

Serial Ultrasonographic Evaluation of Diaphragm Thickness During Mechanical Ventilation in ICU Patients

by

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Abstract

While mechanical ventilation (MV) is life-saving in patients with acute respiratory failure, prolonged mechanical ventilation is associated with numerous potential complications. Recent studies have suggested that the ventilator is a likely cause of the decreased diaphragm force generating capacity (dFGC) seen in mechanically ventilated patients. Further, mode of ventilation has been associated with diaphragm atrophy, which has been identified as a key factor influencing dFGC. Animal studies suggest that even as little as 18 hours of mandatory modes of ventilation lead to diaphragm-muscle atrophy and weakness. If the same is true for human patients, then ventilator-associated diaphragm atrophy and weakness seen in animals may be associated with difficulty to wean in humans. This study utilizes ultrasound to investigate the rate at which diaphragm thickness changes in response to mode of MV in critically ill patients, and validates the reliability of our sonography techniques.

We acquired daily ultrasonographic images of the right diaphragm in the zone of apposition in critically ill patients (n=8) in the ICU of the Royal Columbian hospital. As a control for generalized muscle wasting in the critically ill, we acquired daily ultrasonographic images of the quadriceps from each subject over the period of the study. Patients on all modes of ventilation were included and trends in changes in diaphragm thickness within groups (mandatory modes and assist modes) was determined. Inter-operator and inter-observer reliability tests were conducted with all operators and observers blinded from each other's results.

A mean increase in diaphragm thickness of $8.4 \pm 3.9\%$ was detected over a mean of 5.5 ± 4.3 days in all patients on PS ventilation (n=8), with a mean increase of $1.5 \pm 1.4\%$ per day. Patients ventilated on AC mode (n=4) showed a mean decline in diaphragm thickness of $21.2 \pm 10.8\%$ over 4.5 ± 4.4 days, with an average decrease $4.7 \pm 5.7\%$ per day. Mean decline in quadriceps thickness for all participants in this study (n=8) was $14.4 \pm 13.6\%$ over a mean period of 7.1 ± 4.7 days, an average decline of $2.0 \pm 2.7\%$ per day.

Ultrasound provides a reliable non-invasive method of measuring diaphragm thickness and tracking rates of change in thickness in mechanically ventilated critically ill patients. This may be a useful tool in critical care units to identify patients who may be at risk of weaning difficulties secondary to diaphragms that are weakened as a result of atrophy. Larger studies are needed to correlate diaphragm thickness to diaphragm contractile strength and weaning outcomes.

Keywords: Diaphragm atrophy; Ultrasound; Mechanical Ventilation; Weaning outcome; Assist-control ventilation; Pressure-support ventilation.

*To those who paved the path I now walk,
My elders who placed emphasis of education,
Pioneers in science, medicine and the pursuit of knowledge,
To those who accompanied me on my journey,
My wife and source of inspiration and strength, Joy,
My mother, father, brother and sister,
My aunts, uncles, nephews and nieces,
My colleagues and friends,
To those who will continue this great work and continue to
make innovative discoveries,
To those who will benefit from this work.*

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List of Acronyms

AC	Assist Control
AMV	Assist Mode Ventilation
ANOVA	Analysis of Variance
BMI	Body Mass Index
CIM	Critical Illness Myopathy
CIP	Critical Illness Polyneuropathy
CIPM	Critically Illness Polyneuropathy and Myopathy
CMV	Control Mode Ventilation
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
DD	Diaphragm Dysfunction
dFGC	Diaphragm Force Generating Capacity
Dt	Diaphragm Thickness
FRC	Functional Residual Capacity
ICCs	Intra-class Correlation Coefficients
ICU	Intensive Care Unit
MV	Mechanical Ventilation
PEEP	Positive End Expiratory Pressure
PRVC	Pressure Regulated Volume Control
PS	Pressure support
Qt	Quadriceps Thickness
RASS	Richmond Agitation/Sedation Scale
ROC	Receiver Operating Characteristic
ROS	Reactive Oxygen Species
RT	Respiratory Therapist
SBT	Spontaneous Breathing Trial
SCI	Spinal Cord Injury
SD	Standard Deviation
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
US	Ultrasound
VAP	Ventilator Associated Pneumonia
VIDD	Ventilator Induced Diaphragm Dysfunction
VILI	Ventilator Induced Lung Injury
Vt	Tidal Volume

Executive Summary

While mechanical ventilation (MV) is life-saving in patients with acute respiratory failure, prolonged mechanical ventilation is associated with numerous potential complications. Complications such as ventilator associated pneumonia (VAP), cardiovascular compromise, barotrauma and Ventilator-induced lung injury (VILI) have been recognized for decades as issues to which mechanically ventilated patients in intensive care units (ICU) are susceptible. Recent studies have suggested that the ventilator is a likely cause of the decreased diaphragm force generating capacity (dFGC) seen in mechanically ventilated patients – a condition referred to as ventilator-induced diaphragmatic dysfunction (VIDD). Further, mode of ventilation has been identified as a key factor influencing VIDD. There is an increasing awareness that diaphragm weakness is common in patients undergoing MV and is likely a contributing cause of weaning failure. Difficulties in weaning from MV account for a large proportion of total time spent by ventilated patients in the ICU and prolong length of stay. It is well-established that prolonged ICU stays and MV predispose patients to a greater risk of nosocomial infections and death. Patients with just one episode of nosocomial infection remain in the ICU an average of 11 days longer than patients without nosocomial infection and the cost per patient is significantly increased (by as much as \$38,656). Animal studies suggest that as little as 18 hours of mandatory modes of ventilation can lead to diaphragm-muscle atrophy and weakness. If the same is true for human patients, this ventilator-associated diaphragm atrophy and weakness seen in animals may be associated with difficulty to wean in humans. It is, however, still not clear whether such effects of MV occur in humans and whether the effects, if present, will be amplified due to critical illness. We conducted a single-centre observational study in which we used B-mode ultrasonography to evaluate diaphragm thickness in critically ill patients on MV in the ICU of the Royal Columbian Hospital in New Westminster, BC Canada. This study was a pilot to a larger multicentre study proposed to be conducted in the near future. The proposed multicentre study will focus on using diaphragm thickness, as determined by ultrasonography, as a predictor of weaning failure. This data will allow us to potentially identify at risk patients and allow caregivers to develop interventions that may effectively decrease the risk of poor weaning outcomes by mitigating this treatable

mechanism of weaning failure. The present study serves to validate procedures and provided us with the opportunity to gain invaluable insight into the operations of the critical care unit that will guide us in the design of the aforementioned multicentre study.

Methodology

We acquired ultrasonographic images of the right diaphragm in the zone of apposition in critically ill patients (n=8) in the ICU of the Royal Columbian hospital. As a control for generalized muscle wasting in the critically ill we acquired ultrasonographic images of the quadriceps from each subject over the period of the study. Patients on all modes of ventilation were included and trends in changes in diaphragm thickness within mandatory-mode MV and assist- modes MV groups were determined. Inter-operator and inter-observer reliability tests were conducted with all operators and observers blinded from each other's results.

Results

A mean increase in diaphragm thickness of 0.23 ± 0.03 mm (from 2.5 ± 0.7 mm to 2.7 ± 0.8 mm, 95% CI between 0.2mm to 0.3mm; $8.4 \pm 3.9\%$) was detected over a mean of 5.5 ± 4.3 days in all patients on PS ventilation (n=8), with a mean increase of 0.04 ± 0.03 mm per day ($1.5 \pm 1.4\%$ per day). Patients ventilated on AC mode (n=4) showed a mean decline in diaphragm thickness of 0.4 ± 0.4 mm (from 2.8 ± 0.7 to 2.4 ± 0.8 mm, 95% CI of between 0.1mm to 0.8mm; $21.2 \pm 10.8\%$) over 4.5 ± 4.4 days, with an average decrease of 0.1 ± 0.1 mm per day ($4.7 \pm 5.7\%$ per day). Mean decline in quadriceps thickness for all participants in this study (n=8) was 2.4 ± 2.6 mm (from 15.5 ± 5.5 mm to 13.2 ± 5.1 mm, 95% CI of between 0.6 to 4.2mm; $14.4 \pm 13.6\%$) over a mean period of 7.1 ± 4.7 days, an average decline of $2.0 \pm 2.7\%$ per day.

Conclusion

Ultrasound provides a reliable non-invasive method of measuring diaphragm thickness and tracking rates of change in thickness in mechanically ventilated critically ill patients. This may be a useful tool in critical care units to identify patients who may be at risk of weaning difficulties secondary to diaphragms that were weakened as a result of disuse atrophy. Larger studies may be needed to confirm these findings.

Chapter 1.

Introduction

While mechanical ventilation (MV) is life-saving in patients with acute respiratory failure, prolonged mechanical ventilation is associated with numerous potential complications. Complications such as ventilator associated pneumonia (VAP), cardiovascular compromise, barotrauma and ventilator-induced lung injury (VILI) have been recognized for decades as issues to which mechanically ventilated patients in intensive care units (ICU) are susceptible [Tobin et al, 2001; Dreyfuss et al, 1998].

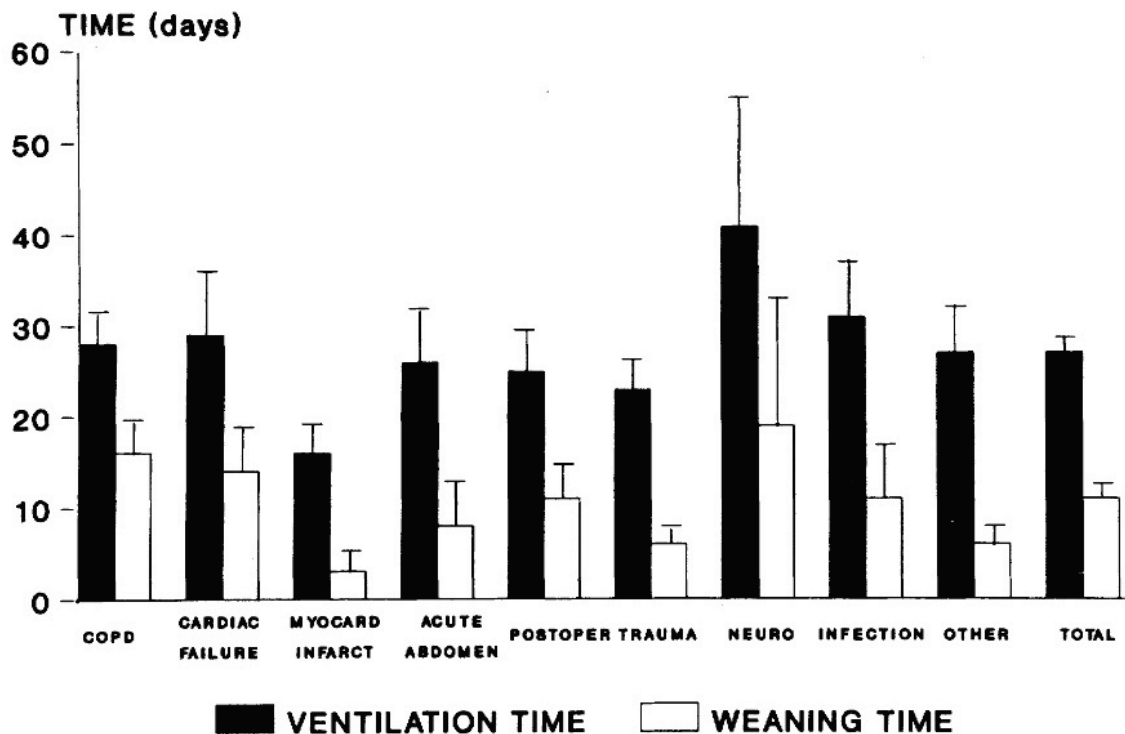


Figure 1. Total duration of mechanical ventilation and the time occupied by weaning in days. Data are mean \pm SEM for each category and the total group of patients [Esteban et al, 1994].

There is increasing awareness that diaphragm weakness is common in patients undergoing MV and is likely a contributing cause of weaning failure [Laghi et al, 2003; Watson et al, 2001; Chang et al, 2005; Petrof et al, 2010; Vassilakopoulos et al, 1998; Harikumar et al, 2009]. Weaning constitutes a large portion – on average approximately 41% [Esteban et al, 1994] – of the time spent in receiving mechanical ventilation (Figure 1). Furthermore, difficulties in weaning patients from MV account for a large proportion of total time spent in the ICU [Esteban et al, 1994]. Inability to wean in a timely manner results in marked increase in ICU Costs [Dasta et al 2005]. The United States devotes \$1.8 trillion annually to health care, which comprises >15% of the U.S. gross domestic product¹. At nearly 5% of the U.S. total healthcare costs, intensive care represents a disproportionate part of this bill [Halpern et al, 2004]. With an attributable cost of \$1,500 per patient-day [Center of Disease Control and Prevention National Nosocomial Infections Surveillance System, January 1992-April 2000], it represents a significant contribution to overall expenses.

In addition to the economic consequences, it is well-established that prolonged ICU stays and MV predispose patients to a greater risk of nosocomial infections and death [Dasta, 2005]. Surveys suggest that more than 20% of all nosocomial infections occur in ICUs [Center of Disease Control and Prevention National Nosocomial Infections Surveillance System, January 1992-April 2000; Stone et al, 2002; Vincent et al, 1995; Pittet et al, 1998]. Nosocomial infections increase morbidity, mortality, costs, and length of stay (LOS) far beyond what is expected based on underlying disease states alone [Jarvis, 1996; Mundy et al, 1999; Wenzel et al, 1995; Digiovine et al, 1999; Dominguez et al, 2001; Slonim et al' 2001; Diaz et al, 1993; Miller' 2003; Haley, 1987; Nelson et al, 1986; Khan et al, 2001]. Patients with just one episode of nosocomial infection remain in the ICU an average of 11 days longer than patients without nosocomial infection [Sieck et al, 1989]. Nosocomial infections increase the cost per patient by ~\$1,909 to \$38,656 and increase LOS in the ICU by an average of 4.3 to 15.6 days [Slonim, 2001; Diaz et al,

¹ Information accessed from the Organization for Economic Co-operation and Development's website at:
http://www.oecd.org/document/16/0,2340,en_2825_495642_2085200_1_1_1_1,00.html

1993; Miller, 2003]. Other studies report that increased hospital stay attributable to nosocomial infections range from 4 to 19 days [Jarvis, 1996; Haley, 1987; Digiovine et al, 1999; Dominiguez et al, 2001; Nelson et al, 1986; Khan et al, 2001, Oris et al, 2002; Whitehouse et al, 2002; Slonim et al, 2001; Wey et al, 1988].

Several studies have suggested that the ventilator is a likely cause of the decreased diaphragm force generating capacity (dFGC) seen in mechanically ventilated patients [Lagi et al, 2003; Watson et al, 2001; Chang et al, 2005] – a condition referred to as ventilator-induced diaphragmatic dysfunction (VIDD) [Vassilakopoulos et al, 2004] because it encompasses both paradoxical movement of the diaphragm as well as diaphragmatic thickness. Further, mode of ventilation has been identified as a key factor influencing VIDD [Jung et al, 2010; Levine, 2008]. In rats, 2 days of controlled mechanical ventilation (CMV) reduced the pressure-generating capacity of the diaphragm by 42%, compared with control animals that breathed spontaneously [Le Bourdelles, 1994]. In contrast, assist modes of ventilation (AMV), which provides support to patients who are able to make spontaneous respiratory efforts (support may be modified based on the patients strength and clinical parameters), may prevent or reduce the deleterious effects seen as a result of CMV [Jung et al, 2010]. However, in assist modes of ventilation such as pressure support mode, high pressure levels may provide almost total ventilator support [Brochard et al, 1989] and may have the same effects on the diaphragm as seen in control modes. It is therefore important to fully understand the parameters of each ventilator mode as this knowledge will be a key factor in choosing the most appropriate mode to meet the patient's needs.

CMV largely replaces spontaneous diaphragmatic activity, resulting in disuse atrophy [Anzueto et al, 1997; Sassoon et al, 2002; Radell et al, 2002]. Animal studies suggest that reduction in dFGC secondary to CMV is strongly correlated with atrophy resulting from diaphragm inactivity [Jung et al, 2010]. A recent human study suggested that 18 to 69 hours of CMV in brain-dead patients resulted in an average of 52-57% reduction in the cross-sectional areas of diaphragm muscle fibers of every type, with an estimated 55% decrease in diaphragm strength [Levine et al, 2008]. Through the assessment of airway occlusion pressure in mechanically ventilated patients (short term: 0.5h; long term >5 days) and the histobiochemical evaluation of biopsy specimens from thoracic surgery patients (MV for 2-3h) and brain dead organ donors (MV for 24-249h),

Jaber and colleagues showed that diaphragm strength progressively decreased with time spent on the ventilator (Jaber et al, 2011). Further, they found that longer periods of MV were associated with significantly greater levels of atrophy and found that this was strongly correlated with diaphragmatic weakness (Jaber et al, 2011). This is of significant importance as weakness may adversely affect weaning outcome [Laghi et al, 2003; Watson et al, 2001; Chang et al, 2005; Petrof et al, 2010; Vassilakopoulos et al, 1998; Harikumar et al, 2009].

B-mode ultrasonography is a reliable, economical, risk free and non-invasive method of measuring muscle thickness [Fukunaga et al, 1989]. In this study we tested the feasibility of utilizing B-mode ultrasound in the tracking of changes in diaphragm thickness in mechanically ventilated critically ill patients. Diaphragm thickness influences diaphragm strength and has been identified as an important variable having direct effect on weaning outcome. The purpose of this study was to determine reliability of our methods and develop ultrasound as a tool that may eventually be valuable in predicting weaning outcomes in critically ill patients.

Rationale

Due to the economic and medical consequences, developing new interventions that shorten length of time spent in the ICU and on MV is of paramount importance. In addition to well-understood factors that contribute to respiratory failure on MV, such as ventilator-induced lung Injury (VILI), barotrauma, atelectasis and biotrauma, an emerging literature suggests that VIDD also plays a major role in determining length of ICU stay and weaning outcome [Harikumar et al, 2009; Vassilakopoulos et al, 1998; Esteban et al, 1994]. The study of brain-dead organ donors by Levine et al. [Levine et al, 2008] may not be representative of critically ill patients on CMV as brain death completely removes neural activation of the diaphragm [Sieck, 2008] and is associated with alteration in the mitochondrial function in skeletal muscle [Kerbaul et al, 2004]. This alteration may induce oxidative stress and subsequent protease activation, resulting in myosin loss [Petrof et al, 2010], which presents as rapid and marked atrophy. Therefore, the extent to which the findings in brain-dead patients can be extended to other patients on CMV is still unclear. Hence, it is important to explore VIDD with other modalities such as

ultrasound in an attempt to understand the changes that occur in the diaphragms of the critically ill.

Levine et al (2008) investigated how CMV influenced changes in diaphragm fiber cross-sectional area (CSA), but neglected to discuss how these changes influenced diaphragm thickness. As type I and type II fibers are present in equal proportions in the human diaphragm (Polla et al, 2004), it is reasonable to take overall change in CSA as the mean of changes in CSA of type I and type II fibers. Levine et al found that a combination of CMV and diaphragm inactivity over 3 days resulted in a mean overall diaphragm fiber atrophy of 55% (type I: 57%; type II: 53%). It is important to note that a 55% decrease in fiber cross sectional area does not translate to an equivalent decrease in diaphragm thickness.

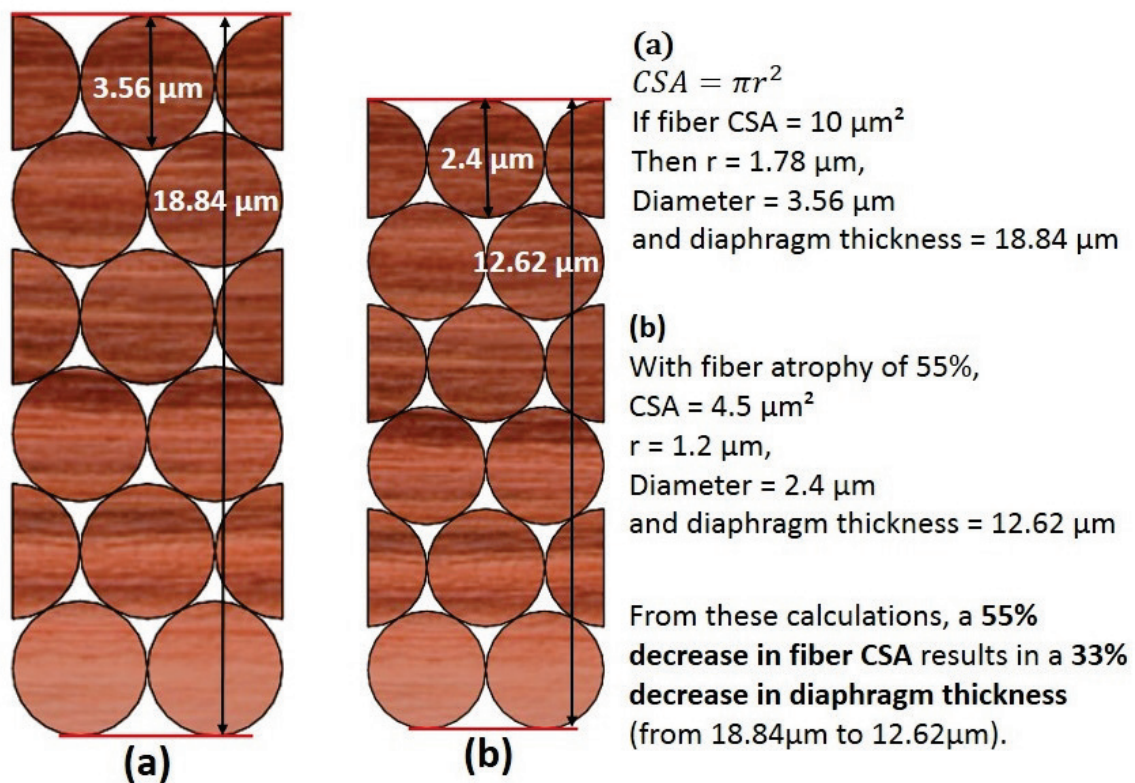


Figure 2. Relationship between fiber cross-sectional area and muscle thickness. (a) baseline diaphragm thickness. (b) atrophied diaphragm.

Assuming all fibers are cylindrical with a circular CSA (Figure 2) and that muscle fiber length remained constant post-atrophy, a 55% decrease in fiber CSA will result in a

33% decrease in muscle thickness. This suggests a rate of atrophy of 11% per day and is 1.8 times the rate (6% per day) suggested by other researchers (Grosu et al, 2012). Furthermore, this supports the hypothesis that brain death accelerates the rate of diaphragm atrophy and highlights the importance of investigating this phenomenon in a population with an intact neural drive.

Kim et al. [Kim et al, 2011] employed M-mode ultrasonography (a diagnostic presentation of the temporal changes in echoes in which the depth of the reflector is displayed on one axis and time is displayed along the second axis, recording motion of the reflector toward and away from the transducer) to assess prevalence of diaphragm dysfunction (DD) during spontaneous breathing trials (SBT) in medical ICU patients and to determine its influence on weaning outcome. They defined diaphragmatic dysfunction as vertical excursion < 10mm or paradoxical movement (movement of the diaphragm opposite to physiological movement, indicative of extreme weakness or paralysis) during the SBT. They found that the group diagnosed with DD had significantly longer weaning times (median 401 vs. 90 hrs, $p < .01$) and total ventilation times (576 vs. 203 hrs, $p < .01$) than the non-DD group. Further, the DD group showed higher rates of primary (defined as requirement for mechanical ventilation within 48 hrs of self-breathing; 83% vs. 59%, $p < .01$) and secondary (defined as a requirement for mechanical ventilation after a successful weaning, i.e., respiratory failure occurring past the 48 hrs of self-breathing; 50% vs. 22%, $p < .01$) weaning failures than the non-DD group, and ICU and hospital lengths of stay were longer in patients with DD than patients without DD. They concluded that the employment of ultrasonography in the diagnosis of DD may prove to be a useful tool in identifying patients at high risk of weaning difficulty. However, they neglected to investigate factors influencing diaphragmatic dysfunction and the natural history of diaphragmatic changes in ICU patients. Diaphragm atrophy secondary to inactivity as a result of CMV may be one possible factor which significantly influences DD [Vassilakopoulos et al, 1998; Harikumar et al, 2009]. More studies are needed to elucidate this topic. Animal studies suggest that even relatively short periods of CMV (as little as 18 hours) lead to diaphragm-muscle atrophy and weakness [Sassoon et al, 2002; Powers et al, 2002]. It is, however, still not clear whether such effects of MV occur in humans and whether the effects, if present, will be amplified due to critical illness. All current studies identifying mode of ventilation as a factor influencing VIDD were

conducted using healthy animal subjects [Radell et al, 2002; Jung et al, 2010]. Critical-illness polyneuropathy and myopathy are common in ICU patients, with a prevalence ranging from 30 to 90%, and may develop quickly after the onset of critical illness [Hough et al, 2007; Khan et al, 2006]. Interactions between muscle inactivity secondary to mechanical ventilation and early development of subclinical polyneuropathy and myopathy may contribute to a more rapid rate of muscle atrophy in critically ill patients [McCool et al, 2008]. The extent to which results of animal studies are applicable to critically ill ICU patients remains to be shown.

Although it is life-saving in patients with respiratory failure (Table 1), mechanical ventilation is also associated with numerous potential complications and can paradoxically create and sustain damage to the lungs [Dreyfuss et al, 1998].. Furthermore, diaphragmatic weakness appears to be very common in patients undergoing MV, having a negative influence on their ability to wean. Although there have been intriguing animal and early ultrasound studies, more human studies are required to better understand how the diaphragm of critically ill patients responds to MV and how this response influences weaning outcomes. Grosu et al (2012) utilized B-mode ultrasonography to determine changes in diaphragm thickness in 7 critically ill patients supported on pressure regulated volume control (PRVC) mode of ventilation. They found that all their patients showed a decline in diaphragm thickness of an average of 6% per day. They neglected to investigate how the diaphragm responds to other modes of ventilation. It is known that level of diaphragm activity in patients on MV is influenced by mode of ventilation, and that morphological changes in the diaphragm are influenced by level of activity. Therefore, it is important to investigate the diaphragm's physiological response to various MV modes. Our study utilized ultrasound to investigate the rate at which diaphragm thickness changed in response to mode of MV in critically ill patients, and made attempts at validating the reliability of our methods. Muscle atrophy influences weakness, hence, in order to develop effective treatment and prevention strategies it is important that we develop tools that will aid in our understanding of this phenomenon as it relates to the diaphragm.

Table 1. Possible Outcomes of Mechanical Ventilation (Howman, 1999)

Reversal of severe hypoxemia

Reversal of acute, severe respiratory acidosis
Relief of respiratory distress
Prevention or reversal of atelectasis
Reversal of respiratory muscle fatigue
Allowance for sedation or neuromuscular blockade
Decrease in systemic or myocardial oxygen consumption
Reduction of intracranial pressure through hyperventilation
Stabilization of chest wall

Chapter 2.

Mechanical Ventilation

The need for mechanical ventilation support is the most common reason for admission to a critical care unit [Saydain et al, 2002]. Explicit indications exist for institution of MV (Table 2); however, they are not well-validated. The decision to institute mechanical ventilation is usually made by the physician at the bedside on clinical grounds and takes into consideration the underlying condition, the likely course of the disease, and the potential response to medical treatment [Kornecki et al, 2009].

Table 2. *Indications for Mechanical Ventilation (Kornecki et al, 2009)*

Respiratory failure
Pump failure
Chest wall dysfunction (e.g., flail chest)
Neuromuscular disease
Central nervous dysfunction (decrease in respiratory drive)
Congenital (e.g., Ondine's curse)
Acquired (e.g., trauma, drugs, infectors)
Pulmonary disease
Ventilation-perfusion mismatch (e.g., pneumonia)
Pulmonary shunt (e.g., acute respiratory distress syndrome)
Reduction in functional residual capacity

Depending on the manufacturer, variations may exist in ventilator parameters. However, there are basic parameters which may be present on all machines: tidal volume and/or minute ventilation, respiratory rate, flow rate or inspiratory time, percent oxygen, and alarm limit settings. The method of inspiratory support provided by the mechanical ventilator is referred to as *mode of ventilation*. It is the specific combination of breathing pattern and control variables to deliver inspiration (Chatburn et al, 2007). The culture of the ICU in each institution and the clinician's experience play vital roles in

the selection of the appropriate mode [Bozyk et al, 2010]. Some modes guarantee a constant volume (volume-targeted or volume-controlled) with each machine breath, whereas other modes guarantee a constant pressure (pressure-targeted or pressure-controlled). Although many variations in modes of ventilation exist, we will discuss the basic modes on which all other modes of ventilation are based.

Overview of Common Modes of Ventilator Support

Volume-Targeted Modes

In a volume-targeted mode, tidal volume (V_t) is the targeted parameter, hence a fixed V_t is delivered with each breath. Volume-targeted modes may be labeled by different names, including controlled mandatory ventilation, continuous mandatory ventilation, and assist/control (AC) mode ventilation, and are the most commonly used modes in the ICU [Santanilla et al, 2008]. If the patient is not making respiratory efforts due to sedation, paralysis, or other factors affecting the respiratory drive, the ventilator delivers breaths at a set respiratory rate and V_t . In volume-triggered modes, the ventilator may be triggered by the patient's attempts to breathe. With the ventilator sensitivity dial set to high levels (-1 to -2 cm H₂O), even minimal efforts by the patient will be detected and the machine will deliver additional breaths at the set V_t . The inspiratory flow rate is fixed and therefore does not change to match the patient's respiratory rate and breathing pattern.

Pressure-Targeted Modes

In pressure support ventilation, pressure is the ventilator's targeted parameter. Dependent on the mode of pressure support, breaths are triggered by the patient and augment the patient's spontaneous inspiratory effort with a pre-set positive pressure level. In all pressure targeted modes, inspiration ends after delivery of the set inspiratory pressure. Two pressure-targeted modes are common: *pressure support ventilation* (in which the patient triggers the ventilator) and *pressure control mode* (in which the ventilator controls the patient's breathing).

Pressure Support Ventilation

In pressure support (PS) ventilation, volume is variable, rather than a fixed V_t as in volume-targeted modes, and is determined by the patient's effort or drive, pre-set pressure level, and various airway resistance and lung compliance factors. Respiratory rate is also determined by the patient and the flow rate is variable, depending on the patient's needs. Pressure support ventilation is commonly thought of as a weaning mode, utilizing low pressure support levels set to overcome resistance in the endotracheal tube and ventilator circuit.

High-level Pressure Support

In contrast to low levels of pressure support typically employed during weaning, high pressure support levels may provide the patient with almost total ventilator support [Brochard et al, 1989]. Similar to AC mode of ventilation, high levels of prolonged pressure support ventilation promote diaphragmatic atrophy and contractile dysfunction (Hudson et al, 2012). Progressively increasing the level of pressure support results in a significant decrease in respiratory rate, effectively decreasing the work of the diaphragm (Brunch et al, 2005). Additionally, at high PS levels, there is significant decrease in diaphragm electrical activity and trans-diaphragmatic pressure, further evidence of decrease in diaphragm activity (Beck et al, 2001). Furthermore, similar to AC ventilation, pressure support ventilation-induced diaphragmatic atrophy and weakness are associated with both diaphragmatic oxidative stress and protease activation (Hudson et al, 2012). Importantly, although prolonged periods of high level PS and mandatory modes of ventilation both promote diaphragmatic atrophy, the speed of PS-induced diaphragm atrophy occurs at a slower rate (Hudson et al, 2012).

Pressure Control Mode

Pressure control ventilation operates in a manner similar to pressure support ventilation in that it relies on a pre-set pressure to determine the volume delivered and volume is variable depending on various factors that affect airway resistance and/or lung compliance. However, in pressure control mode, a respiratory rate is set by the clinician in order to support patients with apnea or an unreliable respiratory drive [Grossbach et al, 2011]. Pressure control mode may be used in patients with acute respiratory distress syndrome to control plateau pressures and V_t [Grossbach et al, 2011]. Patients with

acute respiratory distress syndrome have low lung compliance; therefore, inappropriately high V_t and pressure settings can overstretch and injure the lung. Current strategies in such patients should be focused on limiting V_t and maximal lung stretch. An initial V_t of 6 mL/kg ideal body weight is a reasonable starting point and may be decreased to maintain maximal lung distending pressures less than 30 to 35 cm H₂O [MacIntyre, 2008; MacIntyre, 2013].

Chapter 3.

Important Factors Influencing Rapid Diaphragm Atrophy and Failure to Wean

Oxidative Stress (Mitochondrial Dysfunction)

Numerous studies have shown that mechanical ventilation is associated with an increase in markers of oxidative stress in the diaphragm [Levine et al, 2008; Shanely et al, 2002; Zergeroglu et al, 2003; Falk et al, 2006]. Oxidative modifications become evident within as little as 6 hours following the institution of MV in rats [Zergeroglu et al, 2003]. Other animal studies suggest that diaphragmatic inactivity, secondary to MV, induces diaphragmatic mitochondrial dysfunction resulting in significantly increased mitochondrial reactive oxygen species (ROS) emission, mitochondrial oxidative damage and mitochondrial respiratory dysfunction [Kavazis et al, 2009].

There is evidence that calpain, caspase and ubiquitin-proteasome proteolysis pathways all play significant roles in the development of MV-induced diaphragm atrophy [Petrof et al, 2010]. The initial step of proteolysis, which involves the proteolytic release of myofilaments from their native state, can be accomplished by either calpains or caspases. Since calpains and caspases are activated by ROS [Petrof et al, 2010], an increase in ROS emission during MV may trigger increased proteolytic activity. The partially cleaved and disassembled myofilament proteins are then processed and degraded by the ubiquitin-proteasome system [Petrof et al, 2010].

Systemic antioxidant supplementation has been suggested as a possible mitigation for oxidative stress. However, this method has not been particularly successful in critically ill patients [Mishra et al, 2007; Rinaldi et al, 2009; Victor et al 2009]. It has been suggested by several experts that antioxidants targeted to mitochondria may be of more benefit [Gallay et al, 2010; Subramanian et al, 2010]. Studies investigating effects

of mitochondria-targeting antioxidants have to date only been conducted using animal models. Further studies are needed to refine this proposed method prior to its use in human patients [Fink et al, 2008; Dyson et al, 2009]. For the time being, current preventative measures in humans are primarily based upon allowing persistent diaphragmatic activation during mechanical ventilation [Petrof et al, 2010].

Positive End Expiratory Pressure (PEEP)

Positive end expiratory pressure (PEEP) is a method of positive pressure ventilation used in conjunction with mechanical ventilation; pressure is maintained above the level of atmospheric pressure at the end of exhalation. This is achieved by preventing the complete release of gas during exhalation, usually by means of a valve within the circuit [Dorland's Medical Dictionary]. The main purpose is to increase the volume of gas remaining in the lungs at the end of exhalation, thus reducing atelectasis and the resulting shunting of blood through the lungs and improving gas exchange [Dorland's Medical Dictionary]..

It is established that skeletal muscles atrophy faster when inactive in the shortened position [Jarvinen et al, 1992; Jokl et al, 1983]. Since the increased lung volume at the end of expiration with the use of PEEP would put the passive diaphragm in a relatively shortened position, it is possible that the diaphragm will atrophy at a relatively faster rate. In an animal study, 2 days of CMV with PEEP resulted in significantly more atrophy when compared to a control group on CMV for 3 days (Capdevila et al, 2003). However, it is yet to be confirmed whether critical illness compounds the effects of PEEP. It would be interesting to investigate, in critically ill patients, how PEEP influences rate of diaphragm atrophy.

Critical Illness Polyneuropathy and Myopathy (CIPM)

There is growing recognition that both critical illness and its associated treatments are toxic to muscles and nerves, leading to pathologic changes termed critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) [Hough et al, 2007; Schweickert et al, 2007; Hermans et al, 2008]. Polyneuropathy and myopathy may

have always accompanied sepsis which may be an important predictor of these syndromes.

Systemic Inflammatory response and CIPM

Critical illness, in recent years, has been defined as a syndrome of sepsis and multiple organ failure. Sepsis, a severe systemic response to infection, usually results in early death [Bolton, 2005]. In the United States, > 500,000 patients per year develop sepsis [Riedemann et al, 2003]. However, with improvements in medical and surgical care, survival of many critically ill patients is now prolonged. Despite advances in medicine, the mortality rate is still 30%–50% [Dellinger et al, 2004; Riedemann et al, 2003; Tran et al, 1990], suggesting that there may still be room for improvement in management of sepsis.

In previous years there seemed to have been a confusion of terminology. Terms were being variously applied with no standardized definitions to ensure correct usage of certain key words. In 1992, a consensus conference was convened to do just that. With the recognition that mechanical, chemical or thermal trauma may, in the absence of infection, evoke a severe systemic response, the term “systemic inflammatory response syndrome” or SIRS was proposed [American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis, 1992]. When SIRS is associated with a documented infection, the term “sepsis” should be applied [American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis, 1992]. Thus, bacteria, fungi, viruses, and major trauma of a mechanical, thermal, or chemical nature will induce SIRS [Figure 3], increasing the probability of CIPM.

How SIRS Influences CIPM

Patients with SIRS experience systemic changes in microcirculation secondary to activated cellular and humoral responses [Glauser et al, 1991; Riedemann et al, 2003]. The cellular response involves epithelial and endothelial cells, macrophages, and neutrophils. These facilitate the activation of the humoral response which involves pro-

inflammatory mediators that are activated locally. These cellular and humoral factors interact with themselves and with adhesion molecules, which are increased in the blood of septic patients [Cowley et al, 1994]. This interaction ultimately results in obstruction of capillary flow as adhesion molecules adhere to leukocytes, platelets, and endothelial cells; they also induce rolling neutrophils and fibrin platelet aggregates [Bolton, 2005]. In addition, Nitric Oxide, an endovascular relaxing factor [Palmer et al, 1987], is also activated. This, coupled with the effects of cellular and humoral factors, serves to further slow capillary flow.

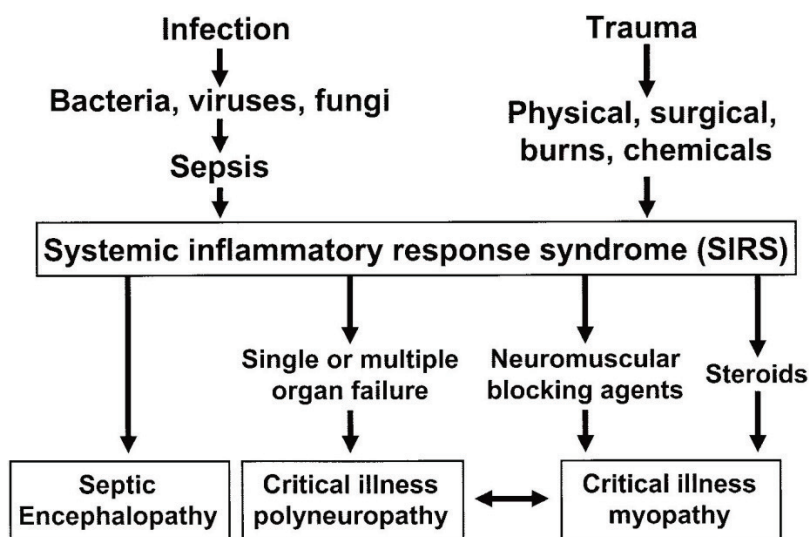


Figure 3: *The various factors associated with the development of the systemic inflammatory response syndrome (SIRS) and its nervous system complications [Bolton, 2005].*

Taken together, all the above stated facts may result in essential nutrients failing to reach the organs. If this persists, despite adequate oxygenation via mechanical ventilation, there will be a severe oxygen deficit at the parenchymal level contributing to multiple organ dysfunction [Glauser et al, 1991].

Acute limb and respiratory weakness, which constitutes CIP, commonly accompany patients with multiple organ dysfunction. CIP, by virtue of decreased neural drive to the diaphragm therefore rendering the muscle inactive, is a major cause of difficulty in weaning patients off MV after respiratory and cardiac causes have been excluded [Vijayan et al, 2005].

As with all living tissues in the body, a disruption in blood flow and impaired delivery of substrates will adversely affect normal functions. In SIRS, disturbances of the microcirculation affect delivery of oxygen and glucose upon which the nervous system depends. Considering this, it is therefore not surprising that patients with SIRS present with symptoms of polyneuropathy. The syndrome is characterized by limb muscle weakness, usually more pronounced distally than proximally, and is often accompanied by atrophy.

CIM is usually associated with the use of intravenous corticosteroids and neuromuscular joint blocking agents – used to facilitate mechanical ventilation in critically ill patients – in addition to SIRS [Bolton, 2002; Lacomis et al, 2000]. The major symptom is flaccid weakness which tends to be diffuse, involving all limb muscles and neck flexors, and often the facial muscles and diaphragm. Thus, these patients may also be difficult to wean from MV [Lacomis et al, 2000].

Along with diaphragm inactivity secondary to MV, CIP and CIM results in rapid atrophy of the diaphragm in critically ill patients requiring a mandatory mode of ventilation. Proper management of sepsis and multiple organ dysfunction syndrome in the ICU are integral to the prevention of CIPM [Bolton, 2005]. In conjunction, interventions that may keep the diaphragm active during MV may be an important step on the road to prevention of ventilator induced diaphragm atrophy and weaning difficulties. Studies investigating the time course of diaphragm atrophy in critically ill patients on MV may give us a better understanding as to the magnitude of the problem, allow ICU medical teams to develop more effective strategies to mitigate weaning difficulties and provide caregivers with information as to the most appropriate time to intervene with treatment plans designed for the prevention of diaphragm weakness.

Chapter 4.

Ultrasonography

Ultrasonography is the visualization of deep structures of the body by recording the reflections (echoes) of pulses of ultrasonic waves directed into the tissues. Diagnostic ultrasonography, as in echocardiography, uses a frequency range of 1 million to 10 million Hertz (cycles per second), or 1 to 10 MHz. Such ultrasound waves are transmissible only in liquids and solids [Dorland's Medical Dictionary].

For assessing body composition, new technologies such as computed tomography (CT) scan, X-ray absorptiometry and ultrasound have advantages over older methods, such as skinfolds and bioelectrical impedance analysis. The major advantage is that they can quantify both fat and muscle thickness and distribution. In order to produce an accurate measurement of subcutaneous fat and overcome the problem of fat compression that is inherent in the skinfold technique, the use of X-ray technology may be employed (Himes et al., 1979; Hawes et al., 1972; Haymes et al., 1976; Stouffer, 1963). However, the applicability of this method for serial evaluations is limited because of radiation exposure. Studies requiring serial evaluations demanded a modality that would eliminate the risk of repetitive radiation exposure. For studies of this nature, ultrasound would be the most appropriate choice.

Acquiring body tissue images via ultrasonography has the same advantages as X-ray or CT scan technology in that fat and muscle thicknesses can be accurately visualized without compression of the tissue. However, ultrasonography is unique in that radiation exposure is eliminated. Another important advantage specific to this study is the ease with which real-time images of soft tissue can be obtained, making ultrasound the ideal modality to evaluate highly functional muscles such as the diaphragm. Original ultrasonographic technology provided a one dimensional image using A-mode ultrasound (only represents elapsed time and thus position of the echo producing

interface) which does not allow for actual images of the tissues to be visualized. B-mode ultrasound is a more technologically advanced method which provides a two-dimensional image of both fat and muscle thicknesses. In this mode, the position of the visualized structure on the display corresponds to the time elapsed (and thus to the position of the echogenic surface) and the brightness of the structure corresponds to the strength of the echo. This allows for better identification and differentiation of the various reflections produced by the sound waves (Ishida et al, 1992).

Fukunaga et al. (1989) compared B-mode ultrasound measurements with direct measurements from cadavers and found that ultrasound was a valid method of measuring both muscle and fat thickness. Ishida et al (1992) assessed, using multiple investigators, the reliability of B-mode ultrasound for the measurement of fat and muscle thickness in human subjects. They found that B-mode ultrasound was a reliable method for measuring both fat and muscle thickness in young adult men and women. Although B-mode ultrasound is a more expensive method of assessing body composition than either skinfolds or bioelectrical impedance analysis, its advantages over these methods include the ability to quantify both fat and muscle thickness/distribution (Ishida et al, 1992). This may be especially important when changes in muscle and fat thickness are of interest.

In this study, we employed B-mode ultrasonography to investigate changes in diaphragm thickness over time in critically ill patients who required mechanical ventilation. This reliable imaging technique provided us with clear images allowing us to accurately track changes in diaphragm thickness.

Along with diaphragm thickness, quadriceps muscle thickness was also evaluated in this study. Muscle ultrasound is an easily available, reliable and quick method for measuring quadriceps muscle thickness. Other methods, such as thigh circumference, are unreliable and often grossly underestimate muscle wasting because they include a measure of the subcutaneous tissue and fat. A more accurate method of measurement is a CT scan; however, this method exposes the patient to radiation and is a more time-consuming study [Appell, 1990]. Although magnetic resonance imaging is accurate for the assessment of cross-sectional areas of muscle, it has not been widely used for research purposes due to the time involved, the cost and competing use in

clinical cases [Reardon et al, 2001]. As with diaphragm thickness, ultrasonography is the modality most suited for performing serial evaluation of the quadriceps muscles. The ease with which the image acquiring protocol is executed, the ability to acquire high resolution images in the ICU and the short time required to perform each quadriceps US exam, made this modality the most appropriate choice for quadriceps muscle imaging in this study.

Chapter 5.

Study Design and Hypothesis

We conducted a single-centre pilot observational study in which we used B-mode ultrasonography to evaluate diaphragm thickness in critically ill patients on MV in the ICU of the Royal Columbian Hospital in New Westminster, BC Canada. We hypothesized that in patients on mandatory mode ventilation, diaphragmatic thickness would progressively decrease over several days following the start of MV. We also evaluated the longitudinal changes of diaphragm thickness in patients who were weaning from the ventilator, where we anticipated that diaphragm thickening would be associated with progression of a patient's ability to generate spontaneous breaths. Further, the predictive value of diaphragmatic thickness for successful liberation from mechanical ventilation was evaluated.

Objectives

Our objective was to evaluate diaphragm thickness in critically ill ICU patients on MV and its changes over time as a function of mode of mechanical ventilation. We proposed to study each subject for up to 14 days from time of enrolment or until extubation, whichever happened first. We aimed to study at least 20 subjects who required MV for at least 72 hours. This study was intended to serve as a pilot for a subsequent, larger multicentre prospective evaluation of diaphragmatic thickness in patients on MV.

Methods and Procedures

Design

This was a single centre observational longitudinal study to evaluate changes in diaphragm thickness in critically ill ICU patients on MV.

Primary Outcome

Diaphragm thickness (via B-mode ultrasonography) measured daily at functional residual capacity (FRC) for 14 days or until extubation or death.

Secondary Outcomes

- Time from intubation to 1st US
- Inter observer variability (kappa score) for evaluating the diaphragmatic thickness of the same US image.
- Inter-rater reliability (agreement): Variability between measured diaphragmatic thickness from US obtained images from the same patient by different operators and observers on the same day.

Patient Characteristics Captured

- Admitting diagnosis
- Age
- Gender
- BMI
- Co-morbidities
- FiO2 average, median, max and min per day
- Sequential Organ Failure Assessment (SOFA) score
- Richmond Agitation/Sedation Scale (RASS)
- Average, median, max and min PEEP per day
- Mode of MV on a daily basis (expressed as a percentage), if not on CMV for 14 days
- Weaning trials, duration and type
- Presence of tracheostomy
- Days in ICU prior to enrolment
- Patient on steroids, start date
- Duration of ICU stay for non-survivors
- Any changes in Mode of ventilation during 1st 14 days
- Any spontaneous breathing trials during 1st 14 days

Inclusion Criteria

Persons who met the following requirements and consented were included in the study:

- Anticipated to require MV > 72 hours
- ≥19 years

Exclusion Criteria

- History of diaphragmatic or neuromuscular disease
- Morbidly obese patients (BMI > 40)
- Declined consent

Methodology

Surrogate decision makers of patients admitted to the ICU who had not been previously enrolled in the study were offered a chance to participate. Informed consent was obtained prior to the subject's inclusion in the study. Diaphragm thickness was measured once per day starting as soon as possible after consent was granted and continuing until the 14th day post-inclusion into the study, extubation, discharged or death, whichever came first.

No participant was sedated or placed on mechanical ventilation by our research team for the purposes of this study. Participants may already have been sedated and mechanically ventilated (for management of their medical condition) prior to commencement of our measurement intervention and/or were awake during their weaning phase.

The US images obtained were saved and stored on an external drive for analysis by research investigators. The data files were randomized by observer C (MW) who randomly re-named each file with a letter-number designation (eg. A12). All operators were blinded from the randomization process. The re-named files were placed in a single folder for analysis. A key was developed by observer C - from which all members of the research team were blinded - that would be used to re-organize the files according to patient and sequence of data acquisition. Thickness measurements were made from the randomized files and results recorded by observer A (CF). Results of measurements

from the randomized files were then re-arranged by observer C according to patient and sequence of acquisition. Graphs for each patient were plotted by observer C from these results. For an inter-observer reliability study, three blinded investigators independently evaluated diaphragmatic thickness in a randomly selected subset of patients (n=5). Inter-observer comparisons were made at a later time. In an inter-operator reliability study, 3 independent operators, who were blinded to each other's results, acquired diaphragm and quadriceps readings from a subset of patients (n=2). Subsequently, the operators made measurements on the acquired images and submitted their results to an independent investigator. The variability in the images and measurements were compared among those obtaining the images.

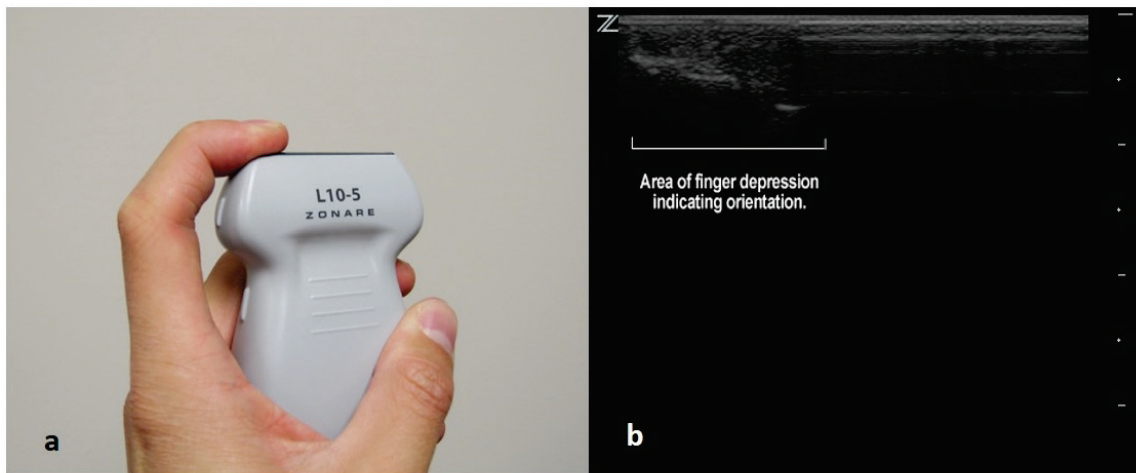
US evaluation of quadriceps muscle thickness was done immediately following each evaluation of diaphragmatic thickness to provide information regarding overall changes in muscle mass in the patient [Gruther et al, 2008]. This allowed for an evaluation of the effects of MV on the diaphragm beyond the catabolic state induced in the ICU.

Ultrasonographic images were acquired by Colin Francis who is a trained physical therapist with 3 years of prior ICU experience after patient consent was obtained (by Suzette Williams – research coordinator). All acquired data was analyzed and reported by Colin Francis and co-investigators.

Technical Aspects of Measuring Diaphragmatic Thickness

Diaphragm Thickness

Real-time movement of the diaphragm was recorded by B-mode ultrasonography using an Echo Blaster 128 Kit (UAB "TELEMED", Dariaus ir Gireno str. 42 Vilnius LT-02189, Lithuania – resolution of 0.1mm) fitted with a 5-10 MHz ultrasound linear transducer (HL9.0/60/128Z) provided by Lungpacer Medical Inc.:



(a) Using finger to push on the marker side of transducer. (b) Aberration from pushing on one side of transducer.

The ultrasound image that appears on the screen should correspond to the same side as the finger applying pressure to the transducer. If not, the transducer is rotated so that the same side that is depressed on the transducer is the same as the aberration that appears on the screen.

Figure 4. Orientation of transducer.

Locate the Diaphragm in the Zone of Apposition to the Ribcage

- Subjects were in the supine position.
 - Precautions were taken to ensure that the patient was lying flat on their back.
 - The head of the bed was lowered to 0° of incline.
 - In cases where the head of the bed could not be laid completely flat due to patient condition, the degree of incline (usually between 10°-20°) during baseline reading was noted and the same degree of incline was set for all subsequent readings.

The probe was oriented with the screen image by applying pressure to one end and noting the position of the image on screen (Figure 4).

- The probe was placed in the 8th or 9th right intercostal space in the midaxillary or anterior axillary line (Figure 5).
- The ultrasound beam was directed perpendicular to the diaphragm; i.e. the probe was positioned perpendicular to the chest wall in a long axis configuration with the left end cephalad.
- The probe position was adjusted until the diaphragm could be clearly visualized (small changes in orientation of probe from its ideal position resulted in distortion or loss of image).

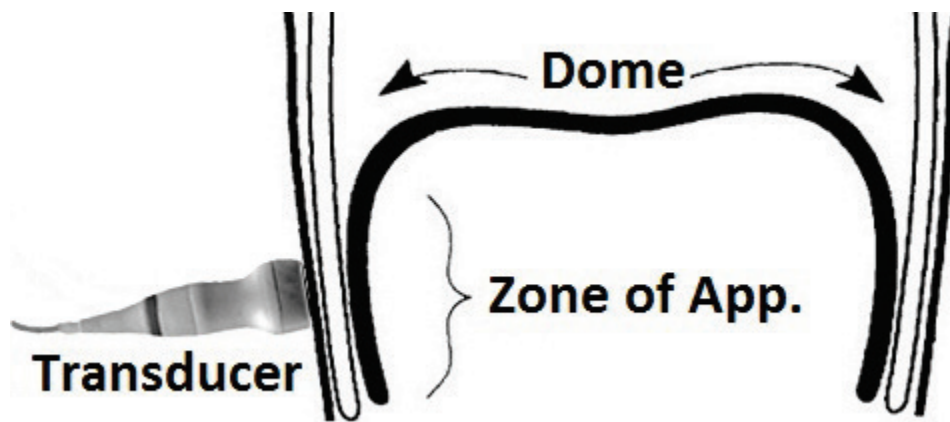


Figure 5. *Transducer placement with respect to zone of apposition of the diaphragm to the ribcage.*

- Once a clear image of the diaphragm was obtained, an indelible ink marker was used to mark the skin at the caudal end of the transducer (Figure 6).

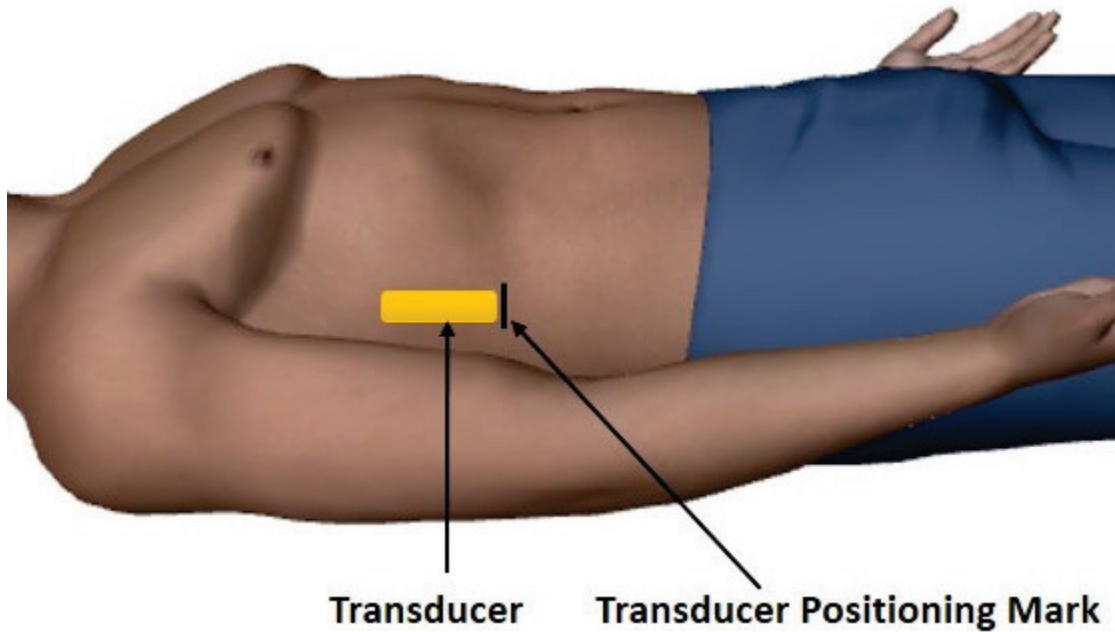


Figure 6. *Placement of Transducer Positioning Mark.*

- All US images were acquired with the transducer in the same position.
- The files were stored in video format and named according to patient number and day of exam.

Identify the Diaphragm

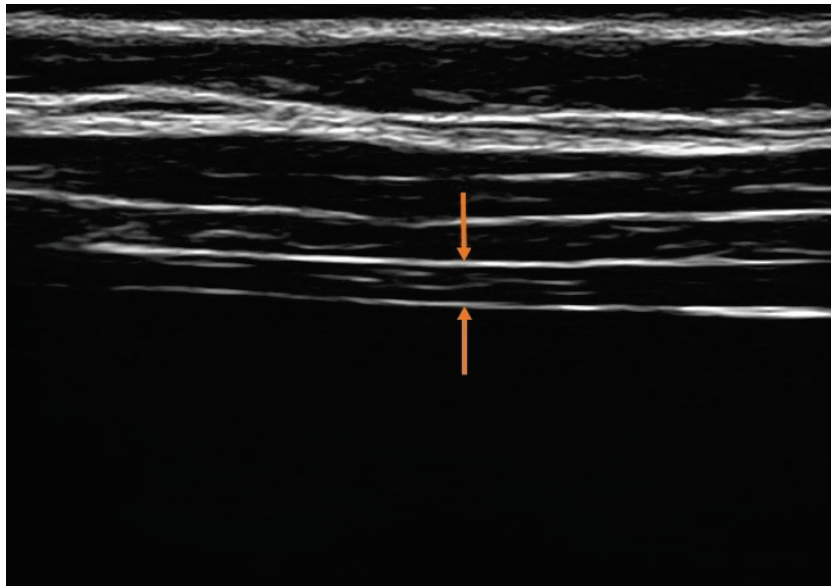


Figure 7. *Echogenic lines representing membranes overlying the diaphragm.*

- The diaphragm is identified as the last set of parallel lines on the image, corresponding to the pleural and peritoneal membranes overlying the less echogenic muscle (figure 7).
- Once identified, real-time movement of the diaphragm was recorded on B-mode (two dimensional) ultrasonography.
- If the patient was triggering the ventilator (as was usually the case in assist modes of ventilation) and there were visible diaphragmatic contractions, at least six consecutive respiratory cycles were recorded.

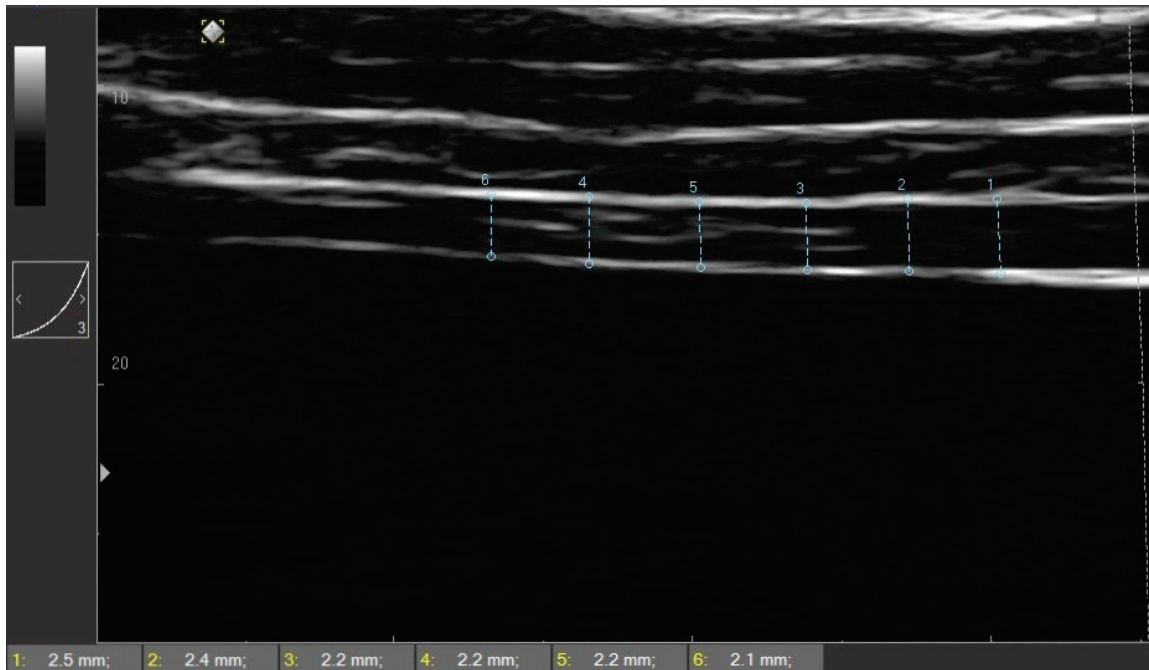


Figure 8. *Measuring end expiratory diaphragm thickness using ‘distance’ measuring tool.*

- End expiratory diaphragm thickness was measured in three consecutive respiratory cycles during the end expiratory pause (Figure 8).
 - The diaphragm thickens as it contracts (Cohn et al, 1997), hence, great efforts were made to ensure that all thickness measurements were performed during the end expiratory pause (when the diaphragm is relaxed).
- Thickness of the pleural and peritoneal membranes are exaggerated by ultrasound (Ueki et al, 1995). Hence, to obtain the most accurate measurement of diaphragm thickness, measurements were made from the middle of the pleural line to the middle of the peritoneal line [Ueki et al, 1995].
- Measurements were averaged and the means reported to the nearest 0.1mm

Failure to Acquire Image

Failure to acquire image was defined as the inability to acquire a discernible image on two consecutive days by two different operators.

- All subjects in which image acquisition failed were excluded from the study.

Measuring Quadriceps Thickness

The technique of quadriceps muscle ultrasound used in this study has been described and validated by Freilich et al (Freilich et al,1995) with modifications to reduce inter-operator variability. Briefly, the thickness of the quadriceps muscle was measured using an Echo Blaster 128 Kit (UAB "TELEMED", Dariaus ir Gireno str. 42 Vilnius LT-02189, Lithuania – resolution of 0.1mm) fitted with a 5-10 MHz linear array transducer. Subjects were positioned in supine with the knees extended and the legs in the neutral position and completely relaxed. Scans were performed at the mid-thigh level, defined as the mid-point between the superior aspect of the patella and the anterior superior iliac spine (ASIS) [Figure 9]. The distance between the ASIS and superior aspect of the patella was measured and the midpoint determined.

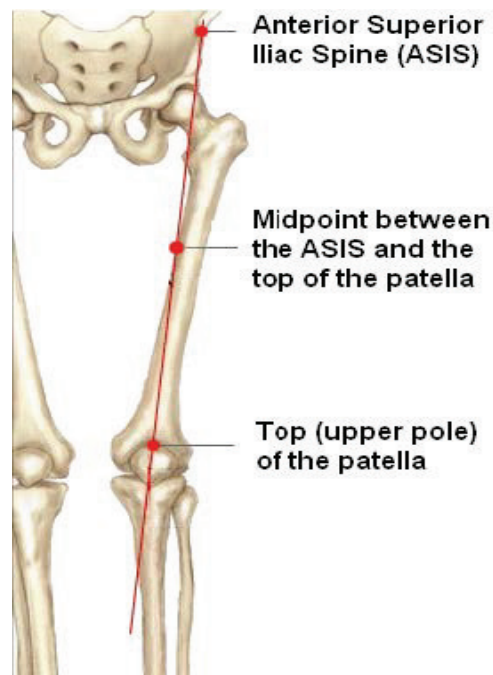


Figure 9. *Midpoint between the ASIS and the superior aspect of the patella.*

Using an indelible ink marker, a mark was placed on the subject's skin at the midpoint (Figure 10a). The transducer was positioned over the midpoint mark perpendicular to the longitudinal axis of the femur (Figure 10b). Once the transducer was positioned over the midpoint mark, a second mark was placed at the distal edge (Figure 10b) to ensure that all consequent readings were acquired from the same position. To ensure consistency, the subject's legs were placed in the neutral position prior to each US exam.

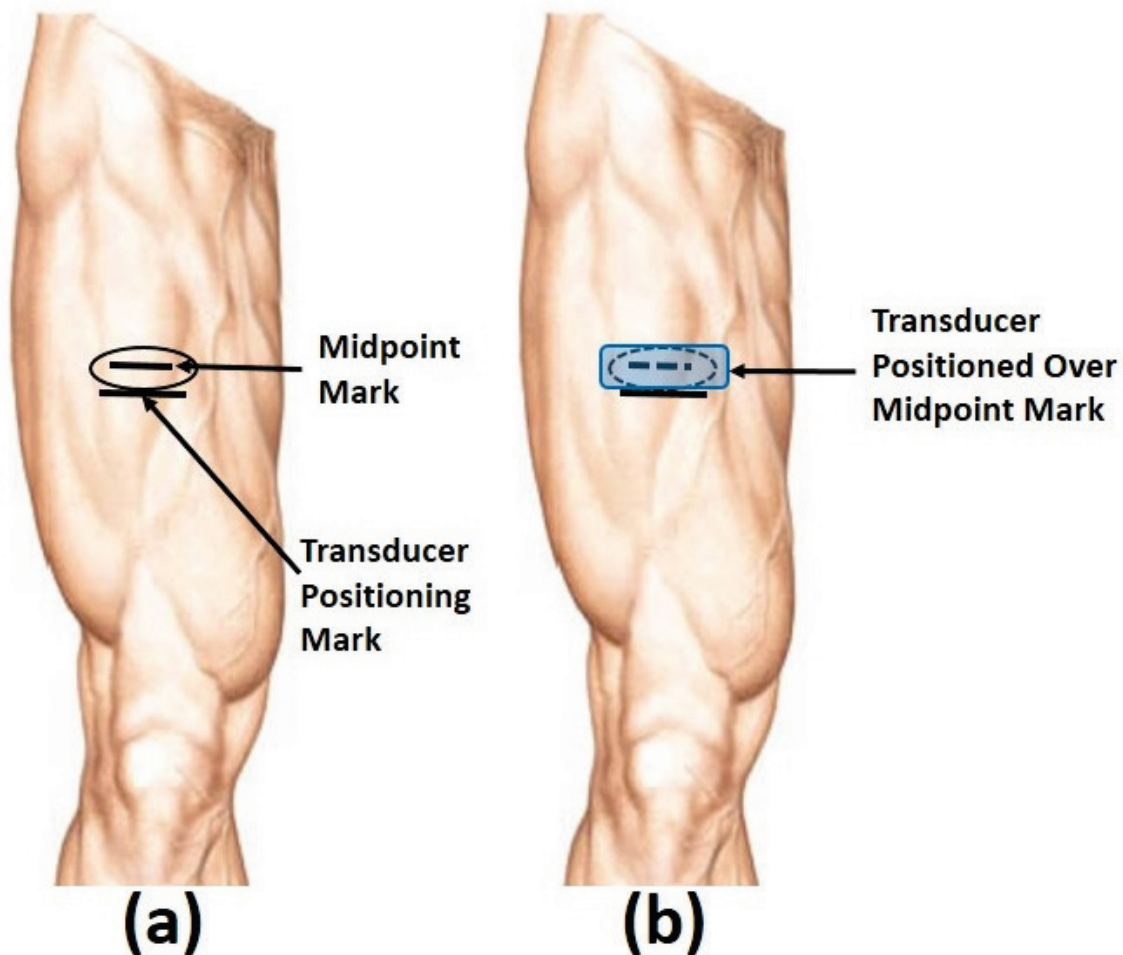


Figure 10. (a) Mark placed at midpoint of the thigh over which the transducer would be positioned. (b) Transducer positioned over midpoint mark with distal edge at the positioning mark.

The quadriceps was visualized using a generous amount of gel and, using the transducer, maximal compression was applied prior to imaging in order to mitigate inter-operator variability (Figure 11).

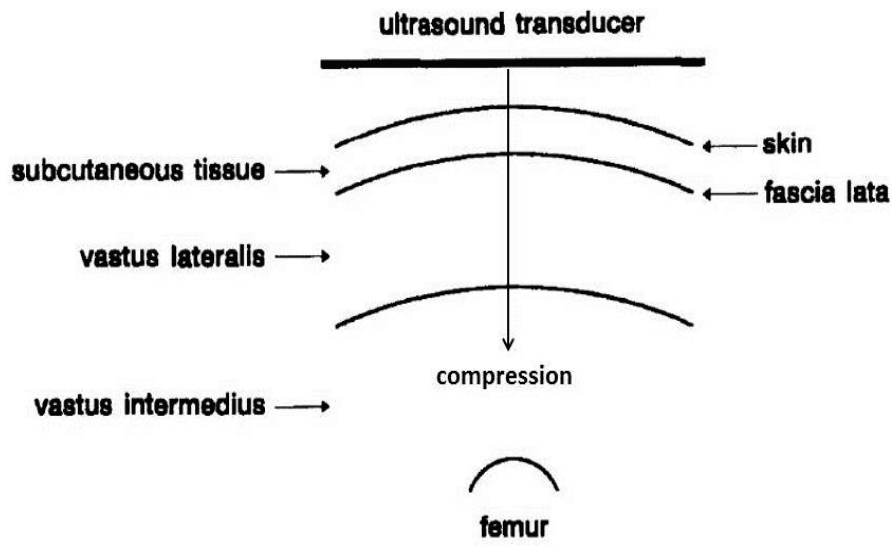


Figure 11. *Maximal compression was applied during image acquisition (Freilich et al,1995).*

Thickness was measured using the machine's electronic callipers, as the distance between the femur and the posterior border of the fascia lata (Figure 12). The scans were completed in approximately 5 min.

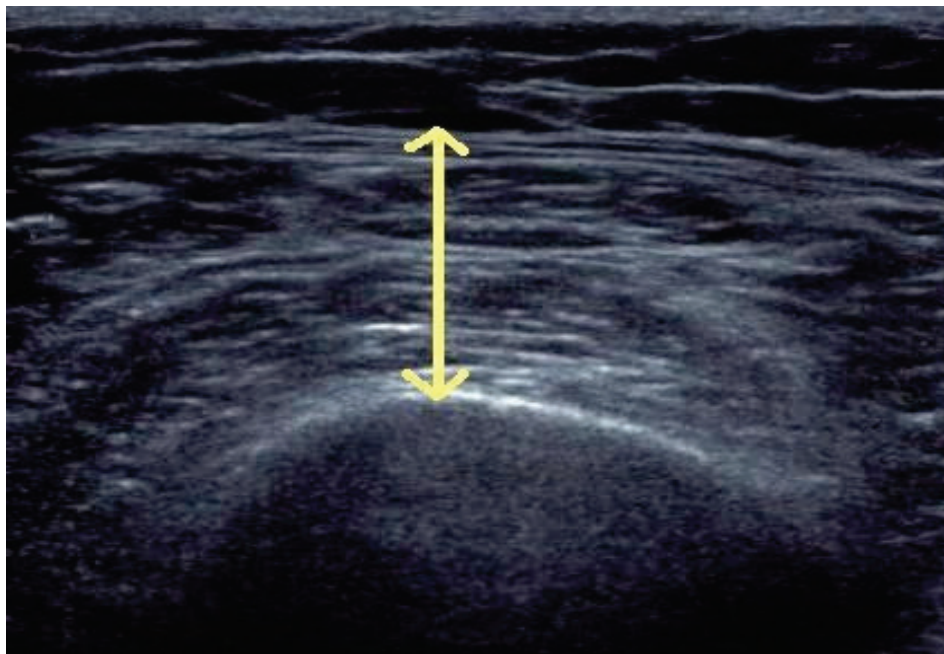


Figure 12. *Measuring quadriceps thickness.*

Confidentiality

The information that we collected from this research project was kept confidential. Information about each subject that was collected during the research was in a locked cabinet and was accessible only by the participating researchers. All files containing information about each participant was labeled with a number rather than the subject's name, with the master file being kept separately in a locked cabinet.

Statistical Analysis

Demographic characteristics were summarized at baseline using descriptive statistics including means (\pm SD) and median for continuous variables and counts and frequencies for categorical variables. All statistical analysis was performed using SPSS v19.0 for Windows.

Diaphragm thickness

Descriptive statistics was used to describe trends within groups. Results were reported as means and standard deviations. Small sample size prevented statistical analysis necessary to determine differences in diaphragm thickness between COPD and non-COPD patients. Both populations were therefore analyzed together. The statistical significance of P value was set at 0.05.

Inter-rater reliability

Agreement between raters (i.e., inter-rater reliability) of measurements was evaluated for all operators (agreement of measurement between operators) and readers (agreement of measurement between readers) using Intra-class correlation coefficients (ICCs). Interclass correlation coefficients and indices of reliability between observers and between operators were calculated.

Sample Size

Each subject served as his/her own control based on baseline Day 1 diaphragm thickness measurements. Sample size for this study was calculated based on studies in which diaphragm thickness was measured using ultrasound imaging in healthy

humans conducted by Wait et al. [Wait et al, 1989] and in SCI patients with paralyzed diaphragms conducted by Gottesman et al. [Gottesman et al, 1997]. Using the sample means and standard deviations of the end-expiratory diaphragm thickness of healthy control subjects (mean: 2.2mm, SD: 0.41mm) in Wait et al.'s study [Wait et al, 1989] and mean thickness of the paralyzed diaphragm (1.7mm) in Gottesman et al.'s study [Gottesman et al, 1997], a significance level of 0.05 and power of 0.80, the calculated sample size required to detect statistically significant changes in diaphragm thickness from baseline is 6 subjects (<http://www.stat.ubc.ca/~rollin/stats/ssize/n1.html>). Due to anticipated technical issues surrounding moderate obesity and image capture and subjects required to conduct sub-study looking at US reliability, the target sample size was 20 subjects.

Anticipated Challenges

Tracking changes in patients' mode of ventilation.

A respiratory therapist (RT) may switch ventilation modes to match a patient's ability to breathe spontaneously in the ICU. If the mode is changed from 'mandatory' to 'assist' mode and the patient starts making voluntary breathing efforts, the rate and/or extent of atrophy of the diaphragm may change.

Mitigation: Records were kept as the modes were changed. Time spent in each mode was recorded as a percentage of total time spent on MV.

Risks, Patient State and Patient Information

Risks

Properly performed, ultrasound imaging is virtually without risk or side effects. Some patients report feeling a slight tingling and/or warmth while being scanned, but most feel nothing at all. In this study, most subjects were unconscious and so did not feel the ultrasound being done. Ultrasound waves of appropriate frequency and intensity are not known to cause or aggravate any medical condition.

Participant's time spent in the study

In most instances, the study ultrasound took 5-10 minutes each for the diaphragm and quadriceps muscle from start to finish. Diaphragm and quadriceps muscle thickness were measured daily for up to 14 days or until discharged or died (whichever came first), thus each subject dedicated approximately 10-150 minutes of their time during the study. This was time required beyond standard care.

Catabolic State of Participants

Some participants were in a catabolic state induced by the ICU. The catabolic state the patients were in was due to illness & immobilization. Our procedures did not in any way influence the patient's health. We performed ultrasound imaging, a procedure that is routinely done in the ICU. In this case, there were no risks to the patient, hence, explaining the procedure to the participant (which was done for all participants and/or their surrogate decision maker) more than likely, did not negatively influence their willingness to participate.

Fear or Anxiety in Participants or Their Families

While being supported by mechanical ventilator is an inclusion criterion for this study, our study did not entail placing patients on the ventilator. A patient being placed on mechanical ventilation is a decision made by the resident intensivist on admission of said patient to the ICU. Ultrasonography is the only tool we utilized to collect data for this study. Ultrasound is a well-established technology and is familiar to most. As there are no risks associated with ultrasound imaging, we did not anticipate any mental discomfort (fear or anxiety) in the participants.

Patient's State of Consciousness

Patients in the ICU who are on mechanical ventilation are often unconscious due to the nature of their illness, over the course of their illness they will often become increasingly more aware due to changes in clinical condition and medications. In some cases, such as severe head injury, it may be necessary for the intensivist to induce a coma. The patient may also be deeply anesthetized to prevent resistance to mechanical

ventilation or as treatment for pain. The patient's unconscious state was in no way influenced by our team.

Accessing Patient's Health Records

Patient's medical records were accessed by Dr. Steven Reynolds (Head of Department of Critical Care, Royal Columbian Hospital) or his designate. The information acquired from these records:

- I. Assisted us in determining the patient's eligibility to participate in the study.
- II. Allowed us to match participants for severity of illness.
- III. Allowed us to maintain a record of participant's mode of MV throughout the study.
- IV. Gave us information on co-morbidities which may have affected outcomes.

Confidentiality, Storage and Disposal of Study Data

All files containing information about each participant were labeled with a number rather than the subject's name, with the master file being kept separately in a locked cabinet located in Dr. Steve Reynolds' office. This was clarified in the study details. Information collected in this study will be held for 2 years, after which all materials identifying participants will be destroyed.

Availability of Physician in the ICU

It was not absolutely necessary for a physician to be on site during the conducting of this study. However, a physician was present in, or on call for the ICU at all times.

Who Was Involved in This Study

Colin Francis was principally involved in all aspects of this Ultrasound Measurement study, with the exception of acquiring consent from participants or their caregiver, which was done by Dr. Reynolds or his clinical research coordinator (Suzette

Williams). All data were acquired and analyzed by Colin Francis with assistance from co-investigators.

Chapter 6.

Results

During the study period, 18 critically ill patients consented to participate. Seven patients were excluded from the study as a result of poor US imaging quality, and 2 were extubated on day 1 post-inclusion, allowing only for the acquisition of baseline readings. One was extubated on day 2 post- inclusion, allowing only for the acquisition of baseline and day 1 data. Of the eligible 8 patients, 4 were female and the mean age was 62 ± 11 yrs. Of the eligible patients, 5 were being treated for sepsis among other complications of critical illness. Intravenous fluid therapy, a treatment used to resolve hemodynamic instability in septic patients, results in tissue edema, making US imaging difficult in most patients and impossible in others. We obtained records of daily fluid changes for each patient from their health records. We calculated fluid balance as the sum of excess fluid from day of intubation to day of baseline image acquisition. Mean positive fluid balance in patients in whom imaging failed was 21,870ml versus 8,257ml in those from whom we successfully acquired images. Patients in whom imaging was not possible or in whom image quality was poor were excluded from the study. Failure to acquire image was defined as the inability to acquire a discernible image on two consecutive days by two different operators.

Reproducibility of Ultrasound Measurements

In a subset of participants, baseline scans were repeated by two additional operators (SW and JW) in order to assess inter-operator reproducibility of the method. The operators were blinded to each other's scans. As none of the operators had previous ultrasound experience, a short training session was conducted, following which competency was gained in performing the exams independently. Each operator made measurements of their images using the Telemed Echo Wave II software. Results were recorded on the form provided and submitted for analysis.

Inter-operator reliability was assessed between two pairs of operators [Operator A (CF) vs. Operator B (JW), and Operator A (CF) vs. Operator C (SW)] (Table 3). Interclass correlation coefficients (to determine level of agreement between results from each pair of operators) and indices of reliability between operators for diaphragm and quadriceps thickness were >0.95, indicating excellent inter-operator reliability. Tables 4 and 5 show differences between measurements made by each operator in individual patients.

Table 3. Reproducibility of Ultrasound Measurements: Inter-Operator Reliability.

	Mean Difference*		P-value		ICC	
	Dt (mm)	Qt (mm)	Dt	Qt	Dt	Qt
Inter-operator (A vs. B; n=6)	0.08	0.18	0.86	0.90	0.976	0.995
Inter-operator (A vs. C; n=6)	0.05	0.41	0.91	0.92	0.982	0.998

*: Difference between mean diaphragm thickness measured by each operator.

Significance was tested using independent t-test.

ICC: Interclass correlation coefficient.

Dt: Diaphragm thickness

Qt: Quadriceps thickness

Table 4. Inter-operator variability: differences between diaphragm thickness measurements by different operators for each patient.

Operator A Dt (mm)	Operator B Dt (mm)	% Difference	Operator A Dt (mm)	Operator C Dt (mm)	% Difference
3.3	3.2	3.0	3.3	3.5	5.7
3.0	3.2	6.1	3.0	2.8	6.7
1.8	1.8	4.4	1.8	1.9	3.7
1.8	1.8	1.1	1.8	1.7	6.8
3.5	3.5	1.1	3.5	3.4	0.9
2.5	2.0	21.0	2.5	2.9	12.8

Table 5. Inter-operator variability: differences between quadriceps thickness measurements by different operators for each patient.

Operator A Qt (mm)	Operator B Qt (mm)	% Difference	Operator A Qt (mm)	Operator C Qt (mm)	% Difference
5.5	5.3	3.6	5.5	5.4	1.8
23.9	24.9	4.0	23.9	23.9	0.0
18.3	17.1	6.6	18.3	17.5	4.4
19.7	18.0	8.6	19.7	18.7	5.1
9.1	8.9	2.4	9.1	9.0	1.1
14.2	13.5	4.9	14.2	13.7	3.5

Inter-observer reliability, shown in Table 4, was assessed between two pairs of observers [Observer A (CF) vs. Observer B (JW), and Observer A (CF) vs. Observer C (MW)]. Previously acquired patient readings for the diaphragm and quadriceps were randomly selected and the files re-named to blind the observers to the patient number and date of acquisition of information. The observers were also blinded to each other's results. Each observer was presented with all the selected patient data files and made measurements on all US images using the Telemed Echo Wave II software. The data was recorded on the provided form and presented for analysis. Interclass correlation coefficients and indices of reliability between observers for diaphragm and quadriceps thickness were >0.95, indicating excellent inter-observer reliability. Tables 7 and 8 show differences between measurements made by each observer in individual patients.

Table 6. Reproducibility of Ultrasound Measurements: Inter-Observer Reliability.

	Mean Difference*		P-value		ICC	
	Dt (mm)	Qt (mm)	Dt	Qt	Dt	Qt
Inter-observer (A vs. B; n=10)	0.01	0.06	0.97	0.97	0.992	0.999
Inter-observer (A vs. C; n=10)	0.03	0.13	0.91	0.94	0.995	0.999

*: Difference between mean diaphragm thickness measured by each observer.
Significance was tested using independent t-test.
ICC: Interclass correlation coefficient.
Dt: Diaphragm thickness
Qt: Quadriceps thickness

Table 7. Inter-observer variability: differences between diaphragm thickness measurements for each patient.

Observer A Dt (mm)	Observer B Dt (mm)	% Difference	Observer A Dt (mm)	Observer C Dt (mm)	% Difference
2.4	2.5	4.0	2.4	2.3	4.2
3.1	3.0	3.2	3.1	3.2	3.1
2.6	2.5	3.9	2.6	2.7	3.7
2.7	2.7	0.0	2.7	2.8	3.6
2.0	2.2	9.1	2.0	2.1	4.8
2.1	2.1	0.0	2.1	2.2	4.6
2.3	2.2	4.3	2.3	2.3	0.0
1.6	1.6	0.0	1.6	1.5	6.3
2.1	2.2	4.6	2.1	2.1	0.0
3.5	3.5	0.0	3.5	3.5	0.0

Table 8. Inter-observer variability: differences between quadriceps thickness measurements for each patient.

Observer A Qt (mm)	Observer B Qt (mm)	% Difference	Observer A Qt (mm)	Observer C Qt (mm)	% Difference
18.1	18.0	0.6	18.1	18.3	1.1
24.4	24.4	0.0	24.4	24.6	0.8
18.3	18.4	0.5	18.3	18.5	1.1
23.6	24.0	1.7	23.6	23.8	0.8
24.5	25.0	2.0	24.5	25.1	2.4
13.5	13.5	0.0	13.5	13.5	0.0
18.6	18.5	0.5	18.6	18.6	0.0
15.3	15.2	0.7	15.3	15.2	0.7
21.3	21.3	0.0	21.3	21.3	0.0
19.5	19.4	0.5	19.5	19.5	0.0

Diaphragm and Quadriceps Thickness

A mean increase in diaphragm thickness of 0.23 ± 0.03 mm (from 2.5 ± 0.7 mm to 2.7 ± 0.76 mm, 95% CI between 0.21 mm to 0.25 mm; $8.4 \pm 3.9\%$) was detected over a mean of 5.5 ± 4.3 days in all patients on PS ventilation ($n=8$), with a mean increase of 0.04 ± 0.03 mm per day ($1.5 \pm 1.4\%$ per day). Patients ventilated on AC mode ($n=4$) showed a mean decline in diaphragm thickness of 0.4 ± 0.4 mm (from 2.8 ± 0.7 to 2.4 ± 0.8 mm, 95% CI of between 0.05 mm to 0.79 mm; $21.2 \pm 10.8\%$) over 4.5 ± 4.4 days, with an average decrease of 0.1 ± 0.1 mm per day ($4.7 \pm 5.7\%$ per day).

Mean decline in quadriceps thickness for all participants in this study ($n=8$) was 2.4 ± 2.6 mm (from 15.5 ± 5.5 mm to 13.2 ± 5.1 mm, 95% CI of between 0.58 to 4.16 mm; $14.4 \pm 13.6\%$) over a mean period of 7.1 ± 4.7 days, an average decline of $2.0 \pm 2.7\%$ per day.

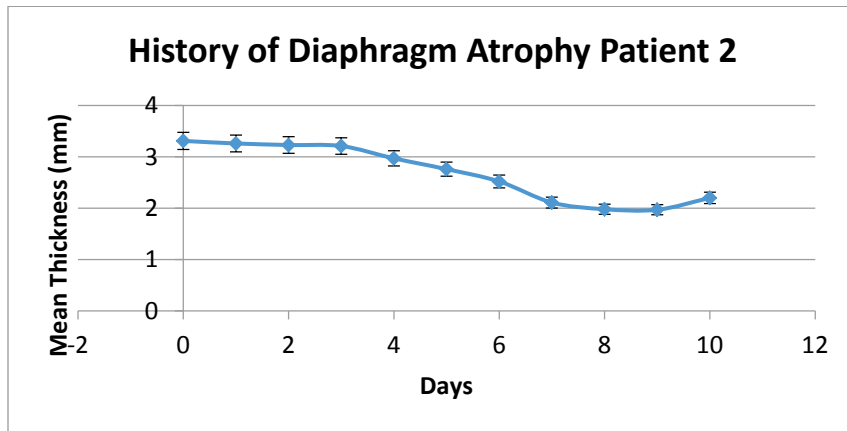


Figure 13. History of diaphragm atrophy in patient 2.

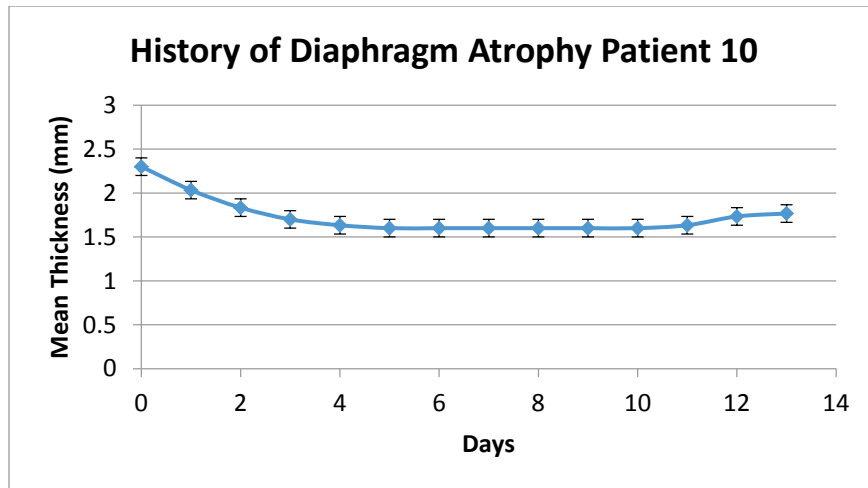


Figure 14. Diaphragm atrophy in patient 10.

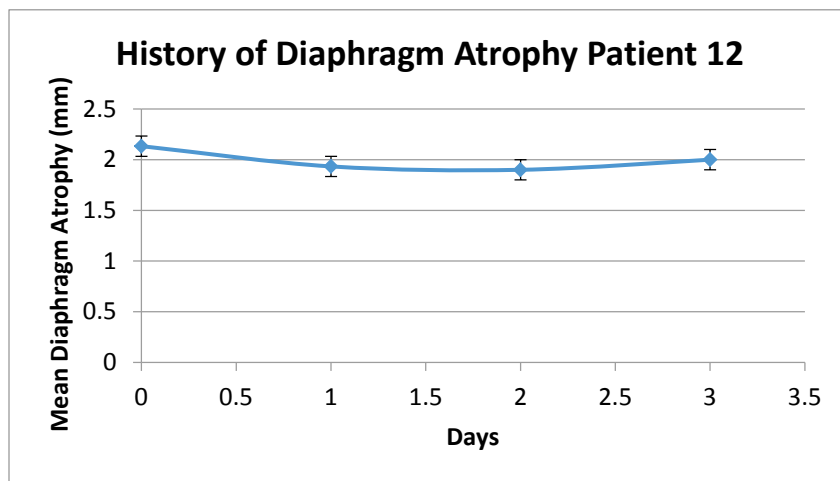


Figure 15. Diaphragm atrophy in patient 12.

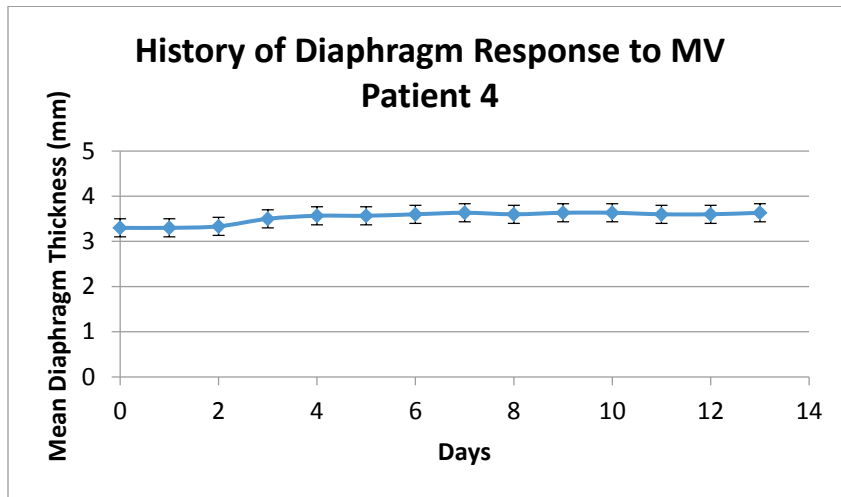


Figure 16. History of diaphragm response to pressure support ventilation in patient 4.

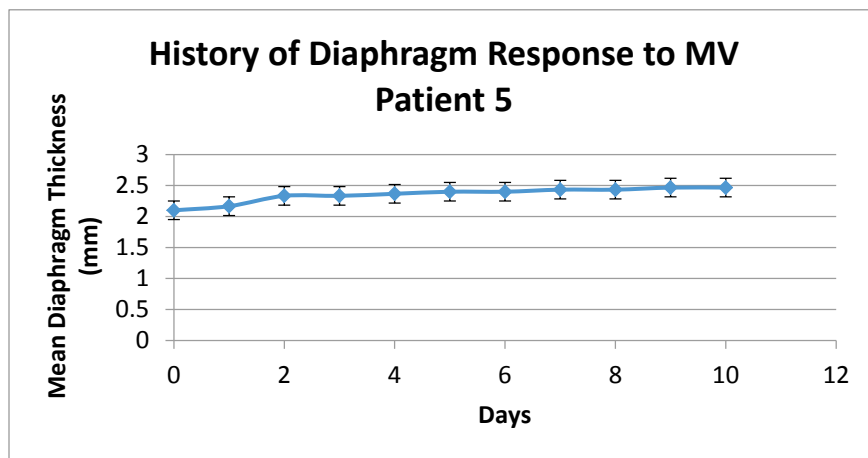


Figure 17. History of diaphragm response to pressure support ventilation in patient 5.

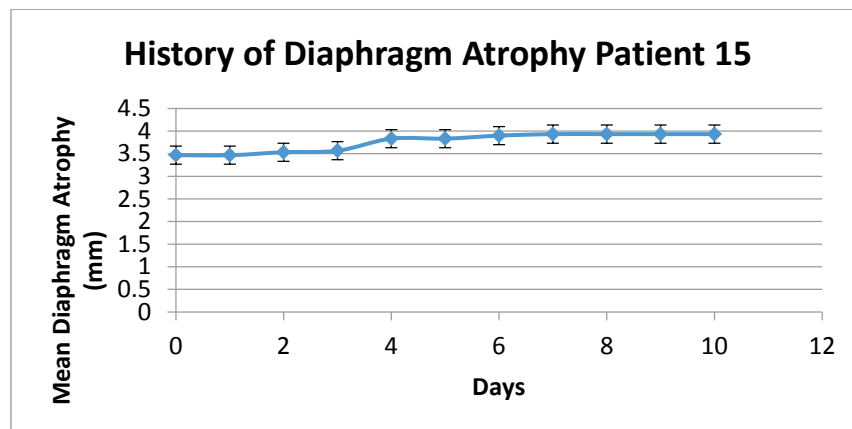


Figure 18. Diaphragm response to pressure support ventilation in patient 15

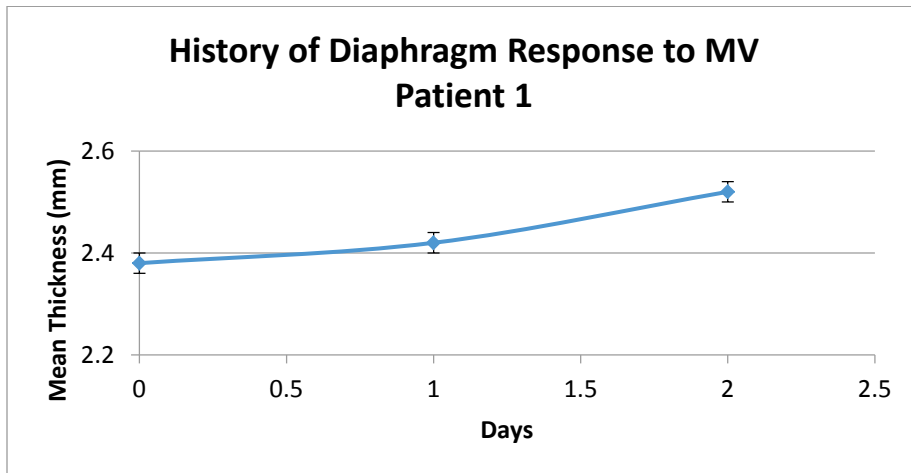


Figure 19. *History of diaphragm response to pressure support ventilation in patient 1.*

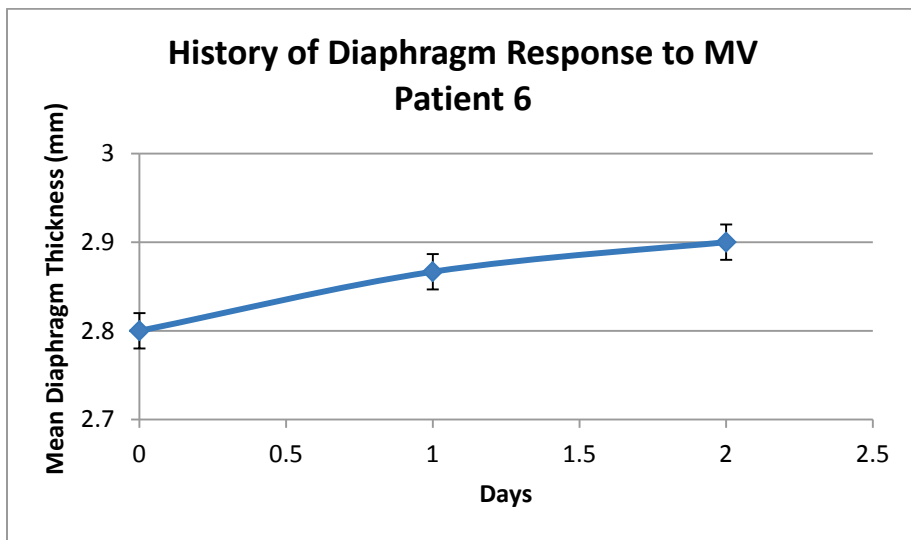


Figure 20. *History of diaphragm response to pressure support ventilation in patient 6.*

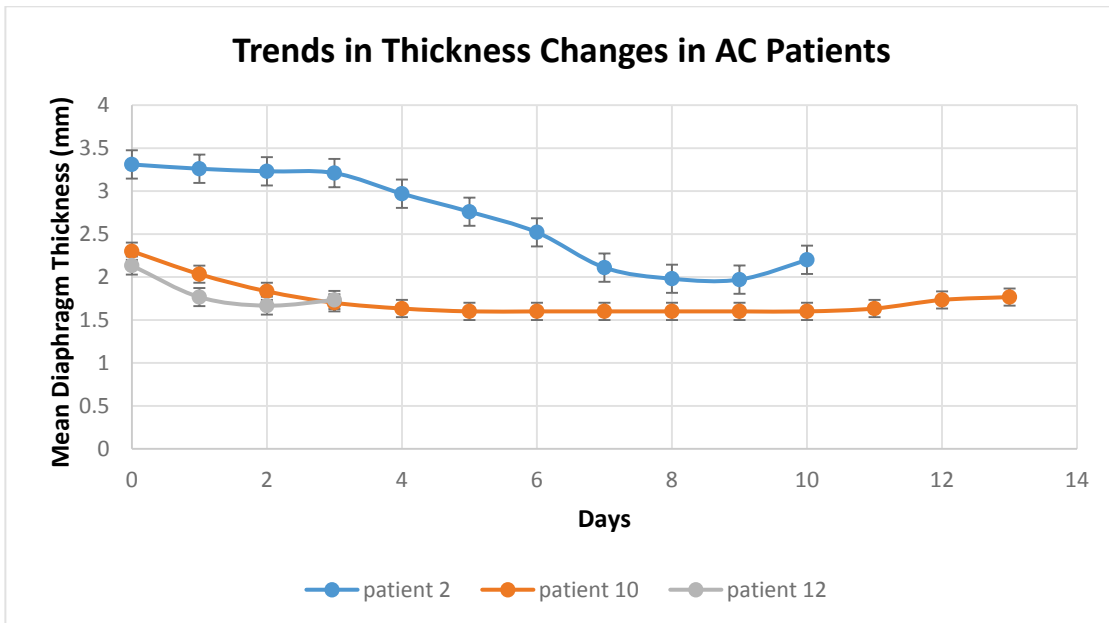


Figure 21. Trends in diaphragm thickness with time for all patients on ACV.

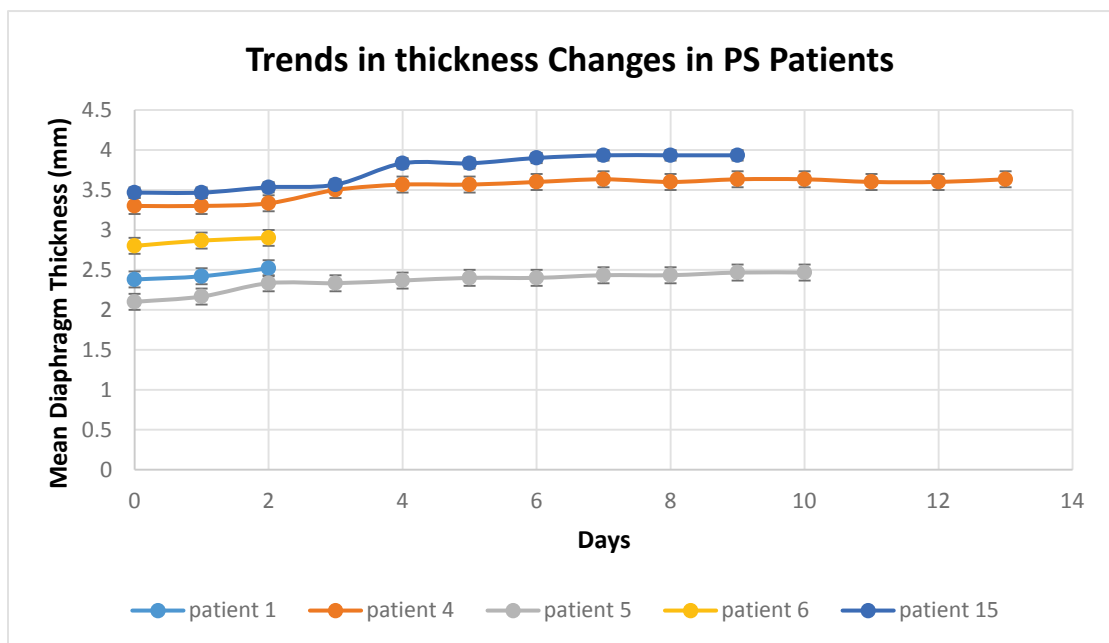


Figure 22. Trends in diaphragm thickness with time for all patients on PSV.

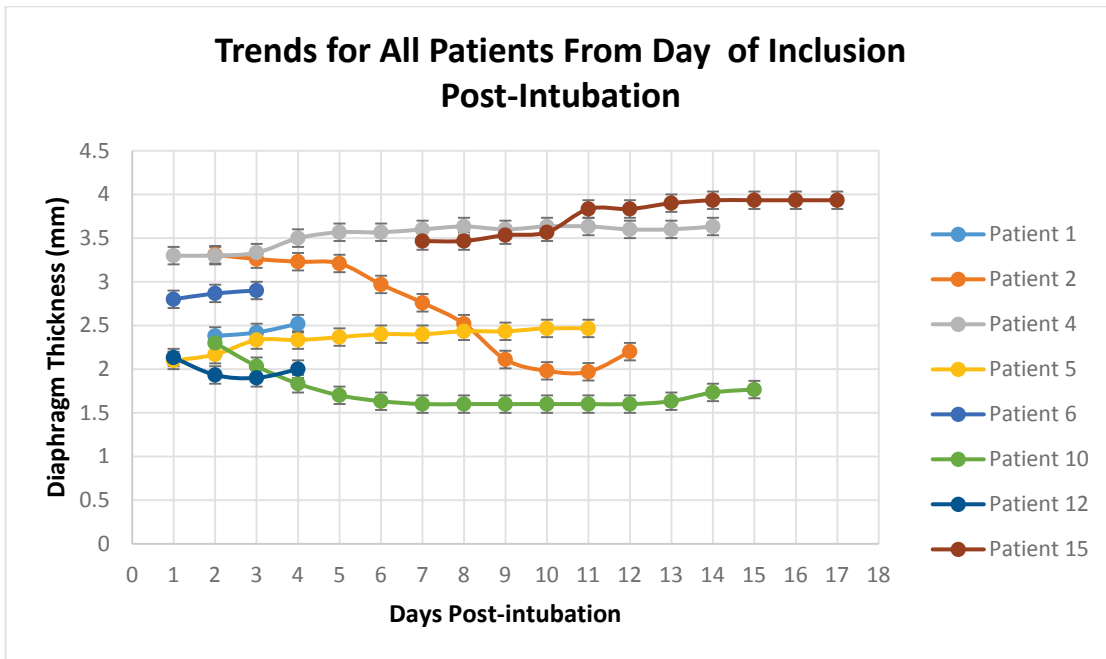


Figure 23. First data point for each patient is represented on day post-intubation.

Chapter 7.

Discussion

The history of diaphragm atrophy in patient 2 is shown in Figure 13. Baseline reading was taken 2 days post intubation. The patient was mechanically ventilated for 6 consecutive days with assist-control mode of ventilation. During this period, all breaths were being delivered by the ventilator and the patient's diaphragm remained inactive. Diaphragm thickness showed a steady rate of decline which plateaued between days 8 and 9 post-inclusion into the study. Mode of ventilation was switched from AC to PS in the pm on day 6. Prior to change in ventilation mode, the diaphragm atrophied 24%, an average of 4% per day over 6 days. As the diaphragm became more active on day 7 (on PS mode), a decrease in rate of decline (from 4% per day between baseline and day 6, to 2% per day between days 7 and 9) was noted between days 7 and 9, and an increase in diaphragm thickness of 0.23mm (from 1.97 to 2.2mm) was detected between days 9 and 10. Over the 9 day period in which a decline in thickness was noted, the diaphragm atrophied a total of 40% (from 3.31mm to 1.97mm) at an average rate of 4.5% per day. The decline in rate of atrophy on implementation of PS ventilation suggests that the mode of ventilation may affect rate of change of diaphragm thickness with time. Further, this also suggests that the magnitude of diaphragm atrophy may have been greater by day 9 had PS not been implemented on day 6.

Patient 10 (figure 14) was included in the study 2 days post-intubation and was supported on AC mode of ventilation. The patient was fully supported by the ventilator for 10 consecutive days and was switched to PS mode on day 10 following data acquisition. During the 10 days on AC mode, the diaphragm showed a decrease in thickness of 30% (from 2.3mm to 1.6mm) by day 5, an average rate of 6% per day. Decline in diaphragm thickness stabilized between days 5 and 10. Following the implementation of PS mode on day 10, an increase in diaphragm thickness of 9.6% (from 1.6mm to 1.8mm) was detected between days 10 and 13, a rate of 3.2% per day.

Patient 12 (figure 15) was intubated and placed on AC mode 24 hours prior to inclusion into the study. A decline of 0.23mm (10.8%) was detected between baseline and day 2, a rate of 5.4% per day. PS was implemented on day 2 post-acquisition of data. Following implementation of PS, an increase in diaphragm thickness of 0.10mm (from 1.9 to 2mm, 5%) was detected between days 2 and 3. Patient 12 was successfully extubated on day 4 prior to data acquisition.

All patients included in the study who were supported on AC at baseline and supported on this mode throughout the study (n=3), were included between 1 and 2 days post intubation (figure 21 and 23). All patients in this group showed similar trends of decline in diaphragm thickness while on AC mode. However, this late entry into the study prevented the acquisition of a true baseline measurement on day of intubation and, since these patients were ventilated by AC mode on intubation, this meant that additional atrophy may have occurred prior to acquisition of first reading. Consequently, total diaphragm atrophy may have been underestimated and may in fact have been greater than what we detected.

While on AC ventilation, patients (n=4) showed a mean rate of decline in diaphragm thickness of $4.7 \pm 5.7\%$ per day. This means that the diaphragms of patients supported on AC mode for at least 2 days prior to inclusion into the study (figure 23) may have already atrophied by at least 10% prior to acquisition of baseline readings. These findings are consistent with data from studies demonstrating rapid diaphragm atrophy secondary to modes of MV that renders the diaphragm inactive [Grosu et al, 2012; Levine et al, 2008; Ayas et al, 1999], and reinforces the deleterious effects of these mandatory modes of ventilation on diaphragm thickness and strength.

We noted an almost immediate attenuation of atrophy in patients in which mode of ventilation was switched from AC to PS during the study. This may be in response to increased diaphragm activity while on PS, eventually resulting in complete cessation of atrophy and commencement of recovery, which presented as an increase in diaphragm thickness. These findings are consistent with data from Futier and colleagues who demonstrated that pressure support ventilation attenuated protein modifications that results in diaphragm atrophy in rats that were mechanically ventilated [Futier et al, 2008].

During the study period, patients 4 and 5 (figures 16 and 17) showed similar trends in changes in diaphragm thickness. These patients were both included in the study 24 hours post-intubation, both ventilated on PS and assessed over 13 and 10 days respectively. Over these periods, diaphragm thickness increased by an average of $0.35\text{mm} \pm 0.03\text{mm}$ (from $2.7 \pm 0.8\text{mm}$ to $3 \pm 0.8\text{mm}$, $12 \pm 4.2\%$), a rate of $1.5 \pm 0.6\%$ per day. Patient 4 reached a maximum thickness of 3.63mm on day 7 post inclusion. There were no changes in diaphragm thickness between days 7 and 13. Increase in diaphragm thickness reached a maximum of 2.47mm by day 9 in patient 5. As with patient 4, thickness changes plateaued from that point until the patient was extubated.

Patient 15 (figure 18) showed similar trends to that seen in patients 4 and 5. However, this patient was included into the study 7 days post-intubation, supported on AC mode for 1 day post-inclusion and switched to PS on day 1 following acquisition of data. No changes in diaphragm thickness were detected between baseline and day 2. However, following institution of PS, an increase in diaphragm thickness of 0.46mm (from 3.47mm to 3.93mm, 11.7%) was detected between days 2 and 7, a rate of 1.95% per day. Similar to patients 4 and 5, increase in diaphragm thickness plateaued towards the end of the study.

Patients 1 and 6 were each assessed over two days (Figures 19 and 20). For patient 1, baseline reading was acquired 2 days post-intubation and 1 day post-intubation for patient 6. These two patients were supported on PS ventilation over the two day evaluation period. As with all participants on PS ventilation, an increase in diaphragm thickness was detected in these patients as their diaphragms became more active while attempting to breathe.

All patients included into our study on PS ventilation (n=5) showed small increases in diaphragm thickness that continued over the course of the study. On intubation, all PS patients were initially placed on AC mode for 1 to 2 days prior to being placed on PS (except patient 15, placed on AC 7 days prior to inclusion) and included into the study. The increase in diaphragm thickness seen in these patients suggests that atrophy may have occurred during time spent on AC mode and that the changes in diaphragm thickness may be a reversal of atrophy resulting from increased diaphragm activity while on PS mode. These patients showed an increase in diaphragm thickness

that plateaued towards the end of the study, suggesting that the plateau thickness may have been true baseline diaphragm thickness.

Further, an increase in diaphragm thickness was detected in all patients (n=8) who either entered the study on PS (n=5; on AC prior to entry into the study) or who were entered into the study on AC and subsequently switched to PS (n=3) during the study period. Those who were switched from AC to PS showed a net increase in diaphragm thickness following institution of PS. These findings suggest that PS mode of ventilation may attenuate and reverse diaphragm atrophy in patients previously ventilated by mandatory MV modes.

The rate of increase in diaphragm thickness in patients on pressure support was $1.5 \pm 1.4\%$ per day, which was $1/3^{\text{rd}}$ the rate of decline seen in the patient ventilated on AC mode ($4.7 \pm 5.7\%$ per day). These results suggest that recovery from the effects of ventilator-associated diaphragm atrophy will require more time than what was necessary for the atrophy to occur. Since diaphragm atrophy is associated with weakness [Laghi et al, 2003; Watson et al, 2001; Chang et al, 2005; Petrof et al, 2010; Vassilakopoulos et al, 1998; Harikumar et al, 2009], this relatively slow recovery may prolong weaning time of patients ventilated on mandatory modes of ventilation for prolonged periods.

It was noted that after a period of 7 days (from time of intubation) on AC ventilation, decline in diaphragm thickness stabilized in patients 10 (figure 23). There was no change in diaphragm thickness between days 7 and 12, following which PS ventilation was instituted, resulting in an increase in thickness. A similar trend was noted in patient 15, who was included into the study on day 7 post-intubation while being supported on AC mode. No changes in diaphragm thickness was detected between baseline and day 1, following which PS ventilation was instituted, resulting in an increase in diaphragm thickness. This may suggest that the decline in diaphragm thickness in patient 15, ventilated on AC mode from intubation to day 8 post-intubation, had stabilized either prior to inclusion into the study or on day 7 (day of inclusion). During this period, the diaphragm remained inactive, possibly suggesting that this cessation of diaphragm atrophy may be the natural behaviour of the diaphragm at specific levels of atrophy. Extrapolating diaphragm atrophy to day of intubation (at a mean rate of 4.7% per day) would show 39% atrophy in patient 10 and 33% in patient 15

by day 7 post-intubation (mean of 36%). These findings raise an interesting question as to whether the decline in diaphragm atrophy seen in AC patients plateau after specific periods, and at what point post-intubation does this plateau occur. If this assumption with regards to plateau in atrophy is true, then we could anticipate this plateau at approximately 60% of baseline thickness (baseline as measured on day of intubation) in patients ventilated on AC mode of ventilation. It is possible that other variables may have influenced this plateau, hence, larger studies are needed to investigate these findings.

In contrast, decline in diaphragm thickness seen in patient 2 (COPD patient) continued beyond day 7 post intubation (figure 23). The diaphragm in individuals with COPD is exposed to oxidative stress and sarcomeric injury (Ottenheijm et al, 2009). It is postulated that in this population, oxidative stress and sarcomeric injury activates the proteolytic machinery, leading to contractile protein wasting (Ottenheijm et al, 2009). It is possible that in this patient, diaphragm inactivity during AC mode of ventilation compounded the level of proteolysis that occurred secondary to oxidative stress, resulting in atrophy beyond the point normally seen non-COPD patients. Further, the diaphragm in this patient had atrophied by 34% by the time the mode of ventilation was switched to PS (8 days post intubation). If our assumptions are correct, we would have expected to see a stabilization in atrophy at approximately this point. Since the decline in thickness was attenuated by the institution of PS ventilation and return of diaphragm activity, we were unable to determine whether stabilization would have occurred at this point or whether atrophy would have continued.

COPD patients (n=3) had thicker baseline diaphragm measurements (between 3.31 and 3.46) when compared to non-COPD patients (n=5) (between 2.10mm and 2.38mm). These groups show strong trends in differences in baseline diaphragm thickness, however, due to small sample size, the groups were analyzed together as we could not determine significance of differences. We understand that respiratory mechanics in these populations are different, and hence, we expect that there will be morphological differences in the diaphragms of these two groups. Further, studies of the structure of the diaphragm at autopsy in patients with COPD have produced inconsistent results [Troyer, 1997]. Hence, it is still not clear as to whether COPD patients have thicker diaphragms when compared to non-COPD patients. It would therefore be interesting to test whether the differences detected in our study could be consistently

detected in a larger population, and also to determine how these differences affect weaning outcome.

The quadriceps muscles of the patients in this study showed a mean rate of decline of 2% per day, which is in agreement with the findings of other researchers (Gerovasili et al, 2009). In contrast, there was a mean decline in diaphragm thickness of 4.7% per day in patients supported on AC mode of ventilation. These findings suggest that the rapid decline in muscle thickness in critically ill patients who require AC mode of ventilation may be limited to the diaphragm.

Conclusion

On the basis of these findings, we conclude that ultrasonography is a reliable method for tracking changes in diaphragm thickness in critically ill mechanically ventilated patients. We have shown feasibility in the use of ultrasonography for tracking progressive diaphragm atrophy and progressive recovery dependent on modes of ventilation. Based on trends seen in these patients, it may be appropriate to apply these methods to larger populations to determine the significance of the changes noted in this study.

Due to the apparent attenuation of the decline in diaphragm thickness seen in patients switched from AC to PS ventilation and increase in diaphragm thickness seen in all other patients following the institution of PS ventilation, it may be reasonable to assume, based on these results, that this mode of MV was the factor influencing these changes. As a decline in diaphragm thickness was noted in all patients ventilated on AC mode, it may be appropriate to assume that the decline in diaphragm thickness was as a result of mode of ventilation. These results suggest that atrophy is attenuated and reversed by a combination of the institution of PS mode and the return of diaphragmatic contractions following a reduction in levels of sedation. How these changes will affect weaning outcomes remain unclear, and we do not know of information in the literature that bears directly on this question. Larger studies are needed to determine the significance of our findings.

We have shown that ultrasonographic assessment of the diaphragm provides a reliable non-invasive measurement of diaphragmatic thickness and degree of atrophy in

critically ill patients on MV. Our results have relevance to patients undergoing MV in whom it has been postulated that unloading of the respiratory muscles and reduction in diaphragm activity may lead to atrophy, diminished force generating capacity and consequently difficulties in weaning. It is not fully elucidated as to the level of diaphragm activity required for preservation of the muscle. It has been demonstrated that brief periods of electrical stimulation (30 minutes/day) was enough to attenuate and reverse diaphragm atrophy in a human subject [Ayas et al, 1999]. This data suggests that the functional integrity of the diaphragm may be maintained by relatively little activation. Consequently, in patients ventilated with PS mode of ventilation, work performed by the diaphragm may be sufficient to prevent atrophy and preserve functional integrity. Taken together, our data and those of Ayas et al suggest that early institution of PS mode of ventilation may attenuate and reverse diaphragm atrophy and may result in improved weaning outcomes.

Future Directions

In keeping with the desire to fully understand the dynamics of diaphragm dysfunction in critically ill patients on MV, a multi-centre study will be conducted that will give us access to a broader data base that will be more representative of the population.

The study will investigate the various populations in the ICU and attempt to show differences in how the diaphragm responds to MV between populations. Gender, age, admitting diagnoses, mode of ventilation and severity of illness will be considered. We will correlate diaphragm thickness to weaning outcome and attempt to determine minimum diaphragm thickness (as a percentage of baseline thickness) required for successful weaning.

Recommendations for Future Studies

Based on findings from this pilot study, amendments to the current study design may be required prior to conducting a larger more definitive study. The current study served to strengthen and validate sonography techniques and to better understand the challenges that may be encountered during subject recruitment in the ICU. Further, the acquisition of preliminary data that would allow us to investigate how the diaphragm

responds to various modes of MV is an important prerequisite to conducting further studies investigating diaphragm thickness as it relates to weaning outcomes.

During the study period, 18 subjects consented to participate. Seven were excluded post-consent as a result of poor image quality and 2 were extubated on day 2 post-inclusion. Of the 7 subjects who were excluded for poor image quality, 6 were as a result of severe edema and 1 was due to a massive pleural effusion. Subjects with severe edema often had high BMI ratings, which in most cases were directly related to their edematous state. Edema decreases the sensitivity of ultrasound resulting in failure to provide a clear image (Saranteas et al, 2008; Pillen, 2010). As we found significant differences in levels of fluid retention between patients from whom we were not able to acquire images and those from whom we were able to acquire images, we believe it is important that, in a larger study, we focus on defining the parameters beyond which acquisition of US images is not possible and exclude all patients that fit this criterion.

The use of high resolution US equipment may improve image quality in future studies. Our current US system has an axial resolution of 0.5mm and lateral resolution of 1mm. The frequency range of the transducers is limited to 5-10MHz. High resolution US systems utilize high sensitivity transducers with relatively broad bandwidths and high frequencies. Axial resolution improves as pulse length decreases, hence, transducers with broader bandwidths and higher frequencies produce higher resolution images. High sensitivity, high resolution US systems may utilize 5-20 MHz transducers that are designed to provide high resolution images at deeper depths than conventional US systems. For example, high resolution systems may produce 15 MHz images that provide penetration equal to that of any 5-10 MHz system. With these systems, axial resolution as low as 385 μm (Pignoli et al, 1986) is possible, allowing for the acquisition of detailed images with highly distinguishable features. A combination of these properties, in addition to an extended system dynamic range, results in images of superior resolution at greater depths. In future studies, it is recommended that high resolution US systems be utilized in the acquisition of images, as acquiring clear images of the diaphragm in obese and edematous patients in the current study proved impossible due to the limitations of the Echoblaster US system.

Although applying maximal compression to the quadriceps muscles during acquisition of US images reduced inter-operator variability, this method made it difficult to distinguish between muscle and fat layers in patients with advanced muscle atrophy. To avoid the reoccurrence of this issue, we will not apply compression in future studies. Instead, we will employ an excess of gel to ensure ease of transmission of US pulses from the full transducer footprint into the muscles, while ensuring that no compression force is applied.

Informed consent was requested from 47 surrogate decision makers during the study period. Of these, 62% declined. All consents were acquired by the research coordinator who approached each decision maker and provided them with the information required to make an informed decision. Since it is important to acquire early consent, approaching families on day of admission is preferred. However, it was discovered that families who were approached on the day of admission of their loved one were more likely to decline consent. Additionally, families were more likely to decline if, rather than being introduced to the study by the research coordinator, their first contact was the assigned nurse, whose only obligation with regards to the study is to give the decision makers the Informed Consent Form. It is possible that this approach may be interpreted as insensitive by the families of potential participants and may influence their choice to not participate. Another possible reason for the high rate of declines could be the attempt to simultaneously gain consent for 2 separate studies. Families tend to be apprehensive regarding the inclusion of their critically ill loved ones into scientific studies. Requesting consent for simultaneous participation in 2 studies compounds this issue. On approaching the families, it is therefore important to be sensitive to each family's state of mind and to tailor how the study is introduced and when the introduction is done. I suggest, that in an attempt to decrease the number of declined consents, guidelines be introduced as to when surrogate decision makers should be approached and who should approach them. Further, guidelines should be introduced to ensure that surrogate decision makers are not required at any one time to consent for more than one study.

In order to conduct a more focused study, stricter exclusion criteria should be implemented and observed. To collect data that is substantial enough to detect correlations between diaphragm thickness and weaning outcome, we will track changes

in diaphragm thickness from intubation to successful weaning to determine the magnitude of diaphragm atrophy and investigate how this influences weaning outcome. To achieve this, we will need to ensure that patients who are expected to be extubated early (less than 72 hrs) are excluded from the study. Further, as weaning outcome will be a variable of interest, we will introduce stricter exclusion criteria regarding severity of illness. These restrictions will allow us to identify the patient populations with the highest probability of survival, and provide us with the opportunity to follow these patients to weaning. Stricter exclusion criteria may result in small samples. To improve recruitment numbers, a multicenter study is recommended.

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Appendices

Appendix A.

Proxy Information and Consent Form



PROXY INFORMATION AND CONSENT FORM

Serial Ultrasonographic Evaluation Of Diaphragm Thickness During Mechanical Ventilation In ICU Patients

Principal Investigator: Dr. Steve Reynolds, MD, FRCPC
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Co-Investigators: Andy Hoffer, PhD
Professor, Department of Biomedical Physiology and Kinesiology
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Colin Francis, BSc. (Hons) PT
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Department of Biomedical Physiology and Kinesiology
Neurokinesiology Laboratory, Simon Fraser University (778)782-5770

Alex Hoffer, BSc (Cand)
Co-op Student
Department of Biomedical Physiology and Kinesiology
Neurokinesiology Laboratory, Simon Fraser University (778) 782-5770

Research Site: Intensive Care Unit
Royal Columbian Hospital
New Westminster, British Columbia

Sponsor: Fraser Health Authority and Simon Fraser University

Funding: Unfunded

Emergency contact number: Pager 604-258-3857. In case of an emergency, Dr. Reynolds can be reached 24 hours per day, 7 days per week.

INVITATION

"You" will refer to the substitute decision maker for those subjects who are incompetent to participate in this study on their own behalf.

You are invited to take part in this research study because we are trying to evaluate diaphragm thickness in critically ill Intensive Care Unit (ICU) patients who are on a ventilator for breathing

Page 1 of 7

Subject or Proxy Consent: Version 9 - 08 July 2013 FHREB approved: 2013 July 17

support. Breathing using a ventilator replaces breathing on your own which results in weakness of the diaphragm muscle fibers from not being used. As the diaphragm becomes weaker, it decreases in thickness. Getting a better understanding of this condition could lead to improved treatments that might help support patients who require a ventilator for breathing.

YOUR PARTICIPATION IS VOLUNTARY

Your participation is voluntary. You have the right to refuse to participate in this study. If you decide to participate, you may still choose to withdraw from the study at any time without any negative consequences to the medical care, education, or other services to which you are entitled or are presently receiving.

Before you decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what will happen to you during the study and the possible benefits, risks and discomforts. You also need to know that there are important differences between being in a research study and being cared for by your doctor. When you participate in a research study, the main goal is to learn things to help other patients in the future. Outside a research study, your doctor's sole goal is to care for your health. Nevertheless, the researchers have a duty of care to all subjects and will inform you of any information that may affect your willingness to remain in the study.

If you wish to participate in this study, you will be asked to sign this form. Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

WHO IS CONDUCTING THE STUDY?

This study is being sponsored by the Fraser Health Authority and Simon Fraser University. This study is being conducted at the Royal Columbia Hospital in New Westminster, British Columbia.

BACKGROUND

When a person is put on a breathing machine we think that the breathing muscles can get weaker. We are not sure how quickly this happens but we know that in some people this leads to problems when they try to breathe on their own without the breathing machine. The diaphragm is at the bottom of your chest separating your lungs from what is in your belly and it is a very strong muscle. In fact, it is main muscle that you use for breathing.

An ultrasound machine is a painless way to see what is happening beneath the skin. It is safe and easy to do. Using an ultrasound we are planning to measure how thick the diaphragm is and how much it changes over 14 days while a person is on a breathing machine.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to determine the use of ultrasound imaging to evaluate diaphragm (the muscle that allows you to breathe) thickness over time in critically ill patients in the ICU. We want to evaluate whether diaphragm thickness will decrease over time following the start of mechanical ventilation (a machine that breathes for you).

This study is an observational study. No treatment will be provided in this study. This study will take place at the Royal Columbian Hospital, and is expected to recruit as many patients as possible by 31 July 2014..

WHO CAN PARTICIPATE IN THE STUDY?

You can take part in the study if:

- You are 19 years of age or older
- You are expected to be on a breathing machine for greater than 72 hours

WHO SHOULD NOT PARTICIPATE IN THE STUDY?

You should not participate in the study if:

- You have a history of a disease affecting the diaphragm or one that cause weakness in your nerves or muscles
- You have a body mass index (BMI) greater than 40 (measure of body fat based on weight and height). If this number is high it makes the ultrasound difficult to do.

WHAT DOES THE STUDY INVOLVE?

Overview of the study

If you qualify for the study, an ultrasound of your diaphragm will be done by an ultrasound operator as soon as possible after you have been intubated (insertion of a tube from the nose or mouth to the lungs to help you breathe). An ultrasound will also be done of your quadriceps (upper leg) muscle to provide information regarding overall muscle thickness

An ultrasound of the diaphragm and quadriceps muscle will be done at baseline (shortly after intubation) and then daily for up to 14 days or until you are able to breathe without the breathing machine

When having the ultrasound done, the operator will place a probe on the skin of your side chest area (diaphragm) or upper leg area (quadriceps) which will take pictures of your diaphragm or quadriceps muscle. The probe of the ultrasound can feel warm or tingle against your skin, however, you will not feel this as you will be unconscious during the time you are on a ventilator.

To ensure that all ultrasound readings are acquired from the same point over the period of the study, skin markers will be used to mark the position of the ultrasound probe. Where possible, four small dots will be placed on the skin to highlight the position of the four corners of the probe. In some places, such as the thigh, it may be more appropriate to mark two lines highlighting the two (long) sides of the probe.

Some participants may be asked to participate in a reliability sub study in which 3 different members of the study team will perform 3 ultrasound evaluations of the diaphragm on the same day. This will be done to ensure that the study team is measuring the diaphragm consistently.

Study Duration

Each ultrasound will take approximately between 5 and 10 minutes.

WHAT ARE THE POSSIBLE HARMS AND DISCOMFORTS?

Risk of Ultrasound

Properly performed, ultrasound imaging is virtually without risk or side effects. Some patients report feeling a slight tingling and/or warmth while being scanned, but most feel nothing at all. In this study, you will be unconscious and so you will not feel the ultrasound being done. Ultrasound waves of appropriate frequency and intensity are not known to cause or aggravate any medical condition.

WHAT ARE THE POTENTIAL BENEFITS OF PARTICIPATING?

There is no direct benefit from being involved in this study. However we hope that the information learned from this study can be used in the future to benefit other people with a similar disease.

WHAT ARE THE ALTERNATIVES TO THE STUDY TREATMENT?

If you decide not to enter this study, you will not have an ultrasound done.

WHAT IF NEW INFORMATION BECOMES AVAILABLE THAT MAY AFFECT MY DECISION TO PARTICIPATE?

You will be advised of any new information that becomes available that may affect your willingness to remain in this study.

WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE?

You have the right to withdraw from the study at any time without any impact to your current and future care. If you choose to enter the study and then decide to withdraw at a later time, all data collected about you during your enrolment in the study will be retained for analysis. It is a legal requirement that these data cannot be destroyed.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or his or her designate and the *Fraser Health Research Ethics Board* for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

You will be assigned a unique study number as a subject in this study. Only this number will be used on any research-related information collected about you during the course of this study, so that your identity [i.e. your name or any other information that could identify you] as a subject in this study will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to insure that your privacy is respected and also give you the right of access to the information about you

that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

AFTER THE STUDY IS FINISHED

There are no interventions involved in this study so that there will be no impact on any subjects after the completion of the study.

WHAT HAPPENS IF SOMETHING GOES WRONG?

By signing this form, you do not give up any of your legal rights and you do not release the study doctor or other participating institutions from their legal and professional duties. There will be no costs to you for participation in this study. You will not be charged for any research procedures. If you become ill or physically injured as a result of participation in this study, medical treatment will be provided at no additional cost to you. The costs of your medical treatment will be paid by your provincial medical plan.

WHAT WILL THE STUDY COST ME?

You will not be paid to participate in this research study. The ultrasounds will be done at no additional cost to you.

WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION?

If you have any questions or desire further information about this study before or during participation, or if you experience any adverse effects, you can contact Dr. Steve Reynolds at (604) 520-4576 or pager at (604) 258-3857.

WHO DO I CONTACT IF I HAVE ANY QUESTIONS OR CONCERNS ABOUT MY RIGHTS AS A SUBJECT?

If you have any concerns or complaints about your rights as a research subject and/or your experiences while participating in this study, contact Dr. Anton Grunfeld and/or Dr. Allan Belzberg, Research Ethics Board [REB] co-Chairs by calling 604-587-4681. You may discuss these rights with the co-chairmen of the Fraser Health REB.

PROXY CONSENT TO PARTICIPATE

**Serial Ultrasonographic Evaluation Of Diaphragm Thickness
During Mechanical Ventilation In ICU Patients**

By signing this consent form I agree that:

- I have read and understood the subject information and consent form.
- I have had the opportunity to ask questions and have had satisfactory responses to my questions.
- I understand that my participation in this study is voluntary and that I am completely free to refuse to participate or to withdraw from this study at any time without changing in any way the quality of care that I receive.
- I authorize access to my health record as described in this consent form.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I understand that all of the information collected will be kept confidential and that the results will only be used for scientific objectives
- I will receive a signed copy of this consent form for my own records.
- I understand that there is no guarantee that this study will provide any benefits to me

I will receive a signed copy of this consent form for my own records. I consent to participate in this study.

Substitute Decision Maker's Signature Printed name Date

Signature of Person Obtaining Consent Printed name Study Role Date

Investigator Signature Printed name Date

My signature above signifies that the study has been reviewed with the study participant by me and/or by my delegated staff. My signature may have been added at a later date, as I may not have been present at the time the participant's signature was obtained.

If this consent process has been done in a language other than that on this written form, with the assistance of an interpreter/translator, indicate:

Language: _____

Was the subject or substitute decision-maker assisted during the consent process in one of ways listed below?

Yes No

If yes, please check the relevant box and complete the signature space below:

- The consent form was read to the subject or substitute decision-maker, and the person signing below attests that the study was accurately explained to, and apparently understood by, the subject or substitute decision-maker (please check if subject is unable to read).*
- The person signing below acted as an interpreter/translator for the subject or substitute decision-maker, during the consent process (please check if an interpreter/translator assisted during the consent process).*

*Signature of Person Assisting
in the Consent Discussion*

Printed Name

Date

**Serial Ultrasonographic Evaluation Of Diaphragm Thickness
During Mechanical Ventilation In ICU Patients**

Version date: 30 April 2013

Patient #: _____

CLINICAL INFORMATION FORM

Year of birth OR Age: _____ OR _____
 yyyy age

Gender: M F

Date of admission: ____/____/____
 dd mm yyyy

BMI: _____

Date and time of intubation: _____

Date and time of 1st US: _____

Time from intubation to 1st US: _____

Initial mode of ventilation: _____

APACHE IV Score: _____

Admitting Category: Medical Surgical

Admitting Diagnosis: _____

Co-morbidities: _____

Admitted From: Ward Emergency OR/IR

Alternative Diagnosis for Distributive Shock: Yes No Possible

**Serial Ultrasonographic Evaluation Of Diaphragm Thickness
During Mechanical Ventilation In ICU Patients**

Version date: 30 April 2013

Patient #: _____

DAILY MEASURES

	day 0	day 1	day 2	day 3	day 4	day 5	day 6	day 7	day 8	day 9	day 10	day 11	day 12	day 13	day 14
US measurement of Diaphragm thickness (mm)															
US evaluation of quadriceps muscle thickness (mm)															
SOFA score															
APACHE IV Score															
RASS score															
PEEP: Minimum															
Max															
Median															
Average															
FiO2: Minimum															
Max															
Median															
Average															
Mode of MV (If mode changes express each mode as a percentage of overall ventilation time for the day)															
Spontaneous Breathing Trial															
Presence of tracheostomy															

Duration of ICU Stay: _____

**Serial Ultrasonographic Evaluation Of Diaphragm Thickness
During Mechanical Ventilation In ICU Patients**

Version date: 30 April 2013

Patient #: _____

CLINICAL INFORMATION FORM

LONG TERM FOLLOW UP:

Time of Tracheostomy: _____

Date of death: _____/_____/_____
 dd mm yyyy

Date of ICU discharge: _____/_____/_____
 dd mm yyyy

Protocol Violation: YES NO

If yes, specify violation(s):

Reason(s):

Appendix C.

Fraser Health Authority Project Approval

FHREB 2012-045

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Fraser Health Research Ethics Board
 FHA, Evaluation and Research Services
 #400, 13450 102nd Avenue, Surrey, BC V3T 0H1
 Phone: 604.587.4436 Fax: 604.930.5425

CERTIFICATE OF FHREB APPROVALS

Official Notification - FHREB Number (to be used on all future correspondence): FHREB 2012-045				
Principal Investigator: REYNOLDS, Steven, MD		Hospital/Facility & Department: Royal Columbian Hospital, Intensive Care Unit		
Institution(s) or Geographical Areas where research will be carried out: Royal Columbian Hospital				
Co-Investigator(s): HOFFER, Andy, FRANCIS, Colin, HOFFER, Alex				
Funding Agencies and/or Corporate Sponsor: unfunded				
Title: Serial Ultrasonographic Evaluation Of Diaphragm Thickness During Mechanical Ventilation In ICU Patients				
Documents Included in this Approval	Date of Approval	Date of Expiry	Type of Approval	Approval of the FHREB
<ul style="list-style-type: none"> Application for Initial Review Dated 2012 May 29 Researcher Response, dated 2012 June 20 Study Proposal, version 2, dated 2012 June 19 Consent Form, version 2, dated 2012 June 19 Subject Notification Letter, version 2, dated 2012 June 19 Substitute Decision Maker Notification Letter, version 2, dated 2012 June 19 	2012 June 27	2013 June 27	Initial Approval; Full Board Review	
<ul style="list-style-type: none"> Amendment Application Form, 2012 November 21 Protocol Version 2, 2012 November 21 Consent Form Version 3, 2012 November 21 	2012 November 27	2013 June 27	Amendment Approval; Delegated Review	

<ul style="list-style-type: none"> • Amendment Application Form, 2012 December 21 • Consent Form Version 4, 2012 December 21 • Case Report Forms, 2012 December 21 	2012 December 27	2013 June 27	Amendment Approval; Delegated Review	
<ul style="list-style-type: none"> • Amendment Application Form, 2013 Feb 07 • Protocol Amendment 3, 2013 February 07 	2013 February 08	2013 June 27	Amendment Approval; Delegated Review	
<ul style="list-style-type: none"> • Amendment Application Form, 2013 February 22 • Protocol Version 3, 2013 February 25 • Consent Form Version 5, 2013 February 20 • Case Report Forms, 2013 February 21 	2013 February 27	2013 June 27	Amendment Approval; Delegated Review	
<ul style="list-style-type: none"> • Amendment Application Form, 2013 March 20 • Consent Form Version 6, 2013 March 20 	2013 March 22	2013 June 27	Amendment Approval; Delegated Review	
<ul style="list-style-type: none"> • Amendment Application Form, 2013 May 28 • Consent Form Version 7, 2013 May 28 • Case Report Forms Version 7, 2013 May 28 	2013 May 30	2013 June 27	Amendment Approval; Delegated Review	
<ul style="list-style-type: none"> • Annual Renewal Form, 2013 June 13 • Researcher Response Form, 2013 June 20 • Consent Form Version 8, 2013 June 20 	2013 June 28	2014 June 28	Annual Renewal; Delegated Review	

<ul style="list-style-type: none"> • Amendment Form, 2013 July 08 • Protocol Version 4, 2013 July 08 • Consent Form Version 9, 2013 July 08 	2013 July 17	2014 June 28	Amendment Approval; Delegated Review	
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CERTIFICATION:

With respect to clinical trials:

1. The membership of the Fraser Health Research Ethics Board complies with the membership requirements for research ethics boards as defined in Part C Division 5 of the Food and Drug Regulations and the Tri-Council Policy Statement.
2. The Fraser Health Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.
3. The Fraser Health Research Ethics Board has reviewed and approved the clinical trial protocol and the informed consent form for the trial which is to be conducted by a qualified investigator named at the specified clinical trial site. This approval of the documentation listed above and the views of the Fraser Health Research Ethics Board have been documented in writing.

With respect to delegated review:

A co-chair of the FHREB has reviewed and approved the documentation listed above for the forenamed research study in accordance with the FHREB Policy on "Ethical Conduct of Research and Other Studies Involving Human Subject", the Tri-council Policy Statement: Ethical Conduct for Research Involving Human", and the "International Conference on Harmonisation Guidance E6: Good Clinical Practice E6: Consolidated Guidelines".

With respect to full board review:

Full FHREB review and approval of the documentation listed above was completed for non-expedited review in accordance with the FHREB Policy on "Ethical Conduct of Research and Other Studies Involving Human Subjects", the Tri-council Policy Statement: Ethical Conduct for Research Involving Human" and the "International Conference on Harmonisation Guidance E6: Good Clinical Practice E6: Consolidated Guidelines".

The FHREB approval for this study expires ONE year from the approval date of this certificate. Researchers must submit a Request for Annual Renewal for ongoing research studies prior to the expiry date in order to receive annual re-approval.

Appendix D.

Telemed Echoblaster 128 Ultrasound System



Echo Blaster 128 CEXT-1Z Kit.



Echo Blaster 128 CEXT-1Z with attached transducer and notebook.