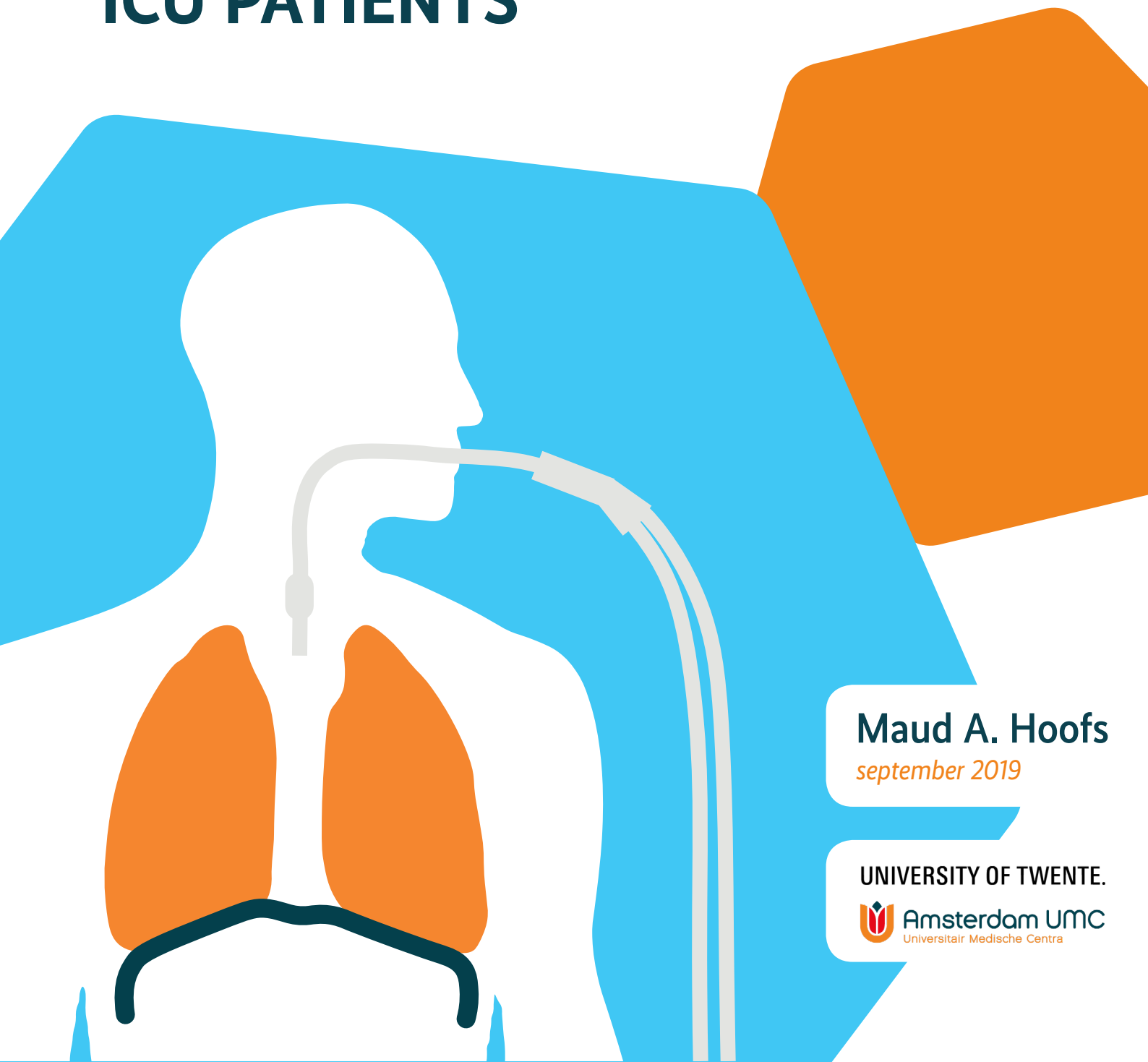
Master Thesis Technical Medicine

NON-INVASIVE DIAGNOSTIC TOOLS FOR THE EVALUATION OF DIAPHRAGM FUNCTION IN MECHANICALLY VENTILATED ICU PATIENTS



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PREFACE

Beste lezer,

In uw handen heeft u mijn afstudeerthesis van de master Technical Medicine, in de richting van Medical Sensing & Stimulation aan de Universiteit Twente. De afgelopen 11 maanden heb ik stage gelopen op de afdeling Intensive Care Volwassenen in het Amsterdam UMC – locatie VUmc te Amsterdam. Ik heb deze stage met veel plezier gedaan maar kon dat niet zonder de bijdrage van verschillende personen, die ik bij deze graag wil bedanken.

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Ik hoop dat u mijn afstudeerthesis met veel plezier zult lezen, ik heb er de afgelopen 11 maanden hard aan gewerkt.

Met vriendelijke groet,

Maud Hoofs

ABSTRACT

INTRODUCTION: Diaphragm dysfunction is a common complication in critically ill mechanically ventilated ICU patients. Monitoring diaphragm function could help in facilitating diaphragm protective ventilation. The current gold standard for assessing diaphragm function, transdiaphragmatic pressure (Pdi), is invasive and has disadvantages. Ultrasound has been proposed as an alternative to assess diaphragm function, but basic measurement options, such as fractional thickening, are not sufficient. More sophisticated ultrasound techniques, speckle tracking and tissue Doppler imaging (TDI), could be used to assess diaphragm function. Furthermore, the airway occlusion pressure in the first 100ms (P0.1) is a measure for respiratory drive and could be of use to assess the pressure produced by all the respiratory muscles. Thus, the aim of this research is to evaluate the role of different non-invasive monitoring tools for the evaluation of diaphragm function in mechanically ventilated ICU patients.

METHODS: Speckle tracking and TDI (color and pulsed wave (PW)) have been tested upon their feasibility in assessing diaphragm function. An algorithm for speckle tracking has been developed and tested by repeated measurements (5 times). Furthermore, color-TDI was tested upon reliability and validity in healthy subjects (n=5) by repeated, simultaneous measurements of flow and breathing along a fixed breathing pattern. M-mode measurements were performed as control measurement.

Besides ultrasound, P0.1 was compared to the pressure generated by all the inspiratory muscles (Pmus) based on two different methods, the Mancebo and the Maquet method, and were compared to control values of ICU patients on supported ventilation (n=14).

RESULTS: Speckle tracking as it was available at the ICU was not feasible to assess diaphragm function. However, developing an algorithm was feasible, and showed a similar mean and small standard deviation, except for some cases where the tracking was unsuccessful.
Pulsed wave TDI was proven to be not feasible. Color-TDI was feasible to assess diaphragm function and had a coefficient of variance of 6.6% per breath. Repeated measurements showed similar coefficient of variances between TDI and M-mode (15% to 11% for inspiration and 10% to 15% for expiration, respectively). Displacement values for M-mode were considerably higher than measured in color-TDI. Color-TDI had a lower correlation for inspiration and expiration (R^2=0.49 $p<0.001$) compared to M-mode (R^2=0.94 $p<0.001$).

P0.1 was not correlated with Pmus, as P0.1 values between 1.5 and 3.5 cmH_2O corresponded to Pmus values between 3 and 21 cmH_2O.

CONCLUSION: More sophisticated ultrasound techniques, speckle tracking and tissue Doppler imaging, as available at the ICU, are not yet applicable to assess diaphragm function. Speckle tracking could potentially be a technique to assess diaphragm function but needs further improvement and testing. P0.1 and Pmus are not correlated and P0.1 does not represent total inspiratory effort of the muscles.

LIST OF ABBREVIATIONS

aCMQ	Automated Cardiac Motion Quantification
Ccw	Compliance of chest wall
CV	Coefficient of variance
ICU	Intensive care unit
P0.1	Airway occlusion pressure developed in 100ms after onset of inspiration
Pab	Abdominal pressure
Pcw	Pressure gradient over the chest wall
Pdi	Transdiaphragmatic pressure
PEEP	Positive End Expiratory Pressure
Pes	Esophageal pressure
Pga	Gastric pressure
Pmus	Pressure generated by all the respiratory muscles
Ppl	Pleural pressure
PW-TDI	Pulsed wave tissue Doppler imaging
SD	Standard deviation
TDI	Tissue Doppler imaging
VC	Vital Capacity
VILI	Ventilator induced lung injury
Vt	Tidal Volume
VTI	Volume time integral
WOB	Work of breathing

CONTENT

1 INTRODUCTION

Mechanical ventilation is started in 45% of the patients admitted to the Intensive Care Unit (ICU) in the first 24-hours of admittance[1]. Patient are weaned from the ventilator as soon as possible as prolonged ventilation is associated with several complications. Complications include poor outcome, pneumonia, delirium, thrombosis and higher health care costs[1]. Prolonged ventilation may lead to ventilator induced lung injury, due to the forces and stress applied to the lungs, and critical illness associated diaphragm dysfunction[1-4]. Research into the direct effects of mechanical ventilation on the inspiratory muscles showed muscle weakness, in which the diaphragm was most affected [5-7]. The acquired respiratory muscle weakness also showed to affect weaning trials as it delayed proper weaning of the ventilator by 7-10 days and increased mortality[8]. Monitoring diaphragm function could help in facilitating diaphragm protective ventilation, however monitoring options- for the diaphragm are limited and to date inadequately used[2]. Furthermore more research is necessary in the most optimal strategy and reference values for diaphragm protective ventilation[9].

To limit ICU acquired diaphragm weakness several measurement options have been proposed over the years. The current gold standard for the assessment of diaphragm function is the measurement of transdiaphragmatic pressure (Pdi) using a nasogastric catheter equipped with air-filled balloons placed in the esophagus and stomach. However, measuring the Pdi is invasive and requires additional technical expertise. Moreover, interpretation of the results can be complex and the results might not be conclusive [2, 10]. Furthermore the balloons used for measuring Pdi are very dependent on placement and volume inside the balloon [2].

Another technique that is increasingly used for the assessment of diaphragm function is ultrasound. Ultrasound has several advantages, such as low-costs, non-invasive, available bed-side and straightforward calculations[11, 12]. However, when considering fractional thickening of the diaphragm a poor correlation ($R=0.28$ $p<0.01$) with transdiaphragmatic pressure was found. Furthermore, the reproducibility of measuring the fractional thickening was low [13, 14]. Basic measurements may therefore not be sufficient for adequate evaluation of diaphragm effort. This indicates a need for more advanced ultrasound measurement techniques such as speckle tracking or tissue Doppler imaging[14-18]. However the feasibility and measurement quality of these techniques has not been tested in ICU mechanically ventilated patients yet.

Another technique which monitors the respiratory drive is the airway occlusion pressure (P0.1) developed in 100ms after onset of inspiration[19, 20]. The P0.1 measurement is non-invasive and is available in almost every modern ventilator. The P0.1 was shown to correlate to work of breathing (WOB)[20] however, using WOB has limitations as volume displacement is needed for WOB to be calculated. The pressure derived from all the respiratory muscles might better correlate to P0.1 as it takes into account pressure changes during isovolumetric contractions.

The aim of this research is to evaluate the role of different non-invasive monitoring tools for the evaluation of diaphragm function in mechanically ventilated ICU patients. Diagnostic

tools include sophisticated ultrasound techniques such as speckle tracking and tissue Doppler imaging, and evaluation of P0.1. The diagnostic tools are believed to improve the non-invasive diagnostic opportunities to evaluate diaphragm function in mechanical ventilated ICU patients.

Part I: BACKGROUND

2 CLINICAL BACKGROUND

2.1 RESPIRATION

The primary function of the respiratory system is the exchange of oxygen and carbon dioxide between the atmosphere and blood. The respiratory system is controlled by rhythmic stimulation of the respiratory muscles by the respiratory control centers in the medulla. The respiratory centers can alter the respiration based on metabolic demands. Metabolic demand is based on the arterial blood gas parameters, PO_2, PCO_2 and pH[21].

The primary muscles of inspiration include the diaphragm and intercostal muscles. During a forced inspiration the accessory muscles are innervated to accommodate with respiration. The accessory muscles of respiration are the sternocleidomastoid, scalenes, trapezii, latissimus dorsi, pectoralis major and minor muscles[21, 22]. During tidal breathing expiration is mainly a passive process, that happens due to the elastic recoil of the lungs. When the load imposed on the respiratory muscles increases or the inspiratory muscles capacity is low, expiratory muscles are activated. The expiratory muscles include the abdominal wall muscles (internal and external oblique, rectoabdominal and transverse abdominal muscles), intercostal muscles and the neck and back muscles[21].

2.2 DIAPHRAGM

The diaphragm is the main muscle of inspiration that separates the thorax and abdomen and contributes for approximately 70% of inspiratory tidal volume in a healthy individual[23]. The diaphragm consists of radiant muscle fibers which connect to a tendinous portion. As the diaphragm is a round structure it has several inserting points, including the sternum, inferolateral rib cage and lumbar vertebral bodies[22].

The diaphragm is innervated through the phrenic nerve that originates from C3 to C5. The diaphragm has a central dome with peripheral elliptical cylinder of muscle fibers called the zone of apposition. During contraction the zone of apposition shortens and a downward displacement of the dome is initiated[22].

The downward displacement of the diaphragm results in an expansion of the thoracic cavity, together with an outward displacement of the lower rib cage results in a negative pleural pressure along with lung expansion. During tidal breathing the intrapleural pressure goes from -5 cmH2O to -10 cmH_2O. Due to pressure change of 5cmH_2O, air will flow into the lungs. Given that normal lung compliance is 100mL/cmH_2O, a tidal breath of around 500mL will be reached[24]. The elasticity of the lung, relaxation of the diaphragm and activation of abdominal muscles result in a decrease of the thoracic cavity causing air to be exhaled and accommodate an exhalation[21] see Figure 1.

2.3 MECHANICAL VENTILATION

Patients who have a (potential) threat to one or more vital functions/organs and require intensive monitoring are admitted to the intensive care. When patients are admitted to the

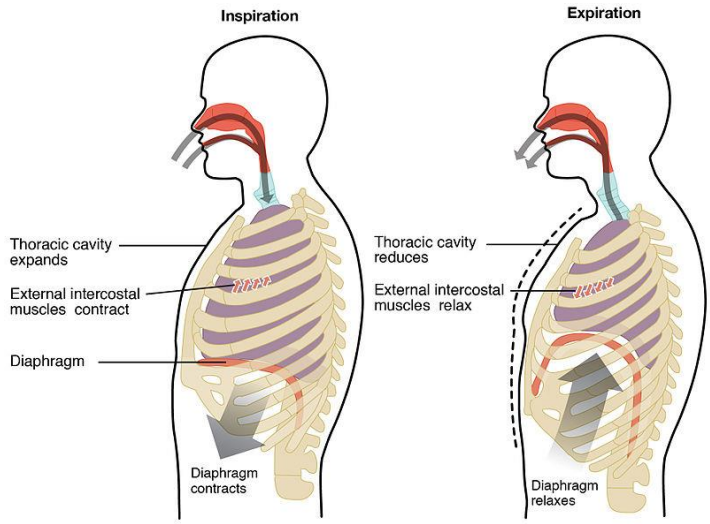

Figure 1 In this figure the dynamics of breathing is displayed. In the left figure the diaphragm moves downwards and the intercostal muscles contract expanding the thoracic cavity, resulting in an inward airflow. In the right figure the diaphragm relaxes, moving upwards again, alongside relaxation of the intercostal muscles, decreasing the thoracic cavity and resulting in the exhalation of air.

Intensive Care Unit (ICU) 45% of these patients need to receive mechanical ventilation in the first 24-hours of admittance[1]. Indications for mechanical ventilation are acute respiratory failure (i.e., acute exacerbation of chronic obstructive pulmonary disease, acute respiratory distress syndrome, pneumonia and pulmonary embolism), coma, and neurological disorders[25]. The main function of mechanical ventilation is to decrease the work of breathing, and to reverse hypoxemia or acute progressive respiratory acidosis[21, 25]. Patients will stay on ventilation until the primary cause for mechanical ventilation is cured. To get the patient off the ventilator the patient will undergo a weaning trial. During a weaning trial the ventilator support is gradually or abruptly withdrawn. The weaning trials are meant to assess the patient's ability to breath without support.

2.3.1 Physiology

Mechanical ventilation can either be invasive or non-invasive depending on the demand of the patient. In the past the ventilators were based on negative pressure, and simulated a decrease in pleural pressure to provide for ventilation. Nowadays ventilation is given through positive pressure ventilation. The function of the ventilator is to decrease the work of breathing and to supply the alveoli and arterial system with oxygen through a provided volume of gas[24, 25].

2.3.2 Types of ventilation

There are many mechanical ventilation modes available, for example pressure-control, volume-control or pressure support ventilation. As is visible from the examples ventilation can be given though controlled or assisted ventilation. In controlled ventilation either the pressure or the volume is set, and every breath is given to the patient according to the set parameters. In controlled ventilation the patient is put on a fixed breathing pattern. In assisted ventilation the patient triggers the ventilation; when the patient triggers the ventilator (i.e., through a drop in airway pressure or flow), the ventilator provides a positive pressure according to the set parameters [24].

2.3.3 Effect of ventilation

Despite being life-saving, mechanical ventilation can also be a potential harm to the patient. Mechanical ventilation can cause damage to the respiratory system also known as ventilator induced lung injury (VILI). Overdistention of the lung is one of the key causes of VILI, and limiting inflation pressure is used as strategy to limit overdistention [26]. Especially the difference between alveolair pressure and pleural pressure (transpulmonary pressure) needs to be kept low to prevent lung stretching. Furthermore lowering the tidal volumes (6ml/ predicted bodyweight) limits the posibbilty of overdistention of the lung (volutrauma) due to the tidal volumes[26]. Additionally atelactrauma, trauma caused by repetitive opening and closing of airway and lung units, also contributes to VILI and setting Positive End-Expiratory Pressure (PEEP) reduces the risk of atelectrauma[26]. Alongside VILI, diaphragm dysfunction has a high prevalence in critically ill patients and is associated with prolonged ventilation and readmission[8, 27]. Ventilator induced diaphragm dysfunction is multifactorial and can be caused by different mechanism, such as disuse atrophy due to ventilator over-assist, or excessive loading when under-assisted.

2.3.3.1 Disuse atrophy of the diaphragm

Levine et al. were the first to describe diaphragm muscle loss in patients on mechanical ventilation. They found a significant lower cross-sectional area in 14 brain-dead organ donors who had been ventilated for 18 to 69 hours before organ harvest compared to patients referred for elective lung cancer surgery. In their research the pectoralis muscle was less affected suggesting the diaphragm is more sensitive to the effects of disuse. The patient group is however not directly comparable to ICU patients[28]. Hooijman et al. studied diaphragm biopsies of ICU patients and found a difference of 25% in cross-sectional area in ICU ventilated patients (mean of 7 days) compared to elective surgery patients[5]. Furthermore Jaber et al. found a decline of 30% in endotracheal tube pressure induced by magnetic stimulation in the first 5-6 days of mechanical ventilation[7]. Similarly, Demoule et al. found that 80% of the patients who have been on mechanical ventilation for more than 5 days develop respiratory muscle weakness[6]. These studies provide evidence of disuse atrophy in mechanically ventilated patients, it might therefore be beneficial to maintain adequate levels of effort during mechanical ventilation to prevent diaphragm weakness due to disuse atrophy[29].

2.3.3.2 Excessive loading of the diaphragm

In contrary to over-assist of the ventilator there is also evidence that under-assist can be harmful for the diaphragm. In an animal study performed by Jiang et al. it was found that when exceeding the fatigue threshold excessive loading led to diaphragm injury[30]. This was also proven in the study performed by Orozco-Levi et al. into diaphragm injury after inspiratory loading. In their study they found sarcomere disruption in all diaphragm samples, which was significantly higher after inspiratory loading and even more evident in patients with COPD[31]. Diaphragm injury after inspiratory loading also affects contractile function as Laghi et al. showed that inspiratory loading caused a decrease in transdiaphragmatic twitch pressure using magnetic stimulation even after 24-hours in 12 healthy subjects[32].

A balance between over-assist and under-assist from the ventilator should be sought to prevent diaphragm weakness in mechanical ventilated patients.

3 TECHNICAL BACKGROUND

To overcome the problems of over-assist and under-assist of the mechanical ventilator monitoring tools are needed. Only with sufficient monitoring tools a diaphragm-protective ventilation strategy can be sought. There are to date several monitoring tools available such as transdiaphragmatic pressure, P0.1, electromyography and ultrasound. For this thesis the focus is on the transdiaphragmatic pressure, P0.1 and ultrasound.

3.1 TRANSDIAPHRAGMATIC PRESSURE

One of the measures to assess the diaphragm is calculating the pressure developed across the diaphragm, the transdiaphragmatic pressure (Pdi). During normal tidal breathing, the pleural pressure decreases and abdominal pressure increases, resulting in the transdiaphragmatic pressure (P_{di}), according in the following formula:

$$P_{di} = P_{ab} - P_{pl} \quad (1)$$

As the abdominal and pleural pressure are not directly measureable surrogates have been proposed in the gastric and esophageal pressure (Pga and Pes, respectively)[33]. As the Pdi is calculated as a difference between Pes en Pga it is assumed to be less influenced by other mechanisms than the diaphragm. During for example intercostal involvement the differences are both transmitted to the abdomen as well as the thorax, leaving the changes in Pdi to be contractions of the diaphragm. The esophageal and the gastric pressure are calculated by air containing latex balloons sealed over catheters, which are placed in the esophagus and in the stomach. Pes was shown to be a useful estimation of the mean pleural pressure and it can help in recognizing the cause of ineffective efforts[11, 33]. Setting up the balloons imposes some difficulties, as the volume of the balloon, the pressure inside the balloon and the dimension of the catheter can all influence the measurements[10]. Furthermore, the catheter needs to be placed at the exact position for the measurement to be interpreted correctly[33]. This makes that the balloons are currently mainly used for research purposes and not widely implemented in routine clinical practice [2, 33].

3.2 ASSESSING BREATHING EFFORT

3.2.1 Po.1

Another non-invasive measure to assess respiratory drive is the airway occlusion pressure, the pressure developed in the occluded airway 100ms after onset of inspiration. During support ventilation the ventilator is occluded for a short time instance in which the patients develops a negative pressure. Whitelaw et al. were the first to measure the P0.1 by taking the decrease in 100ms of an occluded breath. They found the P0.1 to be relatively constant, consistent for every patient and it correlated better with end-tidal CO2 compared to minute ventilation[34].

The P0.1 is considered a good measure of respiratory center output due to several characteristics. The P0.1 is not influenced by any conscious or unconscious reaction as there is a delay of at least 150ms for a respiratory reaction[34]. The airway pressure is independent of the elastic recoil pressure as during an occluded breath at functional residual capacity (FRC)

the elastic recoil of the lungs or thorax is zero. Furthermore no changes in lung volume are seen as there is no flow of gas, and therefore the measurement is independent of flow resistance or compliance of the system. Also no inhibitory reflexes or modification to the force-velocity relationships are induced as there is no change in volume in 100ms[19, 34].

3.2.2 Work of breathing

Work of breathing is the most classic method of measuring breathing effort. Work is the force per certain distance. Work of breathing in the respiratory system is calculated when a pressure changes the volume of the system, see equation 2. Where P is the pressure in cmH2O and V is volume in liters.

$$WOB = P\ (cmH_2O) \times V(L) = \int P\ dv\ (J) \tag{2}$$

Calculating the WOB of every breath requires technical expertise and measurement of Pes. There are some limitations to using the WOB, first WOB is only positive when a volume is displaced, the WOB is insensitive to isometric contractions. Furthermore the frequency and duration of the contractions are not taken into account. The same tidal volume and pressure could be generated in twice the amount of time consuming substantially more energy[11].

Mancebo et al. found a correlation (R ranged from 0.71 to 0.83) between the WOB and the P0.1[20]. A correlation of R=0.71 is however quite low in using the P0.1 value to accurately predict WOB.

3.2.3 Pmus

When respiratory load increases additional muscle groups are recruited. The pleural pressure depends on the pressure generated by all the respiratory muscles (Pmus) and the pressure gradient over the chest wall (Pcw):

$$Ppl = Pmus + Pcw \tag{3}$$

The formula for Pmus:

$$Pmus = Ppl - Pcw \tag{4}$$

Pcw is often calculated by dividing the inspired volume (Vt) by the theoretical compliance of the chest wall (Ccw) (4% of vital capacity (VC)). As Ppl could be estimated by Pes the following formula for Pmus is used,

$$Pmus = Pes - \frac{Vt}{0.04 * VC} \tag{5}$$

During an isovolumetric contraction the WOB would be considered 0, however pressure differences can be obtained. As the Pmus accounts for all the respiratory muscles involved in

respiration and on the contrary of WOB is less dependent volume displacement it might provide a better correlation to the respiratory drive, to P0.1.

3.3 ULTRASOUND MEASUREMENTS OF DIAPHRAGM

3.3.1 General

Ultrasound is widely used in the clinic, as it is bedside applicable, easy to perform and non-invasive. Ultrasound can also be used for the evaluation of diaphragm function [2, 35]. B-mode ultrasound can be used to assess the diaphragm thickness in the zone of apposition. This is done by placing a linear array transducer (> 10 MHz) between the ninth and tenth intercostal space, near the midaxillary line perpendicular to the chest wall see left part of Figure 2. Another way of visualizing the diaphragm can be done by placing a small low-frequency transducer (2-5 MHz) subcostally. The diaphragm is then visualized as a hyperechoic line above the liver or spleen, which approaches the probe during inspiration (i.e., caudal displacement) [36], see Figure 2.

B-mode ultrasound is used in the ICU as a screening tool for diaphragm function. It can be used to evaluate diaphragm motion, diaphragm thickness and muscle contraction[2, 11, 35]. In the B-mode several calculations such as the fractional thickening, changes in absolute

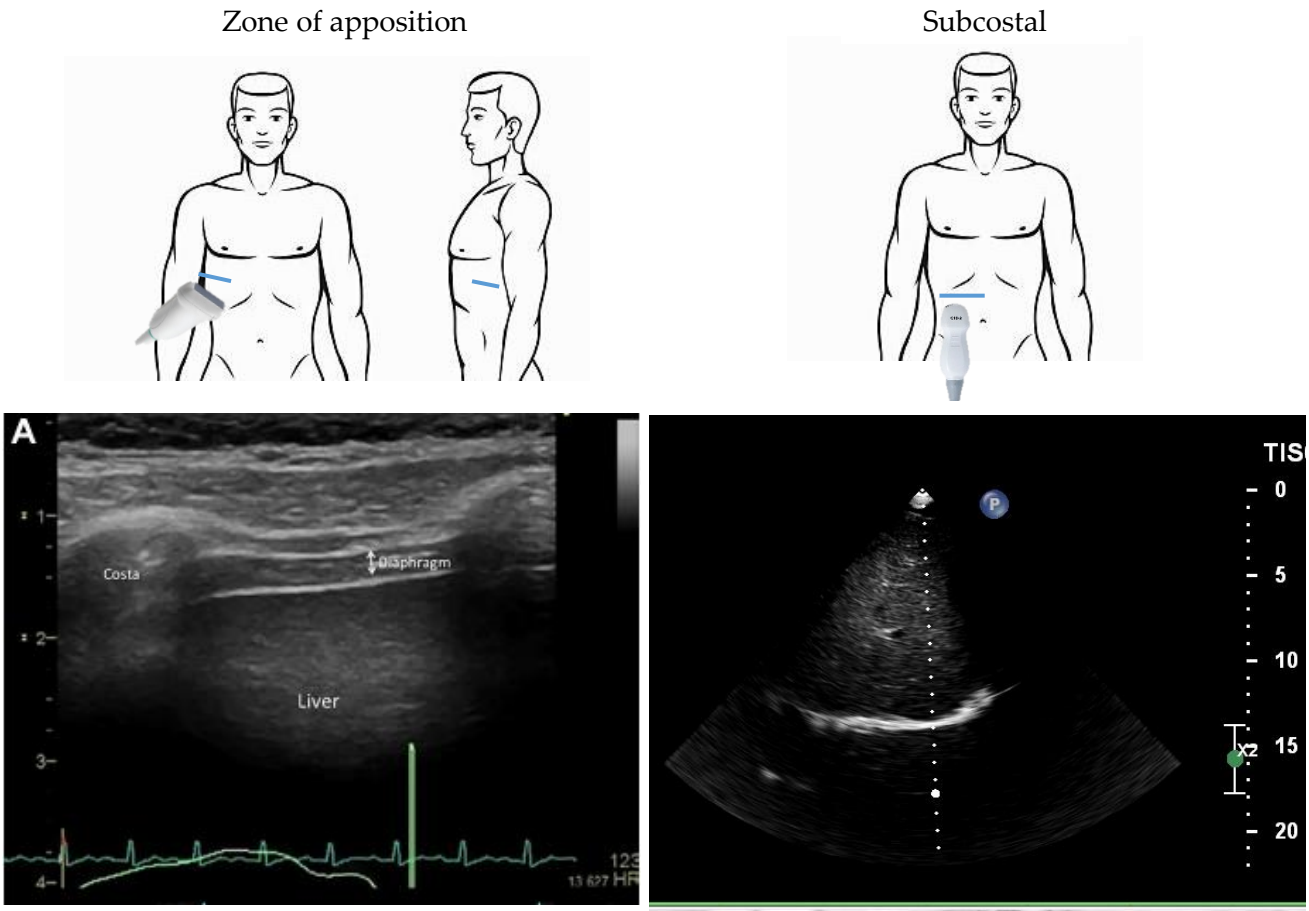

Figure 2 Different ways of visualizing the diaphragm with ultrasound. With on the left side the zone of apposition window and on the right the subcostal window. In the top figures the location of the probe are visualized and marked at the blue lines. The bottom figuress are the corresponding ultrasound images.

thickness and movement of the diaphragm can be performed[2, 11, 14, 37]. Fractional thickening is calculated according to the following formula:

$$Fractional\ thickening = \frac{thickness\ at\ peak\ inspiration - thickness\ at\ end\ expiration}{thickness\ at\ end\ expiration} \quad (6)$$

These calculations are however not sufficient enough to accurately predict the function of the diaphragm. Fractional thickening only had a poor correlation with Pdi (R=0.28 p<0.01)[13, 37]. The diaphragm thickness measured is highly dependent on the placement of the transducer, due to heterogeneity of the diaphragm. Furthermore, the fractional thickening had a high inter-observer variability, with changing diaphragm thickness and thickness fraction within several days, not assumed to be caused by atrophy[37]. This was probably due to the diaphragm only being a very thin muscle (1.7-2 mm) and slight changes in ultrasound angle can already change the measured thickness of the diaphragm. To accurately assess the thickness of the diaphragm the ultrasound needs to accurately assess changes less than 0.5 mm. Depending on the transducer used the minimal measurable distance the ultrasound can measure is calculated according to:

$$\lambda = \frac{v}{f} \quad (7)$$

with λ being the wavelength, v the velocity of sound waves and f the frequency of the transducer. With the speed of sound waves in the human tissue being around 1540 m/s and a 15MHz transducer the smallest wavelength is $(\frac{1540}{15 * 10^6} = 1 * 10^{-4} m =)$ 0.1 mm. The spatial axial resolution, the ability to distinguish between two separate objects, is calculated through:

$$Spatial\ axial\ resolution = \frac{spatial\ pulse\ pusle\ length}{2} = \frac{\#\ of\ cycles * wavelength}{2} \quad (8)$$

The spatial pulse length is the product of the wavelength and the number of cycles in a pulse of ultrasound. Assuming the number of cycles is 2, the spatial axial resolution is $\left(\frac{0.1*2}{2}\right) = 0.1\ mm$ Meaning the smallest sized object that can be detected is 0.1mm. Consequently changes in diaphragm thickness can be difficult to accurately measure. Therefore more sophisticated ultrasound techniques need to be used to accurately assess diaphragm function. More sophisticated analyses include speckle tracking and tissue Doppler imaging and will be compared against the current gold-standard M-mode.

3.3.2 M-mode

From the B-mode image a line can be chosen to assess the movement of the echogenic point on that line. Which results in a movement pattern of the points over time, see Figure 3 for an example. The M-mode for diaphragm is mainly used in the subcostal window, to assess the diaphragm motion as it measures the caudal displacement of the diaphragm during inspiration[2]. The diaphragm moves around 1.6-1.8 cm during quiet breathing and can go up to 7.5 cm during deep breathing[11, 38]. A disadvantages of M-mode is the line dependency, as the movement is visualized over just one linear line. Furthermore if the line is not placed in the same direction of the movement the distance measured could be under or overestimated [16-18].

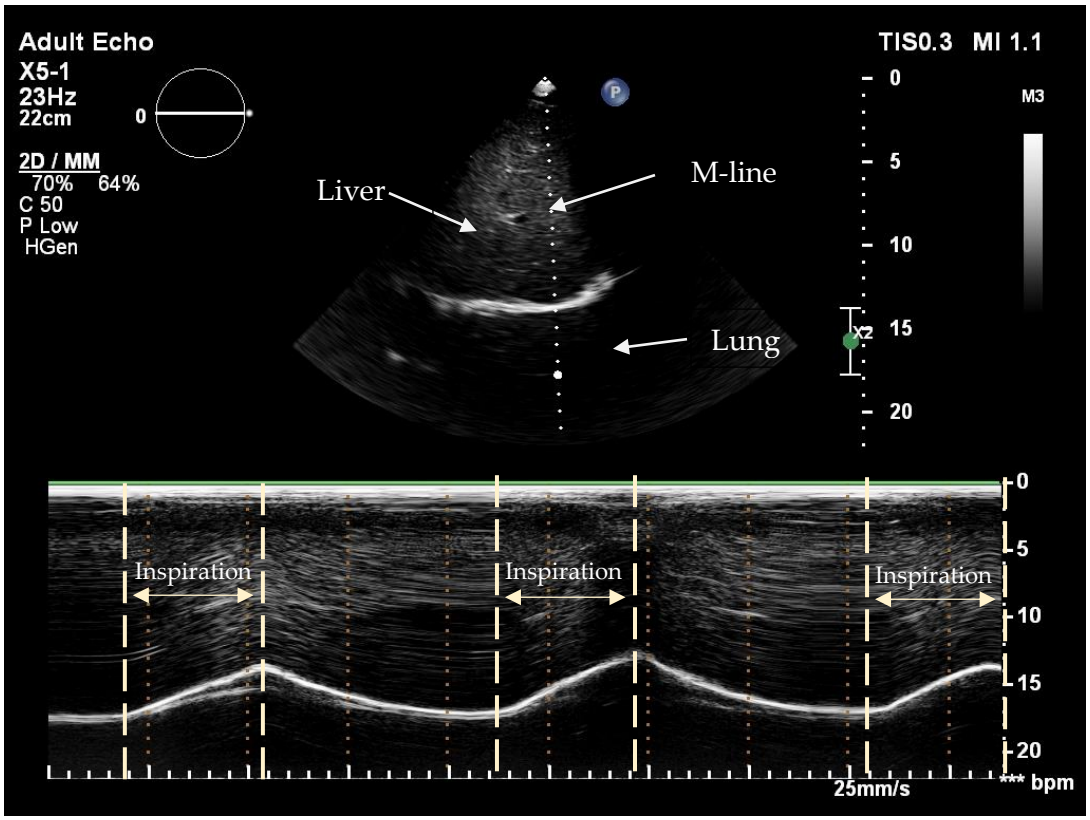

Figure 3 M-mode of the diaphragm, in the subcostal window with three inspirations visible marked in between the dotted lines. The echogenic line in the bottom figure is the tracing of the echogenic diaphragm line along the M-line

3.3.3 Speckle tracking

A method which has been widely used in the cardiology might also be of use in the measurements of diaphragm function when looking at ultrasound is speckle tracking. Speckle tracking is a 2D ultrasound technique that is mainly used in the cardiology to measure the strain of the ventricles. Speckle tracking is a technique that makes use of grey value patterns in ultrasound. A speckle, a grey constant value pattern which is equal to a small region in muscle tissue, is tracked from one frame to another during a contractile cycle. So a speckle is tracked in 2D during a breath, with the tracking being angle-independent and a two-dimensional quantification of the percentage of deformation (strain) and velocity of deformation (strain rate) can be calculated[14]. Strain (ε) and strain rate (ε') are calculated according to the following formula:

$$\varepsilon = \frac{L - L_0}{L_0} \tag{9}$$

$$\varepsilon' = \frac{\delta\varepsilon}{\delta t} \tag{10}$$

In several studies the use of speckle tracking for the diaphragm was tested in healthy individuals and showed to be feasible[14, 39, 40].

In the study by Oppersma et al. (2017) a correlation was found between the strain and strain rate and the Pdi (R^2= 0.72 and 0.80) in healthy subjects[14]. In the study of Oppersma et al. (2017) the ultrasound images were obtained in the zone of apposition view, see left figure of

Figure 2. In their study the strain measurements were done by placing a range of interest on the peritoneal and the pleural line and tracking the movement of the diaphragm, see Figure 4.

In the study done by Goutman et al. (2017) the speckle tracking was used for a different purpose. Instead of using the speckle tracking for strain measurements the speckle tracking was used for diaphragm excursion measurements instead of using the M-mode (see Figure 5)[39]. The absolute excursion of the diaphragm is calculated by using Pythagoras on the measured x and y direction ($excursion = \sqrt{x^2 + y^2}$). One of the disadvantages of M-mode, line dependency of M-mode, is solved when using speckle tracking for the excursion measurements as the absolute excursion is calculated.

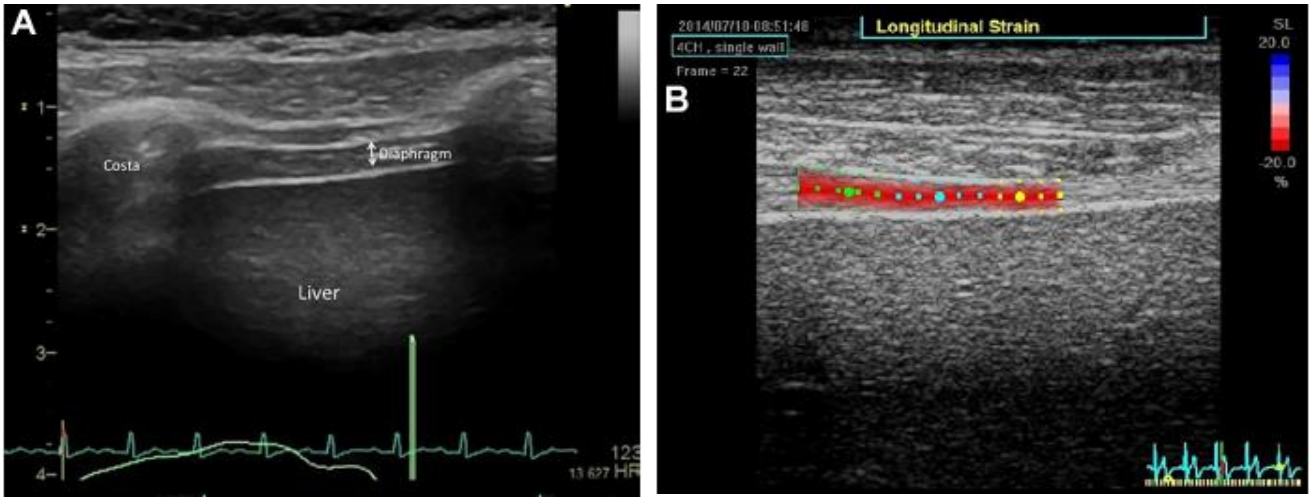

Figure 4 A: B-mode picture of the diaphragm as scanned in Oppersma et al. (2017). Where the diaphragm is visualized as the muscle between two costa, with the liver below the diaphragm. B: Region of interest used for the speckle tracking software of GE Healthcare. Several markers are placed on several speckles, tracking the diaphragm during the contraction.

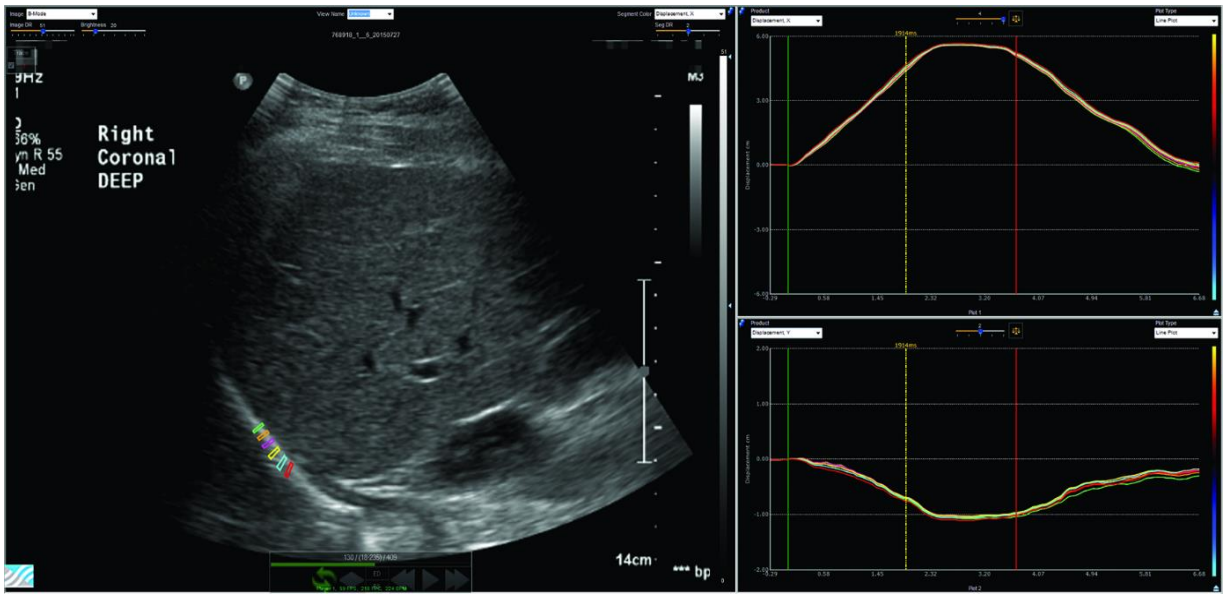

Figure 5 B-ultrasound image on the left with regions selected for speckle tracking, in the subcostal window. On the right the displacement in both the x (top) and y (bottom) direction, with on the x-axis time and y-axis displacement in cm. Image derived from Goutman et al.

3.3.4 Tissue Doppler Imaging

Another ultrasound technique which is borrowed from the cardiology is tissue Doppler imaging (TDI). Tissue Doppler imaging uses the same principle of Doppler, the phenomenon whereby the frequency of a reflected sound is altered by movement of the reflecting surface away or towards the source. When the blood cells are the reflective surface, the shift in frequency provides information regarding the velocity of blood flow, also called the flow Doppler. As every surface that moves creates a frequency shift also the velocities of moving tissue can be used for Doppler analysis. Moving tissue generate low frequency shifts but with high energy. Therefore for TDI to work the settings are the opposite of the settings used in flow Doppler. In TDI the high frequencies are filtered out instead of the low frequencies being filtered out for flow-Doppler [41].

With TDI the velocities of the tissues are calculated. The velocities can either be measured with pulsed wave-TDI (PW-TDI) or color-TDI. PW-TDI is based on the spectral density analysis. Color-TDI is based on the autocorrelation technique. Pulsed wave acquires the velocities only at one point in time whereas color-TDI can acquire similar pixel velocities across a larger image. See Figure 6 for an example of PW-TDI and Color-TDI.

In PW-TDI the Doppler signal from one sample region is collected. The signal is split into different overlapping windows, in each window the frequency content is calculated through Fourier analysis. Resulting in the frequency content over time through a signal spectrum of each window. The resulting Doppler frequency is linearly related to the tissue velocity, thus the frequency content over time represents the velocity of the tissue over time[42].

In color-TDI all the velocities are sampled, meaning a Doppler signal is derived for each depth and ultrasound beam. This is done by sending two pulses successively, and then calculating the difference in phase shift between the two pulses by autocorrelation and repeating this for all the samples. The difference in phase shift can be used to calculate the velocity of the tissue.

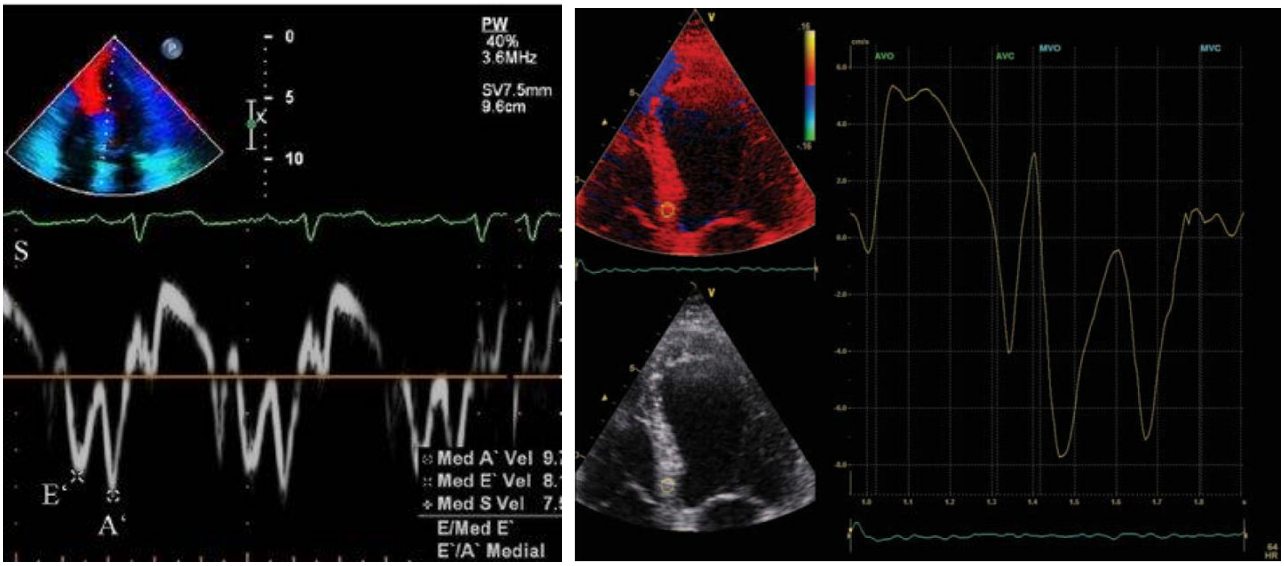

Figure 6 Left figure: PW-TDI of the mitral annulus with peak velocities. In the top window a sample volume is selected and the velocities alongside time are depicted below. Derived from: Kinova et al (2012). Right image: Color-TDI of the ventricle wall with the velocity trace of the yellow represented in the graph on the right. With the average velocity per second. Derived from: Marwick et al. (2007)

When the velocity is estimated for all the parts of the ultrasound image the pixels are color coded based on the velocity. Resulting in an image with different coloring based on the velocity and direction of the velocity. As color-TDI samples different points together it is an average velocity of the tissue, and can sometimes underestimate the velocity due to also integrating the stationary echoes in the velocity integral. The velocities measured are therefore the main velocity of regional contraction instead of specific local function [42, 43].

Only in the last two years has PW-TDI been tested to assess diaphragm function[17, 44]. In the abstract of Soilemezi et al. PW-TDI was used to assess the diaphragm. In their study TDI parameters were compared against similar Pdi parameters, with a significantly high correlation between the TDI-derived maximum relaxation rate and the Pdi maximum relaxation rate ($R=0.93$, $p<0.001$)[17]. Two recent studies also tested the usefulness of PW-TDI on the diaphragm in which it was found to be reliable, correlated to diaphragm pressure and M-mode measurements[16, 18].

No literature was currently found on the use of color-TDI for the diaphragm. In a study by Knegt et al. (2012) M-mode, speckle tracking and color-TDI have been compared in cardiac patients on the mitral annular displacement and they found TDI to be the most robust method of the three, with the lowest inter- and intra-observer variability[45].

As was proven in these various studies TDI could potentially be an ultrasound technique to assess the diaphragm function. As TDI measures the velocity it is beneficial to M-mode as it can assess the contraction velocity as well as the relaxation velocity. M-mode can only measure an average velocity over the whole displacement and does not measure the velocities per time instance. Contraction velocity and relaxation rate could potentially be of use for the clinic as it can tell something about the fatigue of the muscle. This could be of interest during spontaneous breathing trials (SBT) to assess the patients ability to breath without support. When a muscle is fatigued the relaxation rate slows down[46]. When the relaxation rate of the diaphragm can be determined through TDI it could tell something about the physical state of the diaphragm.

Additionally TDI could be of potential use to assess regional contractility and mobility of the diaphragm as the velocities measured can tell something about the mobility of the diaphragm. Cardiology uses TDI for similar reasons to evaluate contractility and mobility of different parts of the ventricle wall[43].

Part II: ULTRASOUND RESEARCH

4 SPECKLE TRACKING: FEASIBILITY

Speckle tracking has been shown in several articles to be a potential superior method of assessing diaphragm contractility compared to conventional techniques. It is superior due to the angle independency, and its possibility to quantify deformation in the strain and strain rate compared to the highly variable fractional thickening[14, 39].

The feasibility of speckle tracking has been shown by these articles, but most of them are on healthy individuals. The feasibility of speckle tracking in ICU patients has not been proven. To use speckle tracking in the ICU it needs to meet certain requirements. Including, feasible to measure (it is possible to measure), the measurement needs to be reliable (repeated measurement give same results) and with a good validity (does it measure what it is supposed to measure). The aim of this research is to test the feasibility of speckle tracking on the ICU.

In order to perform speckle tracking, the following criteria should be met: 1) the equipment available should contain a linear transducer and abdominal/cardiac transducer to visualize both in the subcostal view as well as in the zone of apposition. 2) The available analysis software should be able to perform speckle tracking of the diaphragm.

4.1 TRANSDUCER & ULTRASOUND SETTINGS

To perform the speckle tracking the ultrasound machines and transducers available need to be able to view both windows (zone of apposition and subcostal) and therefore also have a linear and cardiac/abdominal transducer.

For research purposes the ICU has a Philips Epiq 7 ultrasound machine, which is a sophisticated ultrasound machine mostly used in cardiology. The Epiq 7 of the department has a cardiac (X5-1), an abdominal (C5-1) and a general (X6-1) transducer available. Unfortunately on the ICU we do not have a linear probe available for the Epiq 7. As a result the speckle tracking to determine the strain and strain rate is not feasible to measure in the zone of apposition view with this ultrasound machine. The cardiac probe available is sufficient to visualize the diaphragm in the subcostal window.

Furthermore there is a Philips CX-50 ultrasound machine available with a linear, cardiac and abdominal transducer.

4.2 ANALYSIS SOFTWARE

Software for analysis of speckle tracking needs to meet several requirements. First of all it needs to be possible to perform the speckle tracking on the diaphragm, from which either the strain and strain rate or the excursion in x- and y-direction are calculated. Preferably different regions can be tracked at the same time, for both strain/strain rate and excursion measurements.

For the speckle tracking Philips has the Qlab software program which is both available on- and offline for analysis of the ultrasound images, but only for the Epiq 7 derived images. For the CX-50 no speckle tracking analysis can be performed. A part of the Qlab is the Automated

Cardiac Motion Quantification (aCMQ), which is mostly used for assessing myocardial functions. As the software was designed for the ventricles the strain and strain rate are calculated based on the cardiac cycle. For the ventricle a specific overlay is designed to calculate the strain and strain rate of the ventricle walls. For the software to be usable on the diaphragm these settings need to be adjustable.

After testing it was possible to manually adjust the start and end time of the measurement to the start and ending of diaphragm contraction. Additionally it was also possible to change the overlay for the strain and strain rate. Instead of the overlay two self-chosen points were placed and the strain and strain rate was calculated in-between these points.

To use the speckle tracking for excursion measurement it needs to be possible to track a certain region in the 2D-directions. In the Q-lab software it was not possible to select only one region, as it always wants to calculate the strain en therefore needs two selected points. In the process of starting the Q-lab software after selecting the start and end point of contraction two regions are selected and in the distance between these two regions the strain is calculated. However for the excursion measurements we do not want to track the distance between these two regions, but we want to track those single regions. In Q-lab no analysis can be done if there are not two regions selected. And when two regions have been selected it is not possible to trace the excursion of either one of these points as always only the strain and strain rate between these regions are calculated.

As the software and ultrasound machine available at the ICU was not sufficient to perform speckle tracking measurements other solutions were sought to still use speckle tracking software. When looking back at the article written by Oppersma et al. (2017) the software they used for the strain calculations was the EchoPac's Q-analysis tool (General Electric Healthcare). On our ICU all the available ultrasound equipment software is from Philips. Therefore contact was put in place with researchers extensively using the EchoPac software. The researches which developed a specific range of interest for the diaphragm in the speckle tracking software are from a clinic in Aachen. Collaboration was put into place to test whether we could analyze derived ultrasound images from the Philips ultrasound into the EchoPac software. After testing several DICOM files containing diaphragm videos it was evident that the DICOM files from Philips were not compatible with the EchoPac software.

4.3 SUMMARY

Table 1 This table represents an overview of the equipment and software and the available and non-available components.

	Available	Not-available	Remarks
Ultrasound machines			
Philips Epiq 7	- Cardiac transducer - Qlab software	- Linear transducer	
Philips CX-50	- Cardiac and Linear transducer	- Analysis software	
Analysis software			
Philips Qlab	- Strain and strain rate measurement	- Excursion measurements	
GE EchoPac	- Strain and strain rate measurement		Loading difficulties DICOM files

4.4 DISCUSSION

One of the first findings of testing the feasibility of speckle tracking was the absence of a linear transducer on the ultrasound machine with the needed software. On the CX-50, the ultrasound machine with a linear transducer there was no compatible software. For measurements of strain and strain rate of the diaphragm a linear transducer is needed. However on the available ultrasound machine there was no linear probe available. Furthermore after discussing with representatives of Philips the software package needed to perform the strain measurements was not available for linear transducers.

In the test into movement excursion measurements, a different purpose for speckle tracking besides strain and strain rate, also found to be not possible. As the software package was not sufficient and could only measure strain and strain rate other purposes of speckle tracking were also regarded. This finding is contrary to previous studies which have suggested that speckle tracking was suitable to measure for different purposes as in the study performed by Goutman et al[39]. In their study the speckle tracking used for excursion measurements was more accurate compared to just using M-mode. However the program in which they used the speckle tracking was Echo insight, a different available ultrasound analyze tool.

What was also obvious from the test was the inability of DICOM files derived from one manufacturer to be used in a program manufactured by another company. In this study we tried to use the same software as in Oppersma et al[14]. However it was not possible to analyze the data based on the DICOM files from another ultrasound machines. Possibly the analysis tool has different requirements on the DICOM files to be used in the analyze. The DICOM files are introduced so that the in every system the same file type can be imported. The reason it was not possible to import the DICOM files in another company analyze tool is therefore not know. Probably there were certain characteristics of the DICOM files which are needed to be usable in the analyze tool which is only exported when measuring with the same manufacturer's ultrasound machine.

4.5 CONCLUSION

The study into the feasibility has shown that speckle tracking is not yet possible with currently available equipment and software, due to 1) absence of a linear transducer on the Epic 7 and 2) limitations of the current available software analysis software. Therefore, the manufacturer of the ultrasound equipment and software needs to develop their software further or research into developing our own speckle tracking algorithm should be explored.

5 SPECKLE TRACKING: ALGORITHM DEVELOPMENT

As the speckle tracking software packages available were not sufficient enough it was opted to develop our own speckle tracking algorithm to be applied to ultrasound images acquired with the linear transducer of the CX50 Ultrasound machine. Together with a technical medicine intern specialized in imaging, we made a step towards a speckle tracking algorithm that is compatible with the ultrasound images acquired by the ultrasound machines available at the ICU. The aim of this study was to evaluate the feasibility of designing software specifically for speckle tracking of the diaphragm.

For the algorithm to work settings had to adjusted to enhance the speckles. Normally the ultrasound has certain speckle reduction settings in place for better image quality. However for the speckle tracking algorithm to work we needed to keep as much speckles as possible. XRES®, SonoCT, iSCAN and persistence were turned off. XRES, SonoCT and iSCAN are all settings which decreases the amount of speckles visible, to increase image quality. XRES reduces speckles by expanding different grey pixel group to a more dynamic range, more visible to the eye. SonoCT reduces speckles through real time spatial compounding, by averaging different scan angles and averaging out a large degree of the speckles[47] iSCAN automatically optimizes the gain, time gain compensation (TGC) and compression to improve image quality. The TGC compensates the gain for deeper tissue, by keeping in mind the frequency of the ultrasound and the penetration depth of the ultrasound. By switching iSCAN off the gain can be optimized for the region of the diaphragm and no speckles are filtered out[48].

After the settings were optimized the derived images were analyzed based on three steps, 1) image filtering, 2) block-matching and 3) strain and strain rate computations. In step 1) the image filtering was done with singular value decomposition (SVD). A complex method which relies on weighting the principal components present in the ultrasound signal, to select only the tissue specific speckles. More detailed explanation can be found in Maildin et al (2010 et al.) and Bandaru et al (2017) [49, 50]. The second step uses block-matching to track a speckle. A window of $n * n$ samples was selected in the reference frame. In the next frame in the region around the original selected samples the pixels with the same characteristics as the original

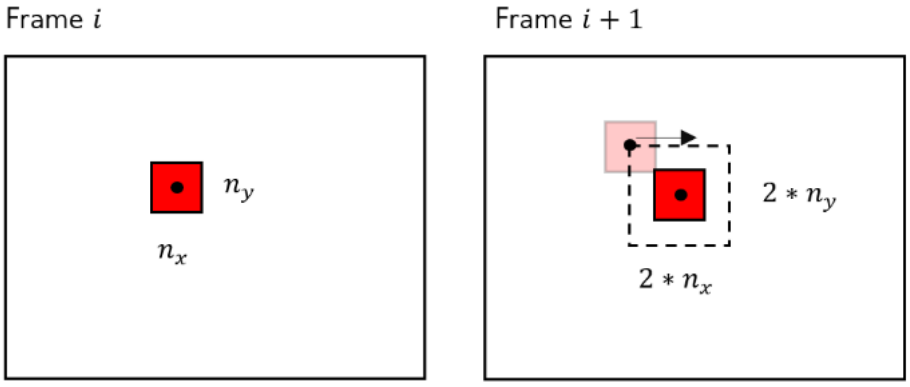

Figure 7 Illustration of block-matching principle. In one frame, a ROI is selected (red square). Around this red square a search window is selected in the consecutive frame. In the search window a square with the same principles is sought and selected as next square.

window is searched and then selected to be the new window, see Figure 7. This is done for all the frames resulting in the tracking of a speckle. In the last step from the tracking of these speckles the strain and strain rate are computed.

When repeating the measurements 5 times per video the algorithm performed well in some cases with a small standard deviation. However, not in all cases the tracking was successful as the speckle moved out of the field of view of the ultrasound measurement. When comparing the mean values of the strain and strain rate derived with the algorithm to other studies it was shown to have similar values.

The algorithm proposed could potentially be of use to measure strain and strain rate of the diaphragm. However, as it works in only some cases the algorithm needs further optimization to be implemented completely in the clinic. Furthermore it has only be tested on one healthy subject and needs to be tested on ICU patients and on a bigger population.

5.1.1 Discussion

The aim of this study was to test the feasibility of speckle tracking in assessing the diaphragm in ICU patients. An important finding was that developing a speckle tracking algorithm for the diaphragm was possible and has potential but needs further testing and improvements.

On the question whether it would be possible to develop an algorithm for the strain and strain rate, we found it was possible to develop an algorithm that can measure the strain and strain rate of the diaphragm. The algorithm could perform the measurements in most cases quite well, in a few cases the speckle tracking was not sufficient as the tracked speckle drifted out of the window. As it works in most of the cases the algorithm has potential but needs some further improvements and implications. In the study of Oppersma et al. found that sometimes the measurements had to be repeated due to incorrect tracking of speckles.

One of the strengths of developing a speckle tracking algorithm is that everything is developed and thought about ourselves. When using software from a certain manufacturer it is usually not know what the software actually does to perform the measurements. In this case there is no black-box and can be altered and improved when ought to be better. However the method has not been tested on a large population or ICU patients and therefore nothing can be said about the exact reliability.

5.1.2 Conclusion

Developing an algorithm to perform the speckle tracking was feasible and has potential, but needs further testing and improvements.

6 TISSUE DOPPLER IMAGING

Another technique which has been proposed as a method of assessing diaphragm function is tissue Doppler imaging (TDI). TDI was shown to be a promising tool in assessing diaphragm function, as it was found to be reliable and it correlated to Pdi and M-mode measurements[16-18]. However, further tests are needed to validate TDI on ICU patients. The aim of this study is to assess the feasibility, reliability and validity of TDI of the diaphragm.

6.1 AVAILABILITY TDI MODES

To test whether TDI is a feasible method to assess diaphragm function several tests have been performed. First of all the feasibility was tested by testing the different methods of TDI (color- and PW-TDI) on the ultrasound machines and the available software for velocity analysis.

The TDI was tested with the cardiac probe in the subcostal window, where the diaphragm is displayed above the liver. The TDI was activated on the Epiq 7 and the range in which the TDI is applied is chosen so that the movement of the diaphragm stays in the set frame. Figure 8 gives an example of ultrasound window with the activated TDI.

Different settings were tested to see whether it would improve image quality. It was found that the scale needed to be adjusted to -2.5 cm/s to +2.5 cm/s as the velocity of the diaphragm stays within that range.

On the Epiq 7 we can measure the color-TDI through their analysis tool, range of interest (ROI). In the ROI mode a certain range can be selected around the movement of the diaphragm which measures the velocity based on the color intensity of the video. This tool then provides a curve with the velocities of the moving diaphragm, see Figure 10.

It is however not possible to export the obtained graph or do some more sophisticated analysis in the software program to the graph. To overcome this problem the graph is exported as image and imported to Engauge Digitizer [51] to convert the image to graph data. The graph data is then imported into MATLAB to perform further analysis, see Figure 11.

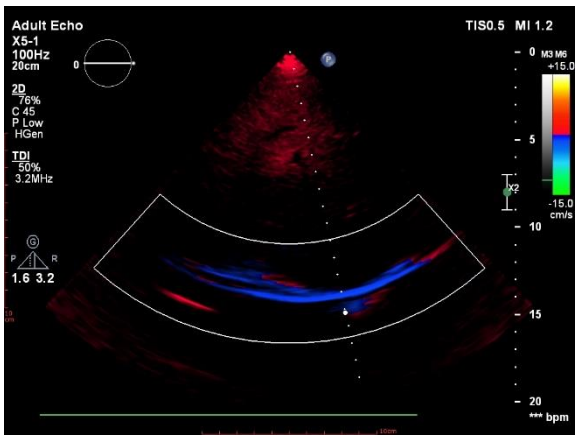

Figure 8 The ultrasound image of the diaphragm in the subcostal window. With the tissue Doppler activated as visible in the color added to the ultrasound image. With the diaphragm colored in blue.

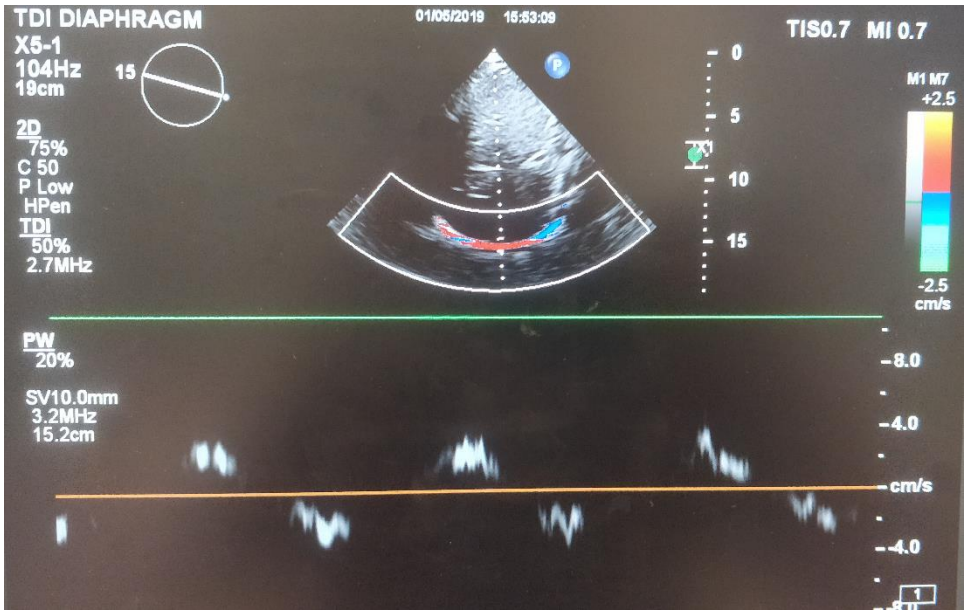

Figure 9 Testing of PW-TDI, in which it can be seen that the sample volume is too small and the tracing of the diaphragm is not correct and incomplete as there is no clear line of the tracing of the diaphragm.

When testing the PW-TDI function, the function could be activated and the sample volume was selected to have the diaphragm move within the sample volume. Nonetheless the sample volume was too small for the total movement of the diaphragm. The sample volume could not be set bigger than 1 cm, as the diaphragm generally moves more than 1cm the diaphragm moved out of the PW-TDI window. Resulting in missed peak velocities, as can be seen in Figure 9.

6.1.1 Discussion

This study was performed to test the availability of tissue Doppler imaging (TDI) at this ICU. One of the first findings of the study included the possibility to use color-TDI on the Epiq 7 ultrasound. On the contrary PW-TDI was not possible to perform due to the sample volume being too small.

With the use of the ROI software package the color-TDI velocities of the diaphragm are determined and can be used for analyses of the diaphragm. However the way in which it actually measures the velocity is not clear. From the data it looks to be measuring the color-TDI, an average value of the velocity based on the color intensity of the signal. The exact mechanism of measuring and the accuracy is however not determined. Even after contact with Philips it was unclear as to whether the ROI of the ultrasound machine is color-TDI. Further testing into the validity and reliability of the data is necessary.

After measuring the TDI it was also feasible to use the derived velocities for further analysis. Not directly online at the ultrasound, but by using Engauge Digitizer the data was digitized and could be used for further analysis. Ideally an online bedside accessible tool is preferred as it provides fast analysis, but for now the offline analysis tool is sufficient.

6.1.2 Conclusion

This study has shown that it is feasible to use color-TDI to assess diaphragm movement. PW-TDI is not possible due to the limitations in sample volume. However the reliability and validity of color-TDI of the diaphragm still need to be determined.

6.2 Reliability and validity study of color-TDI: a pilot study in healthy subjects

As was shown in the previous test, color-TDI could be a possible measure to assess diaphragm ultrasound[16-18]. However for color-TDI to be used in the clinic it also needs to be valid and reliable. Hence the aim of this study if to test the validity and reliability of color-TDI for diaphragm measurements.

6.2.1 Methods

Subjects

For the measurements into the reliability and validity of TDI healthy subjects (n=5) were tested. The subjects had several measurement of both ultrasound as well as simultaneous airflow measurements to compare breathing patterns and ultrasound results.

Measurement setup

First of all the ultrasound machine had to be set to the right settings as mentioned in the availability study mentioned above. To measure the flow we used a pneumotach attached to the BIOPAC system (© BIOPAC Systems Inc.). The flow was calibrated with a 1L syringe.

The ultrasound probe was placed subcostally on the midaxillary line, we only measured the right hemidiaphragm and not the left hemidiaphragm due to the small acoustic window of the spleen. After visualization of the right hemi diaphragm the TDI mode was activated.

Experimental protocol

The subject was asked to held the pneumotach in their mouth and breath along with a fixed breathing pattern displayed on a screen in front of the subject. When the subject was breathing along with the breathing pattern the flow measurement and the ultrasound measurement were started. After 30 seconds the subject was asked to remove the pneumotach from its mouth, the ultrasound was saved automatically and for the flow the correlated breaths were selected in AcqKnowledge® (BIOPAC Systems Inc.) and saved as a separate file.

After the TDI images were obtained the subject was asked to keep breathing along to the breathing pattern. On the ultrasound machine the TDI function was disabled and the M-mode function was activated. The M-mode line was placed as perpendicular as possible to the dome of the diaphragm, in the direction of the movement. When three consecutive breaths were adequately obtained (i.e., diaphragm clearly visible throughout the breath cycle), the M-mode was frozen and the distance and slopes of each inspiration and relaxation were calculated on the ultrasound machine and saved as separate images.

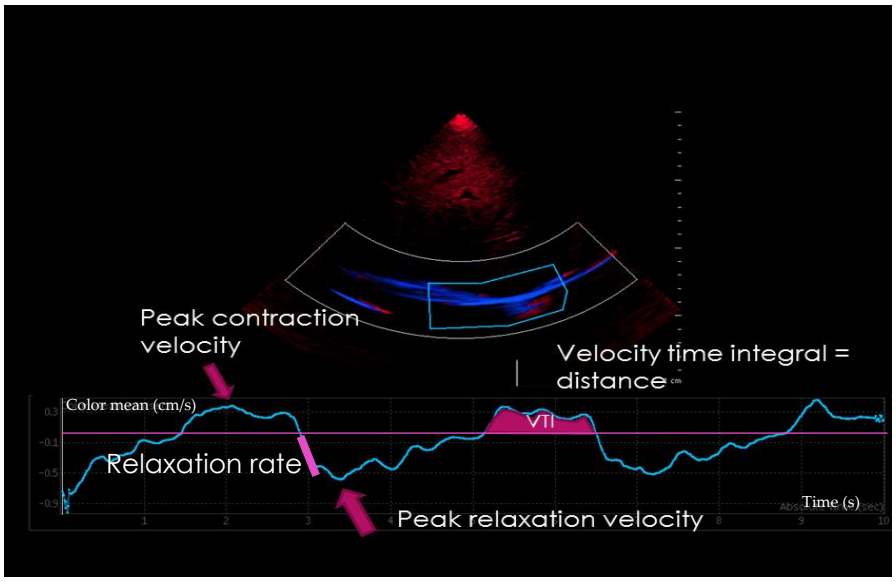

Figure 10 On the top image the ultrasound image with the color-TDI activated as activated in the Philips Epiq 7, with a range chosen for analysis in the blue line around the diaphragm.. In the below part the graph with the different parameters which can be derived from the color-TDI.

To test the reliability the measurements of all the subjects have been repeated three times. As the measurement have been performed for 30 seconds either 3 or 4 breaths were used for the analysis of the repeated breaths.

Data analysis

To be able to perform additional measurements on the derived TDI graph the data was loaded into MATLAB (©The MathWorks, Inc). The derived parameters are based on the study done by Soilemezi et al. and consist of the peak inspiratory velocity, peak expiratory velocity, the integral of the inspiratory and expiratory velocities (distance) and the relaxation rate [17]. For an overview of the parameters see Figure 10. The peak velocities are calculated by automatically selecting the peaks with the function findpeaks. The velocity time integral, a surrogate for distance, is calculated through finding the start and end points of inspiration or expiration and using the function *trapz* to take the integral between these points. Trapz computes the approximate integral using the trapeziodial method with unit spacing. The relaxation rate is calculated by finding the slope of initial part of relaxation. Thus calculating the slope between start expiration and peak relaxation velocity.

Statistical analysis

Statistical analysis were done with SPSS (IBM version 22). Data were analyzed as mean ± standard deviation (SD), except stated otherwise. Statistical difference was indicated by a p value <0.05. Differences between volumes of inspiration and expiration were tested for significant differences using the paired t-test for every measurement. To test the intra variability of the breaths as well as the different measurements the coefficient of variance (CV) was determined as the ratio of the standard deviation to the mean. To assess correlation between TDI parameters and M-mode correlation plots and Bland-Altman figures are made.

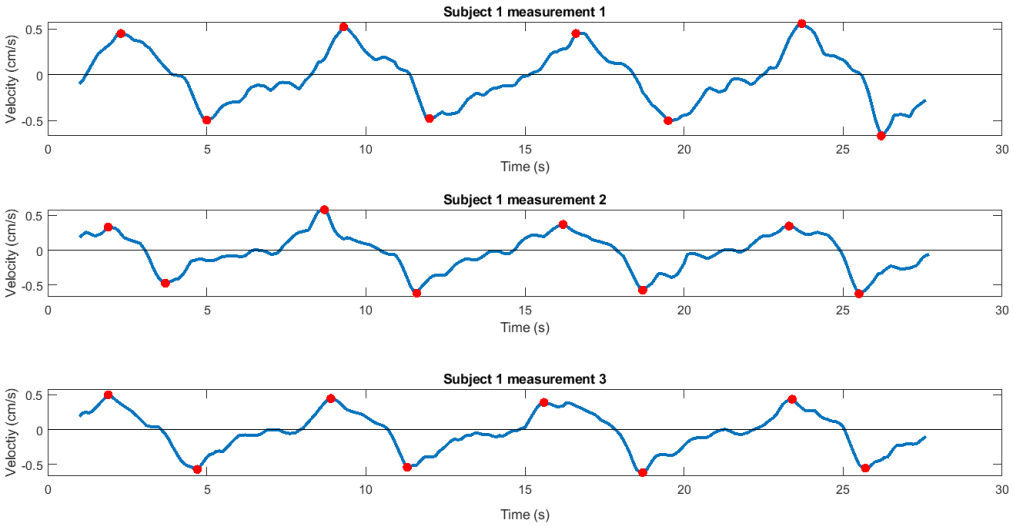

Figure 11 Example of the TDI derived velocities in the validity study, with three measurements of subject 1. In which the blue line is the velocity of the diaphragm as measured in the Philips Epiq 7. The red dots are the maximum and minimum selected. This graph shows the tracing of three measurements and from them it is evident that the breathing is similar for all three measurements. the line follow a similar path and have similar values for the velocity.

6.2.2 Results

To test for the validity and reliability five healthy subjects have been evaluated. An example of the TDI results of one subject is visualized in Figure 11. As shown in the figure because of the fixed breathing pattern the results look quite similar, with similar starting and ending.

6.2.2.1 Repeatability TDI

For the analysis the VTI of the 3 breaths are compared to each other and can be seen in Table 2. The coefficient of variance (CV) is calculated for every subject and measurement, with a total combined CV of 6.6% variability.

Table 2 The VTIi (cm) of the different breaths for each subject of three different measurements (M1 : M3). CV is the coefficient of variation. As can be seen in the table the CV are low, which implies for a similarity in the measurements.

Subject		Breath 1	Breath 2	Breath 3	CV
Subject 1	M1	0.73	0.75	0.72	2%
	M2	0.73	0.64	0.63	8%
	M3	0.62	0.74	0.60	12%
Subject 2	M1	0.48	0.62	0.48	3%
	M2	1.51	1.26	1.55	11%
	M3	1.75	1.99	1.75	8%
Subject 3	M1	1.88	1.85	1.87	1%
	M2	1.73	1.66	1.71	2%
	M3	1.85	1.73	1.81	3%
Subject 4	M1	0.73	0.79	0.85	8%
	M2	0.66	0.64	0.56	9%
	M3	0.90	0.86		3%
Subject 5	M1	1.18	1.36	1.38	8%
	M2	1.87	1.98	1.65	9%
	M3	1.15	1.46	1.26	12%

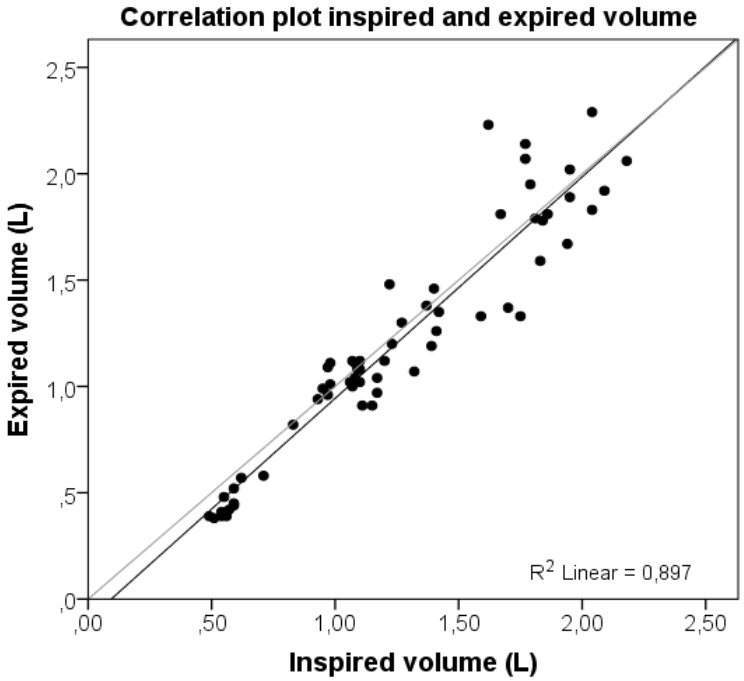

Figure 12 Correlation plot of inspiratory and expiratory volumes with R² of 0.90. The points are along the line of identity, especially at the lower volumes the points lie close to the line of identity (grey line). This correlation plot shows no evident differences between inspired or expired volume.

To test the reliability the values of the velocity time integral have been compared between the different measurements within the subjects. The results are visible in Table 4. The repeated measurements had a CV for VTIi of 15%, for VTIe 10%, M-mode-i 11% and for M-mode-e 15%.

6.2.2.2 Validity

To test whether volumes of inspiration and expiration differ the volumes have been calculated for the different measurements and are shown in Table 3. The volumes of inspiration and expiration do not significantly differ in most cases, only subject 2 has a significant difference between inspiratory and expiratory in all of the measurements. A correlation plot is made in Figure 12 to show the correlation of inspired volume compared to the expired volume. The correlation is very good with an R^2 of 0.90 and the correlation line lying close to the line of identity.

*Table 3 Overview of the volumes inhaled and exhaled based on the flow. Volume in liters. With M1 being measurement 1 etc. * significant difference between inspiration and expiration (p<0.05)*

Subject	Volume inspiration			Volume expiration		
	M1	M2	M3	M1	M2	M3
Subject 1	0.96 ±0.02	0.99 ±0.12	1.05 ±0.05	1.00 ±0.08	1.00 ±0.13	1.06 ±0.06
Subject 2	0.62 ± 0.68*	0.55 ±0.04*	0.55 ±0.04*	0.54 ±0.05*	0.41±0.03*	0.41 ±0.03*
Subject 3	1.44 ± 0.10	1.14 ±0.05*	1.12 ±0.04	1.38 ±0.06	1.02 ±0.09*	1.00 ±0.08
Subject 4	1.79 ±0.24	1.96 ±0.15	1.82 ±0.11	2.07 ±0.16	2.02 ±0.20	1.86 ±0.08
Subject 5	1.56 ±0.24*	1.74 ±0.37	1.25 ±0.13	1.31 ±0.23*	1.58 ±0.22	1.22 ±0.08

To test the validity two measurement options, TDI and M-mode displacement are compared to each other. As shown in Table 4 the difference between M-mode and VTI is substantially different. Only subject 3 had similar value for the inspiratory values of both the M-mode and VTI. For all the other subjects the M-mode has higher values compared to the VTI for both the inspiration and expiration.

Furthermore when comparing the VTI of the inspiration and expiration they are not similar. This can also be seen in Figure 13, there is a moderate correlation with a $R^2 = 0.49$ (p<0.001) Whereas the correlation for the M-mode inspiration and expiration a very good correlation is found, with $R^2 = 0.94$ (p<0.001)(Figure 14).

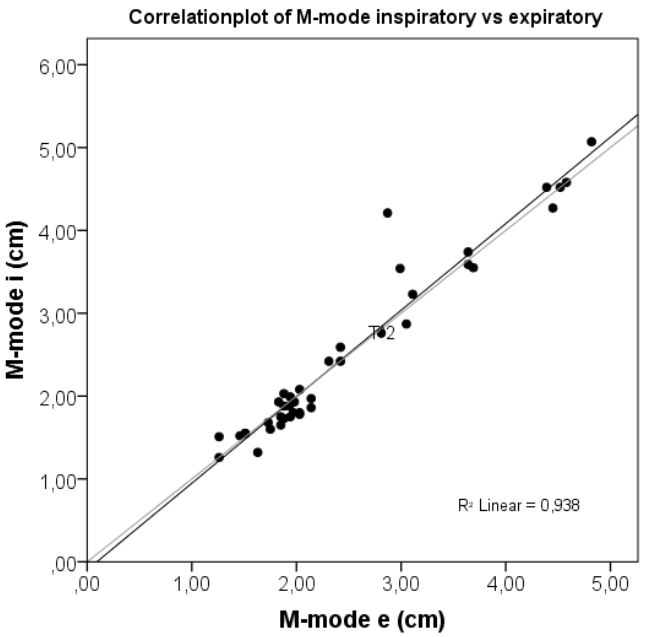

Figure 14 Correlation plot of M-mode, with a R^2 of 0.94.

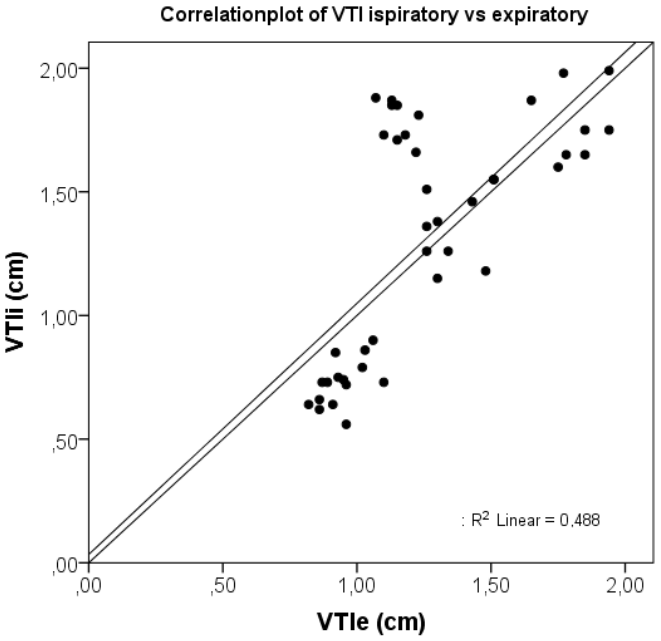

Figure 13 Correlation plot of VTI, with a R^2 of 0.49.

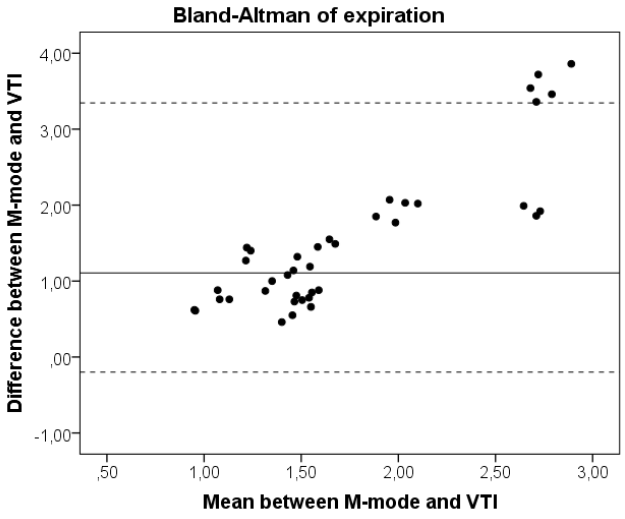

Figure 15 Bland-Altman of M-mode and VTI for expiration.

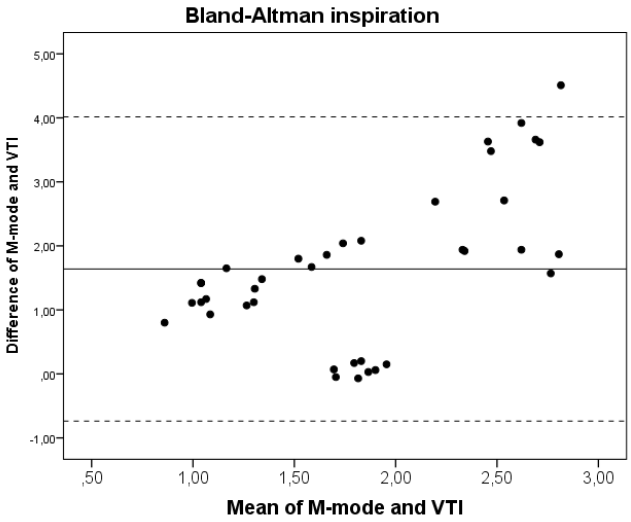

Figure 16 Bland-Altman of M-mode and VTI for inspiration

Table 4 Overview of the derived parameters, where VTIi is the integral of the inspiration and VTIe of the expiration and M-mode i is inspiration and M-mode e is the M-mode distance derived for expiration, values displayed as mean (SD). The mean differences are the differences between VTI and M-mode for either inspiration or expiration.

Subject	VTIi			M-mode i			VTIe			M-mode e			Mean difference inspiration			Mean difference expiration		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Subject 1	0.74	0.67	0.65	2.59	1.76	2.04	0.92	0.80	0.90	2.55	1.88	2.11	1.86	1.20	1.47	1.63	1.07	1.24
	(0.03)	(0.06)	(0.08)	(0.17)	(0.23)	(0.28)	(0.05)	(0.10)	(0.05)	(0.23)	(0.37)	(0.15)	(0.19)	(0.18)	(0.34)	(0.19)	(0.29)	(0.19)
Subject 2	0.53	0.46	0.33	1.60	1.44	1.83	0.80	0.64	0.55	1.70	1.34	1.91	1.07	0.96	1.50	0.88	0.70	1.37
	(0.08)	(0.03)	(0.01)	(0.05)	(0.16)	(0.14)	(0.07)	(0.01)	(0.04)	(0.17)	(0.16)	(0.05)	(0.13)	(0.22)	(0.13)	(0.12)	(0.15)	(0.09)
Subject 3	1.87	1.70	1.80	1.91	1.76	1.71	1.12	1.17	1.16	1.96	1.85	1.78	0.05	0.06	0.12	0.85	0.66	0.65
	(0.15)	(0.04)	(0.06)	(0.13)	(0.10)	(0.34)	(0.03)	(0.04)	(0.06)	(0.08)	(0.10)	(0.13)	(0.11)	(0.11)	(0.12)	(0.04)	(0.11)	(0.16)
Subject 4	0.79	0.62	0.88	3.54	4.64	4.09	0.92	0.80	0.90	2.97	4.62	4.01	2.75	4.02	3.64	1.96	3.70	2.95
	(0.06)	(0.05)	(0.03)	(0.67)	(0.40)	(0.74)	(0.09)	(0.06)	(0.03)	(0.09)	(0.19)	(0.78)	(0.70)	(0.45)	(0.03)	(0.16)	(0.16)	(0.80)
Subject 5	1.30	1.83	1.29	3.50	3.63		1.35	1.70	1.37		3.66		2.19	1.79			1.92	
	(0.11)	(0.17)	(0.16)	(0.34)	(0.10)		(0.10)	(0.09)	(0.06)		(0.03)		(0.45)	(0.20)			(0.07)	

6.3 DISCUSSION

The aim of this research was to test the reliability and validity of color-TDI in a pilot study on healthy subjects. This pilot study tested the different aspects and parameters of color-TDI against the control measurement, M-mode.

The first finding of this study was the repeatability of color-TDI. When comparing the integral of the different breaths (Table 2) a low coefficient of variation (CV) was found. The CV never exceeds 12% with a CV for the total population of 6.6%. Suggesting the consecutive breaths analyzed with color-TDI are repeatable also taking into account some variation in the breathing pattern.

Also repeated measurements were tested on the reliability, by repeating the ultrasound measurements 3 times. The color-TDI had CV values for the VTIi en VTIe of 15% and 10%. When comparing the color-TDI CV values to the M-mode values, similar values were found (11 and 15%). Also suggesting that the CV found for the color-TDI is comparable to M-mode and the variance between measurement likely being because of small physiological differences between the breaths between the measurements. As the breathing pattern was fixed it was believed the subjects were breathing similar between the measurements, however even with the fixed breathing pattern apparently the subjects had some differences in the movement of their diaphragm. The CV found in this study were similar to CV values found in the study of Knegt et al., where they found CV of around 11% for color-TDI and 11% for M-mode[45]. Therefore the repeatability of color-TDI is sufficient to perform measurements.

However, when looking into the validity of color-TDI more dissimilarities were found. First of all when comparing the VTI of inspiration and expiration (Figure 13) the correlation is not very good compared to M-mode inspiration and expiration (Figure 14), with a R^2 of 0.49 compared to 0.94 respectively. The differences in inspiration and expiration in color-TDI can also not be explained with the breathing pattern as the volumes of inspiration and expiration were similar. If the differences between VTIi en VTIe are believed to be real depictions of the movement of the diaphragm, the diaphragm would move differently for inspiration and expiration. Which should also results in differences in volumes in- and exhaled. This is however not the case as was proven in the volumes of inspiration and expiration (see Figure 12 and Table 3). The tidal volumes of inspiration and expiration were is most cases similar, which can also be seen in the correlation with an R^2 of 0.90. So the difference between VTIi en VTIe are not believed to be physiological and thus must be measurement errors of color-TDI.

Furthermore the differences between the measured displacement of VTI and M-mode are also significant. From Table 4 the mean differences show are values of in most cases more than 1cm. This can also be seen from the Bland-Altman plots that show a large bias and wide limits of agreement. Furthermore a trend can be seen as with an increasing average the differences between the measurements tend to get bigger. This finding is contradicting to earlier findings in the literature. In the study of Knegt et al. on the concordance and reproducibility of TDI and M-mode in the assessment of mitral annular displacement they found the displacements measured with color-TDI and M-mode to be similar[45]. The velocities measured were not direct comparable however the bias between M-mode and TDI was 0.08 cm with a standard

deviation of 0.35cm, which is much smaller than our found bias of 1.6cm and standard deviation of 1.2cm. This study was however done on the mitral annulus which is different from measurements of the diaphragm. As the technique and depth of obtaining the images differ. Also their measurements were done with a GE Healthcare ultrasound, which might calculate the color-TDI differently from the Philips ultrasound that we used in this study.

An interesting finding of the correlation plot (Figure 12) between inspiration and expiration is the variance getting bigger for larger tidal volumes. From around 1.5 L the variance has a bigger spread, the tidal volumes inspired in this experiment are also much higher compared to normal tidal volumes. This might be due to the fixed breathing pattern which had 3 seconds of inspiration and 4 seconds of expiration. As this might be longer than a subject normally inspires and expires it results in more volume uptake. When subjects are not breathing along their normal breathing pattern the way in which the volume is expired might also change, maybe due to additional respiratory muscles intervening. Furthermore due to fixed breathing pattern there is a forced inspiration and expiration, it could be that subjects were not fully expired yet when they had to breath in again. The next inhale might therefore also be less than the previous as the subjects are trying to compensate for their tidal volumes and alter their tidal volumes during these different breaths. The smaller tidal volumes might nog be affected due to the breathing pattern being closer to their normal breathing pattern and less affected of the tidal volumes in their total lung volume.

6.3.1 Limitations and strengths

One of the strengths of this study is the validation of color-TDI to both the gold standard M-mode as well as measurements of tidal volumes. By measuring both the M-mode and tidal volume differences in the color-TDI can be explained by the measurement of TDI and are probably not because of physiological changes and differences.

One of the limitations of this study is the limited study subjects used in this study. Only five healthy subjects have been used for this test and from the results can be seen that within the subjects there are a lot of differences in tidal volumes and measured diaphragm excursions in both TDI and M-mode. Expanding the subject size strengthens the results of the reliability and validity study. The differences between inspiratory and expiratory VTI measurements can also be more validated with a larger subject size. Now there are some measurements which show a large deviation from the line of identity in the correlation plot. It is now not know if that is due to the subject or if it is more frequent in different subjects.

6.4 Conclusion

Color-TDI was shown in this study to be a reproducible measure for diaphragm excursion, however the validity of color-TDI is low and needs further improvement before being able to be used in the clinic.

7 GENERAL DISCUSSION ULTRASOUND

The aim of these studies was to test the feasibility, reliability and validity of Tissue Doppler imaging and speckle tracking in the assessment of the diaphragm. In chapter 4 it was proven speckle tracking is not yet possible with the available equipment and software. However as was tested in chapter 5 developing a speckle tracking software was possible and has potential but needs further improvement and tests before implementation in the clinic is possible. Pulsed wave tissue Doppler imaging (PW-TDI) was not possible on the available equipment, nevertheless color-TDI was possible (see chapter 6.1). As color-TDI was possible it was tested on reliability and validity in a pilot study on healthy subjects. Color-TDI was proven to have a good repeatability and reliability but validity was very low as it did not correlate with M-mode and unexplained differences were found between inspiration and expiration.

7.1 CLINICAL IMPLICATIONS

Color-TDI and speckle tracking as it is available on the ICU is not clinical applicable yet. Both speckle tracking and color-TDI have too many shortcomings to date to be used in the clinic. They both have their advantages and could still be of interest in the clinic.

Speckle tracking has already been proven to be superior in assessing diaphragm function to using thickening fraction[14]. Fractional thickening is used to assess atrophy of the diaphragm but is highly dependent on the observer for accuracy[37]. Furthermore it was poorly correlated to Pdi and thus diaphragm function. With the help of speckle tracking the strain and strain rate can be calculated. The strain and strain rate are parameters which tell more about the function of the diaphragm as they take the contractility of the diaphragm into account. Furthermore speckle tracking is angle-independent and thus not influenced by the exact angle of the transducer. If the ultrasound machine is set up correctly, with the right settings for optimal speckle acquisition, it is not dependent on the experience of the observer. If the software could be bedside available and is altered to be easy to use it could quickly notify the observer of the function of the diaphragm function by telling the strain. The strain rate could then be used to assess contraction and relaxation as it tells something about the velocity at which the diaphragm deformation occurs. Excessive strain could tell the clinician something about the patient's effort and could guide ventilation in keeping muscle loading within the preferred range to ensure diaphragm protective ventilation.

TDI and speckle tracking are both hypothetically better measures in assessing diaphragm excursion than M-mode. In this study color-TDI was proven to be not valid for excursion measurements, however this could be a cause of measuring limitations or software limitations. Furthermore PW-TDI was not tested at all as it was not possible to assess the diaphragm in the available settings of the ultrasound machine. PW-TDI if possible has been proven to be correlated to Pdi and has been used to assess peak velocities of the diaphragm[16, 18]. The contraction and relaxation velocities could potentially be used in the clinic to assess diaphragm function during spontaneous breathing trials during weaning of mechanical ventilation. It could show changes in muscle function over time when the velocities decrease before the patient respiratory fails the SBT. Furthermore both color- and PW-TDI could tell something

about the regional function of the diaphragm. Color-TDI can tell something about the overall function of the diaphragm as it is the mean of the selected region and PW-TDI could tell something about specific regions of the diaphragm as it uses small samples volumes.

7.2 FUTURE IMPLICATIONS

Before implementation of these techniques in the clinic future studies and improvements are needed. Color-TDI is bed-side available but was proven not to be valid for the diaphragm in this study. PW-TDI is also very much dependent on the sample volume chosen. If the tracking of the sample is not correct the diaphragm is not correctly traced. Moreover Doppler is angle-dependent and is more effected by background noise, which are all disadvantages of using TDI. TDI might therefore not be the most optimal technique in assessing the diaphragm.

Speckle tracking has showed its potential but needs to be improved further. Developing our own speckle tracking algorithm has benefits of it being it exactly like we want it to be with no black-boxes of manufacturers. However the algorithm did not perform faultless yet. If the algorithm is developed further so that it tracks speckles correctly the strain and strain rate can be determined quickly and provide useful information. The algorithm is now developed in MATLAB but when it needs to be clinical applicable an app could be easier and more useable. Then the diaphragm can be visualized with the ultrasound quickly and the derived images could be uploaded to the software and a strain and strain rate would show up.

Furthermore speckle tracking for assessing diaphragm excursion is better than M-mode excursion. Color-TDI was proven to be less compared to M-mode, but with speckle tracking the excursion is tracked in x and y direction and has no angle dependency. If developed further it could more accurately measure the excursion. However the excursion was proven in just one study by Goutman et al. and has not been used in other studies for the diaphragm[39]. Developing this application of speckle tracking could also be possible and comparable to the software developed for strain measurements. Different speckles could be tracked over time and the distances covered converted to actual diaphragm displacements. This software could then be used in patients in which perpendicular displacement to an M-line is not possible. Which would lead to no under or overestimation of the diaphragm excursion.

7.3 CONCLUSION

In conclusion more sophisticated ultrasound techniques, speckle tracking and tissue Doppler imaging, as available at the ICU, are not yet applicable to assess diaphragm function. Speckle tracking could potentially be a technique to assess diaphragm function but needs further improvement and testing.

Part III: Po.1

8 Po.1 VALIDATION

8.1 INTRODUCTION

The study into the P0.1 value which has been performed has as goal to validate the P0.1 to the patient's effort. The P0.1 is a value which has been used in the clinic to assess patient effort, as it was shown to have a correlation to the work of breathing[20]. The correlation was however not that high with a maximum R of 0.82.

Furthermore when there is no volume displacement the calculated work of breathing is zero, this however does not always imply that there is no work done. When muscles contract but no volume difference is produced, volumetric contraction, according to the formula of WOB (5) the WOB is zero, however the muscles did contract. This would suggest that patient effort is better estimated with the pressure generated by all the inspiratory muscles (Pmus). So this study focusses on finding the relation between Pmus and the P0.1.

8.2 METHODS

8.2.1 Subjects

For the validation of P0.1 we used the airway pressure derived from several ICU patients included in the DiaPro (clinical trial number: NCT03527797) study (n=14). For this study we have 24 hours of data, where from several patients and different hours around 20 breaths have been used for analysis. The patients are all on partially supported ventilation and are included if they are expected to stay on the ventilator for at least 24 hours.

8.2.2 Po.1 analysis

To evaluate the P0.1 several methods of deriving the P0.1 have been analyzed. First of all the method of Maquet has been implemented in MATLAB (© The MathWorks, Inc.), the exact method is explained in the paragraphs below. Mancebo et al. were the first to describe their method of measuring P0.1, this method is also implemented in MATLAB (© The MathWorks, Inc.)[20]. For the validation of these implementations the P0.1 values visible on the monitor of the ventilator (Servo, Maquet) were written down for around 4 or 5 breaths for every hour as control values. An overview of the different P0.1 methods can be seen in Table 5 and Figure 17.

Table 5 Overview of the different methods of determining P0.1 used in this study.

	Maquet P0.1	Mancebo P0.1	Control P0.1
Method	If trigger > 100ms Pressure difference 100ms after drop of 0,5 cmH_2O If trigger < 100ms Gradient between pressure after drop 0f 0,5 cmH_2O extrapolated to 100ms	50ms with the highest gradient extrapolated to 100ms.	Average value of P0.1 visible on monitor of ventilator
Analysis program	MATLAB	MATLAB	Maquet ventilator
Breaths	20 breaths chosen for analysis	20 breaths chosen for analysis	First 4/5 breaths of measurement

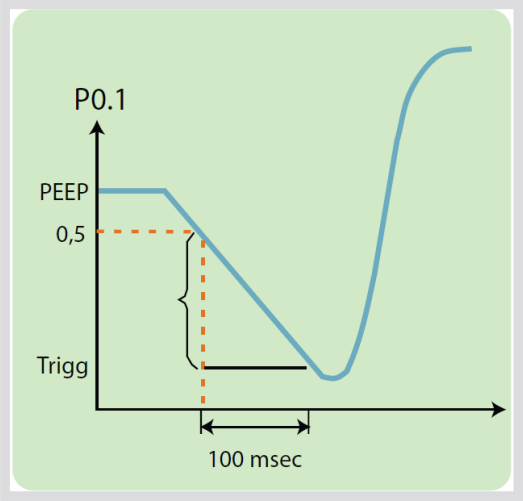

Figure 17 P0.1 method of Maquet, where the P0.1 is calculated after a pressure drop of 0.5 cmH_2O. The pressure between this start point and 100ms later is the P0.1.

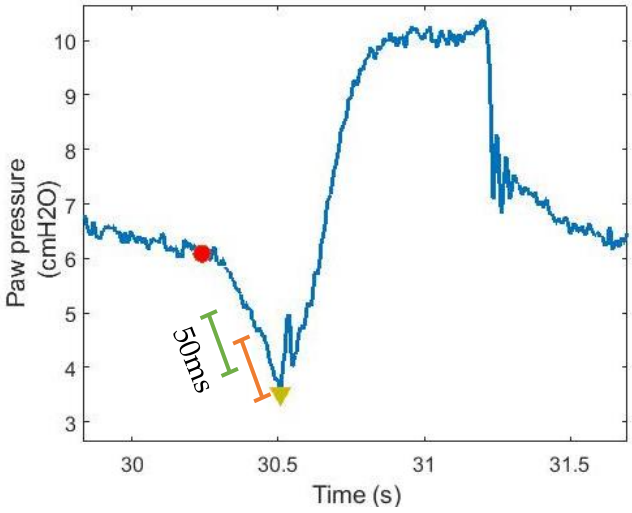

Figure 18 The method of Mancebo for determining P0.1. From the most minimal point windows of 50ms are taken and used to calculate the slope. The slope of 50ms is then extrapolated to 100ms. Two example windows of 50ms are shown.

Maquet method for determining Po.1

The Maquet ventilators have a specific way of calculating the P0.1 value. As the position of the trigger is not always clear they start their 100ms measurement when there has been a pressure drop of 0,5 cmH2O. The moment the pressure has dropped with 0,5 cmH_2O the 100ms starts. The pressure difference 100ms later is the P0.1 value (see Figure 17). If the trigger phase is shorter than 100ms the airway pressure drop is calculated through the gradient of the airway pressure. The gradient of the drop in airway pressure is calculated as a straight line between the start of pressure measurement and the lowest point, this gradient is then extrapolated to a P0.1 value for 100ms.

In MATLAB (© The MathWorks, Inc.) the method of Maquet is implemented by choosing the starting position through the peak of the pressure before the pressure drop and then start

calculations as soon as the pressure is dropped with 0,5 cmH2O. If the drop in airway pressure is more than 100ms the pressure at 0,5 cmH2O + 100ms is taken as calculation point. If the trigger phase is less than 100ms the slope is calculated between the start point and lowest point and is then extrapolated to 100ms. In Figure 19 an example of the two ways the P0.1 point is placed, either with the pressure value taken within the end of the airway pressure drop or extrapolated to a pressure difference based on the gradient of the signal. The differences between the starting point of the pressure and the P0.1 point is the P0.1 value.

Mancebo method for determining Po.1

Mancebo et al. (2000) were one of the first researchers explaining their method of calculating P0.1. In their method they calculate the slope over several windows of 50ms (see Figure 18), the window with the highest slope is extrapolated to 100ms and the pressure difference corresponding to this 100ms is used as the P0.1 value [20]. The Mancebo method is also implemented in MATLAB (© The MathWorks, Inc.) by taking moving windows of 50ms from the minimum of the triggering phase till 200ms back. The highest value of the gradients is used for calculating the P0.1 value, the gradient is then converted into the pressure difference for 100ms.

8.2.2.1 Pmus

The pressure generated by the respiratory muscles (P_{mus}) is calculated with the following equation 4; where P_{cw} is the pressure of the chest wall and P_{es} is the esophageal pressure:

$$P_{mus} = P_{cw} - P_{es} \quad (4)$$

See chapter 3.2.1 P0.1 for more details on the calculation of P_{cw} and P_{es}. The delta values for the Pmus were derived by finding the peak value and subtracting the start value.

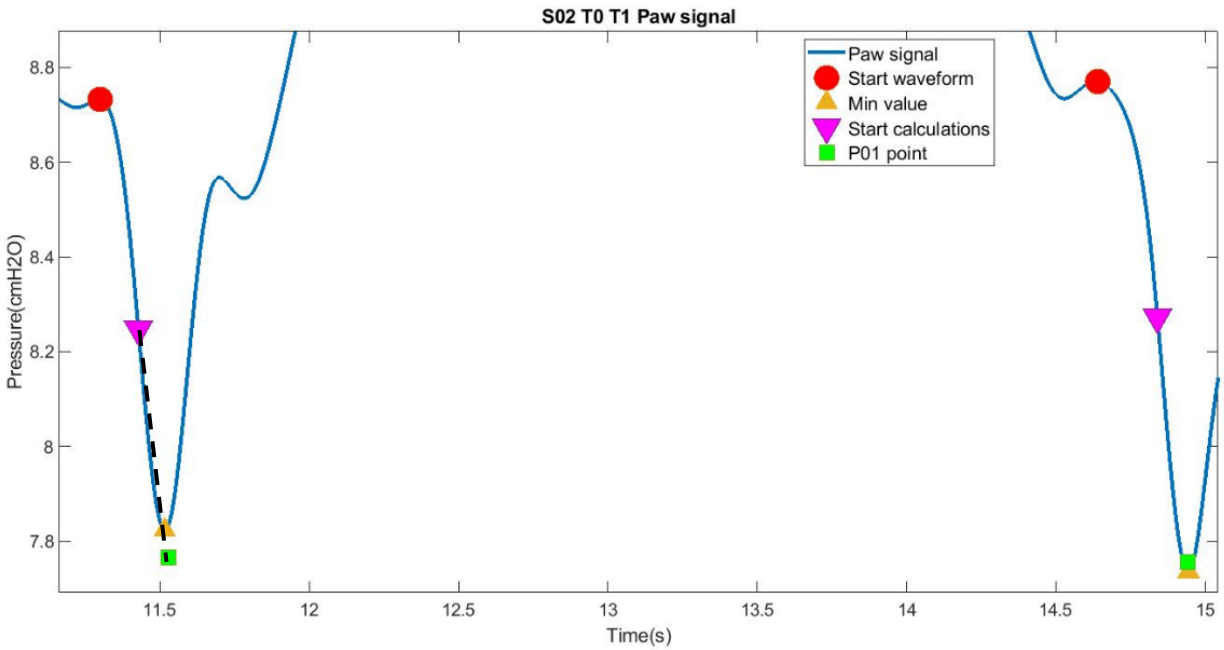

Figure 19 The two methods of determining P0.1 in the Maquet method. In the left graph the P0.1 is extrapolated and put just outside of the paw signal, whereas on the right the P0.1 point is chosen on the paw signal as the 100ms are just within the trigger phase.

8.3 RESULTS

The outcomes of the different P0.1 values from the control values and our measurements are presented in Table 6. It is apparent from this table that the differences between the values written down from the ventilator are similar to the calculated values based on the Mancebo method. Only in subject 18 the measurements are almost half of the measured values and in the second hour this is the other way around.

Table 6 The P0.1 values of the ventilator and our calculations for different patients. With similar values of the control values and the calculated methods, mancebo and maquet.

SUBJECT	MEDIAN CONTROL	MEDIAN MANCEBO	MEDIAN MAQUET
S16_T0_T1	7.2	6.28	5.82
S16_T1_T2	5.1	4.83	4.88
S17_T0_T1	2	2.44	2.62
S17_T18_T19	3.3	3.72	4.02
S17_T19_T20	2.9	2.70	3.32
S18_T0_T1	1.6	3.11	2.97
S18_T1_T2	3	1.82	3.45
S19_T0_T1	2.2	3.34	4.35
S21_T0_T1	5.7	5.40	4.99
S21_T1_T2	3.3	3.06	3.18
S22_T0_T1	1.75	2.26	2.28
S22_T1_T2	2.25	2.31	2.67

Figure 20, Figure 22 and Figure 23 presents the correlation plot between P0.1 and Pmus for the Mancebo method, Maquet and the control method respectively. No correlation was found between the P0.1 and Pmus. What is also evident from the graphs is the large spread of Pmus within the reference values of P0.1. Between 1.5 and 3.5 of P0.1 value the Pmus can be between 3 and 21 cmH2O. Closer inspection of the graph also shows several subjects having P0.1 values above the reference values, with also increasing Pmus values.

The same trend can be seen in Figure 21 as the P0.1 values are displayed against the Pdi values. For the reference values of P0.1 the Pdi has an even bigger range of 0 to 21 cmH2O.

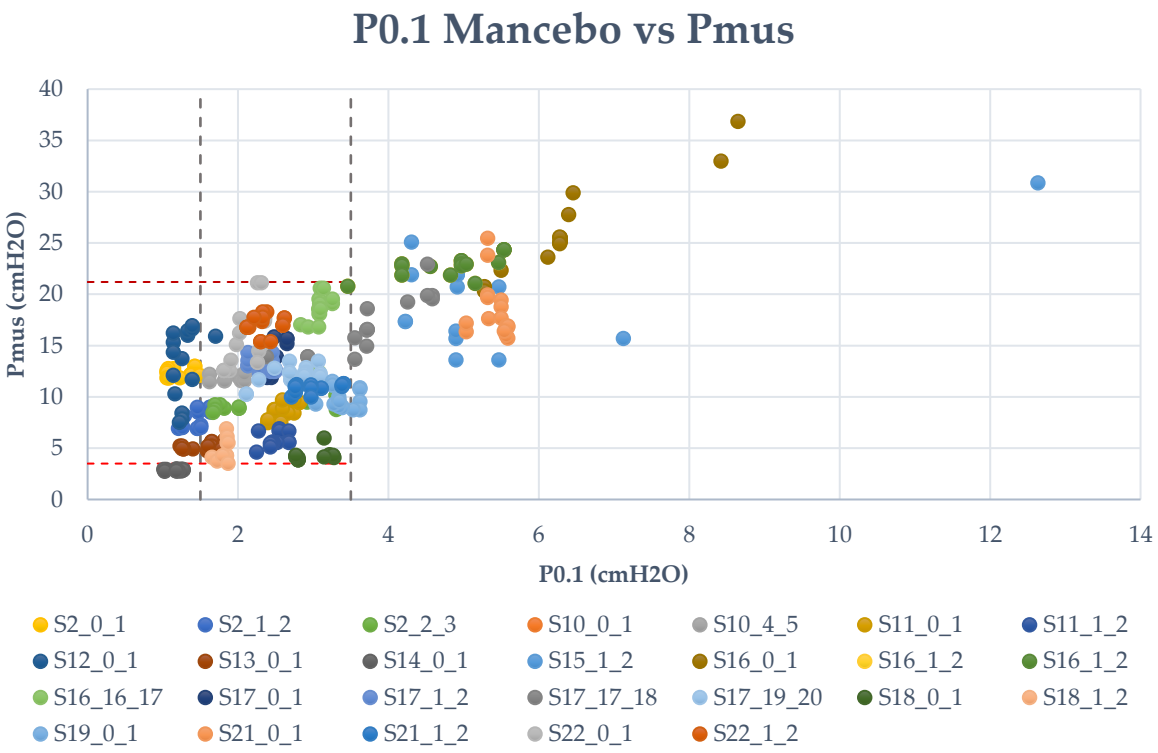

Figure 20 This graph represents the P0.1 values derived from the Mancebo method to the Pmus values. The grey dotted vertical lines represent the P0.1 reference values of a healthy respiratory drive. The horizontal dotted line represents the upper and lower limit of Pmus for the healthy respiratory drive reference values. There is a large spread of Pmus values for different P0.1 values.

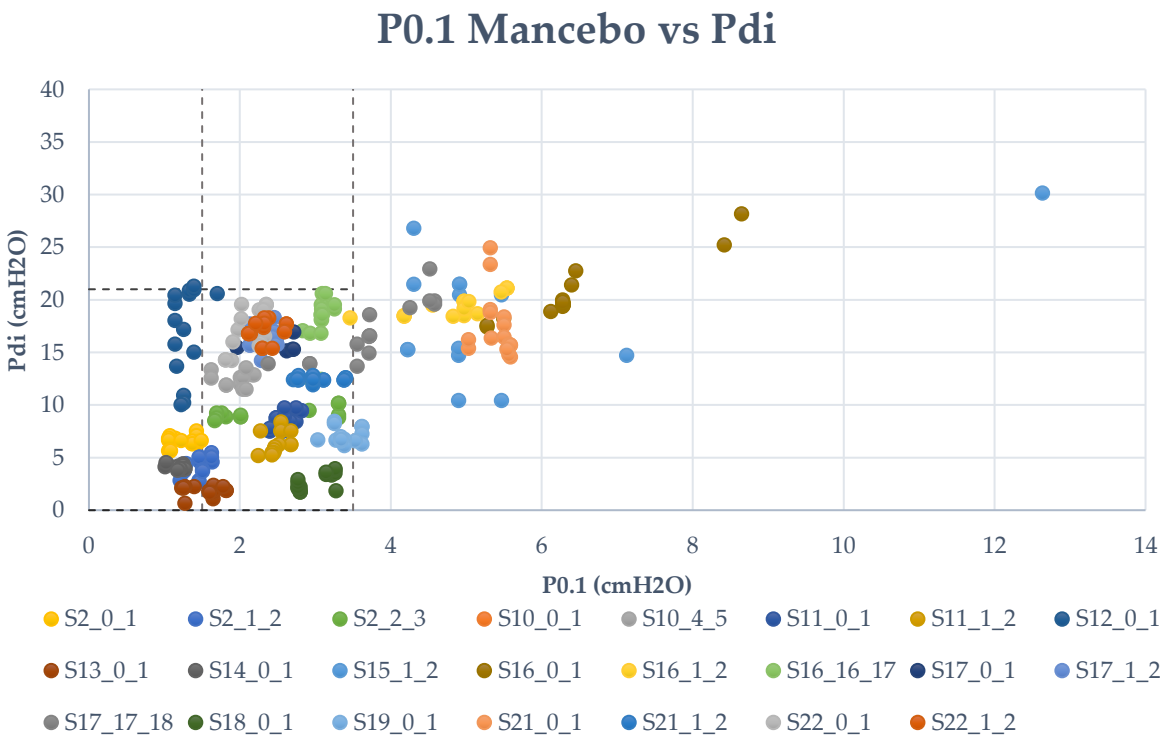

Figure 21 This graph represents the P0.1 values from the Mancebo method to the Pdi values. The grey dotted vertical lines represent the P0.1 reference values of a healthy respiratory drive . The horizontal dotted line represents the upper and lower limit of Pdi for the healthy respiratory drive reference values. In the reference values of P0.1 the Pdi values are wide spread. Indicating no clear correlation.

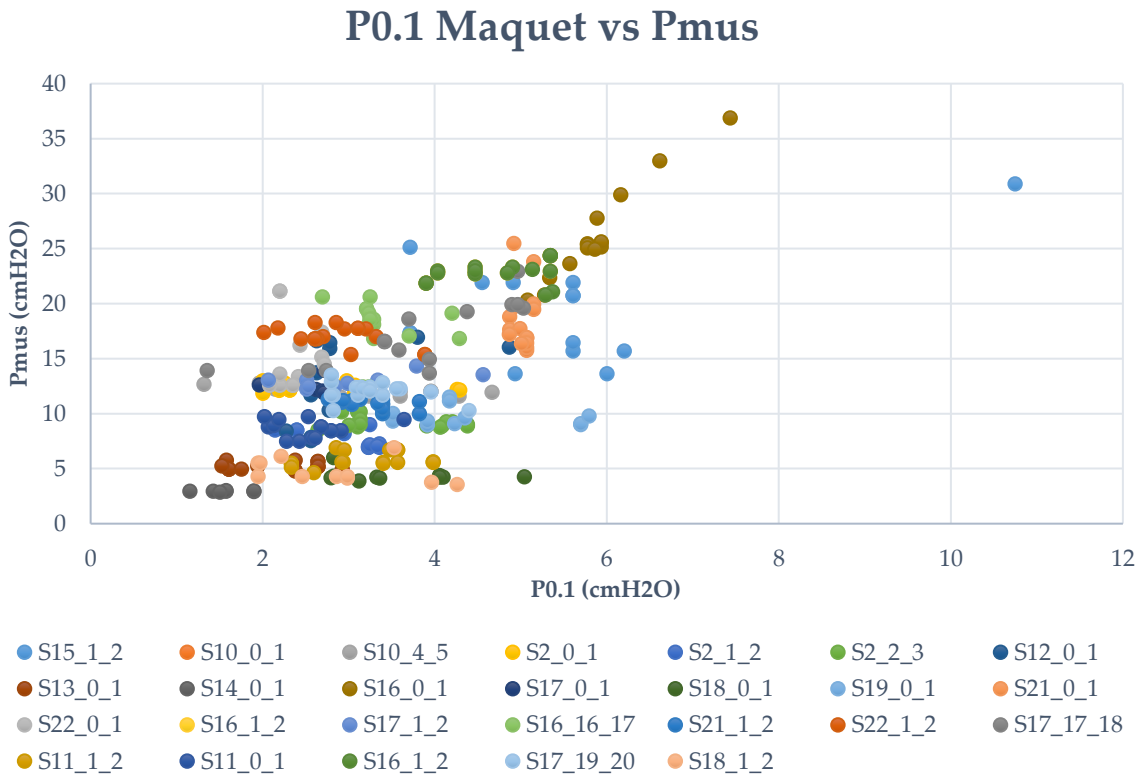

Figure 22 The relation between P0.1 derived through the Maquet method and the Pmus. As can be seen there is a large spread in Pmus values for similar P0.1 values. As from a P0.1 of 2 to 4 there are Pmus values of 4 till 20 cmH2O.

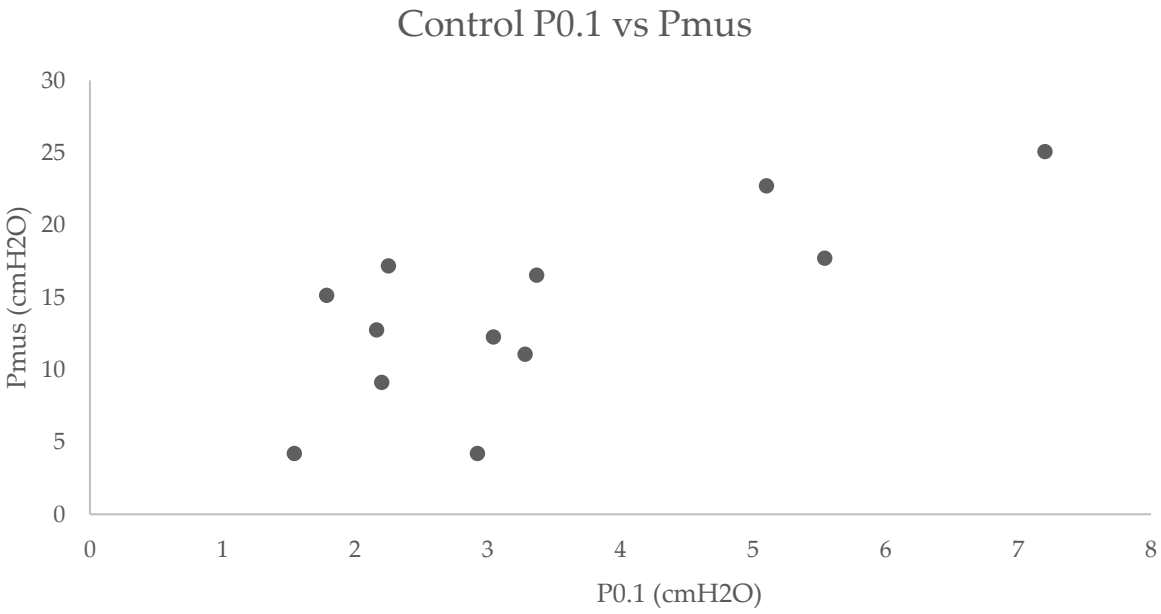

Figure 23 Relation between the Pmus and the control P0.1 values. Each data point represent the average control values of P0.1 and the corresponding Pmus values.

8.4 Discussion

The aim of this study was to test whether it was possible to derive the P0.1 value automatically and it was correlated to Pmus or Pdi.

For the measurement of P0.1 two methods of determining the P0.1 values have been tested, the Mancebo method and the Maquet method and they were validated with control values of the Maquet ventilator monitor. The Maquet method was more difficult to implement as a starting point had to be determined before starting the calculations. This was proven to be difficult as there was sometimes not a clear starting point. Resulting in the start of calculations being set at the wrong time. When comparing the control values to the values derived in the Mancebo and Maquet method (Table 6) the values are in the same ranges. The control values are not directly comparable to the calculated values as just the first few breaths were taken as control values which might not be the exact breaths used in the Mancebo and Maquet calculations. However the values for all the methods are in the same magnitude and therefore the way the calculation are done are probably valid values for P0.1 calculations.

The results of this study show that there is no clear correlation between the P0.1 value and the Pmus as can be seen in Figure 20. Especially when zooming into the reference values for P0.1, when the P0.1 values are between the reference values of 1.5 and 3.5 the Pmus values can range from 3 to 21 cmH2O. This large spread implicate that the P0.1 value cannot be used to estimate Pmus. A possible explanation for this might be that all the factors on which P0.1 is independent of all influence Pmus. P0.1 is a good measure of respiratory neural drive as it is independent of the recoil pressure of the lung and thorax, the resistance of the lung and as there is no volume displacement no modifications are made to the force-velocity relationship[52]. However Pmus is dependent on all of them, as Pmus is dependent on factors influencing pleural pressure and the pressure gradient over the lungs. Pmus is therefore highly dependent on lung volume, elastic recoil pressure of the lung and thorax and the resistance of the lungs[11]. Especially in ICU patients with muscles weakness, the activation of their inspiratory muscles is less, resulting in smaller pressure differences generated. Furthermore, the compliance of the chest wall also influences the Pmus, patients included in the study could have differences in compliance due to their underlying pathophysiology. All these factors could explain the large spread of Pmus values across the reference values of P0.1.

It is interesting to note that in the higher values of P0.1, patient with a higher respiratory drive the Pmus values also increased (see Figure 20). Suggesting that the patients with high respiratory demand are also capable of meeting this demand by increasing their Pmus. As all these patients were on pressure support ventilation it could explain the absence of high respiratory drive with low values of Pmus. When patients with a high respiratory drive cannot meet their respiratory demand by increasing their Pmus they would develop respiratory failure. If they develop respiratory failure they would be switched to controlled ventilation or pressure support would be increased, decreasing their P0.1. Which was also proven by Alberti et al where they proved the P0.1 to be a good parameters to titrate pressure support ventilation[53].

Strengths and limitations

The strength of this study are the high number of breaths analyzed. For every subject 20 breaths have been taken for analysis, with 21 subjects, around 420 breaths have been used for analysis. Furthermore instead of testing one method for P0.1 determination, both the Maquet and the Mancebo method have been tested and implemented.

However the Maquet method needs further improvement as it was proven difficult to implement the starting point of the ventilation triggering, in some cases the starting point was not chosen correctly which could influence the P0.1 value. In most cases the starting point was placed on a point not influencing the final P0.1 value. Furthermore, Pmus is calculated as the difference of the static recoil pressure of the chest wall and the esophageal pressure. The chest wall compliance is an estimation. The exact chest wall compliance might differ and lead to over or underestimation of the Pmus. The estimation has however been widely used in literature and generally accepted measure for chest wall compliance[54].

Another limitation of P0.1 in the current era is the underestimation of P0.1 due to the triggering phase of the ventilators being less than 50ms. Also our implementation of Mancebo could therefore be underestimating the P0.1. If the trigger phase is less than 50ms the gradient calculated is lower, as the window of 50ms is not only placed over the decline in pressure but also on the stable pressure before the pressure drop. Especially patients with high inspiratory drive the P0.1 could be falsely calculated. Taking shorter windows to determine the gradient could potentially solve this problem, but are more influenced by small fluctuations and artefacts in the Paw signal. On random inspection the breaths had triggering phases in most cases for more than 50ms. The short triggering phase could also be a large influence on the Maquet method, when the triggering is short the gradient developed between start of triggering and the lowest point might be lower, which was also seen in study of Telias et al in which they found the Maquet ventilator to have the lowest accuracy[52].

Clinical Relevance

The P0.1 is widely used in the clinic as a measure of respiratory drive. As was proven in this study there is no clear correlation between Pmus and P0.1. Therefore the P0.1 can only be seen as measure of respiratory drive and cannot be used as a measure of the respiratory muscles. Pmus provides a global assessment of all inspiratory muscles and displays patient effort, but as respiratory drive could be higher than the patient can produce the P0.1 and respiratory effort are not linked as was also proven in this study. Therefore P0.1 should primarily be used to assess neural respiratory drive and titrate ventilation and not for assessing patient effort.

8.5 CONCLUSION

The airway pressure drop in 100ms in support ventilation (P0.1) is not correlated to Pmus and Pdi and therefore does not represent total inspiratory effort of the muscles or inspiratory effort of the diaphragm.

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