of thickness are feasible in almost all patients. In healthy subjects, the thickness of individual abdominal wall muscles follows a certain pattern: transversus abdominis < external oblique < internal oblique < rectus abdominis.<sup>96</sup> The thickness of the transversus abdominis muscle measured with ultrasound is strongly correlated with the pressure developed during an expiratory maneuver (assessed by the change in Pga).<sup>94</sup> In addition, the transversus abdominis muscle thickness increase is significantly correlated with the muscle's electrical activity.<sup>93</sup> However, all these studies were performed in healthy subjects, and further studies are needed to determine the reliability and validity of ultrasound assessment of expiratory muscle thickness and function in ICU patients.

### **Other diagnostic tests**

Electrical and magnetic stimulation of the abdominal wall muscles are other methods used to quantify the strength of these muscles.<sup>25,79,81</sup> As these techniques are cumbersome and uncomfortable, they are rarely used either in clinical practice or for research purposes.



**Figure 6. Ultrasound imaging of the abdominal muscles. (a)** Ultrasound image of the rectus abdominis muscle (RA) (top), obtained with the probe placed 2–3 cm above the umbilicus and 2–3 cm from the midline (bottom). **(b)** Ultrasound image of the external oblique muscle (EO), internal oblique muscle (IO) and transversus abdominis muscle (TrA) (top), obtained with the probe placed midway between the costal margin and the iliac crest, along the anterior axillary line (bottom).

Electromyography of the expiratory muscles has been used in research settings to study the timing of expiratory muscle recruitment during respiration,<sup>17,77</sup> but has not reached clinical implementation. Therefore, these techniques are beyond the scope of this review.

## CONCLUSIONS

The expiratory muscles are the “neglected component” of the respiratory muscle pump. Rather as the heart does not comprise only a left ventricle, but also a right one, the respiratory muscle pump is much more than just the diaphragm. In this paper, we have summarized the physiology and pathophysiology of the expiratory muscles, with a special focus on critically ill patients. Expiratory muscles are frequently recruited in critically ill ventilated patients, but a fundamental understanding of expiratory muscle function is still lacking in these patients. Gastric pressure monitoring provides multiple bedside parameters for analysis of expiratory muscle effort, but their clinical implications need to be established.

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# Changes in Respiratory Muscle Thickness during Mechanical Ventilation: Focus on the Expiratory Muscles

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*Critical Care. 2020 Mar 24;24(1):104*

*Author contributions: HdV and ZS contributed equally to this work. Conception and design by LH, ZS, AJ and HdV. Conduction of measurements by ZS, HdV, AJ, and YZ. Statistical analysis by ZS, HdV, HG and PvdV. Preparation of draft by HdV and ZS. All authors critically revised the manuscript and approved the final version.*

*The supplements to this article are available open source from the publisher's website at <https://links.lww.com/ALN/C566>.*

## ABSTRACT

### Background

The lateral abdominal wall muscles are recruited with active expiration, as may occur with high breathing effort, inspiratory muscle weakness, or pulmonary hyperinflation. The effects of critical illness and mechanical ventilation on these muscles are unknown. This study aimed to assess the reproducibility of expiratory muscle (i.e., lateral abdominal wall muscles and rectus abdominis muscle) ultrasound and the impact of tidal volume on expiratory muscle thickness, to evaluate changes in expiratory muscle thickness during mechanical ventilation, and to compare this to changes in diaphragm thickness.

### Methods

Two raters assessed the interrater and intrarater reproducibility of expiratory muscle ultrasound ( $n = 30$ ) and the effect of delivered tidal volume on expiratory muscle thickness ( $n = 10$ ). Changes in the thickness of the expiratory muscles and the diaphragm were assessed in 77 patients with at least two serial ultrasound measurements in the first week of mechanical ventilation.

### Results

The reproducibility of the measurements was excellent (interrater intraclass correlation coefficient: 0.994 [95% CI, 0.987 to 0.997]; intrarater intraclass correlation coefficient: 0.992 [95% CI, 0.957 to 0.998]). Expiratory muscle thickness decreased by  $3.0 \pm 1.7\%$  (mean  $\pm$  SD) with tidal volumes of  $481 \pm 64$  ml ( $P < 0.001$ ). The thickness of the expiratory muscles remained stable in 51 of 77 (66%), decreased in 17 of 77 (22%), and increased in 9 of 77 (12%) patients. Reduced thickness resulted from loss of muscular tissue, whereas increased thickness mainly resulted from increased interparietal fasciae thickness. Changes in thickness of the expiratory muscles were not associated with changes in the thickness of the diaphragm ( $R^2 = 0.013$ ;  $P = 0.332$ ).

### Conclusions

Thickness measurement of the expiratory muscles by ultrasound has excellent reproducibility. Changes in the thickness of the expiratory muscles occurred in 34% of patients and were unrelated to changes in diaphragm thickness. Increased expiratory muscle thickness resulted from increased thickness of the fasciae.

## INTRODUCTION

The respiratory muscle pump is a vital organ that drives alveolar ventilation. The respiratory muscle pump consists of several muscle groups: the diaphragm, which is the main muscle for inspiration; the accessory inspiratory muscles, including the parasternal, external intercostal, scalene, and sternocleidomastoid muscles; and the expiratory muscles, including the lateral abdominal wall muscles, the internal intercostal muscles, and transverse thoracic muscle.<sup>1-6</sup> With impending respiratory failure, mechanical ventilation is a life-saving intervention to support the respiratory pump. However, it is now recognized that mechanical ventilation may have adverse effects on the respiratory muscles.<sup>7-17</sup> Ultrasound studies revealed time-dependent loss of diaphragm thickness.<sup>15,17</sup> Moreover, studies analyzing diaphragm biopsies of ventilated intensive care unit (ICU) patients revealed diaphragm fiber atrophy, impaired contractile protein function, injury, and inflammation.<sup>10-14</sup>

The effects of mechanical ventilation on the expiratory muscles are largely unknown.<sup>1</sup> This is surprising, because these muscles play an important role in airway clearance, prevention of atelectasis,<sup>18-20</sup> and maintaining alveolar ventilation with high breathing effort.<sup>1,6,21</sup> Weakness of the expiratory muscles has been associated with reintubation, rehospitalization, and mortality.<sup>22-25</sup> Although both the diaphragm and the lateral abdominal wall muscles are important components of the respiratory muscle pump, it is unknown whether these muscles respond in a similar fashion to mechanical ventilation and critical illness, i.e., if atrophy of the diaphragm correlates with atrophy of the lateral abdominal wall muscles.

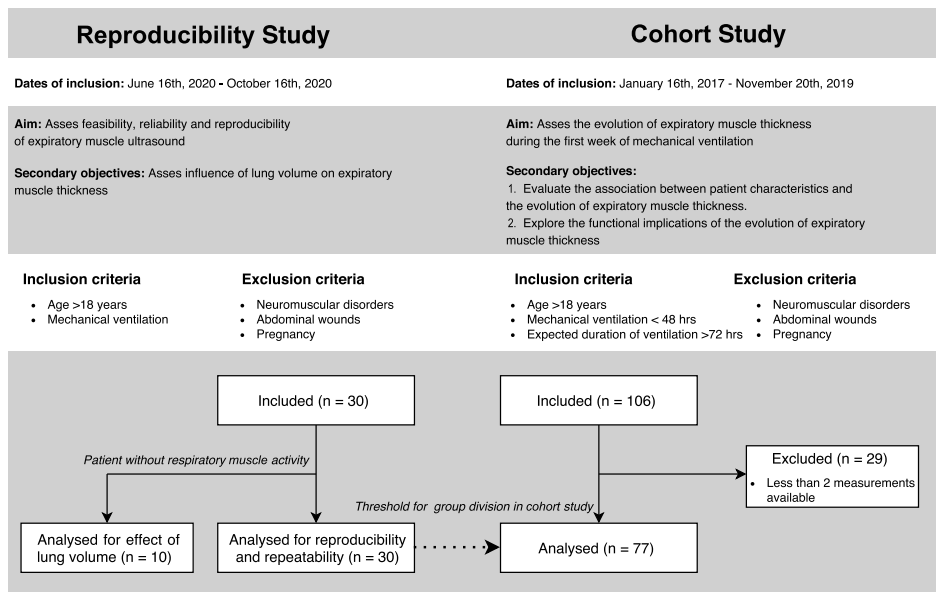
Ultrasound has become a popular tool to investigate diaphragm thickness in ICU patients.<sup>15,26-28</sup> However, very few studies have applied ultrasound to evaluate the expiratory muscle thickness, and therefore the current study aimed to evaluate feasibility and reproducibility of expiratory muscle thickness measurements in critically ill ventilated patients. Because higher lung volume results in caudal displacement of the diaphragm and may as such expand the abdominal wall, we also aimed to assess the influence of lung volume on expiratory muscle thickness (reproducibility study). Second, we aimed to investigate time-dependent changes in the expiratory muscle thickness in critically ill patients during the first week of mechanical ventilation and to evaluate whether changes in expiratory muscle thickness are associated with changes in diaphragm thickness (cohort study). As an exploratory analysis, we assessed whether patient characteristics were associated with the evolution of expiratory muscle thickness and whether the evolution of expiratory muscle thickness was associated with clinical outcomes.

## METHODS

### Study Design and Patients

This prospective, observational study was conducted from February 2017 to October 2020 in a mixed medical surgical academic ICU (Amsterdam University Medical Centers, Location VUmc, Amsterdam, The Netherlands). An opt-out approach for the consent from subjects or their legal representative was used because mechanical ventilation is a requirement for eligibility, and ultrasound measurement is daily routine in this medical center. The study protocol was approved by the local institutional ethics committees and registered on ClinicalTrials.gov (NCT04333186, April 2020). The study was performed in accordance with the ethical standards set forth in the 2008 Declaration of Helsinki and its later amendments. In the current study, the lateral abdominal wall muscles (transversus abdominis muscle, internal oblique muscle, and external oblique muscle) are referred to as the expiratory muscles, unless otherwise stated.

This study consisted of two substudies (**Figure 1**). The reproducibility study tested the feasibility and reproducibility of expiratory muscle ultrasound and assessed the effects of lung volume on expiratory muscle thickness. The cohort study aimed to investigate the evolution of expiratory muscle thickness during the mechanical ventilation in critically ill patients. We used the data from the reproducibility study to determine the



**Figure 1 legend:** Characteristics and flow chart of the reproducibility study and the cohort study.

threshold values to categorize patients into three groups of muscle thickness changes (decreased, no change, and increased) in the cohort study.

In the reproducibility study, adult (more than 18 yr old) ventilated critically ill patients were recruited. Exclusion criteria were past medical history of neuromuscular disorders, abdominal wounds at the proposed location of the ultrasound probe, and pregnancy. Two raters (M.H. and Z.-H.S.) performed the measurements; both had extensive experience in respiratory muscle ultrasound. In one single session, each rater performed ultrasound measurements at the same anatomical location as marked by the first rater within a  $\pm 5$ -min interval. Images were stored for later offline measurements. An intrarater reliability test was performed in a subset of eight patients, in which each rater repeated measurements at the previously marked anatomical site 5 min after the inter-rater session. The raters were blinded to their own and each other's measurements.

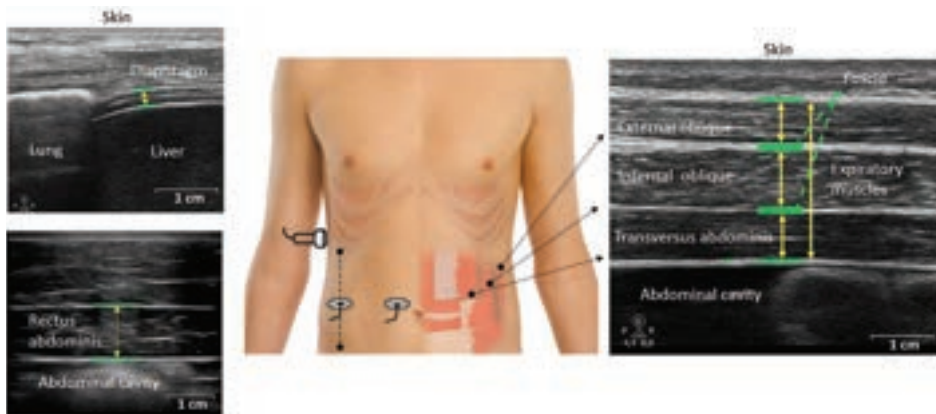
To assess the influence of lung volume on expiratory muscle thickness, ultrasound measurements were repeated in a subgroup of 10 patients in the reproducibility study that showed no signs of respiratory muscle activity during an end-expiratory breath hold. Expiratory muscle thickness was measured at end-inspiratory lung volume (during the last second of a 3-s end-inspiratory occlusion) and at end-expiratory lung volume (during the last second of 3-s end-expiratory occlusion). The difference in lung volume (i.e., delivered tidal volume) between these two measurements was recorded from the ventilator (Servo-U, Sweden). These measurements were performed by a single rater (Z.-H.S.).

The cohort study aimed to assess time-dependent changes of expiratory muscle thickness in critically ill mechanically ventilated patients. Patients admitted to the ICU were screened daily between 9 and 10 am (Monday through Thursday). Patients were eligible for enrolment within 48 h after intubation if the treating physician expected them to remain ventilated for more than 72 h. Exclusion criteria were identical to the reproducibility study. The medical team followed standard clinical protocols for mechanical ventilation and weaning.

### **Ultrasound Examination**

All measurements were performed on the right side with the patient in the supine position. The probe position was marked on the skin after the first measurements to ascertain an identical anatomical location in subsequent measurements. B-mode ultrasound images were acquired using a high frequency (10 to 15 MHz) linear array transducer (CX50, Philips, USA). Expiratory muscle thickness was measured at end inspiration (the frame with minimum thickness within one breath) and included the three individual muscle

layers (**Figure 2**). The mean of the three breaths in one assessment session was saved for further analysis. The measurements were performed daily from Monday to Friday until patients were extubated, discharged from the ICU, transferred to another hospital, or deceased, whichever came first. Detailed methods for ultrasound measurements are described in the legend of **Figure 2**.



**Figure 2 legend:** (Top left) Representative ultrasound image of the diaphragm. The muscle thickness was measured as the distance between the inner layers of the fasciae at end expiration. The probe was located at the zone of apposition between the midaxillary or anterior-axillary line in the 8th to 11th intercostal space. (Bottom left) Representative ultrasound image of the rectus abdominis muscle. The measurement of the muscle thickness was performed at end inspiration and was performed perpendicular to the inner layer of the muscle fascia. The probe was located at approximately 2 to 3 cm above the umbilicus and 2 to 3 cm lateral from the midline. (Right) Representative ultrasound image of the lateral abdominal expiratory muscles, showing three muscles from the top to bottom: external oblique, internal oblique, and transversus abdominis muscles. The measurements of the thickness of expiratory muscles and individual layers were performed at end inspiration and were performed perpendicular to the inner side of the muscle fascia (yellow arrow). The muscle fasciae are presented as green lines. The probe for the lateral abdominal muscles measurement was located approximately on the anterior axillary line, midway between the inferior border of the rib cage and the iliac crest.

## Statistical Analysis

Normality of the distribution of the studied variables was assessed visually on normal probability plots. The data are expressed as mean  $\pm$  SD, median [interquartile range], or frequency (percentage), as appropriate. We used a two-sided significance level of 5% for all analyses. Mean imputation was used for clinical characteristics that were missing. Missing data on muscle thickness during the study period were considered missing at random and were not imputed.

For the reproducibility study, intraclass correlation coefficient models with measures of consistency were constructed (two-way random for interrater and one-way random

for intrarater, respectively). The intraclass correlation coefficient values of the average measures were reported as intraclass correlation coefficient (95% CI). Repeatability coefficient, bias, and the upper/lower limit of agreement were calculated between raters and within each rater.<sup>29–31</sup> We calculated the required sample size for the reproducibility study assuming an intraclass correlation coefficient between two raters of at least 0.85 with 95% CI of width of at most 0.2 and intrarater intraclass correlation coefficient of 0.95 with 95% CI width of at most 0.1. Under these assumptions, 30 patients were required to evaluate interrater reliability, and 16 patients were required to evaluate intrarater reliability (eight patients for each rater to measure twice).

For the cohort study, we used the limits of agreement from the reproducibility study to obtain thresholds for changes in expiratory muscle thickness that were unlikely to arise from measurement variance alone (i.e., to determine the minimal difference in muscle thickness that is likely to be attributable to biologic processes such as atrophy and hypertrophy, as opposed to measurement variance). We used linear regression to estimate the average change in the expiratory muscle thickness for each patient over the first week of study. The study population was divided into three subgroups based on the estimated change in thickness on the last day of measurement (**Figure E1**). If the thickness of the expiratory muscles increased by at least 15% compared with its own baseline on the last day of measurement, a patient was assigned to the increase group. If thickness of the expiratory muscle decreased by at least 15%, a patient was assigned to the decrease group. If relative change was less than 15% in either direction, a patient was assigned to the no change group.

To compare the thickness of the expiratory muscles at different days between the three groups, a linear mixed model design was used with a fixed effect for day of study, group, and group-by-day interaction, a random effect for each patient, and baseline thickness as a covariate. A Bonferroni post hoc correction was applied for the pairwise comparisons. Differences in patient characteristics, baseline ventilator parameters, and clinical outcomes between these three groups were analyzed using ANOVA with post hoc Tukey honest significant difference test, the Kruskal–Wallis test with Dunn post hoc test, or chi-square tests with post hoc tests as appropriate. Post hoc tests were only performed when the overall test was significant.

The association between changes in expiratory muscle thickness and diaphragm thickness was analyzed with a linear regression model, using the estimated difference in thickness on the last day of measurement in the first week for both the diaphragm and the expiratory muscles (**Figure E1**). Given the exploratory nature of the cohort study, no formal sample size calculation was performed. We planned to enroll 100 subjects.

### **Sensitivity Analyses**

Sensitivity analysis models were added after suggestions by the reviewers to evaluate whether the different thresholds to define the three groups derived from the reproducibility study would have resulted in different conclusions. Because patients could have had a variable number of measurements within the first week, we additionally used linear mixed models to estimate the average change of expiratory muscle thickness over time. Linear mixed models were also added after suggestions from the reviewers to test whether changes in thickness were related to baseline characteristics. Linear regression was used to test for associations between the patients' average changes in expiratory muscle thickness (as a continuous parameter) over the first week and clinical outcomes. This approach has more power and does not depend on thresholds. The sensitivity analyses are presented in more detail in the **Supplements**. The data were analyzed with R version 4.0.2 (R Foundation for Statistical Computing, Austria) and SPSS version 26 (SPSS for Windows, IBM Corp., USA).

## **RESULTS**

### **Reproducibility Study: Reproducibility of Expiratory Muscle Thickness Measurements in Ventilated Subjects and Effect of Lung Volume**

Thirty critically ill patients (25 male,  $62 \pm 17$  yr, body mass index =  $25.3 \pm 3.2$  kg/m<sup>2</sup>) were enrolled, and expiratory muscle thickness measurements were obtained in all of these patients. The repeatability and reproducibility for the measurements between and within raters are reported in **table 1**. Intraclass correlation coefficients for the ultrasound measurements of the expiratory muscles were excellent for both interrater and intrarater (interrater intraclass correlation coefficient: 0.994 [95% CI, 0.987 to 0.997], intrarater intraclass correlation coefficient for two raters: 0.998 [95% CI, 0.992 to 1.000] and 0.992 [95% CI, 0.957 to 0.998], respectively). The means of difference caused by repeated measurements were 3.1% with limits of agreement from -13.1 to 6.8% between two raters and 1.4% with limits of agreement from -9.4 to 12.1% for the same rater (**Table 1**).

To assess the effect of lung volume on the expiratory muscle thickness, a subgroup of 10 patients ( $57 \pm 20$  yr, all male, body mass index =  $23.6 \pm 2.6$  kg/m<sup>2</sup>) was analyzed. The mean tidal volume change between two measurements within a subject was  $481 \pm 64$  ml. Mean of difference between the expiratory muscle thickness measured at high lung volume and low lung volume was  $-0.5 \pm 0.4$  mm ( $16.1 \pm 2.9$  mm vs.  $16.7 \pm 3.2$  mm,  $P < 0.001$ ). The thickness decreased by 3.2% after increasing lung volume, with limits of agreement between 0.1 and 6.5% (**Table 1**).

**Table 1.** Reproducibility

	Subjects, n	Mean $\pm$ SD, mm	Repeatability coefficient, mm	Bias $\pm$ SD, %	95% limits of agreement, %	Intraclass correlation coefficient
Interrater	30	13.1 $\pm$ 4.7	1.6	-3.1 $\pm$ 5.1	-13.1 to 6.8	0.994
Intrater (M.H.)	8	13.0 $\pm$ 6.0	1.0	1.4 $\pm$ 5.5	-9.4 to 12.1	0.998
Intrater (ZS)	8	11.7 $\pm$ 4.5	1.6	1.2 $\pm$ 6.5	-11.4 to 13.8	0.991
Volume (high vs low)	10	16.4 $\pm$ 3.0	1.2	-3.2 $\pm$ 1.7	-6.5 to 0.10	0.992

### **Cohort Study: Time-dependent Changes of Expiratory Muscle Thickness in Critically Ill Mechanically Ventilated Patients**

During the study period, 106 patients were enrolled, of whom 29 patients were extubated or died before the second ultrasound measurement was obtained. Accordingly, 77 patients with 331 ultrasound measurements were analyzed. The first ultrasound measurement was performed at a median of 21 [15 to 28] hours after the start of mechanical ventilation. The demographic and clinical characteristics of the study population are presented in **Table 2**.

#### **Baseline Thickness of the Expiratory Muscles**

The baseline median thickness of the expiratory muscles was 13.1 [10.2 to 16.1] mm. We observed a statistically significant association between age and baseline thickness of the expiratory muscles (0.16 mm decrease per year, 95% CI, 0.13 to 0.19;  $R^2 = 0.251$ ;  $P < 0.001$ ) but not between body mass index and baseline thickness and Acute Physiology and Chronic Health Evaluation II and baseline thickness. There was no statistically significant difference in expiratory muscle thickness between male and female patients (13.4 [10.2 to 17.7] mm vs. 12.2 [9.7 to 15.1] mm, respectively;  $P = 0.293$ ).

#### **Changes in Expiratory Muscle Thickness with Mechanical Ventilation**

The limits of agreement of the Bland–Altman plot, constructed on relative differences obtained from the reproducibility study (Figure E3), suggested that within-patient variation due to measurement variance would fall below the 15% limit (Tables E1 and E2). We reasoned that differences above this threshold were likely to be attributed to biologic processes such as atrophy or hypertrophy.

Over the first week of mechanical ventilation, the thickness of the expiratory muscles remained stable in 51 (66%) patients, decreased in 17 (22%) patients, and increased in 9 (12%) patients (**Figure 3**). Significant changes in the expiratory muscle thickness developed as early as the second day of the study. At the second day of the study, the thickness of the expiratory muscles decreased from 15.7  $\pm$  4.3 to 13.9  $\pm$  4.2 mm in the de-

Table 2. Demographics

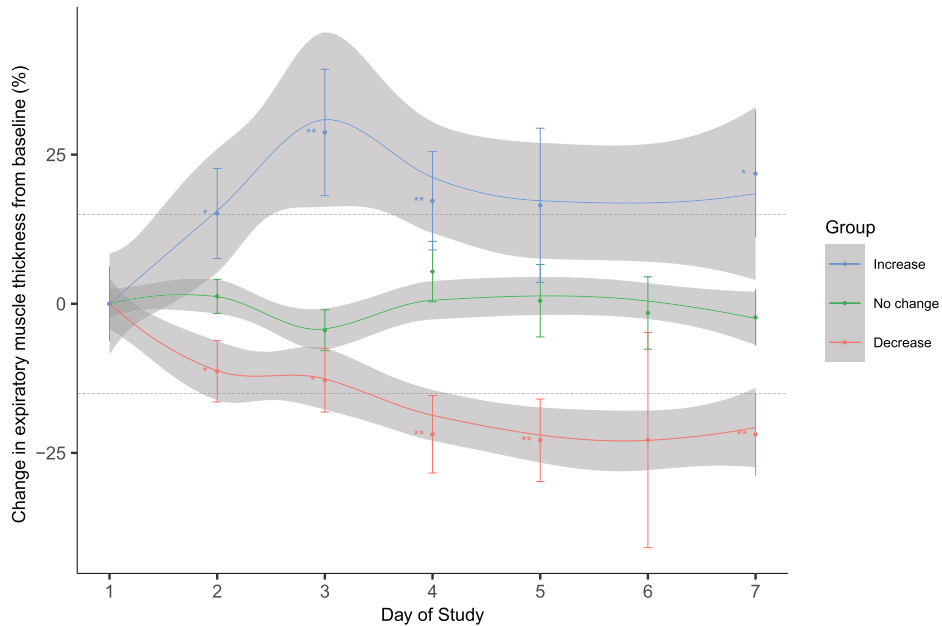
Variables	Overall (n = 77)	no change (n = 51)	decrease (n = 17)	increase (n = 9)	P Value
age, yr	66 [56-70]	64 [56-70]	64 [54-68]	71 [51-73]	0.526
Sex, male	57 (74)	40 (78)	10 (59)	7 (78)	0.269
Body mass index, kg/m <sup>2</sup>	25.0 [23.0-28.8]	24.5 [22.5-29.2]	26.4 [23.9-27.7]	25.2 [23.9-29.8]	0.742
C-reactive protein, mg/l	153 [98-243]	149 [97-222]	168 [97-310]	172 [107-243]	0.847
APACHE II score	21 [13-22]	21 [13-23]	22 [12-22]	18 [11-23]	0.906
Sepsis at admission, n (%)	21 (27)	14 (28)	4 (24)	3 (33)	0.866
Septic shock at admission, n (%)	17 (22)	12 (24)	2 (12)	3 (33)	0.411
Indications for mechanical ventilation, n (%)					0.445
Respiratory dysfunction	25 (32)	14 (27)	7 (41)	4 (44)	
Cardiovascular dysfunction	24 (31)	19 (37)	3 (18)	2 (22)	
Neurologic dysfunction	12 (16)	10 (20)	2 (12)	0 (0)	
Other organ dysfunction	16 (21)	8 (16)	5 (29)	3 (34)	
Medical history, n (%)					
COPD	7 (9)	4 (8)	2 (12)	1 (11)	0.866
Hypertension	20 (26)	13 (25)	5 (29)	2 (22)	0.915
Diabetes	18 (23)	15 (29)	1 (6)	2 (22)	0.139
Ventilator settings at baseline					
Controlled mode of ventilation, h	15 [8-22]	15 [8-21]	16 [6-28]	13 [5-25]	0.901
PEEP, cm H <sub>2</sub> O	8 [6-12]	8 [6-12]	8 [5-11]	10 [5-15]	0.576
Total respiratory rate, breaths/min	22 [19-25]	23 [29-26]	20 [18-24]	22 [18-24]	0.191
Driving pressure, cm H <sub>2</sub> O	13 [10-16]	14 [11-16]	12 [9-23]	13 [8-15]	0.654
Tidal volume per kg of ideal body weight,	6.5 [6.1-7.5]	6.4 [6.1-7.1]	7.4 [6.1-8.2]	6.6 [5.9-7]	0.342

Table 2. Demographics (continued)

Variables	Overall (n = 77)	no change (n = 51)	decrease (n = 17)	increase (n = 9)	P Value
ml/kg ideal body weight					
Pao <sub>2</sub> /Fio <sub>2</sub> ratio	217 [156-317]	235 [152-342]	199 [167-321]	208 [142-234]	0.383
Ventilator settings over the first week*					
Controlled mode of ventilation, h	41 [26-68]	41 [26-55]	48 [26-102]	33 [24.5-54]	0.316
PEEP, cm H <sub>2</sub> O	8 [6-11]	8 [6-11]	8 [5-12]	10 [7-10]	0.683
Total respiratory rate, breaths/min	22 [20-25]	24 [18-26]	22 [18-24]	20 [16-23]	0.079
Driving pressure, cm H <sub>2</sub> O†	12 [9-15]	12 [9-15]	10 [8-18]	10 [6-12]	0.129
Tidal volume, ml/kg ideal body weight	6.5 [6.1-7.6]	6.5 [6.1-7.8]	7.4 [6.1-7.8]	6.5 [6.1-8.3]	0.320
Pao <sub>2</sub> /Fio <sub>2</sub> ratio	212 [169-289]	228 [173-310]	198 [166-229]	189 [155-244]	0.225
Medical treatment over the first week					
Neuromuscular blockers, n (%)	30 (39)	20 (39)	6 (35)	4 (44)	0.900
Corticosteroids, n (%)	24 (31)	15 (29)	6 (35)	3 (33.3)	0.892
Opioids, n (%)	69 (90)	44 (86)	16 (94)	9 (100)	0.363
Vasopressors, n (%)	74 (96)	49 (96)	16 (94)	9 (100)	0.762
Sedatives, n (%)	74 (96)	49 (96)	16 (94)	9 (100)	0.762
Fluid balance, ml	1,935 [-19-4,961]	1,935 [24-5,545]	2,355 [-1,202-4,961]	1,846 [487-4,062]	0.814

**Table 2 legend:** Data are presented as median [interquartile range] or n (%). Missing data were in the range of 2.6 to 6.5%. C-reactive protein (3/74), body mass index (4/73), and tidal volume (2/75), respectively. The driving pressure applied by the ventilator was defined as peak pressure minus expiratory pressure.

crease group ( $P = 0.013$ ) and increased from  $13.7 \pm 7.4$  to  $18.1 \pm 10.5$  mm in the increase group ( $P = 0.007$ ; table E3). No significant differences in clinical parameters, physiologic parameters, or medication was found among the three groups (**Table 2**). In addition, thickness at baseline was not associated with changes in muscle thickness during the first week ( $P = 0.891$ ).

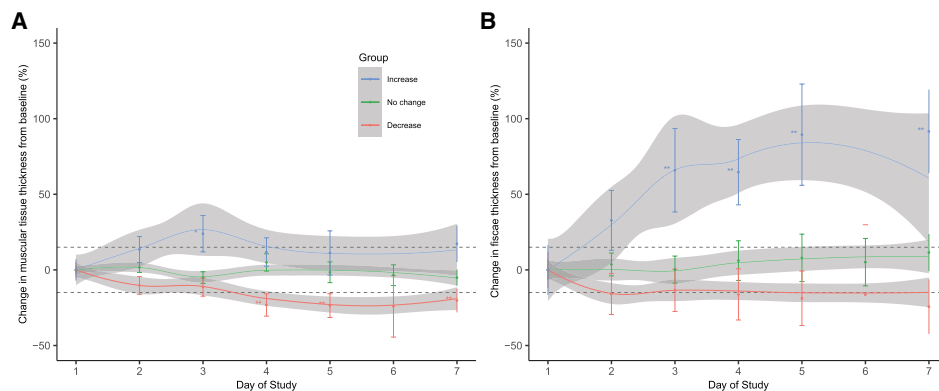


**Figure 3 legend:** Expiratory muscle thickness over the first week of mechanical ventilation. Subjects were divided into three groups based on increase or decrease of the estimated thickness of the last measurement within the first week versus initial thickness. The estimated thickness was obtained with linear regression using all available measurements for each subject. Therefore, the groups reflect the global changes of each patient. The muscle thickness remained stable ( $\pm 15\%$  changes) in 51 (66%) patients, decreased more than 15% in 17 (22%) patients, and increased more than 15% in 9 (12%) patients. Estimated mean and 95% CI are plotted for each group for each day. Trend lines were obtained with local weighted regression. At day 7 of the study, there were 3 patients in the increase group, 8 patients in the decrease group, and 15 patients left in the stable group. At day 6, one measurement was obtained in the decrease group, and no measurements were obtained in the increase group. Compared with the baseline, \* $P < 0.05$ , \*\* $P < 0.001$ .

### ***Differences between Changes in Muscular and Fascia Tissue of the Expiratory Muscles***

Thickness measurements of the expiratory muscles include the superficial and deeper interparietal fasciae (**Figure 2**). Changes in muscle thickness could thus (partly) result from changes in the thickness of these fasciae. Changes in the muscular parts and the fascial parts of the expiratory muscles are shown in **Figure 4**. The time-dependent decrease in expiratory muscle thickness resulted from a decrease in muscular tissue; in

these patients, thickness of the fascia did not change over time. In contrast, the increase in expiratory muscle thickness largely resulted from an increase in thickness of the two interparietal fasciae.



**Figure 4 legend:** Thickness of the muscular tissue and the fascia over the first week of mechanical ventilation. Patients are categorized into three subgroups according to the change in total thickness of the expiratory muscles over time. (A) Compared with the baseline thickness, the thickness of the muscular tissue decreased significantly at day 4 and continuously decreased over the following days. The thickness of muscular tissue remained stable in the increase and no change groups. (B) Compared with the baseline thickness, the thickness of the fasciae increased significantly on day 3 and continuously increased over the following days. Estimated mean and 95% CI are plotted for each group for each day. Trend lines were obtained with local weighted regression. Compared with the baseline, \* $P < 0.05$ , \*\* $P < 0.001$ .

### **Correlation between Thickness Changes of the Expiratory Muscles and the Rectus Abdominis Muscle**

The rectus abdominis muscle is part of the abdominal wall but has a limited role in active expiration.<sup>1,4</sup> Changes of the rectus abdominis muscle thickness were significantly associated with changes in expiratory muscle thickness, although the correlation was weak ( $R^2 = 0.159$ ;  $P < 0.001$ ; Figure E4). Significant associations between changes in total expiratory muscles thickness and their individual layers were detected ( $P < 0.001$ ), with moderate to weak correlation of determination (internal oblique muscle > transversus abdominis muscle > external oblique muscle, with  $R^2$  equal to 0.579, 0.487, and 0.440, respectively).

### **Correlation between Changes in Thickness of the Expiratory Muscles and Diaphragm**

Time-dependent changes in the thickness of the diaphragm were not significantly correlated with the changes in the thickness of the expiratory muscles ( $R^2 = 0.013$ ;  $P = 0.332$ ; Figure E5).

### Clinical Outcomes

No significant differences in clinical outcomes were found among the three groups defined by time-dependent changes in expiratory muscle thickness (**table 3**). A sensitivity analysis was performed to assess the associations between slope of change in expiratory muscle thickness (as a continuous variable) and clinical outcomes (**tables E4 and E5**). A significant association was found between the slope of expiratory muscle thickness and hospital length of stay: more negative slopes in the expiratory muscle thickness (i.e., more loss of muscle mass) were associated with increased hospital length of stay. Hospital length of stay increased by 7.4% (95% CI, 1.6 to 13.1%;  $P = 0.014$ ) per 0.1 mm/day loss of expiratory muscle mass.

**Table 3.** Clinical outcomes

Variable	Overall (n=77)	No Change (n=51)	Decrease (n=17)	Increase (n=9)	p-value
Mechanical ventilation, h	158 [71-335]	125 [67-313]	223 [83-359]	150 [678-317]	0.506
Ventilator-free days at day 28	9 [0-24]	10 [0-25]	0 [0-22]	0 [0-20]	0.482
Tracheostomy	9 (12)	7 (14)	2 (11)	0 (0)	0.483
Reintubation <7 days	12 (16)	8 (16)	2(11)	2 (22)	0.748
Length of ICU stay, days	9 [5-21]	8 [5-22]	10 [7-19]	7 [4-23]	0.676
Length of hospital stay, days	21 [9-36]	22[9 – 36]	15 [11-36]	26 [5-35]	0.975
ICU mortality, n (%)	31 (40)	18 (36)	9 (50)	4 (44)	0.562
Hospital mortality, n (%)	34 (44)	19 (38)	10 (56)	5 (56)	0.334

**Table legend:** Data are expressed as median [interquartile range] or n (%).

## DISCUSSION

This study provides a comprehensive insight into the effects of critical illness and mechanical ventilation on changes in thickness of the most prominent muscle groups of the respiratory pump. These data show that (1) ultrasound is a highly reproducible tool to assess thickness of the expiratory muscles in mechanically ventilated critically ill patients; (2) lung volume in the range of tidal breathing has a significant but small ( $\pm 0.5$  mm, 3% of the total thickness) effect on expiratory muscle thickness; (3) expiratory muscle thickness decreases in 22%, increases in 12%, and remains stable in 66% of critically ill ventilated patients; (4) the observed increase in thickness of the expiratory muscles mainly results from an increase in thickness of the muscle fasciae; and (5) changes in thickness of the expiratory muscles are not associated with changes in the thickness of the diaphragm. As an explorative endpoint, we observed that loss of expiratory muscle mass during the first week of ventilation was associated with increased hospital length of stay.

## Function of the Expiratory Muscles in the ICU

The expiratory muscles are an essential component of the respiratory pump. The lateral abdominal wall muscles are the most prominent expiratory muscles. Activation of the expiratory muscles during breathing occurs when a disbalance develops between load and capacity of the inspiratory muscles, such as with strenuous exercise, low respiratory system compliance, intrinsic PEEP, or low inspiratory muscle capacity as is common in ICU patients.<sup>1</sup>

## Reproducibility of Expiratory Muscle Ultrasound and the Effect of Lung Volume

In the current study, we demonstrate that ultrasound of the expiratory muscles is feasible and highly reproducible in ICU patients. The probe position on the skin was marked to reduce variability in repeated measurements originating from muscle anatomy.<sup>17</sup> The repeatability coefficient for thickness measurements of the expiratory muscles ranged from 1.0 to 1.6 mm, which is higher than the range of 0.2 to 0.4 mm reported for the diaphragm.<sup>17</sup> The origin of this difference is unknown but might be related to the echogenic properties of the muscles (as probes with identical properties were used). Because the expiratory muscles are much thicker than the diaphragm ( $13.2 \pm 3.9$  mm versus  $2.4 \pm 0.8$  mm), the ratio of measurement variance to the thickness of the muscles is equal to 10% in both muscle groups.

Increasing lung volume (passive or active) will result in caudal movement of the diaphragm, which in turn is expected to stretch the abdominal wall muscles. Indeed, the thickness of the expiratory muscles significantly decreased with tidal inspiration. The magnitude of this difference ( $\pm 3\%$  with tidal volume of  $\pm 480$  ml) was, however, much smaller than the difference that was used to categorize patients (15%). It is therefore unlikely that the differences in expiratory muscle thickness observed in the cohort study are explained by differences in lung volume. An earlier study demonstrated that in healthy subjects, breathing from functional residual capacity to residual volume significantly increased expiratory muscle thickness.<sup>32</sup> However, as subjects performed an expiratory maneuver, the increase in thickness in that study was at least partly explained by active muscle contraction.

## Loss of Muscle Thickness

This study used ultrasound to assess whether thickness changes of the expiratory muscles would occur in patients during the first week of mechanical ventilation. The development of expiratory muscle atrophy in critically ill patients has been observed in rectus abdominis muscle biopsies.<sup>11</sup> In vitro contractility of the rectus abdominis muscle was reduced in septic mechanically ventilated patients.<sup>33</sup> Studies using muscle biopsies

are important to identify biochemical pathways involved in the development of atrophy but cannot be used to study time-dependent changes in muscle thickness. Ultrasound provides a more comprehensive overview of the changes in the different muscle groups of the respiratory pump, and it is a feasible technique to study the time-dependent changes in thickness. Of our patients, 22% developed atrophy of the expiratory muscles. These patients could not be identified by specific clinical or physiologic characteristics at baseline. Previous studies have demonstrated that the presence of expiratory muscle weakness in critically ill patients is associated with adverse clinical outcome. Reduced thickness of the expiratory muscles may impair strength and as such negatively affect airway clearance, resulting in atelectasis and pneumonia, especially after extubation.<sup>22,23,25</sup> In our sensitivity analyses, we found that patients who developed expiratory muscle atrophy had significantly longer hospital length of stay, but this finding should be interpreted with caution because this study was not designed to investigate the functional implications of expiratory muscle atrophy. This hypothesis remains to be investigated in a larger sample size, and the data from this study are useful for sample size calculation.

### **Increased Muscle Thickness**

Previous studies reported increased diaphragm thickness in a subgroup of ventilated critically ill patients.<sup>15</sup> In this study, we found that thickness of the expiratory muscles increased in 12% of patients, but interestingly, this increase in thickness was mainly driven by increased thickness of the interparietal fasciae between the three muscle layers. This is a novel and unexpected finding. The muscular fascia is a highly organized connective tissue containing different types of cells (e.g., fibroblasts, myofibroblasts) and extracellular matrix molecules (e.g., ground substance and collagen fibers).<sup>34</sup> This fascia plays a crucial role in transmission, distribution, and absorption of muscle force.<sup>34,35</sup> Both mechanical unloading and loading affect connective tissue collagen synthesis and degradation, thus leading to fascia tissue remodeling.<sup>34,36</sup> This activity-driven adaptation may play a role in regulation of muscle mass and strength.<sup>37,38</sup> However, excessive or repetitive loading to fascial tissue initiates persistent inflammation, inducing macrophages and cytotoxic levels of cytokines, ultimately resulting in tissue damage.<sup>39</sup> Cytokines, such as interleukins, tumor necrosis factor  $\alpha$ , and transforming growth factor  $\beta$ , are fibrogenic cytokines facilitating fibrosis (e.g., fibroblast proliferation and collagen matrix deposition).<sup>34,40,41</sup> Morphological characteristics and function of fascia tissue in respiratory muscles of critically ill patients have not been studied. Future biopsy studies should further elucidate the role of the fasciae in regulating muscle mass and function in ventilated patients and evaluate the clinical implications of increased respiratory muscle fascia thickness.

## **Association between Expiratory Muscles Atrophy and Diaphragm Atrophy**

Another important finding of the current study is that we found no significant association between thickness changes in the expiratory muscles and the diaphragm. The fact that the diaphragm and the expiratory muscles respond differently to mechanical ventilation and critical illness is remarkable, because both muscles act in the same metabolic environment (e.g., level of systemic inflammation, reactive oxygen/nitrogen species, drug exposure, arterial oxygen tension, pH). However, these findings are consistent with earlier studies from our group and others demonstrating that critical illness does not equally affect the different muscles of the respiratory pump.<sup>10,12</sup> For instance, muscle biopsy studies in ICU patients demonstrated different severities of atrophy between the diaphragm and noninspiratory muscles (mostly rectus abdominis muscle).<sup>12</sup>

## **Strengths and Limitations**

The strengths of the current study include the relatively large sample size, simultaneous analysis of different muscles of the respiratory pump, and separate analysis of the muscular fasciae. Several limitations should be acknowledged. First, this is a single-center study conducted in severely ill ventilated patients (hospital mortality  $\pm$  44%). Whether similar results are obtained in other patient categories remains to be investigated. Nevertheless, this study was performed in a large academic ICU admitting a heterogeneous group of ICU patients. Second, we could not evaluate the effects of mechanical ventilation per se on the expiratory muscles but merely the combined effects of critical illness and mechanical ventilation. To precisely investigate the contribution of mechanical ventilation, a nonventilated control group with similar severity of disease should be included. This was not feasible, and therefore the exact contribution of mechanical ventilation should be interpreted with caution. Another limitation of the study is early extubation in many patients, because only one third of the patients remained ventilated by the end of the first week. This might lead to biased observations, because the least-ill and most-ill patients tend to drop out earlier. This form of bias is inherent to cohorts of ICU patients, but it does mean that our results should be interpreted with caution. Further studies are required to confirm the pattern of thickness changes of the expiratory muscles that we have observed and to assess the functional implications.

## **CONCLUSIONS**

The current study demonstrates that ultrasound is a highly reliable tool to assess expiratory muscle thickness in mechanically ventilated critically ill patients. Tidal volume has a significant although small effect on expiratory muscle thickness. Atrophy develops in 22% of the patients and is attributable to loss of muscle tissue; increased expiratory muscle thickness develops in 12% of the patients and is attributed to increased thickness of the interparietal fasciae. Changes in thickness of the expiratory muscles are not associated with changes in diaphragm muscle thickness, indicating that different muscles of the respiratory pump may respond differently to critical illness and mechanical ventilation.

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8

# Activity of the Respiratory Muscles during Expiration in Critically Ill Patients and Healthy Subjects

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*Adapted from Am J Respir Crit Care Med. 2024; 209(7):881-883.*

*Author contributions: HdV and LH designed the secondary analysis. HdV, AJ, MH, HdG, ZS and LH conducted measurements in the original trial. HdV and AJ conducted signal processing and statistical analyses. All authors read and critically revised the manuscript. The supplements to this article are available upon request from the author at [hederdevries@gmail.com](mailto:hederdevries@gmail.com)*

## ABSTRACT

**Rationale:** Expiratory diaphragm activation may facilitate lung recruitment, but has also been proposed as a mechanism for diaphragm injury in ventilated critically ill patients.

**Objectives:** To investigate recruitment patterns of the diaphragm and expiratory muscles during expiration in ventilated critically ill patients and healthy volunteers, and to identify factors associated with expiratory diaphragm recruitment. We hypothesized that patients have more lengthening activations of the diaphragm than healthy subjects, and that co-activation of expiratory muscles increases the force of active lengthening.

**Methods:** Secondary analysis of two studies. Transdiaphragmatic pressure (Pdi) and diaphragm electrical activity (Edi) were measured in patients (n=39) on partially-supported mechanical ventilation and in healthy volunteers (n=19). Pdi and Edi during expiration, the pressure-time product of Pdi, lengthening diaphragm work, the rise in gastric pressure (Pga) and pressure-time product of the expiratory muscles were computed.

**Measurements and main results:** Expiratory diaphragm activity was present in 62% of patients. Median lengthening work of the diaphragm was 1.95J/min (19% of total work). Lengthening work was positively associated with inspiratory effort, and negatively associated with inspiratory support and lung compliance. Co-activation of diaphragm and expiratory muscles occurred in 15% of patients and increased. Critically ill patients had more lengthening work per minute, more expiratory muscle recruitment, and more co-activation of the diaphragm and expiratory muscles compared with healthy subjects.

**Conclusions:** This study demonstrates that the diaphragm remains active during expiration in the majority of critically ill patients, resulting in more lengthening activations. This could be a new mechanism for diaphragm myotrauma.

## INTRODUCTION

Inspiratory flow is generated by contraction of the diaphragm and other inspiratory muscles, while expiration is usually considered to be passive, relying on elastic recoil of the respiratory system.<sup>1,2</sup> However, in an animal model for acute respiratory distress syndrome (ARDS), it was recently demonstrated that the diaphragm remains active during expiration.<sup>3</sup> The magnitude of expiratory diaphragm activity was positively associated with the tendency of lung collapse, leading the authors to conclude that expiratory diaphragm activity is a protective reflex to limit alveolar derecruitment.

Whether adult critically ill patients have expiratory diaphragm recruitment is unknown. This is of importance, as expiratory diaphragm activity may facilitate lung-protective ventilation by limiting tidal lung recruitment, but may also result in lengthening activations of the diaphragm (also referred to as eccentric contractions), a proposed mechanism for diaphragm myotrauma.<sup>4</sup> Simultaneous activation of the expiratory muscles may further increase the risk of diaphragm myotrauma by imposing an increased stress on the lengthening diaphragm.

Accordingly, the aim of this study was to investigate whether lengthening activations are present in ventilated patients. We hypothesized that the diaphragm of ventilated critically ill remains active during expiration, leading to lengthening activations, and that co-activation of expiratory muscles increases the force of lengthening contractions. We also hypothesized that ventilated patients would perform more lengthening activations than healthy subjects. If this hypothesis appears true, it provides a possible new mechanism for critical illness-associated diaphragm weakness.

## MATERIALS AND METHODS

### Study Design

This is a secondary explorative analysis on data from two clinical trials: a randomized-controlled trial in critically ill patients (NCT 03527797) and a physiological study in healthy subjects (NCT 03580720). This analysis was not registered *a priori*. Both studies were conducted in accordance with the ethical standards set forth in the Declaration of Helsinki and its further amendments.

### Participants

The patient cohort (n=39) was recruited at the mixed medical-surgical ICU of a tertiary university hospital (Amsterdam UMC, location VUmc, the Netherlands), and consisted of

adults with acute respiratory failure on partially-supported invasive mechanical ventilation in whom mechanical ventilation was expected to be required for >48 hours.<sup>5</sup> The patients' representatives provided written informed consent.

The healthy cohort (n=19) was recruited at the Faculty of Medicine (Vrije Universiteit, Amsterdam, the Netherlands) and consisted of adults without known cardiac or pulmonary medical history. All volunteers provided written informed consent.

## Procedures

### ***Critically ill patients***

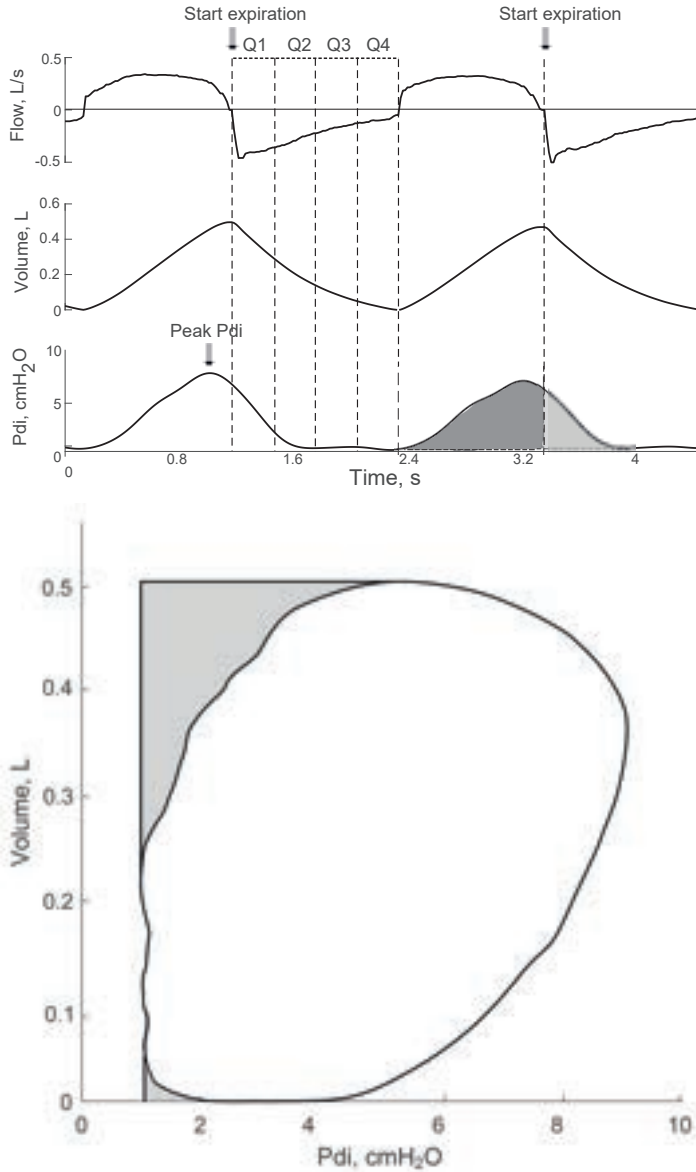
Flow, airway opening pressure (Pao), esophageal pressure (Pes), gastric pressure (Pga), and transdiaphragmatic pressure (Pdi, calculated as Pga – Pes) were recorded as described previously.<sup>5,6</sup> Six patients also had a catheter (NAVA Catheter, Getinge, Sweden) *in situ* to record the electrical activity of the diaphragm (Edi) for clinical purposes. In the original clinical trial, patients were randomized to receive titration of inspiratory pressure support (aimed at achieving Pdi swings between 3-12cmH<sub>2</sub>O, n = 19) or standard-of-care (n = 20).<sup>5</sup>

### ***Healthy controls***

Healthy volunteers were instrumented and connected to a measurement setup in similar fashion as the critically ill patients. All healthy subjects had an Edi catheter *in situ*. Subjects breathed quietly and unimpeded through the flow sensor for several minutes, after which the maximal strength of the diaphragm was assessed (**online supplements**). Next, an inspiratory threshold loading device (Powerbreathe Medical, POWERbreathe International Ltd., UK) was placed in series to the flow sensor. The device did not impede expiration. After breathing unobstructed for several minutes, the threshold load was set to 10%, 20% and 30% of maximal effort for several minutes, to induce a wide range of breathing effort that could theoretically be sustained indefinitely according to the tension-time index.<sup>7</sup> Subjects had 3 minutes of unobstructed resting breathing in between each level to rest.

### ***Signal processing and analyses***

Signal processing and breath-by-breath analyses were done with a custom software (Matlab 2021a, MathWorks, USA) as described in the **Supplements**. In this analysis, the onset of expiration was based on the *onset of expiratory flow* and the end of expiration was set as the *start of inspiratory flow* of the next breath. The expiratory cycle was then divided into four quartiles (Q1 to Q4) with equal length in each breath (**Figure 1A**) as described previously.<sup>3,8</sup> Expiratory diaphragm activity was assessed with Pdi and Edi



**Figure 1 legend:** Analysis of expiratory diaphragm activity. **Left:** Flow, volume, transdiaphragmatic pressure (Pdi) and electrical activity of the diaphragm (Edi) in two breaths in a critically ill patient. Expiration starts at the onset of negative flow and ends at the start of inspiratory flow at the next breath. Expiration was divided into four equal quartiles of equal duration (Q1 to Q4) as shown in the first breath. Mean Pdi of every quartile was calculated, and was normalized to the peak Pdi of the same breath. The neuromechanical coupling was calculated as Pdi/Edi at two points in each breath: during expiration in the middle of Q1, and during inspiration at the same lung volume as the measurement in Q1 (asterisks). The pressure-time product of the diaphragm (PTPdi) was calculated in each breath, and was partitioned in the PTP during inspiration (dark gray) and expiration (light gray) as shown in the second breath. **Right:** Pdi-volume loop. The lengthening work of the diaphragm was calculated as the area of the shaded areas, multiplied by 0.098 to convert the unit to joule. The area enclosed by the Pdi-volume loop (white) represents the positive work of the diaphragm.

during the quartiles of expiration, the neuromechanical efficiency index (NME) during inspiration and expiration, the pressure-time product of the diaphragm during expiration ( $PTP_{di,exp}$ ) and the negative work done by the diaphragm ( $WOB_{neg,di}$ ).

Expiratory muscle activity was assessed with the rise in Pga during expiration, the peak expiratory flow, the pressure-time product of Pga during expiration ( $PTP_{ga}$ ), the pressure-time product of all expiratory muscles ( $PTP_{mus,exp}$ ), and the expiratory work of breathing based on the Campbell diagram ( $WOB_{exp}$ ). More details are available in the **Supplements**.

### Statistical Analysis

Descriptive statistics are expressed as mean  $\pm$  standard deviation, median [interquartile range] or count (percentages), as appropriate. Normality of distributions was assessed visually on normal-probability plots. Log-transformations were applied to convert distributions to normal if required. Since the measurement period in patients lasted 24 hours, the dataset was split into smaller 1-hour recordings and the above parameters were averaged for each of these 1-hour recordings. For healthy volunteers, parameters were averaged per level of inspiratory loading.

Differences in parameters between groups (patients versus healthy volunteers) were assessed with Student's t-test, Wilcoxon log-rank test, or Fisher exact test, as appropriate. Correlations between continuous parameters were assessed with repeated-measures linear mixed-effect models, including fixed effects of group, phase of the respiratory cycle, their interaction terms, and a random effect for each subject. If the interaction term was statistically significant, post-hoc analyses with Bonferroni-corrections were employed to test for differences between groups and/or phase of the respiratory cycle. A two-tailed significance level of 5% was used for all statistical analyses. All the statistical analyses were performed in R version 4.0.1 (R Foundation for Statistical Programming, Vienna, Austria).

Additional details are available in the **online supplements**.

## RESULTS

Characteristics and inspiratory breathing effort in the critically ill and healthy cohorts are summarized in **Table 1**.

**Table 1.** Baseline parameters

Parameter	ICU patients (n = 39)	Healthy subjects (n = 19)	p
Age, years	65 ± 14	29 ± 6	<0.001
Male sex, n (%)	26 (68)	9 (47)	0.314
BMI, kg/m <sup>2</sup>	27 ± 3	23 ± 2	<0.001
Maximal Pdi, cmH <sub>2</sub> O*	31 [17, 58]*	133 [91, 163]	<0.001
Respiratory mechanics			
Respiratory system compliance, ml/cmH <sub>2</sub> O	36 [23,40]	85 ± 25	<0.001
Lung compliance, ml/cmH <sub>2</sub> O	48 ± 28	226 ± 117	<0.001
Chest wall compliance, ml/cmH <sub>2</sub> O	150 ± 57	152 ± 24	0.674
Tidal volume, ml/kg ideal bodyweight	7.6 ± 1.3	10.3 ± 3.5	<0.001
Inspiratory breathing effort			
Respiratory frequency, n/min	23 ± 6	13 ± 4	<0.001
Pdi, cmH <sub>2</sub> O/per breath**	10 [7, 12]	14 [11, 19]	<0.001
PTPdi, cmH <sub>2</sub> O*s/min**	153 [111, 204]	119 [130, 260]	0.131

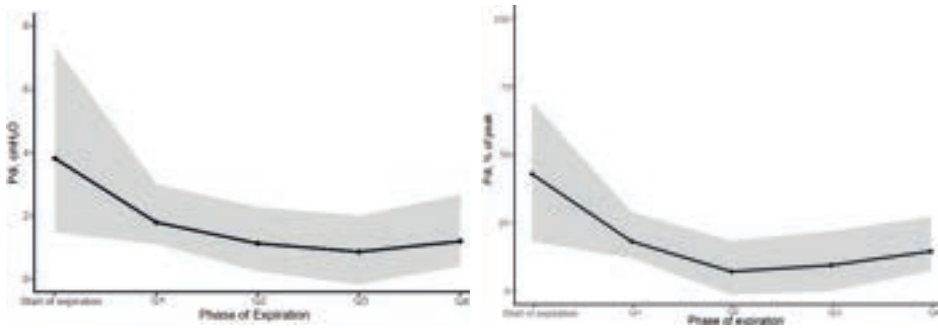
**Table 1 legend:** \*Maximal transdiaphragmatic pressure was known in 7/36 ICU patients, because it was not measured routinely or feasible in the study protocol. \*\*Note that the ICU patients received inspiratory pressure support (10 ± 5 cmH<sub>2</sub>O) while the healthy subjects breathed unassisted.

## Diaphragm Activity During Expiration in the Critically Ill

### Pressure generation and neural drive of the diaphragm during expiration

The evolution of Pdi during expiration in patients is shown in **Figure 2**. At the onset of expiratory flow, the diaphragm developed a median [interquartile range] pressure of 3.9 [1.8 to 7.4] cmH<sub>2</sub>O (39±19% of peak Pdi), while this decreased to 2.0 [1.2 to 3.2] cmH<sub>2</sub>O (20 ±6% of peak Pdi) in the first quartile of expiration. The individual curves are shown in **Figure E1**. Several recruitment patterns were observed: 46% of patients (18/39) demonstrated most diaphragm activity during early expiration and decreased their activity during the rest of expiration (negative regression slopes), 15% (6/39) demonstrated most activity during end-expiration (positive regression slopes), and 38% (15/39) demonstrated continuous activity close to baseline (regression slopes not significantly different from 0).

Median PTPdi during expiration was 12 [1, 19] cmH<sub>2</sub>O\*s\*min<sup>-1</sup>. NME of patients was not different between inspiration and expiration in at the same lung volume (0.71±0.35 vs 0.68±0.18 cmH<sub>2</sub>O/μV, respectively, p = 0.401). Evolution of Edi during expiration is shown in **Figure E2**.



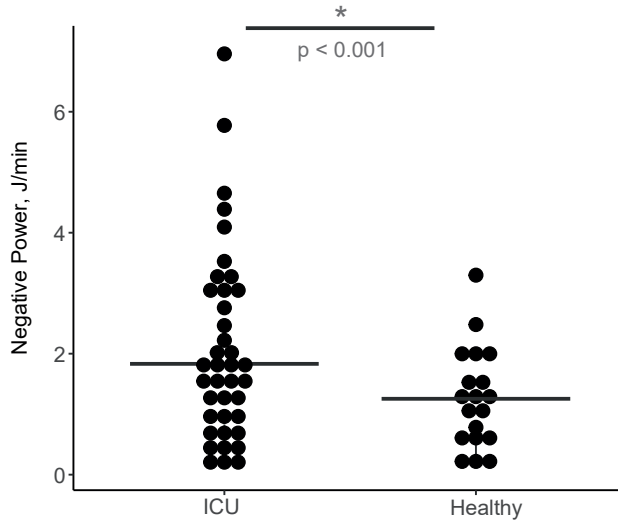
**Figure 2 legend:** Evolution of transdiaphragmatic pressure generation (Pdi, left) and Pdi normalized to peak Pdi (right) during expiration in critically ill subjects. Dots show the median, gray shaded area shows the interquartile ranges.

### ***Lengthening work of the diaphragm***

The lengthening (negative) work of the diaphragm, reflecting the magnitude of pressure generated by the diaphragm while the muscle is lengthening (active lengthening), is shown in **Figure 3**. Among all patients, median lengthening work was 0.08 [0.03 to 0.15] J/breath and 1.95 [0.71 to 3.25] J/minute, equal to 19% of total work performed by the diaphragm. Among only the 24 patients with expiratory diaphragm activity, median lengthening work was 0.14J/breath and 2.9 J/min, equal to 28% of total work performed by the diaphragm.

We explored whether patients with higher or lower active lengthening had different clinical characteristics (**Table 2**). Patients with lengthening diaphragm work above the group median had significantly lower lung compliance, lower inspiratory ventilator support and higher inspiratory diaphragm effort compared with patients demonstrating lower than median lengthening diaphragm work. PEEP, FiO<sub>2</sub>, oxygen saturation and ventilatory ratio were not different. Likewise, in univariate linear models lengthening work of the diaphragm was positively related to inspiratory PTPdi ( $p < 0.001$ ), and negatively related to inspiratory support ( $p = 0.003$ ) and lung compliance ( $p = 0.021$ ), and was not significantly related to PEEP ( $p = 0.349$ ), FiO<sub>2</sub> ( $p = 0.779$ ), SaO<sub>2</sub> ( $p = 0.600$ ) and PaO<sub>2</sub>/FiO<sub>2</sub>-ratio ( $p = 0.793$ ).

Additionally, we explored the effect of titration of pressure support on lengthening work of the diaphragm. Patients in which support was titrated to reach a Pdi of 3-12cmH<sub>2</sub>O per breath had significantly lower lengthening work compared with patients that received standard-of-care (where Pdi was outside of this putative range for 65% of breaths)(5): 1.3 [0.5 to 2.1] versus 2.4 [0.8 to 3.2] J/min, respectively,  $p < 0.001$ .



**Figure 3 legend:** Lengthening work of the diaphragm per minute in critically ill patients and healthy subjects. Each dot represent the average for one subject. The vertical lines show the medians.

#### ***Expiratory Muscle Activity and Co-Activation of the Diaphragm***

Activity of the expiratory muscles is summarized in **Table 3**. In total, 5 out of 39 (13%) patients had a Pga rise  $>2$  cmH<sub>2</sub>O in all of their 24h recordings, and 26 of the 39 (66%) patients had at least one hour where the average Pga rise was  $>2$ cmH<sub>2</sub>O. Expiratory muscle activity (PTP<sub>mus</sub> during expiration) was positively correlated ( $r^2 = 0.22$ ,  $p = 0.012$ ) to expiratory diaphragm activity (PTP<sub>di</sub> during expiration).

**Figure 4** shows the distribution of expiratory diaphragm activity (PTP<sub>di<sub>exp</sub></sub>) and expiratory muscle activity (PTP<sub>mus<sub>exp</sub></sub>) in patients. Co-activation of the diaphragm and expiratory muscles, arbitrarily defined as both PTP<sub>di<sub>exp</sub></sub> and PTP<sub>mus<sub>exp</sub></sub> higher than 25 cmH<sub>2</sub>O\*s\*min<sup>-1</sup>, occurred in 19% of breaths, and was observed in 15% of patients (6/39).

Patients with co-activation of the diaphragm and expiratory muscles had significantly higher active lengthening of the diaphragm compared with patients without co-activation (lengthening work of the diaphragm 4.77 vs 1.86 J/min,  $p < 0.001$ ).

**Table 2.** Differences between high and low expiratory diaphragm effort.

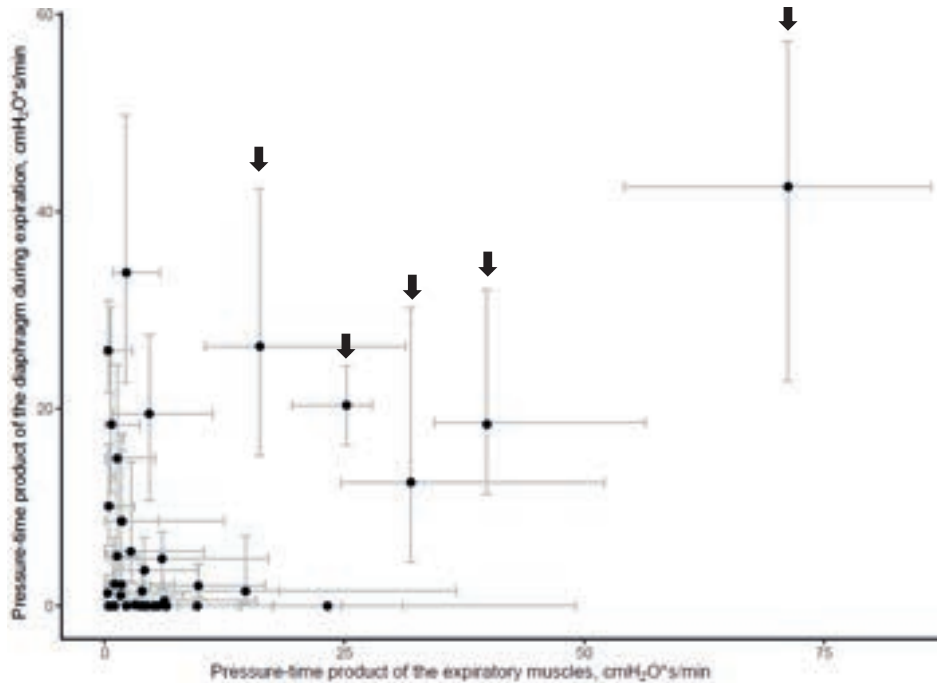
<b>Parameter</b>	<b>Higher expiratory diaphragm effort (n = 20)</b>	<b>Lower expiratory diaphragm effort (n = 19)</b>	<b>p</b>
<b>Demographics and risk-scores</b>			
Age, years	64 (15)	68 (13)	0.549
Sex, # male (%)	12 (60%)	11 (58%)	0.990
BMI	27 (3)	29 (5)	0.076
SAPS score at admission	51 (14)	50 (17)	0.514
APACHE2-score at admission	88 (25)	83 (29)	0.380
RASS score during study	-1 [-3, 1]	-2 [-3, 1]	0.543
<b>Respiratory mechanics</b>			
Compliance respiratory system	35 (14)	43 (16)	0.052
Lung compliance, ml/cmH <sub>2</sub> O	45 (23)	66 (28)	<b>0.021</b>
Chest wall compliance, ml/cmH <sub>2</sub> O	159 (49)	155 (58)	0.822
Tidal volume, ml	517 (116)	519 (98)	0.942
Tidal volume, ml/kg	7.7 (1.2)	7.4 (1.5)	0.509
Respiratory rate, breaths/min	22 (5)	24 (6)	0.829
Pdi, cmH <sub>2</sub> O	11.4 [8.3, 14.6]	8.6 [6.8, 10.3]	<b>0.037</b>
PTPdi, cmH <sub>2</sub> O*s*min <sup>-1</sup>	200 [121, 251]	134 [110, 152]	<b>0.013</b>
<b>Ventilator settings and oxygenation</b>			
Pressure support, cmH <sub>2</sub> O	8 (3)	12 (6)	<b>0.015</b>
PEEP, cmH <sub>2</sub> O	10 (3)	10.16 (4.39)	0.963
SaO <sub>2</sub> , %	95 (2)	94.95 (2.07)	0.647
FiO <sub>2</sub>	50 (15)	45 (8)	0.428
PF-ratio, mmHg	189 (54)	192 (56)	0.913
Ventilatory ratio	1.98 (0.62)	2.26 (0.50)	0.299
<b>Outcomes and risk scores</b>			
ICU mortality, n (%)	3 (15%)	4 (21%)	0.682
Hospital mortality, n (%)	6 (30%)	8 (42%)	0.487
Ventilator-free days at day 28, days	8 [0, 16]	3 [0, 7]	0.135

**Table 2 legend:** All parameters were measured during the expiratory phase of breathing based on flow. PTP, pressure-time product

**Table 3.** Expiratory muscle activity

Parameter	ICU patients (n = 39)	Healthy subjects (n = 19)	p
Peak expiratory flow, ml/s	-740 ± 204	-509 ± 207	<b>&lt;0.001</b>
Rise in Pga during expiration, cmH <sub>2</sub> O	1.2 [0.3, 1.6]	0.3 [0, 1.0]	<b>0.041</b>
PTP of gastric pressure, cmH <sub>2</sub> O*s*min <sup>-1</sup>	13 [6, 39]	8 [2, 17]	<b>0.047</b>
PTP of the expiratory muscles, cmH <sub>2</sub> O*s*min <sup>-1</sup>	17 [1, 21]	0 [0, 3]	<b>&lt;0.001</b>
Expiratory work of breathing, J/breath	0.002 [0, 0.08]	0.01 [0, 0.05]	0.233
Expiratory work of breathing, J/min	0.11 [0.02, 0.24]	0.03 [0, 0.7]	0.173

**Table 3 legend:** All parameters were measured during the expiratory phase of breathing based on flow. Pga, gastric pressure; PTP, pressure-time product



**Figure 4 legend:** Relationship of expiratory diaphragm activity and expiratory muscle activity in individual patients. Dots show median, while the horizontal and vertical gray errorbars depict the interquartile range. There was a significant positive relation between expiratory muscle and expiratory diaphragm activity ( $r^2 = 0.22$ ,  $p < 0.001$ ), mainly driven by 5 patients marked with arrows.

### Comparison to healthy subjects

Patients were significantly older, had lower lung compliance, lower tidal volumes and higher respiratory rates compared with healthy volunteers (**Table 1**).

Evolution of Pdi during expiration in patients compared with healthy subjects is shown in **Figure E3**. The evolution of Pdi during expiration differed significantly ( $p < 0.001$  for the interaction term): patients had a lower Pdi at start expiration ( $3.9 \pm 2.4$  vs  $12.6 \pm 4.1$  cmH<sub>2</sub>O,  $p = 0.018$ ), in Q1 ( $2.0 \pm 1.5$  vs  $9.8 \pm 4.1$  cmH<sub>2</sub>O,  $p = 0.032$ ) and in Q2 ( $1.3 \pm 1.2$  vs  $5.5 \pm 3.1$  cmH<sub>2</sub>O,  $p = 0.044$ ) compared with healthy subjects. PTPdi<sub>exp</sub> was lower in the patients ( $12$  [1, 19] vs  $55$  [31, 62] cmH<sub>2</sub>O\*s\*min<sup>-1</sup>, respectively,  $p < 0.001$ ).

NME was lower in the critically ill compared with healthy subjects ( $0.71 \pm 0.35$  vs  $0.93 \pm 0.42$  cmH<sub>2</sub>O/ $\mu$ V, respectively,  $p = 0.021$ ), but was not different during inspiration and expiration in either group ( $p = 0.401$  for the interaction term).

Patients had lower lengthening work of the diaphragm per breath ( $0.08$  [0.03 to 0.15] vs  $0.12$  [0.07 to 0.19] J/breath,  $p = 0.016$ ), but higher lengthening work per minute ( $1.95$  [0.71 to 3.25] vs  $1.52$  [0.51 to 2.42] J/min, respectively,  $p = 0.045$ , **Figure 3**) compared with healthy subjects.

Patients demonstrated more expiratory muscle activity than healthy subjects (**Table 3**). Co-activation of the diaphragm and expiratory muscles occurred more often in the critically ill (19% vs 5% of all breaths,  $p < 0.001$ ), and was observed in one healthy subject (**Figure 4**).

## DISCUSSION

In this study, we assess whether lengthening activations of the diaphragm occur in critically ill patients on an assisted ventilator mode, and if this is affected by expiratory muscle co-activation. Our results can be summarized as follows: first, a majority of critically ill patients on a supported mode of ventilation exhibit expiratory diaphragm activity (62% of patients), most prominently during early expiration (46% of patients). Second, expiratory diaphragm activity leads to active lengthening in these patients; ~20% of the total of work of the diaphragm is due to active lengthening during expiration, causing patients to have significantly more active lengthening than healthy subjects. The degree of active lengthening of the diaphragm is positively correlated with inspiratory effort, and negatively correlated with lung compliance and inspiratory support. Third, co-activation of the diaphragm and expiratory muscles occurs in 15% of patients, and leads to more active lengthening.

## The Expiratory Brake: Post-Inspiratory Diaphragm Activity

Pellegrini *et al.* demonstrated that electrical activity of the diaphragm continues during expiration in pigs with ARDS. Expiratory diaphragm activity increased when reducing PEEP in this experimental model, which was hypothesized to signify a protective reflex of the diaphragm. Diminishing expiratory diaphragm activity with sedation and passive mechanical ventilation increased atelectasis, fitting the hypothesis that the diaphragm is recruited during expiration to limit atelectasis and tidal lung derecruitment.<sup>3</sup> Data from young infants also demonstrate post-inspiration electrical activity of the diaphragm, which increased when PEEP was reduced, fitting ‘braking’ hypothesis.<sup>8,9</sup> Whether expiratory diaphragm activation occurs in adult patients was unknown.

Our data demonstrate that adult critically ill patients exhibit expiratory diaphragm activity as shown by post-inspiration electrical activity and pressure generation (**Figure 2**). The observation that neuromuscular efficiency of the diaphragm is equal during inspiration and expiration suggests that expiratory diaphragm activation is a controlled process, instead of residual activity due to delayed repolarization of diaphragm muscle fibers or pressure decay caused by repositioning of the (abdominal) organs.

Interestingly, patients with lower lung compliance exhibit higher expiratory diaphragm activity (**Table 2**), which is in line with the ‘diaphragm as brake’-hypothesis. Contrary to earlier studies in infants and pigs,<sup>3,8</sup> expiratory diaphragm activity was not related to PEEP and Pa<sub>o2</sub>/Fi<sub>o2</sub>-ratio in our cohort. A potential explanation for this discrepancy is that pigs<sup>10</sup> and infants<sup>11</sup> have stronger vagal respiratory reflexes as compared to human adults. The strength of these reflexes fades during development to adults.<sup>12</sup> Infants also lack the rigidity of the chest wall to prevent lung collapse, further increasing the likelihood of requiring protective reflexes to prevent airway collapse.<sup>13</sup> Diaphragm activity increased during the last part of expiration (**Figure E1**) in 15% of patients, which probably signifies effort to trigger the next inspiration and not post-inspiration activity *per se*. Indeed, these patients had higher PEEPi than patients that did not show this recruitment pattern (3.2 vs 1.7 cmH<sub>2</sub>O, p<0.001), supporting the hypothesis that this signifies effort to trigger the next breath.

## Expiratory Diaphragm Activation: Braking or Breaking?

Expiratory diaphragm activity might be a double-edged sword in critically ill patients. The diaphragm shifts to a more cranial position when lung volume decreases (expiration), lengthening the diaphragm muscle fibers; if the diaphragm remains active during expiration, this will result in lengthening activations, sometimes referred to as eccentric contractions (although there is no “*contractio*–”, but lengthening). Lengthening activations increase the risk of muscle injury, resulting in greater reductions in force-gener-

ating capacity compared with equal loads of isometric or concentric contractions.<sup>14</sup> Therefore, lengthening contractions have been proposed as a possible mechanism for critical illness-associated diaphragm weakness and myotrauma.<sup>4,15</sup> Whether lengthening activations indeed occur in the diaphragm of ventilated critically ill patients was unknown.

To assess the magnitude of active lengthening, we calculated negative work of the diaphragm with pressure-volume loops (**Figure 1**), which quantifies the amount of force generated by the diaphragm while lung volume is decreasing ('lengthening work'). We assume that the diaphragm must lengthen when lung volume decreases. This method is consistent with computing the negative work done by all respiratory muscles using the Campbell-diagram, but is more specific to the diaphragm.<sup>16-18</sup>

We found that the work generated by the diaphragm while lengthening in patients is significantly higher compared with healthy volunteers at sustainable breathing effort (**Figure 3**). The observation that lengthening work per minute is higher in patients compared with healthy subjects, despite the lower Pdi during expiration in the critically ill, is caused by a larger volume decrease during early expiration in these patients. Indeed, lung compliance was lower and peak expiratory flow was higher in patients. (**Tables 1 and 3**).

Whether the magnitude of active lengthening observed in our study is injurious cannot be derived directly from our data. Extreme lengthening contractions induced by supramaximal electrical stimulation cause immediate damage to diaphragm fibers in dogs.<sup>19</sup> Thirteen percent of patients (5/39) generated >4J/min of lengthening work, which is above known ranges for low to intermediate *inspiratory* effort in healthy subjects.<sup>20,21</sup> This level of work during lengthening activation might be injurious, as cyclic eccentric effort equivalent to intermediate exercise for 30 minutes can rapidly cause ~70% decrease in force generating capacity of skeletal muscle in rabbits.<sup>14</sup> Interestingly, the most common ultrastructural damage observed after lengthening contractions is myofibrillar disruption and infiltration of inflammatory cells,<sup>22</sup> which has been observed in diaphragm fibers of critically ill patients in our earlier study.<sup>23</sup>

### **Expiratory Muscle Recruitment, Friend or Foe?**

Our data demonstrate that expiratory muscle recruitment is common in critically ill ventilated patients, occurring intermittently in 66% and continuously in 13% of. Earlier studies found an association between expiratory muscle recruitment and failed weaning, suggesting that the expiratory muscle might be recruited to support the inspiratory muscles, or that expiratory muscle recruitment signifies unsustainable inspiratory load-

ing.<sup>24,25</sup> Whether these patients recruited their expiratory muscles to aid the inspiratory muscles or to overcome expiratory resistance cannot be derived from our data.

Simultaneous recruitment of the expiratory muscles and diaphragm occurred in 15% of the patients (**Figure 4**), significantly more than in healthy subjects (5%). This behavior could signify an uncoupling of the inspiratory and expiratory muscles.<sup>26</sup> Uncoupling of the diaphragm and expiratory muscles may have increased the stress placed on the diaphragm while lengthening, as patients that demonstrate co-activation of the diaphragm and expiratory muscles had higher lengthening work of the diaphragm. Whether this behavior is protective or injurious requires future evaluation.

### **Clinical Implications and Future Directions**

Expiratory diaphragm activity was positively correlated to inspiratory effort and lung compliance, and negatively correlated to inspiratory support in our cohort. These observations suggest that expiratory diaphragm activity might, in part, be caused by under-assistance and early cycling by the ventilator (a type of asynchrony where the ventilator has cycled off while the inspiratory muscles remain active). Providing adequate inspiratory support or adjusting cycling criteria might alleviate expiratory diaphragm activity. Indeed, patients in which inspiratory support was titrated to obtain Pdi between 3-12cmH<sub>2</sub>O had significantly less active lengthening of the diaphragm. Additionally, advanced monitoring of the diaphragm during inspiration *and expiration* might allow a clinician to detect active lengthening of the diaphragm at the bedside, but this requires either a double-balloon (gastric and esophageal) catheter, or monitoring of diaphragm electrical activity.<sup>27</sup> Larger observational studies are needed to assess incidence of lengthening activations of the diaphragm, and animal studies to establish thresholds for intensity of lengthening contractions to induce diaphragm myotrauma. Additionally, lengthening activation of the diaphragm may develop during inspiration if the accessory inspiratory muscles generate relatively more force than the diaphragm, for instance during paradoxical breathing,<sup>28</sup> or with reversed triggering.<sup>29</sup>

### **Strengths and Limitations**

This study has several strengths. It is the first study to convincingly demonstrate the presence of lengthening activations of the diaphragm in ventilated adult critically ill adults, which has been proposed to be a mechanism for diaphragm myotrauma. In the current study, we conducted an in-depth analysis of diaphragm activity during expiration in critically ill patients and healthy volunteers. We used the reference standard measurements for diaphragm and expiratory muscle activity, including both neural drive (Edi processed from raw diaphragm EMG) and pressure generation (esophageal and gastric manometry), and employed novel parameters to assess the magnitude of

active lengthening. Additionally, our analysis includes every breath taken in 24 hours in critically ill patients and at varying levels of breathing effort in healthy volunteers, limiting the chance for selection bias.

Several limitations must be acknowledged. Only 6 out of the 39 patients had an Edi catheter in situ for clinical purposes during the study period. The pressure and lengthening work of the diaphragm was available in all subjects, however. PEEP,  $\text{FiO}_2$  and cycle criteria were not routinely adjusted in the patients, preventing in-depth assessment of whether expiratory diaphragm activity is a reflex to prevent lung collapse or suboptimal patient-ventilator interaction, which should be addressed in future studies. Our data reflects the magnitude of expiratory diaphragm activity and expiratory muscle activity during real life clinical situations. Second, our study designs and the nature of this secondary analysis did not allow us to investigate the clinical impact of lengthening activations of the diaphragm. Third, the critically ill patients were included at a median of 8 days after start of mechanical ventilation. Whether expiratory diaphragm activity and lengthening activations are more frequent in the early course of transition to assisted ventilation requires further evaluation.

## **CONCLUSION**

This study shows that in critically ill patients on partially supported ventilation, lengthening activations of the diaphragm may develop, and can be exacerbated by co-activation of the expiratory muscles. Adjusting ventilator settings may limit development of lengthening activations. This data provides new insight and a strong rationale for further study in this potential mechanism for critical illness-associated diaphragm weakness.

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# **Part III**

## **Synthesis**

9

## **Summary, general discussion and future directions**



## SCOPE AND CONTENTS OF THE THESIS

In this thesis, we aimed to assess and expand the clinician's toolbox to monitor and control lung stress and respiratory muscle effort, with a long-term aim of limiting the detrimental effects of mechanical ventilation on the lungs and respiratory muscles of critically ill patients. To this end, we have thoroughly studied and described the physiology and assessment of respiratory drive and patient breathing effort<sup>1-3</sup>; we have done prospective studies focused on respiratory physiology in healthy subjects and critically ill patients<sup>4</sup>; we have validated surrogate markers for lung stress and diaphragm effort<sup>5</sup>; and we have conducted a randomized-controlled trial in critically ill patients that applied a new ventilation approach.<sup>6</sup> Strictly a supportive tool, mechanical ventilation on its own will not cure a patient. Doing as little damage as possible during mechanical ventilation is therefore imperative, and is in line with the line from the Hippocratic oath 'first, do no harm'.<sup>7</sup>

In this general discussion, we interpret the meaning of our findings in a broader sense. We also provide future directions for lung- and diaphragm-protective mechanical ventilation, and the expiratory phase of breathing.

## EVIDENCE FOR LUNG- AND DIAPHRAGM-PROTECTIVE VENTILATION, A CATCH-22?

An important hypothesis of this thesis was that maintaining moderate levels of breathing effort during mechanical ventilation would limit the development of respiratory muscle atrophy and load-induced muscle injury.<sup>8-10</sup> This 'diaphragm-protective' approach to mechanical ventilation should be combined with the more-established 'lung-protective' approach to mechanical ventilation, which aims to transmit as little energy as possible to the lungs of critically ill patients by applying low tidal volumes, respiratory rates and driving pressures.<sup>11</sup> Indeed, two expert statements and reviews were published on the combined lung- and diaphragm-protective approach to mechanical ventilation while the research for this thesis was being done.<sup>12,13</sup>

### Disuse atrophy

Because of its central role in this thesis, it is fair to critically evaluate the evidence for diaphragm-protective ventilation. The evidence for *disuse-induced* diaphragm atrophy during mechanical ventilation is compelling. As early as 1988, researchers have consistently observed that the cross-sectional area of diaphragm muscle fibers is decreased in patients that have no diaphragm effort, first in children,<sup>14</sup> and later in critically ill

adults.<sup>15</sup> The reduction in cross-sectional area was more pronounced in diaphragm muscle fibers compared with other skeletal muscles, suggesting that the diaphragm is highly susceptible to atrophy.<sup>15</sup> Later, it was shown that diaphragm strength falls rapidly during the first days of ICU admission when measured objectively with induced efforts, a technique that is reliable even in heavily sedated patients.<sup>16</sup> Our group contributed to understanding the pathways involved in the development of diaphragm disuse atrophy on a molecular level by analyzing diaphragm biopsies from critically ill patients, showing a prominent role for the ubiquitin-proteasome pathway.<sup>17,18</sup> Further trials have shown that keeping the diaphragm active during mechanical ventilation reduces the development of diaphragm weakness,<sup>19–22</sup> proving that the atrophy is caused by disuse and not by critical illness per se. Overall, there is a large basis of evidence showing that preventing diaphragm disuse prevents atrophy and diaphragm weakness.

### **Load-induced injury**

While *disuse*-related diaphragm weakness is relatively established, there is much less evidence supporting *load-induced* injury. Histological data from our own group was amongst the first to show infiltration of inflammatory cells in the diaphragms of some critically ill patients, a pattern that is not compatible with disuse atrophy.<sup>17</sup> Additionally, observational ultrasound data found that the thickness of the diaphragm increases in 12% of ICU patients during the first week of mechanical ventilation, possibly consistent with inflammation and edema development due to load-induced injury the diaphragm.<sup>23</sup> Indeed, these patients were found to have elevated diaphragm effort based on ultrasound measurements, much higher than healthy subjects at rest, fitting the ‘load-induced’ injury hypothesis.<sup>23</sup>

### **Patient self-inflicted lung injury**

Another potential benefit of preventing excessive patient effort is to protect the lungs from patient self-inflicted lung injury.<sup>24</sup> Patients often have an immensely elevated respiratory drive during the early phase of critical illness because of hypoxia, acidemia, fear, and irritants in the airways.<sup>1</sup> The elevated drive leads to high respiratory muscle effort and large negative swings in pleural pressure. This negative pleural pressure elevates lung stress and can lead to lung edema, and even cardiac failure.<sup>25</sup> The increased lung edema can worsen hypoxemia, elevating respiratory drive, leading to a vicious cycle. Additionally, vigorous inspiratory efforts might cause a shift of inhaled air within the lungs, increasing inhomogeneous distribution of lung stress, a phenomenon known as ‘pendelluft’.<sup>26</sup> Lowering patient effort with mechanical ventilation, sedatives or muscle relaxants, can potentially break this cycle and prevent its detrimental effects. Preventing excessive patient effort might therefore prevent load-induced diaphragm weakness and patient self-inflicted lung injury.<sup>24</sup> This is one of the cases where the aims of lung-

protection and diaphragm-protection align. Most of the evidence for self-inflicted lung injury stems from animal studies<sup>26-30</sup>; studies in critically ill patients are highly required. Future trials could randomize patients with early respiratory failure to a ‘conservative’ group, in which patients are managed by the clinician’s discretion using the current standards of care, or an ‘early lung-protection’-group, in which patient effort is rapidly brought down with mechanical ventilation, sedatives, and possibly even neuromuscular blockers or extracorporeal carbondioxide removal. Comparing the progression of lung injury in these groups might reveal whether patient self-inflicted lung injury indeed occurs, and whether an early intervention strategy can limit injury.

### **Confounding or causation?**

Finally, there is uncertainty on whether diaphragm weakness is causally related to patient outcomes, or whether it is a marker of disease severity. Multiple observational trials have shown that diaphragm weakness is prominent in critically ill patients, both at admission to the ICU and emerging during mechanical ventilation.<sup>31-33</sup> Other trials have demonstrated that diaphragm dysfunction is associated with poor patient outcomes, including difficult weaning and prolonged ICU admission.<sup>33-35</sup> One observational trial employed advanced statistical methods (mediation analysis) to infer a certain degree of causation between low diaphragm effort, diaphragm weakness and poor outcomes.<sup>36</sup> A single trial showed that weaning duration can be shortened when improving respiratory muscle strength with training, supporting the hypothesis that diaphragm weakness is causally related to poor outcomes, but the patient population was highly selected.<sup>37</sup> More trials are thus much needed.

The best way to definitively prove the hypothesis that moderate diaphragm effort protects against disuse atrophy, load-induced injury and patient self-inflicted lung injury, might therefore be to conduct a large randomized clinical trial. The scientific basis for this trial might depend heavily on expert opinion and physiological reasoning, but better evidence is unlikely to be obtained without conducting larger outcome-centered trials. A classic Catch-22,<sup>38</sup> but the time for larger trials seems to be now.

## **CHALLENGES IN EVALUATING LUNG- AND DIAPHRAGM-PROTECTIVE VENTILATION**

### **Efficacy and effectiveness**

In Part 1 of this thesis, we have done several studies that can contribute to designing definitive trials on whether a lung- and diaphragm-protective approach to mechanical ventilation benefits patients. First, we describe the physiology of respiratory drive and

the techniques to assess patient breathing effort in Chapters 2 and 3, respectively. Next, we conducted a ‘proof-of-concept’ randomized-controlled trial in Chapter 5. The aim of this trial was to evaluate how many patients have breathing effort outside of putative protective ranges, and how often a patient can be titrated to desired ranges using a strict protocol. We used a labor-intensive protocol (that requires a researcher to be present nearly continuously) to monitor lung stress and diaphragm effort using the reference standard measurements based on esophageal manometry. In the intervention group, the settings of the ventilator were adjusted if patients had breathing effort below or above the predefined target range for breathing effort. Our data show that patients are often outside of putative-protective ranges when not using a titration protocol: only 35% of breaths were within the predefined ‘diaphragm-protective’ range in the control group. Patients in the control group were above the target range for effort roughly ~40% of the time. A minority of patients (~15%) had barely any diaphragm effort, even though they were triggering the ventilator. Applying the titration protocol greatly increases time spent within target ranges, as patients in the intervention group were in the diaphragm-protective range in 81% of breaths. It was not possible to reach 100%, as some patients had extremely elevated respiratory drive.

In a sense, this study established the maximal effect that titration of inspiratory pressure can have on obtaining a desired range of breathing effort in close-to-ideal circumstances (efficacy), using the reference standard measurements and a labor-intensive protocol. It was not possible to get 100% of breaths in the target range for diaphragm effort in the intervention group, likely because the respiratory drive of some patients was so elevated that titration of support alone was insufficient. Use of sedatives or partial neuromuscular blockade might have been successful in these patients.<sup>39</sup> The data from our pilot RCT can prove vital for future trials, as it provides a rough estimate of the incidence of unwanted effort, and an estimate of how effective a titration protocol can be.

### **Target ranges**

An important limitation of our study and for future trials, is that the range of diaphragm effort that we targeted in the intervention group was based mostly on physiological reasoning, observational trials and expert-opinion. It is currently unknown how much diaphragm activity is required to prevent disuse atrophy and load-induced injury. Very low effort might be sufficient to prevent disuse atrophy, as healthy subjects generate a Pdi of 1-3 cmH<sub>2</sub>O per breath during tidal breathing and do not develop atrophy.<sup>2</sup> The diaphragm of critically ill patients operate in a muscle-hostile environment, however, with high levels of circulating cytokines, catabolic states, and frequent use of steroids,<sup>40</sup> so it is possible that more effort is required to prevent atrophy in the critically ill compared with healthy subjects. One observational study using ultrasound found that patients

with a thickening fraction of the diaphragm between 25% and 40% per breath have the highest chance to preserve their diaphragm thickness, and have better outcomes.<sup>23,36</sup> Patients with a thickening fraction below 25% tended to develop atrophy, while patients with a thickening fraction above 40% tended to develop an increase in muscle thickness, possibly consistent with load-induced inflammation. The association between ultrasound-derived parameters of diaphragm effort and the reference standard of transdiaphragmatic pressure is rather poor, however, making it difficult to infer a threshold for transdiaphragmatic pressure that leads to diaphragm injury.<sup>41</sup> Until more data is available, it therefore seems reasonable to target diaphragm effort observed in healthy subjects. The target ranges for lung injury are better established, as trials have shown that patient outcomes improve when targeting volumes below 6ml/kg predicted body-weight.<sup>42</sup> Secondary analyses have attempted to further individualize tidal volumes to the compliance of a patient's respiratory system, and found that having low airway driving pressures, which are essential tidal volumes divided by compliance, correlated even better with improved outcomes.<sup>11</sup> There is likely no cut-off after which lung stress and load-induced injury suddenly occur; higher energy transmitted to the lungs leads to a higher risk of lung injury in a sliding scale: the lower the energy transmitted to the lungs, the lower the chance to develop lower injury.<sup>11,43</sup> The same is likely true for load-induced diaphragm injury, where higher effort makes the diaphragm susceptible for injury on a sliding scale, as suggested by ultrasound data.<sup>36</sup> More studies are required to confirm this hypothesis, however.

A potential study design to answer this question is to construct an animal model for respiratory failure, for instance by broncho-alveolar lavage in pigs.<sup>44</sup> Next, pigs would have to be randomized between different groups of diaphragm effort, targeting no effort, diaphragm effort that is physiological for pigs in health, low diaphragm effort between no effort and physiological effort, and three levels of elevated diaphragm effort. Lung stresses would have to be carefully managed to be as equal as possible in all groups to prevent confounding by global inflammation. After several days of mechanical ventilation, diaphragm biopsies could be taken and compared between groups for single fiber twitch strength and ultrastructural damage.<sup>45</sup> Another possibility would be to conduct a comparable study in critically ill patients with actual respiratory failure, but instead of diaphragm biopsies, weaning duration and diaphragm strength at a set day would be a more feasible outcome. As there is clinical equipoise, it would be ethical to conduct such a trial, but ensuring equal lung stresses would be very complex.<sup>6</sup>

### **Bedside estimates of lung stress and diaphragm effort**

The transpulmonary pressure and transdiaphragmatic pressure, the reference measurements for lung stress and patient effort, respectively, are rarely used in clinical care out-

side of research settings and expertise centers.<sup>46</sup> It was therefore imperative to evaluate whether readily-available bedside measurements of lung stress and diaphragm effort could be used in future trials, which we did in Chapter 6. We assessed the occluded airway pressure (Pocc) and the airway occlusion pressure at 100ms (P0.1), as these parameters can be easily obtained with all mechanical ventilators.<sup>47</sup> Our data shows that both Pocc and P0.1 are too imprecise to estimate the exact lung stress and diaphragm effort in critically ill patients, and therefore they cannot replace esophageal manometry in research studies.

Pocc and P0.1 can reliably detect patients with extremes of lung stress and diaphragm effort, however. This is hopeful, as these patients are theoretically most at-risk of developing lung injury and diaphragm weakness.<sup>12</sup> We show that Pocc correlates better with patient effort and lung stress compared with P0.1. Pocc also has better diagnostic accuracy in identifying patients with extremes of lung stress and diaphragm effort. This is important information, as many ICUs currently use P0.1 in routine care, as automatic measurement of P0.1 is integrated in many mechanical ventilators. Our data might encourage clinicians to measure Pocc instead of P0.1 when they want to assess their patient's respiratory effort, aiming at achieving a Pocc between 7 and 15 cmH<sub>2</sub>O. Automatic assessment of Pocc might be included in future mechanical ventilators, or might be added with new software for current ventilators. Future trials on diaphragm-protective ventilation should use Pocc instead of P0.1 if esophageal pressure is unavailable.

### **Effect size estimates**

A final challenge for designing trials on lung- and diaphragm-protective ventilation concerns the difficulty in estimating a reasonable effect size when designing large trials on lung- and diaphragm-protective ventilation powered on outcomes. 'Strong' outcomes, such as mortality, are multifactorial in critical illness and are not only reliant on mechanical ventilation settings.<sup>48,49</sup> Trials in the ICU setting often do not lead to significant differences in mortality because researchers use over-positive effect size estimates when designing trials, even though their interventions target only a single pathway that contributes to poor outcome.<sup>50</sup> It might therefore be practical to focus on 'softer' outcomes with a direct effect on a patient's quality of life, such as diaphragm strength at liberation from ventilation, ventilator-free days at day 28, and total hospital admission time. Previous studies on interventions that targeted respiratory muscle effort were conducted in small, highly selected patients, however, limiting their external validity in regards to effect size estimation.<sup>37</sup> A reasonable effect size for diaphragm-protective ventilation will therefore be an educated guess, to be refined in future trials.

## **FUTURE PERSPECTIVES FOR LUNG- AND DIAPHRAGM-PROTECTIVE VENTILATION**

### **Detecting lung and diaphragm injury**

A problem that has to be addressed in future studies, is how to act when the aims of lung-protection and diaphragm-protection contradict each other. Many patients have excessively high breathing effort when trying to switch from a controlled mode of ventilation to a supported mode, leading to lung stress and diaphragm effort incompatible with lung- and diaphragm-protective ventilation. The solution is often to sedate a patient once again, and to retry the switch to supported ventilation a few days later. The aim of this approach is that the lungs have more time to recover, making them less susceptible to elevated lung stress when allowing patient effort in the next attempt. Respiratory drive might also be lower when the lungs have recovered as irritant receptors give less feedback to the respiratory control centers. This process might be repeated several times, greatly increasing the time spent on mechanical ventilation in these patients.

One potential solution to this problem could be to include lung inhomogeneity when assessing whether the current level of lung stress is injurious or not for the patient at hand. Currently, we assess either the airway driving pressure or transpulmonary driving pressure when we assess lung stress. These parameters provide an estimate of the average lung stress, as they consider the lung to be a single, homogenous compartment.<sup>51</sup> Mathematical theories have suggested that the same lung stress is much more harmful when applied to an inhomogeneous lung.<sup>52-54</sup> This information could be incorporated in lung stress assessment if we can define a score or factor to express the degree of lung inhomogeneity. This factor would likely be based on CT-scan images and/or electric impedance tomography, or perhaps on lung ultrasound if the technique is developed further. Having a better assessment of lung homogeneity might improve our estimate on whether higher 'average' lung stresses might be accepted. Likely, considering homogeneity would cause clinicians to be more mindful of lung-protection during early critical illness, when lung inhomogeneity is highest, and more focused on allowing patient effort again as soon as the lungs become more homogenous.

It would be a tremendous step forward for studies on lung- and diaphragm protective ventilation if chemical analyses are validated to assess ongoing lung and diaphragm injury. In cardiology, multiple sensitive and specific biomarkers have been validated, including troponin and creatine kinase cardiac band (CK-MB), that are used to detect ongoing loss of cardiac myocytes.<sup>55</sup> Sadly, current markers for lung injury, such as RAGE, SP-D ICAM-1 and IL6, are not specific to the lungs and correlate with all inflammation,<sup>56</sup> and studies on markers for diaphragm injury are in its infancy.<sup>57,58</sup> I hope that a protein

specific to diaphragm fibers is identified that can be measured in peripheral blood or urine, to assess whether the diaphragm is currently undergoing atrophy or load-induced injury. For the lungs, I expect that expired volatile organic compound analysis ('E-nose') could provide highly-sensitive and moderately specific biomarkers patterns for ongoing lung injury in mechanically ventilated patients. This technique has already been used with success in detect lung cancer.<sup>59</sup> Translational studies in critically ill patients have been published recently,<sup>60</sup> and larger validation studies in critically ill patients are ongoing.

### **Experimental interventions**

Several experimental techniques to obtain lung- and diaphragm-protective ventilation require further validation. The application of partial neuromuscular blockade could be an effective intervention in patients with excessively high breathing effort. Instead of completely abolishing patient effort with neuromuscular blockers, a careful titration is applied to obtain a respiratory muscle effort and lung stress in a desired range. This strategy was effective in a pilot trial<sup>61</sup>, but it is unknown whether it is feasible in critically ill patients. One of my personal aims is to further validate this strategy in future trials.

Another possible intervention to use in patients with excessively elevated respiratory drive is extracorporeal carbon-dioxide removal. In this technique, large-bore tubes are inserted in a large vein of the patient to pump blood through a parallel circuit containing an artificial lung. This artificial lung extracts carbon-dioxide, after which the blood is returned to the patient's circulation.<sup>39,62,63</sup> Extra-corporeal carbondioxide removal greatly reduces respiratory drive, but increases risk of bleeding and coagulation.<sup>64</sup> Technical improvements might greatly increase the applicability of this intervention.

Neuromuscular stimulation is a promising technique to prevent disuse atrophy by keeping the respiratory muscles active when patients are deeply sedated, especially during early critical illness. This technique has been attempted with success on the expiratory muscle of critically ill patients.<sup>65</sup> Challenges have to be overcome before electrical stimulation can be applied on the diaphragm of critically ill patients, however. Most parts of the diaphragm lie deeper than the expiratory muscles, making it more difficult to stimulate the diaphragm transcutaneously. Internal pacemakers of the diaphragm have been evaluated in case series in human patients<sup>66</sup>, but these require surgical implantation. Transvenous diaphragm pacemakers have been assessed in pigs,<sup>67</sup> and are currently being developed for human application.

A proposal for a lung- and diaphragm-protective approach to ventilation incorporating the techniques discussed above is presented in **Table 1**.

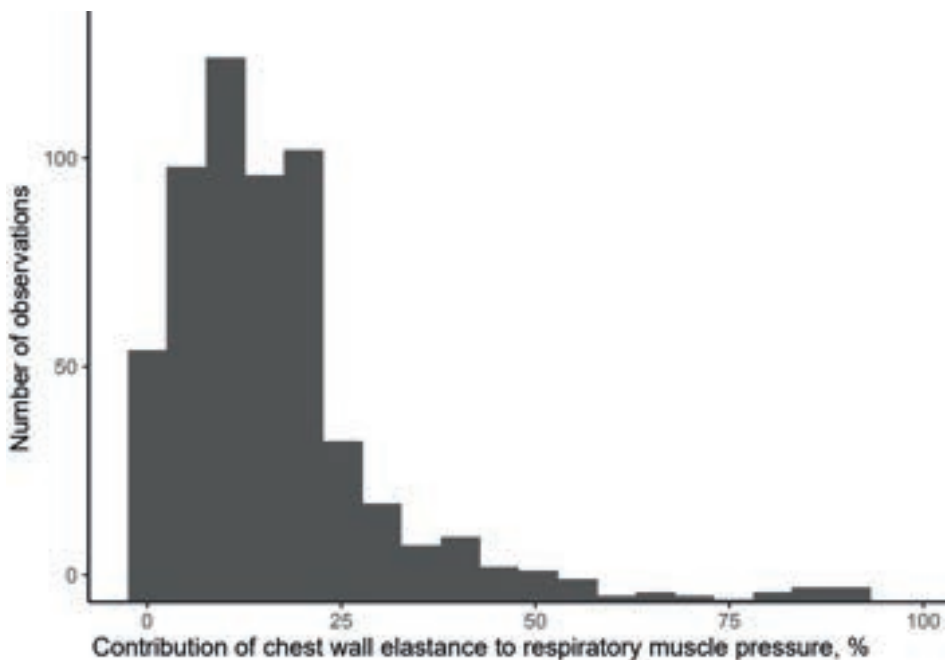
Level	System	Monitoring parameter	Target range	Interventions	Priorities
Basic	Lungs	Tidal volume	6-8 ml/kg	Titration of pressure support	Lung over diaphragm
		Driving pressure	<15 cmH <sub>2</sub> O	Titration of sedatives	
Diaphragm		Estimated PLdyn	<22 cmH <sub>2</sub> O	Neuromuscular blockers	
		Pocc	5-15 cmH <sub>2</sub> O	<i>Partial neuromuscular blockade</i>	
		P0.1	1-4 cmH <sub>2</sub> O		<i>Lung over diaphragm until lung is improving</i>
Intermediate	Lungs	Transpulmonary pressure	<12 cmH <sub>2</sub> O		
Advanced	Diaphragm	Esophageal pressure	5-10 cmH <sub>2</sub> O		
		Electrical activity	5-20 $\mu$ V		
	Lungs	Mechanical power	<12J/min	<i>Extracorporeal CO<sub>2</sub> removal</i>	<i>Balanced approach based on biomarkers and lung homogeneity</i>
		<i>Lung homogeneity</i>	<i>Unknown</i>		
		<i>Biomarkers for lung injury</i>	<i>Unknown</i>		
Diaphragm		Respiratory muscle pressure	Pmus 5-15 cmH <sub>2</sub> O	<i>Electrical stimulation of the diaphragm</i>	
		Transdiaphragmatic pressure	3-12 cmH <sub>2</sub> O		
		Gastric pressure	<2 cmH <sub>2</sub> O		
		Work of breathing	<2J/breath		
		Pressure-time product	50-150 cmH <sub>2</sub> O*s/min		
		Biomarkers for diaphragm injury	<i>Unknown</i>		

**Table 1 legend:** Proposal for a lung- and respiratory-muscle protective approach to mechanical ventilation. Items printed in *italic* require further research.

### Transdiaphragmatic pressure, a golden reference standard?

Another point that has to be addressed in the future is the validity of transdiaphragmatic pressure, the current reference standard for diaphragm effort. Transdiaphragmatic pressure is calculated by subtracting pleural pressure from abdominal pressure, which in clinical practice means to subtract esophageal pressure from gastric pressure. The assumption is that the thorax and abdomen are two compartments, separated only by a completely flaccid diaphragm. Any pressure difference between these compartments is attributed to contractile activity of the diaphragm. This presents some theoretical problems.

First, transdiaphragmatic pressure does not take elastic or resistive forces into account. This differs from the respiratory muscle pressure, which includes the pressure needed to overcome chest wall elastance (respiratory muscle pressure = chest wall recoil pressure – pleural pressure). The elastic recoil pressure of the chest wall on average contributes to 15% of respiratory muscle pressure, but can contribute up to 90% in critically ill patients with stiff chest walls due to edema, pleural effusions or obesity (**Figure 1**).



**Figure 1. Contribution of chest wall elastance to respiratory muscle pressure.** Unpublished data from the DiaPro cohort, including data from 23 patients in whom chest wall elastance was measured. Note that median contribution of chest wall elastance to respiratory muscle pressure is 15%, but that it can range up to 90% in select patients.

It is puzzling that we currently assume that the diaphragm and accessory muscles need to overcome this pressure when we assess them simultaneously, while we ignore this pressure when we assess the diaphragm individually. Likewise, the elastance of the abdominal wall is currently not included in transdiaphragmatic pressure, even though this might influence how much force is required to obtain a pressure change in the abdomen. This might mean that transdiaphragmatic pressure underestimates the force generated by the diaphragm.

Another problem with transdiaphragmatic pressure is the assessment of tonic diaphragm activity. Tonic diaphragm activity might be a relevant phenomenon to protect lung patency,<sup>44</sup> but could also contribute to active lengthening, a proposed mechanism for critical illness-induced diaphragm weakness.<sup>40</sup> When assuming that any difference in pressure between the abdomen and pleural cavity is due to diaphragm contractile activity, it should follow that a baseline diaphragm pressure above 0 cmH<sub>2</sub>O reflects tonic diaphragm activation. However, even after total muscle paralysis, transdiaphragmatic pressure is seldom exactly 0 (mean transdiaphragmatic pressure during paralysis was  $3.2 \pm 2.4$  cmH<sub>2</sub>O, unpublished data from 5 subjects). Thus, the baseline transdiaphragmatic pressure does not seem to reflect tonic diaphragm activity. This can likely be attributed to differences between actual pleural and abdominal pressure compared with esophageal and gastric pressure, respectively, due to the elastance of the esophageal and gastric wall.

Perhaps future techniques can better assess the actual force generated by the diaphragm. Speckle tracking or strain measurement have been validated for cardiac contractions, and pilot studies have evaluated the techniques in the diaphragm.<sup>68,69</sup> Technical improvements are required before these techniques can be implemented in research studies, however. It will be difficult to prove that these techniques outperform transdiaphragmatic pressure, as comparative experiments would by convention use the transdiaphragmatic pressure as the reference standard. If experiments can prove that new measurements of diaphragm force generation have a stronger correlation with oxygen consumption of the diaphragm, or with the amount of diaphragm injury after strenuous exercise, then perhaps transdiaphragmatic pressure can be dethroned.

## **EXPIRATION, NEGLECTED NO MORE**

Most of the studies on mechanical ventilation and respiratory muscle function in the ICU focused on the diaphragm and the inspiratory phase of breathing. To remedy this knowledge gap, we have evaluated the expiratory muscles and the expiratory phase of

breathing in critically ill patients as well in our studies. We summarized the currently knowledge of expiratory muscle function and pathophysiology in critical ill patients in the preamble to part 2. This review shows that expiratory muscle recruitment can have beneficial and detrimental effects in critically ill patients. Expiratory muscle recruitment might assist the inspiratory muscles when the load on the respiratory system increases, thereby preserving minute ventilation. On the other hand, expiratory muscle recruitment might contribute to lung collapse, expiratory flow limitation and air trapping.<sup>3</sup> As is often the case, ‘the dose seems to make the poison’. This review also underlines that it is important to take expiratory muscle recruitment into account when assessing inspiratory muscle recruitment, because expiratory muscle recruitment influences the inspiratory drop in esophageal pressure and the assessment of PEEPi.

Sadly, recruitment of the expiratory muscle is seldom assessed in clinical care and is often overlooked in research studies as well. This is likely because the reference standard, gastric pressure measurement, requires expertise and a dedicated measurement setup.<sup>3</sup> In Chapter 7, we show that ultrasound might be an interesting alternative to assess the expiratory muscles, by showing that measuring the thickness of the expiratory muscles with ultrasound has excellent intra- and interrater reproducibility.<sup>4</sup> Future studies will have to assess whether the change in thickness of the expiratory muscles during expiration correlates to the gastric pressure.

This study also demonstrates that the expiratory muscles decrease in thickness during the first week of mechanical ventilation in 22% of the patients, consistent with atrophy, which had not been described previously. We observed an association between hospital length-of-stay and the decrease in expiratory muscle thickness. Whether this is a causal relation or whether expiratory muscle atrophy reflect disease severity requires further study. Notably, we found that there was no correlation between development of diaphragm atrophy and expiratory muscle atrophy, suggesting that these are completely separate phenomena. Last, this study showed that the thickness of the fasciae of the expiratory muscles increased in 12% of the patients, which was a novel and unexpected finding. No study before had assessed the fasciae of the respiratory muscles. The intramuscular fasciae are a highly organized tissue that plays a crucial role in absorption and transmission of muscle force.<sup>70,71</sup> Biopsy studies are required to elucidate the role of the muscle fasciae in the regulation of muscle function in critically ill patients.

In chapter 8, we combined our acquired knowledge on inspiratory and expiratory muscle assessment by conducting a secondary analysis on data from healthy subjects and critically ill patients. Our aim was to test whether the diaphragms of critically ill patients remain active during expiration, and whether this activation leads to active lengthening.

Expiratory diaphragm activity had been observed in critically ill infants<sup>72,73</sup> and in pigs with ARDS,<sup>44</sup> but whether it occurred in human adults was unknown. Our data show that the diaphragm remains active during expiration in more than half of all patients, and in all of the healthy subjects. This behavior in healthy subjects is consistent with the post-inspirational control of breathing. Post-inspirational activity ceases in healthy subjects when respiratory demands increase to allow for faster expiration <ref breathing matters>. Interestingly, the magnitude of expiratory diaphragm recruitment in critically ill patients was associated with lung compliance: patients with stiffer lungs had more expiratory diaphragm recruitment. This could be consistent with a physiological reflex, wherein the diaphragm attempts to prevent lung collapse in critical illness. We did not adjust PEEP and FiO<sub>2</sub> settings in our study, however, so further validation is required. If expiratory diaphragm activity is indeed a beneficial reflex to increase lung aeration, then our findings might influence ventilator management in the future. For example, we might ‘ramp down’ from inspiratory pressure to PEEP to mimic expiratory diaphragm activation. Another possibility is to use NAVA, a proportional mode of mechanical ventilation, and to keep applying the proportional factor during expiration. Currently, the proportionality of NAVA is switched off as soon as expiration begins, either based on flow or on a maximum of electrical activity compared with the peak of the breath.

We also demonstrate that critically ill patients have more active lengthening than healthy subjects. Whether the magnitude of active lengthening observed in our study is injurious requires further study. Future animal studies might induce a wide range of active lengthening, after which diaphragm biopsies could be done to assess the effect of active lengthening on a structural level.

## CONCLUSION

In this thesis, we aimed to evaluate and improve the tools available to a clinician to obtain lung- and diaphragm-protective mechanical ventilation in critically ill patients. We have discussed the physiology of respiratory drive, the assessment of patient effort, and have shown that it is possible to obtain lung- and diaphragm-protective mechanical ventilation in a highly controlled setting. Additionally, we have shown that the expiratory muscles require more attention in future studies, by demonstrating that the expiratory muscles are at risk of developing atrophy, and that the diaphragm remains active during expiration. I therefore think that ‘lung- and diaphragm-protective’ ventilation should be extended, and instead encompass all the respiratory muscles: Lung- and respiratory muscle-protective ventilation.

Personally, I have learned an incredible number of new skills while doing my PhD research, ranging from conducting physiological measurements, performing signal analysis and statistics, to organizing large projects, designing trials, performing peer reviews and speaking for large audiences. I hope to use these skills to contribute to improving care for critically ill patients. I look forward to doing so in the next decades!

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# Appendices



## ACKNOWLEDGEMENTS / DANKWOORD

Op een dag loop je als onbezorgde coassistent de kamer van de prof op ('hij heet Leo, komt net over uit Nijmegen en heeft nog een project, misschien is het wat?'), en voor je het weet is het 7 jaar later en schrijf je het dankwoord van je proefschrift in de studeerkamer terwijl je vrouw en baby dochtertje op de kamer ernaast liggen te slapen. Wat vliegt de tijd!

Met het afronden van deze laatste paragrafen van mijn proefschrift sluit ik indirect ook een periode van mijn leven af. Een periode waar ik vrijwel elke dag enorm van heb genoten. Al tijdens de bachelor wist ik dat ik tijdens mijn carrière ook de wetenschap wilde bedrijven, en daar heb ik geen spijt van gehad. De mogelijkheid om je ergens vier jaar lang volledig in onder te kunnen dompelen is een bevoorrechtte kans. De vrijheid waarmee dit gepaard ging was heerlijk, en bij vlagen zelf overweldigend. Tot ik aan mijn promotietraject begon was er eigenlijk altijd een uitgestippeld pad geweest om te volgen, met duidelijke korte termijn doelen (volgende tentamen halen, volgende coaschap volbrengen, et cetera). Tijdens mijn promotietraject had ik voor het eerst een langertermijn doel, en mocht ik grotendeels zelf bepalen hoe ik daar kwam. Er was natuurlijk een project omschrijving, maar de invulling daarvan lag voor mijn gevoel altijd open. Daardoor was er niet alleen meer vrijheid dan ooit, maar ook meer verantwoordelijkheid. Ik denk dat precies die twee zaken, vrijheid en verantwoordelijkheid, hetgeen zijn waarvan ik het meest heb geleerd tijdens mijn promotie, en het meest heb genoten.

Ik zal altijd met plezier terugdenken aan de dagen waarop ik op mijn gemakje een ingewikkeld artikel tot op de bodem kon uitpluizen. Of aan het spannende gevoel als na maanden hard werken de data er is, en de eerste analyses en figuren op je scherm verschijnen. Ik kijk zelfs weemoedig terug naar de 40 nachten die ik op een matje op de promovendi kamer heb doorgebracht om de meetopstelling elke twee uur te controleren, hoewel ik daar op het moment zelf niet altijd even gelukkig mee was. Er waren ook momenten dat ik er helemaal klaar mee was, bijvoorbeeld toen ik weer fulltime in de kliniek ging werken en frequent in de weekenden nog aan indieningen of revisies moest werken. Maar aan het eind was dat het allemaal waard en ben ik trots op het resultaat!

Promoveren doe je niet alleen. Natuurlijk is er een groot aantal mensen die ik wil bedanken voor deze prachtige periode uit mijn leven.

Ten eerste wil ik alle patiënten en hun naasten bedanken voor het deelnemen aan het onderzoek. Dit werd toegestaan onder de zeer hevige omstandigheden van een IC

opname. Veel dank, zonder jullie was dit onderzoek niet mogelijk geweest. Ook wil ik alle gezonde vrijwilligers bedanken voor deelname aan de studies.

Dan mijn promotor, **prof. dr. Leo Heunks**. Beste Leo, wat een enorme mazzel heb ik gehad dat jij mijn promotor was! Je bent in meerdere opzichten een groot voorbeeld voor mij en iedereen om je heen. Ten eerste ben je een gedreven en getalenteerd wetenschapper. Je bent altijd zeer enthousiast over de projecten waar je mee bezig bent, en het lukt je om iedereen om je heen mee te nemen in je enthousiasme. Hierbij weet je hechte teams te smeden die samen voor een doel gaan. Je hebt me geleerd om altijd goed te kijken naar de ruwe data, en om dat eerst te snappen voordat er analyses en figuren gemaakt worden. Je blijft altijd kritisch, ook op eigen werk, maar weet bevindingen ook op waarde te schatten. Je probeert nieuwe dingen te leren van elk project, juist als de data andere patronen lieten zien dan we verwacht hadden. Ten tweede ben je een toegeweid begeleider. Je hebt mij steeds precies genoeg vrijheid gegeven om mijn eigen pad te kiezen, maar je deur stond altijd open voor advies of gewoon een praatje. De gevleugelde uitspraak ‘Heb je vijf minuten?’ was vaak het begin van een uren durende discussie. Je wakkerde mijn enthousiasme aan, maar wist ook de haalbaarheid in zicht te houden. Ik waardeer ook erg dat je al de promovendi continu kansen hebt gegeven om te groeien buiten de directe projecten om, bijvoorbeeld door samen peer reviews te doen, of door ons uit te nodigen om bij te dragen aan colleges of masterclasses. Ten derde ben je een empathische arts, die zich tomeloos inzet voor elke patient. Daarbij neem je altijd de tijd om familie uit te leggen wat er speelt en neem je ze mee in je beslissingen, op een manier die voor iedereen te volgen is. Verder ben je een enthousiaste leraar, die de meest ingewikkelde materie simpel weet uit te leggen. Je hebt me geleerd om een presentatie nooit klakkeloos te herbruiken, maar om altijd te proberen er zelf weer iets van te leren. Als laatst ben je ook nog eens een gezellig persoon om mee naar de kroeg te gaan en het over andere zaken dan werk te hebben! Dank voor al deze dingen, ik heb er veel van geleerd. Ik was van plan om op dit punt in het dankwoord nog een steek onder water uit te delen over je voorkeuren qua stad en voetbalteam, maar dat lijkt me precies dit jaar niet zo’n heel goed idee.

Mijn copromotoren **dr. Angélique de Man** en **dr. Pieter Roel Tuinman**. Bedankt dat ook jullie deur altijd voor me open stond. Het was altijd een plezier om met jullie samen te werken, zowel in het onderzoek als in de kliniek. Jullie hebben vele uren tijd gestoken in het lezen en becommentarieren van al mijn stukken, die zeker in het begin lang en wollig waren. De feedback was altijd scherp op de inhoud maar zacht op de persoon, en heeft eraan bijgedragen dat mijn stukken leesbaarder werden en mijn denkproces logischer. **Angélique**, dank in het bijzonder voor de grote aandacht en zorgvuldigheid waarmee je dit alles gedaan hebt. **Pieter Roel**, dank dat je altijd de hoofdlijnen en volgorde van mijn

manuscripten in het oog hield, en dank dat ik altijd met je kon sparren over onderzoek, de kliniek, en levenskeuzes.

Drie personen die ook bijzonder belangrijk zijn geweest in het mogelijk maken van mijn promotie zijn **prof. dr. Armand Girbes**, **Grace Koningstein** en **Hendie Deijkers-Slotboom**. Beste **Armand**, dank voor de mogelijkheid om mijn promotieonderzoek op jouw afdeling te mogen uitvoeren. Jouw vertrouwen in het ‘respiratieteam’ zijn essentieel geweest voor de integratie in de kliniek. De inzet voor de belangen van de afdeling en de Intensive Care zorg in het algemeen hebben grote indruk op me gemaakt. Ook zal ik je wijze lessen over ‘precies genoeg doen’ en de weerbaarheidstrainingen niet vergeten. **Lieve Grace**, zonder jou was er ook nooit iets van mijn onderzoeken terecht gekomen. Je was de spin in het web op de IC, alles wat ik niet wist kwam ik aan jou vragen. En negen van de tien keer loste jij het direct op. Verder stond je deur ook altijd open om te kletsen, had je een goed gevulde snoeppot, en wist je alle roddels. Je was van onschatbare waarde! **Hendie**, ook jij stond altijd klaar om praktische zaken te regelen en deed dit altijd met een glimlach. Dank daarvoor.

De leden van de promotiecommissie **prof. dr. Francis de Man**, **prof. dr. Diederik Gommers**, **prof. dr. Alexander Vlaar**, **dr. Hieronymus van Hees** en **prof. dr. Harm Jan Bogaard**. Dank voor de kritische beoordeling van mijn proefschrift, ik kijk er naar uit om tijdens de verdediging met jullie te sparren over de stukken.

Mijn collega-promovendi van de IC, die ik nu allemaal tot mijn vrienden reken. Jullie hebben er in hoge mate aan bij gedragen dat ik elke dag met veel plezier naar werk ging! **dr. Annemijn Jonkman**, lieve Annie, vanaf dag één hebben we intensief samengewerkt in vrijwel alle projecten die we deden. We werden vaak Jut en Jul genoemd als we weer eens aan kwamen zetten met oesofagusballonen en ons ‘kindje’, de BIOPAC-meetopstelling. Samen waren we de uitvoerende kant van het respiratieteam. We konden ook oneindig praten over andere dingen dan research. Ik heb de oren van je kop gekletst op de Exciting Research kamer, waarbij je af en toe heel suggestief een noise-cancelling koptelefoon opzette als het genoeg was. Je was een groot voorbeeld voor je vakgebied van technisch geneeskundige door echt de brug te slaan tussen de kliniek, technologie en onderwijs. Ook kan je het langst van alle promovendi planken op de vrijdag middag. Jouw ondersteuning bij Matlab en je talent om figuren te maken waren ook van grote waarde voor mijn proefschrift. door jou zijn de uitspraken ‘poah!’ en ‘probleem’n? poar neem’n!’ onderdeel geworden van mijn vocabulaire. Ik kijk er naar uit om in de toekomst te blijven samenwerken! **Bijna-dr. Sander Rozemeijer**, lief Sandertje. Jij werd later onderdeel van de Exciting Research kamer als vitamine C-onderzoeker, en dat is maar goed ook. Als je er vanaf dag één was geweest hadden we nu nog geen letter op

papier gehad. Wij hadden het vooral over zaken die niks met onderzoek te maken hadden. Je platte maar scherpe humor en aanstekelijke lach hebben vooral voor vertraging gezorgd, maar ik zou het niet anders gewild hebben! Ik hoop dat we in de toekomst nog gaan samenwerken, al is het voor alle partijen beter als we niet meer bij elkaar op één kamer zitten. Als er ooit iemand moet flyeren voor me in de Berghain weet ik je te vinden!

**dr. Zhong-Hua Shi**, dear Hua. When we met you were already an intensivist, but this never stopped you from enjoying live in Amsterdam and doing research like a true student. You are curious, smart, funny and hard-working. I greatly enjoyed our discussion about the differences in Chinese and Dutch culture, and our dinners together with Mickey. I hope to keep collaborating in the future!

**Myrte Wennen**, lieve Myrte. Je begon als master student bij Annemijn, maar werd al snel promovenda door je doorzettingsvermogen en enthousiasme. Je bent nieuwsgierig, zorgvuldig en zachtaardig. Ik weet zeker dat je je promotie met succes en plezier gaat afronden.

**dr. Diana Jansen**, ik ken niemand die zo hard kon werken en zo weinig slaap nodig had als jij. Ontzettend knap dat je je promotie volledig naast je opleiding tot anesthesioloog hebt afgerond, maar als iemand dat kon was jij het!

**dr. Harm Jan de Grooth** en **dr. Bob Smit**. Jullie waren al bijna klaar toen ik begon en waren dus automatisch de senioren met voorbeeldfunctie. **Harm Jan**, dank voor alle prikkelende discussies die we gevoerd hebben over statistiek, fysiologie en het ongrijpbare begrip causaliteit. Jouw talent om ingewikkelde analyses helder uit te leggen en tactisch antwoord te geven op peer-reviewers is van grote waarde geweest. We zullen in de toekomst zeker nog samenwerken. **Bob**, jij bleef altijd positief over onderzoek, zelfs als alle resultaten anders waren dan gedacht. Ook heb ik zelden zo'n snelle groei in bankdruk-vermogen gezien als bij jou aan het einde van je promotie.

The-boys-next-door, de 'data scientists' dr. **Lucas Fleuren**, **Luca van Roggeveen**, **dr. Tingjie Guo** en **Bart van Dijk**. **Lucas**, af en toe hoor ik nog steeds in gedachten jouw typerende lach over de gang bulderen. Je was altijd vrolijk en bereid om te sparren over vanalles. Verder ben je iemand die vol overgave zijn eigen weg kiest en alles met een succes volbrengt, ga zo door! En laat het duidelijk zijn, elke wetenschapper werkt met data, de term 'data scientist' slaat inherent nergens op. **Luca**, je bent eigenzinnig en komt op waar je voor staat. Soms vuriger dan handig is, maar altijd met passie! Ik wens je veel succes met je eigen bedrijf. **Tingjie**, dank voor alle leuke discussies over

taal en grafische kaarten. Fantastisch dat je een aanstelling hebt in Leiden, ik hoop dat je nog lang hier bij ons blijft! **Bart**, je besloot enkele maanden nadat we elkaar leerde kennen dat promoveren niet het pad voor je was, en hebt op eigen kracht je weg naar de Intensive Care weer gevonden. Ik denk dat deze route veel beter bij je past, we zien elkaar op de werkvloer!

Ook met jullie opvolgers **Ameet Jagesar, Tariq Dam, Amne Moussa** en **Martijn Otten** heb ik vele gezelligheid beleefd, ik wens jullie veel succes met het afronden van jullie promoties. Begin op tijd met het maken van jullie boekje, is mijn advies.

De echo-boys **dr. Mark Haaksma, Jasper Smit** en **dr. Mica Heldeweg**, ook wel bekend als Pieter Roel's Angels. **Markie Mark**, the real diaphragm star. Je begon als student bij Pieter Roel, maar wist me toch op rechts in te halen en bent eerder gepromoveerd. Ook lag je altijd goed bij alle verpleging en kreeg je daardoor alles voor elkaar. Als ik ooit vragen heb over echo of het middenrif ben jij degen die ik zal bellen. **Jasper**, jij nam de tijd om goed over alles na te denken en ook echt de natuurkunde te begrijpen. Ik denk dat de radiologie goed bij je past, ik zal je bellen als er weer eens een D-dimeer verhoogd is. **Mica**, cityboy, jij bent door je promotie heen gerold en doet precies waar je zin in hebt, ga zo door!

**Dr. Jenny Juschten**, lieve Jenny. Je hoorde niet duidelijk bij een van de bovenstaande promovendi-teams, maar was toch duidelijk onderdeel van de groep. We delen een voorliefde voor techno en Berlijn. Ook wij zullen elkaar nog zeker tegenkomen, misschien op de werkvloer en anders op de dansvloer.

**YingRui Zhang**, dear YingRui. You were very brave to come to the Netherlands to do research, and you did great! Thank you for all your help with the studies. I am sure you have a great career ahead of you.

**Ilias Attaye**, we gingen zo vaak naar de sportschool maar zijn nog steeds niet vierkant. We houden vol!

Middenrif-onderzoekers **prof. dr. Coen Ottenheijm** en **dr. Marloes van den Berg**. Beste **Coen**, dank voor alle discussies over de basale fysiologie en de gezellige borrels. Je hebt een feilloos instinct voor nieuwe, unieke richtingen voor het middenrif onderzoek, en ik weet zeker dat we in de toekomst nieuwe projecten gaan doen. Lieve **Marloes**, jij had altijd oneindige energie en enthousiasme. Ik denk dat dat je goed van past komt in Amerika, het land van de bravoure!

Alle TG'ers die direct of indirect hebben bijgedragen aan mijn projecten, en die ik nog niet genoemd heb: **Jonne Doorduyn, Babette van de Werff, Judith Elshof, Esmee de Boer** en **Minke Holleboom**. Dank voor jullie hulp, en veel succes en jullie verdere carrière! Ik weet zeker dat de technische geneeskunde in toenemende mate een belangrijke rol gaat spelen in de gezondheidszorg.

Verder wil ik alle stafleden van de Intensive Care van het VUmc bedanken die ik nog niet genoemd heb: **Paul Elbers, Jack Haitzma, Eric Lust, Patrick Thorat, Jan Jaap Slijkstra, Evelien van der Heijden, Birkitt ten Tusscher, Harry Gelissen en Sandra Stapel**. Dank dat jullie mij betrokken bij de behandeling van patienten met lastige ademmechanica, en dank voor het sparren over de klinische toepassing van het onderzoek. Ook alle AIOS uit de tijd dat ik promoveerde wil ik bedanken voor hun hulp, gezelligheid en vertrouwen.

Research-verpleegkundige **Erna Alberts** en **Ingrid van den Hul**. Ik kon altijd bij jullie terecht voor logistieke vragen, hulp bij metingen en natuurlijk de laatste roddels. Ik verliet jullie kamer altijd met een glimlach. **Ronald Driessen**, bedankt voor alle ondersteuning bij opvragen van data uit Epic, en voor je inzichten in de opstelling van Ajax.

Ook alle verpleegkundigen van de Intensive Care wil ik bedanken. Jullie hielpen me altijd met de metingen, zelfs als de apparatuur hopeloos in de weg stond, en hielden me gezelschap tijdens de 'nachtdiensten'.

Alle assistenten, stafleden en verpleegkundigen van de vooropleiding Interne in het OLVG, inclusief de cardio en de IC, dank voor de prachtige tijd! Mede door jullie had ik elke week weer zin om aan de slag te gaan, ook als ik weer hele weekenden aan revisies had gewerkt. Ook dank aan de assistenten, stafleden en verpleegkundigen van de longziekten van AmsterdamUMC, het voelde als thuiskomen toen ik hier weer aan de slag ging.

Verder wil ik mijn vrienden **Mark Vuurberg, Jelle Bruin en Luc Severeijns** bedanken voor de nodige afleiding tijdens de promotie. De frequente avonden kaarten, bierdrinken en stappen, en de mooie vakanties gaven me elke keer weer energie. Ook wil ik iedereen van mijn waterpolovereniging **De Dolfijn** bedanken, en in het bijzonder mijn (ex-)teamgenoten **Sebastiaan Lambalk, Joost Krommenhoek, Timothy Lont, Misja Langeler, Willem Sjerps, Nick Stocker, Felix Kraneveld, Tarek Othman, Jan Poel, Jan Roest, Marco Tuijnman, Arno Wartenbergh, Robert Muller, Thomas van Lammeren, en Eric Romeijn**, en hun **fantastische vriendinnen en vrouwen**. De avonden

in het clubhuis, de barbecues, de vakanties, de festivals, en soms zelfs waterpolo, het zijn elke keer hoogtepunten waar ik energie en steun uit haal. Veel dank!

Mijn familie **Henk de Vries, Ingrid van Westing, Myrthe en Naomi, en alle aanhangsels**. Zusjes, jullie zijn fantastisch! We hebben het als kind al gezellig gehad met elkaar, en zien elkaar nu steeds meer door de groeiende familie. **Myrthe**, je hebt een heerlijk gezinnetje met Baba Ali en mijn drie lieve nichtjes Kaileena, Ariana en Iselin. Je scherpe humor en inzicht in taal blijven me verrassen. **Naomi**, je bent een fantastische tante voor Femke. Ook jij kiest lekker je eigen pad in het leven, ga zo door! **Vaders**, je bent altijd een inspiratie geweest. Een betrokken arts, een bevlogen onderwijzer en schrijver, een kritisch wetenschapper en ook nog eens de beste vader (en opa!) op aarde die altijd voor ons klaar stond, ik had niet beter kunnen wensen. Tijdens mijn promotie heb ik vaak met je gespard over stukken, en had je altijd scherpe inzichten. Ik was als kind altijd al trots dat jij boeken schreef 'voor de dokterschool'. Nu heb ik er ook eentje geschreven, en ik weet zeker dat jij nu trotst bent. **Mama**, ook jouw onvoorwaardelijke steun, zorg en liefde zijn van groot belang voor mij. Je luisterde altijd naar ons en stimuleerde ons om te doen wat we wilden. Je staat positief in het leven en hebt ons geleerd altijd open te staan voor iedereen. Ook ben je een fantastische oma voor al je kleinkindjes!

Mijn schoonouders **Rolf en Eljoma van Dam**, en zwager **Lucas**. Dank dat ik altijd welkom ben, en er dan een pak Strawberry Hill klaar staat. Ik voel me altijd thuis bij jullie. Mijn katten **Edgar en Toulouse**, jullie harige koppies en dolle streken vrolijken me altijd op.

Dan als laatste **Carmen van Dam**. Al ruim 12 jaar ben je mijn steun en toeverlaat. Je bent mijn beste vriendin, mijn echtgenote, mijn vaste spar- en discussiepartner, en sinds kort ook de moeder van ons kindje. Het begon als echte kalverliefde tijdens de opleiding, maar ondertussen is ons relatie zo sterk als staal. Zonder jouw hulp met dingen plannen, vaak tot frustratie aan toe, was ik nooit gekomen waar ik nu was. Je kan altijd honderd ballen tegelijk in de lucht houden, en vergeet dan ook niet aandacht te besteden aan je familie en vrienden. Sinds kort hebben ons prachtige **Femke**, waar jij een geweldige moeder voor bent. Ik ben super benieuwd hoe ze wordt als ze opgroeit! Ik kijk uit naar de rest van mijn leven samen met jou. Dit boek draag ik dan ook aan je op, het was zonder jou nooit gelukt.



## PHD PORTFOLIO

Name PhD student: Heder de Vries

PhD period: 2017 - 2021

Supervisor & co-supervisors: Leo Heunks, Pieter Roel Tuinman, Angelique de Man

### 1. PhD training

	Year	ECTS
<b>General courses</b>		
- Research integrity	2017	1.0
- Data management	2017	0.15
- BROK (Basis Regelgeving en Organisatie voor Klinisch onderzoekers)	2017	1.5
- Time management	2017	0.70
- Scientific Writing in English	2019	3.0
- Statistics with R	2019	3.0
<b>Specific courses</b>		
- EPIC for clinical researchers	2017	0.40
<b>Seminars, workshops and master classes</b>		
- LIVES Masterclass Mechanical Ventilation	2018	2.0
- Patient controlled ventilation	2017	0.25
<b>Presentations</b>		
- TOPICS in IC (invited speaker, national congress)	2017	0.3
- ESICM (abstract presentation, international congress)	2018	1.0
- Foshan rehabilitation congress (invited main speaker, Chinese national congress)	2019	2.0
- ERS (invited speaker, international masterclass)	2020	2.0
<b>(Inter)national conferences attendee</b>		
- Lage Landen (LaLa) congress	2017	0.25
- ESICM	2018	
- ESICM	2019	
<b>Other</b>		
- Monthly research meetings ACS research institute	2017-2021	1.0
- Weekly research meetings Diaphragm Research Group	2017-2021	4.0
- Supervision by and discussions with PhD team	2017-2021	3.0
- Conducting peer reviews for international journals	2020-2021	0.5
- ACS PhD Retreat (attendee and abstract presentation)	2019	1.0

### 2. Teaching

	Year	ECTS
<b>Lecturing</b>		
- EDIC I exam trainer, lectures about hypoxemia	2020	1
- Lectures about mechanical ventilation for the bachelors of Medicine and Biomedical Sciences	2018-2019	0.3
<b>Tutoring, Mentoring</b>		
- Thesis mentor for Master students of Medicine	2018	2.0

## Appendices

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### Supervising

- |  |           |     |
|--|-----------|-----|
| - Supervising two Medicine students and one Technical Medicine student during their scientific internship in the Intensive Care, including writing of the theses | 2018-2020 | 2.0 |
|--|-----------|-----|
- 

### Other

- |   |           |   |
|---|-----------|---|
| - Giving unwanted lectures on random topics to my roommates to distract myself from doing actual work | 2017-2021 | 0 |
|---|-----------|---|
- 
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### 3. Committees

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	Year	ECTS
- Member of the ACS PhD teaching committee	2017-2020	2.0
- Chairman of ProVUmc, the PhD committee of VUmc	2018-2020	2.0

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**Total ECTS:** 36.35

## LIST OF PUBLICATIONS

1. Wüst RCI, **de Vries HJ**, Wintjes LT, Rodenburg RJ, Niessen HWM, Stienen GJM: Mitochondrial complex I dysfunction and altered NAD(P)H kinetics in rat myocardium in cardiac right ventricular hypertrophy and failure. *Cardiovasc Res* 2016; 111:362–72
2. Jansen D, **de Vries HJ**, Heunks LMA: Acetylcholine receptor antagonists in acute respiratory distress syndrome: Much more than muscle relaxants. *Crit Care*. 2018; 22(1):132.
3. **de Vries HJ**, Jonkman A, Shi Z-H, Spoelstra-de Man A, Heunks L, Vries H de, Jonkman A, Shi Z-H, Man AS, Heunks L, de Vries HJ, Jonkman A, Shi Z-H, Man AS, Heunks L: Assessing breathing effort in mechanical ventilation: physiology and clinical implications. *Ann Transl Med* 2018; 6:387–387
4. **de Vries HJ**, Jonkman AH, Tuinman PR, Girbes ARJ, Heunks LMA: Respiratory Entrainment and Reverse Triggering in a Mechanically Ventilated Patient. *Ann Am Thorac Soc* 2019; 16:499–505
5. Shi Z-HZ-H, Jonkman A, **de Vries HJ**, Jansen D, Ottenheijm C, Girbes A, Spoelstra-de Man A, Zhou J-XJ-X, Brochard L, Heunks L: Expiratory muscle dysfunction in critically ill patients: towards improved understanding. *Intensive Care Med* 2019; 45:1–11
6. Jonkman AH, Roesthuis LH, Boer EC De, **de Vries HJ**, Girbes ARJ, Hoeven JG Van Der, Tuinman PR, Heunks LMA: Inadequate assessment of patient-ventilator interaction due to suboptimal diaphragm electrical activity signal filtering. *Am J Respir Crit Care Med*. 2020;202(1): 141-144.
7. **de Vries HJ,\*** Jonkman AH,\* Heunks LMA: Physiology of the Respiratory Drive in ICU Patients: Implications for Diagnosis and Treatment. *Crit Care*. 2020; 24(1):104
8. Jongh FHC de, **de Vries HJ**, Warnaar RSP, Oppersma E, Verdaasdonk R, Heunks LMA, Doorduyn J: Ventilating two patients with one ventilator: technical setup and laboratory testing. *ERJ Open Res* 2020; 6:00256–2020
9. Jonkman AH, Frenzel T, McCaughey EJ, McLachlan AJ, Boswell-Ruys CL, Collins DW, Gandevia SC, Girbes ARJ, Hoiting O, Kox M, Oppersma E, Peters M, Pickkers P, Roesthuis LH, Schouten J, Shi Z-H, Veltink PH, **de Vries HJ**, Shannon Weickert C, Wiedenbach C, Zhang Y, Tuinman PR, Man AME de, Butler JE, Heunks LMA: Breath-synchronized electrical stimulation of the expiratory muscles in mechanically ventilated patients: a randomized controlled feasibility study and pooled analysis. *Crit Care* 2020; 24
10. Shi Z, **de Vries HJ**, Vlaar APJ, Hoeven J Van Der, Boon RA, Heunks LMA, Ottenheijm CAC: Diaphragm Pathology in Critically Ill Patients with COVID-19 and Postmortem Findings from 3 Medical Centers. *JAMA Intern Med*. 2021; 181(1):122-124.
11. Withers A, Man TCC, D’cruz R, **de Vries HJ**, Fisser C, Ribeiro C, Shah N, Hollebecke M Van, Vosse BAH, Heunks L, Patout M: Highlights from the respiratory failure and mechanical ventilation 2020 conference. *ERJ Open Res*. 2021 Feb 8;7(1):00752-2020
12. **de Vries HJ,\*** Shi ZH,\* Grooth HJ De, Jonkman AH, Zhang Y, Haaksma M, Ven PM Van De, Man AAME De, Girbes A, Tuinman PR, Zhou JX, Ottenheijm C, Heunks L: Changes in Respiratory Muscle Thickness during Mechanical Ventilation: Focus on Expiratory Muscles. *Anesthesiology* 2021; 134:748–59
13. Jansen D, Jonkman AH, **de Vries HJ**, Wennen M, Elshof J, Hoofs MA, Berg M Van Den, Man AME De, Keijzer C, Scheffer GJ, Hoeven JG Van Der, Girbes A, Tuinman PR, Marcus JT, Ottenheijm CAC, Heunks L: Positive end-expiratory pressure affects geometry and function of the human diaphragm. *J Appl Physiol* 2021; 131:1328–39
14. Haaksma ME, Smit JM, Heldeweg MLA, Nootgedacht JS, Atmowihardjo LN, Jonkman AH, **de Vries HJ**, Lim EHT, Steenvoorden T, Lust E, Girbes ARJ, Heunks LMA, Tuinman PR: Holistic Ultrasound to Predict Extubation Failure in Clinical Practice. *Respir Care* 2021; 66:994–1003

## Appendices

15. Nossent EJ, Schuurman AR, Reijnders TDY, Saris A, Jongerius I, Blok SG, **de Vries HJ**, Duitman JW, Vonk Noordegraaf A, Meijboom LJ, Lutter R, Heunks L, Bogaard HJ, Poll T van der: Pulmonary Procoagulant and Innate Immune Responses in Critically Ill COVID-19 Patients. *Front Immunol.* 2021; 12:664209.
- 16a. **de Vries HJ**, Jonkman AH, Grooth HJ de, Duitman JW, Girbes ARJ, Ottenheim CAC, Schultz MJ, Ven PM van de, Zhang Y, Man AME de, Tuinman PR, Heunks LMA: Lung- and Diaphragm-Protective Ventilation by Titrating Inspiratory Support to Diaphragm Effort: A Randomized Clinical Trial. *Crit Care Med* 2022; 50:192–203
- 16b. **de Vries HJ**, Grooth HJ De, Heunks LM: The authors reply. *Crit Care Med.* 2022; 50(9):e732-e734
17. Jonkman AH, Holleboom MC, **de Vries HJ**, Vriends M, Tuinman PR, Heunks LMA: Expiratory Muscle Relaxation-Induced Ventilator Triggering: A Novel Patient-Ventilator Dyssynchrony. *Chest.* 2022; 161(6):e337-e341.
18. Dam TA, Roggeveen LF, Diggelen F van, Fleuren LM, Jagesar AR, Otten M, **de Vries HJ**, Gommers D, et al.: Predicting responders to prone positioning in mechanically ventilated patients with COVID-19 using machine learning. *Ann Intensive Care.* 2022; 12(1):99.
19. **de Vries HJ**, Tuinman PR, Jonkman AH, Liu L, Qiu H, Girbes ARJ, Zhang Y, Man AME De, Grooth HJ De, Heunks L: Performance of Noninvasive Airway Occlusion Maneuvers to Assess Lung Stress and Diaphragm Effort in Mechanically Ventilated Critically Ill Patients. *Anesthesiology* 2023; 138:274–88
20. **de Vries HJ**, Drummond G: Neuromuscular Blockade Improves Results in Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med.* 2024; 209(5):478-481
- 21a. **de Vries HJ**, Jonkman AH, Holleboom MC, Grooth HJ de, Shi Z, Ottenheim CA, Man AM de, Tuinman PR, Heunks L: Diaphragm Activity During Expiration in Ventilated Critically Ill Patients. *Am J Respir Crit Care Med.* 2024; 209(7):881-883.
- 21b. **de Vries HJ**, Heunks L: Reply to Akoumianaki et al.: Diaphragm Activity During Expiration in Ventilated Critically Ill Patients – Expiratory Asynchrony Is Important. *Am J Respir Crit Care Med* 2024. ePub ahead of print.

\*shared first authorship

## CURRICULUM VITAE

Heder de Vries was born in Amsterdam in 1992, and has lived there ever since. His parents Henk de Vries and Ingrid van Westing are both general practitioners (huisarts), who had met each other at the Vrije Universiteit during a social event of the medical faculty (MFVU). He has fond memories of his childhood in Osdorp where he lived with his parents, his sisters Myrthe and Naomi, multiple cats, and a piano. After finishing gymnasium at the 'Nicolaas Lyceum' in Amsterdam, Heder did not know what to study. He had broad interests ranging from biology and computer sciences to languages and history. In the end, he decided to be incredibly original and started to study Medicine at the same faculty as his parents. Continuing his streak of originality, he met his girlfriend (now wife!) Carmen van Dam at the Medical faculty, at a social event of the MFVU.

At the end of his medical internships (coschappen), Heder once again did not know which direction to go as he enjoyed a wide variety of specialties in the medical field, ranging from internal medicine, cardiology and neurology to surgery and gynaecology. He decided to do a final internship at the Intensive Care Department of the VU, which immediately felt like a bull's eye. At the ICU, he could treat patients using knowledge from almost all fields of medicine combined with state-of-the-art technology. He met Leo Heunks, a pulmonologist-intensivist who had just accepted a position of professor (Hoogleraar) at the department. After a few brief discussions they worked out that a PhD trajectory would be a great follow-up, and luckily a grant was available for a fulltime position.

Heder greatly enjoyed his time as a PhD candidate at the Intensive Care department, owing to all the cheerful times 'working' with his peers, the limitless 'short' discussions with his supervisors, and the direct integration of his acquired knowledge into clinical practice. After four years of PhD training, he started his medical specialization as a pulmonologist first at the OLVG and then at AmsterdamUMC, while finishing his PhD on the side.

Apart from work, Heder plays the piano, is goalkeeper in a waterpolo team, enjoys long discussions at the bar with friends and strangers, infrequently attends techno parties, and likes to play videogames (but never has the time anymore). He currently lives happily in Amsterdam with his wife Carmen, baby daughter Femke, two cats and a piano.