OXYGENATION AND PULMONARY MECHANICS IN CRITICALLY ILL CHILDREN RECEIVING MECHANICAL VENTILATION: A COMPUTATIONAL PHENOTYPE AND MACHINE LEARNING APPROACH

A Dissertation Presented

By

Craig David Smallwood

to

The Department of Bioengineering

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

in the field of

Bioengineering

Northeastern University
Boston, Massachusetts

April 2018
ACKNOWLEDGMENTS

Thanks and glory be to God, the Son and the Holy Spirit, forever and ever. Thank you for your grace, your strength, your wisdom and for granting me the peace of mind and good health necessary to complete this work.

This work would not have been possible without the support of Northeastern University, the Department of Bioengineering and my dear advisor Dr. Andrew Gouldstone. Dr. Gouldstone’s encouragement, his superhero ability to wrangle complex topics, ceaseless enthusiasm for discovery and innovation and importantly, his humor have modelled what it is to be a great professor. Indeed, I am extremely thankful for his support and guidance and remain greatly indebted.

Thank you to my committee members at Northeastern University, Dr. Jeffrey Ruberti and Dr. Sagar Kamarthi. Your lessons inside the classroom and the laboratory have taught me a great deal about the field, the scientific method and will be something I carry with me throughout my career.

I am extremely grateful to my colleagues and mentors at Boston Children’s Hospital and to the Division of Critical Care Medicine. Dr. Nilesh Mehta, whose encouragement, scientific curiosity and enthusiasm have had a significant impact on me, not only as a scientist but also as a person. Dr. John Arnold, whose thorough understanding of the pediatric pulmonary system, his thoughtful and timely critiques on how to effectively communicate science and most importantly, his high expectations have pushed me higher and have helped to mold me as a scientist and as a person. Thank you.

To my parents, whose love, guidance and lessons in determination are with me in whatever I pursue, thank you for your encouragement and example.

No one is more important to me on this planet than my loving, beautiful and supportive wife, Erika, and my beautiful daughter Sadie. Sadie, whose unending curiosity and adorable emulation of my ‘research’ fills my heart. Erika, thank you for your enduring and daily love, your support in all I pursue and all the amazing things you do. Thank you.

Craig Smallwood
Northeastern University
April 2018
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ABSTRACT

Mechanical ventilation (MV) is a lifesaving therapy applied to critically ill children. A component of MV, positive end-expiratory pressure (PEEP) is often increased to improve ventilation efficiency thereby improving gas exchange. PEEP may ameliorate or exacerbate lung injury. PEEP optimization is clinically important and predicting physiologic response is desirable. Despite this, there is a paucity of literature to guide the clinician at the bedside. Importantly, time-series physiologic data are available for MV patients in the pediatric intensive care unit. However, these data have not been adequately explored in the literature. Therefore, we sought to 1) quantify the time required for oxygenation and pulmonary system compliance changes in children requiring mechanical ventilation, 2) quantify the empirical probability of PEEP changes implemented by expert clinicians that result in positive effects on oxygenation, pulmonary mechanics and dead-space fraction and identify clinical features associated with positive response and 3) extract computational phenotypes from time-series physiologic data and develop a model to predict PEEP response during MV in children.
Equilibration time for oxygenation and compliance was computed. PEEP changes were quantified as either a responder (condition improvement) or a non-responders (condition worsening) and the empirical probability of a clinician implementing a change that improved the patient’s condition within was quantified. Features from continuous mechanical ventilation variables were extracted and used to train a model in order to predict improvements in ventilation efficiency subsequent to changes in PEEP.

A total of 265 subjects were enrolled and 1327 PEEP change cases were analyzed. Equilibration requires 38 and 71 minutes for respiratory system compliance and oxygenation respectively; the latter was directly observed to be dependent upon severity of illness. The empirical probability of improving a patient’s condition following a PEEP change by clinicians was ~59% and ~48% for PEEP increases and decreases respectively. Responders to increased PEEP had higher oxygen requirements and ventilator support. A total of 27 computable phenotypes were identified and incorporated into a prediction model. These phenotypes incorporated features that are not typically assessed by clinicians at the bedside. The area under the receiver operator characteristic curve was 0.82 and 0.90 for classifying response to PEEP increases and decreases respectively. In the future, these methods may play an important role in optimizing care during pediatric MV.
1. INTRODUCTION

Acute respiratory failure (ARF) is a common condition that requires invasive mechanical ventilation, but individualized therapeutic targets remain elusive. ARF can be caused by pulmonary disease, infection, airway instability, shock or neurologic disorders. Recent studies show that mechanical ventilation is applied to nearly 800,000 patients in the United States each year and carries a substantial risk of mortality and financial burden; $27 billion, or 12.0% of all hospital costs each year. At the individual level, cost of mechanical ventilation can be as much as $1500 per day. Methods and techniques are needed to individualize care, reduce morbidity, duration of ventilation and cost.

Gleaning robust representations of pediatric pathophysiology is especially difficult because the underlying causes of disease span body systems and physiologic processes, creating complex nonlinear relationships among observed measurements. Specifically, ventilator induced lung injury (VILI) occurs as a result of inappropriate setting of ventilator parameters and is affected by many known and unknown risk factors. At this stage, efforts to reduce VILI have primarily focused on limiting stress and strain of the lung parenchyma through reduced peak airway pressure ($P_{peak}$), tidal volumes and the application of positive end-expiratory pressure (PEEP). PEEP is used to modulate oxygenation support and limit VILI by preventing atelectasis and facilitating alveolar recruitment. In general, lung
protective ventilation incorporates low tidal volumes (6ml/kg ideal body weight), plateau pressure $\leq 30$ cmH$_2$O and ideal PEEP.$^9,^{10}$ In the adult literature, a strategy for PEEP titration remains elusive; published randomized controlled clinical trials have not agreed.$^{11-13}$ In children, there have been no definitive clinical trials and leading scientists have stated that the mechanisms by which PEEP is beneficial are not well understood and require further investigation.$^{14,9}$ Prospective randomized controlled clinical trials are difficult or even futile in this population and alternative means of assessing and improving ventilator care are needed.$^{15}$ In these cases, interventions are designed at the population level and result in a one-size fits all strategy based on only a narrow snapshot of clinical data. However, heterogeneity in both admitting diagnosis and individual subject pathophysiology preceding mechanical ventilation creates a significant challenge for generating effective clinical interventions. The work of Meade et al titrated PEEP based only on oxygen requirement.$^{11}$ Such trials have shown us that more data that better describes the clinical scenario are needed to individualize and optimize ventilator care to reduce risk of mortality, length of stay in the intensive care unit and cost. The paucity of data outlining a strategy for pediatric PEEP titration means that bedside clinicians are forced to implement unproven strategies. These decisions are inherently heterogeneous and vary by institution, medical unit and amongst individual clinicians.$^{16}$
In this work, an approach that leverages intervention heterogeneity by application of computational phenotyping, identification of meaningful representations of a clinical scenarios and the provision of a basis for new models of pulmonary pathophysiology is described. Typically, continuous data are clinically ignored but could offer a rich area of discovery into the pathophysiology of critically ill, mechanically ventilated patients.

The present work identifies variable associations with clinically relevant factors (oxygenation, pulmonary mechanics and dead-space fraction) as a function of PEEP and developed models needed to accurately predict response. Phenomics is the area of biology concerned with the measurement of traits of organisms especially as it relates to disease. Here, computational phenotype data will be extracted from the data feeds of technology continuously applied to subjects during mechanical ventilation. Data mining and machine learning on the other hand have increasingly been employed to detect novel patterns in data and develop models that incorporate a large number of variables that have complex and nonlinear relationships. However, these techniques have not been widely applied to problems in children with acute respiratory failure receiving mechanical ventilation. The research is centered on three progressive yet complementary objectives:
1. Quantify the equilibration time required for oxygenation and respiratory system compliance response following increases in positive end-expiratory pressure

2. Quantify the empirical probability of positive response to PEEP; the rate at which clinicians are able to identify cases when positive end-expiratory pressure should be increased and decreased based on oxygenation, respiratory system compliance and dead-space ventilation

3. Extract computational phenotypes from time-series physiologic data and develop a model to predict response to changes in positive end-expiratory pressure
2. **PEDIATRIC MECHANICAL VENTILATION**

The pulmonary system’s main function is respiration; the exchange of O\textsubscript{2} and CO\textsubscript{2} gas through the lungs. During normal breathing, a pressure gradient is formed between the thoracic cavity and the ambient atmosphere as the ventilatory muscles contract. The gradient moves air from the environment into the lungs using a series of conducted airways until the gas reaches the terminal lung unit, the alveoli. It is within the alveoli that gas exchange occurs. Diffusion of gases (both O\textsubscript{2} and CO\textsubscript{2}) occurs at the level of the alveolar-capillary membrane. As blood passes through a network of small capillaries that envelope the alveoli, O\textsubscript{2} is taken up into the blood and CO\textsubscript{2} is excreted into the alveolar space. As the breathing muscles relax, the pressure gradient reverses and gas is forced from the lung to the ambient environment.

Respiratory failure is defined as the inability of a patient to achieve adequate levels of O\textsubscript{2} uptake and CO\textsubscript{2} removal that matches the metabolic demand of the body.\textsuperscript{18} The main 2 types of respiratory failure: 1) hypoxemic respiratory failure, where adequate oxygenation cannot be maintained and 2) hypercapnic respiratory failure, where appropriate CO\textsubscript{2} levels cannot be maintained.\textsuperscript{19} Infants and young children have an increased risk of respiratory failure relative to their adult counterparts. This risk arises from the fact that the immune system is immature, there are differences in airway anatomy and they are poorly equipped to sustain
increased work of breathing, which is required during illness since the proportion of fatigue-resistant type 1 muscle fibers has not yet peaked.\textsuperscript{20-22}

In severe cases, placement of an artificial airway and application of mechanical ventilation is required to ensure safe and effective oxygenation and ventilation. A mechanical ventilator is a device that employs positive pressure in order to sustain artificial respiration through the provision of $O_2$ and elimination of $CO_2$. This chapter will provide a brief overview of basic mechanical ventilation concepts and a review of pediatric mechanical ventilation. Areas of research that are needed in order to improve outcomes for critically ill children with hypoxic respiratory failure who require mechanical ventilation will be highlighted.

2.1 Mechanical ventilation: basic concepts

Unlike spontaneous breathing, where a negative pressure gradient is achieved through contraction of the inspiratory muscles, mechanical ventilation utilizes positive pressure. Upon patient connection to a mechanical ventilator, positive pressure is generated at the interface to generate a pressure gradient and facilitate air movement into the lungs. At its most basic, the components of a positive pressure breath include the peak airway pressure ($P_{peak}$), positive end-expiratory pressure ($PEEP$), inspiratory time ($T_i$), respiratory rate ($RR$) and fraction of inspired oxygen ($FiO_2$). The difference between the $P_{peak}$ and $PEEP$ make up the ventilating pressure (or $\Delta P$) and is the pressure needed to generate a given breath. $PEEP$ is a
distending pressure needed to ensure that, upon expiration, the lungs do not collapse, and adequate inflation is maintained for subsequent breaths.\textsuperscript{23,24} In Figure 2.1, the mechanical ventilator, breathing circuit and connections are depicted.\textsuperscript{25} A flow control valve opens at point (a) while a flow control valve at point (e) is constricting. This has the effect to pressurize the gas in the breathing circuit and fresh gas travels from point (a) down the inspiratory limb of the breathing circuit to point (b) where it enters the humidifier. The gas is then heated and humidified to 37°C and 100% relative humidity.\textsuperscript{26} Next, the gas leaves the inspiratory limb of the breathing circuit at point (c) and continues to the patient at point (d). A bifurcation at point (d) in the breathing circuit ensures that upon inspiration, fresh gas from the inspiratory circuit is inhaled through the endotracheal tube and travels to the lungs where gas exchange occurs. The ventilator then cycles into expiration; the valve at point (a) is constricted, pressure in the breathing circuit decreases to PEEP and the breath is expired through the endotracheal tube, passed the bifurcation at point (d) and travels down the expiratory limb of the breathing circuit. The expired breath enters the mechanical ventilator at point (e) and is discharged to the atmosphere at the ventilator exhaust port.
A number of parameters are measured during mechanical ventilation, including but not limited to: inspired and expired tidal volume ($V_t$), total respiratory rate ($RR_{total}$), ventilating pressures, partial pressure of CO$_2$ in the exhaled breath ($PetCO_2$), oxygen saturation ($SpO_2$) and others. An example of mechanical ventilation waveforms along with where some parameters can be visualized is depicted in Figure 2.2. The $V_t$ is the volume of a given breath and typically ranges from 5-8ml/kg. In a 10kg pediatric subject, this translates to 50-80ml. $PetCO_2$ has been referred to as the 6th vital sign and is a marker of ventilation and is often used to approximate the partial pressure of CO$_2$ in the arterial blood and calculate indices of ventilation efficiency such as dead-space ventilation (cf. Chapter 4.).$^{27-29}$ $SpO_2$ is the oxygen saturation by plethysmography and is measured with a non-invasive
finger probe continuously for patients in the pediatric intensive care unit (PICU).

\( SpO_2 \) for healthy children is \( \geq 95\% \) and is incorporated into important indices of oxygenation in order to quantify severity of illness and response to therapies and interventions.\textsuperscript{30,31}
Mechanical ventilation is applied in order to maintain adequate oxygenation and ventilation. Ventilation is principally modulated by adjusted $V_t$ and $RR$ (combined, the expired minute ventilation, $V_E$, where $V_E = V_t \times RR$). Oxygenation is primarily modulating by adjusting $F_{O_2}$ and mean airway pressure ($P_{mean}$). The primary
determinant of $P_{\text{mean}}$ is $\text{PEEP}$, so practically, oxygenation is modulated by adjusted $\text{PEEP}$ during mechanical ventilation.

### 2.2 Pediatric mechanical ventilation practice

At the end of the 20th century, intensive care practitioners in the PICU had achieved important, albeit limited insights into pediatric mechanical ventilation. The major shift came from an effort to normalize gas exchange (both oxygenation and ventilation parameters) and begin to adopt what would evolve into ‘lung protective ventilation’. Other important insights included reducing the peak pressure and tidal volumes used to reduce the lungs exposure to toxic pressures that can exacerbate lung injury as well as the application of positive end-expiratory pressure in order to reduce the risk of atelectasis. Another important feature of pediatric hypoxic respiratory failure and lung injury was that the cause of injury (underlying disease process) was an important feature that affected risk of mortality. It is also widely understood that children are not simply little adults; meaning that data from adult trials of mechanical ventilation cannot be utilized conclusively to inform care of the pediatric patient. Despite these important insights, much remains unknown and more work is needed in order to improve outcomes for mechanically ventilation children.
2.2.1 High versus low PEEP

The use of PEEP in the context of acute lung injury was first described by Ashbaugh et al in critically ill adult patients.\textsuperscript{23} Since that time, the application of PEEP has become standard practice during mechanical ventilation. Clinical trials designed to assess whether high or low PEEP is optimal during pediatric mechanical ventilation have not been definitive. Adult trials have demonstrated improvements in ventilator free days (the number of days a subject did not require mechanical ventilation in the hospital), need for rescue therapy (such as high-frequency oscillatory ventilation and extra-corporeal membrane oxygenation) but showed no differences in mortality between cohorts exposed to low versus high PEEP.\textsuperscript{11,12} In another prospective clinical trial, no differences in mortality of morbidity were observed between high (~13 cmH\textsubscript{2}O) and low (~8 cmH\textsubscript{2}O) PEEP.\textsuperscript{13} Interestingly, a non-linear effect of severity of illness has been shown to be an important factor in the likelihood of response to increased levels of PEEP and overall mortality, suggesting that a tailored approach to PEEP, assessing an individual subject's condition may be beneficial.\textsuperscript{37} Recently, a multi-center retrospective investigation noted that PEEP levels below a prescribed level increased risk of mortality during mechanical ventilation.\textsuperscript{38} Large clinical studies have informed important changes in clinical practice but the titration and optimization of PEEP is still not well understood in children.
2.2.2 Treatment protocols for pediatric mechanical ventilation

A limited number of treatment protocols for the management of pediatric mechanical ventilation have been put forth in the literature.\textsuperscript{39-41} However, many of these have been translated directly from adult data and fail to adequately control for differences between pediatric and adult pathophysiology and care in the intensive care unit.\textsuperscript{42,43} Given the paucity of validated pediatric treatment protocols, no one-size fits all protocol is widely available and work in this area is needed.

2.2.3 Lung protective ventilation

Lung protective ventilation has been informed by large clinical studies in order to assuage ventilator induced lung injury (VILI), which occurs as a result of inappropriate setting of ventilator parameters and is affected by many known and unknown risk factors.\textsuperscript{4-7} At this stage, efforts to reduce VILI have primarily focused on limiting the exposure of the lung parenchyma to excessive peak airway pressures ($P_{\text{peak}}$), reducing tidal volumes and applying PEEP. In general, lung protective ventilation incorporates low tidal volumes (6ml/kg ideal body weight), plateau pressure $\leq 30$ cmH$_2$O and ideal PEEP.\textsuperscript{9,10} A feature of lung protective ventilation is permissive hypercapnia, whereby the targets for arterial partial pressure of CO$_2$ ($PaCO_2$) are relaxed. $PaCO_2$ during normal breathing is maintained at a level $\sim 35$-$45$ mmHg along with an arterial blood pH $\sim 7.35$-$7.45$. During acute illness, $PaCO_2$ can rise as the patient’s disease progresses, and their ability to increase respiratory
effort fails to match metabolic demand. In the past, lung volumes and the pressures required to deliver those volumes were increased. The increased pressure is known to contribute to VILI and adversely affect mortality and morbidity. Permissive hypercapnia prescribes a pH target of $>7.25$ and allows $PaCO_2$ to rise to levels greater than 45 mmHg. A lower pH and $PaCO_2$ target mean that lower volumes and pressures can be applied to the patient via the mechanical ventilator and minimize the exposure to toxic overdistension of diseased lung units.$^{44,45}$

### 2.2.4 Mode of ventilation

There are limited data in the literature that demonstrate superiority of any single mode of ventilation for subjects with hypoxic respiratory failure or acute respiratory distress syndrome.$^{46-48}$ In adult ICUs, volume-control, assist-control mode is most often utilized. On the other hand, pressure-control is the most widely applied mode of ventilation in the pediatric population.$^{49}$ The work of the pediatric acute lung injury consensus conference (PALICC) group determined that there is no recommendation on a specific ventilator mode for this patient population.$^9$ Instead, recommendations include using patient-specific tidal volumes ($V_t$) according to disease severity: $V_t = 3–6$ mL/kg ideal body weight (IBW) for patients with poor respiratory system compliance, and $V_t = 5–8$ mL/kg IBW for patients with better respiratory system compliance. Overall however, low $V_t$ is underutilized
in children in the first 24 hours of illness. Ward et al observed that when the definition of low $V_t$ was expanded to include $V_t$ up to 8 mL/kg IBW, the frequency of low $V_t$ use increased to only 58–60%, which suggests a large proportion of patients receiving $V_t$ higher than the recommended cutoff. There are no randomized, controlled trials to support the notion that 8 mL/kg is worse for a pediatric patient than 6 mL/kg. Nevertheless, the impact of a low $V_t$ strategy in adults has had important implications in the PICU and targets of 5-7 ml/kg are often cited for pediatric patients with hypoxic respiratory failure and acute respiratory distress syndrome. Observational data, have not shown a relationship between $V_t$ and mortality in mechanically ventilated children, regardless of the severity of disease.

2.2.5 Sedation management

Sedation is an essential component of the medical management of children requiring mechanical ventilation. Sedation enhances safety and comfort of children but comes with some important limitations and risks. Sedation carries the risk of prolonged duration of mechanical ventilation, induced neuromyopathy and increases the risk of delirium, a disturbed state of consciousness characterized by restlessness, incoherence and confusion. A large prospective sedation management for pediatric patients with acute respiratory failure study was designed
to assess the effect of protocolized sedation management upon mortality, duration of ventilation and adverse event rate.\textsuperscript{55} Although the study failed to demonstrate a difference in the primary end-point, mortality, the authors noted reductions in overall sedation use and number of adverse events. More recently, patient-ventilator interactions have become an important quality marker during mechanical ventilation.\textsuperscript{56-58} Sedation titrated to ensure patient comfort and synchronization with the mechanical ventilator, while not blunting the respiratory effort completely is an important clinical goal. Sedation management during mechanical ventilation is a potential confounding factor that can affect how an individual subject may respond to and interact with the mechanical ventilator. Therefore, it is essential that work in this area include markers of respiratory effort, patient-ventilator dyssynchrony and contribution to overall minute ventilation when designing algorithms to predict response and better understand the physiologic effects of PEEP.

2.2.6 Recruitment maneuvers

A recruitment maneuver, whereby high airway pressures are transiently applied to a patient in order to resolve atelectasis has been investigated in the context of pediatric hypoxic lung injury and acute respiratory distress syndrome. Only a handful of investigations have been conducted in the pediatric population.\textsuperscript{59,60} Although the studies have noted that oxygenation can be improved,
the effects are only transient, and the studies were not powered to ascertain whether this improvement in oxygenation results in a mortality benefit or reduction in duration of mechanical ventilation. Indeed, there is insufficient evidence to recommend recruitment maneuvers as a standard of care in mechanically ventilated pediatric patients. Instead, clinicians are forced to rely on clinical judgement and bedside experiments, modulating PEEP incrementally to achieve the desired physiologic effect.

2.3 Implications

In mechanically ventilated children with hypoxic respiratory failure, titration of PEEP is done to improve oxygenation through the recruitment and stabilization of alveoli. However, PEEP can ameliorate or exacerbate lung injury. PEEP changes are frequently made at the bedside but little guidance exists in the pediatric literature. The physiologic rationale for increasing PEEP in most cases is to improve functional residual capacity, reduce physiologic dead-space fraction, shunt fraction and ventilation/perfusion mismatch. Although the use of moderate to high levels of PEEP have been shown to be safe in the pediatric population, widespread and consistent application has not been recommended. Decisions are inherently heterogeneous and vary by institution, medical unit and amongst individual clinicians. Furthermore, clinical interventions for the majority of studies are designed at the population level. While
this strategy has made important contributions to the advancement of mechanical ventilation up until this point, it can result in a one-size fits all approach based on a narrow snapshot of clinical data. Important features of a critically ill pediatric patients include heterogeneity in admitting diagnosis and individual subject pathophysiology during mechanical ventilation. More data, recorded continuously and processed to adequately describe the clinical scenario of a patient is needed to individualize and optimize ventilator care.
3. DECISION SUPPORT DURING MECHANICAL VENTILATION

3.1 Introduction

Decision support in the context of modern medicine is about predicting future events based on a thorough evaluation and understanding of a patient’s present condition. One of the earliest forms of predicting health dates to the time of Hippocrates (460 B.C. to 377 B.C.). Hippocrates was a student of natural history and the progression of disease; he noted the association of environmental factors (access to water and food) with disease. Hippocrates was a champion of prognosis, which he described as the “importance of being able to foretell the course of an illness”, believing that it is an essential part of treating the diseased. Indeed ‘Hippocratic facies’ was a technique he outlined to forecast death based upon observed patient signs and symptoms.

The signs to watch for in acute diseases are as follows. First study the patient’s facies; whether it has a healthy look and in particular whether it be exactly as it normally is. If the patient’s normal appearance is preserved, this is best; just as the more abnormal it is, the worse it is... – Hippocrates

Indeed, modern medicine has evolved to not only include the physical appearance of a patient (as described by Hippocrates), but various blood tests, imaging diagnostics, assessments of pain and mobility and many more. More
recently, continuous-in-time (or time-series) physiologic parameters are available in the context of critical illness and mechanical ventilation. However, quantifying those aspects of time-series patient data that are associated with health and those associated with disease, as in Hippocratic facies, has not been adequately described in the literature for mechanically ventilated patients.

Caring for the mechanically ventilated patient is becoming increasingly complex, especially in the context of the intensive care unit. Randomized controlled trials are expensive, time consuming and in some patient populations, extremely difficult or even futile. Alternative means of assessing and improving bedside medicine are needed to individualize care, reduce morbidity, duration of mechanical ventilation and cost. The potential for better care based on the application of methods to extract clinical insights based on existing data found in the medical record, bedside clinical devices, imaging modalities and clinical assessment is important and should be addressed. The potential impact is profound and could touch all aspects of medicine including clinical care, billing, administrative scheduling and even facilitated home care. Presently, a multitude of data can be collected, but it’s use has not yet been optimized. In the sections that follow, a general overview of key concepts is completed to serve as a primer in decision support development and application in the field of critical care medicine and mechanical ventilation. A review of the relevant literature pertaining to the
application of clinical decision support to the mechanically ventilated subject and
the principles of computational phenotyping are also provided.

3.2 Overview of Essential Concepts

3.2.1 Computerized Decision Support

It is useful to begin by defining several important terms that are frequently
utilized in describing computerized decision support, associated systems and
analysis.

Computerized decision support (CDS) is a branch of clinical decision
support in the form of applications embedded within the medical record, web and
smart-phone applications, various bedside tools and online references. CDS has
been studied for several decades. As early as the 1950s and 60s, work was being
done to leverage mathematical and computerized methods to aid medical
diagnosis.\textsuperscript{73,74} CDS has been shown to be an efficient type of decision support in
some clinical environments, reducing practice variance, augmenting clinician
decision making and improving quality.\textsuperscript{73-77}

3.2.2 Types of Clinical Data

For a subject admitted to the intensive care unit and receiving mechanical
ventilation, there are disparate data types that must be considered when storing,
accessing and deriving insights from the data. Structured data elements are those
that document patient information using controlled vocabulary rather than a text narrative or other unstructured means. An example would be a flow sheet row in the medical record where a clinician would record respiratory rate. Data from pick-down lists, such as those utilized to document breath sounds, or capnographic data are also examples of structured data. In most cases, structured data are preferred since the data are relatively easy to query, manipulate and process.

Unstructured data is a term that has gained popularity in recent years and goes hand-in-hand with ‘big data’. These are data that cannot be readily mapped to a specific field with known characteristics. Often, unstructured data are stored without a clear purpose for later use or it is very difficult or impossible to impose a structure on it. Examples include clinical notes where a clinician can free text an entry, most imaging, and a few other sources (typically outside the electronic health record).

There is a need to integrate these data types in order to achieve the maximum clinical, quality and business value. There are efforts in the field to adopt standards that facilitate the flow of data. One such effort is the clinical document architecture (CDA), an important standard in the United States that seeks to incrementally structure data and provide interoperability. As these standards are implemented, the hope is that individual institutions, departments and teams will be able to more readily access and extract value from these data.
3.2.3 Data Collection and Warehouse

Data collection at the bedside is particularly daunting, especially since a single subject can be connected to several devices that output different types of data and at different frequencies. First and foremost, the admission-discharge transfer feed, which contains important patient identifiers is used to associate the patient with the bed-space, medical record and other data sources. A data warehouse is a central location for all data that an enterprise or hospital collects. These data can include those stored directly in the electronic health record (including medication administration record, physiologic data, treatments, notes, etc.), incorporated into the admission-discharge transfer (ADT), continuous physiologic data from the monitor and mechanical ventilator, imaging (radiologic, ultrasounds, etc.), billing, as well as other sources. Increasingly, institutions are implementing data architecture that streamlines the collection of data from multiple locations to a central repository for patient care, quality improvement and research.

3.2.4 Data Mining and Data Science

As the field of artificial intelligence has progressed over the past 30 years, data mining has been of prominent interest among researchers in the field. Data mining is the science of extracting useful information from data sets and spans several disciplines, including statistics, data management, artificial intelligence, machine learning, pattern recognition and others. A researcher engaged in data
mining will address data collection, storage and retrieval, data cleaning, data reduction, visualization, algorithm development, machine learning, statistical analysis and will need to balance statistical and computational issues.

Increasingly, the role of the data scientist is one that spans various industries and all levels of enterprise decision making. A data scientist is a person at the intersection of substantive expertise (domain knowledge), math and applied statistics, machine learning, and coding skills. On one hand, all scientists deal with data and one may prefer to bestow the title of data scientist upon anyone dealing with data and statistics. However, for our purposes, this is referred to as traditional research. As more data is collected, the importance of machine learning, hacking and coding skills are required to achieve the maximum value out of our patient’s data. It is in the best interest of the field of medicine to have people with extensive substantive expertise (respiratory therapists, doctors, nurses and other clinicians) gain the skills needed to become data scientists. One of the issues facing a data scientist with little knowledge in the field is solving problems that either 1) don’t exist, or 2) are obvious to clinicians in the field. Data scientists with keen awareness of clinical practice, especially as it pertains to mechanical ventilation will be excellently positioned to achieve insights into pathophysiology and development of useful CDS tools that will have a clinical impact.
3.2.5  Artificial Intelligence

The definition of artificial intelligence (AI) can be controversial depending on the applied domain (computer science, data science, statistics, science fiction, etc.). The English mathematician, and widely recognized father of artificial intelligence, Alan Turing, devised what is known as the ‘Turing Test’ of computer intelligence.\textsuperscript{86} Turing proposed that if a computer could mimic human behavior, and in so doing fool a human into believing they were interacting with a human, that computer could be defined as possessing intelligence. More broadly, artificial intelligence is defined as the branch of computer science dealing with the simulation of intelligent behavior in computers and the capability of a machine to imitate intelligent human behavior.\textsuperscript{87}

3.2.6  Machine Learning

Machine learning is a subset of artificial intelligence that provides a mechanism to learn from data and improve from experience without being explicitly programmed.\textsuperscript{88} This is particularly useful in the context of medicine since it may not be completely necessary to explain all the variance in a given subject, but to get a reasonable approximation of system performance or subject health in an effort to provide individualized care.

In general, there are two principal types of learning utilized within machine learning that a researcher can employ to extract knowledge from a given dataset:
supervised and unsupervised learning. Supervised learning is the term used to describe a problem where a discrete outcome is known a priori. Techniques within supervised learning utilize a labelled dataset that has two components: 1) a set of inputs (typically a vector of data containing either continuous variables, categorical variables or a combination of both and 2) a target, or outcome. This is collectively referred to as the training data and is used to train the machine learning algorithm.

On the other hand, unsupervised learning is the machine learning task of uncovering hidden structure or relationships within an unlabeled dataset. An unlabeled dataset is one where no target or outcome exists. An example of unsupervised learning is the application of a cluster analysis technique to detect distinct phenotypes of subjects with a common clinical diagnosis. In this case, this information may reveal differences in clinical characteristics and prognosis for a given diagnosis, such as bronchiectasis.

In addition to the two principal types of learning, a third type of learning called semi-supervised learning exists. Semi-supervised learning is where input data are a mixture of both labelled and unlabeled cases. In this case, the prediction problem is comprised of identifying the organizational structure of the data as well as the predictions. Often, these algorithms extend the functionality of other methods.

Some examples of machine learning algorithms seen in the medical literature included tree-based methods, discriminant analysis, regression models...
(multiple and logistic), support vector machine, k nearest neighbor and neural networks. An important aspect of applying machine learning in healthcare is the interpretability of the algorithm. Tree based algorithms, discriminate analysis (depending upon the discriminant function) and support vector machines (depending on the function used) are generally preferred for their improved interpretability. Support vector machines and discriminate analysis have been applied to research problems in the intensive care unit and during mechanical ventilation. Selecting a machine learning algorithm should be a balance of overall performance (accuracy), duration of time needed for training and interpretability.

3.2.7 Classification and regression

In general, machine learning is employed to make a prediction or observation about a variable and can be broadly divided into regression and classification problems. A regression problem is one where the output is a continuous variable in either space or time. During mechanical ventilation, it may be desirable to predict continuously the oxygenation ($SpO_2$) and ventilation ($PaCO_2$) of a subject as a result of some clinical intervention. In the context of a regression, an algorithm could be constructed to predict the $SpO_2$ and $PaCO_2$ of a subject at any point in time; PEEP is increased, $SpO_2$ and $PaCO_2$ are predicted to be 93% and 42mmHg respectively. On the other hand, a classification approach may be to
simply categorize a PEEP change as generally good or generally bad (either a positive or negative response). It is important to note that many problems can be posed as either a regression or classification problem (each with benefits and drawbacks). It is essential to understand the clinical problem, objective of the decision support tool you are developing and statistical performance of the algorithm when deciding which methodology is most appropriate.

3.2.8 Decision Support Algorithms During Mechanical Ventilation

Decision support algorithms employed during mechanical ventilation have been demonstrated in the literature. These algorithms have been primarily implemented in order to alert clinicians to the presence of a specific syndrome and ensure adherence to established practices. Other areas of research include closed-loop control of inspired oxygen, automated waveform analysis and decision support to predict physiologic changes to individual mechanical ventilator settings. Some examples of studies that sought to achieve a decision support tool during mechanical ventilation are outlined in Table 2.1.
Table 3.1. Computerized decision support during mechanical ventilation.

<table>
<thead>
<tr>
<th>Class of Computerized Decision Support Tool</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Alert Management</td>
<td>Ventilator induced lung injury\textsuperscript{96}</td>
</tr>
<tr>
<td></td>
<td>Inspired oxygen\textsuperscript{98-101}</td>
</tr>
<tr>
<td></td>
<td>Ventilation of the neonatal subject\textsuperscript{102}</td>
</tr>
<tr>
<td>Protocol/Guideline</td>
<td>Adherence to mechanical ventilation goals\textsuperscript{103}</td>
</tr>
<tr>
<td></td>
<td>Acute respiratory distress syndrome\textsuperscript{97,104}</td>
</tr>
<tr>
<td></td>
<td>Tidal volume surveillance\textsuperscript{105}</td>
</tr>
<tr>
<td></td>
<td>Weaning\textsuperscript{106}</td>
</tr>
<tr>
<td>Research</td>
<td>Titrating mechanical ventilator settings\textsuperscript{107}</td>
</tr>
<tr>
<td></td>
<td>Waveform analysis\textsuperscript{108}</td>
</tr>
</tbody>
</table>

Other decisions support platforms exist in the broader ICU context. Such systems include the VISICU and BioSign and Visensia platforms.\textsuperscript{109-111} Simply enabling more widespread and easy access to clinical data has not been shown to improve risk of ICU mortality or length of hospital stay overall.\textsuperscript{111} However in a smaller cohort of subjects, the sickest patients, a reduced mortality risk has been observed, but mortality risk was increased in increased in the less sick patients. Indeed, what is needed is not simply more data, but a method to incorporate a wide variety of data, perform automated analyses and push alerts to clinicians.

3.3 Computational Phenotyping

3.3.1 Limitations of the electronic health record

The electronic health record (EHR) is an essential component as it contains the bulk of patient data available in a hospital. An EHR can contain data from a
physiologic monitor but also affords clinicians to manually input a number of variables. This presents a problem.

The data are often inaccurate or missing which has an adverse effect on predictive power of models.\textsuperscript{112,113} The error included in the EHR can occur at multiple points: during the patient assessment, interpretation of results, transcribing results into the record and even be influenced by billing requirements.\textsuperscript{114} These challenges pose a significant problem when health record data is naively used for clinical research. Though not directly related to mechanical ventilation, an important example of inappropriately utilized health record data is seen in a study of community-acquired pneumonia.\textsuperscript{115} In this study, patients who were admitted to the emergency department and died quickly had large amounts of data omitted from the medical record. Accordingly, repeating this study revealed that the healthiest patients (who also have less data charted in the emergency department) had the highest risk of mortality and the sicker patients had a lower risk, a misleading and erroneous finding.\textsuperscript{116}

Fortunately, the limitations of the EHR can be circumvented. Increasingly, medical devices offer built in connectivity that affords automated recording of physiologic data directly to a server without the need for clinician intervention (apart from making the necessary connections at the bedside). For example, tidal volume (the size of a breath) is an important variable measured during mechanical ventilation. Tidal volume has traditionally been assessed by bedside clinicians by
looking at the data display of the mechanical ventilator. The clinicians would then remember this value, walk to a computer terminal and input the variable into the EHR. Instead, one can record the tidal volume automatically and continuously and store these data in a server for future research. This process has two important benefits: 1) the potential for human error is reduced or altogether mitigated and 2) the data can be recorded at a much higher frequency. Therefore, utilizing automatically recorded data may reduce the risk of data error being incorporated into predictive models.

3.3.2 Time-series data

Most predictive models applied in medical literature are cross-sectional and only consider physiologic features at the present time to predict outcomes at a fixed point in the future. Increasingly, time-series data are recorded during hospitalization as noted previously. Time-series data is defined as “a collection of random variables indexed according to the order they are obtained in time”. Practically, data in the intensive care unit is referred to as time-series if it is collected continuously and at regular intervals. For example, a heart rate signal obtained every 5 seconds would be deemed a time-series data element. But on the other hand, if a clinician records the heart rate at discrete and different time points in the medical record, this would typically not be referred to as time-series data, even though the signal does indeed exist in time. This distinction is important since
decision support algorithms developed from the medical record have been implemented more often than those that incorporate higher frequency data but are associated with important risks and limitations.\textsuperscript{118-120}

In the context of predictive modelling, Kennedy et al describe a generalized approach to analyzing time-series data and incorporating these findings into various models.\textsuperscript{121} The steps proposed to incorporate time-series data are outlined in Table 2.2.\textsuperscript{121}

<table>
<thead>
<tr>
<th>Table 3.2. Proposed steps required to incorporate time-series data into prediction model.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Selecting candidate variables</td>
</tr>
<tr>
<td>2. Specify measurement parameters</td>
</tr>
<tr>
<td>3. Define data format</td>
</tr>
<tr>
<td>4. Define time window duration and resolution</td>
</tr>
<tr>
<td>5. Calculate latent variables for candidate variables not directly measured</td>
</tr>
<tr>
<td>6. Calculate time-series features as latent variables</td>
</tr>
<tr>
<td>7. Create data subsets to measure model performance effects attributable to various classes of candidate variables</td>
</tr>
<tr>
<td>8. Reduce the number of candidate features</td>
</tr>
<tr>
<td>9. Train models</td>
</tr>
<tr>
<td>10. Measure model performance characteristics</td>
</tr>
</tbody>
</table>

### 3.3.3 Phenotype extraction

For features such as age, height, weight, presence or absence of a disease, etc., limited feature extraction can be done. However, for continuous time-series data (heart rate, blood pressure, airway pressure, etc.), data can be transformed or represented as a number of features. These features can vary in complexity.\textsuperscript{122}
Features as simple as the mean, maximum, minimum and variance during a specified time period can provide important information about the state of a mechanically ventilated subject at a given period in time. Where a lot of computation is done is extracting more complex features in continuous data such as linear correlations, stationarity, signal entropy and many more. Recently, Fulcher et al described a computational framework for automated time-series phenotyping.\textsuperscript{122,123} The time-series phenotyping framework can be applied to a variety of research problems, including disease diagnosis, understanding pathophysiology and linking genotypes to phenotypes or diseases.\textsuperscript{114,124,125} However, the framework has thus far not been adequate applied to mechanically ventilated patients admitted to the intensive care unit.

\subsection*{3.4 Opportunities in Mechanical Ventilation}

Medical devices at the bedside collect vast amounts of data, only a fraction of which are entered into the electronic health record and available for clinical decision making. Increasingly, these data are being collected for quality and research purposes at many medical centers in the United States and throughout the world. Thus far, agreement between CDS and clinician recommendations has demonstrated to be generally good in both adult and pediatric mechanically ventilated patients for certain clinical problems.\textsuperscript{106,107,126} In the future, however, a computerized system should not be targeting to equal clinician recommendation
performance, but rather to exceed it. Conceivably, a system could be developed to apply mechanically ventilation in a nearly closed-loop fashion. However, it is more likely that immediate advancements in medicine will be achieved by the incorporation of automated decision support. Medical data from disparate sources is compiled, processed and fed to the clinician at a pertinent time and in a way that is easily interpreted. The utility of continuous physiologic and mechanical ventilator data and the extraction of computational phenotypes has not been thoroughly studied and represents a ripe opportunity for discovery and decision support development during mechanical ventilation.
4. OBJECTIVES

Pediatric mechanical ventilation and more specifically the titration of PEEP is not well understood. PEEP may ameliorate or exacerbate lung injury. PEEP optimization is clinically important and predicting physiologic response is desirable. Automatically recorded time-series physiologic data has important benefits over manually charted data entered into the electronic health record. Increasingly, these data are available during mechanical ventilation in the pediatric intensive care unit.

This work will lay the foundation for critical care computational phenotyping during mechanical ventilation and provide important insights into the fundamental understanding of oxygenation and pulmonary mechanics during mechanical ventilation in children. The long-range objectives of this work are to provide near real-time decision support tools to clinicians for the prediction of oxygenation and pulmonary mechanics response to ventilator changes and provide alerts for subjects likely to benefit from changes. We anticipate that the insights gleaned and algorithms constructed will significantly enhance efforts by researchers and clinicians in critical care and have practical benefits at the hospital level by potentially improving outcomes such as duration of ventilation and cost of care.

Oxygenation, respiratory system compliance and dead-space ventilation are often clinically related but are physiologically distinct in children receiving mechanical ventilation. Oxygenation is a function of pulmonary system
performance, cardiac output, available hemoglobin. On the other hand, compliance is primarily a function of lung mechanics, chest wall compliance and airway resistance; all of which can be affected by pathophysiologic processes. For these reasons, oxygenation, respiratory system compliance and dead-space ventilation will be evaluated separately. It is physiologically reasonable to suspect that the underlying factors affecting improvements or worsening are different during increases and decreases in PEEP and therefore one may suspect that the computational phenotypic expression of certain features will be different. For this reason, separate models are trained for PEEP increases and decreases.

Robust representations of pediatric oxygenation during mechanical ventilation is clinical important but elusive. Oxygenation response depends on underlying causes of disease that span body systems and physiologic processes, creating complex nonlinear relationships among observed measurements. We will probe physiologic time-series data to extract computational phenotypes that are representative of oxygenation response and construct a new theoretical model of oxygenation during mechanical ventilation. The research is centered on three progressive yet complementary objectives and is outlined in the following chapters:

1. Quantify the equilibration time required for oxygenation and respiratory system compliance response following increases in positive end-expiratory pressure (CHAPTER 6).
2. Quantify the empirical probability of positive response to PEEP; the rate at which clinicians are able to identify cases when positive end-expiratory pressure should be increased and decreased based on oxygenation, respiratory system compliance and dead-space ventilation (CHAPTER 7).

3. Extract computational phenotypes from time-series physiologic data and develop a model to predict response to changes in positive end-expiratory pressure (CHAPTER 8).
5. METHODS

In this section, the general methods that applied across objectives. Objective-specific methods are outlined in the chapters that follow as appropriate.

5.1 Subjects

Subjects for this work were considered eligible if they were admitted to the medical-surgical intensive care unit (ICU) at Boston Children’s Hospital, age < 18 years and received invasive mechanical ventilation for a period >24 hours. The study was approved by the institutional review board at Boston Children’s Hospital (IRB-P00021911) and need for written informed consent was waived due to the fact that only existing records would be utilized. All data were collected from January 1, 2015 to February 14, 2017.

5.2 Data collection

Upon subject admission to the ICU, the bedside clinician connected the medical device-interfacing module (IntelliBridge EC10, Philips Healthcare, Andover, MA) between the mechanical ventilator (Servo-I, Getinge AB-Maquet, Gothenburg, Sweden) and the bedside physiologic monitor (IntelliVue MP90, Philips Healthcare, Andover, MA). Data were recorded at a frequency of 0.2 Hz (corresponding to a sample once every five seconds) to a research server. Data could then be extracted with a proprietary data export tool (Analytics Platform V1,
Etiometry Inc., Boston, MA). Time-series data were recorded for the duration of invasive mechanical ventilation in the ICU. Demographic and outcome data were abstracted from the medical record for each subject by implementing SQL code to interact with a relational database (SQL Server V11.0.7, Microsoft Corporation, Redmond, WA). Additionally, the primary diagnosis was recorded according to the International Classification of Diseases published by the World Health Organization (Revisions 9 and 10, Clinical Modification).128

5.3 Data aggregation and database construction

A retrospective cohort of mechanically ventilated children admitted to the pediatric intensive care unit at Boston Children’s Hospital were utilized. Physiologic monitor (heart rate, respiratory rate, plethysmographic oxygen saturation and blood pressure), mechanical ventilation (25+ variables including: \( P_{\text{peak}} \), \( P_{\text{EEP}} \), inspired oxygen concentration, pulmonary compliance, airway resistance, etc.), demographic and outcome data will be utilized to construct the parent database. A multivariate time-series with \( P \) variables and length \( T \), will be represented as a matrix \( \mathbf{X} \in \mathbb{R}^{P \times T} \). An schematic of the database is depicted in Figure 5.1.
Figure 5.1. Schematic of the database.

For two subjects, the different data components are depicted. For outcome data, LOS = length of stay, the matrix $\mathbf{X} \in \mathbb{R}^{P \times T}$, the processed matrix contains only those variables that are included in the analysis is processed with interpolation and filtering methods, results represent those phenotype features that are extracted from each variable $P$.

An example of a mechanically ventilated subject and associated continuous data streams is depicted in Figure 5.2.
Figure 5.2. Example of the continuous data streams obtained during mechanical ventilation.

5.4 Signal preprocessing

Although dozens of variables are collected from the physiologic monitor and mechanical ventilator, not all variables are collected on every subject. For example, arterial blood pressure requires the insertion of an indwelling arterial catheter.\textsuperscript{129,130} Indwelling arterial catheters carry an increased risk of thrombus, embolism, bleeding and hospital acquired infection.\textsuperscript{131,132} For these reasons, invasive blood pressure (as is measured with an indwelling arterial catheter) is only applied to a small proportion of subjects and for a limited amount of time. Therefore, these data were not reliably and continuously recorded for the population and had to be eliminated. A manual inspection of all available data was completed on the
population to ensure selection of those variables that were recorded continuous and reliably for all subjects in the dataset.

The following variables were found to not be routinely captured at a high frequency and large gaps in data were frequently observed: inspiratory airway resistance, expiratory airway resistance invasive and non-invasive blood pressure. Therefore, these variables were excluded from the time-series analysis but still included as a static feature as part of the description of the population. In all, a total of 22 variables were included in the processed data matrix; data are outlined in Table 3.1.
<table>
<thead>
<tr>
<th>Name</th>
<th>Abbreviation</th>
<th>Units</th>
<th>Typical Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak inspiratory pressure</td>
<td>$P_{\text{peak}}$</td>
<td>cmH2O</td>
<td>22</td>
</tr>
<tr>
<td>Positive end-expiratory pressure</td>
<td>$\text{PEEP}$</td>
<td>cmH2O</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory rate (total)</td>
<td>$R_{\text{total}}$</td>
<td>breaths/min</td>
<td>20</td>
</tr>
<tr>
<td>Respiratory system compliance</td>
<td>$C_{RS}$</td>
<td>ml/kg/cmH2O</td>
<td>0.5</td>
</tr>
<tr>
<td>Respiratory rate (spontaneous)</td>
<td>$R_{\text{spontaneous}}$</td>
<td>breaths/min</td>
<td>15</td>
</tr>
<tr>
<td>Fraction of inspired oxygen</td>
<td>$\text{FiO}_2$</td>
<td>Fraction</td>
<td>0.4</td>
</tr>
<tr>
<td>Expired minute ventilation</td>
<td>$V_e$</td>
<td>L/kg/min</td>
<td>0.08</td>
</tr>
<tr>
<td>Inspired minute ventilation</td>
<td>$V_i$</td>
<td>L/kg/min</td>
<td>0.08</td>
</tr>
<tr>
<td>Spontaneous minute ventilation</td>
<td>$V_{e,\text{spontaneous}}$</td>
<td>breaths/min</td>
<td>0.06</td>
</tr>
<tr>
<td>Mean airway pressure</td>
<td>$P_{\text{mean}}$</td>
<td>cmH2O</td>
<td>10</td>
</tr>
<tr>
<td>End-tidal carbon dioxide</td>
<td>$P_{\text{aCO}_2}$</td>
<td>mmHg</td>
<td>40</td>
</tr>
<tr>
<td>Carbon dioxide elimination</td>
<td>$V_{\text{CO}_2}$</td>
<td>ml/kg/min</td>
<td>5</td>
</tr>
<tr>
<td>Expired tidal volume</td>
<td>$V_{e}$</td>
<td>ml/kg</td>
<td>6</td>
</tr>
<tr>
<td>Inspired tidal volume</td>
<td>$V_{i}$</td>
<td>ml/kg</td>
<td>6</td>
</tr>
<tr>
<td>Pressure in the first 100ms</td>
<td>$P_{100}$</td>
<td>cmH2O</td>
<td>0.5</td>
</tr>
<tr>
<td>End-expiratory flow</td>
<td>$V_{ee}$</td>
<td>L/kg/min</td>
<td>0.001</td>
</tr>
<tr>
<td>Ventilator work of breathing</td>
<td>$W_{OB,\text{vent}}$</td>
<td>Joules/L</td>
<td>1</td>
</tr>
<tr>
<td>Ambient pressure</td>
<td>$P_b$</td>
<td>mmHg</td>
<td>760</td>
</tr>
<tr>
<td>Heart rate</td>
<td>$HR$</td>
<td>beats/min</td>
<td>100</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td>$Sp_{O_2}$</td>
<td>%</td>
<td>95</td>
</tr>
<tr>
<td>Estimate of arterial oxygen</td>
<td>$P_{aO_2,\text{est}}$</td>
<td>mmHg</td>
<td>80</td>
</tr>
<tr>
<td>Dead-space fraction</td>
<td>$V_{d}/V_{i}$</td>
<td>Fraction</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Both the physiologic monitor and mechanical ventilator offer built-in preprocessing that is inclusive of artifact detection. However, these signals are often still corrupted by noise and artifact. Since the data included in the present work
were generated from real-world medical cases, interruptions in select signals or monitoring occurred from time to time. In Figure 5.3, the steps used to handle these cases, where $x$ is the variable of interest, $m(x)$ is a function to identify length of missing data.

![Diagram](image.png)

*Figure 5.3. Algorithm to identify and handle missing data.*
5.5 Interpolation of missing data

In order to apply an interpolation method that best approximated the missing data, a series of tests were performed. The testing involved taking a sample of real data, eliminating a portion of the real data to simulate a gap, applying various interpolation methods (linear, piecewise cubic, nearest and previous). This test was repeated for different variables and 2 time scales (10 second and a 2 minute gap). An example of the interpolation methods applied to a 10 second gap of a single physiologic variable is shown in Figure 5.4.
Figure 5.4. Example of interpolation algorithms on end-tidal CO$_2$ with 10 seconds of missing data.

It is apparent, that for a 10 second section of missing data, the linear interpolation method performed very well. An example of the interpolation methods applied to a 2-minute gap of a single physiologic variable is shown in Figure 3.5.
As is depicted in Figure 5.5, the increased duration of the missing data reduced the capacity of any of the interpolation methods tested to accurately portray the missing data. The performance of the linear and nearest interpolation methods was similar at this duration of missing data. However, since the majority of missing data in the dataset was on the order of seconds and not minutes, interpolation was implemented using a 1-dimentional linear method. An important feature of working with pediatric subjects is the difference in physiologic parameters as a
function of size, weight and sex making it difficult to apply a simple band-pass filter. Further, most of the work in time-series critical care artifact detection surrounds waveform signals from the electrocardiogram.

5.6 Filtering physiologic time-series data

Although there is a paucity of literature directing approaches for time-series mechanical ventilation data artifact detection, band-pass, low-pass and Savitzky-Golay filters have been applied to time-series data. For heart rate, a band-pass filter was implemented at conditions representative of physiologic plausibility (30 to 300 bpm) and a low-pass filter was applied to respiratory rate. For other variables, several filters were tested in order to ascertain a method that achieved the best balance of 1) reduction in what could be identified clinically as artifact and 2) the preservation of local data phenomenon. In Figure, 3.6 different filtering methodologies are depicted.
Figure 5.6. Example of filtering algorithms on peak inspiratory pressure ($P_{peak}$).

Of note, the moving average algorithm removed artifact (spike detected at ~44 minutes in Figure 5.6) but completely obliterated the local data phenomenon of the signal. The robust local regression and Savitzky-Golay filters performed reasonable well at reducing the artifact (~44 minutes in Figure 5.6). However, the Savitzky-Golay filter was superior in its ability to preserve the local data phenomenon. Therefore, the Savitzky-Golay filter (frame length = 5) was selected as it offered the
best balance of reducing artifact while preserved the local data phenomenon. This filter was applied on time-series data and was designed to sufficiently reduce noise and artifact while preserving local data phenomenon that could be obliterated with alternative filtering algorithms such as moving average or other methods. An example of the filter applied to tidal volume and peak inspiratory pressure is shown in Figure 5.7.

Figure 5.7. Example of filtering applied to mechanical ventilation variables. A: tidal volume (Vt) and B: peak inspiratory pressure (P_{peak}).
5.7 Data normalization

Normalization of individual parameters is important in a pediatric population since signals are expected to change as the child grows. For instance, the expected heart rate of a newborn may be 140 bpm, but for a 16-year old child, the same value of 140 bpm would indicate a significant physiologic derangement. Therefore, data were normalized to either body weight (for respiratory parameters tidal volume, minute ventilation, carbon dioxide elimination, end-expiratory flow rate) and Z-scores were computed for heart rate and respiratory rate. A Z-score is defined by the following:

$$Z = \frac{(x - \mu)}{\sigma}$$

Where $x$ is the observed measurement, $\mu$ is the expected measurement from a population mean and $\sigma$ is the standard deviation of the population.

5.8 Identification and labeling of cases
Each individual subject time-series will include several discrete cases. A case is defined as a time period surrounding a change in PEEP on the mechanical ventilator. These cases occur when the bedside clinician decided that a change in PEEP was required and implemented this change. In Figure 5.8, a schematic of the identification of this time point and extraction of predictor data (information preceding the PEEP change) and target data (information about the outcome of the PEEP change) is shown. Let us say that we have $N$ multivariate time series, each with $C$ cases, $P$ variables and $K$ binary labels. The $T$ vectors are stacked in $X$, to one vector $x$. We are left with $N$ labeled cases $\{x_i, y_i\}_{i=1}^N$, where $x_i \in \mathbb{R}^F$, $y_i \in \{0,1\}^K$, $F = PC$. Each case will be mapped over a clinically relevant binary space. The areas of clinical importance are oxygenation, respiratory system compliance and dead-space fraction. In the following sections, these factors are described.

*Figure 5.8. Example of predictor and target time window.*
5.9 Markers of pediatric lung health

During pediatric mechanical ventilation, composite indices of oxygenation, respiratory system compliance and dead-space ventilation fraction are useful to quantify severity of lung injury, gauge response to therapy and predict risk of mortality.\textsuperscript{34,144-147}

In the sections that follow, oxygenation, respiratory system compliance and dead-space ventilation fraction will be discussed and later utilized as important metrics of illness severity in Chapters 6-8.

5.9.1 Oxygenation

Oxygenation status of subjects is best described in relation to the proportion of inspired oxygen: $\frac{SpO_2}{FiO_2}$, where $SpO_2$ is the oxygen saturation as measured by the bedside pulse oximeters and $FiO_2$ is the fractional inspired concentration of oxygen delivered to the patient by the mechanical ventilator.\textsuperscript{148,149}

The SF ratio is limited since it ignores the mean airway pressure, an important mediator of oxygenation in mechanically ventilated children. Therefore, the oxygenation index ($OI$) is often applied.\textsuperscript{150}

$$OI = \frac{P_{mean} \times FiO_2}{PaO_2}$$
Where $P_{\text{mean}}$ is the mean airway pressure applied, $FiO_2$ is the fraction of inspired oxygen expressed as a percentage and $PaO_2$ is the partial pressure of oxygen in the arterial blood.

One of the limitations of $OI$ is the fact that an arterial blood sample is required to obtain $PaO_2$\textsuperscript{151}. Therefore, a clinical surrogate, the oxygen saturation index ($OSI$) that can be continuously applied has been proposed and validated in mechanically ventilated children\textsuperscript{152}. The $OSI$ utilized plethysmographic oxygen saturation ($SpO_2$).

The advantage of $SpO_2$ over $PaO_2$ is that it is non-invasive and continuously recorded.

$$OSI = \frac{P_{\text{mean}} \times FiO_2}{SpO_2}$$

Where $SpO_2$ is the oxygen saturation as measured by plethysmography.

### 5.9.2 Respiratory system compliance

During mechanical ventilation, the interaction between the device and the child is primarily dependent on the mechanical properties of the pulmonary system. The Equation of Motion, which states that pressure required to deliver a gas volume into the lungs ($P_T$) is a function of the elastic ($P_E$) and resistive ($P_R$) properties of the whole respiratory system\textsuperscript{1}:

\begin{itemize}
  \item Since the inertial forces are negligible during mechanical ventilation, this term has been eliminated from the description for the sake of brevity
\end{itemize}
\[ P_T = P_E + P_R \]

Pulmonary compliance \((C)\) and tidal volume \((V_T)\) determine the elastic properties of the respiratory system and the flow \((V)\) and airway resistance \((R)\) determine the resistive properties:

\[ P_E = \frac{V_T}{C} \]
\[ P_R = \dot{V} \times R \]

Combined:

\[ P_T = \left( \frac{V_T}{C} \right) + \dot{V} \times R \]

Therefore, \(V_T, C, V\) and \(R\) determine the pressure required to deliver a breath during ventilation. Pulmonary compliance is defined as the change in volume from beginning to the end of the respiratory cycle \((\Delta V)\) per unit change in pressure \((\Delta P)\).

\[ C = \frac{\Delta V}{\Delta P} \]
\[ C = \frac{V_T}{P_T} \]

5.9.3 Dead-space fraction

In general, the dead-space fraction of the respiratory system is a metric of cardiopulmonary system efficiency and a marker of disease severity during mechanical ventilation. It describes the proportion (fraction) of inspired gas that is involved in gas exchange. The fraction ranges from 0 to 1.0, where low numbers mean that a smaller portion of the inspired breath is not involved in gas exchange and higher values mean the
majority of the breath does not exchange $\text{O}_2$ or $\text{CO}_2$. In general, a healthy patient who is not mechanically ventilated with a dead-space fraction $\sim 0.3$, severely ill mechanically ventilated children can have a dead-space fraction from 0.4 – 0.9. Although levels higher than 0.8 are infrequently seen and often indicative of extremely severe disease

$$F_{\text{ECO}_2} \times V_T = F_{\text{ICO}_2} \times V_D + F_{\text{ACO}_2} \times V_A$$

Volume of $\text{CO}_2$ in mixed expired air is equal to the volume of $\text{CO}_2$ coming from dead space plus the volume of $\text{CO}_2$ coming from the alveoli. Where $F =$ concentration expressed as a fraction, $E$ is the mixed expired, $I$ is the inspired and $A$ is the alveolar gas.

Since $F_{\text{ICO}_2}$ is approximately equal to zero, the first term is eliminated. Then, substituting $V_d$ for $(V_T - V_{D\text{CO}_2})$ and $F_{\text{ETCO}_2}$ for $F_{\text{ACO}_2}$.

$$F_{\text{ECO}_2} \times V_T = F_{\text{ETCO}_2}(V_T - V_{D\text{CO}_2})$$

$$F_{\text{ECO}_2} \times V_T = F_{\text{ETCO}_2} \times V_T - F_{\text{ETCO}_2} \times V_{D\text{CO}_2}$$

$$V_{D\text{CO}_2} \times F_{\text{ETCO}_2} = V_T(F_{\text{ETCO}_2} - F_{\text{ECO}_2})$$

$$\frac{V_{D\text{CO}_2}}{V_T} = \frac{F_{\text{ETCO}_2} - F_{\text{ECO}_2}}{F_{\text{ETCO}_2}}$$

And since $F_{\text{CO}_2} = \frac{P_{\text{CO}_2}}{P_{\text{total}}}$

$$\frac{V_D}{V_T} = \frac{P_{\text{ETCO}_2} - P_{\text{ECO}_2}}{P_{\text{ETCO}_2}}$$

And since $P_{\text{ECO}_2}$ is not typically computed automatically by the ventilator, it was calculated.

$$P_{\text{ECO}_2} = \left(\frac{V_{\text{CO}_2}}{V_E}\right) \times (P_b \times P_{\text{H}_2\text{O}})$$
Substituting \( \left( \frac{V_{CO_2}}{V_E} \right) \times (P_b - P_{H2O}) \) for \( P_{ECO_2} \).

\[
V_D = \frac{P_{ETCO_2} - \left( \frac{V_{CO_2}}{V_E} \right) \times (P_b - P_{H2O})}{P_{ETCO_2}}
\]

Assuming \( P_b \) is equal to 760 mmHg and since the gas was heated to 37°C and fully saturated, \( P_{H2O} \) is equal to 47 mmHg.

\[
V_D = \frac{P_{ETCO_2} - \left( \frac{V_{CO_2}}{V_E} \right) \times (713)}{P_{ETCO_2}}
\]

5.10 Computational phenotype extraction

The term computational phenotype is a relatively new term derived from *computational*, relating to the process of mathematical computation, especially as it relates to the use of computers and *phenotype*, an individual’s observable characteristics that result from the interaction of its genotype with the environment. The word phenotype comes from the Greek ‘*phainien*’ meaning to show and ‘*typoes*’ meaning type. A *computational phenotype* is a computable definition of a characteristic, condition or medical event that is derived from healthcare data processed by a computer.\(^{153}\) Computational phenotyping is an emerging area of research and has begun to be applied in some areas of medicine.\(^{154}\)
Although thousands of methods and iterations exist in the literature, a set of ~200 methods (including autocorrelation, auto-mutual information, stationarity, entropy, correlation dimension, linear and non-linear model fits, and measures from the power spectrum) is enough to form a concise summary of the different behaviors of time-series data. Fulcher et al, describe a methodology to quantify a wide range of time-series properties and highlights the opportunity to extract computational phenotypes from medical time-series data. These techniques have been applied in some areas of bioengineering, but applications on medical time-series data have not yet been studied.

In the present work, a variable map for matrix X is extracted from the function $g : \mathbb{R}^{P \times t} \rightarrow \mathbb{R}^F$ where $g$ is a function utilized to extract various phenotypes from the medical time-series data and mapped to a vector of features $\mathbf{x} \in \mathbb{R}^F$ and stored in each subject's respective result array.

5.11 Phenotype Selection

Because a multitude of phenotypes are extracted from the physiologic time-series data, it is necessary to select a small subset that is most important. In general, a methodology for feature selection, or in this case, phenotype selection is implemented with respect to design considerations, interpretability and predictive
accuracy. Design considerations include computational cost; memory usage and speed. Interpretability is an important component of working with medical data since it is desirable to maintain an ability to understand what factors are contributing to the model (or at least when practicable to do so). Predictive accuracy is principally optimized by reducing overfitting, which can readily happen with too many features. Practically, overfitting pertains to the generalizability of findings to data outside the test set. In some cases, data reduction is implemented in order to transform many features into a single variable or input. Principal component analysis (PCA) and discriminant analysis (DA) are some examples. These procedures can reduce the number of features required to construct a model, and therefore decrease the likelihood of overfitting the model. However, implementing PCA and DA make it difficult to interpret the model after it has been constructed.

On the other hand, feature selection, whereby a small subset of features or phenotypes are taken from a larger set. With feature selection, one can both reduce the number of variables and preserve the interpretability of the model (if applicable).

In general, there are two types of feature selection algorithms: filters and wrappers. A filter feature selection algorithm uses general information about the variables to select those most associated with the target. This standard method will often utilize univariate analysis, whereby ability of each variable to discriminate between groups is quantified with a p-value. However, this does not consider the
interaction between features or the fact that selected features may contain redundant information. In the latter case, features that are passed through may not actually be needed.\textsuperscript{161}

5.11.1 Least Absolute Shrinkage and Selection Operator (LASSO)

Least absolute shrinkage and selection operator (LASSO) is a regression method that works by penalizing the size of regression coefficients. By doing so, some (or many) parameter estimates can be exactly zero. As the penalty increases, the closer to zero the estimates become. LASSO has been applied in other areas of medical research and yielded selected features that provide good prediction models.\textsuperscript{162}

For a nonnegative value of $\lambda$, LASSO solves the following problem.

$$
\min_{\beta_0, \beta} \left[ \frac{1}{2N} \sum_{i=1}^{N} (y_i - \beta_0 - x_i^T \beta)^2 + \lambda \sum_{j=1}^{p} |\beta_j| \right]
$$

Where, $N$ is the number of observations, $y_i$ is the target at observation $i$, $x_i$ is the input data vector of length $p$ at observation $i$, $\lambda$ is a nonnegative parameter corresponding to a single value of Lambda and both $\beta_0$ and $\beta$ are scalar vectors of length $p$.

After the LASSO procedure is completed on the phenotype data, a subset of phenotypes is identified and utilized to train the prediction models. Details of the models tested, and validation procedures are described in Chapter 8.
6. EQUILIBRATION TIME REQUIRED FOR RESPIRATORY SYSTEM COMPLIANCE AND OXYGENATION RESPONSE FOLLOWING CHANGES IN POSITIVE END-EXPIRATORY

6.1 Abstract

Objective: Increases in positive end-expiratory pressure (PEEP) are implemented to improve oxygenation through the recruitment and stabilization of collapsed alveoli. However, the time it takes for a PEEP change to have maximum effect upon oxygenation and pulmonary compliance has not been adequately described in children. Therefore, we sought to quantify the time required for oxygenation and pulmonary system compliance changes in children requiring mechanical ventilation.

Design: Retrospective analysis of continuous data

Setting: Multidisciplinary intensive care unit of a pediatric university hospital

Patients: Mechanically ventilated pediatric subjects

Interventions: A case was eligible for analysis if during a 90-minute window following an increase in PEEP, no other changes to the ventilator were made, ventilator and physiologic data were continuously available and a positive oxygenation response was observed. Time to 90% ($T_{90}$) of the maximum change in oxygenation and compliance was computed. Differences between oxygenation and
compliance $T_{90}$ were compared using a paired t-test. The effect of severity of illness (by oxygen saturation index; OSI) upon oxygenation and compliance was analyzed.

Measurements and Main Results: A total of 200 subjects were enrolled and 1150 PEEP change cases were analyzed. Of these, 54 subjects with 171 PEEP change case were included in the analysis (67% were responders).

Changes in dynamic compliance ($T_{90} = 38$ minutes) preceded changes in oxygenation ($T_{90} = 71$ minutes; $P < 0.001$). Oxygenation response differed depending on severity of illness quantified by OSI; lung dysfunction was associated with a longer response time ($P = 0.001$).

Conclusions: $T_{90}$ requires 38 and 71 minutes for dynamic pulmonary compliance and oxygenation respectively; the latter was directly observed to be dependent upon severity of illness. To our knowledge, this is the first report of oxygenation and compliance equilibration data following PEEP increases in pediatric mechanically ventilated subjects.
6.2 Introduction

Increases in positive end-expiratory pressure (PEEP), with concomitant increases in plateau pressure are frequently applied to mechanically ventilated subjects in order to improve oxygenation through the recruitment and stabilization of collapsed alveoli. Thus, in the atelectatic lung, increasing PEEP effectively permits the modification of functional residual capacity (FRC). Following increases in PEEP and improvement in FRC, reductions in physiologic dead-space fraction, shunt fraction and ventilation/perfusion mismatch are often observed. Recruitment maneuvers, whereby significant increases in airway pressure are applied, have been demonstrated to be safe in the pediatric population. However, there is no consensus on the utility of such maneuvers as evidence has yet to demonstrate a clear benefit in terms of a reduction in duration of ventilation or in hospital mortality. Therefore, the widespread application of recruitment maneuvers by sustained inflation is not recommended. Application of PEEP in adult subjects with lung injury has been shown to improve oxygenation, pulmonary compliance and functional lung recruitment. Although long-term benefits of very high levels of PEEP are not needed and may be injurious in some cases. In contrast to recruitment maneuvers, clinicians often titrate PEEP and plateau pressures incrementally (perhaps 1-4 cmH₂O) to achieve oxygenation targets.
However, the time required at the new PEEP level for maximum physiologic effect to be observed is not well understood in pediatric subjects.\textsuperscript{168,169} Additional research is required to optimize the timing methods of PEEP titration.\textsuperscript{9,170} Furthermore, there are no data reporting the time required to observe maximum therapeutic goal such as improvement in oxygenation and/or respiratory system compliance ($C_{rs}$) effects after increasing PEEP in mechanically ventilated children. Therefore, we sought to describe the time required to achieve maximum oxygenation and dynamic compliance following PEEP increases in children with respiratory failure as well as assess the effects of severity of lung injury on equilibration times.

6.3 Materials and Methods

Subjects were eligible for inclusion in the study if they were admitted to the pediatric intensive care unit (PICU), were less than 18 years of age, were mechanically ventilated > 24 hours and demonstrated hypoxic respiratory failure during the course of mechanical ventilation (oxygen saturation index > 5).

6.3.1 Data collection

Upon subject admission to the ICU a medical device-interfacing module (IntelliBridge EC10, Philips Healthcare, Andover, MA) was used to connect the mechanical ventilator (Servo-I, Getinge AB-Maquet, Gothenburg, Sweden) and the bedside physiologic monitor (IntelliVue MP90, Philips Healthcare, Andover, MA).
The ventilator was calibrated according to manufacturer’s recommendations and tubing compensation was activated for all subjects. Data were recorded at a frequency of 0.2 Hz to a research server for the duration of invasive mechanical ventilation in the ICU. Data were then extracted with a data export tool (Analytics Platform V1, Etiometry Inc., Boston, MA). Demographic and outcome data were abstracted from the electronic medical record for each subject and the diagnosis was recorded according to the International Classification of Diseases published by the World Health Organization (Revisions 9 and 10, Clinical Modification) and binned to either primary respiratory, surgical procedure, neurologic, sepsis or ‘other’.128

6.3.2 Data aggregation, database construction and signal preprocessing
Physiologic parameters (heart rate, respiratory rate, oxygen saturation and blood pressure), mechanical ventilation variables (including: $P_{\text{peak}}$, PEEP, inspired oxygen concentration, $C_{\text{RS}}$, airway resistance, etc.), demographic and outcome data were utilized to construct the database. Both the physiologic monitor and mechanical ventilator offer built-in preprocessing that is inclusive of artifact detection. However, these signals can still be corrupted by noise and artifact.139 A band-pass filter was applied to physiologic data in order to remove data beyond the physiologic range according to established methods.142 For the mechanical ventilator data, a 1-minute median filter was applied.

6.3.3 Identification and analysis of individual PEEP cases
In order to adequately assess the time course of oxygenation and compliance changes, the time points at which PEEP was increased were identified. A case was defined as a period of 90-minutes following an increase in PEEP. Cases were eligible for inclusion in the analysis if no other ventilator changes were made (including a fixed delta pressure, no changes in respiratory rate or inspiratory time, $\text{FiO}_2$ was permitted to be changed) during the 90-minute window. Responders were defined as a sustained improvement in oxygenation following the increase in PEEP. Oxygenation (defined as oxygen saturation index; $\text{OSI} = \text{FiO}_2 \times \text{MAP} \times 100 / \text{SpO}_2$) and respiratory system compliance ($C_{RS}$) were smoothed by applying a 5-minute median filter. Next, the maxima for $\text{OSI}$ and $C_{RS}$ were identified at the 90-minute point. The percentage increases at 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80 and 90 minutes were recorded for both $C_{RS}$ and $\text{OSI}$. Each case was stratified by severity of hypoxemic lung dysfunction by $\text{OSI}$ according to the PALICC consensus on pediatric acute respiratory distress syndrome.$^9$

### 6.3.4 Statistical analyses

The D’Agostino and Pearson omnibus test was used to assess the normality of the data. Normally distributed data are presented as mean ± SD and non-normally distributed, continuous variables are presented as median (interquartile range). Data were fit to a one-term power series similar to previous studies in adult subjects and is shown in the summary figures.$^{171}$ A paired t-test was utilized to compare the
equilibration times between OSI and $C_{RS}$ as well as the differences of OSI equilibration between subjects with and without hypoxic lung dysfunction. Data aggregation, cleaning and analyses were conducted using MATLAB (V9.1.0.441655, The Mathworks Inc., Natick, MA). Statistical analyses were performed using Prism® (V6.0h, GraphPad Software, Inc., La Jolla, CA) and SPSS (V23.0.0, IBM Corporation, Armonk, NY).

The protocol was approved by the institutional review board and need for informed consent was waived since the study was limited to the review of health information previously recorded.

6.4 Results

A total of 200 subjects were enrolled in the study and 1150 PEEP change cases were analyzed. Of these, 171 PEEP change cases in 54 subjects met quality and data standards and were included in the analysis. The median (IQR) number of cases per subjects was 2 (1-4). A description of the population is shown in Table 4.1.
Table 6.1. Description of the study population. *Continuous values are expressed as median (interquartile range) unless otherwise indicated.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (IQR)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>2.4 (0.8 - 8.7)</td>
</tr>
<tr>
<td>Sex, n female (%)</td>
<td>97 (49)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>10.8 (7.5 - 29)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>77 (63 - 116)</td>
</tr>
<tr>
<td>CMV duration (days)</td>
<td>5.1 (2.3 - 7.9)</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>9.2 (5.0 - 19.3)</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>10.6 (3.3 - 30.5)</td>
</tr>
<tr>
<td>Primary diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>56 (28)</td>
</tr>
<tr>
<td>Surgical</td>
<td>46 (23)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>25 (12.5)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>11 (5.5)</td>
</tr>
<tr>
<td>Other</td>
<td>60 (30)</td>
</tr>
</tbody>
</table>

The proportion of PEEP increases that were 1, 2 and ≥ 3 cmH₂O were 92%, 7% and 1% respectively. Synchronized intermittent mandatory ventilation was utilized in all subjects (54% of cases utilized pressure targeted modes and 46% of cases were volume targeted). In responders, $T_{90}$ was 38±27 minutes and 71±12 minutes for compliance and oxygenation respectively ($P < 0.001$). Overall, there was a reduction in OSI by 13% following the PEEP increase in responders ($P = 0.004$) and $SpO_2/FiO_2$ increased from 223 to 246 ($P < 0.001$). $C_{RS}$ improved 0.49 ml/cmH₂O/kg (0.41–0.61) to 0.56 ml/cmH₂O/kg (0.42–0.70); $P < 0.001$. HR decreased following the PEEP change from 120 bpm (106 – 138) to 118 bpm (103
– 136) (P = 0.02). Mean blood pressure and carbon dioxide elimination were similar preceding and following the PEEP increase in responders: 74 mmHg (61 – 86) versus 73 mmHg (61 – 85) (P = 0.64) and 5.2 ml/kg/min (4.2 – 6.5) versus 5.0 ml/kg/min (4.2 – 6.9) (P = 0.60). Spontaneous respiratory rate (RRsp) was similar before and after the PEEP change (P = 0.07). The proportional increase in OSI and CRS for responders is depicted in Figure 4.1A.

Figure 6.1. Comparison of increases in dynamic pulmonary compliance and oxygenation. The mean±SD are denoted by the circles and whiskers, δ(%) is the change in either oxygen saturation index (OSI = FiO2 x MAP x 100 / SpO2) or respiratory system compliance (CRS) relative to the maxima at each time point. A: responders (those who had an increase in oxygenation following PEEP increase), OSI improved by 13% and CRS improved by 14% during the monitoring time-frame in responders, B: non-responders (no change in oxygenation or worsening following PEEP increase).

Oxygenation response differed depending on severity of illness; OSI > 5 was associated with a longer response time (P = 0.001, Figure 4.2). In non-responders,
$T_{50}$ was 65±12 and 64±13 for oxygenation and $C_{RS}$ respectively ($P = 0.68$). The proportional decreases in oxygenation and $C_{RS}$ are depicted in Figure 4.1B.

Figure 6.2. Time required to achieve increases in $\text{SpO}_2/\text{FiO}_2$. Time required to achieve increases in $\text{SpO}_2/\text{FiO}_2$ following an increase in PEEP dependent upon severity of illness by oxygen saturation index. The mean±SD are denoted by the circles and whiskers. $\delta(\%)$ is the change in $\text{SpO}_2/\text{FiO}_2$ relative to the maxima observed.
6.5 Discussion

Understanding the time it takes to realize the full effect of a PEEP change is clinically important, both to allow sufficient time to observe maximum clinical benefits as well as prevent excessive delay between adjustments or additional interventions. In responders, changes in $C_{RS}$ preceded improvements in oxygenation and the time to oxygenation equilibration was longer for subjects with hypoxic lung injury. In non-responders, $C_{RS}$ and oxygenation decreased simultaneously.

Nearly all studies assessing equilibration times of oxygenation are focused on adult subjects and most evaluate response following changes in $FiO_2$ without changes PEEP. Fildissis et al examined adult ICU subjects and determined the equilibration time to be just over 8 minutes after increasing the $FiO_2$ by 0.3.\textsuperscript{172} In adult mechanically ventilated subjects, Cakar et al demonstrated that 90\% of oxygenation response occurs within 5 minutes after increasing $FiO_2$ by 0.2.\textsuperscript{173} For PEEP maneuvers, Tugrul et al determined that the average equilibration time for oxygenation was 20 minutes in adults with acute respiratory distress syndrome following a pressure-volume maneuver and setting the PEEP 2 cmH$_2$O above the lower inflection point.\textsuperscript{171} They also note that the time to equilibration varied from 1 to 70 minutes. Important differences exist between Tugrel et al and the present study. First, a much greater increase in PEEP as well as the application of the pressure-volume maneuver, likely resulted in more aggressive and rapid
recruitment. In the current study, the majority of PEEP increases were only 1 and 2 cmH₂O. This may partially account for the much longer average equilibration time noted in the current study, 71 minutes versus the 20 minutes observed by Tugrul et al. Second, the patient populations are different. Pediatric patients with ARDS have unique physiologic characteristics when compared with adult subjects including a more compliant chest wall, retained surfactant activity and fundamentally different immune system responses. Further, oxygenation is an important clinical target in pediatric subjects as it is associated with lower mortality during acute respiratory distress syndrome versus mechanics in the adult literature.

There are limited data describing the duration of time required to maximally decrease oxygenation and \( C_{RS} \) following modest PEEP changes. As such, the observation that maximal decreases in OSI and \( C_{RS} \) occur essentially simultaneously will need to be reproduced in future investigations.

In the present study, it was anticipated that the equilibration times following PEEP maneuvers would be longer than those reported for \( FiO_2 \) maneuvers. Increases in PEEP, with a concomitant increase in plateau pressure are implemented to improve oxygenation through the recruitment and stabilization of collapsed alveoli. We documented an increase in \( C_{RS} \) from 0.49 ml/cmH₂O/kg (0.41–0.61) to 0.56 ml/cmH₂O/kg (0.42–0.70) that may be associated with an increase in end-expiratory lung volume. It is unclear that this 14% improvement in
$C_{RS}$ would be clinically meaningful in all subjects. In subjects with low $V_t \,(4\text{-}6\text{ml/kg}),$ a 14% improvement may be meaningful and afford further titration of mechanical ventilation but on the other hand, an improvement in compliance for a child receiving 7-8ml/kg may not be important. In either case, following improvements in $C_{RS}$ additional time is required to transport oxygen to the alveolar-capillary membrane as redistribution of blood flow within the lungs may occur and this likely explain the delayed improvement in oxygenation.

The effects of increased $PEEP$ on cardiac output should be considered as well. Although there are no clear data in the pediatric literature, it is conceivable that increases in $PEEP$ (and intrathoracic pressure) can reduce cardiac output and have the effect to prolong or interfere with the equilibration time to improved oxygenation. However, since the $PEEP$ changes in the present study were relatively modest, it is not clear that this would play a significant role in the observed equilibration times. In adults with diffuse lung injury, reduction in cardiac output may improve oxygenation in some cases.\textsuperscript{178} In this case, reduction in blood flow may primarily be in regions of poorly ventilated lung tissue, having the effect to reduce shunt and improve $V/Q$. Although we did not directly measure cardiac output in the present study, crude surrogates ($HR, BP$, carbon dioxide elimination; $VCO_2$) were assessed. We did not observe clinically important differences in HR, blood pressure or $VCO_2$ following $PEEP$ increases in responders and therefore the effect of reduced cardiac output is unlikely. More work in this area is indicated.
There are important procedural limitations to the present study that should be considered. First, the study was retrospective in nature and therefore an investigational protocol that guided the titration of PEEP was not utilized. However, decisions about when and how much to increase the PEEP were made by the bedside clinicians who generally adhere to an institutional guideline for the care of children with PARDS. Admittedly, this introduces variability in care. However, the trial was designed to be a pragmatic assessment of bedside care and the incorporation of clinician-to-clinician variability reflects usual care. Second, we did not measure oxygenation invasively by arterial blood gas sampling. OSI and S/F have been demonstrated to be acceptable surrogates for oxygenation index (OI) and $PaO_2/SpO_2$ in children with lung injury who have $SpO_2 \leq 97\%$. The agreement between invasive and non-invasive measures of oxygenation is slightly worse as $SpO_2$ approaches the non-linear portion of the oxyhemoglobin saturation curve ($SpO_2 96-97\%$). However, the use of OSI and S/F is generally accepted in the range 80-97%. Third, we utilized the volume calculation available on the mechanical ventilator (Servo-I) that may underestimate the true volumes and affect the accuracy of $C_{RS}$ measurements. However, since the primary objective of the current work was to quantify the change in $C_{RS}$, and significant changes in tubing compliance may not be likely to occur over a short time period, the effects of this limitation on the equilibration time is limited. Although the absolute measurements of $C_{RS}$ should be interpreted with caution, especially in infants and young children.
Fourth, the study cohort consisted of a heterogeneous mix of underlying conditions that required mechanical ventilation and was therefore not homogenous. Again, our cohort likely reflects the mix of conditions and severity of illness observed in the PICU and therefore is a pragmatic description of response to PEEP increases. We did not control for level of consciousness. Use of sedatives and paralytic agents was at the discretion of the providing team and therefore variation between subjects is likely. However, we did not note differences in spontaneous breathing in the time before and after the PEEP changes, limiting the degree to which level of consciousness is likely to affect the results. Lastly, the PEEP changes analyzed in the present study were modest and therefore the equilibration times we report may not apply to PEEP changes outside this ranges observed.

Future work should be done in order to identify subject characteristics associated with positive or negative responses to PEEP and the effects on equilibration times.

6.6 Conclusions

This study demonstrates that in the context of modest PEEP increases in children with hypoxic respiratory failure, 38 and 71 minutes for dynamic pulmonary compliance and oxygenation are adequate for observing improvements. Compliance preceded oxygenation improvements. Equilibration time for oxygenation was dependent upon severity of illness. To our knowledge, this is the
first report of oxygenation and compliance time-course data secondary to PEEP changes in pediatric mechanically ventilated subjects. These findings may aid clinicians and researchers in determining the optimal time required between changes in PEEP.
7. EMPIRICAL PROBABILITY OF POSITIVE RESPONSE TO PEEP CHANGES AND MECHANICAL VENTILATION FACTORS ASSOCIATED WITH IMPROVED OXYGENATION

7.1 Abstract

Objective: Positive end-expiratory pressure (PEEP) is titrated to improve oxygenation during mechanical ventilation. PEEP may ameliorate or exacerbate lung injury. It is clinically desirable to identify factors that are associated with a clinical improvement or deterioration following a PEEP change. However, these factors have not been adequately described in the literature. Therefore, we quantify the empirical probability of PEEP changes resulting in positive effects on oxygenation, pulmonary mechanics and dead-space fraction. Further, we identify readily obtainable clinical factors that are associated with positive response in children receiving mechanical ventilation.

Design: Retrospective analysis of continuous data

Setting: Academic hospital multidisciplinary intensive care unit

Patients: Mechanically ventilated pediatric subjects

Interventions: During a PEEP increase (PEEP_increase), a responder was defined as anyone who exhibited an improved SpO2/FiO2 (S/F); non-responders demonstrated a worsening S/F in the hour following. For cases where PEEP was decreased (PEEP_decrease), a responder was anyone who maintained or increased S/F; non-
responders demonstrated a worsening S/F. Features from continuous mechanical ventilation variables were extracted and differences in these features between responders and non-responders were tested using Mann-Whitney U and Chi-square tests.

Measurements and Main Results: A total of 286 PEEP change cases were eligible for analysis in 76 subjects. Of the PEEP_increase cases, the empirical probability of positive response was 56%, 67% and 54% for oxygenation, mechanics and dead-space fraction respectively. The median S/F increase was 13. For PEEP_decrease, the empirical probability of acceptable response was 46%, 53% and 46% for oxygenation, mechanics and dead-space fraction respectively. PEEP_increase responders had higher $FiO_2$ requirement (70.8 versus 52.5%; $P < 0.001$), mean airway pressure (14.0 versus 12.9 cmH$_2$O; $P = 0.029$) and oxygen saturation index (9.9 versus 7.5; $P < 0.01$) versus non-responders. For PEEP_decrease, no statistically significant differences in demographic or ventilator parameters were observed.

Conclusions: In children requiring mechanical ventilation, the responder rate was modest for both PEEP_increase and PEEP_decrease cases. These data suggest PEEP titration often does not have the desired clinical effect and predicting which patients will manifest a positive response is complex, potentially requiring more sophisticated means of assessing individual subjects.
7.2 Introduction

In mechanically ventilated children with hypoxic respiratory failure, titration of positive end-expiratory pressure (PEEP) is typically implemented to improve oxygenation through the reversal of atelectasis and prevention of further alveolar collapse. However, PEEP can ameliorate or exacerbate lung injury. PEEP changes are frequently made at the bedside but little guidance exists in the pediatric literature to predict who is likely to respond to an intervention. The physiologic rationale for increasing PEEP in most cases is to improve functional residual capacity, reduce physiologic dead-space fraction, shunt fraction and ventilation/perfusion mismatch. Although the use of moderate to high levels of PEEP have been shown to be safe in the pediatric population, widespread and consistent application has not been recommended. Oxygenation is an important clinical target in pediatric subjects as it is associated with lower mortality during severe illness, acute respiratory distress syndrome (ARDS). Despite the importance of oxygenation, there is a paucity of investigations reporting the proportion of PEEP changes that are associated with a positive response and investigations targeting PEEP management are needed. Therefore, we sought to quantify the proportion of PEEP changes that had a positive effect on oxygenation in children receiving mechanical ventilation and identify factors that could be readily obtained at the bedside that are associated with response.
7.3 Methods

Subjects were enrolled in the study if they were admitted to the pediatric intensive care unit (PICU), age was less than 18 years, received mechanical ventilation > 24 hours, continuous mechanical ventilation data were recorded during that time period and they exhibited hypoxic respiratory failure defined as an oxygen saturation index ≥5.9

All subjects were mechanically ventilated (Servo-I, Getinge AB-Maquet, Gothenburg, Sweden) and connected to a bedside physiologic monitor (IntelliVue MP90, Philips Healthcare, Andover, MA). A medical device-interfacing module (IntelliBridge EC10, Philips Healthcare, Andover, MA) was used to connect the mechanical ventilator and monitor to a research server. Data was recorded at a frequency of 0.2Hz for the duration of invasive mechanical ventilation in the ICU. Demographic and outcome data were abstracted from the medical record for each subject and the diagnosis was recorded according to the International Classification of Diseases published by the World Health Organization (Revisions 9 and 10, Clinical Modification) and binned to either primary respiratory, surgical procedure, neurologic, sepsis or other.128

Both the physiologic monitor and mechanical ventilator offer built-in preprocessing inclusive of artifact detection. However, these signals can still be corrupted by noise and
artifact. A band-pass filter was applied to physiologic data in order to filter out data that is beyond the physiologic range according to established methods.

A case was defined as a 2-hour period: 1-hour preceding and 1-hour following a change in PEEP since this has been shown to be the time required to achieve equilibration of pulmonary compliance and oxygenation following modest changes in PEEP level in mechanically ventilated children. A quality function was built to ensure that only ‘clean’ cases were analyzed. A clean PEEP case was defined as one where no ventilator changes were made (other than PEEP and FiO₂); the PEEP change was sustained for > 1-hour.

For cases where the PEEP was increased, a responder was defined as a case that exhibited any improvement in either oxygenation by \( \text{SpO}_2/\text{FiO}_2 (S/F) \), respiratory system compliance (\( C_{RS} \)) or dead-space fraction (\( V_d/V_l \)); \( x_{\text{post}} - x_{\text{pre}} > 0 \) (for \( x = S/F, C_{RS}, V_d/V_l \)). For cases where PEEP was decreased, a responder was defined as a case where \( S/F, C_{RS} \) or \( V_d/V_l \) was maintained; \( x_{\text{post}} - x_{\text{pre}} \geq 0 \) (for \( x = S/F, C_{RS}, V_d/V_l \)).

The D’Agostino and Pearson omnibus test was applied to test the normality of the data. Since the data were not normally distributed, continuous variables are presented as median (interquartile range). Subjects had multiple cases where PEEP was increased or decreased. To account for this, generalized estimating equations were utilized to compare continuous demographic and respiratory features and categorical features between responders and non-responders (by \( S/F \)).
aggregation, cleaning and analyses were conducted using MATLAB (V9.1.0.441655, The Mathworks Inc., Natick, MA). Statistical analyses were performed using SPSS® (V23.0, IBM Corp., Armonk, NY). The protocol was approved by the institutional review board.

7.4 Results

There were 265 subjects evaluated for study inclusion (189 were excluded; 30 had age > 18 years, 69 were ventilated for < 24 hours and 90 subjects were excluded due to no PEEP change cases that passed quality metrics). In total, 76 subjects demonstrated PEEP change cases that were included in the analysis. A description of the population is shown in Table 7.1.
Table 7.1. Description of the study population. * Continuous values are expressed as median (interquartile range) unless otherwise indicated.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (IQR)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.9 (0.9 - 6.6)</td>
</tr>
<tr>
<td>Sex, n female (%)</td>
<td>38 (50)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>10.3 (7.1 - 20.0)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>80 (65 - 109)</td>
</tr>
<tr>
<td>Vent duration (days)</td>
<td>5.7 (3.4 - 14.4)</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>11.0 (5.7 - 20.9)</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>22.0 (7.5 - 108.1)</td>
</tr>
<tr>
<td>Primary diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>25 (33)</td>
</tr>
<tr>
<td>Surgical</td>
<td>18 (24)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Other</td>
<td>22 (29)</td>
</tr>
</tbody>
</table>

The number of PEEP cases that were analyzed was 286 (166 increases and 120 decreases). The PEEP was increased by 1, 2 and ≥ 3 cmH₂O in 58%, 26% and 16% of the cases respectively. The PEEP was decreased by 1, 2 and 3 cmH₂O in 80%, 17% and 3% of the cases respectively. In the PEEP_increase cases, the empirical probability of positive response was 56%, 67% and 54% for S/F, Crs and Vd/Vt respectively. For PEEP_decrease, the empirical probability of acceptable response was 46%, 53% and 46% for oxygenation, mechanics and dead-space fraction.
respectively. The distribution of oxygenation, $C_{RS}$ and $Vd/Vt$ responses are depicted in Figures 7.1, 7.2 and 7.3 respectively.

Figure 7.1. Distribution of oxygenation response following a PEEP increase. Where $\delta \text{SpO}_2/\text{FiO}_2$ is difference, expressed as a percentage in the hour following a PEEP change relative to the hour preceding the change.
Figure 7.2. Distribution of oxygenation response following a PEEP increase. Where $\delta C_{RS}$ is difference, expressed as a percentage in the hour following a PEEP change relative to the hour preceding the change.
There were statistically significant differences in ventilation parameters in the 1-hour preceding the PEEP change in the PEEP\textsubscript{increase} group; responders had higher FiO\textsubscript{2} (70.8 versus 52.5%; $P < 0.001$), higher mean airway pressure (14.0 versus 12.9 cmH\textsubscript{2}O; $P = 0.029$) and increased oxygen saturation index (9.9 versus 7.5; $P < 0.01$) were observed in the 1-hour preceding the PEEP change in responders compared to non-responders (Table 5.2.).
Table 7.2. Comparison between PEEP responders and non-responders following a PEEP increase. Responders were defined as those demonstrating oxygenation improvement in the 1-hour following the PEEP change relative to the preceding 1-hour. OSI = oxygen saturation index, ΔPEEP = change in PEEP.

<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>Responders</th>
<th>Non-responders</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{\textsubscript{dynamic}} (ml/kg/cmH\textsubscript{2}O)</td>
<td>0.42 (0.25 - 0.53)</td>
<td>0.44 (0.29 - 0.50)</td>
<td>0.598</td>
</tr>
<tr>
<td>PEEP (cmH\textsubscript{2}O)</td>
<td>8 (6 - 10)</td>
<td>7 (5 - 8)</td>
<td>0.438</td>
</tr>
<tr>
<td>SpO\textsubscript{2} (%)</td>
<td>95 (93 - 97)</td>
<td>94 (93 - 96)</td>
<td>0.450</td>
</tr>
<tr>
<td>P\text{peak} (cmH\textsubscript{2}O)</td>
<td>24 (22 - 28)</td>
<td>23 (20 - 26)</td>
<td>0.205</td>
</tr>
<tr>
<td>FiO\textsubscript{2} (%)</td>
<td>71 (55 - 86)</td>
<td>52 (46 - 65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vt (ml/kg)</td>
<td>6.0 (5.0 - 7.2)</td>
<td>6.7 (5.3 - 7.2)</td>
<td>0.427</td>
</tr>
<tr>
<td>RR (breaths/min)</td>
<td>28 (24 - 36)</td>
<td>27 (24 - 32)</td>
<td>0.367</td>
</tr>
<tr>
<td>P\text{\textsubscript{mean}} (cmH\textsubscript{2}O)</td>
<td>14.0 (11.9 - 16.5)</td>
<td>13.0 (10.8 - 14.8)</td>
<td>0.029</td>
</tr>
<tr>
<td>OSI</td>
<td>9.9 (7.4 - 14.8)</td>
<td>7.5 (5.7 - 8.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>ΔPEEP (cmH\textsubscript{2}O), n (%)</td>
<td>1 (1 - 2)</td>
<td>1 (1 - 2)</td>
<td>0.732</td>
</tr>
<tr>
<td>1</td>
<td>59 (63)</td>
<td>37 (51)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>19 (20)</td>
<td>24 (26)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>14 (15)</td>
<td>11 (15)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>
Table 7.3. Comparison between PEEP responders and non-responders following a decrease in PEEP. Responders were defined as those demonstrating oxygenation improvement in the 1-hour following the PEEP change relative to the preceding 1-hour. OSI = oxygen saturation index, ΔPEEP = change in PEEP.

<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>Responders</th>
<th>Non-responders</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\textsubscript{dynamic} (ml/kg/cmH\textsubscript{2}O)</td>
<td>0.45 (0.38 - 0.60)</td>
<td>0.48 (0.32 - 0.54)</td>
<td>0.413</td>
</tr>
<tr>
<td>PEEP (cmH\textsubscript{2}O)</td>
<td>8 (7 - 10)</td>
<td>8 (7 - 11)</td>
<td>0.676</td>
</tr>
<tr>
<td>SpO\textsubscript{2} (%)</td>
<td>96 (95 - 97)</td>
<td>96 (93 - 97)</td>
<td>0.729</td>
</tr>
<tr>
<td>P\text{peak} (cmH\textsubscript{2}O)</td>
<td>24 (22 - 26)</td>
<td>25 (21 - 27)</td>
<td>0.928</td>
</tr>
<tr>
<td>FiO\textsubscript{2} (%)</td>
<td>54 (50 - 64)</td>
<td>52 (47 - 73)</td>
<td>0.588</td>
</tr>
<tr>
<td>V\text{t} (ml/kg)</td>
<td>6.8 (6.0 - 7.7)</td>
<td>6.1 (5.6 - 7.3)</td>
<td>0.227</td>
</tr>
<tr>
<td>RR (breaths/min)</td>
<td>27 (23 - 32)</td>
<td>30 (25 - 38)</td>
<td>0.222</td>
</tr>
<tr>
<td>P\text{mean} (cmH\textsubscript{2}O)</td>
<td>13.7 (11.9 - 15.7)</td>
<td>13.4 (12.0 - 16.6)</td>
<td>0.937</td>
</tr>
<tr>
<td>OSI</td>
<td>7.4 (6.2 - 11.6)</td>
<td>7.5 (6.4 - 11.3)</td>
<td>0.811</td>
</tr>
<tr>
<td>ΔPEEP (cmH\textsubscript{2}O), n (%)</td>
<td>1 (1 -1)</td>
<td>1 (1 -1)</td>
<td></td>
</tr>
<tr>
<td>-3</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>-2</td>
<td>9 (16)</td>
<td>12 (19)</td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>45 (80)</td>
<td>51 (80)</td>
<td></td>
</tr>
</tbody>
</table>

For PEEP\textsubscript{increase} group, the median (IQR) change in $S/F$ was 13 (-5 to 30) and -19 (-40 to -7) for responders and non-responders respectively. For decreases in PEEP, the responder rate was 47% and there were no statistically significant differences in demographic or ventilation parameters between responders and non-responders (Table 5.2B.). For the PEEP decrease group, the median (IQR) change in $S/F$ was 8 (3 - 21) and -8 (-16 to -3) for responders and non-responders respectively. There were no differences in age, weight, height or sex between responders and non-responders for either the PEEP\textsubscript{increase} or PEEP\textsubscript{decrease} group.
7.5 Discussion

Quantifying the proportion of PEEP changes having a positive or acceptable effect on oxygenation in children is important. Our data show that when increasing PEEP as a part of routine care, oxygenation was improved in just over half (56%) of the cases. Responders demonstrated worse lung injury relative to non-responders with significantly greater $F_iO_2$ requirements, mean airway pressure and oxygen saturation index in the hour preceding the change. On the other hand, just under half (47%) of cases demonstrated acceptable oxygenation following a decrease in PEEP. There were no differences in the demographic or ventilator features between PEEP decrease responders and non-responders.

Most pediatric experimental and clinical investigations including PEEP titration has been done in combination with a recruitment maneuver. Few studies in the pediatric literature have assessed the titration of PEEP without a recruitment maneuver. In the adult literature, end-expiratory transpulmonary pressure, dynamic compliance, dead-space, electrical impedance tomography, computed tomography and ultrasonography have been proposed as methods to individualize or assess PEEP titration. In a cohort of adult subjects with ARDS, Pintado et al assessed the utility of an individualized approach to setting PEEP based on best pulmonary compliance. The authors did not report
the success of individual *PEEP* changes but did note in the compliance-guided group, the $P_dO_2/FiO_2$ ratio was 146 compared to 133 in the control group. However, this finding was not statistically significant and represented only a trend. In the present study, we sought to quantify the number of *PEEP* changes that would be classified as responders or non-responders. Further, mechanically ventilated children have been noted to have distinct pathophysiologic characteristics during lung injury compared to adults; children have increased chest wall compliance, preserve the function of surfactant during lung injury and have different immune response that is different from adult subjects. Head-to-head comparison with adult studies must be done with this in mind.

Weaning from mechanical ventilation includes stepped reduction in ventilator support (including *PEEP*) and comprises up to 40% of the total duration of ventilation. In children, efforts to introduce protocols for ventilator weaning have demonstrated mixed results. Inappropriate application of *PEEP* can result in alveolar over-distension, increased work of breathing, worsening ventilation-perfusion matching as well as effects on the circulatory system and distribution of blood flow within the lung itself. These factors could delay weaning and prolong duration of mechanical ventilation. The fact that we were unable to identify factors associated with a positive weaning response underlines these findings.
There are important limitations to the present study that should also be considered. The study was conducted retrospectively and therefore the PEEP increases and decreases were not strictly controlled. However, as this study was designed to assess the prevalence of responders and non-responders to current practice (“usual care”), a protocol could not be designed to ascribe specific conditions for PEEP titration. The definitions for positive response to PEEP increases and decreases may not be acceptable for all patients and conditions. For instance, a stricter definition for positive response would only reduce the proportion of responders. Subjects enrolled in the present study demonstrated a mix of demographics and underlying conditions; therefore, application of the findings to specific diseases may not be appropriate without further study. However, the cohort largely reflects a mix of conditions and severity of illness that is typically seen in large academic PICU environment.

7.6 Conclusions

In children requiring mechanical ventilation with hypoxic respiratory failure, the empirical probability of a positive response was not much better than the flip of a coin (ranging from 46 to 67%). These data suggest PEEP titration is a difficult clinical problem and improved methods for responder identification are needed. Factors associated with a positive response include the baseline PEEP level, higher peak inspiratory pressure, higher FiO₂, higher mean airway pressure and
increased oxygen saturation index. Decreasing *PEEP* is particularly difficult since we were unable to identify any factors associated with desired clinical result. These data provide baseline performance data for *PEEP* titration and may provide valuable information for future methods needed to aid clinicians in identifying subjects likely to benefit from or tolerate a change in *PEEP*. 
8. PREDICTING PHYSIOLOGIC RESPONSE TO CHANGES IN POSITIVE END-EXPIRATORY PRESSURE IN MECHANICALLY VENTILATED CHILDREN: A COMPUTABLE PHENOTYPE AND MACHINE LEARNING METHOD

8.1 Abstract

Objective: Positive end-expiratory pressure (PEEP) is often increased to improve ventilation efficiency thereby improving gas exchange during pediatric mechanical ventilation. Although it is clinically important to optimize PEEP in this population, there is a paucity of literature to guide the clinician at the bedside. Gleaning robust representations of pediatric pathophysiology is especially difficult because the underlying causes of disease span body systems and physiologic processes, creating complex nonlinear relationships among observed measurements. Increasingly, time-series physiologic data are available for mechanically ventilated subjects in the intensive care unit. However, these data have not been adequately explored in the literature. Therefore, we sought to apply time-series computable phenotyping on time-series physiologic data and develop a model to predict PEEP response in mechanically ventilated children.

Design: Retrospective analysis of continuous data

Setting: Academic hospital multidisciplinary intensive care unit

Patients: Mechanically ventilated subjects < 18 years of age
Interventions: Time-series data from the patient monitor and mechanical ventilator were abstracted 1-hour preceding and 1-hour following a PEEP change. PEEP increase (PEEP\textsubscript{increase}), a responder was defined as anyone who exhibited an improved dead-space fraction ($Vd/Vt$); non-responders demonstrated a worsening $Vd/Vt$ in the hour following the PEEP change. Features from continuous mechanical ventilation variables were extracted and used to train a support vector machine model in order to predict $Vd/Vt$ response to changes in PEEP. The performance of the model was assessed by calculating the area under the receiver operator characteristic curve (AUROC) and computing measures of diagnostic accuracy.

Measurements and Main Results: In all, 393 PEEP change cases were included in the analysis in 83 subjects. A total of 27 computable phenotypes were identified and incorporated into the model. The AUROC was 0.82 and 0.90 for classifying response to PEEP increases and decreases respectively. The overall diagnostic accuracy was 0.75 for PEEP increases and 0.84 for PEEP decreases.

Conclusions:
The model classified responders to increases and decreases in PEEP with reasonable accuracy. The model performed better for those cases when PEEP was decreases. In the future, these methods may play an important role in optimizing care of the mechanically ventilated pediatric patients.
8.2 Introduction

Positive end-expiratory pressure (PEEP) is often increased to improve ventilation efficiency and gas exchange during pediatric mechanical ventilation. However, PEEP can ameliorate or exacerbate lung injury. Although it is clinically important to optimize PEEP in this population, there is a paucity of literature to guide clinicians at the bedside. The physiologic rationale for increasing PEEP is often to reduce physiologic dead-space fraction, improve oxygenation and lung mechanics as well as improve shunt fraction and ventilation/perfusion mismatch. Ratios of dead-space to tidal volume ratio (Vd/Vt) has been associated with pediatric disease severity and success of ventilator weaning. Although the use of increased levels of PEEP has been shown to be safe in this population, widespread application within the pediatric intensive care unit has not been recommended and further work in this area is needed.

Methods and techniques are needed to individualize care, reduce morbidity and duration of ventilation in the pediatric population. Traditionally, gleaning robust representations of pediatric pathophysiology is especially difficult because the underlying causes of disease span body systems and physiologic processes, creating complex nonlinear relationships among observed measurements. This presents an important problem when designing experiments and transcribing medical data in a traditional sense. However, the increased connectivity of bedside
medical devices as well as the availability of sophisticated time-series data analytics and machine learning offer an important opportunity in the modern intensive care unit.

Therefore, we sought to apply time-series computable phenotyping on time-series physiologic data and develop a model to predict PEEP response in mechanically ventilated children. A number of computable phenotypes are extracted from continuous physiologic data, important phenotypes are identified and used to train a machine learning model to identify those cases where a subject is likely to see an improvement in gas exchange following a manipulation of PEEP.

8.3 Methods

Subjects were eligible for inclusion in the study if they received mechanical ventilation for > 24 hours in the pediatric intensive care unit (PICU), age was less than 18 years, continuous mechanical ventilation data were recorded during that time period and they exhibited hypoxic respiratory failure defined as an oxygen saturation index ≥ 5.9

Mechanical ventilation was applied using the Servo-I (Getinge AB-Maquet, Gothenburg, Sweden) and connected to a physiologic monitor (IntelliVue MP90, Philips Healthcare, Andover, MA). The mechanical ventilator was interfaced to the monitor using the IntelliBridge medical device-interfacing module (model EC10, Philips Healthcare,
Andover). Data was recorded at a frequency of 0.2Hz for the duration of stay in the ICU. The variables included were peak inspiratory pressure ($P_{\text{peak}}$), positive end expiratory pressure ($\text{PEEP}$), total respiratory rate ($RR$), respiratory system compliance ($CRS$), spontaneous respiratory rate ($RR_{\text{spontaneous}}$), fraction of inspired oxygen ($FiO_2$), expired minute ventilation ($Ve$), inspired minute ventilation ($Vi$), spontaneous minute ventilation ($Ve_{\text{spontaneous}}$), mean airway pressure ($P_{\text{mean}}$), end-tidal CO$_2$ concentration ($P_{\text{etCO}_2}$), volumetric CO$_2$ elimination ($VCO_2$), expired tidal volume ($V_e$), inspired tidal volume ($V_i$), estimate of the pressure in the first 100ms of the breath ($P_{100}$), end-expiratory flow rate ($V_{ee}$), work of breathing of the ventilator ($W_{\text{OB ventil}}$), barometric pressure ($P_b$), heart rate ($HR$), oxygen saturation ($SpO_2$) and dead-space fraction ($Vd/Vt$).

Demographic and outcome data were abstracted from the medical record for each subject and the diagnosis was recorded according to the International Classification of Diseases published by the World Health Organization (Revisions 9 and 10, Clinical Modification) and binned to either primary respiratory, surgical procedure, neurologic, sepsis or other.

Data preprocessing

Because the procedures included in computable phenotype extraction often require the input data to be completely intact (no gaps in data), 1-dimensional linear interpolation was implemented for each variable. Further, the physiologic monitor and mechanical ventilator offer built-in preprocessing but signals can still be corrupted by noise and artifact. Band-pass and low-pass filters were applied to filter out data that was not
physiologically plausible according to established methods. A Savitzky-Golay filter was applied to mechanical ventilation data in order to remove noise and artifact but preserve local data phenomenon. Further, normalization of individual parameters is important in a pediatric population since signals are expected to change as the child grows. Data were normalized to either body weight (for respiratory parameters tidal volume, minute ventilation, carbon dioxide elimination, end-expiratory flow rate) and Z-scores were computed for heart rate and respiratory rate.

8.3.1 Case identification

For an individual subject, a case was defined as a 2-hour period, to include a 1-hour period preceding and 1-hour period following a change in PEEP. We have previously demonstrated that a period ~60 minutes is necessary to observe physiologic effects from modest changes in PEEP. A quality function was built to ensure that only ‘clean’ cases were analyzed. A clean PEEP case was defined as one where no ventilator changes were made (other than PEEP and FiO2); the PEEP change was sustained for > 1-hour. For cases where the PEEP was increased, a responder was defined as a case that exhibited any improvement in $Vd/Vt$; $[Vd/Vt_{\text{post}} - Vd/Vt_{\text{pre}}] > 0$. For cases where PEEP was decreased, a responder was defined as a case where oxygenation was maintained; $[Vd/Vt_{\text{post}} - Vd/Vt_{\text{pre}}] \geq 0$.

8.3.2 Computable phenotype extraction
In most clinical investigations involving mechanical ventilation data, descriptive statistics are typically computed. However, since time-series data recorded at a relatively high frequency (compared to data transcribed in the electronic medical record), various representations of individual signals can be computed. Although thousands of methods exist in the literature, a set of 219 methods (including autocorrelation, auto-mutual information, stationarity, entropy, correlation dimension, linear and non-linear model fits, measures from the power spectrum and outlier quantification) provides a robust summary of the different behaviors of time series analysis. These methods have been applied in some areas of bioengineering, but applications on medical time-series data have not yet been studied. We quantify a wide range of time series properties, computable phenotypes according to existing methods.

8.3.3 Feature selection and model training

A small number of computable phenotypes were selected from the total set of phenotypes by implementing the least absolute shrinkage and selection operator according to established methods (LASSO). A support vector machine (SVM) is a supervised machine learning algorithm that is applied to a wide variety of pattern recognition and classification problems and achieves good discriminative power in various healthcare data applications. A separate model was trained for all cases where the PEEP was increased (PEEP↑SVM) and where the PEEP was
decreased (PEEP↓_{SVM}). To protect against overfitting and to assess model performance a 5-fold cross validation was performed.

8.3.4 Statistical analyses

The D’Agostino and Pearson omnibus test was applied to test the normality of the data. Since the data were not normally distributed, continuous variables are presented as median (interquartile range). To assess model performance, the area under the receiver operator characteristic curve was calculated as well as the diagnostic accuracy, sensitivity, specificity, positive and negative predictive values and the positive and negative likelihood ratios. Data aggregation, cleaning and analyses were conducted using MATLAB (V9.1.0.441655, The Mathworks Inc., Natick, MA).

The protocol was approved by the institutional review board.

8.4 Results

A total of 393 PEEP change cases were included in the analysis in 83 subjects. A general description of the population is shown in Table 8.1. Each of the 219 computable phenotype procedures were applied to each of the 22 variables included in the analysis.
Table 8.1. Description of the population.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (IQR)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>2.1 (0.8 – 8.0)</td>
</tr>
<tr>
<td>Sex, n female (%)</td>
<td>36 (43)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>11 (7.7 - 28.0)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>80 (66 - 116)</td>
</tr>
<tr>
<td>Vent duration (days)</td>
<td>5.8 (3.1 – 10.2)</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>12.0 (6.9 – 21.4)</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>20.2 (6.4 – 49.2)</td>
</tr>
<tr>
<td>Primary diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>23 (28)</td>
</tr>
<tr>
<td>Surgical</td>
<td>23 (28)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>21 (25)</td>
</tr>
</tbody>
</table>

In all, 4818 computable phenotypes were quantified. Selection by LASSO identified a total of 27 computable phenotypes and were incorporated into the SVM model. The AUROC was 0.82 and 0.90 for classifying response to PEEP increases and decreases respectively. The overall diagnostic accuracy was 0.75 for PEEP increases and 0.84 for PEEP decreases. The performance of the models is depicted in Table 8.2.
Table 8.2. Model performance results.

<table>
<thead>
<tr>
<th>Model type</th>
<th>PEEP↑ (SVM (Gaussian))</th>
<th>PEEP↓ (SVM (linear))</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUROC</td>
<td>0.82</td>
<td>0.90</td>
</tr>
<tr>
<td>Diagnostic accuracy</td>
<td>0.75</td>
<td>0.84</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.75</td>
<td>0.81</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.75</td>
<td>0.87</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>0.79</td>
<td>0.86</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>0.71</td>
<td>0.82</td>
</tr>
<tr>
<td>Positive Likelihood Ratio</td>
<td>3.05</td>
<td>6.22</td>
</tr>
<tr>
<td>Negative Likelihood Ratio</td>
<td>0.33</td>
<td>0.22</td>
</tr>
</tbody>
</table>

The receiver operator characteristic curves for the PEEP↑_{SVM} and PEEP↓_{SVM} models are depicted in Figures 8.1 and 8.2 respectively.

Figure 8.1. Receiver operator characteristic curve for the PEEP increase model.
Figure 8.2. Receiver operator characteristic curve for the PEEP decrease model.

A visual description of the included computable phenotypes and each subject included in the analyses is depicted in Figure 8.3. Data were standardized to zero mean.
Figure 8.3. A visual summary of the computable phenotypes including in the models. Each row corresponds to a phenotype and each column corresponds to an individual subject. The cases were organized such that responders are on the left (Responder +) and non-responders are on the right (Responder -). The results were standardized to zero mean. Values above the mean were depicted in red and values below the mean are depicted in green.

Some differences across the phenotypes can be noted at the individual level. A responder and non-responder are depicted in Figure 8.4.
Figure 8.4. A comparison of the phenotype expressions of a responder (+) and non-responder (-). Each row corresponds to a phenotype and each column corresponds to an individual subject. The cases were organized such that responders are on the left and non-responders are on the right. The results were standardized to zero mean. Values above the mean were depicted in red and values below the mean are depicted in green. Note the differences in phenotype ‘vco21918’; the responder was below the population mean and the non-responder was above the mean. ‘vco21918’ corresponds to the stationary of carbon dioxide elimination rate (VCO₂).
The top types of computable phenotypes were those assessing stationarity, linear and non-linear model fits and outlier quantification. The included variables were the preceding $Vd/Vt$, $SpO_2$, $HR$, $WOB_{rem}$, $P_{100}$, $VCO_2$, $PetCO_2$, $P_{mean}$, $VE_{spontaneous}$, $VE$, $PEEP$ and $P_{peak}$.

8.5 Discussion

In mechanically ventilated children with hypoxic respiratory failure, the prediction models demonstrated diagnostic accuracy of 75% and 84% for $PEEP$ increases and decreases respectively. The performance of the present models are superior to the empirical probability of improved condition following clinician directed alterations in $PEEP$ (cf. Chapter 4). The empirical probability of improved pulmonary condition defined as an improvement in dead-space fraction was 53.9% when increasing $PEEP$ and 46.3% when decreasing $PEEP$.

The majority of pediatric investigations involving $PEEP$ titration has been done in combination with a recruitment maneuver. In the pediatric literature, few studies have assessed the titration of $PEEP$ without a recruitment maneuver. However, typical management of the child during mechanical ventilation includes the modest titration of $PEEP$ (in increments ranging from 1-3 cmH$_2$O). In a large multicenter, randomized controlled trial, a strategy included lung recruitment maneuvers and $C_{RS}$ guided $PEEP$ titration versus low $PEEP$ demonstrated an increase in 28-day mortality. In this study, the authors note the
findings did not support routine lung recruitment combined with \textit{PEEP} titration. Although this seems to suggest, at least in adult subjects with moderate to severe acute respiratory distress syndrome (ARDS) that \textit{PEEP} titration may not be beneficial, it’s not clear to what degree optimizing $C_{RS}$ has on overall lung health. In the present study, we selected to use $Vd/Vt$ as the target since has been associated with pediatric disease severity and success of ventilator weaning.\textsuperscript{197,198} Further, children have different pathophysiologic characteristics during lung injury relative to adults. Children have increased chest wall compliance, they preserve the function of surfactant during injury have immune responses different than those of adult subjects.\textsuperscript{174-176} For these reasons, it is difficult to make generalizations about pediatric mechanical ventilation based on adult data.

There are limitations to the present investigation that should also be considered. The nature of the study, being retrospective, precluded the strict control of how and when changes in \textit{PEEP} where made. Factors pertaining to the subjects sedation regimen were not included. However, since spontaneous breathing parameters, including $RR_{\text{spontaneous}}$ and $V_e_{\text{spontaneous}}$, the end effects of any sedative or paralytic agents on the respiratory system are largely captured. Indeed, this approach may be superior to one that only includes dosing information for sedatives or paralytic agents. For example, subject A is receiving a high absolute dose of a sedative but manages to retain spontaneous breathing and subject B is receiving a modest absolute dose but is not breathing at all. One would expect that the fact that
subject A is breathing spontaneously, this may relevant when designing an algorithm to predict physiologic response; if only dosing information was captured, this information would be omitted. Subjects enrolled in the present study demonstrated a mix of demographics and underlying conditions; therefore, application of the findings to specific diseases may not be appropriate without further study. However, the cohort largely reflects a mix of conditions and severity of illness that is typically seen in large academic PICU environment.

8.6 Conclusions

The model classified responders to increases and decreases in PEEP with reasonable accuracy. The model performed better for those cases when PEEP was decreased. Of note, many computable phenotypes that were passed to the model describe characteristics of physiologic variables that are not readily identified at the bedside. In the future, these methods may play an important role in optimizing care of the mechanically ventilated pediatric patients.
CONCLUSIONS

In this work, the time required for equilibration of oxygenation and respiratory system compliance following a change in positive end-expiratory pressure (PEEP) was quantified, the empirical probability of clinical improvement following PEEP changes was assessed, phenotypes of time-series physiologic data were extracted and a model was developed to predict response to PEEP changes. In the context of modest PEEP increases in children with hypoxic respiratory failure, 38 and 71 minutes for respiratory system compliance and oxygenation are adequate for observing improvements. Compliance preceded oxygenation improvements. Equilibration time for oxygenation was dependent upon severity of illness. This is the first report of oxygenation and compliance time-course data secondary to PEEP changes in pediatric mechanically ventilated subjects. This finding will have an impact on clinical practice and future research. The clinical impact may be that clinicians should take a ‘wait and see’ approach to PEEP titration, especially since the full effects aren’t realized for ~1 hour following a change. These data may also help future investigators select a time frame following PEEP changes that can be targeted to gauge effectiveness. Indeed, this was an important and necessary step of working towards a prediction model in the present work.

The empirical probability of a positive response to PEEP changes was not much better than the flip of a coin (ranging from 46 to 67%); suggesting PEEP
titration is a difficult clinical problem and improved methods for responder identification are needed. Factors associated with a positive response include the baseline PEEP level, higher peak inspiratory pressure, higher FiO\textsubscript{2}, higher mean airway pressure and increased oxygen saturation index. Decreasing PEEP is a particular issue since clinically available factors associated with the desired clinical result could not be identified; suggesting that more sophisticated methods are required. These data provide baseline performance data for PEEP titration and may provide valuable information for future methods needed to aid clinicians in identifying subjects likely to benefit from or tolerate a change in PEEP.

The feasibility of phenotype extraction from time-series physiologic data was demonstrated. Many computable phenotypes that were selected and passed to the model describe characteristics of physiologic variables that are not readily identified at the bedside. The prediction model classified responders to increases and decreases in PEEP with good accuracy, 75 and 84% respectively. This performance was superior to the empirical probability of improvement where positive response rates were 54 and 46% for PEEP increases and decreases respectively. The model performed better for those cases when PEEP was decreased, highlighting the need for sophisticated bedside phenotyping and prediction models. In the future, these methods may play an important role in optimizing care in the intensive care unit and lay the foundation for a rich area of discovery in pediatric mechanically ventilated children.
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APPENDIX

Copy of institutional review board letter of approval.

Boston Children’s Hospital
Institutional Review Board (IRB)
300 Longwood Avenue
Mailstop RCH 3164
Boston, MA 02115
Tel: (617) 355-7022
Fax: (617) 730-0226
www.bostonchildrens.org/research/irb

Principal Investigator Craig Smallwood
Protocol Number IRB-P00021911
Protocol Title Retrospective analysis of critically ill children requiring mechanical support:
Identifying factors associated with prolonged duration and effects of adjunct therapy on gas exchange

Date: March 29, 2016

NOTICE OF EXPEDITED APPROVAL
IRB Approval Date: 3/29/2016
IRB Activation/Release Date: 3/29/2016
IRB Expiration Date: 3/28/2017

The Institutional Review Board has approved the above referenced protocol through expedited review procedures as
permitted under 45 CFR 46.110, category 5.

Risks were determined to be minimal with no potential for direct benefit.

The IRB has determined that you have met the regulatory requirements necessary in order to obtain a waiver of
informed consent/authorization.

The occurrence of unanticipated problems should promptly be reported to this office. Any revisions, amendments, or
changes to the protocol require prior IRB approval. The IRB has asked this office to notify investigators that clinical
investigation protocol files are subject to audits at some future time.

Sincerely,

Robleinscky Dominguez, IRB Administrator
For the Institutional Review Board

Tell us how we are doing! https://www.surveymonkey.com/s/irbsatisfactionsurvey