MONITORING THE DIAPHRAGM IN CRITICALLY ILL PATIENTS USING ELECTROMYOGRAPHY:

INTERPRETING THE EAdi SIGNAL AND QUANTIFYING PATIENT EFFORT

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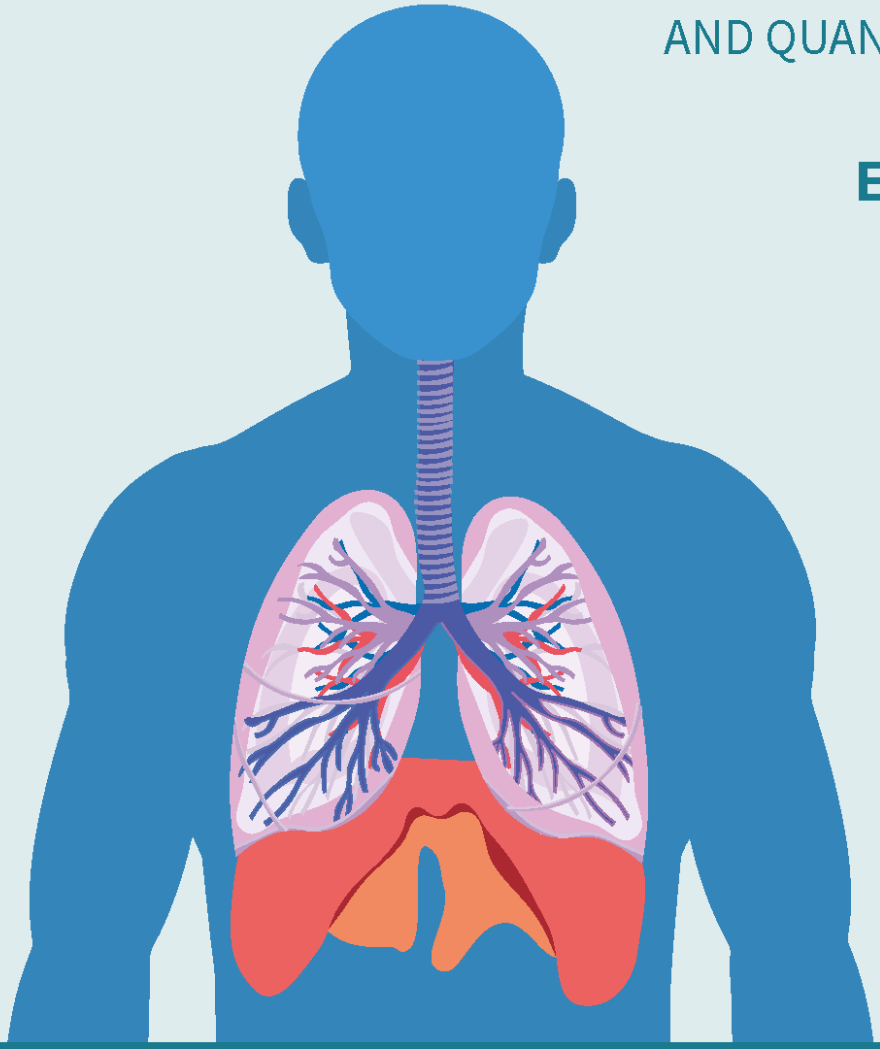

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Monitoring the diaphragm in critically ill patients using electromyography:

interpreting the EAdi signal and quantifying patient effort

Esmée C. de Boer

Preface

Beste lezer,

Voor u ligt mijn afstudeerthesis van de master Technical Medicine, waar ik heb gekozen voor de richting Medical Sensing and Stimulation, aan de Universiteit Twente. De afgelopen 11 maanden heb ik rondgelopen op de Intensive Care Volwassenen van Amsterdam UMC, locatie VUmc. Ik heb genoten van dit jaar en heb enorm veel geleerd, waarvoor ik een aantal mensen wil bedanken.

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Ik hoop dat u deze thesis met veel plezier zal doorlezen.

Met vriendelijke groeten,
Esmée de Boer

Abstract

INTRODUCTION: Diaphragm protective ventilation requires monitoring of patient effort. Multiple techniques have been developed to do so, including diaphragmatic electromyography (EAdi) and oesophageal manometry. However, widespread adaptation of these techniques at the bedside is currently limited, due to for instance technical difficulties in signal filtering and complex interpretation of waveforms. In addition, EAdi does not provide a direct measure of breathing effort. Aims of this thesis were to improve understanding of the EAdi signal processing (study 1) and to translate this signal to a functional measure (study 2). At last, this thesis aims to improve the reliability of oesophageal pressure (Pes) measurements (study 3), which are validated using expiratory holds.

METHODS: The three studies listed above are tested in mechanically ventilated patients (study 1, n=4 and study 3, n=10) or healthy subjects (study 2, n=15). Study 1 compared the EAdi signal on one hand to electromyograms (EMG) with cardiac artefacts and on the other hand to transdiaphragmatic pressure (Pdi) signals (or Pes if Pdi was not available). As such, it was investigated whether peaks with a small amplitude, that were seen in the EAdi signal, were functional diaphragmatic contractions. Study 2 correlated EAdi to the pressure generated by the respiratory muscles (Pmus), a measure for patient effort. Data were obtained by applying increasing levels of inspiratory threshold loading, ranging from 10% to 80% of maximal Pdi. The relationship was assessed using linear regression. In study 3 a continuous ratio of airway pressure (Paw) and Pes was calculated during patient effort under an expiratory hold. In doing so, the minimal duration of an expiratory hold sufficient to verify Pes measurements was determined.

RESULTS: Analysis showed that the small amplitude peaks seen in the EAdi signal are no functional diaphragmatic contractions, but are rather disturbances caused by depolarisation of the heart. Using improved filtering techniques, we found that the correlation between EAdi and breathing effort varied among subjects and could not be predicted using physiological parameters. The correlations did not improve when correcting for flow. Regarding the Pes measurements, the Paw/Pes ratio became close to unity during an expiratory hold after a median of 198 ms [IQR 84-364 ms] after onset of patient effort. This yields a gain in time of 676 ms [IQR 392-828 ms] with regard to applying an expiratory hold until Pes and Paw reach a minimum.

CONCLUSION: We conclude that (1) the algorithm of Maquet ventilators to compute EAdi is insufficient in filtering cardiac disturbances. Optimisation of the algorithm improves EAdi signal quality, increasing its reliability and possibly leading to clinical implementation of EAdi monitoring parameters. Furthermore, (2) the EAdi signal cannot yet be used to estimate patient effort at the bedside. Including factors that influence the relationship between EAdi and patient effort, such as thoracoabdominal configuration, might improve the correlation. Last, (3) the duration of an expiratory hold to verify Pes measurements can be reduced. The proposed method might be embedded in the ventilator software, allowing near continuous calculation of the Paw/Pes ratio in the future and hence, improving reliability of Pes measurements.

List of abbreviations

ARDS	Acute respiratory distress syndrome
AUC	Area under the curve
Ccw	Compliance of the chest wall
CMV	Continuous mandatory ventilation
COPD	Chronic obstructive pulmonary disease
CSV	Continuous spontaneous ventilation
$E_{0.1}$	Electrical activity in the first 100 ms of a diaphragmatic contraction
EAdi	Electrical activity of the diaphragm
ECG	Electrocardiogram
EMG	Electromyogram
ICU	Intensive care unit
IMV	Intermittent mandatory ventilation
IQR	Interquartile range
MV	Mechanical ventilation
NAVA	Neurally adjusted ventilatory assist
NME	Neuromuscular efficiency
NVE	Neuroventilatory efficiency
$P_{0.1}$	Airway pressure in 100 ms after start of patient effort
Pab	Abdominal pressure
Pao	Airway opening pressure
Paw	Airway pressure
Pcw	Pressure over the chest wall
Pdi	Transdiaphragmatic pressure
Pes	Oesophageal pressure
PEEP	Positive end-expiratory pressure
PEEPi	Intrinsic positive end-expiratory pressure
Pi,mean	Mean inspiratory pressure
Pi,max	Maximal inspiratory pressure
Pga	Gastric pressure
P_L	Transpulmonary pressure
Ppl	Pleural pressure
Pmus	Pressure generated by all respiratory muscles
Pmo	Mouth pressure
Pplat	Plateau pressure
PTP	Pressure-time product
PVBC	Patient-ventilator breath contribution
RMS	Root mean square
Tee	Thickness at end expiration
Tei	Thickness at end inspiration
TF	Thickening fraction
TTI	Tension-time index
VC	Vital capacity
VIDD	Ventilator-induced diaphragm dysfunction
VILI	Ventilator-induced lung injury
Vt	Tidal volume
WOB	Work of breathing

Table of contents

1 - Introduction

Mechanical ventilation (MV) is a lifesaving intervention in patients with acute respiratory failure and is the cornerstone of modern intensive care unit (ICU) care. Almost 50% of the ICU patients in the Netherlands is mechanically ventilated, a therapy that is started based on acute respiratory failure, caused by e.g. coma, acute exacerbation of chronic obstructive pulmonary disease (COPD) and neuromuscular disorders [9, 10]. Respiratory failure results from an imbalance between respiratory load and inspiratory muscle capacity [2]. By taking over the patient's work of breathing, MV restores this balance and improves gas exchange [2, 11].

Despite these benefits, the application of MV may cause complications. The therapy may give rise to ventilator-associated pneumonia, tracheal injuries, haemodynamic compromise and/or lung injury. The latter is called ventilator-induced lung injury (VILI) [10, 12]. To limit VILI a lung protective ventilation strategy is developed, aiming to limit the amount of mechanical stress that is applied to the lungs by the ventilator or by the patient's own effort [10, 12, 13]. To prevent overdistension of the lung, the clinician targets and limits parameters as Vt and Pplat and PEEP is used to prevent atelectasis and injury from inspiratory stretch [14]. Prolonged ventilation is associated with increased length of stay on the ICU, morbidity and mortality and therefore one should not postpone the initiation of weaning. While postponing of weaning can lead to complications, premature onset of it also has its risks, such as severe cardiopulmonary decompensation [15]. Therefore, the moment of when one begins with weaning is important.

Regarding the diaphragm, MV may induce ventilator-induced diaphragm dysfunction (VIDD), a loss of diaphragmatic force-generating capacity specifically linked to the use of MV [16]. VIDD is associated with atrophy, oxidative modifications, structural injury and muscle fibre remodelling and has adverse effects on clinical outcomes in critically ill patients and weaning from the ventilator [16, 17]. Therefore, diaphragm-protective ventilation is developed to prevent VIDD [17, 18]. This strategy strives to maintain an appropriate level of inspiratory diaphragmatic effort while avoiding potentially injurious forms of patient-ventilator asynchrony. The optimal level of diaphragm effort is unknown, but it is thought that it is best to maintain a relatively low effort similar to that of healthy individuals [19]. VIDD is namely caused by both high and low levels of breathing effort [17]. As a consequence, diaphragmatic-protective ventilation requires direct monitoring of diaphragmatic effort.

There are several tools for monitoring diaphragm effort. First, using ultrasound the function of the diaphragm can be assessed. Thickness of the diaphragm can be tracked over time and diaphragm contractile effort can be represented with the thickening fraction, the percentage increase in thickness during inspiration [20]. Although ultrasound is non-invasive and widely available, the technique requires training and provides intermittent data [21]. Second, in the oesophagus manometry measurements can be performed, providing oesophageal pressure (Pes). When adding gastric pressure measurements, transdiaphragmatic pressure (Pdi) can be monitored. These manometry measurements are the gold standard of measuring inspiratory effort under MV and give direct output. However, placement of an oesophageal balloon and interpretation of the results require expertise [22]. Third, the electrical activity of the diaphragm (EAdi) can be calculated from diaphragmatic electromyography (EMGdi), measured with surface electrodes or electrodes embedded on a nasogastric tube [23]. EAdi represents neural drive, but as normal values are not determined yet and the algorithm to obtain EAdi from EMGdi is not yet optimal, interpretation of the measurements is difficult and clinical use is hampered [5, 11]. Fourth, a non-invasive, reliable method to measure respiratory drive during MV is airway occlusion pressure [19].

EAdi represents phrenic nerve activity and thus neural drive, while the other methods described above are caused by this neural drive [24]. Hence, the time between actual initiation of a breath and measuring the initiation of this breath is shorter when using EAdi compared to e.g. oesophageal manometry. Furthermore, the algorithm by which EAdi is calculated from EMGdi can be optimized, which will increase reliability of the EAdi signal. Last, if less catheters are needed for clinical care patients will have more freedom of movement, with its own advantages, including increased patient comfort. Therefore, this thesis focuses primarily on the EAdi signal: on further understanding this signal and quantifying inspiratory effort using EAdi. Furthermore, the validation procedure of oesophageal manometry measurements is discussed in this thesis.

2 - Research questions

This thesis primarily focusses on the EAdi signal, but also other monitoring methods are studied. Therefore, multiple research questions will be answered.

Small amplitude peak study

As the activity of the diaphragm (EAdi) is closely correlated with neural drive and can be measured continuously, it seems a reliable source of measuring patient effort [11]. However, as can be seen in 1, peaks with a low amplitude (red arrows) are seen in the EAdi signal of which the origin is unknown, but subject of debate. During neurally adjusted ventilatory assist (NAVA) these small amplitude peaks can cause inspiratory flow, which is wanted if the small amplitude peaks are caused by diaphragmatic depolarisation. However, if the origin is e.g. crosstalk of adjacent muscles or noise due to cardiac depolarisation, it is not wanted that these small amplitude peaks cause inspiratory flow. Therefore, the origin of the small amplitude peaks should be determined and to do so, the following research question is drawn up:

What is the origin of the small amplitude peaks in the Maquet filtered EAdi signal of mechanically ventilated ICU patients?

It is hypothesised that the small amplitude peaks are artefacts due to inadequate filtering of cardiac disturbances. To test this, the following subquestions are formulated:

1. Are the small amplitude peaks caused by the diaphragm?
2. If so, has this diaphragmatic depolarisation functional meaning?

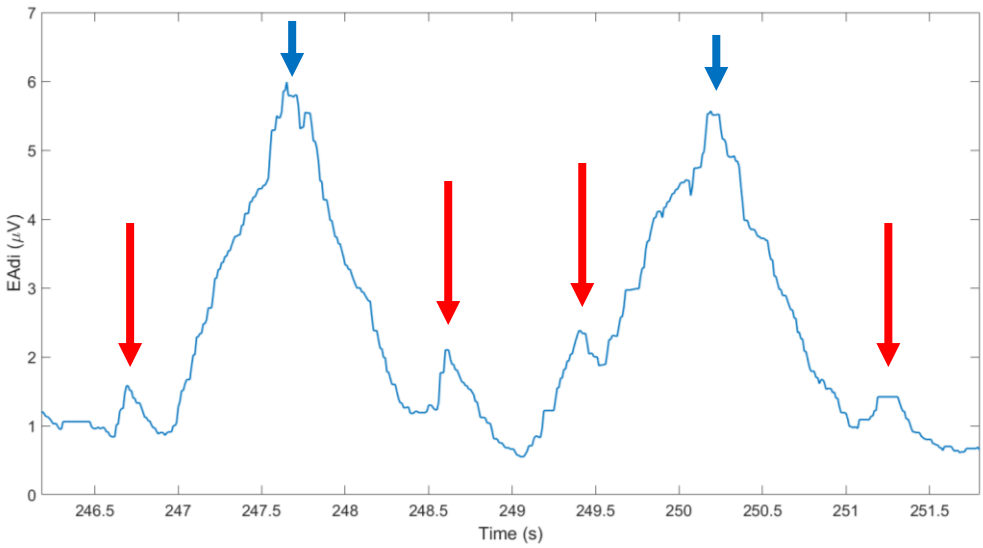

Figure 1: Electrical activity of the diaphragm of a patient with two diaphragmatic contractions, indicated with the blue arrows. The origin of the small amplitude peaks, indicated with red arrows, is unknown.

Edi2Pdi study

The pressure generated by the respiratory muscles (Pmus) is a measure for patient effort and is based on Pes measurements [8]. Although Pes measurements acquired with an oesophageal balloon catheter are extensively used for research purposes, they are not used routinely in clinical care [25]. This is due to limitations of the oesophageal balloons, such as their filling volume. Therefore, another measure could be used to estimate Pmus. The correlation between EAdi and patient effort is well described [4, 6, 8, 26]. In 2013 Bellani et al. found a linear relationship between EAdi and Pmus in patients in a supported mode of ventilation [8], which is described in more detail in the Technical background. However, this was only in a small

range of effort, as Pmus ranged from 0 to 10 cmH_2O. Therefore, we tested whether EAdi can give us an estimate of Pmus in a broad physiological range. Furthermore, in earlier analysis done in previous graduation research the relationship between EAdi and Pdi was investigated. We continue this project by aiming to find a conversion factor to compute Pdi from EAdi.

Can EAdi provide a clinical relevant estimation of patient effort?

The following subquestions are drawn up in order to answer this question:

1. Can a conversion factor be found to estimate Pdi based on EAdi?
2. What is the relationship between EAdi and Pmus in healthy volunteers?

Baydur study

As said, oesophageal balloon catheters are used to measure Pes. To validate the position and filling volume of an oesophageal balloon, the Baydur manoeuvre is performed. An expiratory hold is applied for at least one breath, during which the ratio of airway pressure (Paw) and Pes is measured. During the expiratory occlusion, the change in Paw and Pes should be identical as there is no change in lung volume and thus no change in P_L. Therefore, Pes measurements are considered reliable when the Paw/Pes ratio has a value between 0.8-1.2 [27]. However, it is unknown if a shorter expiratory hold could be sufficient for validation of Pes measurements. Since this would be beneficial as it is less uncomfortable for patients and might allow near continuous calculation of this ratio by the ventilator in the future, it lead to the following research question:

What is the minimal duration of an end-expiratory hold in order to obtain a reliable Paw/Pes ratio in ICU patients on partially-supported modes of ventilation?

Answering these three research questions will give insights on the functioning and monitoring of the diaphragm. As such, this graduation research contributes to the final goal of increasing comfort of the patient during mechanical ventilation and reducing harmful effects of mechanical ventilation by being able to set the settings of the ventilator more in accordance with the patient's demand.

3 - Clinical background

Respiratory system

The main function of the respiratory system is facilitating the exchange of oxygen and carbon dioxide between the human body and the atmosphere. This is accomplished by integrating the following processes: pulmonary ventilation (the inward and outward movement of air in the lungs), gas exchange in the lungs and tissues, transport of gases by the blood and overall regulation of respiration [28]. Figure 2 shows the different elements of the respiratory system and relevant pressures, which will be described next.

The lungs have the tendency to collapse, which is known as elastic recoil. On the contrary, the chest wall tends to pull the thoracic cage outwards, thus having an elastic recoil pressure opposite to the lungs. In equilibrium the elastic recoil pressures of the lungs and chest wall are equal, keeping the thoracic cavity at the same volume. The chest wall and lungs are not connected directly, but via the intrapleural space. As the elastic recoil of the lungs and chest wall is opposite, the pleural pressure (Ppl) is less than atmospheric pressure [1]. Hence, in equilibrium Ppl is negative.

A change in the balance between the elastic recoil pressures of the lungs and chest wall causes a change in volume of the thoracic cavity. Activation of respiratory muscles, including the diaphragm, intercostal muscles, abdominal muscles and accessory muscles, lowers Ppl. This causes a pressure gradient relative to atmospheric pressure and consequently, air flows into the lungs. Furthermore, the elastic recoil pressure of the lungs is affected by pulmonary disease, e.g. pulmonary fibrosis [1].

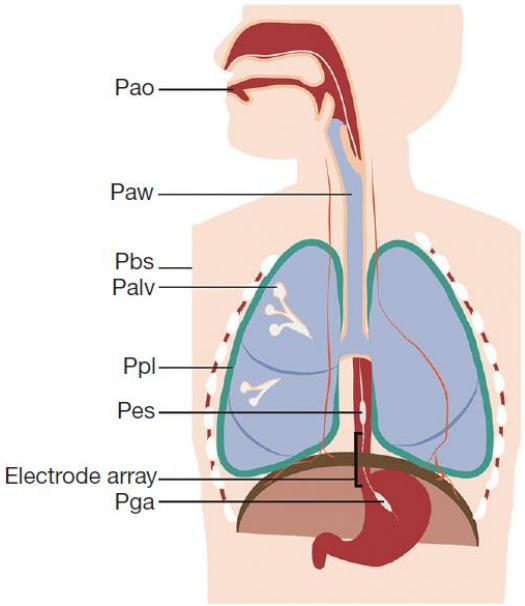

Figure 2: Schematic presentation of the respiratory system and relevant pressures [2].

Physiology of spontaneous breathing

During quiet inspiration the diaphragm contracts, causing the thoracic cavity to increase and the abdominal cavity to become smaller. As a consequence, Ppl drops and abdominal pressure (Pab) increases, causing a pressure gradient over the diaphragm: transdiaphragmatic pressure (Pdi) [29]:

$$Pdi = Pab - Ppl \quad (1)$$

In clinical practise, Pab is substituted by gastric pressure (Pga) and Ppl by oesophageal pressure, as Pab and Ppl cannot be measured directly. Although the pressure is not uniform throughout the pleural space due to gravity and regional inhomogeneities, Pes is a useful estimation of Ppl in the dependent lung regions [14]. The decrease in Ppl leads to a pressure difference over the lungs: transpulmonary pressure (P_L), resulting in inspiration. P_L can be calculated by subtracting Ppl from the airway opening pressure (Pao):

$$P_L = Pao - Ppl \quad (2)$$

During higher effort or a forced inspiration the accessory muscles of inspiration are used: scalene muscles, sternocleidomastoid muscles, neck and back muscles and upper-respiratory-tract muscles. Contraction of these muscles contributes to decreasing Ppl [1, 2]. Also relaxation of the accessory expiratory muscles helps to decrease Ppl [28].

Quiet expiration is passive, achieved by relaxation of the inspiratory muscles. However, during a forced expiration or if airway resistance is increased (e.g. during asthma) expiratory muscles are used: abdominal muscles (internal and external oblique, rectus abdominis and transverse abdominis), internal intercostal muscles and neck and back muscles. Contraction of the abdominal muscles increases Pab, forcing the diaphragm to move cranially, which on its turn elevates Ppl, and as such expiratory driving pressure [1]. Furthermore, the internal and external obliques and rectus abdominis result in downward movement of the lower rib cage, increasing Ppl [30].

Changes in Ppl cause changes in P_L, which ultimately drives ventilation. Ppl is dependent on the pressure generated by the respiratory muscles (Pmus) and the pressure gradient over the chest wall (Pcw):

$$\Delta Ppl = \Delta Pmus + \Delta Pcw \quad (3)$$

Like this, the pressure generated by all of the respiratory muscles can be calculated as follows:

$$\Delta Pmus = \Delta Ppl - \Delta Pcw = \Delta Ppl - \frac{\Delta V}{Ccw} \approx \Delta Pes - \frac{\Delta V}{4\%\ VC} \quad (4)$$

where ΔV is the tidal volume, Ccw chest wall compliance and VC the vital capacity, the maximal amount of air a person can breathe out after a maximal inspiration [2, 31]. Ccw can be calculated as the slope of a pressure-volume loop, made with Pes during passive inflation under controlled mechanical ventilation. However, in order to do so, spontaneous activity of the patient should be halted with heavy sedation or by hyperventilating the patient. Alternatively, it is widely accepted to estimate Ccw as 4% of vital capacity, in which is corrected for age, gender and height and the assumption is made that Ccw is linear over the range of volumes that is studied [31].

Just like other skeletal muscles, respiratory muscles are stimulated by neural excitation at the motor endplate. The muscle membrane (sarcolemma) is depolarised by this stimulus, causing actin and myosin filaments to slide, resulting in shortening of the muscle. Physiological relationships that can influence muscle contraction are the force-length relationship, force-velocity relationship and the force-frequency relationship. The force-length relationship indicates that the length of a muscle before contraction influences the amount of force that can be generated by the muscle. At the optimal length maximal force can be generated. For the inspiratory muscles the optimal length is near residual volume, while the optimal length of the expiratory muscles is at total lung capacity. The interaction between velocity of muscle shortening and frequency of stimulation on one hand and the force that can be generated by the muscle on the other hand are covered in the force-velocity and force-frequency relationships, respectively [30].

Regulation of ventilation

Ventilation is controlled by respiratory centres in the central nervous system, located primarily in the medulla. The ventilatory control mechanism not only establishes the automatic rhythm for contraction of the respiratory muscles, but also adjusts this rhythm to adapt to

changes in metabolic demand, mechanical conditions (e.g. changing posture) and non-ventilatory behaviour (e.g. speaking) [1]. The phrenic nerve transmits the action potentials from the central nervous system to the diaphragm, the main respiratory muscle [1, 32].

Anatomy of the diaphragm

The diaphragm is a double-dome shaped muscle of 2-3mm thick in healthy adults, which separates the thoracic and abdominal cavities. The domes are innervated by the left and right phrenic nerve, which both arise from C3 through C5 [30, 33]. The diaphragm consists of muscle fibres that converge onto a central tendon. Based on the insertion of the muscle fibres the diaphragm is divided into three parts, see Figure 3. First, the muscle fibres of the sternal diaphragm insert along the xiphoid process. Second, the muscle fibres of the crural diaphragm attach to lumbar vertebral bodies. The crural diaphragm is comprised of the left and right crus, which form the oesophageal hiatus. Third, the fibres inserting on the inferolateral rib cage form the costal diaphragm. The muscle fibres of the costal diaphragm that directly appose to the lower rib cage are known as the zone of apposition. Diaphragmatic contraction leads to shortening of the zone of apposition, causing the central tendon to move caudally [1, 30].

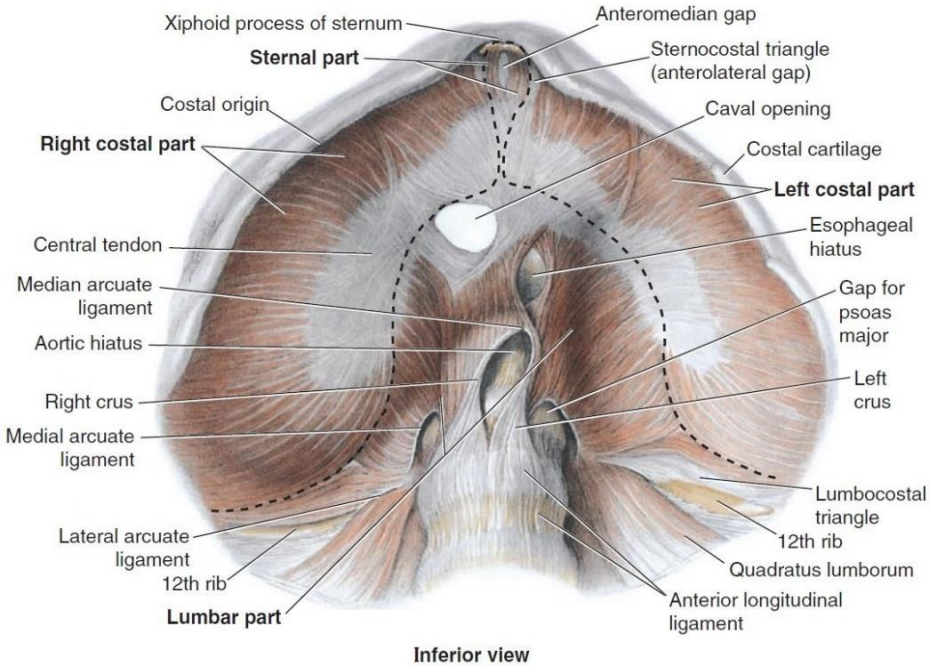

Figure 3: Anatomy of the diaphragm [1].

Acute respiratory failure

Almost half of the ICU patients in the Netherlands is mechanically ventilated [9]. The therapy is started in patients with acute respiratory failure, whose respiratory system cannot maintain adequate gas exchange. Acute respiratory failure can be divided based on failure in oxygenation or carbon dioxide exchange. In type I respiratory failure, or hypoxaemic respiratory failure, the lungs cannot oxygenate mixed venous blood sufficiently, resulting in an arterial oxygen pressure lower than 60 mmHg. The most common underlying pathophysiological mechanisms are shunting and a ventilation-perfusion mismatch. Causes of type I respiratory failure include acute respiratory distress syndrome and COPD. Type II respiratory failure, or hypercapnic respiratory failure, refers to the failure of the lungs to eliminate carbon dioxide. This results in respiratory acidosis (pH < 7.35) and an arterial carbon dioxide pressure higher than 50 mmHg. The pump function of the respiratory system fails, causing alveolar hypoventilation. Causes of type II respiratory failure include central nervous system disturbances, such as anaesthesia; neuromuscular diseases, such as myasthenia gravis; elevated breathing workload, such as in COPD; and increased dead space, such as in pulmonary embolism

[10]. By taking over the patient's work of breathing and facilitating lung inflation, MV maintains adequate oxygenation and ventilation [2, 11].

Mechanical ventilation

The modes of MV are divided based on three parameters: the control variable (volume or pressure), the breath sequence and the targeting scheme. There are three breath sequences: continuous mandatory ventilation (CMV), intermittent mandatory ventilation (IMV) and continuous spontaneous ventilation (CSV). Mandatory breaths are ventilator driven, while spontaneous breaths are triggered and cycled by the patient. During CMV, all breaths are started by the ventilator, without influence of the patient. Breathing effort is therefore completely taken over by the ventilator. During IMV, patients can trigger set mandatory breaths during a short timeframe at the end of expiration and before delivery of the next mandatory breath. In addition to a set rate of breaths per minute that are delivered by the ventilator, the patient can trigger additional breaths. During CSV all breaths are triggered by the patient and supported by the ventilator, resulting in a shared breathing effort. The targeting scheme refers to a feedback loop between ventilator settings and ventilator outputs to achieve set goals e.g. proportional assist ventilation [10]. Proportional assistance can e.g. be regulated based on the electrical activity of the diaphragm, which is called neurally adjusted ventilatory assist (NAVA). During NAVA a patient receives support proportional to the EAdi signal. With a nasogastric catheter EAdi is measured throughout every breath, as a result of which variations in neural respiratory output directly change the ventilatory assistance [11]. While a spontaneous breath occurs due to a decrease in Ppl relative to positive end-expiratory pressure (PEEP), a ventilatory breath is given by applying positive pressure.

Ventilator-induced lung injury

Due to application of positive pressure, MV may cause harmful stretching of lung tissue, leading to ventilator-induced lung injury (VILI). By looking at the factors causing this lung stress, VILI can be subdivided into barotrauma, volutrauma, atelectrauma and biotrauma. Barotrauma occurs due to high airway pressures. This may lead to alveolar rupture, subsequently causing air to leak in the surrounding soft tissues, such as the subcutis. Volutrauma is caused by excess stress at the end of inspiration. The application of too high volumes causes local overdistention of the most compliant lung areas and regional differences in lung compliance result in heterogeneous distribution of air throughout the lungs. This causes deformation of lung areas above its resting volume, exerting stress on alveolar epithelial cells and capillary endothelial cells. Atelectrauma develops when alveoli repeatedly close (at end expiration) and open (during inspiration). Especially between aerated and atelectatic lung areas shear stress is elevated, causing functional and structural alterations. Mechanical injury causes the release of inflammatory agents, which worsen local tissue damage and may promote extrapulmonary multiorgan dysfunction. This is termed biotrauma [10, 12]. A lung protective ventilation strategy is developed to limit harmful stress caused by MV. Overdistension of the lung is prevented by limiting Vt and Pplat. Furthermore, atelectasis and cyclic opening and closing of alveoli is prevented by applying adequate PEEP [10, 14].

Ventilator-induced diaphragm dysfunction

Also the respiratory muscles of ICU patients are affected. Critical illness-associated diaphragm weakness is a term that describes respiratory muscle weakness in ICU patients [34]. Factors inducing weakness of the respiratory muscles include sepsis [35], inflammation [36], drug use [37] and metabolic derangements [38]. Furthermore, the main respiratory muscle may be injured by MV, termed ventilator-induced diaphragm dysfunction (VIDD) [16]. Multiple causes of myotrauma can be appointed. Firstly, the most important mechanism that induces diaphragm dysfunction is disuse atrophy, caused by suppression of inspiratory effort [39]. Although the precise mechanisms are unknown, inactivity of the diaphragm leads to atrophy of myofibrils and mitochondrial dysfunction, resulting in contractile dysfunction. Ventilator

overassist already leads to atrophy within a few days [39]. Secondly, contraction against an excessive load damages the diaphragm (concentric load-induced injury) and causes inflammation and diaphragm weakness [40]. Thirdly, contraction during lengthening of the diaphragm, called eccentric contraction, injures the diaphragm (eccentric load-induced injury). Eccentric loading is proven to be more injurious to the diaphragm than concentric loading [41]. Lastly, excessive PEEP shortens the resting length of diaphragm. Consequently, to maintain the optimal length of sarcomeres, the amount of sarcomeres along the length of a muscle fibre might be reduced. This is called longitudinal atrophy [42]. When PEEP decreases acutely, such as during a weaning trial, the diaphragm may be overstretched above its optimal length. This causes a reduction in diaphragm function [19].

VIDD has adverse effects on clinical outcomes in critically ill patients and weaning from the ventilator [16, 17]. Therefore, a diaphragm-protective ventilation strategy is developed, which aims for appropriate levels of inspiratory diaphragmatic effort without inducing damaging patient-ventilator asynchronies. Although the optimal level of diaphragm effort is unknown, a relatively low level of effort, similar to that of healthy individuals, is thought to be best [19]. Hence, diaphragm-protective ventilation requires monitoring of the patient's demand, which will be described in the next chapter.

4 - Technical background

Quantifying breathing effort

Ultrasound

In the respiratory system, force is usually estimated as pressure and muscle shortening as change in lung volume or displacement of chest wall structures [31]. One of the techniques used to evaluate breathing effort is ultrasound. Thickness of a muscle can be tracked over time, caudal displacement during tidal breathing can be visualised and the thickening fraction (TF) can be calculated. The TF is the magnitude of increase in thickness as percentage increase in thickness [20]:

$$TF = \frac{Tei - Tee}{Tee} \cdot 100\% \quad (5)$$

where Tei is the thickness of the muscle at end inspiration and Tee at end expiration. Although ultrasound is non-invasive and widely available, the technique requires training and provides intermittent data [21].

Pressure

All pressures in the respiratory system can be measured or estimated, of which the measurement of Pes and Pga will be described in more detail below. Multiple parameters can be extracted from the many pressures existing in the respiratory system. The absolute differences in amplitude of pressure curves (Pes, Pga and Pdi) are for example suitable for bedside evaluation of breathing effort. Furthermore, the decrease in airway pressure in 100ms after onset of tidal inspiratory effort against an occluded airway ($P_{0.1}$) can be used for bedside evaluation of neural respiratory drive [43]. Moreover, advanced evaluation of pressure curves allows the calculation of the work of breathing (WOB), pressure-time product (PTP) and tension-time index (TTI). WOB is calculated as follows [31]:

$$WOB = Pmus \cdot V = \int_{t_0}^{Ti} Pmus \, dV \quad (6)$$

where t_0 is the beginning of inspiratory flow, Ti the end of inspiration and V the tidal volume. When integrating pressure over time instead of volume, the PTP is obtained:

$$PTP = P \cdot t = \int_{t_0}^{Ti} P \, dt \quad (7)$$

in which P is the used pressure and t the time. Global respiratory muscle activity can be assessed when Pmus is used and, hence, PTPmus is calculated. When Pdi is used PTPdi can be calculated as a measure for diaphragm effort [31]. TTI relates the average inspiratory pressure (Pi,mean) to the maximal inspiratory pressure (Pi,max) that a patient can generate:

$$TTI = \frac{Pi,mean}{Pi,max} \cdot \frac{Ti}{Ttot} \quad (8)$$

where Ti/Ttot is the relative duration of inspiration to a full breath cycle. Both Pmus and Pdi can be used to assess global respiratory muscle effort and diaphragm effort, respectively. WOB and PTP are gold standard parameters to measure respiratory muscle effort, but as they are difficult to obtain and interpret, they are hardly used in clinical care [2, 31]. Due to sedation and motivation maximal voluntary efforts are hindered in critically ill patients. As a result Pi,max, and thus TTI, are difficult to acquire [31].

Electromyography

Another technique to evaluate breathing effort is electromyography, in which the temporal and spatial summation of muscle fibre action potentials is acquired. Neural control of breathing is tightly matched to activity of the diaphragm and therefore multiple techniques are used to obtain EMG of the respiratory muscles, e.g. surface electrodes and electrodes affixed to a

catheter [31, 44, 45]. Although surface EMG is non-invasive, its signal quality decreases due to cross talk of adjacent muscles, movement artefacts, fat and oedema [23]. These disadvantages are partly overcome by measuring EMG using a catheter with electrodes affixed to it. This allows computation of EAdi, which is discussed in more detail below. Using EAdi the patient-ventilator breath contribution (PVBC) index, neuroventilatory efficiency (NVE) index and neuromuscular efficiency (NME) index can be calculated [46-48]. During NAVA, the PVBC estimates the relative contribution of the patient to the total tidal volume generated by the patient and ventilator together. The ability to generate volume for a given electrical activity is described by the NVE:

$$\mathrm{NVE} = \frac{\mathrm{Vt}}{\mathrm{EAdi}} \tag{9}$$

The NME also reflects the efficiency of the diaphragm, as it expresses the coupling between electrical activity and the generated pressure:

$$\mathrm{NME} = \frac{\mathrm{Pdi}}{\mathrm{EAdi}} \tag{10}$$

Although these parameters have added value in monitoring diaphragm function and titrating ventilator support, currently they are not extensively used in clinical practise. This is caused by the fact that the reliability of these parameter is affected by insufficient EAdi filtering of the ventilator [46, 47].

Computation of EAdi

The first step in the calculation of EAdi is placement of a dedicated nasogastric catheter with nine electrodes (i.e., one ground electrode and eight bipolar electrodes) affixed to it in the oesophagus. The catheter goes through the crural part of the diaphragm to measure crural EMGdi, see Figure 2 [2]. The crural EMGdi represents global diaphragm activation, although this relationship may not be valid at extreme chest wall configurations [5, 45]. By taking the root mean square of the crural EMGdi, the electrical activity of the diaphragm can be quantified [5]. As EAdi can be measured continuously, it helps to detect the degree of patient-ventilator asynchrony [22, 27]. However, as the electrical activity of the heart is larger than the electrical activity of the diaphragm, the heart distorts the EAdi signal. Furthermore, the EAdi signal can be influenced by crosstalk of adjacent muscles, such as the abdominal muscles. Sedatives supress the respiratory muscle activity and therefore influence EAdi as well [25, 27]. Other disturbances in EAdi are noise, electrode motion artefacts and oesophageal peristalsis [3]. Last, neuromuscular transmission and muscle fibre membrane excitability should be intact, as the catheter measures the spatial and temporal summation of action potentials from recruited motor units [24].

The first step in computing EAdi is applying the double subtraction technique. From the eight bipolar electrodes on the catheter seven EMGdi signal pairs are obtained [25, 49]. As the right side of Figure 4A illustrates, first the centre of the electrical active region of the diaphragm (EARdictr) is found, using the three electrode pairs with the most negative correlation coefficients. Subtraction of the signals of the electrode pairs 10 mm distal and 10 mm caudal from EARdictr is called the double subtraction technique and provides one raw EMGdi signal, as can be seen in Figure 4B. The polarity of noise is the same in signals from the electrode pairs 10 mm distal and 10 mm caudal from EARdictr, while the polarity of the activity of the diaphragm is reversed in both signals [3]. As such, the double subtraction technique not only finds the electrode pair with the most information, but also increases the signal to noise ratio in this signal.

Although it is known that Maquet, the manufacturer of the ventilator used at our ICU, computes the root mean square and, subsequently, corrects for residual signal disturbances, the exact steps are patented and therefore unknown to us. To be independent of this black box, we obtain the raw EMGdi ourselves, from which we calculate EAdi with our own algorithm. Our algorithm starts with the double subtraction technique as well.

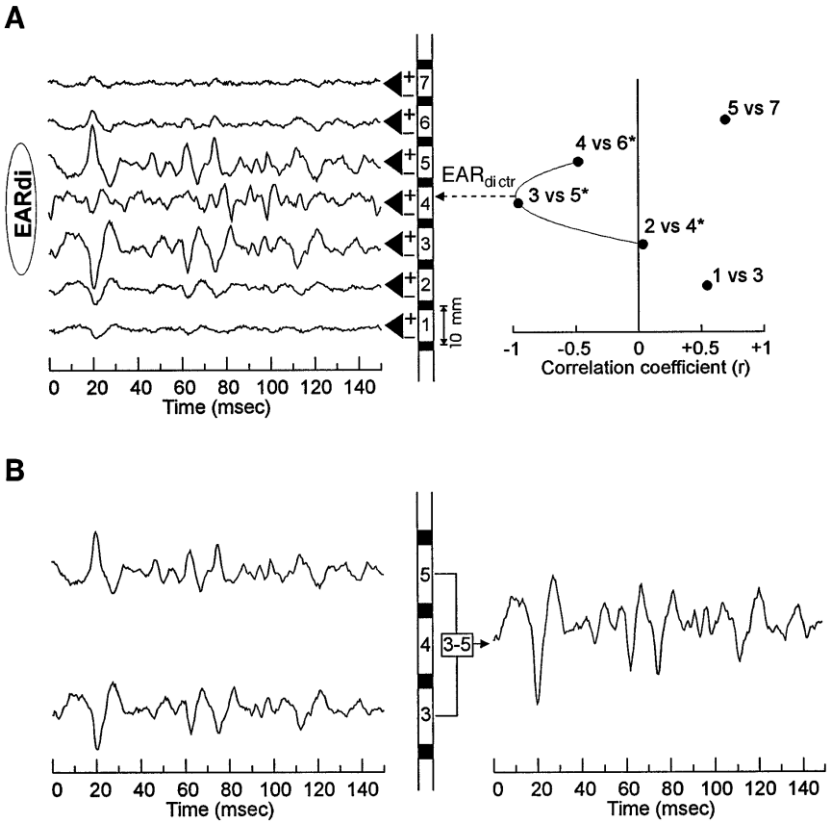

Figure 4: A: Determination of the centre of the electrical active region of the diaphragm (EARdictr) using the three most negative correlation coefficients (right) of electrode pairs, made with eight electrodes positioned on an EAdi catheter (middle). B: Electrode pairs 10 mm caudal and 10 mm distal to the EARdictr are used for double subtraction and provides one raw EMGdi signal [3].

The second step in our algorithm to compute EAdi is electrocardiogram (ECG) cancellation. This is done using two methods: using wavelet transformation, based on the article of Zhan et al. [50] and using template subtraction. These methods are combined, as they both work on a different part of the signal. Wavelet transformation is better at deleting ECG artefacts when there is no diaphragm activity, while template subtraction deletes ECG artefacts more properly during diaphragm activity. Furthermore, template subtraction works better than wavelet transformation when the heart rate is not constant.

Of the signal without ECG artefacts the root mean square (RMS) is taken and lastly a moving average filter is used. This moving average filtered signal is the EAdi signal. The steps taken in our algorithm to calculate EAdi from the eight separate electrode signals are summarised in Figure 5.

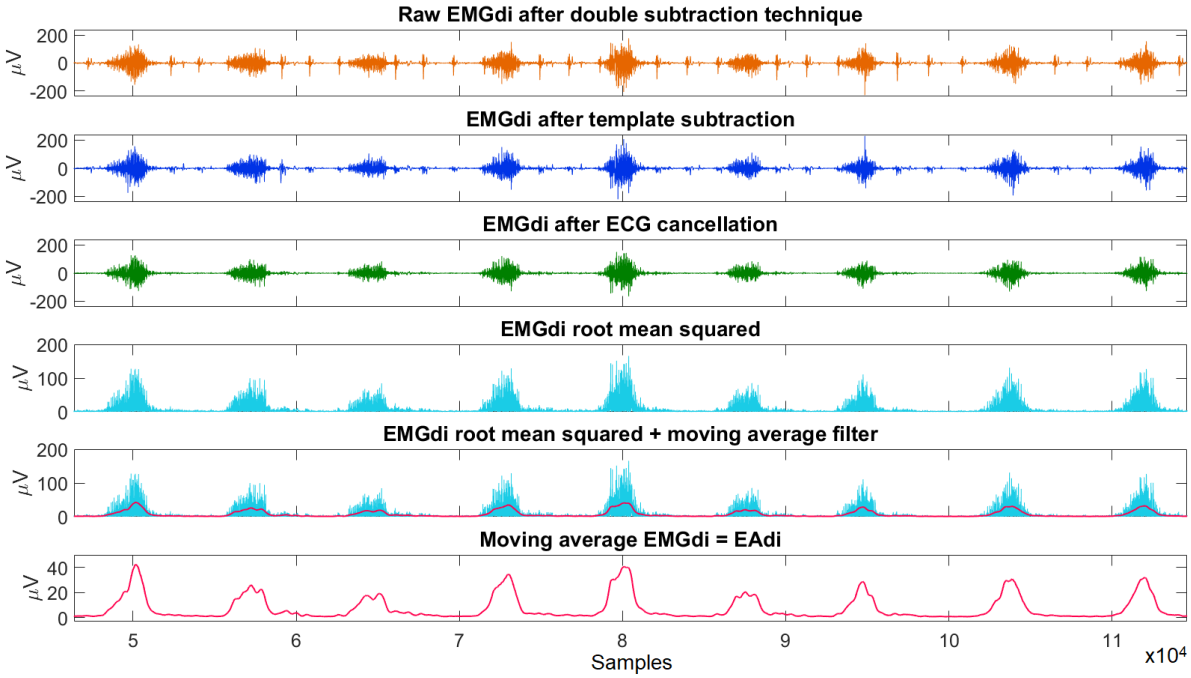

Figure 5: Subsequent steps that are taken in our algorithm to compute EAdi.

Measuring Pes and Pga

As discussed before, Ppl can be estimated using Pes [14]. Pes can be measured in different ways: using balloon catheters, liquid-filled catheters or catheter-mounted microtransducers [31]. Of these methods, the balloon catheter is used most widely to measure Pes. An air-containing latex balloon is sealed over a catheter with spirally arranged holes, which transmits the pressure to a pressure transducer outside of the body [31, 51]. The catheter is placed in the lower third of the oesophagus, at approximately 35-45 cm from the nares, and as the balloon lies posterior to the heart, cardiac oscillations in the pressure signal are a characteristic of a correct position [52]. For an accurate transmission of pressure, the balloon is filled with air until it is fully distended. This makes sure that there is an open connection between the lumen of the catheter and the inside of the balloon. Subsequently, most of the air is removed from the balloon in order to prevent overestimation of the pressure [31]. If also Pga, to approximate Pab, is measured, a second balloon (either fixed to the oesophageal balloon catheter or mounted on a second catheter) is positioned. As the balloon should be placed in the stomach, it should be placed beyond the point where the cardiac oscillations were seen, which is at least 45 cm from the nares [52].

To validate the filling volume and position of the oesophageal balloon, the Baydur manoeuvre or positive pressure occlusion test are performed. The Baydur manoeuvre is used on patients with spontaneous inspiratory efforts: an expiratory hold is applied for at least one breath, during which the ratio of airway pressure (Paw) and Pes is measured. On patients without spontaneous inspiratory efforts the positive pressure occlusion test is performed: their thorax is compressed during the expiratory hold and again the Paw/Pes ratio is calculated. Pes measurements are considered reliable when the Paw/Pes ratio is close to unity [27]. Balloon volumes should be checked frequently during measurements, as the accuracy of Pes measurements depends on the amount of air injected in the balloon [22]. An overfilled balloon can overestimate the pressure, while an underfilled balloon does not properly transmit Pes [51]. Furthermore, as the balloon tends to deflate, re-evaluation of balloon volumes is necessary to ensure reliable measurements over time [22].

Despite these drawbacks, the balloon catheter is used more frequently to measure Pes than the other methods mentioned above. Liquid-filled catheters should be flushed regularly to avoid clogging of the holes and to keep the system free of air bubbles. Furthermore, pressure is always measured at the end of the catheter, which may not be the optimal site. Catheter-mounted microtransducers have a performance compared to that of balloon catheters. Handling during long measurements is probably easier than that of balloon catheters, due to the fact that there are no balloons that can deflate and that they may be easier to tolerate for a patient. However, also these catheters measure pressure at a focussed point, which may not be the optimal site. Moreover, these catheters are more expensive than balloon catheters and may be difficult to sterilise and reuse [31]. Due to these limitations, Pes measurements are not used routinely for clinical care [25]. Since the calculation of Pmus is based on Pes measurements, as explained in Equation (*4*), another measure should be used to estimate Pmus for an estimation of patient effort.

Relationship between EAdi and patient effort

In 2013 Bellani et al. showed a linear relationship between EAdi and Pmus in ten mechanically ventilated patients in a small physiological range (Pmus ranged from 0 to 10 cmH_2O) [8]. They presented that the EAdi-Pmus relationship was highly variable between patients, but that it was stable within patients. As such, they demonstrated that Pmus could be estimated based on $P_{0.1}$/EAdi obtained during an end-expiratory hold.

The relationship between EAdi and Pdi is described extensively, although both linear [24, 53] and curvilinear relationships [4-6, 26] are found. Grassino et al. found a curvilinear relationship between EAdi and Pdi in healthy subjects, obtained during inspiratory occlusions under a controlled thoracoabdominal configuration, assuming an isometric contraction. They discovered that the EAdi-Pdi relationship primarily depends on this thoracoabdominal configuration, rather than lung volume [26]. Their result is in accordance with the idea that diaphragm length is more influenced by abdominal displacement than e.g. lung volume (force-length relationship). Subsequently, in the following paper they investigated the relationship during inspiration with constant flow, again with a controlled configuration of the thorax and abdomen. Also during these dynamic manoeuvres they found a curvilinear relationship and concluded that inspiratory flow influences this relationship as well (force-velocity relationship) [4]. Both papers include Pdi values ranging from 0 to 60 cmH2O [4, 26]. Moreover, Beck et al. studied the relationship during a controlled configuration of thorax and abdomen and found a curvilinear relationship in healthy subjects over the entire physiological range of Pdi. They verified the findings of Grassino et al., concluding that diaphragm activation is not influenced by chest wall configuration or lung volume [5]. A later study of Beck et al. in mechanically ventilated patients showed a linear relationship between EAdi and Pdi [24]. Sinderby investigated the relationship in healthy individuals and patients with COPD and prior polio infection, in which they found a linear relationship between EAdi and Pdi. Goligher et al. studied the relationship in healthy individuals in the entire physiological range of Pdi. They found a curvilinear relationship and showed that this relationship is affected by inspiratory flow and motion of the diaphragm [6]. This is also in agreement with the above mentioned studies of Grassino et al. and Beck et al. [4, 5, 26]. An earlier graduation study in healthy individuals in the entire physiological range of Pdi found that a linear model could not describe the EAdi-Pdi relationship in all subjects. Furthermore, the found correlations were very heterogeneous between subjects and no conversion factors were found that could predict Pdi based on EAdi [7]. Results of the mentioned studies are shown in Figure 6.

Fauroux et al. found that the effects of the force-velocity relationship during pressure support ventilation can be eliminated by including flow. They showed that at any level of EAdi the PTPdi was reduced when flow was increased and that PTPdi was more influenced by flow than EAdi, in accordance with the force-velocity relationship. They showed a linear relationship

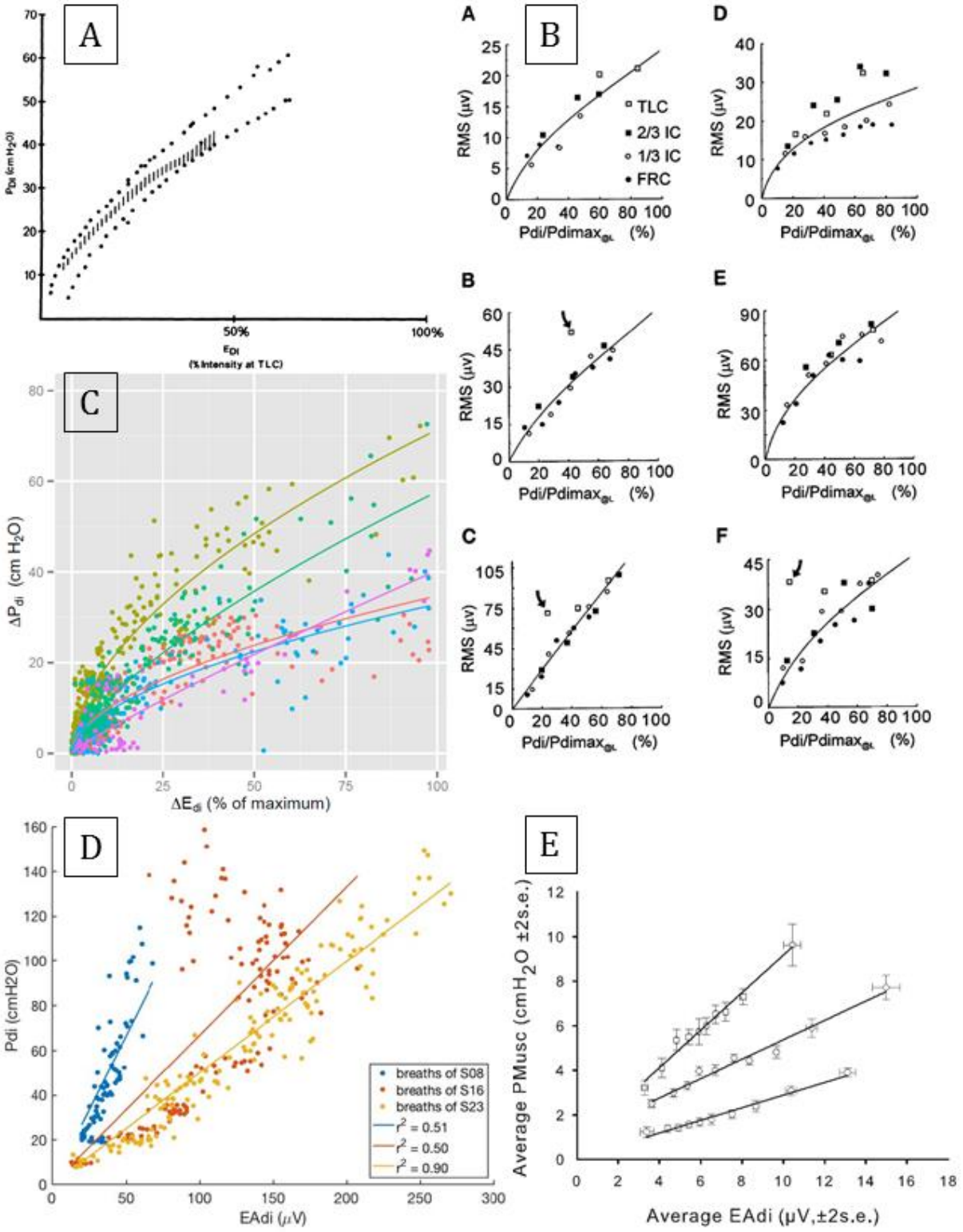

Figure 6: Overview of previously reported relationships between the electrical activity of the diaphragm (EAdi, Edi or RMS) and transdiaphragmatic pressure (Pdi) or respiratory muscle pressure (Pmus): A) The curvilinear relationship found by Goldman et al. between EAdi and Pdi [4]. B) Beck et al. found curvilinear EAdi-Pdi relationships in five out of six patients. One subject showed a linear relationship [5]. C) Goligher et al. described a curvilinear relationship between EAdi and Pdi. Each colour represents a subject [6]. D) Previous graduation research found that the EAdi-Pdi relationship was not in all subjects linear. The different colours represent different subjects [7]. E) A linear relationship was found between EAdi and Pmus by Bellani et al. [8].

during spontaneous breathing and showed that the relationship at high flow became linear when correcting for flow [54].

5 - Small amplitude peak study

Introduction

Measuring the EAdi signal is one of the techniques to monitor neural respiratory drive [23]. Furthermore, this signal is used for providing assisted mechanical ventilation [11]. As in this signal peaks are seen with an unknown origin, it is uncertain whether treatment and/or ventilator settings should be changed based on these small amplitude peaks or that ventilator software for EAdi signal filtering should be optimised. By determining the origin of the small amplitude peaks, the reliability of the EAdi signal will improve. It is hypothesised that the peaks with small amplitudes are a result of inadequate ECG filtering [46, 47]. This chapter focusses on finding the origin of the small amplitude peaks in the EAdi signal.

Methods

Subjects

For this proof of concept study mechanically ventilated patients from the ICU of Amsterdam University Medical Centre, location VUmc, with both an EAdi catheter and Pes and/or Pdi catheter in situ were prospectively included in the period May to July 2019. Patients should have an EAdi signal with clear diaphragmatic contractions, defined as a positive deflection with an amplitude of minimally 2 μV and a duration of at least 400 ms. Patients with diaphragm paresis or paralysis were not included. As signals were compared within a patient, patients were their own control and a convenient sample size of 15 patients was thought to be sufficient for answering the research question.

Design

This is an observational study and therefore randomisation and blinding are not applicable.

Methods of measurement

Included patients had an EAdi catheter (Edi Catheter ENFit, Maquet Critical Care, Solna, Sweden) and in some cases also an oesophageal balloon catheter (CooperSurgical Inc., Trumbull, Connecticut, USA) in situ. A pneumotach (Adult flow sensor, Hamilton Medical, Bonaduz, Switzerland) was placed between the patient and the mechanical ventilator (Servo-i or Servo-U, Maquet Critical Care, Solna, Sweden) to measure flow. Furthermore, a splitter was made for us in order to acquire the raw EMGdi and EAdi of the ventilator simultaneously. Flow, pressure and raw EMGdi are recorded by a CE-certified measurement setup (BIOPAC MP160, BIOPAC Systems Inc., Goleta, California, USA) with a sample frequency of 2000 Hz and are stored offline. Flow, pressures and EAdi are recorded with a sample frequency of 100 Hz and are also stored for offline analysis. Hence, the signals that will be used are raw EMGdi, EAdi, flow, airway pressure (Paw) and Pdi (or Pes if Pdi was not available).

First, EAdi will be compared to an EMG signal that contains ECG artefacts, which says something about the probability that the small amplitude peaks are caused by ECG filtering. When there is an ECG artefact at every time stamp that there is a small amplitude peak in EAdi, the probability that the small amplitude peaks are caused by interference of the electrical signal of the heart enlarges. Second, EAdi will be compared to Pdi, or if this signal is not available to Pes, which points out whether there is a functional diaphragmatic contraction. If no positive or negative deflections are seen in respectively Pdi or Pes at the time stamps of small amplitude peaks, there is no functional diaphragmatic contraction or no contraction of the diaphragm at all. Paw (which is the same as the pressure applied by the ventilator) and flow are used to determine mechanical inflations. By combining the outcome of all comparisons, a conclusion can be drawn about the origin of the small amplitude peaks in EAdi.

In the EAdi signal, a diaphragmatic contraction was defined as a positive deflection with an amplitude of minimally 2 μV and a duration of at least 400 ms with a simultaneous increase in flow, based on previous literature [46]. Peaks with an amplitude of at least 2 μV, but without a consequent rise in flow were considered small amplitude peaks.

Analysis

The stored signals were analysed offline with Matlab version 2017a (MathWorks, Natrick, Massachusetts, USA). First, Paw and, depending on the signals available, flow and Pes were resampled. To smoothen the signals a little bit and to remove artefacts caused by resampling, a moving average filter with a window of 15 ms was applied to Paw, Pes, Pdi and/or flow. Furthermore, offset and drift were removed from the flow signal. Since the recordings from the ventilator and Biopac were not started and ended at the same time, the signals were synchronised based on expiratory holds done during the measurements.

In order to obtain EMGdi with cardiac artefacts, first the eight raw EMGdi signals were band-pass filtered with cutoff frequencies of 30 and 400 Hz. Next, noise from the electricity grid was removed with a 50 Hz band-stop filter. The double subtraction technique, as described in the Technical background, was used to make a single EMG signal from the eight raw EMGdi signals. This signal contains information about both EMGdi and ECG. The pressure signals and EMG signal containing ECG artefacts were downsampled in order to plot them in one figure with and compare them to EAdi. Since we hypothesised that the small amplitude peaks are artefacts due to ECG removal, EAdi, EMGdi with ECG artefacts and Pdi were plotted above each other. In this way the hypothesis could be tested visually.

Results

Signals were recorded in four mechanically ventilated patients, all in a supported mode of ventilation. The duration of recordings differed per patient, ranging from 4 minutes up to 14 minutes. In each patient the entire recording was visually inspected for small amplitude peaks. Of one patient an epoch with small amplitude peaks in the EAdi signal is shown below. Epochs containing small amplitude peaks of two other patients with small amplitude peaks are presented in Appendix A1. The recordings of one patient did not contain small amplitude peaks and is therefore not shown.

Small amplitude peaks can be seen in the EAdi signal in Figure 7, which clearly have a regular pattern. When comparing the EAdi signal with the EMG signal with cardiac artefacts, it can be seen that the heart beats every time there is a small amplitude peak. This indicates that the small amplitude peaks are caused by depolarisation of the heart. Furthermore, a drop in Pdi is seen simultaneously with the small amplitude peak, further strengthening the hypothesis. A functional contraction of the diaphragm elevates Pdi, while a cardiac contraction causes a drop in Pdi.

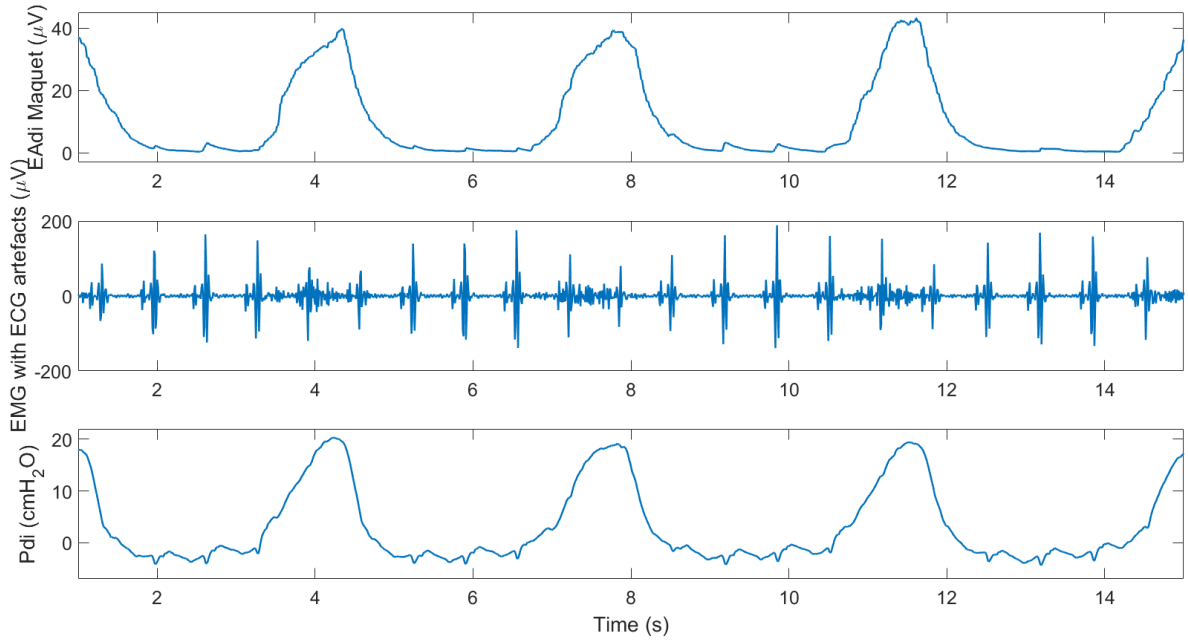

Figure 7: Epoch of a recording of EAdi as analysed by Maquet (top graph), EMG with cardiac artefacts (middle graph) and Pdi (bottom graph). In the EAdi signal small amplitude peaks can be seen.

Discussion

The results show that small amplitude peaks between two subsequent breaths in the EAdi signal are no functional diaphragmatic contractions, but artefacts due to cardiac contractions. Dependent on the mode of ventilation and the amplitude of diaphragmatic contractions, small amplitude peaks can cause patient ventilator asynchronies. Hence, the filtering algorithm on a Maquet ventilator to compute EAdi should be optimised. Furthermore, treatment strategy of a patient should not be changed based on these small amplitude peaks.

To our knowledge no previous studies are performed focusing on finding the origin of peaks with small amplitudes that are seen in the processed EMG of the diaphragm, although it is proposed that they are caused by suboptimal filtering of ECG artefacts [46, 47]. A strength of our study is the fact that EAdi is compared to an EMG signal that contains cardiac artefacts, recorded at the same location in the human body as the EAdi signal. Due to this, delay caused by transmission of the electrical current from the heart to e.g. ECG electrodes is prevented. Furthermore, in all patients pressure curves were recorded, allowing us to draw conclusions regarding functional diaphragmatic contractions.

However, several limitations should be acknowledged. First, the amount of data for answering the research question is not extensive. At our ICU patients not often receive both a balloon catheter and an EAdi catheter and due to time limitations the period of data collection could not be extended. By including more patients, we expect to find the same results as shown above. However, by including more patients, a stronger conclusion can be drawn about the origin of the small amplitude peaks. Second, although all signals were synchronised based on expiratory holds, additional synchronisation was necessary. It became apparent that the part of the algorithm that calculates the ECG artefacts caused this signal to shift earlier in time, although we could not find the exact steps in the algorithm that caused this shift. To remove the possibility that a small amplitude peak and heartbeat were paired wrongly, additional synchronisation was performed using the pressure curves. The additional synchronisation is described in more detail in Appendix A2. Third, although available, non-invasive techniques such as surface EMG or ultrasound were not used. As ultrasound could not be recorded with the measurement setup and data files are images instead of matrices with numbers, correct synchronisation would have been difficult. Moreover, it is unknown whether ultrasound

resolution is good enough to see small diaphragmatic contractions. Regarding surface EMG, signal quality decreases due to cross talk of adjacent muscles, fat, movement artefacts and oedema [23]. Furthermore, because of the distance between a surface electrode and the diaphragm, is it uncertain whether diaphragmatic depolarisations causing small voltage differences are picked up by the electrode. As a consequence, no conclusions about a functional diaphragmatic contraction could have been drawn if no contraction was seen on either ultrasound or surface EMG.

Of the four patients studied, one did not show small amplitude peaks in the EAdi signal. In this signal the algorithm of the Maquet ventilator removed disturbances caused by cardiac depolarisations correctly, which can be explained by the possibility that the patient had a high signal to noise ratio.

Whether small amplitude peaks lead to unwanted ventilatory patterns is dependent on the mode of ventilation. In controlled or ventilated modes of ventilation, EAdi is not used for determining the ventilatory breath or support, respectively, that a patient receives. However, during NAVA changes in the neural respiratory output directly lead to a change in the ventilatory support. Moreover, during NAVA patients with relatively low EAdi peaks will be hindered more by small amplitude peaks than patients with relatively high EAdi peaks. In the latter the proportionality factor will be >1, damping the small amplitude peaks. Therefore, also the voltage difference caused by diaphragmatic depolarisation determines whether small amplitude peaks cause unwanted ventilatory patterns.

Conclusion

It can be concluded that the small amplitude peaks in the EAdi signal are artefacts caused by depolarisation of the heart instead of them being functional contractions of the diaphragm. Therefore, treatment and/or ventilator settings should not be changed based on small amplitude peaks. Additionally, the algorithm of Maquet to compute EAdi should be optimised to remove these small amplitude peaks from the signal. This increases reliability of the EAdi signal and might allow clinical implementation of monitoring parameters, i.e. PVBC, NME and NVE.

6 - Estimation of patient effort from EAdi

Introduction

To ensure lung-protective and diaphragm-protective ventilation, patient effort should be monitored. Besides measuring the EAdi signal directly, as described in the previous chapter, also the pressure generated by the respiratory muscles (Pmus) can be measured. An oesophageal balloon is used to do this, but due to limitations such as filling status, oesophageal balloons are not used routinely in clinical care [25]. To circumvent the use of oesophageal balloons, the relation between EAdi and Pmus or EAdi and Pdi are studied. Linear or curvilinear correlations are described, but in small physiological ranges [4, 8, 26]. It is hypothesised that EAdi and Pmus are linearly correlated in a broad physiological range, although the correlation is hypothesised to be very heterogeneously among subjects.

Methods

Subjects

For this physiological study 23 healthy volunteers were measured at the clinical research laboratory in the ICU of Amsterdam University Medical Centre, location VUmc. A BROK-certified investigator obtained written informed consent prior to screening. Screening consisted of a short medical history taking, physical examination and ECG evaluation. As such, it was ensured that participants were in good physical condition and able to undergo a loading protocol. Table 1 shows the inclusion and exclusion criteria. The study protocol was approved by the medical research ethics committee of the VUmc (METc VUmc).

Table 1: Inclusion and exclusion criteria of Edi2Pdi study

Inclusion criteria	Exclusion criteria
Age ≥ 18 years	History of cardiac and/or pulmonary disease, or current cardiac/pulmonary symptoms, or medication use
Signed informed consent	History of pneumothorax
	Contra-indications for nasogastric tube placement: • Recent epistaxis (3 months) • Current upper airway, oesophageal, gastric and/or mouth pathology • Coagulopathy, either due to drugs or disease
	Contra- indication for magnetic stimulation (cardiac pacemakers)

Design

Given that this is a proof of concept study, randomisation and blinding are not applicable.

Methods of measurement

Included participants were instrumented with a dedicated nasogastric catheter, with which Pes and Pga could be measured simultaneously (Nutrivent™, Sidam Biomedical solution, Modena, Italy). Next, an EAdi catheter was inserted (Adult 8Fr 125 cm EDI catheter, Maquet Critical Care, Solna, Sweden). Flow and tidal volume were measured with a pneumotach (Adult flow sensor, Hamilton Medical, Bonaduz, Switzerland). Furthermore, a nose clip was placed to prevent air leakage via the nostrils. Flow, pressures and EMGdi were recorded at a sample frequency of 2000 Hz by a CE-certified measurement setup (BIOPAC MP160, BIOPAC Systems Inc., Goleta, California, USA), which stored the data for offline analysis. Adequate position and filling status were verified by using multiple short occlusions as described in literature [55].

After the catheters were placed correctly and calibration was performed, the measurements started. First, the participants breathed quietly for 15 minutes in order to get comfortable with the measuring instruments and to get a baseline measurement. Maximal inspiratory muscle strength (Pi,max) was measured during a one second inspiratory hold and a sniff, at both functional residual capacity and residual volume. Subjects had visual feedback during this manoeuvre and repeated the measurement three times, of which the highest value was selected as Pi,max. Subsequently, the participants underwent a loading protocol. A threshold loading device (Power Breathe Medic Plus, POWERbreathe Ltd, Warwickshire, UK) was attached to the inspiratory arm of the pneumotach. As such, loading levels of 10%, 20%, 30%, 40%, 50%, 60% and 80% of Pi,max were imposed on the subjects. Of every level at least 10 breaths were measured. To ensure that fatigue would not arise, participants could rest between the loaded breaths. After breathing quietly for 15 minutes in order to rest, measurements stopped and the measurement instruments were removed. The measurements were performed by a BROK-certified member of the study team and a medical doctor was present to ensure the safety of subjects. All of the medical devices that were used are CE-certified and are utilised within their intended use. A flowchart of the measurements can be seen in Appendix B1.

Analysis

The stored signals were analysed offline with Matlab version 2017a (MathWorks, Natrick, Massachusetts, USA). First, offset and drift were removed from the flow signal. Next, a moving average filter with a window of 40 ms was used to remove small fluctuations from the flow and Pes signals. Pmus was calculated using Equation (4), described in the Clinical background. The needed volume was calculated from the flow signal, as volume is the integral of flow. Furthermore, vital capacity (VC) was calculated using the summary equations of reference values that were published by the European Respiratory Society in 1983, that are based on age, gender and height [56].

To compute EAdi, first the eight raw EMGdi signals were band-pass filtered with cutoff frequencies of 30 and 400 Hz. Next, noise from the electricity grid was removed with a 50 Hz band-stop filter. The double subtraction technique, as described in the Technical background, was used to make a single EMG signal from the eight raw EMGdi signals. Subsequently, template subtraction and discrete wavelet transformation were used to remove ECG artefacts. The output was squared and filtered with a moving average filter with a window of 267 ms to obtain EAdi.

During previous graduation research in which this data was used, epochs with useful data were selected visually. As data outside these epochs contain artefacts and oesophageal spasms, the selected epochs were also used in this study. This previous study focussed on the correlation between EAdi and Pdi. Hence, correlation plots of EAdi and Pdi were made, of which they tried to estimate the correlation with a conversion factor. In an attempt to finding a correct conversion factor to compute Pdi from EAdi, we came up with multiple possibilities to compute the conversion factor:

1. $\frac{\text{maximal slope in P0.1 of Pmo}}{\text{maximal slope in E0.1}}$
2. $\frac{\text{maximal slope in P0.1 of Pmo}}{\text{maximal slope in whole EAdi peak}}$
3. $\frac{\text{AUC in P0.1}}{\text{AUC in E0.1}}$
4. $\frac{\text{AUC in P0.1}}{\text{AUC in E0.1 at same indices as P0.1}}$

in which AUC is the area under the curve of the mentioned signal. $E_{0.1}$ is the rise in electrical activity in the first 100ms of a diaphragmatic contraction. A diaphragmatic contraction is defined as a positive deflection with a minimal duration of 400 ms and an amplitude of at least 2 μV.

In all four of the above options the first step was to determine the start of a breath in Pmo and EAdi. Subsequently, the indices of P0.1, E0.1 and EAdi peak were calculated. For the first and second option, the maximal slope was calculated as the minimum (Pmo) or maximum (EAdi) of the derivative. The AUC, used in option 3 and 4, is calculated using trapezoidal numerical integration. The four options were applied to individual breaths, after which the conversion factor was calculated as the median over these individual breaths.

Additionally, to make a new correlation plot of EAdi and Pdi, EAdi was divided into steps of 10% of EAdi,max. Per step the median of delta EAdi's and subsequent delta Pdi's were calculated. Their correlation was visualised in a scatter plot with a linear regression line.

Subsequently, the relationship between EAdi and Pmus was investigated. After processing the data as described above, delta's of EAdi and Pmus were calculated. To visualise the correlation, these delta's were plotted in a scatter plot with a regression line.

Results

23 healthy subjects were recruited, of which three were excluded as the nasogastric catheters were not tolerated. Four subjects were excluded due to a low signal to noise ratio of the EAdi signal and of one subject data was not saved due to technical difficulties. The demographic information of the remaining 15 subjects is shown in Table 2.

Table 2: Main characteristics of the study population

Subject	**Gender**	**Age (year)**	**Height (cm)**	**BMI (kg/m²)**
S1	F	32	173	23.8
S2	F	32	173	24.8
S3	F	28	170	22.5
S8	F	27	175	20.3
S9	M	39	183	23.9
S11	M	25	183	20.9
S12	M	23	185	19.9
S13	M	24	183	24.1
S14	M	43	187	22.0
S16	F	31	163	21.1
S17	M	26	170	24.9
S20	F	27	184	22.1
S21	F	24	180	22.5
S22	F	28	167	20.4
S23	M	29	186	23.4
Mean ± SD	**F (8/15)**	**29 ± 5.6**	**177 ± 7.7**	**22.4 ± 1.7**

Abbreviations: F = female, M = male, BMI = body mass index

To conclude whether Pdi can be estimated from EAdi, multiple conversion factors are calculated. Figure 8 shows Bland Altman plots of the four methods described above to calculate the conversion factor. All four plots show low agreement.

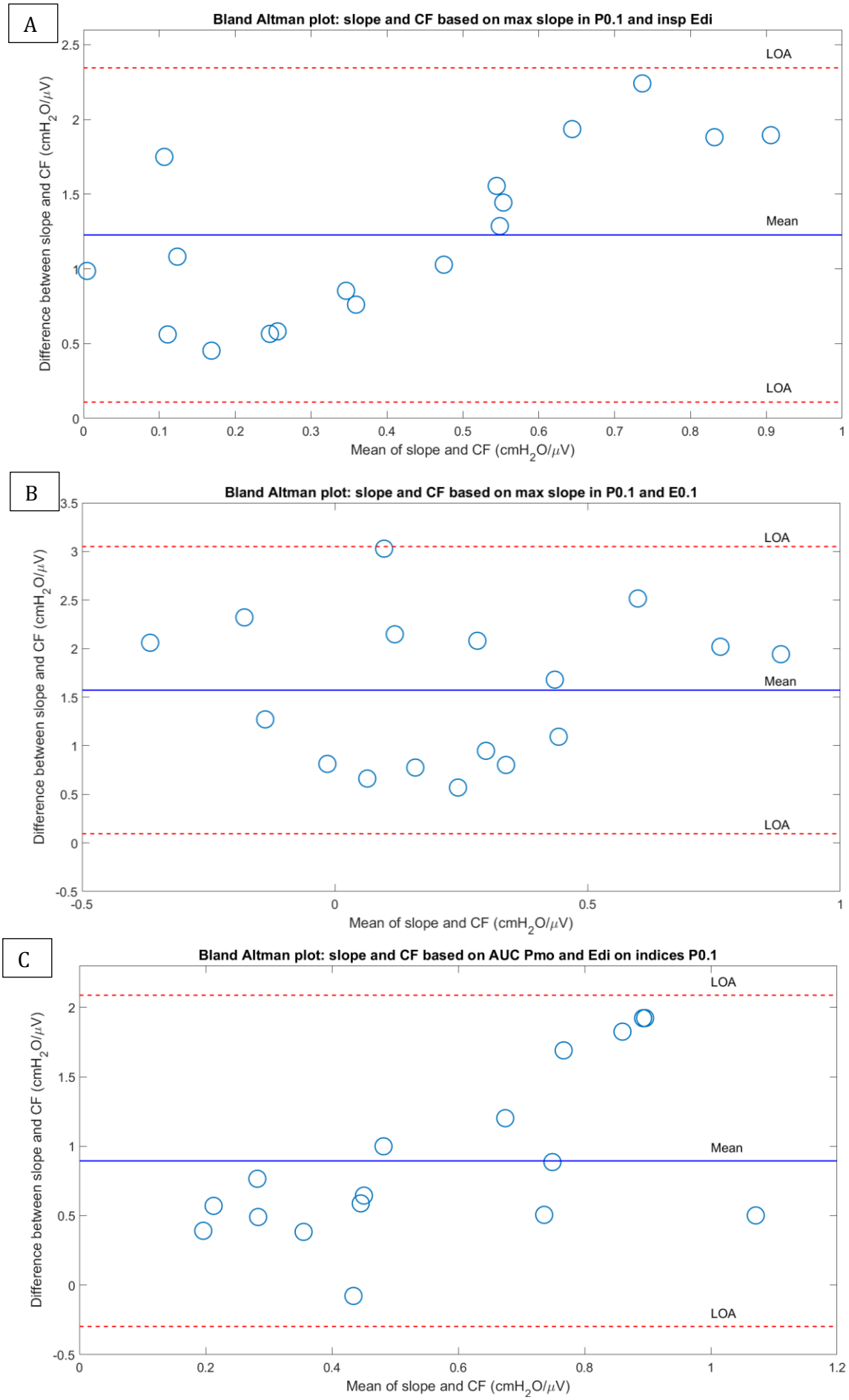

Figure 8: Bland Altman plots of the four different ways to calculate the conversion factor to calculate Pdi from EAdi. The four methods of calculation of the conversion factors are described above in the Methods section. Each dot represents one subject.

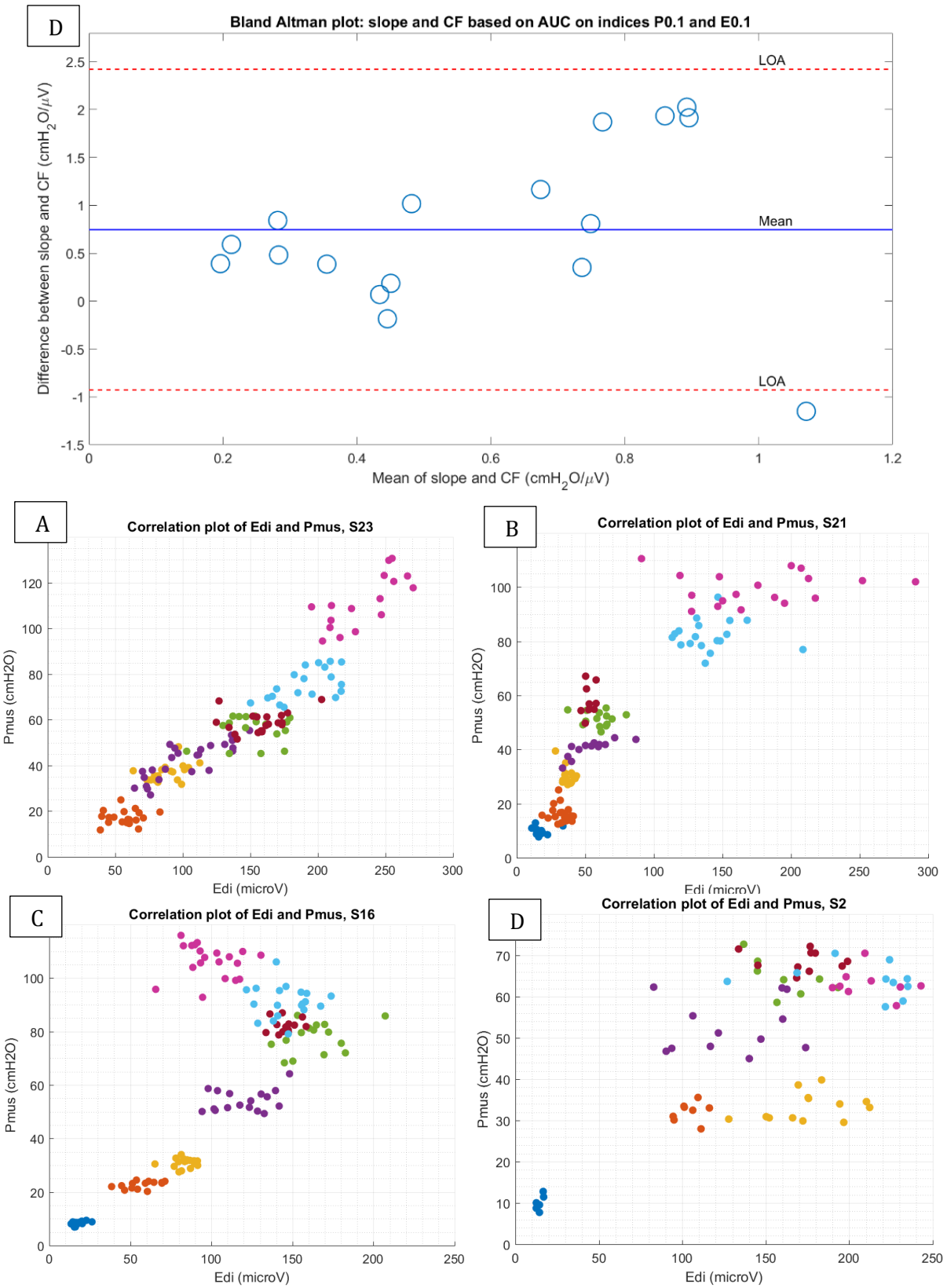

Figure 9: Type of trends seen in the correlation plots of EAdi and Pmus. A) Linear trend. B) Trend in which a plateau is reached in Pmus. C) Delta EAdi decreases, while delta Pmus increases with increased loading. D) Breaths are gathered in a cloud. The colours represent the different loading levels: dark blue – unloaded, orange – 10%, yellow – 20%, purple – 30%, green – 40%, red– 50%, light blue – 60% and pink– 80% of Pdi,max. Each dot represents a breath.

Turning now to the relationship between EAdi and Pmus, four different trends were seen in the correlation plots. Figure 9A shows a linear trend that was seen in four subjects. The trend of the correlation plots of three patients, however, reaches a plateau, presented in panel B. Panel C shows a decrease in delta EAdi, while delta Pmus increases with increased loading. This was seen in four subjects. Last, panel D shows a trend in which all breaths, apart from the breaths without loading, are gathered in a cloud, which was seen in three subjects. When applying linear regression, the average r^2 over all subjects was 0.64±0.19. Correction for flow did not improve correlation and even worsened the correlation, as the average r^2 of linear regression decreased to 0.42±0.16.

Discussion

The main findings of this study can be summarised as follows: (1) EAdi and patient effort are not linearly correlated in every subject and therefore, (2) the assumed linear correlation is not correct in all healthy subjects in a wide physiological range. However, (3) not all trends in the correlation plots can be physiologically explained.

The first step in this research was finding a conversion factor to estimate Pdi from EAdi, while the rest of this study mainly focused on finding a correlation between EAdi and Pmus. Pmus can be influenced by several factors, such as the activation of accessory muscles, which is not the case when using Pdi. However, as Pmus is a measure of patient effort, we thought that it would be it more clinically relevant than using Pdi.

Not all trends that were seen in the correlation plots of EAdi and Pmus were as expected and those trends were different than presented in previous literature. The linear trend (Figure 9, panel A) is in accordance with previous literature [8]. Also between EAdi and Pdi linear [24, 57] and curvilinear [4-6, 26] relationships are described. Possible explanations for the unexpected relationships were conceptualised and will be discussed based on the seen trends. Technical difficulties were ruled out by assessing which leads were used for calculation of the EAdi signal. As in all subjects leads in the middle of the catheter were used for computation of EAdi, the possibility that the diaphragm moves out of range of the catheter is ruled out.

One of the trends shows an increase in neural drive, while the generated pressure levels reach a plateau (Figure 9, panel B). Beck et al. showed that the diaphragm can generate less pressure for a given EAdi at higher lung volumes, as would be expected based on the force-length relationship [5]. Furthermore, by estimating the Ccw as 4% of VC, the assumption is made that Ccw is linear over the volumes studied. However, this assumption may not be true at high loading levels. At these loading levels the thoracic wall expands more, leading to a stiffer thoracic wall and thus, an overestimated Ccw. As a result, the calculated Pmus may be underestimated. Moreover, Fauroux and colleagues showed that an increase in flow rate can increase the velocity of contraction, as a consequence of the force-velocity relationship [54]. However, when we corrected for flow, the correlation coefficients became less. This can be explained by the used threshold loading device. When the subjects overcame the threshold, flow immediately peaked in contrast to a graduate increase in flow e.g. during spontaneous breathing.

Another trend showed a decreasing neural drive, while the generated pressure increased with increased loading (Figure 9, panel C). EMGdi of the crural diaphragm is used as a measure for global activation of the diaphragm. However, this relationship is only shown to be linear up to 75% of Pdi,max [5]. Above this value EMGdi underestimates the global diaphragm activation. However, in this study EAdi already decreases from 50% of Pdi,max. Therefore, global diaphragm activation underestimation can only explain the decrease in the highest loading level of 80% of Pdi,max. The force-velocity relationship can be another explanation for a decreased EAdi during increased loading [5]. The conduction velocity increases at high loading, resulting in an underestimated EAdi signal.

A strength of this study is that a broad physiological range is studied, since healthy subjects are used instead of patients. Furthermore, to make the translation to clinical practise easier, we did not control thoracoabdominal configuration. Mechanically ventilated patients may also breath with different breathing patterns. Another strength is the fact that EAdi was calculated with our own algorithm. Because of this, a more extensive analysis of the EAdi signal was possible in comparison to using the EAdi signal as filtered by the ventilators. Furthermore, irregularities of the EAdi signal could be tracked down to the raw EMGdi.

Limitations should be acknowledged. First, Ccw was estimated based on 4% of VC, possibly inducing an underestimation of Pmus at high loading levels. It would be better to calculate the true Ccw, although this is nearly impossible, as it includes sedating or hyperventilating subjects. Second, an inspiratory threshold loading device is used to vary the pressure that was generated by the inspiratory muscles. However, as the device is placed at the opening of the mouth, Pmo is varied rather than Pmus. This might lead to missing values (see Figure 9, panel D).

This study shows that multiple relationships are seen between EAdi and Pmus. This implies that the relationship is dependent on force-length and force-velocity relationships, as shown in previous literature [4-6, 26], and that a linear relationship is not sufficient to describe the correlation. More research has to be done before Pmus can be estimated based on EAdi at the bedside. It is recommended that the force-length and/or force-velocity relationships are taken into account in future research. E.g. by including respiratory inductance plethysmography measurements, thoracoabdominal configuration and, hence, the force-length relationship can be integrated. Furthermore, a model of the respiratory system could give insights in the parameters affecting neuromechanical coupling. This would provide further understanding of the relationship between EAdi and Pmus.

Conclusion

To conclude, this study shows that EAdi cannot yet provide a clinical relevant estimation of patient effort in the entire physiological range in healthy individuals. Multiple relationships are seen between EAdi and Pmus and they might be influenced by the force-velocity and force-length relationships. A reasonable approach to tackle this issue could be to take thoracoabdominal configuration into account in future research.

7 - Minimal duration of expiratory holds to verify oesophageal pressure measurements

Introduction

Besides the EAdi signal, described in the previous two chapters, also oesophageal manometry is used to monitor patient effort [22]. Oesophageal pressure measurements are increasingly used as state-of-the-art monitoring technique in ventilated ICU patients. To test the filling volume and position of an oesophageal balloon, the ratio between Paw and Pes should be close to unity during an expiratory hold [27]. As a shorter expiratory hold is less uncomfortable for patients, this study focusses on determining the minimal duration of an expiratory hold to validate oesophageal pressure measurements.

Methods

Subjects

Data of 10 mechanically ventilated patients from the ICU of Amsterdam University Medical Centre, location VUmc, were used. Patients were ventilated in a partially supported mode and had two oesophageal balloon catheters in situ. Data were collected for the DiaPro study (Clinical Trials number: NCT03527797) and therefore recruitment of patients was in accordance with their inclusion and exclusion criteria, shown in Table 3. Recruitment took place based on the electronic health record.

Table 3: Inclusion and exclusion criteria for data used for Baydur length study

Inclusion criteria	Exclusion criteria
Age ≥ 18 years	Neuromuscular disorder
Signed informed consent	Severe bleeding diathesis (thrombocytes < $50 \cdot 10^9$/L, aPTT > 80 sec)
Mechanically ventilated ICU patient on NAVA or pressure support ventilation	Recent upper airway surgery
Mechanical ventilation is expected to continue for at least 24 hours	Proved air leakage in the pleural cavity

Design

This is an observational study and therefore randomisation and blinding are not applicable.

Methods of measurement

Included patients had an oesophageal balloon catheter (Nutrivent™, Sidam Biomedical solution, Modena, Italy) in situ. A pneumotach (Adult flow sensor, Hamilton Medical, Bonaduz, Switzerland) was placed between the patient and the mechanical ventilator (Servo-i or Servo-U, Maquet Critical Care, Solna, Sweden) to measure flow. Flow, Paw and Pes were recorded by a CE-certified measurement setup (BIOPAC MP160, BIOPAC Systems Inc., Goleta, California, USA) with a sample frequency of 250 Hz and were stored for offline analysis. During the measurement Baydur manoeuvres were performed, of which those with a value between 0.8 and 1.2 are stored as separate data files and used for data analysis.

Analysis

Offline analysis was done with Matlab version 2017a (MathWorks, Natrick, Massachusetts, USA). First, a moving average filter with a window of 40 ms was applied to Pes and Paw to smoothen these signals. Subsequently, the start of patient effort was determined in these signals, just like the maximum (Paw) or minimum (Pes). This was checked by visually inspecting whether the start of patient effort was defined as the start of drop in pressure. If this

was not the case, the start of patient effort was changed manually as the start of drop in pressure. Next, the delta drop in both pressures and the ratio Paw/Pes were calculated. Since a Baydur manoeuvre is considered reliable if this ratio is between 0.8-1.2, only manoeuvres with a ratio in this range were used for further analysis. Of these manoeuvres, Paw and Pes were synchronised based on the start of patient effort and a continuous Paw/Pes ratio was calculated. Subsequently, it was determined how many milliseconds after the start of patient effort the Paw/Pes ratio reached the reliable range of 0.8-1.2 and stayed stable for 40 ms thereafter. The value of 40 ms was chosen arbitrarily, based on visual inspection of the data. Lastly, we calculated the median amount of time, after the start of patient effort, after which the Paw/Pes ratio was stable in the reliable range for at least 40 ms.

The results are visualised in figures, in which the onset of patient effort is represented by a blue asterisk. The time that the Paw/Pes ratio is within the reliable range of 0.8-1.2 is depicted as a green line. Since in clinical practice the Paw/Pes ratio is calculated as the ratio of the maximal drops in pressure of Paw and Pes, the range is only shown till the minima of Paw and Pes. The first moment in time that the ratio is in the range for at least 40 ms is indicated by a red cross. The time between the red cross and minima of Paw or Pes is the gain in time that can be achieved.

Results

Figure 10 presents Paw, Pes and the ratio of Paw and Pes during an expiratory hold of a representative subject. As described above in the Method section, the time between the blue asterisk and the red cross is calculated. The median time between the start of inspiratory effort and the red cross is 198 ms [IQR 84-364 ms]. As such, an expiratory hold of 410 ms from the start of patient effort proves to be sufficient for validation of Pes measurements. Compared to giving an expiratory hold till the pressures reach a minimum, the method described above provides a gain in time of 676 ms [IQR 392-828 ms].

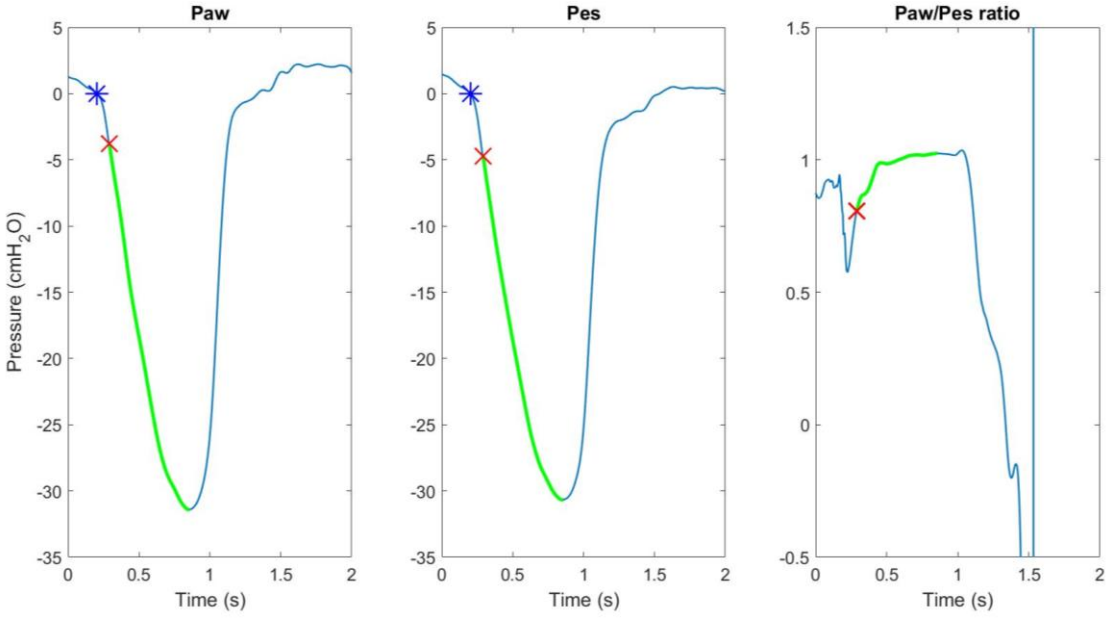

Figure 10: Airway pressure (Paw), oesophageal pressure (Pes) and the Paw/Pes ratio during one expiratory hold. The blue asterisk show the onset of patient effort. The green lines show the period of time that the Paw/Pes ratio is in the reliable range of 0.8-1.2. The red cross indicates the first moment that the ratio is stable in the reliable range for at least 40ms. Per expiratory hold manoeuvre the time between the blue asterisk and red cross is calculated.

Discussion

To our knowledge no previous literature is available in which the length of an expiratory hold for validation of Pes measurements was questioned. Strengths of this study are the reasonable amount of occlusions analysed and the fact that data are obtained from ICU patients. This gives insights in clinical conditions instead of trying to translate conclusions based on data of healthy volunteers to clinical practise.

However, a limitation of this study is the arbitrarily chosen time that the Paw/Pes ratio should be in the range of 0.8-1.2. By analysing more data it should be determined whether these 40 ms are chosen correctly. Furthermore, the study was conducted in a single centre and therefore generalisability of the results should be assessed.

Intrinsic positive end-expiratory pressure (PEEPi), neuromuscular paralysis and expiratory muscle activity can alter the curves of Paw and Pes. Chiumello and colleagues showed that neuromuscular paralysis and PEEP applied by the ventilator do not influence the Paw/Pes ratio [58]. However, they used delta drops in pressure for calculation of the ratio instead of the method used in this study. Therefore, and to study the effect of expiratory muscle activity and PEEPi, it should be assessed whether the proposed method can be used in patients with PEEPi, neuromuscular paralysis and expiratory muscle activity.

When implementing the proposed method in the ventilator software, not all breaths will be close to unity after 410 ms. Therefore, we propose to prolong the expiratory hold if unity is not reached after applying the expiratory occlusion for 410 ms until Paw and Pes reach a minimum. That way, the ratio of the delta drops in pressure can be calculated. If this ratio is close to unity the measurement is accepted, but otherwise the position and filling volume of the oesophageal balloon should be checked manually.

Conclusion

This study shows that an expiratory hold for verification of oesophageal pressure measurements can be reduced to 410 ms after the start of patient effort. In the future, automatic expiratory occlusions may be implemented within the ventilator software. This enables a continuous verification of oesophageal balloon measurement, increasing its clinical value.

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9 - Appendix

A1. Small amplitude peaks in remaining patients

Epochs of recordings with small amplitude peaks of two patients are shown below. When comparing the EAdi signal (top graph) with the EMG signal with cardiac artefacts (middle graph) of Figure 11, it can be seen that the heart beats every time that a small amplitude peak is seen. However, the pressure signal (bottom graph) shows a lot of fluctuations, which makes interpretation of this signal difficult. Nevertheless, based on experience it is concluded that the small amplitude peaks are not caused by functional diaphragmatic contractions, but rather by activity of the heart.

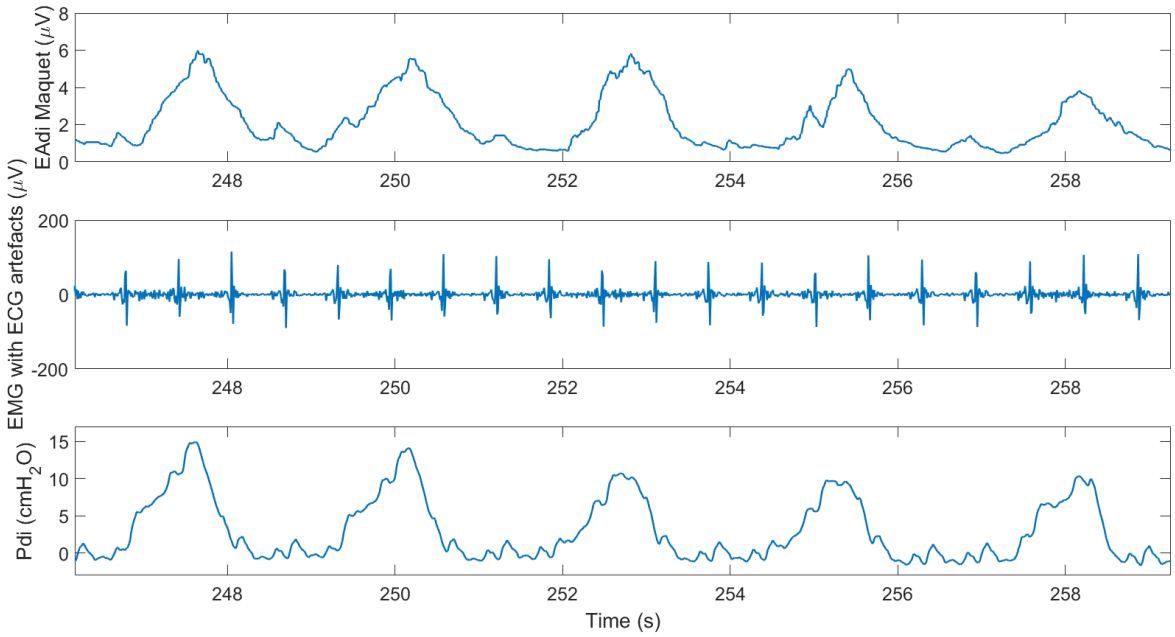

Figure 11: Epoch of a recording of EAdi as analysed by Maquet (top graph), EMG with cardiac artefacts (middle graph) and Pdi (bottom graph). In the EAdi signal small amplitude peaks can be seen.

The oesophageal balloon of the subject shown in Figure 12 was broken, due to which the Pes and Pdi signals were not reliable and only EAdi and the calculated ECG artefacts are shown. One small amplitude peak can be seen in the EAdi signal (top graph) and simultaneously the heart contracted, as can be seen in the bottom graph.

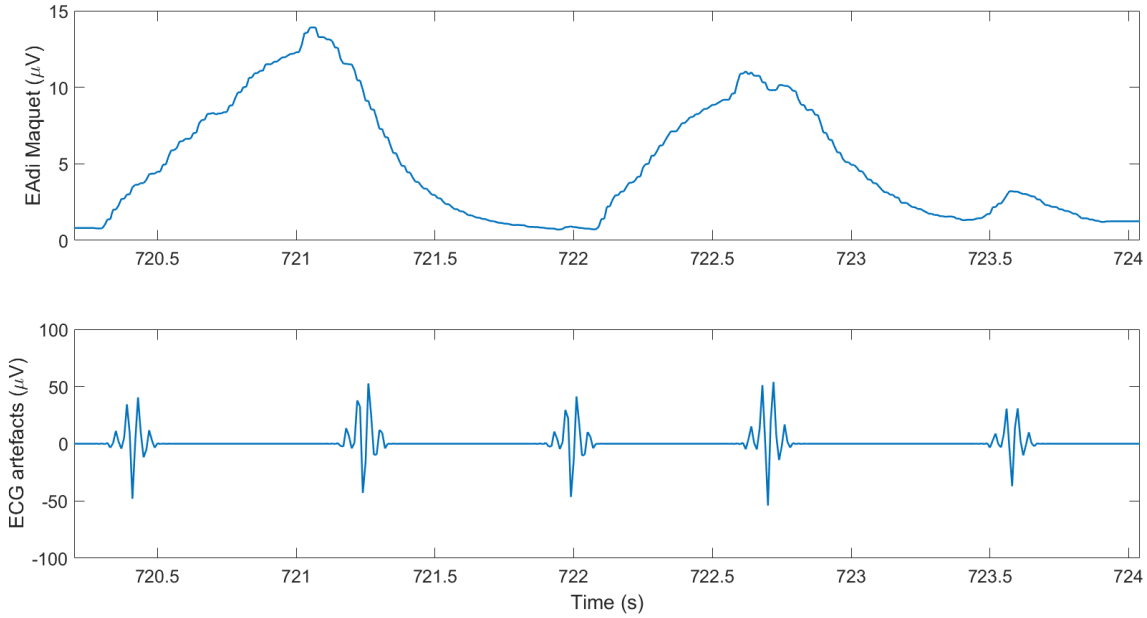

Figure 12: Epoch of a recording of EAdi as analysed by Maquet (top graph) and calculated cardiac artefacts (bottom graph). In the EAdi signal a small amplitude peak can be seen.

A2. Additional synchronisation of the small amplitude study

In the small amplitude peak study all signals (EAdi, Pdi or Pes and EMG with cardiac artefacts) were synchronised based on expiratory holds. However, additional synchronisation was necessary, since the part of the algorithm that calculates the ECG artefacts caused this signal to shift earlier in time. This additional synchronisation was done manually per patient by pairing recognisable diaphragmatic contractions in the EAdi and pressure signals.

B1. Flowchart of measurements of Edi2Pdi study

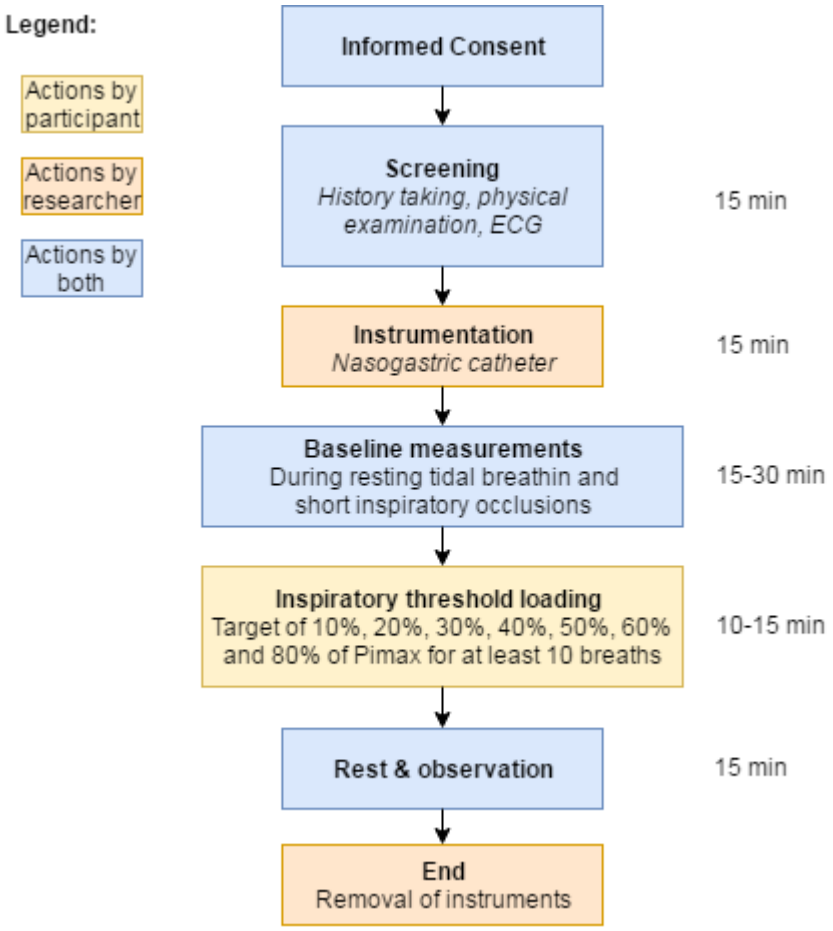

Figure 13: Flowchart of the measurements per participant that are performed in the Edi2Pdi study.