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Evaluation of Various Inspiratory Times and Inflation Pressures During Airway Pressure Release Ventilation

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An Evaluation of Various Inspiratory Times and Inflation Pressures During Airway Pressure Release Ventilation

Formal Dissertation Report

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We hereby certify that this dissertation, submitted by Tim W. Gilmore, conforms to acceptable standards and is fully adequate in scope and quality to fulfill the dissertation requirement for the degree of Doctor of Philosophy in Health Science.

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Abstract

There are few recommendations on how best to apply certain modes of mechanical ventilation. The application of Airway Pressure Release Ventilation (APRV) includes strategic implementation of specific inspiratory times (I-times) and particular mean airway pressures (MAWP) neither of which is standardized. This study utilized a retrospective analysis of archived electronic health record data to evaluate the clinical outcomes of adult patients that had been placed on APRV for at least 8 hours. 68 adult subjects were evaluated as part of a convenient purposive sample. All outcomes of interest (surrogates) for short-term clinical outcomes to include the PaO2/FiO2 (P/F) ratio, Oxygen Index and Oxygen Saturation Index (OI; OSI), and Modified Sequential Organ Failure Assessment (MSOFA) scores showed improvement after at least 8 hours on APRV. Most notably, there was significant improvement in P/F ratio ($p = .012$) and OSI ($p = .000$). Results of regression analysis showed P low as a statistically significant negative predictor of pre-APRV P/F ratio with a higher initial P low coinciding with a lower P/F ratio. The regression analysis also showed MAWP as a significant positive predictor of post-APRV OSI and P high and P low as significant negative predictors of post-APRV MSOFA scores. In summary, it was found that settings for P high, Plow, and T low in addition to overall MAWP and Body Mass Index (BMI) had significant correlation to impact at least one of the short-term clinical outcomes measured.

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Table of Contents

List of Tables

Chapter 1: Introduction

Introduction to Chapter 1

Millions of patients are hospitalized in the U.S. each year, and roughly 3% of all who are admitted to an acute care institution will require positive pressure ventilation (PPV) (Wunsch et al., 2010). In an intensive care environment, there are multiple approaches to artificially ventilating patients, and the means by which a patient is ventilated is well-known to affect the patient's course of care and, most importantly, outcomes (Serpa Neto, Cardoso, Manetta, & et al., 2012). It has been established that PPV is anti-physiologic and contributes to morbidity and mortality under certain conditions (A. Esteban et al., 2013). Furthermore, there is a correlation between ventilation volume, airway pressure, and the development of ventilator-induced lung injury (VILI) ("Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome," 2000).

Although recent animal studies have attempted to establish a type of strain threshold at which lung damage occurs, there is lacking evidence as to which entity—dynamic strain (such as volutrauma) or static strain (such as barotrauma)—primarily contributes to principal lung injury (Protti et al., 2013; Protti et al., 2011). Volutrauma, caused by generalized lung overdistention, and barotrauma, caused by high transpulmonary pressures, are each known to contribute to overall VILI (Beitler, Malhotra, & Thompson, 2016), but it may be the avoidance of atelectrauma, which is caused from cyclic opening and closing of the lung, that is most effective in VILI prevention (Cressoni et al., 2017). Some studies suggest that an open lung approach is ideal because it prevents atlectrauma (Cressoni et al., 2017). Additionally, the management of specific mean airway pressures (MAWP) is more protective than the traditional approach of

targeting conservative inspiratory volumes (Kacmarek, Villar, et al., 2016). However, there is no consensus regarding how best to specifically apply pressure modes of PPV.

Airway Pressure Release Ventilation (APRV), in particular, is a mode of PPV that offers an alternative to conventional ventilation strategies. Moreover, in several small-scale, observational studies, PPV with APRV has been shown to improve overall oxygenation and allow a shorter intensive care unit stay with fewer days on the ventilator (E. G. Daoud, H. L. Farag, & R. L. Chatburn, 2012). Specifically, APRV mode allows for sustained inflation of the lung over a more prolonged period than other pressure modes of PPV (E. G. Daoud et al., 2012), resulting in less cyclic opening and closing of lung units (E. G. Daoud et al., 2012; Habashi, 2005; Protti et al., 2013). In this chapter, the investigator will highlight the need for further study in this arena as well as certain proposed steps in which to accomplish the study. Additionally, the investigator will outline individual entities relating to the study plan and the execution thereof.

Background and Statement of the Problem

It has been estimated that nearly 3% of all hospitalized patients will receive invasive mechanical ventilation, and the mortality rate is significant for this population due, in part, to the development of VILI (A. S. Slutsky & Ranieri, 2014; Wunsch et al., 2010). There are multiple factors that contribute to VILI, and neither open lung approach or conservative volume ventilation strategies absolutely prevent the development of this detrimental condition. Of the variety of PPV strategies that seek to minimize incidence of lung injury, it has been established that protective ventilation, minimizing lung stretch by managing mean airway pressure, is preferred over traditional volume targeted ventilation (Curley, Laffey, Zhang, & Slutsky, 2016).

Although temporary PPV is a common, potentially life-saving, modality, clinicians must recognize that it is one that poses significant risks (A. s. Esteban et al., 2013; Klompas, 2013; Arthur S. Slutsky & Ranieri, 2013). However, there is little published data on recommendations of exactly how to implement specific ventilator modes. Moreover, there remains a gap in knowledge of how to manage the continual application of certain modes of PPV. Pressure targeted modes of mechanical ventilation, albeit part of a protective lung strategy (Rittayamai et al., 2015), require the healthcare provider to maintain astute awareness of the dynamics of pressure application during breath delivery.

Multiple studies have suggested that the cyclic recruitment and de-recruitment of lung units, known as atelectrauma, are a primary cause of acute lung injury (ALI) with detrimental outcomes (Chiumello et al., 2008; Cressoni et al., 2017; Serpa Neto et al., 2012; Arthur S. Slutsky & Ranieri, 2013; "Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome," 2000). However, almost no data exists as to the specific means in which to minimize this distinctive sort of lung stress and strain. Both open lung approach and conservative tidal volume ventilation are preferred in patients with Acute Respiratory Distress Syndrome (ARDS) (Kacmarek, Villar, et al., 2016; "Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome," 2000); however, no definitive ideal mode of PPV exists for all patients.

It has been suggested that judicious use of positive end-expiratory pressure (PEEP) and inspiratory-to-expiratory ratios of 1:1 or greater, also considered inverse-ratio ventilation (IRV), can be useful in minimizing lung damage during PPV attributed to prolonged inflation times and de-recruitment prevention (Ehab G. Daoud, Hany L. Farag, & Robert L. Chatburn, 2012; Spieth

et al., 2015), and the APRV mode of PPV is one method to protectively ventilate a variety of patient populations that may require IRV (Burchardi, 1996; Diaz et al., 2011; Francesca Facchin, 2015; Kollisch-Singule et al., 2014). There is no consensus, however, as to the specific means by which IRV should be applied, since several studies that utilize animal or mathematical models have been inconclusive (Daoud & Chatburn, 2014; Arthur S. Slutsky & Ranieri, 2013).

Relevance, Significance, and Study Purpose

In acute care, the respiratory therapist (RT) is charged with caring for and managing patients that are placed on mechanical ventilation, also known as PPV. Among physicians and RTs alike, there is varying opinion regarding the best means in which to artificially ventilate patients, as there are many choices in mode, breath delivery, and various other parameters that can be controlled by the operator of the PPV machine. Numerous studies address the nature of PPV and overall clinical implications; however, few have identified specific strategies that effectively allow patients to be mechanically ventilated, short-term, while protecting against VILI.

At the turn of the century, one paramount study ("Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome," 2000) established that lower tidal volumes are preferred to higher tidal volumes during PPV; however, end inspiratory pressure must also be considered to prevent VILI (Protti et al., 2011). A substantial number of patients placed on PPV are ventilated using a type of pressure-controlled mode, rendering volume to be a function of the particular pressure applied and the overall pulmonary mechanics. Both volume and pressure modes of PPV offer advantages individually; however, modes of PPV in which pressure is controlled has gained favor as a means to employ a protective lung strategy (Rittayamai et al., 2015). The APRV

mode, specifically, offers a variety of options that will manipulate breath delivery while absolutely controlling the application of pressure during the breath cycle, which is also considered a mode of PPV recommended for patients with already developing or concomitant lung injury (Burchardi, 1996; E. G. Daoud et al., 2012; J. B. Downs & Stock, 1987).

Mechanical ventilation via PPV has long been known to induce ALI and contribute to overall morbidity and mortality in acute care patients (de Prost, Ricard, Saumon, & Dreyfuss, 2011). As ventilation strategies and modes of PPV have evolved, there has been little improvement in overall incidence of ALI and associated mortality rates (Erickson, Martin, Davis, Matthay, & Eisner, 2009; A. Esteban et al., 2013). The current fourth generation mechanical ventilators allow for more autonomy in delivering positive pressure breaths. However, this increased capability requires more decision-making when implementing a modern mode of PPV. Because PPV poses significant risk, regardless of the mode (Rittayamai et al., 2015), clinicians must remain perspicacious when seeking both to prevent and treat VILI as well as ALI.

Although, microprocessor-controlled, later-model ventilators are more sensitive to patient biofeedback, improperly implemented modes of PPV can have deleterious effects on the lung (de Prost et al., 2011). Clinicians are able to apply and limit specific ventilation pressure and maintain relative control of many aspects of the breath cycle (Kacmarek, 2011), yet there are many variables to consider in order to ventilate safely a multiplicity of patient populations.

From the advent of PPV in the early 1900s to the current versions of microprocessor-controlled machines with graphical user interface, mechanical ventilation has changed dramatically (Kacmarek, 2011). With advancements in PPV breath delivery options, various modes of mechanical ventilation have been introduced that allow clinicians more choices in how

the respiratory cycle can be manipulated (Tobin, 2001). More is also known regarding what contributes to VILI. However, a significant portion of mechanically ventilated patients are still developing VILI, occasionally described as ALI or vent-propagated Acute Respiratory Distress Syndrome (ARDS) (Erickson et al., 2009). Unfortunately, there is disagreement concerning the application of certain modes of PPV, and mortality attributed to mechanical ventilation remains high (Erickson et al., 2009; A. Esteban et al., 2013).

As is it difficult to quantify actual lung stress and strain during PPV, the evaluation of plateau pressure and tidal volumes are considered the surrogates for assessing this metric (Chiumello et al., 2008), and a protective lung strategy remains the preferred approach to minimize stress and strain (Rittayamai et al., 2015). In order to prevent VILI, tidal volumes must be kept within an acceptable range, lower than 6 ml/kg of predicted body weight (Serpa Neto et al., 2012; "Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome," 2000), and the recommended plateau pressure should be maintained lower than 30 cmH20 (de Prost et al., 2011).

A special type of pressure-targeting mode, APRV, promotes an open lung concept (Lachmann, 1992) and is considered to be part of a protective lung strategy in the application of PPV (E. G. Daoud et al., 2012; Tobin, 2001). Although APRV permits the clinician to maintain a consistent plateau pressure, there is no consensus, or established guideline, with respect to the safest threshold for the absolute prevention of ALI (Rittayamai et al., 2015). It is also unknown whether APRV mode employed with higher inspiratory times (I-times) and lower plateau pressures results in better clinical outcomes when compared to APRV mode employed with shorter I-times and higher plateau pressures.

This study investigated association between various settings in the APRV mode and short term clinical outcomes of interest. Because there is a general lack of data as to what specific I-times and sustained pressures allow for maximal oxygenation and best short term outcomes, this study sought to distinguish whether there is a superior way in which to implement and manage the APRV mode of PPV. If specific settings are associated with better clinical outcomes, clinicians should be able to initiate more purposefully the APRV mode for patients prior to the development of VILI. Likewise, as the study revealed certain predictors of clinical outcomes, the findings will hopefully stimulate further study into this area, allowing for more standard initial PPV setting recommendations for patients that will receive APRV or for those patients who have already developed ALI or ARDS.

Elements

Hypotheses

Overall, in APRV mode, the use of a longer I-time results in ideal mean airway pressure, less pulmonary stress and strain due to less cyclic opening and closing of the lung, and, therefore, overall better clinical outcomes as evidenced by better PaO2/FiO2 ratio, Oxygenation Index (OI), Oxygen Saturation Index (OSI), and Modified Sequential Organ Failure Assessment (MSOFA) scores when compared to the use of shorter I-times in a similar patient population.

H_0: There is no relationship between the length of I-time and short-term clinical outcomes, such as PaO2/FiO2 ratio, OI, OSI, and MSOFA scores.

H_1: If there is a relationship between the length of I-time and short-term clinical outcomes, patients ventilated with longer I-times will demonstrate better short-term clinical outcomes, as evidenced by better P/F ratio, OI, OSI, and MSOFA scores, than patients ventilated with shorter I-times *because of the application of ideal mean airway*

pressures.

Theories

The theoretical framework that guided this research is founded in the evidence-based medicine model of best clinical practice ("Evidence-based Medicine. A new Approach to Teaching the Practice of Medicine," 1992). Moreover, the investigator sought to integrate the theory of evidence-based medicine into bedside clinical practice (K. Walshe & T. G. Rundall, 2001) through the adoption of the presupposition that if an intervention or therapy is shown to improve the overall course of care of a large group of similar patients, then that particular intervention or therapy should be considered as best practice in a similar patient population, provided that no other published data suggests the antithesis. Walshe and Rundall (2001) highlighted the fact that there exists relatively unexplained, eclectic variations in clinical practice patterns, and, for decades, evidence has been produced that emphasizes this gap between research and clinical practice. This study sought to allow a translation of research into bedside clinical practice.

In a review by Tabak et al. (Tabak, Khoong, Chambers, & Brownson, 2012), 61 different models of current theories and frameworks were evaluated for specific modalities of dissemination and implementation of research into practice. Unfortunately, available measures to confirm implementation of any research is generally lacking given the broad spectrum of a particular application in various settings. Additionally, the general small sample size of numerous studies may hamper the overall development, evaluation, and use of standard measures (Tabak et al., 2012).

Upon study conclusion, the investigator adopted an analogous model for disseminating and implementing the study results as originally proposed by Funk, Tornquist, and Champagne

(Funk, Tornquist, & Champagne, 1989). Furthermore, as most dissemination practices lack consistency and broad impact, it would be important to mimic an already established model type of persuasive communication, or diffusion, of innovation as cited in a review by Wilson et al. (Wilson, Petticrew, Calnan, & Nazareth, 2010).

Research Question

Do patients ventilated with longer I-times, in APRV mode, have better short-term clinical outcomes compared to patients ventilated in the same mode with shorter I-times? These so-called short-term clinical outcomes will encompass a variety of metrics to include P/F ratio, OI, OSI, and MSOFA score (Dechert, Park, & Bartlett, 2014; Ferreira, Bota, Bross, Melot, & Vincent, 2001; Grissom et al., 2010; Rawat et al., 2015; Vincent et al., 1996). The investigation of long-term clinical outcomes is of interest; however, it was not investigated during this study since a retrospective analysis of archived EHR data does not allow for long-term follow-up or confirmation of post hospital stay mortality.

Definition of Terms

Conceptual

All of the following definitions have been extracted from Egan's *Fundamentals of Respiratory Care* (Kacmarek, Stoller, & Heuer, 2016) and may be further defined in the following "Operational" section.

Airway-Pressure Release Ventilation (APRV) – form of pressure ventilation that uses two levels of continuous positive airway pressure in an intermittent mandatory ventilation breathing pattern

Barotrauma – physical injury sustained as a result of exposure to ambient pressures above normal, most commonly secondary to positive pressure ventilation (e.g. pneumothorax and pneumomediastinum)

Positive End-Expiratory Pressure (PEEP) – application and maintenance of pressure above atmospheric at the airway throughout the expiratory phase of positive pressure mechanical ventilation

Ventilator-induced lung injury (VILI) – lung injury which occurs as a result of excessive pressure and/or volume during mechanical ventilation

Volutrauma – alveolar overdistention and damage caused by ventilation with high peak inflation pressures

Operational

Airway-Pressure Release Ventilation (APRV) – a specific mode of PPV, originally described by in 1987 (J. B. Downs & Stock, 1987) as a type of continuous positive airway pressure (aka CPAP) in which unusually long I-times are utilized at higher held pressure levels

Barotrauma – lung injury caused by the delivery of excess pressure during PPV

Inverse Ratio Ventilation (IRV) – inspiratory times during PPV that exceed expiratory times, typically in order to increase mean airway pressure at lower peak distending pressures

Positive End-Expiratory Pressure (PEEP) – above ambient pressure applied to the lung that persists during a resting state, at end exhalation during PPV

Positive Pressure Mechanical Ventilation (PPV) – above ambient pressure applied to the airway/lungs during artificial mechanical respirator use

Ventilator-induced lung injury (VILI) – lung damage, typically qualified by the presence of pulmonary edema on chest x-ray or clinical presentation that develops during and as a consequence of PPV

Volutrauma – lung injury caused by the delivery of excess volume during PPV

Description of Variables

Dependent

This study included dependent variables indicative of certain short-term clinical outcomes after being placed on mechanical ventilation in the APRV mode for at least 8-24 hours. These dependent variables were comprised of changes in the following variables between the time of APRV implementation and at least 8-24 hours thereafter: P/F ratio, OI, OSI, and MSOFA score (Dechert et al., 2014; Ferreira et al., 2001; Grissom et al., 2010; Rawat et al., 2015; Vincent et al., 1996).

Independent

This study included many independent variables as a function of each patient's already executed course of care. These variables included:

1) patient demographics such as: age, sex, race, height, weight, and diagnosis

2) specific unit of care

3) time from intubation to initiation of APRV

4) total continuous duration on APRV

5) variables immediately prior to being placed on APRV such as:

- inhaled fractional concentration of oxygen (FiO2)
- mean airway pressure (MAWP)
- arterial partial pressure of oxygen (PaO2)
- oxygen saturation (SaO2 or SpO2)
- pre-APRV ventilator mode

6) APRV initial settings such as:

- time high (T high)

- pressure high (P high)
- time low (T low)
- pressure low (P low)
- pressure support (PS)
- APRV average tidal volume (Vt)
- PS average Vt

7) conditions at initiation of APRV such as:

- Glasgow coma scale (GCS)
- bilirubin
- mean arterial pressure (MAP)
- creatinine (Cr)

8) APRV settings after at least 8 hours to include:

- time high (T high)
- pressure high (P high)
- time low (T low)
- pressure low (P low)
- pressure support (PS)
- APRV average tidal volume (Vt)
- PS average Vt

Covariates

Several covariates should be considered in a retrospective study of this type to include: comorbid conditions and/or differential diagnoses that may alter the course of care outside of the original respiratory failure as well as the following: 1) time delay to APRV, 2) individual settings

on APRV, 3) primary and secondary diagnoses, 4) unit of management (SICU, MICU, NeuroICU, Other), and 5) total continuous duration on APRV. The presence and progression of organ failure as it relates separately to metrics such as the MSOFA score (Ferreira et al., 2001; Grissom et al., 2010; Vincent et al., 1996) as well as the model of ventilator used are also considered covariates.

Rationale

Downs and Stock introduced a newer mode of PPV, APRV, to the healthcare market circa 1987. The original study was small ($N = 10$) and utilized animal models (dogs), comparing APRV with one other traditional mode of PPV. As a novel approach to applying Continuous Positive Airway Pressure (CPAP), the findings suggested that APRV was a viable mode to treat ALI, because arterial oxygenation improved and peak airway pressures were maintained at a lower level than a more traditional mode (J. B. Downs & Stock, 1987). The next year, the same group conducted the first human trial of APRV with similar findings; patients with ALI were successfully ventilated at lower peak airway pressures when compared to traditional PPV (Garner, Downs, Stock, & Rasanen, 1988). A patent was issued to Dr. Downs the same year for his invention of the new PPV mode (J.B. Downs, 1988).

After two landmark studies were published (J. B. Downs & Stock, 1987; Garner et al., 1988), multiple variable studies were conducted to evaluate the efficacy of APRV. Eventually, APRV was established as a means for implementing a protective lung strategy for the non-injured lung as well as a recommended early treatment for ALI or ARDS (Habashi, 2005; Varpula et al., 2004). There are no studies, however, that have evaluated specific I-times and the relationship between the resulting MAWP and short-term clinical outcomes.

Assumptions

Certain assumptions were made in order to proceed with this study, resulting in study validity and continuing relevance as well as application to bedside care. To begin, as this study employed a retrospective analysis of archived EHRs, the investigator assumed the information technology (IT) department extraction team had adequately surveyed the entire UH EHR in order to acquire the particular purposive sample that met inclusion criteria. Although seemingly a limitation, the investigator further assumed that the archived EHR data was entered into the medical record in its original form by each clinician and/or healthcare provider in an accurate manner for each individual patient, yielding the data as such. The data extracted was raw data and treated as such.

In broader terms, various pragmatic assumptions were considered. As PPV has been utilized for many years (Kacmarek, 2011), one would assume that this means of artificial ventilation will continue. Additionally, after almost three decades, the APRV mode persists and is currently being used in the local Shreveport/Bossier City, Louisiana area with success. Nevertheless, APRV mode use is not prevalent across the US and is mainly used as a rescue mode only (E. G. Daoud et al., 2012). There is an assumption that if evidence-based data were presented to suggest that the APRV mode could be utilized in a certain manner to influence positive clinical outcomes, more institutions would adopt this mode of PPV as an adjunct to standard of care (K. Walshe & T. Rundall, 2001).

Summary

In summary, the investigator sought to identify certain clinical implications of longer I-times compared to shorter I-times in APRV mode, examining specific metrics considered surrogates for clinical outcomes as previously described. This retrospective study was conducted

via a partnership between Louisiana State University Health Sciences Center in Shreveport (LSUHSC-S) and University Health (UH) Hospital and may offer clinicians practical insight as to the best means in which to mechanically ventilate ventilate patients in a mode such as APRV, providing additional awareness to the specific application of PPV in order to assist patients who have already developed VILI.

Chapter 2: Review of the Literature

Introduction to Chapter 2

The implementation and management of mechanical ventilation are complex processes with no current standard across the medical disciplines. Although much data exists on its use, a majority of studies only describe PPV as implemented within the categorical application of the generically controlling either volume or pressure (Rittayamai et al., 2015; A. S. Slutsky & Ranieri, 2014; Tobin, 2001). Since current, fourth generation mechanical ventilators offer numerous modes, it is imperative that the clinician managing PPV be aware of the potential deleterious effects specific modes can have, whether used in the short-term or over longer periods. It has been proposed that future mechanical ventilators will offer decision support (Kacmarek, 2011), but, currently, the physician and RT are the primary decision makers in the application and management of PPV. A review of the literature reveals a convoluted plethora of animal studies, various recommendations, and overall disagreement related to the use of PPV.

From the advent of PPV in the early 1900s to the current versions of microprocessor-controlled machines with graphical user interface, mechanical ventilation has changed dramatically (Kacmarek, 2011). Using advancements in PPV breath delivery options, various modes of mechanical ventilation have been introduced that allow clinicians more choices in how the respiratory cycle can be manipulated (Tobin, 2001). More is also known as to what contributes to VILI. However, a significant portion of mechanically ventilated patients are still developing VILI, occasionally described as ALI or vent-propagated ARDS (Erickson et al., 2009), and agreement is lacking in how certain modes of PPV should be applied. Furthermore, mortality attributed to mechanical ventilation remains high (Erickson et al., 2009; A. Esteban et al., 2013).

As is it difficult to quantify actual lung stress and strain during PPV, the evaluation of plateau pressure and tidal volumes is considered the generic surrogates for assessing this metric (Chiumello et al., 2008), and a protective lung strategy remains the preferred approach to implementation and execution of PPV (Rittayamai et al., 2015). In order to prevent VILI, tidal volumes must be kept within an acceptable range, lower than 6 ml/kg of predicted body weight (Serpa Neto et al., 2012; "Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome," 2000) with a recommended plateau pressure maintained lower than 30 cmH2O (de Prost et al., 2011). Several traditional *volume*-targeting modes of mechanical ventilation permit the controlled application of flow to deliver a, so-called, safe volume, while other traditional *pressure*-targeting modes utilize the application of pressure to achieve variable volumes with consistent plateau pressures (Rittayamai et al., 2015).

A special type of pressure-targeting mode, APRV, promotes an open lung concept (Lachmann, 1992) and is considered a part of a protective lung strategy of PPV (E. G. Daoud et al., 2012; Tobin, 2001). Although APRV permits the clinician to manage a consistent plateau pressure, there is no consensus, or established guideline, as to the safest threshold in the absolute prevention of ALI (Rittayamai et al., 2015). It is also unknown whether APRV mode employed with higher I-times and lower plateau pressures has better clinical outcomes than if utilized with shorter I-times and higher plateau pressures.

Historical Overview

Mechanical Ventilation

Mechanical ventilation, in its modern form, has been a mainstay of healthcare since the early 1900s and has developed into the fourth generation of microprocessor-controlled machines in common use today (Kacmarek, 2011; A. S. Slutsky, 2015). Some might contest that the first account of artificial respiration is found in the antiquity of the Holy Bible's 2 Kings 4:34, in which it is noted, "Then he [Elisha] went up and lay on the child, putting his mouth upon his mouth… the flesh of the child became warm" (New Living Translation). Historically, artificial respiration by means of PPV can be traced back in the scientific literature to Vesalis' 1543 *De Humani Corporis Fabrica* treatise on anatomy in which he recorded:

> But that life may be restored to the animal, an opening must be attempted in the trunk of the trachea, into which a tube of reed or cane should be put; you will then blow into this, so that the lung may rise again and take air. (Singer, 1943)

Robert Hook further expanded the knowledge of PPV through his canine experiments in which he explains, in detail, the use of PPV via bellows for successful resuscitation (Hook, 1666).

During the 1700s, several paramount physiologic discoveries, including that of oxygen and its use in respiration, temporarily altered the view of mouth-to-mouth resuscitation modalities (A. S. Slutsky, 2015), but a century later saw the advent of the precursor to our most common form of PPV. Circa 1864, Alfred Jones invented one of the first negative pressure ventilators (Jones, 1864), which would become the template for the "iron lung" that was originally introduced by Alfred Willez in 1876, also known as the "spirophore" (Emerson & Loynes, 1978). In 1929, Drinker and Shaw developed the first widely used iron lung, originally purposed to treat patients with polio (Drinker & Shaw).

As of the 1940s, negative pressure ventilation was mainstream, but this would soon change when the polio resurgence reached its peak during the 1950s. Famously, Bjorn Ibsen is credited with leading the charge to convert patients from negative pressure ventilation to PPV. Incidentally, this led to the formation of intensive care units, resembling what is known today (*Anaethesia and the Practice of Medicine: Historical Perspectives*, 2007).

Mechanical ventilation during the polio epidemic of the mid-twentieth century still employed negative pressure, but this was soon replaced with PPV as a mainstay of care. Currently, almost all critically-ill patients requiring respiratory support will be placed on some form of PPV. Of the multiplicity of various mechanical ventilators and modes of PPV, there remains little consistency in how PPV is applied and almost no consensus in how to manage this life-saving, yet anti-physiologic, intervention.

VILI

It has long been known that artificial respiration, especially via PPV, can cause injury. In 1744, it was first described that mouth-to-mouth was preferred above the use of bellows as Fothergill noted, "the lungs of one man may bear, without injury, as great a force as those of another man can exert; which by the bellows cannot always be determined" (Fothergill, 1744). During the polio epidemic, investigators recognized that PPV could induce damage to lung structure (Avignon, Hedenstrom, & Hedman, 1956). The term "respirator lung" was eventually coined in 1967 to describe the development of "heavy lungs" that resulted from certain post mortem pathological findings in patients that had undergone PPV ("Respirator Lung Syndrome," 1967). It is now better understood that PPV is not only deleterious to the lung but can also result in widespread harm to other organ systems as a result of PPV-induced inflammation (Plotz, Slutsky, van Vught, & Heijnen, 2004).

A paradigm shift began shortly after the work by Ashbaugh et al. in 1967 when the term ARDS was first described as a type of sudden manifestation of lung injury as a result of indiscriminate stimuli (Ashbaugh, Bigelow, Petty, & Levine, 1967). Arguably, Mead et al. are credited with the early conceptualization of VILI through the use of theoretical models in an attempt to assess elastic mechanical properties of the lung. The authors concluded that "mechanical ventilation, by applying high transpulmonary pressures to heterogeneously expanded lungs, could contribute to the development of lung hemorrhage and hyaline membranes" (Mead, Takishima, & Leith, 1970, p. 602). A more formal concept of, so-called, VILI has eventually been accepted but only well after the work of both Ashbaugh and Mead et al. introduced the notion that PPV could be of detriment under certain conditions.

Irrespective of the particular terminology used in the past, mechanical ventilation via PPV has long been known to cause ALI and contribute to overall morbidity and mortality in acute care patients (de Prost et al., 2011). The application of excessive transpulmonary pressure as well as the delivery of above physiologic tidal volumes individually have been shown to cause VILI in animal models (Dreyfuss & Saumon, 1998). Ventilator-*associated* lung injury might be a more appropriate term as it is virtually impossible to prove the ventilator as a single cause of ALI ("International Consensus Conferences in Intensive Care Medicine: Ventilator-associated Lung Injury in ARDS. This official conference report was cosponsored by the American Thoracic Society, The European Society of Intensive Care Medicine, and The Societe de Reanimation de Langue Francaise, and was approved by the ATS Board of Directors, July 1999," 1999); however, VILI remains the most common term used to describe ALI that develops during mechanical ventilation. Although VILI is indistinguishable from other forms of lung injury, it is still widely accepted that mechanical ventilation has the potential to worsen acute

lung disease (Curley et al., 2016; Parker, Hernandez, & Peevy, 1993). Specific VILI cannot absolutely be proven, but a recent review by Curley et al. reiterated the ever-growing body of knowledge surrounding the evidence that PPV causes injury and eludes a cellular response (Curley et al., 2016).

As ventilation strategies and modes of PPV have evolved, there has been little improvement in overall incidence of ALI and mortality rates (Erickson et al., 2009; A. Esteban et al., 2013). The current fourth generation mechanical ventilators allow for more autonomy in delivering positive pressure breaths, but this increased capability requires more decision-making when implementing a modern mode of PPV. PPV poses significant risk, regardless of the mode (Rittayamai et al., 2015), and clinicians must remain astute when seeking not only to prevent but also to treat VILI and ALI.

Although microprocessor-controlled, later-model ventilators are more sensitive to a patient's biofeedback, improperly implemented modes of PPV can have deleterious effects in the lung (de Prost et al., 2011). Clinicians are able to apply and limit specific ventilation pressure and maintain relative control of many aspects of the breath cycle (Kacmarek, 2011), yet there are numerous variables to consider in order to ventilate safely an array of patient populations. In summary, VILI is a consequence of several mechanisms that include: 1) barotrauma, resulting from excessive pressures; 2) volutrauma, resulting from excessive volumes; 3) atelectrauma, from cyclic closing and reopening of alveolar units; and 4) biotrauma, resulting from the cytokine/inflammatory mediator release as a result of PPV (Dreyfuss & Saumon, 1998).

APRV

Downs and Stock introduced a newer mode of PPV, known as APRV, to the healthcare market circa 1987. Their original study was small *(N* = 10) and utilized animal models (dogs),

comparing APRV with one other traditional mode of PPV. As a novel approach to applying CPAP, the findings suggested that APRV was a viable mode to treat ALI because arterial oxygenation improved, and peak airway pressures were maintained at a lower state than the traditional mode (J. B. Downs & Stock, 1987). The next year, the same group conducted the first human trial of APRV with similar findings in that patients with ALI were able to be successfully ventilated at lower peak airway pressures compared to traditional PPV (Garner et al., 1988). Subsequently, a patent was issued to Dr. Downs the same year for his invention of the new PPV mode (J.B. Downs, 1988).

After two landmark studies (J. B. Downs & Stock, 1987; Garner et al., 1988) were published, scores of variable types of studies were conducted to evaluate the efficacy of APRV. Eventually, APRV was established as a means for implementing a protective lung strategy for the non-injured lung as well as a recommended early treatment for ALI or ARDS (Habashi, 2005; Varpula et al., 2004). More recently, it has been suggested that early implementation of APRV prevents VILI in the normal lung (Emr et al., 2013; F. Facchin & Fan, 2015). Overall, however, there remains a lack of specific recommendation on how best to apply this protective ventilation strategy (Jain et al., 2016).

It is well established that the APRV mode of PPV allows opportunity to mechanically ventilate patients, utilizing a protective lung strategy as the mode allows for sustained inflation of the lung over a more prolonged period than does traditional IRV (E. G. Daoud et al., 2012), resulting in less cyclic opening and closing of lung units (E. G. Daoud et al., 2012; Habashi, 2005; Jain et al., 2016; Protti et al., 2013). In addition to being a pressure-targeting breath delivery mode, APRV allows one to set extended I-times for application of IRV (Habashi, 2005). Unlike traditional IRV, APRV is pressure-targeted breath delivery with sustained pressures for

prolonged I-times that allow for maximal recruitment of lung units, avoiding atelectrauma. Furthermore, the patient is allowed to breath spontaneously at maximal inflation pressure, so ventilator asynchrony is less of an issue than during traditional IRV (E. G. Daoud et al., 2012).

The APRV mode offers opportunity not only to prevent VILI but also to treat ALI and ARDS. This IRV pressure-targeted mode is a form of CPAP applied beyond the traditional timeframe in which patients are usually in control of their preferred I-time. Under spontaneous conditions, the time taken to inspire is almost identical to the time taken to expire. Similarly, during PPV in traditional CPAP mode, patients choose their own I-time, rarely exceeding the time of expiration. Katz and Marks established that CPAP, compared to spontaneous conditions while intubated, allowed for a decrease in a patient's work of breathing (WOB) (Katz & Marks, 1985). The understanding of the benefits of CPAP has changed over the years, and APRV mode has gained recognition as a more effective PPV mode in the allowance of spontaneous breathing (E. G. Daoud et al., 2012; Varpula et al., 2004).

When APRV was originally introduced into healthcare, it was touted as a mode of PPV that mimicked CPAP; however, unlike CPAP, APRV allows for continuous pressure application for a prolonged time period while conserving the patient's ability to trigger spontaneous efforts. The major difference between traditional CPAP and APRV lies in the fact that, in APRV, pressure is applied similar to IRV pressure-targeted modes, but only APRV allows patients to continue breathing spontaneously at a sustained inflation pressure. A short release time allows for ventilation to be accomplished regardless of a patient's spontaneous efforts (J. B. Downs & Stock, 1987).

Relevant Theory

Stress and Strain

It has been established that a conglomeration of events leads to the development of VILI (Curley et al., 2016). Of these events, none can be identified as an individual causative factor. It is, however, the process of cyclic opening and closing and the over distention of alveolar units that lead to excessive stress and strain in the lung and contributes to the overall development of VILI (Chiumello et al., 2008; Protti et al., 2013; A. S. Slutsky & Ranieri, 2014). In humans, it is difficult to quantify stress and strain; however, several parameters have been suggested as being analogous to such.

A paramount study published in the *New England Journal of Medicine*, in 2000, confirmed that in patients with ALI, ventilation with smaller tidal volumes (6 ml/kg) results in better clinical outcomes when compared to ventilation with traditional tidal volumes (12 ml/kg). This trial, executed by the "ARDSnet" group, additionally found that extra pulmonary organ failure and mortality were decreased in the lower tidal volume group ("Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome," 2000). In 2007, a study by Terragni et al. suggested that implementation of lower tidal volumes (6 ml/kg) may not be sufficient to protect from lung injury. The group concluded that simply limiting tidal volume, even at plateau pressures $\leq$ 30 cmH2O, may not be sufficient protection for certain patients with large areas of non-aerated lung (Terragni et al., 2007). Other studies have explored the concept of using even lower tidal volumes (< 6 ml/kg), indicating that volume-targeted ventilation with tidal volumes lower than 6 ml/kg might enhance lung protection, ultimately preventing VILI (Bein et al., 2013; Terragni et al., 2009).

Under a majority of circumstances, pressure-targeted modes of PPV are preferred to volume-targeted modes for lung protection (Rittayamai et al., 2015). And, although lower tidal volume ventilation compared to conventional tidal ventilation is associated with better clinical outcomes (Neto et al., 2015; Serpa Neto et al., 2012), pressure-targeted ventilation is more protective against VILI. Needem et al. evaluated the use of volume-limited ventilation as compared to the use of pressure-limited ventilation in a large prospective cohort, noting that lung protective ventilation via pressure-limited modes was associated with a substantial long-term survival benefit in patients with ALI (Needham et al., 2012). In patients with ARDS, Amato et al. suggested that driving pressure (ΔP), comparing tidal volume to respiratory-system compliance, may be a more sensitive indicator of risk as opposed to individual tidal volume or plateau pressure (Amato et al., 2015). In 2016, the "LUNG SAFE" study by Laffey, et al. concluded that both lower plateau and lower driving pressures are associated with improved survival in ARDS (Laffey et al., 2016). The overwhelming concept remains that "VILI originates from the interaction between the mechanical power transferred to the ventilable lung parenchyma and the anatomo-pathological characteristics of the latter" (Gattinoni et al., 2016, p. 1574).

Time Constants

In 1955, a well-known joint study between the John Hopkins University School of Medicine and Harvard Department of Physiology explored the concept of varying individual lung unit compliance, finding this variance is attributed to both volume-elastic and flow-resistive properties (Otis et al., 1956). The group's findings led to the concept of what would eventually be understood as the pulmonary time constant. As a product of both lung compliance and overall system resistance, a time constant is the time required to passively inflate and deflate each lung

unit. Ideally, under normal conditions, 95% of alveoli will be inflated within three time constants (0.25 seconds). However, with lung disease, irrespective of cause, either or both lung compliance and airways resistance is often distorted so that filling time for each individual unit can be extremely variable (Kacmarek, Stoller, et al., 2016).

In certain cases, longer I-times may be required to satisfy one time constant. If I-time is inadequate, filling volume remains insufficient, and alveolar ventilation is decreased. Furthermore, inadequate filling contributes to the development of widespread atelectasis, contributing to more stress and strain in the lung leading to VILI (A. S. Slutsky & Ranieri, 2014). The use of longer I-times, beyond customary initial setting for traditional modes of PPV, may assure that atelectrauma from under inflation during inspiration is avoided altogether.

Current Recommendations of APRV Use

To date, studies comparing APRV to conventional PPV have yet to demonstrate any significant difference in mortality outcomes (Gonzalez et al., 2010; Maxwell et al., 2010; Varpula et al., 2004). Even though the oxygenation benefit of APRV use has been well established (E. G. Daoud et al., 2012), there remains an overall lack of consensus concerning when to implement this mode of PPV. The additional challenge remains as to how one should manage this non-conventional mode, given the current lack of recommendations.

Two of the more common published management strategies of APRV simply include generic recommendations for setting the four primary variables of: 1) lung inflation pressure (P high), 2) lung inflation time (T high), 3) lung deflation pressure (P low), and 4) lung deflation time (T low). The recommendations of both Habashi and Modrykamien et al. suggest that it is best to target I-times of at least 4 seconds with a strategy of matching pre-APRV, conventional ventilator plateau pressure as a starting point for P high. Both published strategies suggested

setting T low to target inducement of auto PEEP with an initial P low setting of 0 cmH2O (Habashi, 2005; Modrykamien, Chatburn, & Ashton, 2011). To date, there is still no single APRV recommendation widely accepted in respiratory care. Furthermore, over the last 30 years of APRV use, studies have rarely evaluated similar settings in order to assess the efficacy of a single APRV strategy (Jain et al., 2016).

Summary of Literature

There is little published data on how exactly to implement and apply certain ventilator modes. Specifically, there seems to be an overall knowledge gap in how best to manage newer modes of PPV after their implementation. Both the physician and RT remain the primary decision-makers in the process of both initiating and managing PPV. After the initial decision of choosing the proper mode, the clinician must decide how best to manipulate and maintain PPV in a dynamic environment, and few published recommendations exist outside of generic suggestions.

Lung protective strategies during PPV have been associated with a substantial long term survival benefit for patients with ALI (Needham et al., 2012), and APRV offers a means to achieve high-level lung protection (Jain et al., 2016). Although no specific recommendations have necessarily been widely adopted, APRV is a mode well-known to offer a means to achieve better oxygenation and produce less stress and strain on lung tissue (E. G. Daoud et al., 2012; Emr et al., 2013; F. Facchin & Fan, 2015). Two of the more commonly recommended published strategies (Habashi, 2005; Modrykamien et al., 2011) are based on animal studies and theoretical considerations and do not address whether a specific I-time is preferred to another. More studies are indicated to identify the best means in which to apply the APRV mode. It remains unknown

whether it is best to target higher I-times with lower plateau pressures or whether shorter I-times with higher plateau pressures would be more favorable to the prevention and treatment of ALI.

Chapter 3: Methodology

Introduction to Chapter 3

There are many modes of PPV, and each allows various options of implementation and management (Metnitz et al., 2009). Of the choices in PPV modes, pressure-targeted modes have been shown to be more lung protective compared to volume-targeted modes (de Prost et al., 2011; Lachmann, 1992; Rittayamai et al., 2015), and further developments in ventilator technology have contributed to favoring IRV as a preferred technique to achieve lung protection, while enhancing oxygenation (Burchardi, 1996; Lachmann, 1992; Protti et al., 2013). APRV mode, also known as Bivent® or BiLevel®, (Chopra, Vardhan, & Chopra, 2014) allows the employment of a protective lung strategy similar to typical pressure-targeted IRV. However, APRV mode allows for sustained inflation of the lung over a more prolonged period than does traditional IRV (E. G. Daoud et al., 2012), resulting in less cyclic opening and closing of lung units (E. G. Daoud et al., 2012; Habashi, 2005; Protti et al., 2013).

No definitive data exists concerning how APRV should be applied in order to *prevent* VILI compared to applying APRV to *treat* ALI. This quantitative study evaluated subjects in the intensive care environment of an academic medical center who were placed on PPV via APRV. The retrospective analysis sought to compare subjects' responses to longer I-time versus shorter I-time settings and to identify which setting for I-time resulted in better clinical outcomes as indicated by P/F ratio, OI, OSI, and MSOFA scores. This chapter will provide a summary of the research design and methodology, rationale, threats, strengths and weaknesses of design, subjects' discussion, reliability and validity, overall resources required, data collection and analysis procedures, as well as the limitations and delimitations of the study.

Pilot Study

A pilot study was completed during the NSU Winter Term in 2016 as part of the requirement in the HSP 9007: Research Practicum course. The pilot was of similar format to this larger, more detailed dissertation study but provided only limited data. However, with $N = 20$, the pilot provided insight into the induction of longer I-times with the application of lower MAWP during PPV. The findings suggested that, in APRV, ventilation with longer I-times at lower MAWP tended to result in better short-term clinical outcomes as evidenced by better/lower OI and OSI.

Although the pilot study did not render statistically significant results, it could be appreciated that longer I-times resulted in better OI and OSI, in general. Additionally, the pilot provided an experience in order to allow corrections for future studies along the same topic. In conclusion, the pilot study showed promise in revealing that there may be a correlation between how APRV is implemented and managed, and it may show the effect on certain short-term clinical outcomes.

The pilot revealed there is opportunity for more studies related to the topic as well as a need to study other modes of PPV. The lower OI and OSI after implementing APRV with longer I-times may indicate that a longer I-time approach is more desirable and a safer means in which to utilize the APRV mode, overall. There is an expectation that clinicians would be offered great insight into how best to approach the implementation and management of APRV as the topic is studied further. Also, the pilot, as well as this dissertation study, could culminate into a template for other studies of any of the various modes of PPV commonly used in modern-day clinical practice.

Research Design and Methodology

This quantitative study evaluated adult subjects in an intensive care environment who were placed on the APRV mode of PPV at a large academic medical center between October 1, 2013 and October 1, 2016. The investigator performed a retrospective analysis of archived EHR data in order to evaluate subjects' responses to various I-times quantified and described per short-term clinical outcomes among the diagnostic tests evaluated. Each patient's settings on APRV and coinciding parameters as well as concomitant clinical diagnostic values included in the prior independent variables list (Ch. 1) were acquired in alignment with the specific timeframe in which APRV was employed. The subjects' ventilator settings as well as other ventilator parameters and diagnostic values were evaluated. As the main independent variable, the I-time category ("short" or "long"), was determined based upon a yield from the stepwise regression analysis related to the T-high setting as a predictor.

The harvesting of archived EHR data allowed specific insight into a patient's course of care, and clinical outcomes centered on the patient being mechanically ventilated in APRV mode. Once subject information was compiled and all raw data accounted for, demographics were appraised for central tendency, and I-time was evaluated for normal frequency distribution. As the main outcomes of interest, the pre-APRV dosing and post-APRV dosing P/F ratio, OI, OSI, and MSOFA scores were also calculated for each patient, representative of validated predictors of clinical outcomes (Dechert et al., 2014; Ferreira et al., 2001; Grissom et al., 2010; Rawat et al., 2015; Vincent et al., 1996).

Rationale

The theoretical framework that guided this research is founded in the evidence-based medicine model of best clinical practice ("Evidence-based Medicine. A new Approach to Teaching the Practice of Medicine," 1992). A recent survey in Respiratory Care confirmed there is limited consensus among practitioners in implementing and managing APRV (Miller, Gentile, Davies, & MacIntyre, 2017), and this study sought to establish the ideal means of implementing the APRV mode of PPV.

Study Setting

This study was conducted at an academic medical center in the Southern US. Primarily, all raw data extraction was performed electronically on the medical center campus, but a majority of data analysis occurred campus wide and off site. Some of the secondary data extraction was performed off-campus but only within the confines of the prior-approved IRB protocol. All study procedures were performed electronically, utilizing the investigator's personal, secured laptop computer with no direct or indirect investigator/subject interaction. This retrospective analysis was an extraction of archival data within a large EHR database.

Subjects

Sample size

Although a conservative target was 100 total subjects with a minimal expectation of 60 based upon the fact that 20 were extracted as part of the pilot study, the purposive sample yielded 68 total subjects, overall. All subjects that met inclusion criteria were to be extracted from the UH database from within the dates specified (3-year timeframe) and included as part of the sample population for this study. One barrier to identifying all eligible subjects was that the investigator depended upon the UH information office to do the comprehensive search and was

only given access to subjects that were identified initially. A power analysis was not performed as all subjects meeting inclusion criteria were included, and the study population was a function of the original UH report rendering.

Inclusion and Exclusion Criteria

All subjects, 18 years or older, for which APRV PPV was ordered were considered as having met inclusion criteria during the initial Information Office search of the archived EHR. Thereafter, only subjects identified as having received APRV for a minimum of approximately 8 hours consecutively were included. Preferably, subjects had undergone APRV PPV for at least 12-24 hours consecutively; however, due to low sample size, subjects receiving APRV for at least 8 hours consecutively were included to prevent a loss of power during the analysis. Only adult subjects at the academic medical center with documented APRV PPV between October 1, 2013 and October 1, 2016 were included in the study.

Only subjects not receiving APRV for at least 8 hours were excluded initially. There were subjects that received APRV just under the 8 hours that were included after re-evaluation of the overall subject number. After the initial UH report was compiled, subjects that were placed on APRV but found without their settings documented were also excluded. Moreover, any patient lacking the information necessary to calculate neither the P/F ratio, OI, OSI or MSOFA score were not included. Instances such as known aspiration, improper intubation, and complicated interventions during the ICU stay should be considered exclusion criteria to be evaluated on an individual basis. However, these incidents could not be confirmed through a simple EHR retrospective analysis. Moreover, any patient found with a pre-existing terminal condition, such as end-stage renal disease or aggressive forms of cancer, would also potentially

need to be excluded but were not necessarily accounted for during this study in consideration of the short-term follow up.

Specific Procedures

Institutional Review Board (IRB) approval was sought via the typical protocol of the academic medical center as well as through Nova Southeastern University (NSU). Once IRB approval at both institutions was obtained, a data extraction report request was submitted to the UH Information Office. This team performed a comprehensive, retrospective extraction of the EHRs for all adult subjects who were admitted to UH in the intensive care environment and who received PPV via APRV mode between October 1, 2013 and October 1, 2016. This retrospective search allowed purposive sampling of a population that met inclusion criteria for the study.

Based upon all the initially submitted protocol and inclusion criteria, 102 potential subjects were identified. Once the UH EHR data from the initial sample had been compiled in a formal report, the complete applicable EHR numbers and all pertinent information were made available to the investigator via secured email. The complete EHR of all subjects was then accessible to the investigator within the confines of the approved IRB protocol, and it was noted that many initially listed did not meet inclusion criteria of having received APRV for at least 24 hours. Shortly after the report was received, the investigator made a decision to separate out any subject that was not placed on APRV for at least 8 consecutive hours as this represents a typical 8-hour working shift in a hospital setting. Several subjects that received APRV just under the 8 hours were included after re-evaluating the total subject number. The overall goal remained identifying patients who received APRV for at least an average of 12-24 hours; however, the loss of power was also considered in broadening the selection to include those receiving APRV for a shorter time frame (at least 8 hours). The final yield was $N = 68$.

The UH medical information office had compiled certain data into a Microsoft® Excel spreadsheet, creating a specific database of information that highlighted only the selected fields requested on the approved IRB protocol for the original 3-year time period. Requested fields that were initially reported with no data were able to be verified and completed by doing manual data extraction for each applicable subject. This tedious process allowed other measures or variables, such as onset of APRV and exact ventilator settings, to be verified.

A data collection tool (DCT) form (Appendix A) was created to allow the investigator to acquire specific information in a usable format directly from the UH report/spreadsheet. Manual data extraction from the EHR was necessary to ensure complete information in the 2-page DCT form. This search was performed for each subject specifically by MRN and required acquiring certain information by an evaluation of a flowsheet or other report. During this process, various data items from the original UH report were able to be confirmed to assure accuracy of the bulk information originally provided by the UH Information Office. After all DCT forms were completed, an electronic database was created utilizing FileMakerPro software. The electronic database was exactly templated from the original DCT. The electronic database allowed for all DCT forms data to be input into a usable electronic format that could be converted back to a Microsoft® Excel spreadsheet that was directly input into Statistical Package for the Social Sciences (SPSS) to allow statistical analyses.

Once the initial raw data extraction was performed and all possible missing fields were accounted for on both the original spreadsheet and DCT forms, the P/F ratio, OI, OSI, and MSOFA scores were calculated for each subject's pre-APRV and post-APRV dosing. The secondary Excel spreadsheet (edited version of the original spreadsheet report) was utilized to input the mathematical formulas required to render specific P/F ratio, OI, and OSI for each

subject. In addition, an "if, then" formula was created in Excel in order to calculate pre-APRV and post-APRV MSOFA scores for all subjects. All complete data was then transferred from the DCT forms into the electronic database, converted into an Excel spreadsheet, and transferred directly into SPSS. The final rendering included the following for each subject:

- Name, MRN
- Age (years), sex, height (inches), weight (pounds)
- Intensive care unit (ICU) assigned: Medical, Surgical, Neuro, Other
- Vent mode prior to APRV initiation

Pre-APRV Settings and Parameters:

- Initial inhaled fractional concentration of oxygen (FiO2): %
- Positive End-Expiratory Pressure (PEEP): cmH2O
- Peak inspiratory pressure (PIP): cmH2O
- Mean airway pressure (MAWP): cmH2O
- Oxygen saturation (SpO2): %

Initial APRV Settings and Parameters and Post-APRV Dosing Settings and Parameters:

- I:E ratio
- FiO2 (%)
- T high (sec)
- T low (sec)
- Respiratory rate (RR) spontaneous: breaths per minute (bpm)
- RR total: bpm
- Tidal volume (Vt) exhaled: milliliters (ml)
- VT spontaneous: ml

- P high (cmH2O)
- P low (cmH2O)
- PIP (cmH2O)
- MAWP (cmH2O)
- Minute ventilation/volume (Ve)
- PaO2 (mmHg)
- SpO2 (%)

In order to acquire the MSOFA scores at APRV initiation as well as post-APRV dosing, the following additional parameters were acquired:

- Serum bilirubin (mg/dl)
- Mean arterial blood pressure (mmHg)
- Confirmation of use and dose of vasopressor medication
- Glasgow coma scale (GCS)
- Serum creatinine (mg/dl)

A sub-score was assigned to each subject based on mean arterial blood pressure and serum creatinine score, templated from the original MSOFA table by Grissom et al. (Grissom et al., 2010). Thereafter, a pre-APRV initiation and post-APRV dosing P/F ratio, OI, OSI, and MSOFA score were calculated for each subject. The serum bilirubin was used from the original SOFA metric and scored accordingly to replace the jaundice and icterus account on the MSOFA version. Nevertheless, a MSOFA score was calculated for each subject in order to appreciate any significant pre-APRV and post-APRV change.

Statistical Analyses

The overall sample demographics data were appraised, and specific metrics were calculated by descriptive statistics for age, sex, race, height, weight, and body mass index (BMI). Additionally, the primary independent variable, initial I-time setting, was initially appraised for normal distribution. Pertinent clinical data was evaluated and reported as a conglomerate. The change scores for the outcomes of interest (dependent variables) were also calculated to identify any statically significant result. Correlation matrixes were created to evaluate whether any relationship existed among the categorical and continuous variables. A bivariate analysis was performed for all categorical variables. An additional correlational matrix was created linking predictor variables to change in dependent variable scores, both pre-APRV and post-APRV. A bivariate analysis of categorical variables and change scores was performed. A multiple regression analysis was conducted to identify significant predictors for any of the four dependent variables: P/F ratio, OI, OSI, and MSOFA scores.

Once pertinent data was accounted for, specific metrics regarding the entire purposive sample were calculated, as reported. The investigator conducted data analysis via SPSS version 23 and 24 by descriptive and inferential statistics, as applicable. A $p < .05$ was considered statistically significant; however, each perceived clinically significant variable was reported as such. A stepwise regression analysis was performed to identify any bivariate between outcomes and predictors. A p-value ≤ 0.2 to start was considered statistically significant for all covariates. For each outcome variable, the difference between the two groups was considered clinically relevant based on published research among the topic as well as expert opinion. The difference was considered statistically significant only if the differences between the two groups were at $p \leq .05$. The study sought to evaluate whether there is an I-time associated with ideal clinical

outcomes; however, certain covariates should be accounted for and individually ruled out as having significant influence on a clinical outcome separate from the I-time on a case-by-case basis.

Instruments and Measures

No special instruments were required for this study outside of what would be customary for a retrospective analysis of archived EHR data. A laptop was used to receive, store, and process study data. There were various undisclosed computer programs used during the UH initial report compilation process by the Information Office, assumed to be a part of the standard data extraction and reporting approach. An institution-assigned, personal laptop computer was utilized as well as various software to include Microsoft Office (Word and Excel) as well as SPSS, version 23 and 24 for all statistical analyses. All measures were reported as originally rendered from the extraction process via EHR. No parameters or values were altered beyond the literal, original iteration.

The P/F ratio, OI, OSI, and MSOFA scores were all calculated utilizing original versions of the required variables. The applicable equations are listed in the later subtitled "Metrics" section. Statistical measures were performed utilizing SPSS, version 23 or 24, and reported as originally output.

Reliability and Validity

There are certain assumptions that an EHR contains both reliable and valid information. A review by Chan, Fowles, and Weiner (2010) evaluated reliability and validity of extracting and abstracting from EHR data. The group appraised 35 prior studies of EHR data quality and found that data reliability was questionable for, mainly, the problem and medication lists. Their study revealed an overall variance among institutions' practice of documentation and data extraction

methods, and it was concluded that overall EHR data quality varies among institutions (Chan et al., 2010).

In this study, the EHR data was taken at face validity, as certain archived information would have been auto-generated. Other parameters were entered into the EHR by a credentialed clinician; therefore, a potential for occasional error did exist. The secondary data extracted from archived EHRs was not manipulated and was recorded as it appeared in the original EHR annotation. For this study, the EHR was considered a secondary source, as the patient's real-time diagnostic monitors and support devices were considered the primary source. Other information, such as yielded by some equipment with direct communication with EHR, will have been auto-generated directly from the primary source; however, all EHR data was considered secondary.

A majority of what was extracted from the EHR was numerical. In order to acquire the patient's primary diagnosis, as well as to confirm the necessary metrics, the investigator combed through various electronic flowsheets and archived spreadsheets, or similar documentation, only as applicable to the extraction criteria as prior annotated. All raw data were initially transcribed from the UH-provided report/spreadsheet onto a DCT form (Appendix A) created specifically based on the original protocol. Additional missing data was copied verbatim from the EHR, and once the DCT forms were complete, they were transcribed into a tailored electronic database that allowed conversion back to an Excel spreadsheet for the purpose of transmission into SPSS.

A systematic approach to extracting the EHR archived data was maintained during the course of study. In order to avoid potential transcription error, the investigator systematically extracted all initial missing data by recording directly from the EHR and was the only acquisitioner thereof. Unfortunately, there may be confounding variables such as comorbidities,

whether confirmed or not, and other unreported entities that may affect clinical outcomes unrelated to the original exposure of interest (I-time). This was not necessarily confirmed in this study.

All surrogates used as predictors of short-term clinical outcomes were based upon well-published, validated instruments and were calculated as represented in the literature (Dechert et al., 2014; Ferreira et al., 2001; Grissom et al., 2010; Rawat et al., 2015; Vincent et al., 1996). The validity of the raw data, initially extracted by the UH team, is assumed and based solely upon the fact that the established academic medical center regularly produces retrospective analyses and is accustomed to such requests. Moreover, there were several steps integrated in order to confirm, firsthand, the validity of the report data. To note, the investigator revisited each subject's EHR a minimum of two times, confirming both the date and time of APRV initiation as well as the manually documented PPV settings and parameters for each subject.

Strengths and Weaknesses of Design

Strengths

The major strength of this retrospective study design lies in the fact that large amounts of archived EHR data were accessible and assumed to be accurate as part of the legal medical record. The utilization of archived data allowed the investigator access to the information via MRN search and allowed several avenues to confirm the accuracy of the originally submitted UH report. The health information of subjects could easily be secured as only the MRN would be able to identify study subjects, and this MRN number was kept secure at all times on the DCT forms kept in the investigator's locked office or all electronic study files stored on the investigator's password-protected computer.

Because the dissertation committee included a variety of experts (Respiratory Therapist, Pulmonologist, and Psychometrician/Statistician), the mentoring and steering helped maintain a high level of integrity of study design and implementation. Furthermore, the study design was modeled after the structure of a typical retrospective analysis of ICU patients receiving PPV.

Weaknesses

The most notable weakness was the susceptibility of uncorrected confounding or bias. Data collection errors were possible as can occur in any study, whether prospective or retrospective. An additional primary weakness of this retrospective study design lies in the fact that the archived EHR data had been mostly entered into the system manually, at some point, by a variety of healthcare providers. In a typical EHR, one can assume that there is some degree of margin for error, although conclusions about EHR data quality, in general, have yet to be clearly presented in the literature (Chan et al., 2010). Over a 24-hour period, however, it should be highly unlikely that multiple clinicians are entering in ventilator settings with error, and at this particular academic medical center, a majority of lab results are auto-generated into the EHR once results are attained.

Because EHR had only been implemented in October of 2013, there was a limited data set given the design of a retrospective analysis of only archived EHR data. Additionally, even though the investigator assumed, based on firsthand experience, that a large number of potential subjects would be identified having received APRV for at least 24 hours, only 68 were included in this study once inclusion criteria were applied. The small sample size decreased the power of the study, overall, but was a function of this study, being a retrospective investigation of a non-standardized approach to APRV at a single academic medical center.

Threats

The most significant threat to this retrospective analysis of archived EHR data was the low purposive sample population size. Upon completion of the pilot project (See "Pilot Study Summary" section), it was noted that it should be necessary to expand the timeline in which EHRs were evaluated from 1 year to 3 years. Furthermore, a strategic planning meeting was held with the Chief Information Officer (CIO) and Lead IT data extractor prior to the implementation of this study. Both the CIO and Lead IT data extractor were informed of the study goals and creative means in which subjects meeting inclusion criteria could be potentially identified and successfully added to a raw data report. Nevertheless, only patients that had EHR available (established at UH, October, 2013) were considered, given the timeline and procedures of this study.

The timely documentation of PPV settings could be questionable, dependent upon the scenario and when the documentation was performed as well as being dependent upon the particular documenting clinician and how detailed their EHR account. As the EHR PPV data will primarily yield what was manually entered, the investigator must make the assumption that the information found in the EHR was entered with accuracy and by only those whom possess the privilege to do so with the applicable credentials and password-protected access.

Reflexivity

Arguably, inherent bias exists for any investigator. As an RT and bedside clinician that often manages PPV, there is a degree of preference toward certain modes and particular care practices. However, in this study, only the data acquired was evaluated as the investigator had no direct contact with subjects or providers. Likewise, there was no direct involvement with the

process of ordering or managing any of the subjects on PPV, neither was there any influence on subject selection as inclusion criteria were pre-determined as originally outlined.

Resource Requirement

This study required a continued partnership between UH Shreveport, the Louisiana State University (LSU)-affiliated academic hospital, and LSU Health Sciences Center (HSC) Shreveport School of Allied Health. UH granted the investigator permission to access particular archived EHRs as an extracted retrospective data set shortly after IRB approval. The LSUHSC Shreveport IRB was involved with the receiving and monitoring of all electronic study proposal documents as well as with the decision for approval of the drafted protocol. Both the UH Medical Information office as well as the UH IT support staff were involved with the process of initial data extraction.

The LSUHSC Shreveport medical library as well as the NSU library resources were utilized for the literature review, and both were further utilized for research of topics related to this study. A majority of all data collection, archive, and analyses was conducted electronically by the investigator, utilizing a secured, password-protected laptop computer. However, several individuals assisted as mentors during study execution to include the following Dissertation Committee members: Dr. Guy Nehrenz (Chair), Dr. Robert Walter (Clinical Expert), and Dr. Patrick Hardigan (Statistical Expert). The investigator was allotted research time as part of the expectation for all unclassified faculty at the LSUHSC Shreveport School of Allied Health Professions. No additional funding was necessary to support this effort.

Timeline

This study began immediately after: 1) approval of the initial research proposal (Chapters 1, 2, and 3) by the Dissertation Committee, 2) NSU IRB approval, and 3) LSUHSC Shreveport

IRB approval. Once initial NSU IRB and LSU IRB approval was obtained, the study remained under Center-level status. It should be noted that, as a result of the pilot study, the original LSU IRB protocol remained with expedited approval status until 2018. Tentatively, the primary raw data extraction process was completed on August 11, 2017 with final database completion shortly after secondary data was finalized on August 22, 2017. Preliminary data analysis was performed immediately thereafter with continued evaluation of all data ongoing until just prior to the initial draft of the Formal Dissertation Report (10.10.17).

As a pilot study had already been completed and the data analysis revealed a potentially clinically but non-statistically significant result, the investigator efficiently proceeded seeking to build further upon the original pilot concept. The pilot was also used as a general template in which to design this particular study. Overall, the study idea began in late 2016, culminating to official implementation immediately after IRB approval by both NSU and LSUHSC Shreveport.

Ethical Considerations and Review

This study required the approval of both the NSU IRB and LSUHSC Shreveport IRB. Additionally, because of the long-existing partnership with UH Hospital, it was necessary that certain UH officials provided services in order for this study to be carried out. All patient data were kept secure in order to assure study subject privacy and maintain compliance with the Health Insurance Portability and Accountability Act. Additionally, this assurance of security allowed the investigator to uphold the fundamental ethical principle of nonmaleficence.

The LSUHSC Shreveport IRB committee, along with all applicable personnel and offices, provided preliminary review, approval, surveillance, and auditing of all study procedures to assure human protection of all the research subjects to be included. Additionally, the Dissertation Chair and Committee was charged with advising and guiding the investigator

(Doctoral Candidate) during the process of proposal drafting and study implementation. Informed consents were waived, and there was no intervention or subject interaction with the investigator. All study data were treated with utmost respect, and no patient identifiers were released to any entity nor were directly referenced in any of the submitted materials.

Funding

No additional funding was necessary to support this effort. Please refer to the "Resource Requirement" section for more information.

Management of Data

In summary, the investigator performed a retrospective analysis of archived EHR data. UH Shreveport, the LSU-affiliated academic hospital, granted the investigator permission to access particular archived EHRs as an extracted retrospective data set after the IRB protocol was approved. The harvesting of the archived EHR data was initially performed by the UH IT department extraction team through the UH Information Office, rendering a raw data spreadsheet with accompanying medical record (MR) numbers and creating a specific database of information that highlighted only the selected fields requested on the approved IRB protocol. The EHR data included original patient data from the study time period: October 1, 2013 and October 1, 2016.

This formal report, with complete applicable EHR numbers, was made available to the investigator via secured email. At this juncture, the complete EHR of all subjects was then accessible to the investigator within the confines of the approved IRB protocol and allowed the investigator to perform additional data extraction for any missing fields. The health information of subjects remained secured as only the MRN would be able to identify study subjects, and this MRN number was kept in an electronic spreadsheet of which only the investigator had password-

protected access on an institution-assigned personal lap top computer stored in the investigator's locked office.

A DCT form (Appendix A) was created in order to highlight all variables to be studied. After a final version of the tool was utilized to compile all raw data into a more organized format in which to study variables of interest, an electronic database was created utilizing Microsoft FileMakerPro. This database replicated all fields of the DCT, allowing direct export into a new spreadsheet that would ultimately feed data into SPSS.

The secondary data extracted from archived EHRs was not manipulated, recorded as it appeared in the original EHR annotation. A majority of what was extracted from the EHR was numerical. In order to acquire necessary metrics, however, the investigator combed through various flowsheets and annotations within the EHR, or similar documentation, to fill in any missing fields first into the DCT, then transfer into the electronic database. Once all available preliminary data had been entered into the electronic database, all missing fields were accounted for by manually combining through the EHR, once again, to identify available potential additional data. Certain missing fields were filled in with the best available data to coincide with study variables as best as possible (See "Reliability and Validity" section, under "Special Considerations" subheading).

Upon study conclusion and after Dissertation Formal Report approval by the committee, all electronic data will be stored electronically on the investigator's password-protected lap top, and all DCT forms will remain filed in the investigator's secured office, according to IRB protocol for a period of up to 3 years. Thereafter, all hard copies of data (DCT forms) will be shredded and all electronic study files deleted.

Data Analyses

Safeguards

The NSU and LSU IRB-approved protocol was implemented for this study via the methodology as outlined in this Chapter (Ch. 3). Initial data was extracted directly from UH EHR archives by the UH Information Office and integrated into a formal report by the IT Department, which was made available to the investigator. Moreover, the investigator explored additional archival data within the confines of the IRB-approved protocol, seeking to assure that the methodology implementation was consistent with the purpose of the research. Thereafter, exact values from the EHR were recorded manually onto a DCT form (Appendix A). Once additional raw data had been collected manually, all data were transcribed from the DCT form into an electronic database. The database was exactly templated from the DCT forms to represent pre-APRV initiation parameters and diagnostic values as well as those same values and parameters an average of 8-24 hours after APRV mode was implemented. The database was converted to a Microsoft® Excel spreadsheet and, subsequently, into SPSS to allow data analysis.

During the initial data analysis, the investigator consulted the Dissertation Committee statistical expert for steering and thereafter received support in proceeding with the more sophisticated statistical processing. After initial statistical analyses were complete, consulting services were sought for assistance with regression analysis and the interpretation thereof. Only what was originally rendered from the compilation of all raw data was input into the SPSS software as data fields. All data analyses, thereafter, were performed via SPSS as a function of the original data set.

Metrics

As this quantitative study employed a retrospective analysis of archived EHR data, the investigator sought to appreciate short-term clinical outcomes by evaluating the changes in the P/F ratio, OI, OSI, and MSOFA scores between onset of APRV use and cessation after at least 8 hours of continual use. Initially, overall sample population demographics were evaluated in order to appraise the characteristics of all subjects. Additionally, an I-time distribution plot was created in order to preliminarily evaluate for non-normality of the main independent variable (exposure of interest) of study. All dependent variables were calculated for subjects both prior and after having received APRV. Change in dependent variables was derived by subtracting post-APRV P/F ratio, OI, OSI, and MSOFA from pre-APRV P/F ratio, OI, OSI, and MSOFA.

The goal was to test the original hypothesis that, overall, in APRV mode, the use of a longer I-time results in ideal mean airway pressure, less pulmonary stress and strain due to less cyclic opening and closing of the lung, and, therefore, overall better clinical outcomes as evidenced by better P/F ratio, OI, OSI, and MSOFA scores when compared to the use of shorter I-times in a similar patient population. Multiple regression analysis was conducted to identify significant predictors for any of the four dependent variables of P/F ratio, OI, OSI, and MSOFA scores. Different regression models were created for each of the dependent variables. Also, different multiple regression analyses were conducted for pre-APRV and post-APRV data. A level of significance of 0.05 was used in the multiple regression analysis. An independent variable was considered a significant predictor of the dependent variable if the *p*-value was less than or equal to the level of significance value.

In alignment with seeking to answer the original research question "Do patients ventilated with longer I-times, in APRV mode, have better short-term clinical outcomes

compared to patients ventilated in the same mode with shorter I-times?", the following parameters and diagnostic values were acquired directly from each subject's EHR as a means of eventually assessing the main outcomes of interest: FiO_2, PaO_2, MAWP, and SpO_2. A standard equation was used in order to input these values for calculating OI as follows: (FiO_2 x MAWP) / PaO2 x 100 (Dechert et al., 2014). Due to the intermittent unavailability of a PaO_2 during the study subjects' clinical care, pulsatile oxygen saturation (SpO_2) was used to replace the PaO_2. This replacement allowed the calculation of a modified OI (OSI) as a surrogate for the more traditional OI via an equation as follows: (FiO_2 x MAWP/SpO_2 x 100) (Rawat et al., 2015). Additionally, the following was acquired in order to allow the calculation of each patient's initial MSOFA score: SpO2, FiO2, presence of documented jaundice or bilirubin level, mean arterial pressure with confirmation of the presence or absence of pressor treatment (eg. Dopamine and Dobutamine), Glasgow coma scale score, and serum creatinine. The MSOFA score was calculated based on the original presented table by Grissom et al. (2010) in order to derive a 0 to 4 total number (Grissom et al., 2010). The serum bilirubin was used from the original SOFA metric to replace the jaundice and icterus account on the MSOFA version, but this did not affect score calculation as the original alignment between MSOFA and original SOFA scoring was maintained. BMI was calculated for each subject and evaluated accordingly based on the traditional equation: (mass(kg) / height^2(m)) x 703 ("Reprint: 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults," 2013).

The P/F ratio, OI, OSI, and MSOFA score calculated for each subject represents a short-term outcome metric, as each in clinical practice, represent an established, validated gauge of patient prognosis (Dechert et al., 2014; Ferreira et al., 2001; Grissom et al., 2010; Rawat et al., 2015). The P/F ratio, introduced in 1974 (Horovitz, Carrico, & Shires, 1974), has been studied

extensively and found as an accurate predictor of mortality (Cooke et al., 2008). As P/F ratio decreases, predicted mortality increases. The OI during the first 4 days of PPV is well-known to correlate with a 28-day survival and mortality outcome. As OI increases, survival decreases, and predicted mortality increases (Dechert et al., 2014). As with OI, the OSI is also inversely related to mortality; when either OI or OSI increases, predicted mortality increases (Rawat et al., 2015). As with OI and OSI, the SOFA and MSOFA scores are highly predictive of clinical outcomes associated with mortality in that a higher MSOFA score indicates an increase in mortality risk (Ferreira et al., 2001; Grissom et al., 2010).

Each calculation for the dependent variables was performed on an Excel spreadsheet by inputting the applicable formula for each subject, utilizing parameters prior to APRV initiation and post-APRV dosing. An "if, then" formula was created in Excel in order to calculate pre-APRV and post-APRV MSOFA scores for all subjects. All univariate statistics for categorical variables are reported as frequencies with proportions. For continuous variables, the number, mean, and standard deviation were reported. Where relevant, the minimum and maximum due are included due to the number of subjects and relatively non-normal distribution of the data (Lang, 2006).

Subject demographics and pertinent clinical data were calculated to represent the pre-APRV and post-APRV period and to highlight initial APRV parameters. The change in scores for all dependent variables were calculated, and correlations for associate between continuous measures were also performed. Moreover, a bivariate analysis was performed for all categorical variables, and an additional correlational matrix was created, linking predictor variables to change in dependent variable scores, both pre-APRV and post-APRV. A final bivariate analysis of categorical variables and change scores was performed. The main independent variable, I-

time (T high) was evaluated, along with other continuous and categorical variables by multiple regression analysis to identify significant predictors for any of the dependent variables: P/F ratio, OI, OSI, and MSOFA. Any p-value < .05 was considered statistically significant; however, some associations are reported at $p > .05$, as calculated.

Special Considerations

As all data acquired were based on values only accessible within an archived EHR, certain special considerations were warranted. Initial MSOFA scores were calculated within a window of less than or equal to 2-hours either just prior to or just after APRV initiation. Because the time in which APRV was initiated tended to be random, lab results did not always exactly coincide with the particular onset time. It was found that most labs were acquired every 12 to 24-hour period depending on physician's order and the protocol of the particular unit of care. Post-APRV dosing, MSOFA scores were computed based on the required lab inputs in order to allow scoring. Those labs not coincidentally available were sought out and acquired up to a period of 48 hours after APRV was terminated. This was necessary as patients received APRV for variable timeframes and had labs acquired equally as random. Values as close as possible to the exact time of APRV cessation were used even if recorded from different panels.

The SpO2 and FiO2, as well as MAWP, were readily accessible within a timeframe of 1-2 hours either pre-APRV or post-APRV dosing, so OI and OSI score calculations were relatively unaffected. For post-APRV dosing individual metrics, the labs coinciding most with the timeframe immediately post-APRV were used, but if a particular single lab result was not available for that time, the next available missing lab result was utilized (not beyond a period up to 48 hours after APRV dosing). When available, the invasive arterial mean arterial blood pressure was utilized as opposed to the non-invasive. For GCS scores, the attempt was to utilize

the most coincidental record as applicable to pre-APRV and post-APRV timeframe; however, for post-APRV dosing, available GCS scores up to 6 hours later were used. There were subjects that received APRV just under the 8 hours which were included after re-evaluation of the initial overall subject number.

Format for Presenting Results

This study sought to identify a preferred means in which to apply APRV mode of PPV, evaluating I-time as the main independent variable and exposure of interest. Given the primary hypothesis of this study, it is important to present I-time as a viable predictor of short-term clinical outcomes for patients receiving APRV within the context of how other parameters are directly or indirectly affected by this setting. Certain other correlations as a quantifiable relationship, albeit negative or positive, and also, covariates that affect outcomes, separate of I-time, are reported as well as any other relationship among variables or any found relation of variables to clinical outcomes. Overall, the study results section includes a statement that addresses whether the data analysis offers support to or refutes the original hypothesis.

Data was compiled in order to 1) detail all of the general subject characteristics, allowing the reader to appraise the study population demographics, 2) provide a summary to overview the study clinical data results, and 3) provide the results of the outcomes of interest (dependent variables). Additionally, correlational matrixes are provided for both pre-APRV and post-APRV clinical outcomes. The details of a bivariate analysis are presented in order to appreciate any statistically significant association among categorical and continuous variables. Correlational matrixes of predictor variables and change scores both pre-APRV and post-APRV are also presented. The investigator furthermore highlights an additional bivariate analysis of categorical variables and change scores, and the multiple regression analysis results are summarized.

Generalized study results will be disseminated among the clinical community via local, state, or national presentation in addition to being published in a high impact scientific journal.

Regression Analysis

In this exploratory study, multiple regression analysis was conducted to identify significant predictors for any of the four dependent variables of P/F ratio, OI, OSI, and MSOFA scores. Different regression models were created for each of the dependent variables. Also, different multiple regression analyses were conducted for pre-APRV and post-APRV data. A level of significance of 0.05 was used in the multiple regression analysis. An independent variable was considered a significant predictor of the dependent variable if the *p*-value was less than or equal to the level of significance value.

As the main outcomes of interest (dependent variables) were the change in P/F ratio, OI, OSI, and MSOFA after at least 8 hours on APRV, the initial predictor variables (independent variables) included: 1) Age at APRV onset, 2) height, 3) weight, 4) BMI, 5) pre-APRV MAWP, 6) T high (I-time), 7) T low, 8) P high, 9) P low, and post-APRV MAWP. Certain other variables could be considered clinically relevant but not necessarily statistically significant. A level of significance of 0.05 was used in the multiple regression analysis. An independent variable was considered a significant predictor of the dependent variable if the *p*-value is less than or equal to the level of significance value.

The investigator sought to identify correlations of surrogates for short-term outcomes (P/F ratio, OI, OSI, and MSOFA) with the predictor variables as prior described in order to indicate whether a regression effect was statistically significant. Moreover, a model summary was evaluated via SPSS in order to appreciate particular relationships among the independent

and dependent variables. The investigator sought to identify predictors of best short-term clinical outcomes.

Model Building Strategy

Although the SPSS software was utilized for the actual stepwise regression analyses, below were the general proposed prediction models to be utilized for the purpose of identifying significant relationship between dependent and independent variables:

- Main model: most feasible outcome of interest:
    - Δ P/F ratio* = (T_{High} + P_{High} Δ + initial MSOFA score)

**P/F ratio was replaced with ΔOI ratio, ΔOSI, or ΔMSOFA although the core model remained as described*

- Exploratory model: to include exploratory variables – potential confounders
    - Δ P/F ratio** = (T_{High} + P_{High} + Δ MSOFA score) P_{High} setting + P_{Low} setting + I-time + MAWP

***P/F ratio was replaced with ΔOI ratio, ΔOSI, or ΔMSOFA although the core model would remain as described*

Procedure

The investigator began with no predictors within the stepwise model. A predictor was entered, or removed, based on partial *F*-tests according to *t*-tests for the slope parameters obtained. The final model was identified when no more predictors could be justifiably entered or removed from the stepwise model. Both the alpha-to-enter (α_E) and alpha-to-remove (α_R), by SPSS default, was kept at 0.2 in order to avoid the elimination of potential impactful predictors.

Step 1: Each of the one-predictor models was fitted, that is, regressed y on x_1, y on x_2, etc. Of all predictors, whose t-test P-value is less than $\alpha_E = 0.2$, the first predictor put into the stepwise model had the lowest P-value.

Step 2: The predictor with the lowest P-value ($\alpha_E < 0.2$) was deemed the "best" single predictor. Each two-predictor models were fitted to include the particular "best" single predictor - regressing y on $x1$ and $x2$, y on $x1$ and $x3$, etc. Each predictor thereafter that had a t-test value of $\alpha_E < 0.2$ was included in the stepwise model as a sequential predictor. If a second predictor was identified, then each predictor was entered into the stepwise model to evaluate whether the significance of the first predictor was somehow affected. If the t-test P-value for testing $\beta 1 = 0$ rendered the $\alpha_R > 0.2$, x_1 was removed from the model.

Step 3: If both x_1 and x_2 were to be included in the two-predictor stepwise model after aligning with the procedures as prior described, the investigator fit each of the three-predictor models that include x_1 and x_2 as predictors, regressing y on x_1, x_2 and x_3, regressing x_1, x_2 and x_4, etc. Of those predictors, whose t-test P-value is $\alpha_E < 0.20$, the third predictor put in the stepwise model was the predictor that had the smallest t-test P-value. If x_3 was deemed the "best" third predictor, then it was entered into the stepwise model. If a third predictor is identified, then each predictor was entered into the stepwise model to evaluate whether the significance of the first and second predictor was somehow affected. If the t-test P-value for testing $\beta 1 = 0$ or $\beta 2 = 0$, then rendering the $\alpha_R > 0.2$, the applicable predictor was removed from the model.

Results and Interpretation: Limitations and Delimitations

This study was primarily limited by the number of subjects ($N = 68$) whose EHRs were made available to the investigator due to the limited number of UH patients who met the inclusion criteria. Furthermore, a main delimitation of this study lies in the fact that the sample was drawn from a single academic medical center in the Southern US. A significant limitation of this study was the dependence upon archived EHR information as the source of all data. Although the EHR is considered legal documentation, its accuracy is not infallible (Häyrinen, Saranto, & Nykänen, 2008).

The timeframe in which this study was conducted may have limited the investigator's ability to re-visit the raw data once transferred into the Microsoft® Excel spreadsheet and released via email by the UH Information Office. Additionally, there were several confounding variables that may have affected overall outcomes not necessarily attributed to I-time setting or PPV. For example, it was not possible to account for comorbidities or other non-ventilator associated acute events in each subject. A large portion of subjects who require mechanical ventilation may be found with significant non-pulmonary disease (Wunsch et al., 2010) that may alter the course of care and outcomes. This alteration would cause a potential skew of certain diagnostic parameters and clinical outcomes.

Additionally, many subjects had labs available only within 12-24 hours of the time APRV was stopped. This availabilitymay have caused calculated MSOFA scores to be somewhat less accurate than if a prospective study was accomplished that could guarantee lab values absolutely concurrent with APRV use.

Summary

In summary, the investigator sought to execute the methodology in a clear, comprehensive, and detailed manner in order to assure accurate results and to allow other researchers to reproduce the study (Roberts, 2010). A systematic approach to searching the EHR and extracting data was imperative and assured via a step-by-step approach as outlined throughout the methodology (Ch. 3). To ensure the validity and generalizability of the results, the methodology was carried out with high fidelity, with every subject DCT being verified at least twice. The study results should offer insight into how better to ventilate patients placed in APRV mode.

In the next chapter (Ch. 4), the study results are outlined in detail to allow the reader an appreciation for the overall summative outcomes. As there may be clinically relevant results that are not necessarily statistically significant and vice versa, one must take this into account as findings are presented and appraised. The expectation is to link study results back to the original hypothesis in hopes of answering the general question of: Do patients ventilated with longer I-times, in APRV mode, have better short-term clinical outcomes compared to patients ventilated in the same mode with shorter I-times?

The major strength of this study lies in the fact that no other similar study has been identified in the literature, so this study is the first of its kind. Moreover, this study should be of great value to the particular academic medical center from which the EHRs were extracted, offering insight into best clinical practice.

Chapter 4: Results

Introduction to Chapter 4

As stated in Chapter 1, this quantitative study examined the relationship between inspiratory time, inflation pressures, and surrogates for short-term clinical outcomes during mechanical ventilation via the APRV mode of PPV. This chapter is organized in terms of how the original research question was addressed, how patients were selected as a convenient, purposive sample from an academic medical center EHR, and what can be appreciated from the findings. The subject demographic information is listed in Table 1. The original outcomes of interest were the change in subject's P/F ratio, OI, OSI, and MSOFA scores, and it was investigated as to what degree any of the categorical or continuous variables studied effected these clinical outcomes.

Within the confines of both the LSUHSC Shreveport and NSU-approved IRB protocols, a retrospective analysis of archived EHR data was performed to include 68 subjects. The results presented are the product of tedious EHR review and meticulous data analysis of what was rendered from the retrospective search. All data was initially recorded by the UH Information Office in original form as extracted from the initial EHR inquiry. Thereafter, the initial raw data was transcribed from the preliminary spreadsheet into a more organized format onto DCT forms (Appendix A). After the electronic database was constructed and filled in with all information from the DCT forms, the data was transferred exactly into SPSS. All statistical analyses were performed using version SPSS version 23 or 24, and results are presented in the original format as yielded.

Data Analysis Results

All available data was analyzed for each subject in the sample population *(N* = 68). Both descriptive and inferential statistics were calculated for all subjects, as reported. Furthermore, all pertinent findings are reported, as applicable to the original research question and hypothesis. All data analyses were performed utilizing Microsoft® Excel and SPSS version 23 or 24.

Subjects

The convenient, purposive study sample population was a result from the yield of an original inquiry performed by the UH Information Office, producing a total of 68 subjects that met inclusion criteria. The overall study sample population demographics (Table 1) revealed subjects tended to be near middle age *(N* = 68; M = 46.3 years) with a majority of subjects being Caucasian *(n* = 44; 64.7%) and male *(n* = 49; 72%), most of whom received care in the SICU (*n* = 42; 61.7%). It was noted that subjects, on average, were classified as clinically obese (M BMI = 30.9).

Table 1: Subject Demographics

(*n* = 68)	**($\bar{x}$; min-max, SD)**
Age, yr,	46.39 (18-84, 16.77)
Height, in	68.10 (53-76, 4.87)
Weight, lbs	204.50 (66-356, 55.30
BMI	30.90 (13.32-59.23, 7.86)
(*n* = 67)	**n (%)**
Sex, male	49 (72.13)
Race	
White	44 (65.67)
Black	23 (34.32)
(n = 59)	**n (%)**
MICU	14 (23.72)
SICU	42 (71.18)
Neuro ICU	1 (1.69)
Other	2 (3.38)

SICU - Surgical Intensive Care Unit
MICU - Medical Intensive Care Unit
Neuro ICU – Neurosurgical Intensive Care Unit

Pre-APRV

Table 2 provides an overview of clinical data. Although one subject was missing documentation as to which mode of PPV subject was placed prior to being placed on APRV, of the overall sample (*N* = 67), most subjects had been placed in PRVC (*n* = 30; 44.8%) or PS mode *(n* = 23; 34.3%) prior to APRV initiation with 100% FiO2 being the most prevalent setting for pre-APRV FiO2 (23.9%). Pre-APRV mean airway pressure in subjects was variable (M = 15.03) but most commonly found at 12-13 cmH2O (*n* = 13; 19.4%). Subject's pre-APRV SpO2 was also variable (IQR = 6) but found most commonly to be 94-100%. It was not possible to deduce the precipitating event that led to a decision to place a patient on APRV, and no consistent pattern could be appreciated for initial settings.

Table 2: Clinical Data

Pre-APRV Mode	**n (%)**
PRVC	30 (44.77)
PC	8 (11.94)
PS	23 (34.32)
Unknown	6 (8.95)
	n, $\bar{x}$ (SD)
MAWP	63, 15.03 (5.75)
FiO2	65, 70.98 (22.08)
Pre-APRV Initiation:	**n ($\bar{x}$; min-max, SD)**
SpO2	67 (93.46; 78.00-100.00, 4.98)
P/F ratio[1]	44 (96.39;26.00 – 222.50, 44.09)
Pre-APRV OI[2]	43 (27.34; 5.42-88.46, 14.55)
Pre-APRV OSI[3]	63 (18.99, 6.73-75.00, 9.67)
Pre-APRV MSOFA[4]	58 (8.96, 2.00-17.00, 3.20)
APRV Initial Parameters:	**n ($\bar{x}$; min-max, SD)**
Thigh, sec	65 (6.30; 0.90-11.00, 2.65)
Tlow, sec	61 (1.21; .40-10.00, 1.41)
Phigh, cmH2O	65 (24.2; 18.00-35.00, 3.33)
Plow, cmH2O	68 (3.51; 0.00-15.00, 4.47)
MAWP, cmH2O	66 (21.87; 4.00-31.00, 4.28)
Post-APRV Dosing	**n ($\bar{x}$; min-max, SD)**
Total Time on APRV,hrs	68 (19.27; 6.80-24.96, 5.49)
SpO2	68(93.51; 70.00-100.00, 5.47)
P/F ratio[1]	21(147.27; 33.75-300.00, 71.63)
Post-APRV OI[2]	21 (19.81; 4.19-56.29, 14.12)

Post-APRV OSI[3]	68 (12.27; 1.68-26.66, 5.75)
Post-APRV MSOFA[4]	58 (8.79; 2.00-17.00, 3.16)

[1]PaO2/FiO2
*[2]Oxygen Index = (FiO2*MAWP)/PaO2*100*
*3Oxygen Saturation Index = (FiO2*MAWP)/SpO2*100*
[4]Modified Sequential Organ Failure Assessment Score

It was not common to have a PaO2 available that coincided with APRV initiation nor even a few hours surrounding the implementation of APRV, thus SpO2 was used as a surrogate for this value in order to acquire MSOFA scores at or near onset of APRV. The available pre-APRV MSOFA scores (n = 58) revealed a majority of subjects were considered at greater than normal risk category ($\bar{x}$ = 8.9; s = 3.2).

APRV Dosing

There was an initial target of identifying only potential subjects that had been placed on APRV for a 24-hour period, but, due to low sample size, it was determined to include all patients that had received at least 8 hours of APRV consecutively. Incidentally, a few were added having received APRV for just under the 8-hour total window. On average, subjects received APRV consecutively for 19.27 hours (min-max = 6.80-24.96; SD = 5.49). Post-APRV SpO2 was higher than pre-APRV SpO2, but the difference was not statistically significant.

PPV settings among subjects were highly variable, and no particular underlying pattern was noted. The average setting for I-time (T high) was 6.30 seconds with high variability noted (0.9 sec to 11.0 secs). PPV settings for T low, P high, and P low were also highly variable (see Table 2).

Main Outcomes of Interest

A paired t-test was performed to compare the change in all scores for the dependent variables. There was noted improvement in P/F ratio, OI, OSI, and MSOFA scores, on average,

for all subjects (see Table 3). There was statistically significant improvement in change scores for both P/F ratio (44.28 average increase; p = 0.12) and OSI (6.34 average decrease; p = 0.00).

Table 3: Outcomes of Interest (Dependent Variables)

Δ Score: Pre-Post APRV	n ($\bar{x}$, SD)	*p*-value
P/F Ratio	18(-44.28, 66.42)	.012
OI	18(8.77, 20.44)	.086
OSI	63(6.34, 9.50)	.000
MSOFA	52(.096, 2.45)	.778

Paired t-test performed

Correlational Matrixes

Tables 4, 5, 6, and 7 provide an overview of all correlational matrixes results. Although the original independent variable (I-time) did not prove to correlate with statistical significance with any of the four dependent variables (P/F ratio, OI, OSI, and MSOFA), it is well established that I-time has a direct impact upon various parameters during PPV via APRV (E. G. Daoud et al., 2012). The following variables were found to have statistically significant correlation with surrogates for pre-APRV clinical outcomes:

P/F ratio: None

OI: Initial MAWP, $r(41) = .348$, $p < .05$

OSI: Initial P high, $r(58) = .294$, $p < .05$; Initial MAWP, $r(61)$, $p < .05$

MSOFA: Initial P low, $r(56) = .385$, $p < .01$

The following variables were found to have statistically significant correlation with surrogates for post-APRV clinical outcomes:

P/F ratio: BMI, $r(19) = .457$, $p < .05$

OI: BMI, $r(19) = -.478$, $p < .05$; P low, $r(19) = .466$, $p < .05$

OSI: T low, $r(61) = -.260$, $p < .05$; P high, $r(63) = .418$, $p < .01$; MAWP, $r(66) = .577$, $p < .01$

MSOFA: P high, $r(53) = .360$, $p < .01$

Regarding change scores, the only pre-APRV variable found to have statistically significant correlation with a clinical outcome was initial P low with ΔOI: $r(16) = -.545$, $p < .05$. In reference to change scores, no post-APRV variables were found to have statistically significant correlation with clinical outcomes. However, in consideration of the low sample size, APRV duration, P high, and MAWP could be viewed as impactful based on the close proximity of each variable to statistical significance in correlation to one of the four clinical outcomes evaluated.

Table 4: Correlation Matrix for Clinical Outcomes: Pre-APRV

		P/F ratio	OI	OSI	MSOFA
Age	*Corr.*	0.200	-0.168	0.001	0.230
	Sig.	0.192	0.282	0.991	0.082
	N	44	43	63	58
Height	*Corr.*	-0.079	0.172	0.170	0.036
	Sig.	0.609	0.269	0.183	0.790
	N	44	43	63	58
Weight	*Corr.*	0.170	-0.124	0.099	0.210
	Sig.	0.271	0.427	0.442	0.114
	N	44	43	63	58
BMI	*Corr.*	0.216	-0.209	0.017	0.233
	Sig.	0.160	0.179	0.894	0.079
	N	44	43	63	58
Pre-APRV MAWP	*Corr.*	0.012	0.099	0.086	0.045
	Sig.	0.942	0.549	0.519	0.745
	N	40	39	59	54
Initial Thigh	*Corr.*	-0.115	0.192	0.062	-0.233
	Sig.	0.473	0.235	0.639	0.084
	N	41	40	60	56

Initial Tlow	*Corr.*	-0.080	-0.224	0.113	0.178
	Sig.	0.626	0.176	0.407	0.207
	N	39	38	56	52
Initial Phigh	*Corr.*	-0.126	0.159	.294*	0.235
	Sig.	0.425	0.321	0.022	0.084
	N	42	41	60	55
Initial Plow	*Corr.*	-0.045	-0.03	0.063	.385**
	Sig.	0.770	0.848	0.622	0.003
	N	44	43	63	58
Initial MAWP	*Corr.*	-0.054	.348*	.292*	0.154
	Sig.	0.729	0.022	0.02	0.257
	N	43	43	63	56

* Correlation is significant at the 0.05 level

** Correlation is significant at the 0.01 level

Table 5: Correlation Matrix for Clinical Outcomes: Post-APRV; At Cessation

		P/F ratio	**OI**	**OSI**	**MSOFA**
Age	*Corr.*	0.047	-0.180	0.040	0.235
	Sig.	0.838	0.434	0.746	0.075
	N	21	21	68	58
Height	*Corr.*	-0.344	0.298	0.020	0.087
	Sig.	0.127	0.189	0.87	0.514
	N	21	21	68	58
Weight	*Corr.*	0.283	-0.362	-0.103	0.183
	Sig.	0.214	0.106	0.404	0.168
	N	21	21	68	58
BMI	*Corr.*	.457*	-.478*	-0.088	0.193
	Sig.	0.037	0.028	0.474	0.148
	N	21	21	68	58
APRV Duration	*Corr.*	-0.296	0.308	-0.027	0.008
	Sig.	0.193	0.174	0.830	0.950
	N	21	21	68	58
Thigh	*Corr.*	0.148	0.147	0.123	-0.167
	Sig.	0.535	0.535	0.336	0.232
	N	20	20	63	53

Tlow	*Corr.*	-0.025	-0.210	-.260*	-0.068
	Sig.	0.918	0.373	0.040	0.630
	N	20	20	63	53
Phigh	*Corr.*	-0.067	0.090	.418**	.360**
	Sig.	0.773	0.698	0.001	0.007
	N	21	21	65	55
Plow	*Corr.*	-0.329	.466*	0.128	0.227
	Sig.	0.146	0.033	0.311	0.095
	N	21	21	65	55
MAWP	*Corr.*	-0.141	0.336	.577**	0.167
	Sig.	0.542	0.136	.000	0.209
	N	21	21	68	58

* Correlation is significant at the 0.05 level

** Correlation is significant at the 0.01 level

Table 6: Correlation Matrix of Predictor Variables and Change Scores: Pre-APRV

		Δ P/F ratio	**Δ OI**	**Δ OSI**	**Δ MSOFA**
Age	*Corr.*	0.063	-0.022	-0.062	-0.191
	Sig.	0.804	0.932	0.628	0.176
	N	18	18	63	52
Height	*Corr.*	0.105	0.156	0.139	-0.098
	Sig.	0.678	0.535	0.278	0.489
	N	18	18	63	52
Weight	*Corr.*	-0.019	0.078	0.165	-0.103
	Sig.	0.941	0.758	0.196	0.468
	N	18	18	63	52
BMI	*Corr.*	-0.064	-0.012	0.084	-0.070
	Sig.	0.801	0.964	0.515	0.622
	N	18	18	63	52
Pre-APRV MAWP	*Corr.*	-0.397	0.188	-0.050	-0.137
	Sig.	0.115	0.47	0.709	0.346
	N	17	17	59	49
Initial Thigh	*Corr.*	-0.458	0.281	0.031	0.038
	Sig.	0.074	0.292	0.817	0.795
	N	16	16	60	50
Initial Tlow	*Corr.*	0.371	-0.334	0.093	0.087

	Sig.	0.158	0.206	0.496	0.561
	N	16	16	56	47
Initial Phigh	*Corr.*	-0.288	0.408	0.142	-0.139
	Sig.	0.247	0.093	0.280	0.341
	N	18	18	60	49
Initial Plow	*Corr.*	0.407	-.545*	-0.051	0.075
	Sig.	0.094	0.019	0.692	0.595
	N	18	18	63	52
Initial MAWP	*Corr.*	-0.371	0.338	0.166	-0.020
	Sig.	0.130	0.170	0.195	0.893
	N	18	18	63	50

* Correlation is significant at the 0.05 level

** Correlation is significant at the 0.01 level

Table 7: Correlation Matrix of Predictor Variables and Change Scores: Post-APRV; At Cessation

		Δ P/F ratio	**Δ OI**	**Δ OSI**	**Δ MSOFA**
APRV Duration	*Corr.*	0.267	-0.23	-0.214	-0.081
	Sig.	0.284	0.359	0.092	0.570
	N	18	18	63	52
Thigh	*Corr.*	-0.256	-0.122	-0.017	0.052
	Sig.	0.322	0.642	0.901	0.727
	N	17	17	58	47
Tlow	*Corr.*	0.137	0.243	0.063	0.079
	Sig.	0.601	0.346	0.640	0.595
	N	17	17	58	47
Phigh	*Corr.*	-0.284	0.437	0.024	-0.257
	Sig.	0.254	0.070	0.852	0.075
	N	18	18	61	49
Plow	*Corr.*	0.215	-0.226	0.025	0.100
	Sig.	0.391	0.368	0.848	0.495
	N	18	18	61	49
MAWP	*Corr.*	-0.434	0.214	-0.179	-0.149
	Sig.	0.072	0.393	0.162	0.293

N	18	18	63	52

* Correlation is significant at the 0.05 level.

** Correlation is significant at the 0.01 level.

Bivariate Analyses

Tables 8 and 9 provide an overview of the bivariate analysis results. In evaluation of categorical variables, no statistically significant relationship was found between categorical variables and P/F ratio and OI. However, the ICU in which subjects were managed while on APRV bears statistical significance with post-OSI (p = .022) and both pre-MSOFA (p = .014) and post MSOFA (p = .030) showing empirical relation. Additionally, ICU in which subjects were managed was found with statistically significant relation to Δ P/F ratio (p = .034). This could be considered simple artifact and not clinically meaningful.

Table 8: Bivariate Analyses

	Pre-P/F Ratio		**Post-P/F Ratio**	
	n ($\bar{\bar{x}}, SD$)	p-value	n ($\bar{\bar{x}}, SD$)	p-value
Sex		.848		.096
Male	30(95.50, 44.52)		14(126.445, 60.094)	
Female	14(98.30, 44.75)		7(188.928, 79.025)	
Race		.706		.343
White	29(98.22, 44.88)		13(157.64, 84.63)	
Black	15(92.86, 43.84)		8(130.42, 43.12)	
ICU		.345		.397
MICU	10(87.24, 31.72)		5(121.91, 93.29)	
SICU	24(100.56, 46.72)		10(164.67, 69.07)	
Pre-APRV Mode:		.163		.997
PRVC	22(103.810, 53.306)		10(150.311, 77.178)	
PS/CPAP	11(81.879, 33.993)		5(150.091, 105.727)	

	Pre-OI		**Post-OI**	
	n ($\bar{\bar{x}}, SD$)	p-value	n ($\bar{\bar{x}}, SD$)	p-value
Sex		.522		.102
Male	29(28.04, 16.28)		14(22.81, 15.70)	
Female	14(25.89, 10.51)		7(13.83, 8.20)	
Race		.217		.929
White	28(25.01, 11.80)		13(20.07, 17.19)	
Black	15(31.68, 18.33)		8(19.51, 7.90)	
ICU		.555		.305
MICU	10(29.12, 10.06)		5(28.65, 21.69)	
SICU	24(26.27, 17.37		10(16.88, 10.89)	
Pre-APRV Mode:		.292		.508
PRVC	21(25.03, 12.97)		10(19.15, 15.11)	
PS/CPAP	11(32.34, 20.06)		5(26.17, 19.67)	

	Pre-OSI		**Post-OSI**	
	n ($\bar{\bar{x}}, SD$)	p-value	n ($\bar{\bar{x}}, SD$)	p-value
Sex		.198		.983
Male	45(19.78, 10.80)		49(12.26, 6.18)	
Female	18(17.03, 5.77)		19(12.29, 4.61)	
Race		.660		.791
White	40(19.35, 11.11)		44(12.13, 5.62)	
Black	23(18.36, 6.64)		24(12.53, 6.08)	
ICU		.312		.022
MICU	14(20.74, 6.73)		14(15.59, 5.22)	
SICU	39(18.16, 11.04)		42(11.54, 5.83)	
Pre-APRV Mode:		.322		.583
PRVC	28(17.56, 6.83)		30(11.75, 5.58)	
PS/CPAP	23(20.68, 13.52)		23(12.64, 6.00)	

	Pre-MSOFA		**Post-MSOFA**	
	n ($\bar{\bar{x}}, SD$)	p-value	n ($\bar{\bar{x}}, SD$)	p-value

Sex		.303		.739
Male	42(9.21, 3.36)		42(8.88, 3.17)	
Female	16(8.31, 2.75)		16(8.56, 3.24)	
Race		.441		.777
White	40(9.20, 3.05)		37(8.70, 3.16)	
Black	18(8.44, 3.55)		21(8.95, 3.23)	
ICU		.014		.030
MICU	12(10.91, 3.11)		13(10.38, 2.66)	
SICU	37(8.13, 2.83)		36(8.27, 3.26)	
Pre-APRV Mode:		.625		.390
PRVC	25(9.32, 3.50)		25(9.20, 3.35)	
PS/CPAP	19(8.78, 3.56)		18(8.27, 3.47)	

Table 9: Bivariate Analyses of Categorical and Change Scores

	Δ P/F Ratio	**Δ OI**	**Δ OSI**	**Δ MSOFA**
	p-value n ($\bar{\bar{x}}, SD$)	*p*-value n ($\bar{\bar{x}}, SD$)	*p*-value n ($\bar{\bar{x}}, SD$)	*p*-value n ($\bar{\bar{x}}, SD$)
Sex	.597	.627	.314	.427
Male	12(-37.79, 64.70)	12(10.04, 24.91)	45(6.99, 10.37)	38(-0.05, 2.59)
Female	6(-57.26, 74.09)	6(6.23, 6.64)	18(4.72, 6.85)	14(0.50, 2.02)
Race	.977	.318	.589	.964
White	11(-44.65, 70.82)	11(4.28, 15.71)	40(6.76, 11.17)	35(0.08, 2.54)
Black	7(-43.70, 64.35)	7(15.83, 26.02)	23(5.61, 5.65)	17(0.11, 2.31)
ICU	.034	.059	.663	.738
MICU	4(-1.92, 15.29)	4(-5.73, 10.32)	14(5.15, 7.06)	11(0.18, 1.77)
SICU	8(-78.28, 81.41)	8(17.46, 27.01)	39(6.27, 10.85)	33(-0.06, 2.73)
Pre-APRV Mode:	.207	.493	.365	.210
PRVC	8(-25.08, 55.05)	8(4.62, 15.05)	28(5.33, 7.46)	22(-0.22, 2.67)
PS/CPAP	5(-88.19, 89.68)	5(16.76, 34.67)	23(8.03, 12.36)	16(.75, 2.04)

Regression Analysis

Multiple regression analysis was conducted to identify significant predictors for any of the four dependent variables of P/F ratio, OI, OSI, and MSOFA scores. Different regression models were created for each of the dependent variables. Also, different multiple regression analyses were conducted for pre-APRV and post-APRV data. A level of significance of 0.05 was used in the multiple regression analysis. An independent variable was considered a significant predictor of the dependent variable if the *p*-value was less than or equal to the level of significance value.

Pre-APRV Results

For the pre-APRV data, the independent variables included the age, height, weight, BMI, Pre-APRV MAWP, T high, T low, P high, P low, and APRV MAWP. Tables 10 to 13 summarize the results of the different multiple regression analyses to determine which pre-APRV scores of the independent variables are significant predictors of the pre-APRV scores of P/F ratio, OI, OSI, and MSOFA.

Table 10 summarizes the results of the multiple regression analysis to determine which are significant predictors of pre-APRV P/F ratio. The regression results showed that the model fit of the regression model (F (10, 20) = 1.40, p = 0.25) generated was insignificant indicating that the regression model did not have an acceptable model fit. The r-square value of the regression model was 0.41, which indicates a moderate effect size and that the combined effects of all independent variables captured 41% of the variance in predicting the pre-APRV P/F ratio. The investigation of the individual impacts showed that only the pre-APRV P low (t (30) = -2.12, p = 0.05) was a significant predictor of pre-APRV P/F ratio. This was the only *p*-value less than the level of significance value. Investigation of the unstandardized beta coefficient value showed that pre-APRV P low negatively predicted pre-APRV P/F ratio. A one score increase in pre-

APRV P low will result to a 5.27 increase in the pre-APRV P/F ratio. This means that the higher the pre-APRV P low, the lower the pre-APRV P/F ratio.

Table 10: Multiple Regression Results of Predictors of Pre-APRV P/F Ratio

Model		Unstandardized Coefficients		Standardized Coefficients	T	Sig.
		B	Std. Error	Beta		
1	(Constant)	3.53	503.62		0.01	0.99
	Age	-0.04	0.63	-0.01	-0.07	0.95
	Height	1.60	7.65	0.14	0.21	0.84
	Weight	-0.79	1.36	-0.87	-0.58	0.57
	BMI	7.70	8.92	1.14	0.86	0.40
	Pre-APRV MAWP	0.11	1.69	0.01	0.07	0.95
	APRV Initial T High	-8.82	4.44	-0.50	-1.99	0.06
	APRV Initial T Low	42.53	22.68	0.49	1.88	0.08
	APRV Initial P High	-9.88	7.11	-0.54	-1.39	0.18
	APRV Initial P Low	-5.27	2.49	-0.45	-2.12	0.05*
	APRV Initial MAWP	8.32	6.95	0.59	1.20	0.25

Note. $F(10, 20) = 1.40$, $p = 0.25$, R Square (R^2) = 0.41, $n = 30$
a. Dependent Variable: APRV initial P/F ratio
b. Predictors: (Constant), APRV Initial MAWP, Height, APRV Initial P Low, Age, Pre-APRV MAWP, BMI, APRV Initial T Low, APRV Initial T High, APRV Initial P High, Weight
*Significant at level of significance of 0.05

Table 11 summarizes the results of the multiple regression analysis to determine which are significant predictors of pre-APRV OI. The regression results showed that the model fit of the regression model (F (10, 20) = 1.18, p = 0.36) generated was insignificant indicating that the regression model did not have an acceptable model fit. The r-square value of the regression model was 0.41, which indicates a moderate effect size and that the combined effects of all independent variables captured 41% of the variance in predicting the pre-APRV OI. The investigation of the individual impacts showed that all independent variables of age (t (30) =

0.10, $p = 0.92$), height (t (30) = 0.59, $p = 0.56$), weight (t (30) = -0.13, $p = 0.90$), BMI (t (30) = -0.18, $p = 0.86$), Pre-APRV MAWP (t (30) = 0.65, $p = 0.52$), T high (t (30) = 120, $p = 0.25$), T low (t (30) = -0.99, $p = 0.34$), P high (t (30) = 1.00, $p = 0.33$), P low (t (30) = 0.94, $p = 0.36$), and APRV MAWP (t (30) = -0.53, $p = 0.60$) were not significant predictors of pre-APRV OI. This was because all the p-values were greater than the level of significance value.

Table 11: Multiple Regression Results of Predictors of Pre-APRV OI

Model		Unstandardized Coefficients		Standardized Coefficients	T	Sig.
		B	Std. Error	Beta		
1	(Constant)	-88.93	166.46		-0.53	0.60
	Age	0.02	0.21	0.02	0.10	0.92
	Height	1.49	2.53	0.42	0.59	0.56
	Weight	-0.06	0.45	-0.20	-0.13	0.90
	BMI	-0.52	2.95	-0.24	-0.18	0.86
	Pre-APRV MAWP	0.36	0.56	0.12	0.65	0.52
	APRV Initial T High	1.76	1.47	0.31	1.20	0.25
	APRV Initial T Low	-7.40	7.50	-0.27	-0.99	0.34
	APRV Initial P High	2.34	2.35	0.40	1.00	0.33
	APRV Initial P Low	0.77	0.82	0.21	0.94	0.36
	APRV Initial MAWP	-1.22	2.30	-0.27	-0.53	0.60

Note. $F(10, 20) = 1.18$, $p = 0.36$, R Square (R^2) = 0.41, $n = 30$

a. Dependent Variable: APRV initial OI

b. Predictors: (Constant), APRV Initial MAWP, Height, APRV Initial P Low, Age, Pre-APRV MAP, BMI, APRV Initial T Low, APRV Initial T High, APRV Initial P High, Weight

Table 12 summarizes the results of the multiple regression analysis to determine which are significant predictors of pre-APRV OSI. The regression results showed that the model fit of the regression model (F (10, 37) = 0.69, $p = 0.73$) generated was insignificant indicating that the regression model did not have an acceptable model fit. The r-square value of the regression model was 0.16, which indicates a low effect size and that the combined effects of all independent variables captured 16% of the variance in predicting the pre-APRV OSI. The

investigation of the individual impacts showed that all independent variables of age (t (47) = 0.08, p = 0.94), height (t (47) = 0.23, p = 0.82), weight (t (47) = 0.17, p = 0.87), BMI (t (47) = -0.23, p = 0.82), APRV MAP (t (47) = 0.72, p = 0.48), T high (t (47) = 0.87, p = 0.39), T low (t (47) = 0.95, p = 0.35), P high (t (47) = 0.25, p = 0.80), P low (t (47) = -0.18, p = 0.86), and MAWP (t (47) = 0.19, p = 0.85) were not significant predictors of pre-APRV OSI. This was because all the p-values were greater than the level of significance value.

Table 12: Multiple Regression Results of Predictors of Pre-APRV OSI

Model		Unstandardized Coefficients		Standardized Coefficients	T	Sig.
		B	Std. Error	Beta		
1	(Constant)	-26.10	101.60		-0.26	0.80
	Age	0.01	0.10	0.01	0.08	0.94
	Height	0.35	1.54	0.15	0.23	0.82
	Weight	0.04	0.26	0.24	0.17	0.87
	BMI	-0.39	1.73	-0.27	-0.23	0.82
	Pre-APRV MAWP	0.25	0.35	0.13	0.72	0.48
	APRV Initial T High	0.77	0.88	0.20	0.87	0.39
	APRV Initial T Low	2.48	2.61	0.19	0.95	0.35
	APRV Initial P High	0.32	1.24	0.09	0.25	0.80
	APRV Initial P Low	-0.08	0.45	-0.03	-0.18	0.86
	APRV Initial MAWP	0.22	1.18	0.08	0.19	0.85

Note. F(10, 37) = 0.69, p = 0.73, R Square (R^2) = 0.16, n = 47

a. Dependent Variable: APRV initial OSI

b. Predictors: (Constant), APRV Initial MAWP, Height, APRV Initial P Low, Age, Pre-APRV MAP, BMI, APRV Initial T Low, APRV Initial T High, APRV Initial P High, Weight

Table 13 summarizes the results of the multiple regression analysis to determine which are significant predictors of pre-APRV MSOFA score. The regression results showed that the model fit of the regression model (F (10, 32) = 1.43, p = 0.21) generated was insignificant indicating that the regression model did not have an acceptable model fit. The r-square value of the regression model was 0.31, which indicates a moderate effect size and that the combined effects

of all independent variables captured 31% of the variance in predicting the pre-APRV MSOFA score. The investigation of the individual impacts showed that all independent variables of age (t (42) =1.01 , p = 0.32), height (t (42) = 1.02, p = 0.32), weight (t (42) =-0.87 , p = 0.39), BMI (t (42) = 0.94, p = 0.35), APRV MAP (t (42) = 0.99, p = 0.33), T high (t (42) = -0.03, p = 0.98), T low (t (42) = 1.37, p = 0.18), P high (t (42) = 0.04, p = 0.97), P low (t (42) = 1.11, p = 0.27), and MAWP (t (42) = -0.18, p = 0.86) were not significant predictors of pre-APRV MSOFA score. This was because all the p-values were greater than the level of significance value.

Table 13: Multiple Regression Results of Predictors of Pre-APRV MSOFA Score

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-23.17	26.86		-0.86	0.40
	Age	0.03	0.03	0.16	1.01	0.32
	Height	0.41	0.41	0.64	1.02	0.32
	Weight	-0.06	0.07	-1.24	-0.87	0.39
	BMI	0.43	0.46	1.13	0.94	0.35
	Pre-APRV MAWP	0.09	0.09	0.17	0.99	0.33
	APRV Initial T High	-0.01	0.24	-0.01	-0.03	0.98
	APRV Initial T Low	0.91	0.67	0.26	1.37	0.18
	APRV Initial P High	0.01	0.33	0.01	0.04	0.97
	APRV Initial P Low	0.14	0.13	0.21	1.11	0.27
	APRV Initial MAWP	-0.06	0.32	-0.07	-0.18	0.86

Note. $F(10, 32) = 1.43$, $p = 0.21$, R Square (R^2) = 0.31, $n = 42$
a. Dependent Variable: APRV initial MSOFA Score
b. Predictors: (Constant), APRV Initial MAWP, Height, APRV Initial P Low, Age, Pre-APRV MAP, BMI, APRV Initial T Low, APRV Initial T High, APRV Initial P High, Weight

Post-APRV Results

For the pre-APRV data, the independent variables included the age, height, weight, BMI, APRV duration, T high, T low, P high, P low, and MAWP. Tables 14 through 17 summarizes the results of the different multiple regression analyses to determine which post-APRV scores of

the independent variables are significant predictors of the post-APRV scores of P/F ratio, OI, OSI, and MSOFA.

Table 14 summarizes the results of the multiple regression analysis to determine which are significant predictors of post-APRV P/F Ratio. The regression results showed that the model fit of the regression model (F (10, 9) = 0.65, p = 0.75) generated was insignificant indicating that the regression model did not have an acceptable model fit. The r-square value of the regression model was 0.42, which indicates a moderate effect size and that the combined effects of all independent variables captured 42% of the variance in predicting the post-APRV P/F Ratio. The investigation of the individual impacts showed that all independent variables of age (t (19) = -0.25, p = 0.81), height (t (19) = -0.68, p = 0.51), weight (t (19) = 0.49, p = 0.64), BMI (t (19) = -0.31, p = 0.77), APRV duration (t (19) = -0.92, p = 0.38), T high (t (19) = 0.76, p = 0.47), T low (t (19) = 0.38, p = 0.71), P high (t (19) = 0.29, p = 0.78), P low (t (19) = -0.39, p = 0.71), and MAWP (t (19) = -0.09, p = 0.93) were not significant predictors of post-APRV P/F Ratio. This was because all the p-values were greater than the level of significance value.

Table 14: Multiple Regression Results of Predictors of Post-APRV P/F Ratio

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	818.64	1105.38		0.74	0.48
	Age	-0.40	1.60	-0.08	-0.25	0.81
	Height	-12.05	17.71	-0.76	-0.68	0.51
	Weight	1.83	3.71	1.22	0.49	0.64
	BMI	-6.64	21.75	-0.70	-0.31	0.77
	APRV Duration	-4.04	4.39	-0.28	-0.92	0.38
	Post-APRV T high	9.04	11.87	0.33	0.76	0.47
	Post-APRV T low	14.75	38.50	0.15	0.38	0.71
	Post-APRV P high	1.43	4.92	0.10	0.29	0.78
	Post-APRV P low	-2.20	5.63	-0.13	-0.39	0.71

Post-APRV MAWP	-0.32	3.70	-0.03	-0.09	0.93

Note. $F(10, 9) = 0.65$, $p = 0.75$, R Square (R^2) = 0.42, $n = 19$
a. Dependent Variable: Post-APRV P/F ratio
b. Predictors: (Constant), Post-APRV MAWP, APRV Duration, Height, Age, Post-APRV P low, Post-APRV T low, Post-APRV P high, BMI, Post-APRV T high, Weight

Table 15 summarizes the results of the multiple regression analysis to determine which are significant predictors of post-APRV OI. The regression results showed that the model fit of the regression model (F (10, 9) = 1.40, p = 0.31) generated was insignificant indicating that the regression model did not have an acceptable model fit. The r-square value of the regression model was 0.61, which indicates a strong effect size and that the combined effects of all independent variables captured 61% of the variance in predicting the post-APRV OI. The investigation of the individual impacts showed that all independent variables of age (t (19) = -0.53, p = 0.61), height (t (19) = 1.69, p = 0.13), weight (t (19) = -1.31, p = 0.22), BMI (t (19) = 1.19, p = 0.26), APRV duration (t (19) = 0.96, p = 0.36), T high (t (19) = -0.42, p = 0.68), T low (t (19) = -0.39, p = 0.71), P high (t (19) = -0.71, p = 0.50), P low (t (19) = 0.82, p = 0.43), and MAWP (t (19) = 1.02, p = 0.33) were not significant predictors of post-APRV P/F Ratio. This was because all the p-values were greater than the level of significance value.

Table 15: Multiple Regression Results of Predictors of Post-APRV OI

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-282.92	179.02		-1.58	0.15
	Age	-0.14	0.26	-0.15	-0.53	0.61
	Height	4.84	2.87	1.55	1.69	0.13
	Weight	-0.79	0.60	-2.66	-1.31	0.22
	BMI	4.20	3.52	2.22	1.19	0.26
	APRV Duration	0.68	0.71	0.24	0.96	0.36
	Post-APRV T high	-0.81	1.92	-0.15	-0.42	0.68
	Post-APRV T low	-2.41	6.24	-0.12	-0.39	0.71

Post-APRV P high	-0.57	0.80	-0.19	-0.71	0.50
Post-APRV P low	0.75	0.91	0.23	0.82	0.43
Post-APRV MAWP	0.61	0.60	0.28	1.02	0.33

Note. $F(10, 9) = 1.40$, $p = 0.31$, R Square (R^2) = 0.61, $n = 19$
a. Dependent Variable: Post-APRV OI
b. Predictors: (Constant), Post-APRV MAWP, APRV Duration, Height, Age, Post-APRV P low, Post-APRV T low, Post-APRV P high, BMI, Post-APRV T high, Weight

Table 16 summarizes the results of the multiple regression analysis to determine which are significant predictors of post-APRV OSI. The regression results showed that the model fit of the regression model (F (10, 59) = 3.33, p = 0.002) generated was significant indicating that the regression model has an acceptable model fit. The r-square value of the regression model was 0.40, which indicates a moderate effect size and that the combined effects of all independent variables captured 40% of the variance in predicting the post-APRV OSI. The investigation of the individual impacts showed that that only the post-APRV MAWP (t (60) = 2.98, $p < 0.001$) was a significant predictor of post-APRV OSI. This was the only p-value less than the level of significance value. Investigation of the unstandardized beta coefficient value showed that post-APRV MAWP positively predicted post-APRV OSI. A one score increase in post-APRV MAWP will result to a 0.54 increase in the post-APRV OSI. This means that the higher the post-APRV MAWP will result in a higher post-APRV OSI.

Table 16: Multiple Regression Results of Predictors of Post-APRV OSI

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-59.85	34.74		-1.72	0.09
	Age	-0.03	0.04	-0.07	-0.60	0.55
	Height	0.91	0.52	0.75	1.74	0.09
	Weight	-0.16	0.08	-1.55	-1.94	0.06
	BMI	0.89	0.51	1.27	1.73	0.09
	APRV Duration	-0.14	0.13	-0.13	-1.08	0.29

Post-APRV T high	0.03	0.33	0.01	0.10	0.92
Post-APRV T low	0.03	1.51	0.00	0.02	0.98
Post-APRV P high	0.26	0.20	0.19	1.32	0.19
Post-APRV P low	0.25	0.16	0.18	1.58	0.12
Post-APRV MAWP	0.54	0.18	0.43	2.98	0.00*

Note. $F(10, 59) = 3.33$, $p = 0.002$, R Square (R^2) = 0.40, $n = 60$
a. Dependent Variable: Post-APRV OSI
b. Predictors: (Constant), Post-APRV MAWP, APRV Duration, Height, Age, Post-APRV P low, Post-APRV T low, Post-APRV P high, BMI, Post-APRV T high, Weight
*Significant at level of significance of < 0.05

Table 17 summarized the results of the multiple regression analysis to determine which are significant predictors of post-APRV MSOFA score. The regression results showed that the model fit of the regression model (F (10, 40) = 2.03, p = 0.06) generated was insignificant indicating that the regression model did not have an acceptable model fit. The r-square value of the regression model was 0.34, which indicates a low effect size and that the combined effects of all independent variables captured 34% of the variance in predicting the post-APRV MSOFA score. The investigation of the individual impacts showed that post-APRV P high (t (50) = 2.35, p = 0.02) and P low (t (50) = 2.39, p = 0.02) were significant predictors of post-APRV MSOFA score. These were the only p-values less than the level of significance value. Investigation of the unstandardized beta coefficient value showed that both post-APRV P high and P low positively predicted post-APRV MSOFA score. A one score increase in post-APRV P high will result to a 0.29 increase in the post-APRV MSOFA score. A one score increase in post-APRV P low will result to a 0.26 increase in the post-APRV MSOFA score. This means that the higher the post-APRV P high and P low will result in a higher post-APRV MSOFA score.

Table 17: Multiple Regression Results of Predictors of Post-APRV MSOFA Score

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		

1	(Constant)	-22.95	21.02		-1.09	0.28
	Age	0.02	0.03	0.09	0.61	0.55
	Height	0.35	0.32	0.53	1.08	0.29
	Weight	-0.06	0.05	-1.04	-1.16	0.26
	BMI	0.44	0.31	1.18	1.40	0.17
	APRV Duration	-0.01	0.09	-0.02	-0.15	0.88
	Post-APRV T high	-0.20	0.20	-0.15	-1.01	0.32
	Post-APRV T low	-0.55	1.25	-0.07	-0.44	0.66
	Post-APRV P high	0.29	0.13	0.37	2.35	0.02*
	Post-APRV P low	0.26	0.11	0.33	2.39	0.02*
	Post-APRV MAWP	0.01	0.11	0.01	0.05	0.96

Note. $F(10, 40) = 2.03$, $p = 0.06$, R Square (R^2) = 0.34, $n = 50$
a. Dependent Variable: Post-APRV MSOFA Score
b. Predictors: (Constant), Post-APRV MAWP, APRV Duration, Height, Age, Post-APRV P low, Post-APRV T low, Post-APRV P high, BMI, Post-APRV T high, Weight
*Significant at level of significance of < 0.05

Given that this study examined both absolute values and changes in all clinical outcome scores (P/F ratio, OI, OSI, and MSOFA) at two time points (T0 and T'X'), there was the potential for subjects to continue receiving APRV beyond the recorded time. Additionally, not all subjects had available metrics to calculate both pre-APRV or post-APRV dependent variables.

Summary

The data bears clinical implication in several ways. One can appreciate that the overall sample may not render an accurate representation of the entire patient population nor does it necessarily exactly align with the average expectation in what is seen during local patient care. However, study results may offer insight into better practice. Certain findings such as the effect of MAWP on certain clinical outcomes can be viewed as indirectly supporting the original hypothesis. As it is well-known that I-time affects MAWP (Burchardi, 1996), this study confirmed that I-time is a setting of great importance. Likewise, particular settings can directly

or indirectly affect short term clinical outcomes and arguably end organ function. In the upcoming Chapter 5, specific clinical implications and relevancy to bedside care are discussed in detail. It is important to note that results from this study should only be interpreted as presented, although there is an alignment with the theory from prior studies of APRV as a mode of stabilization for alveolar units.

Chapter 5: Discussion

Introduction to Chapter 5

This study yielded both expected and unforeseen results. It was to be assumed, based upon the small pilot performed prior to this larger-scale study, that results of this study would have been relatively concurrent or, at the least, continuing in alignment with the results of the pilot. However, there are a few items of particular interest discussed in detail within this chapter. As the results are further presented and discussed, the investigator urges the reader to be aware of variables that have not necessarily been linked into the study but may be thought of as an influencer nonetheless. The study may be underpowered given the relatively small sample size, but there are specific results worth noting that bare both statistical as well as clinical significance.

Various limitations apply to this study and will be discussed. Several interesting findings have immediate applicability to current bedside care and allowed the investigator immense insight into particular practice patterns at the large academic medical center of study. All retrospective data was treated as such, and all results were appraised by the investigator in the capacity of a doctoral-candidate level researcher and licensed, practicing Respiratory Therapist. The following results and accompanying interpretations are meant to provide the reader with a detailed understanding reflective of the investigator's overall body of work.

Discussion and Interpretation of Results

Demographics

At the large academic medical center in which the study was conducted, based upon observation of the local demographics and patient population, it was expected to have sampled a cohort comparable to the overall general demographic. However, study results yielded a

predominant Caucasian sample population as opposed to the more prevalent African American patient population. It was not necessarily expected to have a predominant middle-aged sample nor was it expected that only 68 subjects could be identified over a 3-year period from the EHR archives, having received APRV for a minimum of 8 hours consecutively. It is suspected there were undoubtedly potential subjects that were not captured during the initial data extraction by the UH IT team, but this is only speculation based upon the experience of the investigator in having cared for multiple patients over many years that consistently received APRV. In this study, a majority of the subjects were cared for in the SICU; however, it should be noted that patients are often managed by the MICU service in the SICU environment. This management could be a confounder in delineating PPV management preferences among the ICUs.

Clinical Data

There was some difficulty acquiring all pertinent ventilator settings for some subjects as documentation was variable and occasionally lacking. Upon contacting the RT department, it was found that no specific policy existed for documentation requirements of ventilator settings and parameters. Moreover, it was noted upon re-review of subject's EHRs that certain subjects had emergent events that necessitated rapid intubation and placement on PPV. Other subjects were removed from APRV prior to the 24-hour target period based upon varying provider preferences. Certain documented APRV settings revealed that several patients were only placed on APRV as a mode but did not have technical APRV implemented as originally purposed (i.e., I-time < 1 sec; I:E < 1:1).

On average, subjects received higher MAWP during APRV as compared to their prior PPV mode, but this did not result in overall higher subject SpO2 after APRV initiation. This may be attributed to the fact that some subjects were placed on APRV as a rescue mode while

their clinical status was deteriorating. Likewise, as evidenced by the pre-APRV MSOFA scores, end organ dysfunction may have been developing simultaneously. Although average I-time (T high) during APRV for subjects was 6.3 seconds, there was disparity among the overall sample (min-max: 0.9 sec – 11.0 sec). This could be attributed to provider preference or even misplaced caregiver documentation, exchanging I-time with the inspiratory ratio of the I:E. In summary, it was assumed that all EHR documentation was accurate and all data manually entered was done so without error.

Outcomes of Interest

For the main study dependent variables, referred to as short-term clinical outcomes, all showed improvement. The change in P/F ratio, OI, OSI, and MSOFA were all in a desirable direction with a statistically significant change in P/F ratio and OSI. Because the number of subjects ascribed to each group was highly variable, there may have been a greater effect appreciated if a larger number of subjects were sampled. There was difficulty acquiring a PaO2 on most subjects as this metric is only available through an arterial blood gas (ABG) procedure. A majority of patients do not receive daily ABGs nor did the time of onset of APRV or cessation thereof necessarily coincide with the timeframe in which the ABG may have been acquired according to typical institution protocol or ordering provider preference. Moreover, as prior outlined in the "Special Considerations" section, other data required for calculation of dependent variables was lacking owing to smaller sample size of the individual groupings for pre-APRV and post-APRV change scores.

The P high, P low, the MAWP, and subject's BMI each impacted one or more clinical outcomes. It is unknown whether the impact was a function of a stand-alone variable or whether a conglomerate of several entities rendered the effect. However, it is well-known in clinical

practice that, mathematically, P high and P low directly affect MAWP. It is also known that patients with higher BMI typically have less desirable clinical outcomes and higher mortality overall (Calle, Thun, Petrelli, Rodriguez, & Heath, 1999). The study revealed that a lower setting for P high, P low, T low, and overall lower target MAWP were associated with a better OI, OSI, and MSOFA score. In consideration of MSOFA score as a validated indicator of acuity and predictor of mortality, patients in this study tended to be at moderate risk overall. This may have affected outcomes unrelated to PPV management.

The regression analysis identified P low as a significant predictor of pre-APRV P/F ratio (not causal). MAWP was identified as a significant predictor of post-APRV OSI (contributing factor). Finally, P high and P low were identified as significant predictors of post-APRV MSOFA scores (contributing factor). The results of the regression revealed that the higher the P low, the lower resulting P/F ratio (undesirable), while the higher the MAWP, the higher the OSI (undesirable). Additionally, the higher the P high and P low, the higher the MSOFA score (undesirable). In summary, both P high and P low should be kept as low as possible while a higher MAWP should only be targeted in order to increase OSI.

The study dependent variables were considered surrogates for short-term clinical outcomes and should only be regarded as such. There is no one metric that absolutely represents a desirable clinical outcome. Likewise, there is no known PPV setting or parameter that is an exclusive influencer of a short-term clinical outcome. It would have been highly valuable to be able to follow each subject's entire course of care in order to investigate whether change scores for P/F ratio, OI, OSI, and MSOFA metrics continued to trend in the same direction as in this retrospective analysis. As well, a prospective study might offer an opportunity in which to

guarantee the acquisition of certain parameters, such as PaO2, with the target of building a larger, more consistent sample size for each outcome.

APRV Current Considerations

A recent study confirmed that there is variable opinion on APRV management among PPV practitioners (Miller et al., 2017). In the current literature, however, APRV is still recommended as a protective mode of PPV, favored above a majority of traditional modes for ARDS management (Perinel-Ragey, Baboi, & Guerin, 2017). Perhaps the greatest attraction of APRV use is the ability to limit cyclic opening and closing of lung units, which allow more stability and the implementation of optimal PEEP by means of preventing de-recruitment during the expiratory phase, and not by PEEP setting alone, such as in a traditional mode of PPV. A recent review by Niemen et al. (2017) suggests that APRV allows for personalization of PEEP, generating intrinsic PEEP in order to stabilize the lung and avoid VILI (Nieman et al., 2017). It will be interesting to monitor for future studies in this area of research to appreciate any developments in suggested starting parameters for APRV initiation of more specific management strategies as a whole.

APRV, in general, is thought to reduce overall lung stress and strain by diminishing dynamic alveolar heterogeneity (Kollisch-Singule et al., 2016). Moreover, a 2013 systematic review by Andrews et al. suggested that, in high risk patients, the early application of APRV may prevent progression to ARDS (Andrews et al., 2013). One of the most well-known published studies of APRV cites that "APRV seems to have a similar safety profile to low tidal volume ventilation" (Maxwell et al., 2010), but it is not recommended to utilize APRV as a rescue mode. Additionally, the originator of APRV, along with colleagues, recommends the incorporation of a "physiology driven" approach with individualized ventilator setup in addition

to adopting a view that P High and T High should not necessarily be considered concurrent entities (Evans, Stawicki, Eiferman, Reilley, & Downs, 2011). Although almost no studies have addressed specific initial settings, Madden et al. recommends setting a P_{low} of 0 cmH2O in order to optimize CO2 clearance (Madden et al., 2016), but this does not address oxygenation.

Implications for Practice

Currently, there is a lack of agreement among ordering providers, institutional protocol, and RTs, alike, on when and how PPV should be implemented. There is also no consensus, specifically, on how PPV should be managed (Miller et al., 2017). This study revealed a congruency with this ideal. Results were not absolutely conclusive based upon a most likely underpowered sample. Moreover, a study of this kind requires one to evaluate all results in perspective for which population was evaluated. Not all bedside practice involves a patient population akin to subjects of this study. However, patients at other institutions with comparable acuity and risk levels may greatly benefit from specific APRV employment over longer periods of time as evidenced by the appreciable improvement seen for all dependent variables in this study.

It was evident that no particular standard for ordering APRV or managing APRV settings existed, either between different ICUs or among the same ICU. It seemed as if the ordering provider had the greatest bearing on initial settings implementation, but it is difficult to identify a trend with an *N* of 68. Certain covariates, as well as individual comorbidities and pre-existing conditions, were unable to be evaluated. Other potential confounders were identified but not tested, such as the fact that subjects had highly differing precipitating events that led to APRV initiation and a highly variable time delay between intubation and APRV implementation.

Furthermore, it was empirically noted that certain providers ordered similar APRV settings on all patients, regardless.

Our local institution should greatly benefit from the findings of this study, in that it seems as if a lower P high, P low, and MAWP could be attributed to a more positive short-term clinical outcome based upon the dependent variables of this study. Although I-time (T high) did not render a statistically significant relationship with any of the dependent variables, one should appreciate that a lower P high was attributed to a lower (more desirable) MSOFA score. It has long been known that MAWP affects oxygenation and that I-time directly affects MAWP during PPV (Boros, 1979). Also, longer inflation times allow for maintenance of MAWP at lower peak pressures while decreasing cyclic opening and closing of lung units (E. G. Daoud et al., 2012). In this study, subjects received a highly variable I-time, and it would be recommended for future similar studies that outliers be discarded to prevent confounding.

Overall, this study offers insight to all clinicians that manage PPV, especially those who regularly manage APRV. Based upon the study results, the investigator recommends the following during APRV initiation and management: 1) utilize the lowest possible P high and P low to achieve acceptable oxygenation and CO2 clearance, 2) closely attend to T low, titrating as necessary but maintaining IRV, and 3) allow for lowest possible MAWP while allowing for adequate inflation and acceptable oxygenation.

Implications for Further Research

Further research is certainly warranted to explore the deeper concepts surrounding APRV implementation and prolonged application of this specialized mode. Although APRV is an established protective mode of PPV, a majority of studies have only utilized analogue models, animals, or a small population of particularly specific subjects. This study gives insight into a

small, moderate risk population of patients managed on APRV for a short period of time. There remains much opportunity for more exploration of the topic. Ideally, a randomized control trial of a larger cohort should be identified in which APRV was maintained for at least 24 hours consecutively. A prospective study may allow for better congruency between true SOFA scores and other validated metrics within the realm of a pre-APRV and post-APRV evaluation.

It is still unknown whether specific APRV settings directly affect long-term outcomes and mortality. Additionally, though the results of this study showed that P high, P low, and MAWP affect a short-term clinical outcome, data is still lacking as to what particular settings might be recommended as starting points in the general adult population. It is important to note that applicability to a general population of those receiving PPV has yet to be determined. Moreover, a larger study, templated and based on this study's methodology, should be considered in order to appreciate a greater effect should one be realized.

Limitations and Delimitations

Several limitations and delimitations were noted in this study. Arguably, the greatest limitation of this study is that it is underpowered given the yield of only 68 subjects from a retrospective search of the EHR within a 3-year period. Because all data acquired was gleaned retrospectively, a major limitation was the fact that the EHR system was only recently adopted, beginning circa October, 2013. This timeframe absolutely limited the timeframe in which data could easily be acquired in a comprehensive manner without data mining through traditional paper charts. In the future, it is recommended to target a longer timeframe in order to capture a greater cohort of subjects.

Even after planning in advance and working directly with the UH Information Office, it was initially difficult to identify all particular patients that received APRV for at least exactly 12-

24 hours consecutively. This timeframe limitation contributed to the overall low sample population. It was noted during the review of raw data from the original full EHR that there was a lack of documentation on ventilator flowsheets with occasional missing parameters and settings, highly dependent upon the timeframe in which the original input occurred and also variable according to the healthcare provider documenting the events.

In reviewing the actual EHR to manually extract additional information to satisfy the missing fields from the initial report, there was some difficulty in identifying lab values exactly concurrent with onset, cessation, or APRV, so the investigator set a timeframe range allowable for recording. As previously mentioned, PaO2 was also not commonly acquired as it is not standard practice when patients are relatively stable and have available non-invasive SpO2 monitoring.

Recommendations

It is recommended that future investigation related to this study topic evaluate a greater timeframe in order to capture a potentially larger sample population. Additionally, it may be worthwhile to develop a prospective study evaluating this same ideal as well as evaluate a broader scope of clinical outcomes both short term and long term. A prospective study would allow more control over time delay for APRV initiation, total time on APRV, and congruency with lab results concurrent with particular outcomes of interest.

A multi-center, prospective study should be designed that would include a large number of subjects that could be investigated in a more controlled manner. A study to include more time aligned lab and other parameter acquisition with concurrent APRV initiation is recommended. Additionally, a study that reports outcome metrics after a more consistent APRV dosing (i.e., each subject receiving 24-48 hours continuous APRV) may render more appreciable results. In

summary, no study design is without flaw, but the more variables that are accounted for and controlled, the higher likelihood results would be applicable to a more general population.

Summary

In conclusion, there is no stand-alone metric able to predict an absolute clinical outcome. Neither can the implications of this study be applied explicitly to similar populations. This study simply suggests that there may be an ideal way to ventilate patients in the APRV mode under certain conditions. A larger study to include more subjects followed over a longer period of time is recommended. The incorporation of other outcome measures would also be necessary in order to assume more comprehensively the P/F ratio, OI, OSI, and MSOFA scores that were most affected by the specific variables identified in the correlational matrixes, bivariate analyses, and regression analysis.

The identified predictors of P high, P low, and MAWP impacting the short-term clinical outcomes should only be considered in alignment with and within the parameters of this specific study. In order to account for covariates, such as those associated with particular comorbidities as sepsis, organ failure, and genetic predisposition, a more in-depth evaluation of these particular variables would be necessary.

Although the EHR is considered an accurate database of patient information, there is potential for human error in the recording process. This study gives insight into the potential of exploring preferred ways in which to artificially ventilate patients, withholding the compounding of stress, strain on the lungs, and the long-term effects thereof. It should be noted that with longer I-times, inflation pressures are expected to be slightly lower as compared with shorter I-times when pressure is applied over less time. The ordering provider ultimately influences what settings are initiated at onset of APRV. Likewise, the managing medical team, overall, certainly

impacts the patient's course of care and may influence the manipulation of mechanical ventilation.

This study confirms that settings for APRV should not be chosen arbitrarily and that the purposeful application of APRV could have both positive and negative effects that influence more than just oxygenation. In alignment with the prior published recommendations of both Habashi and Modrykamien et al., the investigator would not disagree that it is still a good strategy to set T low to target inducement of auto PEEP with an initial P low setting of 0 cmH2O (Habashi, 2005; Modrykamien et al., 2011). However, the results of this dissertation study would suggest also that both P high and MAWP should be applied judiciously and maintained as low as possible in order to promote better short-term clinical outcomes.

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Appendix:

Appendix A: Data Collection Tool

**All missing (undocumented) fields will be designated: "#"*

MRN: _____

Adm Date/Time: _____; _____

Disch Date/Time: _____; _____

DOB: _____; _____ (Age at onset of APRV: yrs)

Sex: Male; Female **Race**: _____

Height (flowsheets, tabs): _____ (in)

Weight (flowsheets, tabs): _____ (lbs)

Dx ARDS? (ICD-9: 518.82; ICD-10: *J80*): Y(1)/N(2)

Provider # *during APRV management:* _____

ICU stay *during APRV management*: MICU (1), SICU (2), Neuro ICU (3), Other (4)

Time from intubation to initiation of APRV (hrs): _____ . __

Respiratory status *immediately* **prior to initiation of APRV**:

Prior Vent mode: PRVC/PCVG (1); PC (2); PS/CPAP (3); VC (4); unknown (5): _____

Pre-APRV, Main setting: (PC level, Vt, PS): _____

FiO2: _____ (%)

PEEP: _____ (cmH2O)

PIP: _____ (cmH2O)

MAP: _____ (cmH2O)

SpO2: _____ (%) PaO2: _____ (mmHg)

APRV *initial* settings:

I:E: _____

FiO2: _____ (%)

T high: _____ (secs) Phigh: _____ (cmH2O) HR: _____ (bpm)

T low: _____ (secs) Plow: _____ (cmH2O) RR: _____ (bpm)

PIP: _____ (cmH2O) MAWP: _____ (cmH2O)

RR spont: _____ (bpm)

RR: total: _____ (bpm) Ve: _____ (l/min)

Vt exhaled: _____ (mls) PaO2: _____ (mmHg); Time: _____

Vt spont: _____ (mls) SpO2: _____(mmHg); Time: _____

Variables post-APRV at least 24 hours: *total hours on APRV* when below values recorded: ____

I:E: _____

FiO2: _____ (%)

T high: _____ (secs) Phigh: _____ (cmH2O) HR: _____ (bpm)

T low: _____ (secs) Plow: _____ (cmH2O) RR: _____ (bpm)

PIP: _____ (cmH2O) MAWP: _____ (cmH2O)

RR spont: _____ (bpm)

RR: total: _____ (bpm) Ve: _____ (l/min)

Vt exhaled: _____ (mls) PaO2: _____ (mmHg); Time: _____

Vt spont: _____ (mls) SpO2: _____(mmHg); Time: _____

MSOFA Score **<u>at initiation of APRV</u>**:

SpO2: _____ (%)

FiO2: _____ (%)

(Liver): Presence of documented scleral icterus or jaundice ___ yes ___ no

Bilirubin: _____ (mg/dL)

MArtBP: _____ (mmHg)

Hypotn level:_____ (**Score***)

*no hypot = **0**; MAP<70 = **1**; on vasopressors, dopamine<5μg/kg/min or dobutamine any dose = **2**; dopamine >5μg/kg/min or Epi/Norepi<0.1μg/kg/min = **3**; dopamine > 15μg/kg/min or Epi/Norepi>0.1μg/kg/min = **4**)

GCS: _____

Creatinine: _____ (*level*)

Creatinine: _____ (**Score***)

*Cr<1.2mg/dL (<106μmol/L) = **0**; Cr 1.2-1.9 mg/dL (106-168 μmol/L) = **1**; Cr 2.0-3.4mg/dL (177-301μmol/L) = **2**; Cr 3.5-4.9mg/dL (309-433 μmol/L) Or UO<500ml/day = **3**; Cr>5.0mg/dL (>442μmol/L) = **4**

SOFA (Sequential Organ Failure Assessment) Score **<u>after on APRV at least 24 hours:</u>**

total hours on APRV when below values recorded: ____

SpO2: _____ (%)

FiO2: _____ (%)

(Liver): Presence of documented scleral icterus or jaundice ___ yes ___ no

Bilirubin: _____ (mg/dL)

MArtBP: _____ (mmHg)

Hypotn level:_____ (**Score***)

*no hypot = **0**; MAP<70 = **1**; on vasopressors, dopamine<5μg/kg/min or dobutamine any dose = **2**; dopamine >5μg/kg/min or Epi/Norepi<0.1μg/kg/min = **3**; dopamine > 15μg/kg/min or Epi/Norepi>0.1μg/kg/min = **4**)

GCS: _____

Creatinine: _____ (*level*)

Creatinine: _____ (**Score***)

*Cr<1.2mg/dL (<106μmol/L) = **0**; Cr 1.2-1.9 mg/dL (106-168 μmol/L) = **1**; Cr 2.0-3.4mg/dL (177-301μmol/L) = **2**; Cr 3.5-4.9mg/dL (309-433 μmol/L) Or UO<500ml/day = **3**; Cr>5.0mg/dL (>442μmol/L) = **4**