

Exploring the Impact of One-Lung Ventilation on Post-Operative Pulmonary Complications in Thoracic Surgery

By

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Abstract

This thesis investigates the predictive power of various ventilatory parameters, particularly peak inspiratory pressure (PIP), in relation to post-operative pulmonary complications (PPCs) in patients undergoing one-lung ventilation during thoracic surgery. This thesis demonstrates that PIP levels during one-lung ventilation are predictive of PPCs, with results suggesting that the rate of risk for PPCs increases exponentially as PIP levels rise.

A comprehensive exponential pressure dose-response model was developed to better describe patient exposure, incorporating both the magnitude and duration of all PIP setpoints the patients were exposed to during surgery. This model provided enhanced predictive power for PPCs and correlated significantly with observed tidal volume drift (TV-Drift), a potential intraoperative indicator of lung injury. The findings underscore the importance of considering both PIP levels and exposure time in the management of one-lung ventilation.

Additionally, this thesis proposes TV-Drift as a potential intraoperative biomarker of lung damage, noting that it was increased in patients who developed PPCs compared to matched controls.

This thesis concludes with recommendations for future research, including the validation of the exponential pressure model, further exploration of TV-Drift as a biomarker, and the development of real-time monitoring tools to improve patient outcomes after thoracic surgery and one-lung ventilation.

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Dedication

To my sweet Maia.

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List of Abbreviations

ARDS	Acute Respiratory Distress Syndrome
AWP	Airway Pressure
AWF	Airway Flow
COPD	Chronic Obstructive Pulmonary Disease
DLCO	Diffusion Capacity for Carbon Monoxide
FEV1	Forced Expiratory Volume in One Second
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
ILD	Interstitial Lung Disease
LPV	Lung Protective Ventilation
MV	Mechanical Ventilation
OLV	One Lung Ventilation
PBW	Predicted Body Weight
PCV	Pressure Control Ventilation
PEEP	Positive End Expiratory Pressure
PIP	Peak Inspiratory Pressure
PPC	Post-operative Pulmonary Complication
TI	Inspiratory Time
TLC	Total Lung Capacity
TLV	Two Lung Ventilation
TV	Tidal Volume
TV-Drift	Tidal Volume Drift

VCV	Volume Control Ventilation
VILI	Ventilator Induced Lung Injury

Chapter 1: Introduction

1.1 Overview

Every year, approximately 2.4 million surgeries are performed in Canada, with most surgeries conducted under general anesthesia requiring mechanical ventilation (MV) [1], [2], [3], [4].

Unlike natural breathing, where air is drawn into the lungs by creating negative pressure, mechanical ventilation uses positive pressure to push air into the lungs via an endotracheal tube.

This fundamental difference in the mechanism of breathing increases the risk of lung injury, particularly during lung surgeries, which are essential for managing conditions such as lung cancer—the leading cause of cancer-related deaths in Canada [1], [2], [3], [4].

Lung surgeries, such as those for the treatment, staging, and diagnosis of lung cancer, present unique challenges due to the need for one-lung ventilation (OLV). During OLV, only one lung is ventilated while the other lung is collapsed to allow the surgeon access to the lung being operated on. This practice, while necessary, significantly increases the potential for lung injury, especially in patients with pre-existing lung conditions like chronic obstructive pulmonary disease (COPD) or interstitial lung disease (ILD). These patients are particularly vulnerable to the adverse effects of OLV, which can lead to post-operative pulmonary complications (PPCs) such as pneumonia, acute lung injury, and, in severe cases, respiratory failure [1], [2], [3], [4]. Given these risks, the concept of lung-protective ventilation—strategies aimed at minimizing lung injury by carefully controlling ventilatory parameters like peak inspiratory pressure (PIP) and tidal volume (TV)—has become increasingly important in thoracic surgery. However, the application of protective ventilation strategies during OLV is not yet well understood, and there is no consensus on the optimal settings to prevent lung injury. A major clinical challenge is that there are competing interests during lung surgery. Excessive airway pressures and tidal volumes

are both potentially harmful, yet reducing these parameters may cause inadequate gas-exchange which can also be harmful [1], [2], [3], [4]. This trade-off makes it difficult to make evidence-based decisions regarding the most protective ventilator strategy during surgery. Additionally, the variability in patient responses and the complexity of the surgical environment further complicate the establishment of standardized protective measures.

1.2 Problem Definition

One-lung ventilation (OLV) presents a significant challenge in thoracic surgery, particularly because it requires ventilating only half of the lung space, often in patients with pre-existing compromised lung function. These patients are at heightened risk of post-operative pulmonary complications (PPCs), which are a major cause of morbidity and mortality. Despite the critical importance of ventilatory management during OLV, nature of the damage caused by setpoints for ventilation parameters such as peak inspiratory pressure (PIP) and tidal volume (TV) are not well understood [1], [2], [3], [4]. This lack of clarity leads to inconsistent care practices across Canada [5], potentially increasing the risk of PPCs. Developing a deeper understanding of how OLV settings may increase risk of PPCs is essential to improving patient outcomes and reducing the incidence of PPCs in this vulnerable population.

1.3 Objectives

The primary objective of this thesis is to enhance the understanding of how ventilatory settings during one-lung ventilation (OLV) in thoracic surgery increase the occurrence of post operative pulmonary complications (PPCs). To achieve this, the research is structured around the following specific objectives:

1.3.1 Lung Pressures

The objective of this research is to investigate the role of peak inspiratory pressure (PIP) during one-lung ventilation (OLV) in relation to post-operative pulmonary complications (PPCs).

Although PIP is not a direct measure of lung pressure in Pressure-Controlled Ventilation (PCV) it remains a critical parameter in ventilatory management by limiting plateau pressures. Given that the available data was derived from pressure controlled OLV, this study specifically explores the significance of PIP as a surrogate marker for lung stress and its potential impact on the incidence of PPCs during OLV. By focusing on PIP, this research aims to contribute to the understanding of how ventilatory setpoints for pressures influence lung injury and to inform strategies for minimizing PPCs in thoracic surgery.

1.3.2 Lung Volumes

Tidal volume (TV) management is a key focus in protective ventilation strategies, especially during one-lung ventilation (OLV) in thoracic surgery. High tidal volumes can cause lung overdistension (volutrauma), leading to ventilator-induced lung injury (VILI). Studies suggest that lower tidal volumes, around 6 mL/kg predicted body weight (PBW), are associated with better outcomes and reduced lung injury. However, the relationship between tidal volume and post-operative pulmonary complications (PPCs) remains complex, with some studies indicating that low tidal volumes alone may not be sufficient. This research investigates how tidal volume settings during OLV influence PPCs, aiming to validate and potentially refine current recommendations to minimize lung injury.

1.3.3 Finding Intraoperative Biomarkers

One of the goals of this research is the identification of an intraoperative biomarker that could serve as an indicator of lung injury during surgery rather than relying on the later observation of post-operative pulmonary complications (PPCs). Such a biomarker would be invaluable for

researchers by allowing for a more detailed investigation of the progression of lung injury during surgery. Additionally, it would offer clinicians real-time feedback, enabling them to adjust ventilatory settings promptly to mitigate injury. While the specific nature of this biomarker was not predetermined, the study evaluates potential indicators, with the goal of identifying a reliable and actionable metric. This could enhance the ability to prevent PPCs by enabling timely intervention based on intraoperative monitoring.

1.4 Thesis Structure

This chapter provides an overview of the work demonstrated in this thesis and the structure of the chapters. Chapter two is the background of this thesis and provides an overview of the anatomy and physiology of the lung, details of mechanical ventilation, and the relevant signals. The context of lung surgery, post-operative pulmonary complications (PPCs), and patient risk factors are also described. One-lung ventilation (OLV) is explained, and past research along with current recommendations for the management of OLV are discussed.

Chapter three describes the methods of the thesis. The demographics of the dataset are presented, followed by detailed descriptions of the Python implementations used to clean, parse, and extract relevant data from raw ventilation signals. The features used in the statistical tests are introduced here, including the novel tidal volume drift (TV-Drift) as a potential intraoperative biomarker of lung injury during Pressure-Controlled Ventilation (PCV).

Chapter four is the results section. Included in this chapter are descriptions of the specific statistical tests and presentation of their outcomes. The statistical tests focus on evaluating how setpoints for PIP and TV impact the rates of PPCs. A significant focus is placed on recognizing that patients often experience a range of ventilator settings. To address this, a novel model is developed that accounts for exposure to multiple ventilator setpoints over time.

Chapter five provides a discussion of the results, the potential findings and limitations of each statistical test are also discussed.

Chapter six provides concluding remarks including conclusive summary of the study and suggested future work to further investigate the findings.

Chapter 2: Background

2.1 Anatomy & Physiology

2.1.1 Anatomy of the Lung

When we breathe the air in air travels in a network composed of the nose, pharynx, larynx, trachea, bronchi, bronchioles, and lungs. The lungs consist of hundreds of millions of specialized tissue sacs called alveoli, together this combined tissue of alveoli is called the lung parenchyma [6]. Alveoli are the primary location of the gas exchange for the body. Gases are exchanged with a capillary network that surround the alveoli.

2.1.2 Gas Exchange

Within a minute of being born we must begin to breathe, and the cessation of this breathing is not compatible with life. Breathing involves something called gas exchange the primary function of which is to exchange CO_2 from our blood with O_2 from the outside air. O_2 is essential for our cells to generate energy through oxidative phosphorylation. It is this process that generates the energy we need to survive. One of the byproducts of this energy production process is CO_2 , if CO_2 is allowed to build up in our body our blood will become too acidic. Therefore, respiratory gas exchange is essential to bring in the oxygen required to create our energy and expel the CO_2 waste product.

2.1.3 Breathing Mechanics

One respiratory cycle involves inhalation and exhalation. During inhalation fresh air is moved from the surrounding environment into the lung for gas exchange. Following this in exhalation, the air will then be expelled once again into the environment completing the cycle [7].

In order to understand how the body moves air in and out of the lungs we must remember the physics of airflow. Air moves from one region to another whenever there is a pressure difference. The air will move from an area of higher pressure to an area of lower pressure.

2.1.3.1 Inspiration

To move air into the lung the body must create a pressure differential between the pressure in the outside environment, atmospheric pressure, and the pressure within the lung. The body does this by changing the volume of the lung [8]. This leads to another physical property of gasses we must recall which is Boyle's law [9], expressed in the following formula:

$$P_1V_1 = P_2V_2$$

As the volume of a space increases the pressure will decrease, unless more air is added.

The body needs air to move from the external environment into the alveoli, since this is where gas exchange will take place. Therefore, we must make the alveolar pressure a low-pressure zone so the air will move there. The pressure within the alveoli is commonly referred to as intra-alveolar pressure. The body can temporarily lower the intra-alveolar pressure by using muscles to expand the lung. The expansion of the diaphragm causes an increase in volume of the pleural space and a decrease in the pleural pressure. The decrease in pleural pressure and increase in pleural space volume pulls on the lung to expand. This expansion reduces the pressure in the alveoli according to Boyle's law and this creates a pressure differential with atmospheric pressure.

Since the alveoli and the surrounding environment are connected through a series of airways these two spaces will equalize their pressures by creating airflow. Air will flow from the higher atmospheric pressure to the lower alveolar pressure, thereby filling the lungs with air. It should

be noted that inspiration is an active process since it requires use of muscles and energy to expand the lungs and draw in air.

2.1.3.2 Expiration

Lungs have a natural elasticity that stores energy like a rubber band. As it is filled with air it stretches the lungs much like a stretching a rubber band. When expiring air, the pressure differential is created due to the elasticity of the lung. This increases the pressure in the lung relative to atmospheric pressure and therefore air will move out of the lung into the surrounding environment. It is also possible to create active forced expiration by squeezing muscles like the abdominals.

2.1.4 Volumes and Capacities in the Lung

At different times during the respiratory cycle there are different volumes and capacity associated with the lungs that are given names so they can be differentiated.

2.1.4.1 Residual Volume

Firstly, it is important to note that the lungs never fully deflate. Even after a maximum forceful expiration there is still some air that remains. This air is called the residual volume [10]. If there was no residual volume in the lungs they would collapse and be difficult to reopen [11].

2.1.4.2 Tidal Volume

This is the volume of air that moves in and out of the lungs during normal quiet breathing conditions. This amount of air can be expired using only passive exhalation [12].

2.1.4.3 Inspiratory/Expiratory reserve volume

This is the amount of air that can be forcibly inhaled or exhaled past the normal tidal volume [12].

2.1.5 Pressures Relating to the Lung

2.1.5.1 Atmospheric Pressure

This is the pressure of the environment outside the lung. This is often used as a reference for other pressures within the lung. If a pressure is negative then it is negative relative to atmospheric, if positive it is greater than atmospheric and if it is 0 then it is equal to atmospheric pressure.

2.1.5.2 Intra Alveolar Pressure

This represents the pressure inside the alveoli, this changes during different phases of breathing. It should be noted that there are on average 480 million alveoli in the lung [13]. Any notion of measurable “alveolar pressure” therefore represents the average pressure of these alveoli [14].

2.1.5.3 Intra Pleural Pressure

This represents the pressure within the pleural space. This pressure is created by the adhesion between the visceral pleura, parietal pleura and the diaphragm. This adhesion is created with surface tension and is what allows us to expand our lungs by expanding our diaphragm. The intra pleural pressure should always be lower than the intra alveolar pressure. Due to a combination of competing forces and the adhesion of the pleural layers this pressure is kept at approximately -4mmHg relative to the intra alveolar pressure.

2.1.5.4 Trans Pulmonary Pressure

This pressure is defined by the formula:

$$P_{tp} = P_{alv} - P_{ip}$$

It is the difference between alveolar pressure and the pleural pressure. As the transpulmonary pressure increases, the lung volume increases. This pressure can be understood as the distending force or in other words the amount of pressure required to keep the lung open at the current volume [15]. Due to the elasticity of the lung as the volume of the lung increases it gets harder to continue to stretch it.

2.1.6 Lung Compliance and Elastance

“Compliance is the ease with which an elastic structure stretches. Compliance is, therefore, basically a measurement of the elastic resistance of a system” [16]. With regards to the lung, compliance describes the increase in lung volume for a marginal increase in transpulmonary pressure. It is defined by the formula:

$$C = \frac{\Delta V}{\Delta P_{tp}}$$

Where:

$$\begin{aligned}\Delta V &= \text{change in lung volume} \\ \Delta P_{tp} &= \text{change in transpulmonary pressure}\end{aligned}$$

Elastance is the inverse of compliance:

$$E = \frac{1}{C} = \frac{\Delta P_{tp}}{\Delta V}$$

It can be thought as the returning force. Compliance is the force required to stretch the lung open when moving air in and the elastance is that same force but working oppositely to move the air back out and return the lung to its original shape.

Measuring the compliance of the lung generally has two methods. The two methods give rise to two different names, static compliance and dynamic compliance.

2.1.6.1 Static Compliance

This is measured only when airflow is zero, muscles are relaxed and pressures within the lung have been equalized. This is an attempt to completely isolate and measure the effect of the elastic resistance of the lungs. It can be difficult to achieve perfect muscle relaxation in a conscious individual but when the patient is paralyzed static compliance can be measured.

2.1.6.2 Dynamic Compliance

This is the continuous measurement of compliance and represented as the slope in a PV loop for the lung [17]. The big difference between static and dynamic is that dynamic compliance is measured with airflow present. This means that the effect of airway resistance is included in the compliance measurement.

2.2 Mechanical Ventilation

Mechanical ventilation (MV) utilizes a machine to assist with the work of breathing for a patient [18]. They were first used in mass scale in the 1960s [19]. During thoracic surgeries, such as the ones explored in this study, patients will be under general anesthesia. Anesthesia impairs pulmonary function and adequate gas exchange since they lose control of somatic muscle, therefore they must be mechanically ventilated.

There are many ventilation modes that will describe in general how a mechanical ventilator will interact with the patient. Each ventilation mode is a combination of the selection of control variable and ventilation sequence [19].

2.2.1 Ventilation Sequence

Mechanical ventilator cycles can be divided into four phases similar to respiratory cycles of the lungs: inspiration, expiration, transition from inspiration to expiration and transition from expiration to inspiration.

When the ventilated patient is under anesthesia and chemically paralyzed the ventilator must control all phases of breathing, this is referred to as continuous mandatory ventilation [20]. This is the mode used in the ventilation data collected within our study.

2.2.2 Ventilation Control Variables

Mechanical ventilators require a control variable. Control in this context means the variable that can be set by the operator and will be used as feedback for the setpoint of the machine [19]. Due to the properties of the lung including lung compliance and airway resistance we can derive a pressure-volume (PV) loop for the lung. For each lung volume there is an associated pressure.

We cannot arbitrarily choose a certain pressure and volume that we want to set the lung to since they are linked through the properties of the organ.

Practically this means that we can only choose to control or drive respiration through pressure or volume at any given time [19]. The non-controlled variable will be dependent on the value set for the controlled variable. This is the meaning of ventilation control settings. If we set the machine to pressure control ventilation (PCV) mode, then pressure will become the driving variable. The volume measurement will therefore be dependent on the pressure setpoint and the opposite for volume control ventilation (VCV) mode. Because data analysis in this thesis will focus on PCV, VCV signals are discussed in the Appendix.

2.2.3 Airway Flow

By convention inspiratory flow is taken to be positive and expiratory flow is negative.

2.2.3.1 Inspiratory Flow in PCV

During PCV, the inspiratory flow is a result of the applied pressure from the ventilator, airway resistance, and compliance. Flow into the lung decreases as the pressure in the lung rises and therefore the pressure differential decreases. This can be seen in the following equation [21]:

$$f = \left(\frac{\Delta P}{R_{aw}} \right) e^{-\frac{t}{\tau}}$$

Where:

$$\begin{aligned} f &= \text{Airway flow} \\ \Delta P &= \text{Pressure applied to airway above PEEP} \\ R_{aw} &= \text{Airway resistance} \\ t &= \text{Time since start of inspiration} \\ \tau &= \text{Time constant from resistance and compliance} \\ e &= \text{natural logarithm base} \end{aligned}$$

The ventilator will constantly adjust flow so that the inspiratory pressure is maintained at the set level [22]. PCV inspiratory flow waveforms will descend to zero given sufficient inspiratory time.

In Figure 2.1 we can see what happens to PCV inspiratory flow waveforms when changing inspiratory time. In the first two breaths the flow is not able to descend all the way to zero. In the third breath inspiratory time is increased giving additional volume and allowing flow to descend to zero, this is important because with zero flow indicates pressure equalization between the ventilator and the lungs. Increasing the inspiratory time beyond this point will not continue to increase the volume of the lung as flow has already descended to zero.

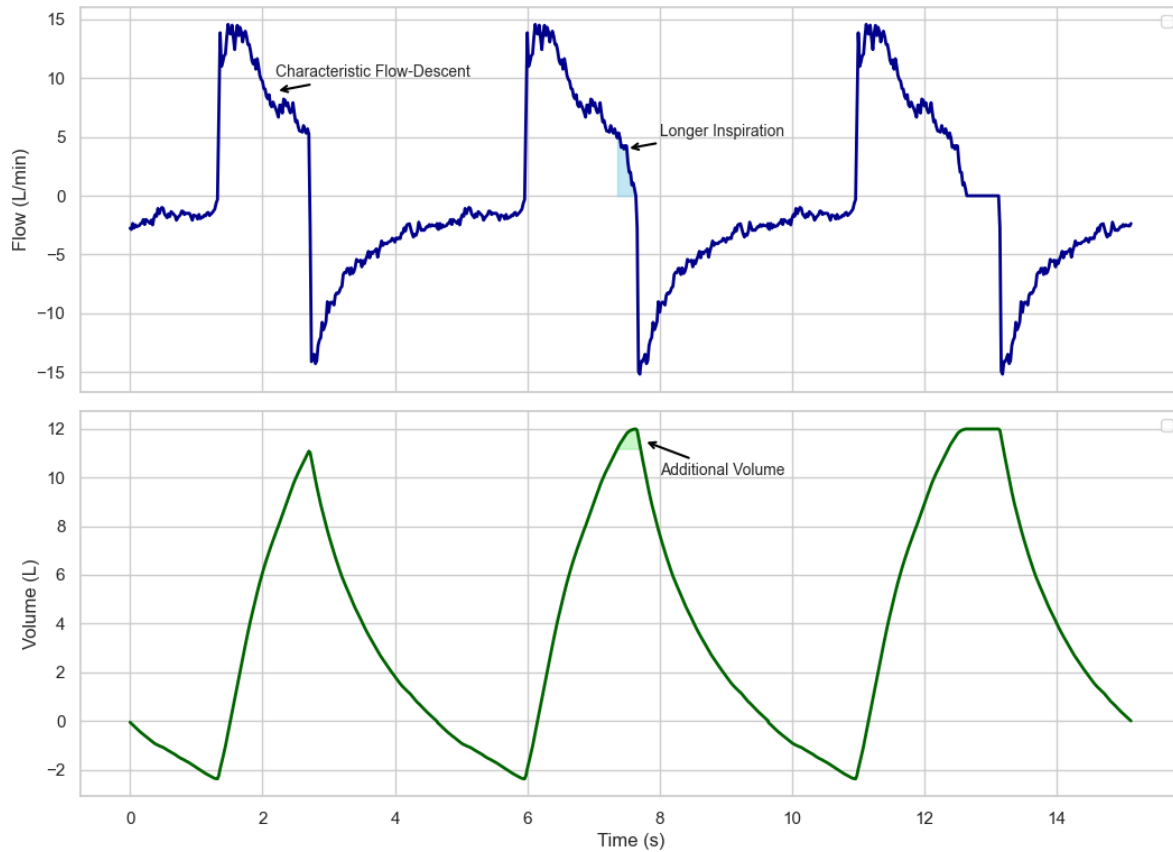


Figure 2.1: Pressure-controlled ventilation (PCV) with the characteristic flow-descent. The prolongation of inspiratory time in the second cycle shows an additional amount of volume produced compared to the first cycle. Extending inspiratory time beyond this point does not increase volume, as shown in the third cycle (Adapted from [22]).

Upon observing the inspiratory phase of the PCV flow signal we can discern two phases. The first is the initial peak which is due to the pressurization of the system. The second phase is the descending phase [22]. Due to inspiratory flow's dependence on lung characteristics during PCV we can gain some insight to changing lung properties from this second phase of the measured airflow signal. The shape of this descending portion is dependent on the compliance and resistance of the respiratory system [22]. In Figure 2.2 we can see that increasing resistance and holding compliance constant the shape of the flow curve is altered and becomes flatter. When compliance increases and resistance remains constant the signal maintains its descending shape but is interrupted earlier.

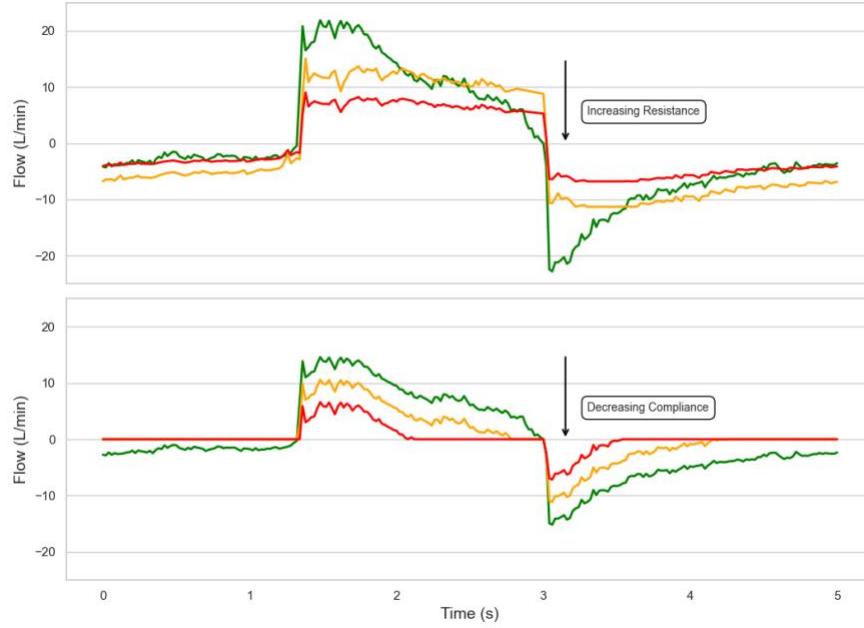


Figure 2.2: Different flow shapes at different mechanical loads during pressure-controlled ventilation. Top plot shows resistance variations. Bottom plot shows compliance variations (Adapted from [22]).

2.2.3.2 Expiratory Flow Waveform

The expiratory flow waveform is normally passive during controlled mechanical ventilation.

Once stretched open the elasticity of the lung causes it to return to its resting shape dictated by the balance of pressures between the lung and the pleural space. We can model the expiratory flow mathematically with an equation similar to the inspiratory flow during PCV.

$$f = -\left(\frac{P_{alv}}{R_{aw}}\right)e^{-\frac{t}{\tau}}$$

2.2.4 Airway Pressure

2.2.4.1 What is Airway Pressure

Pressure applied by the ventilator to the respiratory system is measured as airway pressure (AWP). It must be understood that the AWP measurement does not directly reflect the pressures within the lung. There are multiple factors that contribute to the measured AWP which can be described by the equation of motion in the following way [23]:

$$P_i = P_{el} + P_{res} + P_0$$

$$P_i = \left(\frac{V}{C}\right) + (\dot{V} \times R_{insp}) + P_0$$

Where:

P_{aw} = Airway pressure

P_{tp} = Transpulmonary elastic pressure applied at lung

P_{res} = Pressure to overcome airway resistance

P_0 = Initial alveolar pressure at beginning of inspiration

f = Airway flow

R_{insp} = Airway resistance during inspiration

V = Volume in the lung

C = Respiratory system compliance

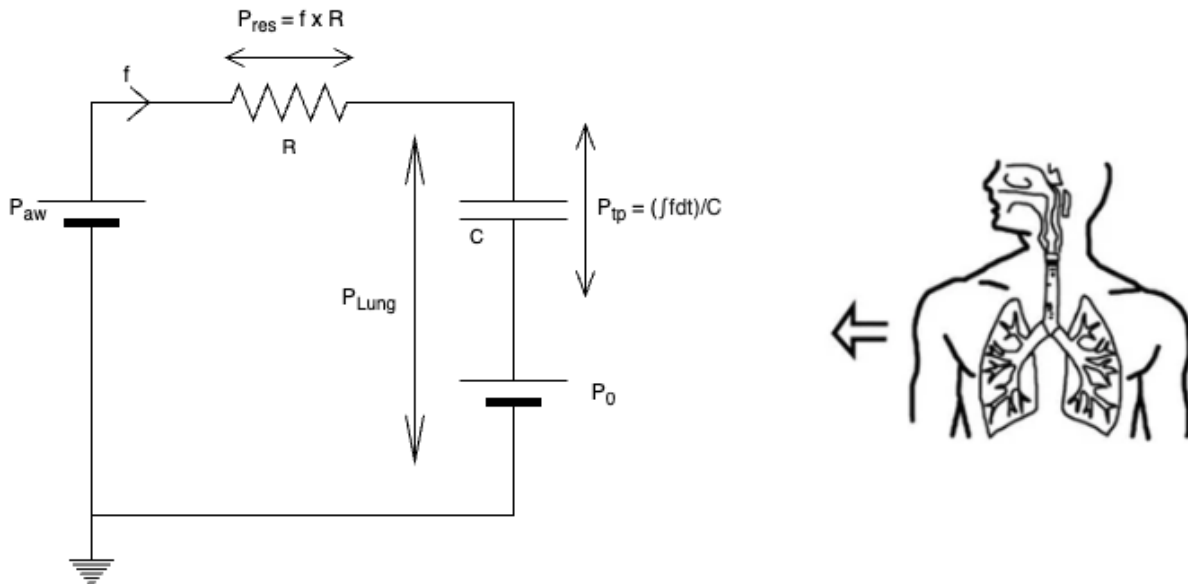


Figure 2.3: The diagram shows a circuit representation of the above formulas. By making some assumptions the lung can be represented by a circuit diagram. This represents how different pressures combine to create AWP during mechanical ventilation.

The term $(f \times R)$ models the pressure created to overcome the resistance of the airways. The term $\frac{V}{c}$ represents the pressures necessary to overcome the elastic forces of the lung at a particular volume V .

This simplified formula can only be applied when modeling the lung as a single compartment. These are just estimations, due to the lung being a complex network of many airways and alveoli that will be filled with air. However, these formulas can still be used with some accuracy at specific parts of the respiratory cycle and they demonstrate the difference between AWP and lung pressure.

2.2.4.2 Airway Pressure in PCV

During PCV the pressure is set by the ventilator, and it is the flow waveform that is dependent on the lung properties. The airway pressure will quickly rise to the set point which is called peak inspiratory pressure (PIP) and remain there for the majority duration of the inspiratory time. If the inspiratory time is of sufficient length for the airway flow to reach zero then PIP becomes equal to plateau and can be used to estimate alveolar pressure [21]. This can be understood in the context of the circuit diagram shown in Figure 11. If flow (current) is zero, then the pressure (voltage) P_{aw} will be equal to the pressure (voltage) P_{Lung} .

2.2.5 Breathing Mechanics of Positive Pressure Ventilation

As discussed previously, it is necessary to create a pressure differential to create air flow into the alveolar sacs. When we breathe normally this pressure differential is created by decreasing pressure in the alveoli. Some types of mechanical ventilators also operate in this manner which is called negative pressure mechanical ventilation [24]. However, most mechanical ventilators used in hospitals today and the ventilators used in this study use positive pressure for ventilation.

Mechanical ventilation can be invasive or non-invasive, but this study focuses on invasive ventilation. It is invasive because the ventilator delivers air to the lung through an endotracheal tube which must be inserted in a process called intubation. They create airflow by creating positive pressure in this tube [25].

There are several differences in the mechanics of respiration that occur due to ventilation by positive pressure instead of negative pressure. Transpulmonary pressure does not change between these two modes since the force required to distend the lung is the same. However, the way which we provide this distending force is much different. Most notable is that alveolar pressures reach much higher levels in positive pressure ventilation. This is because we are essentially pushing the lung open through the alveoli instead of pulling it open through the pleural space.

2.3 Lung Resection Surgery

Also known as a pulmonary resection, a lung resection is an operation in which lung tissue is removed. This could be a small part of the lung up to the entire lung itself.

This surgery can be performed either minimally invasively or as an open surgery depending on the specific situation. However, today most lung surgeries are performed using a small incision on the side of the body not requiring open surgery [26].

2.3.1 Type of lung surgery

The goal of lung resections can either be to entirely remove the section of the lung or to sample of the lung for diagnostic purposes, this is referred to as a biopsy.

There are five categories of lung resections including the wedge resection, segmentectomy, lobectomy and pneumonectomy. These differ in the amount of lung tissue removed. The amount

of tissue removed will depend on the reason for the surgery and the amount tissue that is diseased or cancerous.

2.3.2 Post operative pulmonary complications

The term postoperative pulmonary complication (PPC) refers to nearly any complication impacting the respiratory system following anesthesia and surgery. These complications are diverse in definition, frequently occurring, significantly detrimental to patient outcomes, and challenging to predict [27].

This study used a prospective, validated classification system (Ottawa Thoracic Morbidity & Mortality) which categorizes pulmonary complications into Atelectasis, ARDS, Initial Ventilator Support > 48 hours and Pneumonia [28].

Indications

Lung cancer is the second most common cancer in the United States and the leading cause of cancer related mortality [29]. The primary cure for lung cancer is lung resection surgery.

Therefore, many lung resection surgeries are used to remove cancerous lung tissues. However, lung resection surgery is used to treat other tumor related conditions such as metastatic tumors to the lungs, benign lung tumors. It can also be used to removed tissue damaged from diseases such as bronchiectasis, emphysema, abscess and trauma to the lung [26].

2.3.3 Pulmonary Function Tests

These are tests that can be conducted to evaluate the performance of a patients' lungs and to assess their risks for undergoing lung surgery. These tests are performed pre-operatively with the patient awake and breathing spontaneously. Values are often expressed as a percentage of predicted such as FEV1% predicted. The percentage represents the patients test value compared

to what would be expected given the patients demographic (matched to their sex, age, race, height and weight etc.) [30].

2.3.3.1 FEV1

This is the amount of air expired within the first second of forceful expiration [31]. Low FEV1 has been found to be a predictor of post-operative pulmonary complications [32], [33]

2.3.3.2 FVC

This is the amount total amount of air the patient is able to expire after a deep breath and a maximal effort forced exhalation [31].

2.3.3.3 FEV1/FVC

This represents the percentage of the patient's FVC that is expired in one second [31]. Low FEV1/FVC has been found to be a predictor of post-operative pulmonary complications [34].

2.3.3.4 DLCO

DLCO stands for the diffusing capacity of the lungs for carbon monoxide. This metrics represents the diffusion capability of the lungs or "the lungs' ability to transfer gas from inspired air to the bloodstream" [35]. Low DLCO has been found to be a predictor of post-operative pulmonary complications in past research [32], [33], [36], [37]

2.3.4 Lung Diseases

2.3.4.1 Chronic Obstructive Pulmonary Disease (COPD)

COPD is a common disease with widely varying symptoms and degree of severity. It is characterized by airflow limitation. This disease is associated with structural changes to the lung causing airways to narrow and decreasing lung elasticity [38]. COPD is caused by prolonged exposure to harmful particles or gasses causing inflammation, the most common cause of COPD

worldwide is smoking [38].

Pulmonary function tests are essential for diagnosing and understanding effects of COPD. A ratio of $\frac{FEV1}{FVC} < 0.7$ confirms diagnosis of COPD [38], this means that the patient can expel less than 70% of their lung capacity in one second. This is due to multiple factors. One of the structural changes related to COPD is referred to as emphysema. This involves an inflammatory response in the lung leading to destruction of alveoli and elastin [38]. Recall that exhalation is generally a passive process involving the natural elasticity of the lung. The destruction of elastin decreases the natural elasticity of the lung leading to reduced passive exhalation force and air trapping. Air trapping involves the collapse of smaller airways in the lung during exhalation. The elasticity of the lung holds them open in a healthy lung but in a lung with COPD there is not enough elasticity to hold them open and their narrowing or entire collapse leads to obstruction [38], [39].

2.3.4.2 Restrictive Lung Disease

Restrictive lung diseases are a set of pulmonary disorders characterized by spirometry. Restrictive disease cause reduced distensibility of the lung. This can be confirmed in spirometry by reduced total lung capacity (TLC) [40]. Restrictive diseases reduce the amount the lung can expand. This is differentiated from obstructive disorders which affect flow rates rather than lung expansion.

2.3.4.3 Interstitial Lung Disease (ILD)

These are a set of heterogenous lung disorders characterized by shared clinical, radiographic, physiologic or pathologic factors. They all involve inflammation and fibrosis (scarring) that affects the alveoli, alveolar ducts and bronchioles [41]. Fibrosis of the lung's tissues lead to permanent decrease in ability to carry oxygen. As the disease progresses and the amount of scar

tissue increases it becomes more difficult to breathe due to destroyed air sacs and increased stiffness of the tissues [42]. The cause of ILD is still unknown but contributing factors include exposure to irritants from smoking or from environment and family history among others.

2.3.4.4 Lung Cancer

Refers to cancerous tumors originating in the lung. Approximately one in four cancer deaths in Canada is attributed to lung cancer, making it the leading cause of cancer-related mortality in the country. In 2023, over 31,000 Canadians are expected to receive a lung cancer diagnosis, and the disease is projected to claim the lives of more than 20,000 Canadians [43]. Lung Surgery is the standard treatment option if the patient is well enough to undergo the surgery [44].

2.4 One Lung Ventilation

2.4.1 Description

One lung ventilation (OLV) is also sometimes called single lung ventilation, this procedure involves collapsing one of the lungs and ventilating the other. A lung should be collapsed to allow surgical operation on that lung. In addition to allowing surgical exposure to the collapsed lung, OLV can provide protection to the ventilated lung. Proper placement of the ventilator tube protects the ventilated lung from damage due to lavage fluids, blood or purulent secretions from the operated lung [45].

2.4.2 Challenges of OLV During Lung Surgery

By nature of OLV clinicians are challenged with providing adequate gas exchange for the patient in only half the lung space. Additionally, patients receiving OLV during lung surgeries often present with a variety of comorbidities such as the lung diseases discussed in a previous section. Historically OLV strategy focused on reversing hypoxemia and hypercapnia with less concern on potential damage to the lung due to MV. Since then, the concept of ventilator induced injury

(VILI) has been introduced. VILI shows how damage can be caused to the lung due to high tidal volumes or lung pressures [46]. This realization often now presents clinicians with a difficult decision between potential damage due to high pressures and tidal volumes versus hypoxia and hypercapnia [47].

2.4.3 Ventilator Induced Lung Injury

There are several proposed methods of lung injury due to MV. These include barotrauma, volutrauma, atelectrauma and biotrauma.

Barotrauma is caused by damage to the lung parenchyma due to high distending pressures within the lung. The distending pressure is described in a previous chapter, this is transpulmonary pressure. High transpulmonary pressures create a large stress on the tissue that can lead to damage or even rupture [46], [48].

Volutrauma refers to damage caused by excessive tidal volumes in the lung which stretches the alveoli. This concept describes injury damage caused by excessive lung expansion rather than elevated pressure [46], [48].

Atelectrauma is strain due to repeated collapse and reinflation of the alveoli. This has two effects, firstly the repeated collapse and reinflation cycle causes a strain force that can fatigue the tissue leading to damage and inflammation. Secondly, since the alveoli are connected through interalveolar septae, the collapse of one alveoli can cause damage to surrounding alveoli [48].

Biotrauma describes the aftereffects of physical damage such as barotrauma, volutrauma and atelectrauma. This damage causes the release of intracellular mediators. Cells can be injured directly by these mediators or they can be injured indirectly through cell-signalling pathways [48].

2.4.4 Lung Protective Ventilation

The settings and techniques used during MV can affect the patient's risk of developing VILI and subsequent pulmonary complications as a result. Our better understanding of VILI has led to a concept called lung protective ventilation (LPV) [46]. LPV is a set of guidelines for what the tidal volume, plateau pressure, positive end expiratory pressure or fraction of inspired oxygen settings should be. These are informed by research and theory with the aim of reducing harm to the lungs caused by mechanical ventilation.

LPV was originally shown to be effective in reducing mortality in patients with acute respiratory distress syndrome (ARDS) in the intensive care setting where patients were undergoing mechanical ventilation of **both** lungs for days or weeks. The LPV strategy focused on low tidal volumes and low distending pressures (6ml/kg predicted body weight). This strategy led to decreased mortality compared to patients receiving 12ml/kg predicted body weight [46], [49]. However, evidence of the trade-off made between oxygenation and LPV was already present in MV of two lungs since the LPV group had lower oxygenation than the unprotected group. It took around 15 years after this influential publication to show that low tidal volumes also benefitted patients without ARDS [50].

2.4.4.1 Lung protective ventilation during one lung ventilation

LPV guidelines have now achieved widespread use during MV including by anesthesiologists in the operating room with the hope of reducing postoperative pulmonary complications. However, thus far LPV has not been investigated with adequately powered trials for OLV [46]. OLV has elevated risk for VILI and postoperative pulmonary complications than MV on two lungs due to its unique challenge [46]. Past research has suggested that some LPV strategies during OLV could be beneficial for patient outcome. There are many aspects of protective ventilation but the

two that will be most focused on in this research are the role of tidal volume and peak inspiratory pressure.

2.4.4.2 Tidal volume

Low tidal volumes are an important part of lung protective ventilation strategy for two lung ventilation (TLV) and there is some evidence that this is beneficial in OLV. Ventilation with high tidal volumes has been shown to cause volutrauma [51], [52]. There has been some conflicting evidence from other studies. A meta-analysis of randomized trials on low versus high TV during OLV in patients undergoing thoracic surgery showed a lower incidence of pulmonary infiltrations and ARDS, but the incidence of PPCs did not differ between both strategies [46], [53]. Furthermore, another study found that a TV of 8 to 9 mL/kg pbw was associated with fewer PPCs. In the large proportion of the patients, the large TV during OLV was inversely proportional to the incidence of respiratory complications [46], [54].

Despite this the 2022 edition of Management of One-Lung Ventilation recommends that, “although adequately powered trials are still missing for a strong recommendation of low protective TV during OLV, values should not exceed 6 ml/kg pbw in most cases” [46]. However, this comes with the caveat that for patients who have severe COPD or severe hypercapnia, 6-8ml/kg PBW should be considered.

2.4.4.3 Peak inspiratory pressure

Peak inspiratory pressure (PIP) can be used in PCV mode to limit plateau pressures. Plateau pressure is a surrogate measure for alveolar pressure and therefore an important clinical variable for protective ventilation. It is important to remember that PIP is only equal to plateau pressure in the case that flow reaches zero at end of inspiration. It is recommended that plateau pressures be ideally kept below 25cmH₂O [46]. The PIP can therefore be set during PCV to ensure plateau pressures are below this threshold.

2.4.4.4 Positive end expiratory pressure

During one-lung ventilation (OLV) the dependent lung can be compressed by the mediastinum, intraabdominal structures, and surgical manipulation, leading to a decrease in functional residual capacity (FRC). Positive end-expiratory pressure (PEEP) can help maintain lung units open at the end of expiration, thereby preventing atelectasis and increasing FRC above the lung's closing capacity. Additionally, using appropriate levels of PEEP may allow ventilation to occur within the linear portion of the pressure-volume curve of the respiratory system, which helps minimize atelectrauma [46], [55]. Current recommendations for PEEP are 5–10 cmH₂O in most patients, 3–12 cmH₂O range possible depending on the other ventilator settings [46].

2.4.4.5 Inconsistent application of protective ventilation

Without concrete evidence supporting protective ventilation guidelines, clinicians remain uncertain about the optimal strategies to employ during OLV. A 2018 multi-institutional cross-sectional survey of anesthesiologists at high-volume Canadian tertiary and university centers demonstrated significant variation in ventilation management practices [56]. This heterogeneity, particularly in defining and implementing lung-protective ventilation strategies, reflects a lack of consensus among practitioners. Such variation underscores the critical need for further research with aims to systematically investigate OLV. This thesis aims to address these gaps by contributing to the development of evidence-based recommendations and a more standardized approach, ultimately ensuring both improved and more consistent care for patients undergoing OLV.

Chapter 3: Methods

3.1 Data Collection

Our study is a prospective observational cohort study involving 446 adult patients undergoing lung surgery at the Health Sciences Center in Winnipeg. Patients arrive in the operating room and undergo general anesthetic according to the anesthesiologist's discretion. During the surgery and time of OLV, TrendFace™ software was used to record de-identified real-time data from the ventilation machine. Patients will undergo routine post-operative care. We will not be asking anesthesiologists to purposely expose patients to higher airway pressures, tidal volumes or hyper-oxygenation during OLV.

3.2 Data Description

Data collected falls into two categories, perioperative data and intraoperative data.

Perioperative data refers to patient and surgery characteristics that are collected before and after the time of surgery. They include baseline measurements of patient lung function, patient characteristics and surgical information that is recorded before or after completion. This information is recorded into an excel spreadsheet. Patient characteristics and lung function recordings are made before the surgery while specific surgical data were recorded during and after the surgery.

Much of the intraoperative data is recorded during the surgery from a ventilator this is output in csv format. The recording software used is called IX trends, this software allows a laptop to communicate with the ventilator in the operating room. A research assistant attends each surgery where they connect the laptop to the ventilator via a serial cable in order to record data. Data recorded by the ventilator includes a wide variety of signals. In this study the signals of interest

are the airway flow and the airway pressure signals which have been explained in the Mechanical Ventilation section of the Background (2.2).

Figure 3.1 has been provided to show an example of the .csv file containing ventilator data. It can be seen there is a variety of signals recorded at different sampling frequencies. Timestamp in milliseconds since Unix Epoch denotes when the sample was taken. Note the columns for the signals of interest, “AWP-AWAY(cmH20)” which is airway pressure and “AWF-AWAY(l/min)” which is airway flow.

	A	B	C	D	E	F	G	H	I	J	K
1	Milliseconds since 01.01.1970	I-I(mV)	ABP-ABP(mmHg)	II-II(mV)	III-III(mV)	AWP-AWAY(cmH2O)	Compound ECG-aVR(mV)	AWF-AWAY(l/min)	Pleth-PLETH(-)	Compound ECG-V(mV)	Compound ECG-II(mV)
1274	1561051554342.00	0.035	84.125	-0.095	-0.135	4.608	0.005	-46.863	2024	-0.035	-0.08
1275	1561051554344.00	0.03		-0.09	-0.125						
1276	1561051554346.00	0.03		-0.09	-0.125		0			-0.035	-0.075
1277	1561051554348.00	0.03		-0.09	-0.125						
1278	1561051554350.00	0.03	82.125	-0.09	-0.125	4.574	0	-46.33	2137	-0.035	-0.07
1279	1561051554352.00	0.03		-0.09	-0.125						
1280	1561051554354.00	0.035		-0.095	-0.135		0			-0.035	-0.07
1281	1561051554356.00	0.035		-0.095	-0.135						
1282	1561051554358.00	0.035	80.625	-0.095	-0.135	4.641	0	-46.963	2245	-0.035	-0.07
1283	1561051554360.00	0.035		-0.095	-0.135						
1284	1561051554362.00	0.035		-0.095	-0.135		0			-0.035	-0.07
1285	1561051554364.00	0.035		-0.095	-0.135						
1286	1561051554366.00	0.035	79.688	-0.095	-0.135	4.674	0	-47.563	2348	-0.04	-0.065
1287	1561051554368.00	0.035		-0.095	-0.135						
1288	1561051554370.00	0.04		-0.1	-0.145		0			-0.04	-0.065
1289	1561051554372.00	0.04		-0.1	-0.145						
1290	1561051554374.00	0.04	79.188	-0.1	-0.145	4.674	0	-45.763	2445	-0.035	-0.065
1291	1561051554376.00	0.04		-0.1	-0.145						
1292	1561051554378.00	0.04		-0.1	-0.145		0			-0.035	-0.065
1293	1561051554380.00	0.035		-0.095	-0.135						
1294	1561051554382.00	0.045	78.875	-0.095	-0.145	4.708	-0.005	-46.397	2537	-0.035	-0.065
1295	1561051554384.00	0.045		-0.095	-0.145						
1296	1561051554386.00	0.045		-0.095	-0.145		-0.005			-0.04	-0.06
1297	1561051554388.00	0.045		-0.095	-0.145						
1298	1561051554390.00	0.045	78.438	-0.095	-0.145	4.741	-0.005	-46.663	2623	-0.04	-0.06
1299	1561051554392.00	0.045		-0.095	-0.145						
1300	1561051554394.00	0.045		-0.095	-0.145		-0.005			-0.04	-0.06
1301	1561051554396.00	0.045		-0.095	-0.145						
1302	1561051554398.00	0.05	77.812	-0.1	-0.155	4.741	-0.005	-46.93	2703	-0.04	-0.06
1303	1561051554400.00	0.05		-0.1	-0.155						
1304	1561051554402.00	0.05		-0.1	-0.155		-0.005			-0.04	-0.06
1305	1561051554404.00	0.05		-0.1	-0.155						
1306	1561051554406.00	0.06	77	-0.1	-0.165	4.708	-0.005	-46.03	2776	-0.04	-0.06
1307	1561051554408.00	0.055		-0.095	-0.155						
1308	1561051554410.00	0.055		-0.095	-0.155		-0.005			-0.04	-0.06

Figure 3.1: Screenshot of raw ventilator data when opened in Microsoft Excel.

3.2.1 Data Selection and Grouping

Data was recorded before and throughout the course of the study, Figure 3.2 illustrates a timeline of data recording and usage over the course of the study.

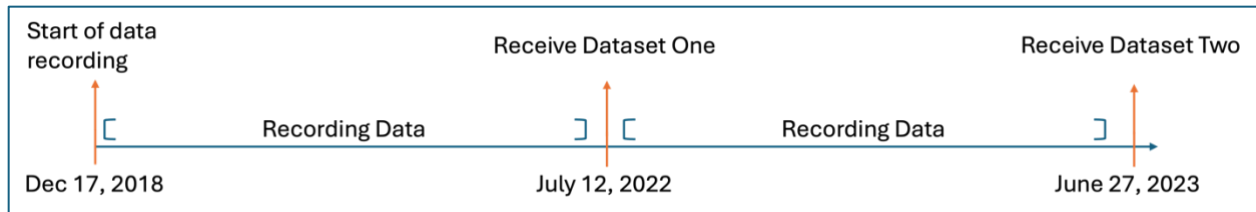


Figure 3.2: Timeline depicting when patient data was received by researchers over the course of the study.

Since recording of data was ongoing throughout the study data was received in two parts as dataset one and dataset two. Datasets one and two were combined to create dataset three, which is also known as the full dataset. Unless otherwise specified all results presented in this thesis refer to the dataset three which includes dataset one and dataset two.

The full dataset consisted of perioperative data for 446 patients however, of these 446 patients there were only 229 patients with ventilator data for the signals of interest (airway flow and airway pressure). Some patients did not have ventilator data due to technical problems during recording but mostly due to inability of the research assistant to enter the operating room during Covid 19.

Twenty-three patients with ventilator data were removed from the dataset for the following reasons: excessive noise, combination volume control and pressure control ventilation, confirmed surgical problem causing postoperative pulmonary complication. Three of these patients had a postoperative pulmonary complication.

After removal of the above specified patients the dataset was grouped into patients who were ventilated using only VCV or PCV. A summary of this can be seen in Figure 3.3.

Dataset Three Grouping and Removals

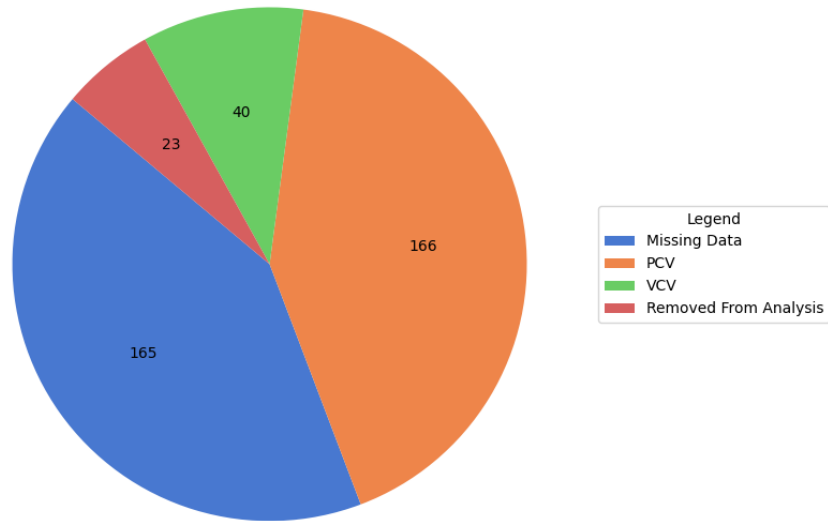


Figure 3.3: The dataset consists of 394 patients before removals and groupings, this figure details the removal and grouping.

The ratio of pulmonary complications to non-pulmonary complications varied in groups divided by PCV and VCV. This can be seen in the table below.

Table 1: Table depicting the number of patients with pulmonary complications who were ventilated with PCV or VCV mode.

	PPC	No PPC	Total
PCV	18	148	166
VCV	2	38	40

Due to the relatively higher number of patients with pulmonary complications in the PCV group as well as the larger overall group size, this group was selected for analysis in this study.

3.2.2 Data Distributions in PCV Group for Dataset

The following is a series of figures depicting representing distributions of relevant demographic features within the PCV group from the dataset.

3.2.2.1 Patient Demographics

Table 2: Patient Population overview in PCV Dataset N=166. Patients with PPC N=18.

	n	%
Sex		
Male	79	47.6
Female	87	52.4
	Mean (SD)	Median
BMI	29.03 (6.19)	28.34
DLCO	81.99 (19.76)	83.00
FEV1	91.38 (23.15)	90.00
FVC	97.99 (19.85)	97.00

3.2.2.2 Surgery Data

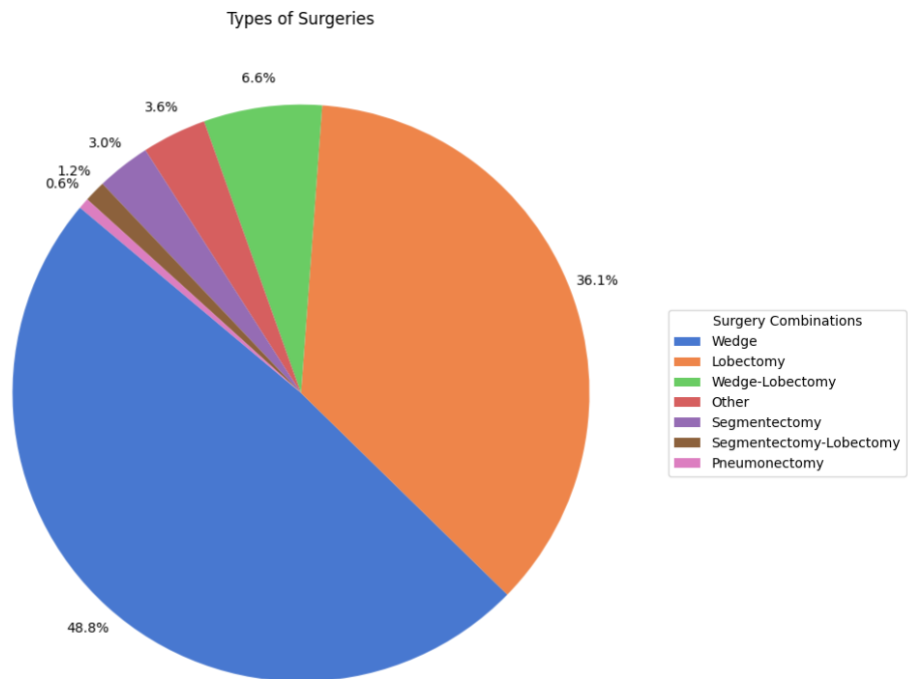


Figure 3.4: This figure shows the distribution of the type of surgeries in the PCV subgroup of dataset.

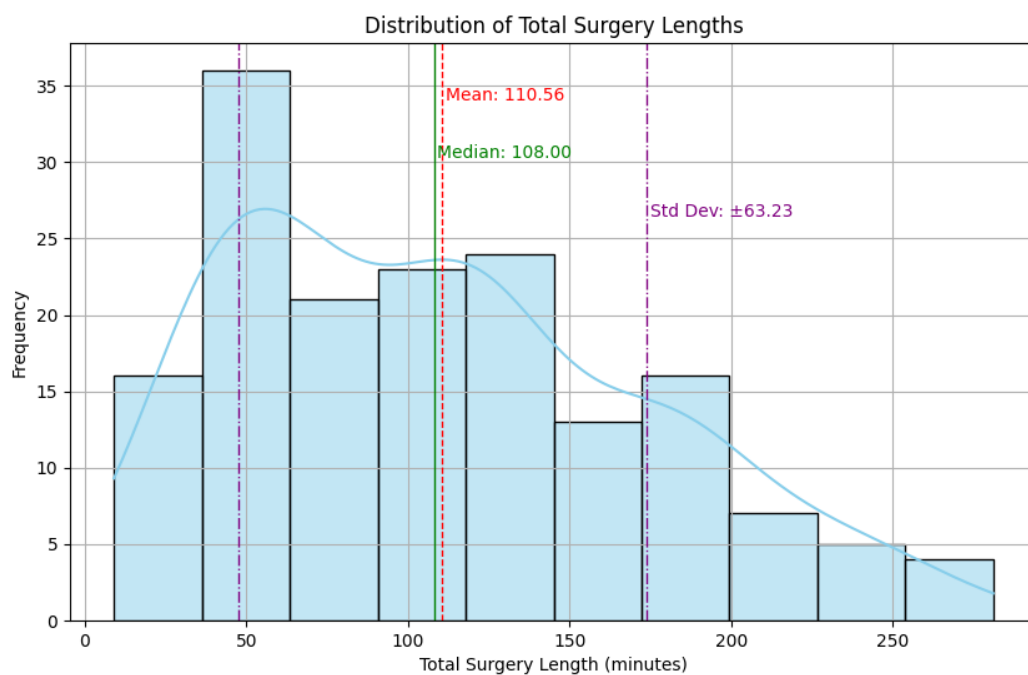


Figure 3.5: This figure shows the distribution of total surgery lengths in the PCV subgroup of dataset.

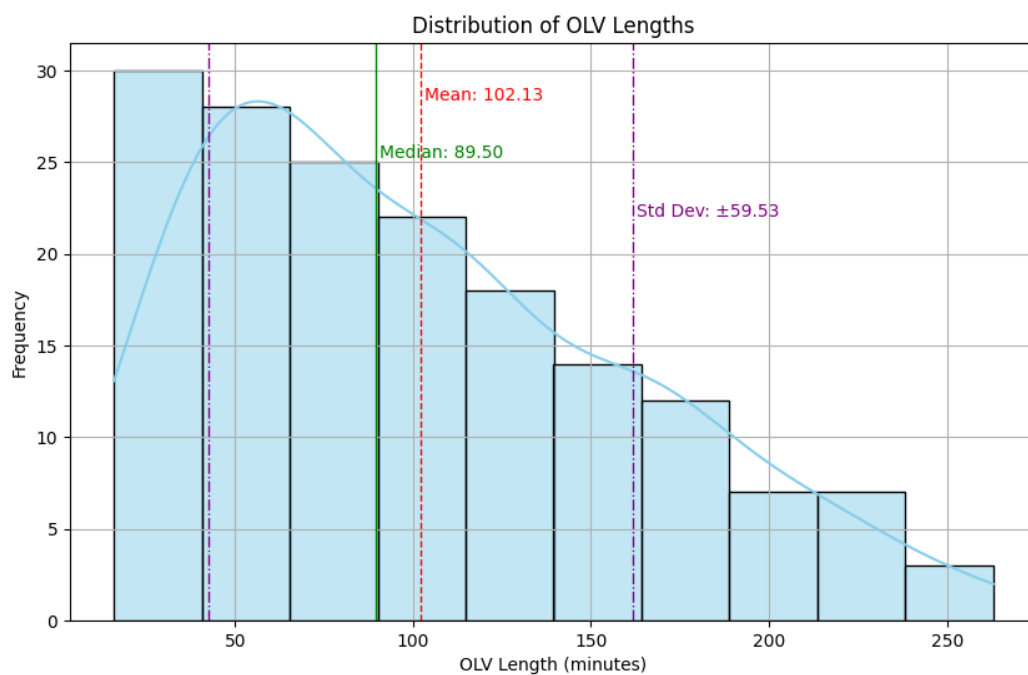


Figure 3.6: This figure shows the distribution of one lung ventilation lengths in the PCV subgroup of dataset.

3.3 Data Processing

Ventilation Data was recorded for 229 patients using TrendFace™ software. There were over 30 parameters recorded however, the two signals of interest are airway pressure (AWP) and airway flow (AWF).

3.3.1 Pre-Processing

3.3.1.1 *Missing Signals*

Due to difficulties with recording not all signals were captured for each patient. The signals of interest were unable to be recorded for a portion of the patients included in the study. Patients without the signals of interest were removed (n=165) from analysis as detailed in section 3.2.1.

3.3.1.2 *Grouping based on type of ventilation*

The type of ventilation used will determine which type of feature can be extracted from the signals and could be an underlying confounding variable if used in the same analysis. It is for these reasons that the patients were grouped by the ventilation control variable used during their surgery, VCV or PCV. Only surgeries with PCV were selected for analysis this was detailed in section 3.2.1

3.3.1.3 *Resampling Data*

Some data collected from different surgeries had inconsistent sampling periods between 6-10ms. In the ventilator data each sample point is denoted by a time in milliseconds since the Unix Epoch. Therefore, all surgeries were resampled to 20ms using python libraries for pandas. Points were interpolated using linear method.

3.3.1.4 *Manual Cleaning of Noise*

Problems during recording can cause artifacts in signal capture. Portions of the recorded signal that are noisy are difficult to remove without manual revision of the signals.

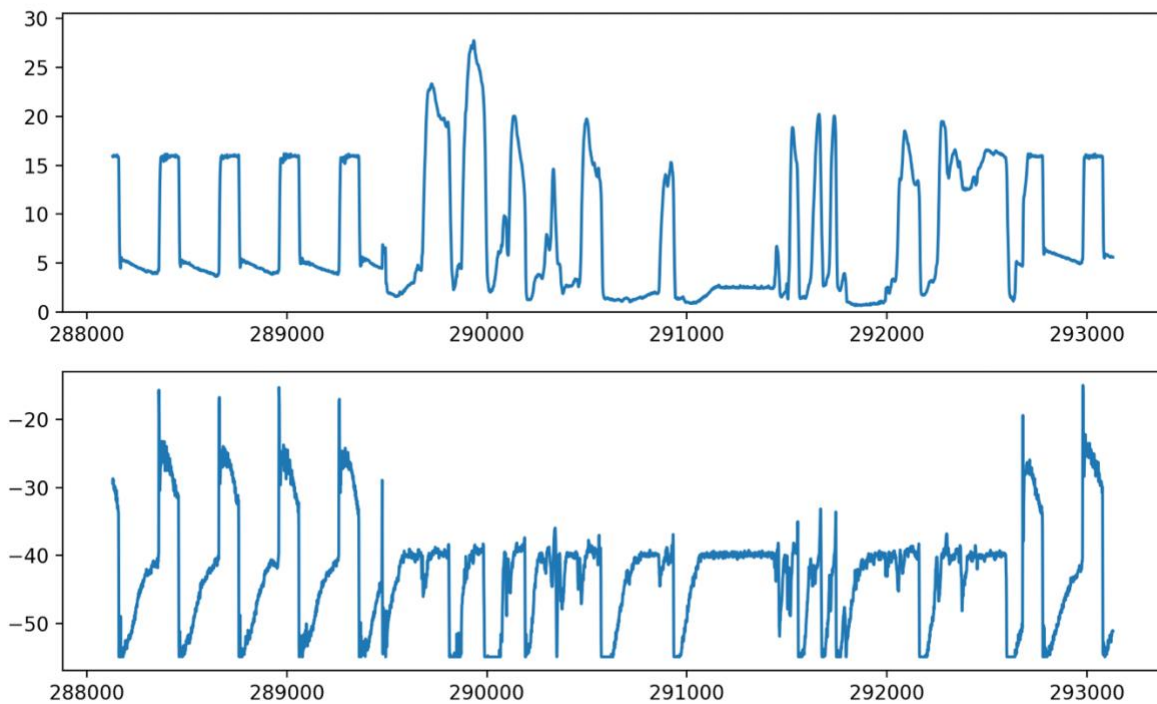


Figure 3.7: This view shows raw ventilator signal data from a portion of a surgery. The top plot shows AWP, the bottom shows AWF. This window shows multiple respiratory cycles. This figure is depicting a portion of the surgery which has recording noise that should be removed.

Figure 3.14 shows a portion of the signal that should be removed due to noise. Since the signals were very long, a software was created using python to navigate through the signals one window at a time.

First, an overall view of the surgery was displayed, the user would inspect for possible trouble spots and then click on either side of where they want to navigate through. Cursor location was shown with a red bar and coordinates displayed in bottom left.

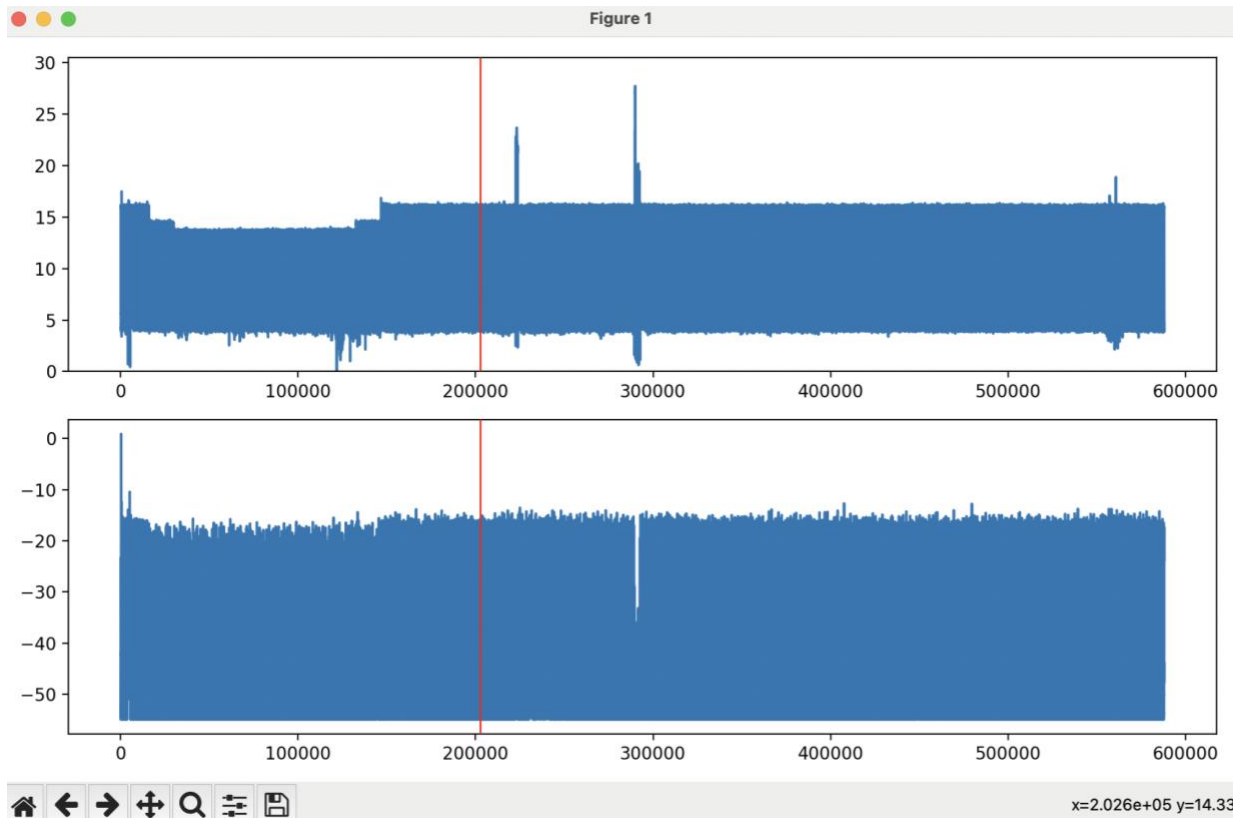


Figure 3.8: This is the first view given in the signal cleaning software. Both AWP (top) and AWF (bottom) signals can be seen for the entire surgery. The cursor is marked by a red line on both plots. Sections of the surgery are selected by mouse clicks for further detailed inspection.

After this window views such as in Figure 3.14 are shown where the user can click on either side of parts of the location that should be removed. When removing portions of the signal it is important that the ends are relatively consistent. Figure 3.8 shows proper placement of an endpoint, which should be at the end of a respiratory cycle and right before the rising edge of the pressure wave signaling the start of the next respiratory cycle.

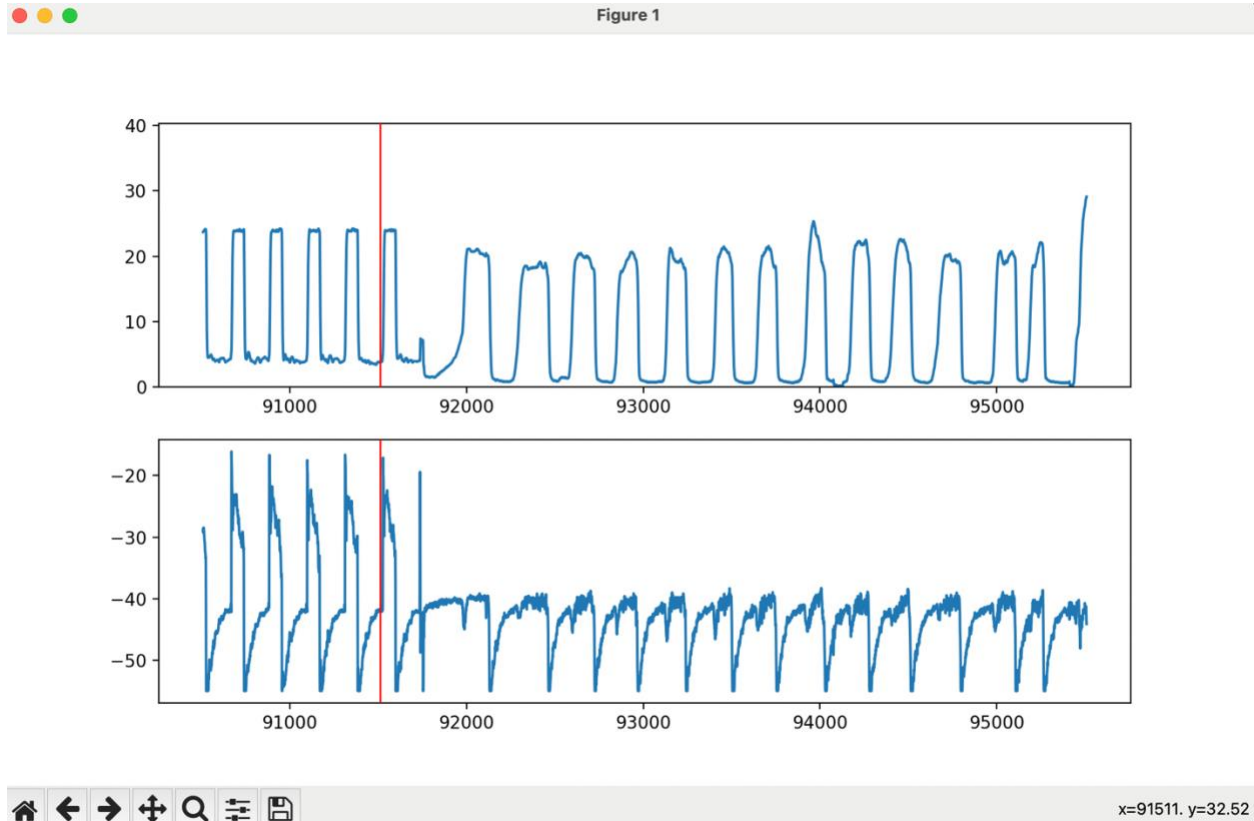


Figure 3.9: Here are the ventilatory signals AWP (top) and AWF (bottom) for a portion of the surgery that was selected for manual cleaning. Parts to be cut out are marked by a cursor. The cutting point should be consistently placed at the beginning of a respiratory cycle.

3.3.1.5 Splitting the surgery duration into individual respiratory cycles

A python function was created to automatically split the surgery into individual breaths, two algorithms were tested and analyzed by visual inspection. Both algorithms use the airway flow signal to detect split points for respiratory cycles. The first utilizes low pass filtering and checked for zero crossings in the flow signal. The second was determined to have better accuracy. This algorithm uses python library `scipy.signal.find_peaks` to find peaks in the first derivative of the flow signal. It calculates the mean and standard deviation and then uses that as a filter to find only peaks greater than 3 standard deviations from the mean. This was used to ignore peaks in slope related to noise. This high peak in the first derivative accurately finds the index of the

sharp increase in flow signal due to start of inspiration and this is used as a split point. In order to remove inaccurate split points any breaths that were not in range [2.5 seconds, 16 seconds] were removed, these breath lengths would correspond to respiratory rates not in range compatible with appropriate mechanical ventilation.

3.3.1.6 Valid Respiratory Cycles Selection

As a final check to ensure there are no respiratory cycles that were incorrectly processed in some way a python function was created to filter out invalid signals. First each signal is checked to determine if it is numeric. Then all numeric signals are averaged together to create one signal that is somewhat characteristic of an appropriate ventilator signal for AWP or AWF respectively. Each signal is then cross correlated with the average signal and is above the set threshold should be included in analysis, the threshold selected by visual inspection was 0.7. This was done for both the AWF and the AWP signals. All respiratory cycles that had cross correlation below threshold for either AWF or AWP were removed.

3.3.1.7 Shifting flow signals

For an unknown reason flow signals recorded had a vertical shift such that they needed to be corrected to have meaningful results when integrating to get volume. To correct for this the mean value was subtracted from the signal.

3.3.1.8 Shifting volume signals

Due to artifacts in flow signals some of the volume signals were shifted vertically such that volume was negative. Volume signals were all shifted to such that the minimum value of the

volume signal was zero. Implied by this is an assumption that net volume change of the lung for each respiratory cycle is zero.

3.3.1.9 Alignment of Signals

When individual respiratory cycles are extracted, the signals are not aligned in their arrays.

When plotted they did not appear ordered and are difficult to inspect visually or apply further analysis.

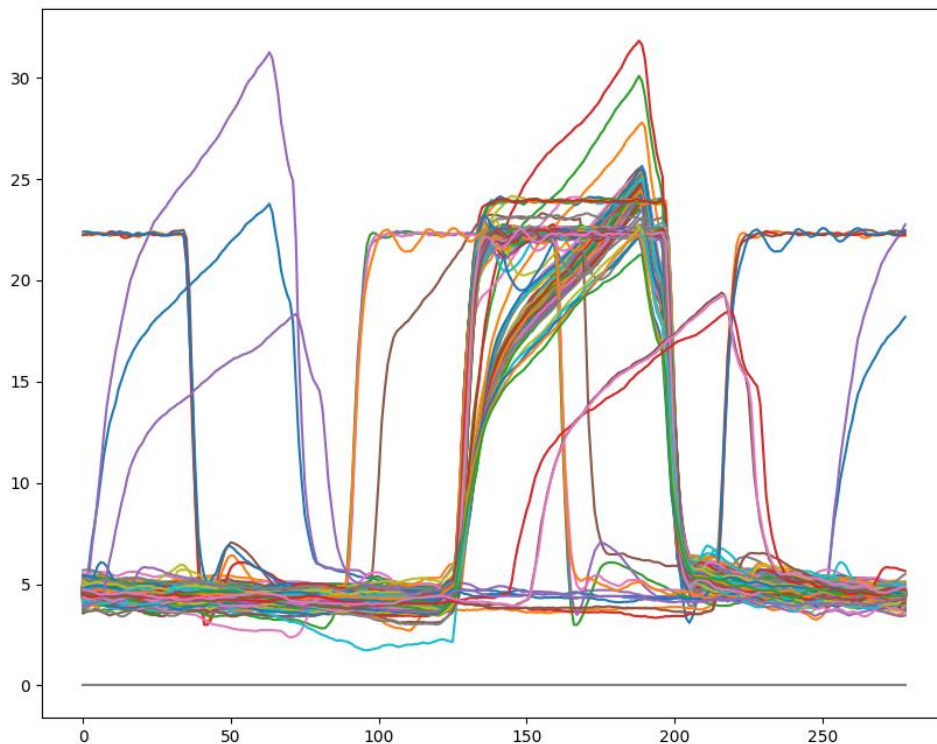


Figure 3.10: This figure shows AWP signals for individual respiratory cycles that have been plotted overlapping one another. As can be seen the signals are not aligned. X-axis represents array index position.

Figure 3.10 shows the pressure signals of respiratory cycles that have been extracted from a surgery. As can be seen these signals are not aligned and there is quite a bit of variation in the signal shape. A robust algorithm to align the signals was created using python functions. This

algorithm seeks to align the pressure signals and the flow signals on the falling edge of the pressure signal. The falling edge was chosen because it is the most consistent edge point since exhalation of the air from the lungs is a passive process. The inspiration portion of the signal is active and variable as it is controlled by the ventilator.

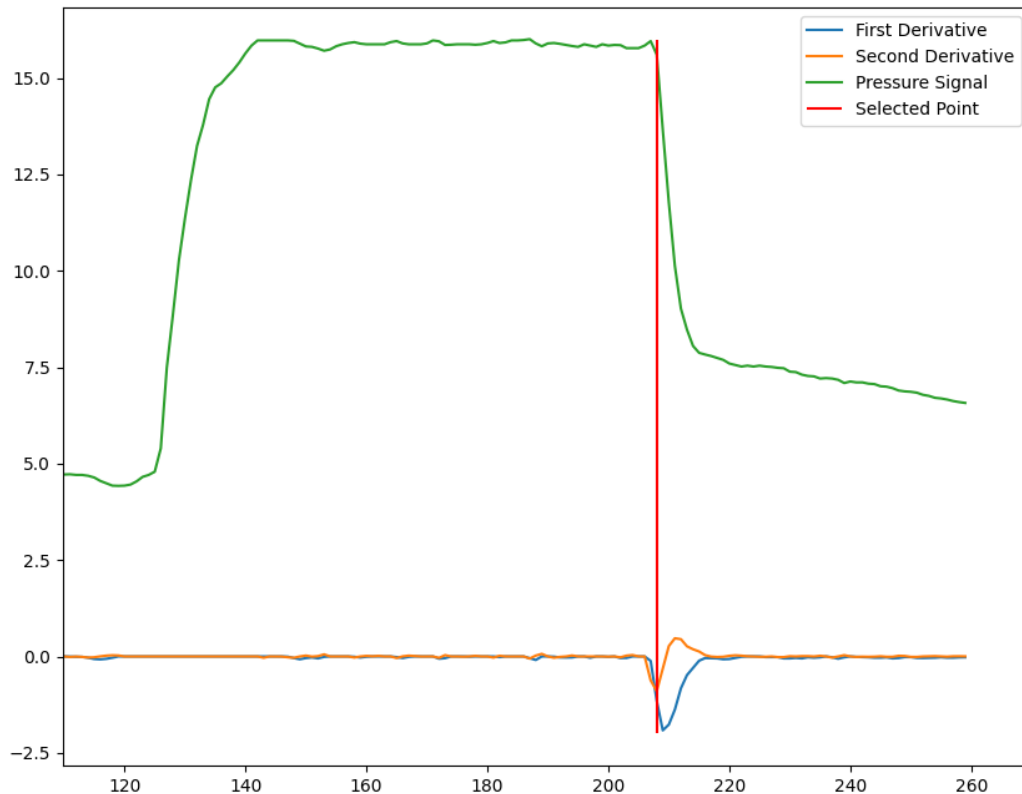


Figure 3.11: This figure illustrates the process of finding the falling edge of the AWP signal for alignment purposes. The red line denotes the alignment point selected by the algorithm. This point pertains to the local minima of the second derivative that is closest to the global minimum of the first derivative.

The function starts by taking the first and second gradient of the pressure signal. It then finds the largest negative slope point in the function; this should correspond to the exhalation slope. The first derivative is highly resistant to noise on the AWP signal since the descent from PIP to PEEP is often abrupt and the largest magnitude change anywhere in the signal. However, this point

should not be used to align the signals since the point of maximum downward slope can occur at inconsistent points in the signal. Additionally, the exhalation pressure downslopes could not be compared if their start points are misaligned. Instead, we should find the point corresponding to the end of inspiration and the start of expiration. This is done by finding the local minimum in the second gradient function closest to the global minimum downward slope. The second derivative local minima closest to the first derivative global minima is used to have more consistent results when noise is introduced. The second derivative is far less resistant to noise than the first derivative and when aligning signals with noise the number of local minima increase due to many points with high concavity. Therefore, this is why the second derivative local minima closest to the first derivative global minimum is used to capture the alignment point.

This alignment point found by the algorithm can be seen in the Figure 3.11, after this point is found, it is shifted to the middle of the array and the flow signal is shifted by the same amount to maintain alignment.

After all signals from Figure 3.10 are shifted in this manner the result is shown in Figure 3.12 where the signals can be more easily compared.

This algorithm for signal alignment was implemented as a python function.

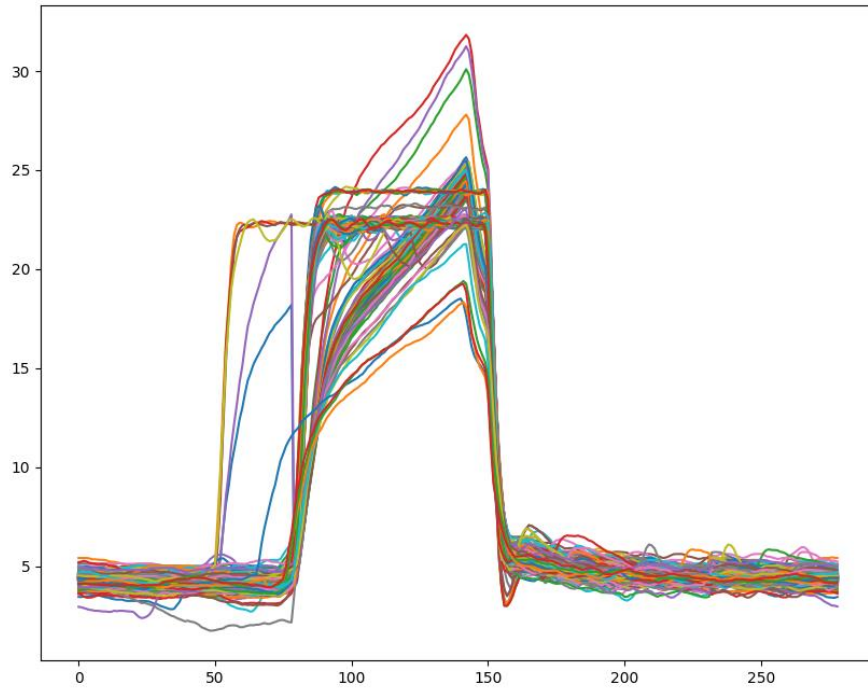


Figure 3.12: This figure depicts the result of the alignment function after being used on misaligned AWP signals extracted from a surgery.

3.4 Feature Extraction

There are two broad categories of features extracted during this research: perioperative and intraoperative feature types.

The use of the term perioperative feature during this thesis will refer to patient and surgery characteristics that are collected before and after the time of surgery while intraoperative features will refer to features extracted from data collected during the surgery. Within the intraoperative features category, we can further divide features into respiratory cycle features and surgery wide features. Respiratory cycle features refer to features that can be extracted individually from each respiratory cycle throughout a surgery. Surgery wide features are features that can be used to represent the surgery as a whole but are derived from the respiratory cycle features within that surgery.

One of the challenges explored during this thesis is that our resolution for damage occurring to a patient is only at a surgery wide level, which is the presence of a postoperative pulmonary complication. This means in the presence of a postoperative pulmonary complication; we can only say that perhaps at least one of the respiratory cycles within the surgery caused damage. Our pulmonary complication surgery wide label does not shed light on which individual respiratory cycles might have been problematic. Shedding light on this is, in fact, the end goal of the research work, discovering features of damaging respiratory cycles. However, as previously stated, since the presence of a post-operative pulmonary complication is, by definition, available only for an entire surgery, determining information about respiratory cycle features can only be done by using the surgery wide features in attempt.

The general outline for intraoperative features used within this study are the followings:

1. Extract features from each respiratory cycle in recorded data.
2. Summarize respiratory cycle features into surgery wide features.
3. Determine relationship between surgery-wide feature and Pulmonary Complication.

3.4.1 Perioperative Features

These features are patient and surgery characteristics that are collected before and after the time of surgery. They include baseline measurements of patient lung function and surgical information that is recorded after completion. These features are considered risk factors for the development of PPCs (based on existing evidence and literature).

3.4.1.1 Diffusion capacity of the lungs for carbon monoxide

The diffusion capacity of the lungs for carbon monoxide (DLCO) is used to test to diffusion capability of the lungs and has been explained in the Pulmonary Function Tests section of the Background. This has been shown to be an important diagnostic indicator interstitial lung disease

and has been shown to be one of the most powerful pre-operative predictors of pulmonary complications.

3.4.1.2 Forced expiratory volume in one second

Forced expiratory volume in one second (FEV1) is captured during spirometry tests and refers to the amount of air a patient can forcefully expel in one second. It is an important diagnostic indicator of multiple lung diseases and shown to be a predictor of pulmonary complications. It has been discussed in further detail in a Pulmonary Function Tests section of the Background.

3.4.1.3 Forced vital capacity

Functional vital capacity (FVC) is measured during spirometry tests and refers to the maximum amount of air that the patient moves in and out of their lungs during maximum inhalation and exhalation. It can help predict lung diseases and can be a predictor of pulmonary complications. It is discussed in further detail in the Pulmonary Function Tests section of the Background.

3.4.1.4 Type of Surgery

During lung surgery different types of surgery refer to how much of the lung is removed and where it is removed from. In this study surgeries were ordered into 5 categories, wedge resection, segmentectomy, lobectomy and pneumectomy. These are ordered by how much lung tissue is removed during the process of the surgery.

3.4.1.5 Length of Surgery

The length of the surgery is recorded in real-time by a research assistant or nurse who is in the operating room during the surgery. It has been shown to have predictive power for pulmonary complications [46].

3.4.1.6 Length of one-lung ventilation

The length of time for OLV is recorded by a research assistant or nurse who is in the operating room during the surgery. This feature was used in statistical tests to determine if length of OLV has predictive power for pulmonary complications.

3.4.2 Respiratory Cycle Feature Processing Functions

Some utility functions were written in python to assist in the extraction of multiple respiratory cycle features.

3.4.2.1 Constant pressure periods

It is helpful to identify periods of stabilized pressure especially during constant pressure ventilation. In PCV, the pressure wave is approximately a square wave. In this case the top part of the square corresponds to the pressure during the inspiration process and the bottom part corresponds to the expiration process. Separating these parts from the full respiratory signal can be helpful for analysis. The Pressure during the expiration process is called positive end expiratory pressure and this is common to both PCV and VCV ventilation.

Extraction was done using a python function. First the derivative of the pressure signal is taken, and z-scores are calculated for each point. A signal mask is then created for z-scores less than the threshold. This threshold is determined by inspection of resulting signals, increasing the threshold improves accuracy on clean signals but decreases noise prevention. The threshold should be changed depending on whether extracting periods from PCV or VCV signals. By only keeping points with low slope, we are left with the constant pressure parts of the signal. The collection of data points has a time and magnitude. These points are then clustered using k clustering into two groups based on their magnitudes. This creates two groups of data points

corresponding to the constant pressure expiration period and the constant pressure inspiration period which can be seen in Figure 3.13.

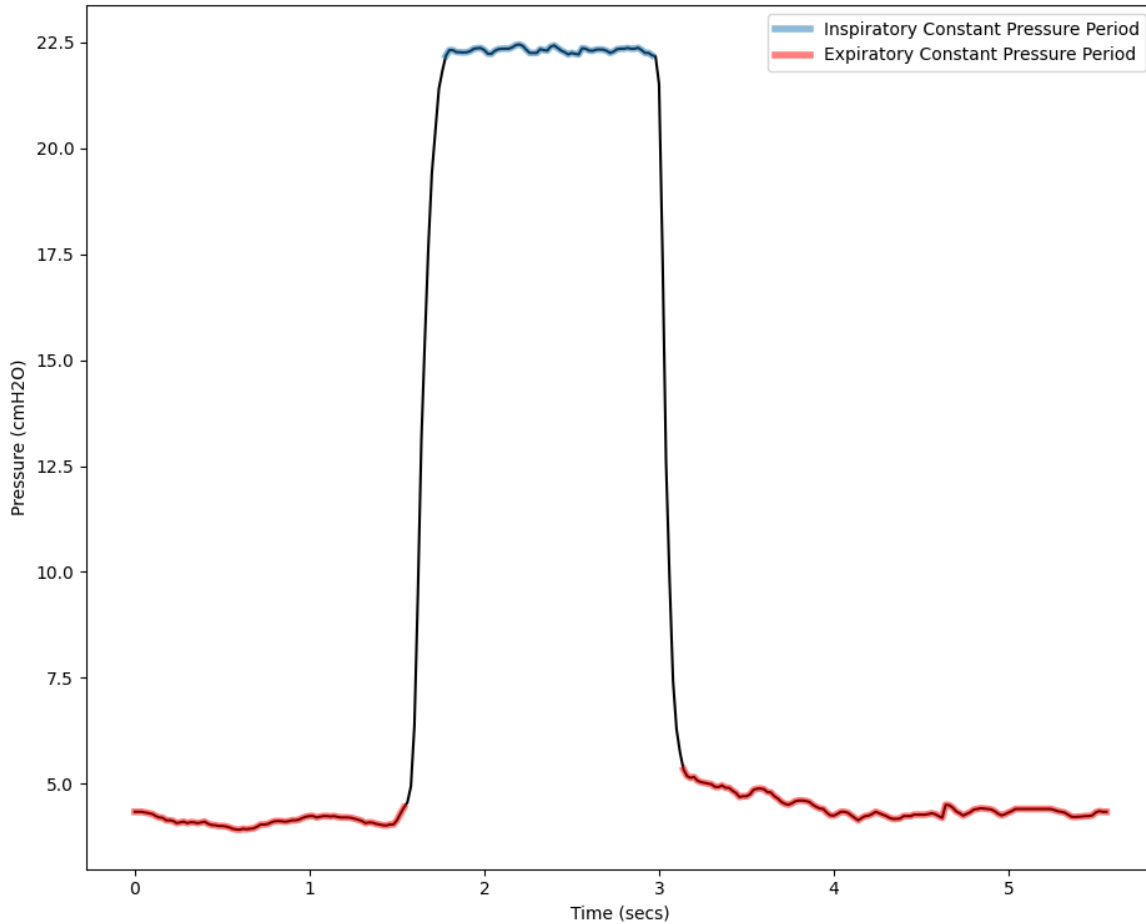


Figure 3.13: This figure was created using the finding constant pressure periods function. The red part of the signal are the indexes that were returned as part of the expiratory constant pressure period. The blue part of the signal is the indexes that correspond to the inspiratory constant pressure period. These are overlayed on the input signal to the function in black.

3.4.2.2 Finding inspiration and expiration phases

Inspiration and expiration phases of the respiratory cycle are important to be identified primarily so they can be used to create other features that will be used. First the constant pressure periods are obtained explained in Constant pressure periods. Using this output and the original signal the inspiration and expiration periods indexes are found for the AWP and AWF signals. As shown in

Figure 3.14 the inspiratory and expiratory portions of the AWP and AWF signals are excised for analysis.

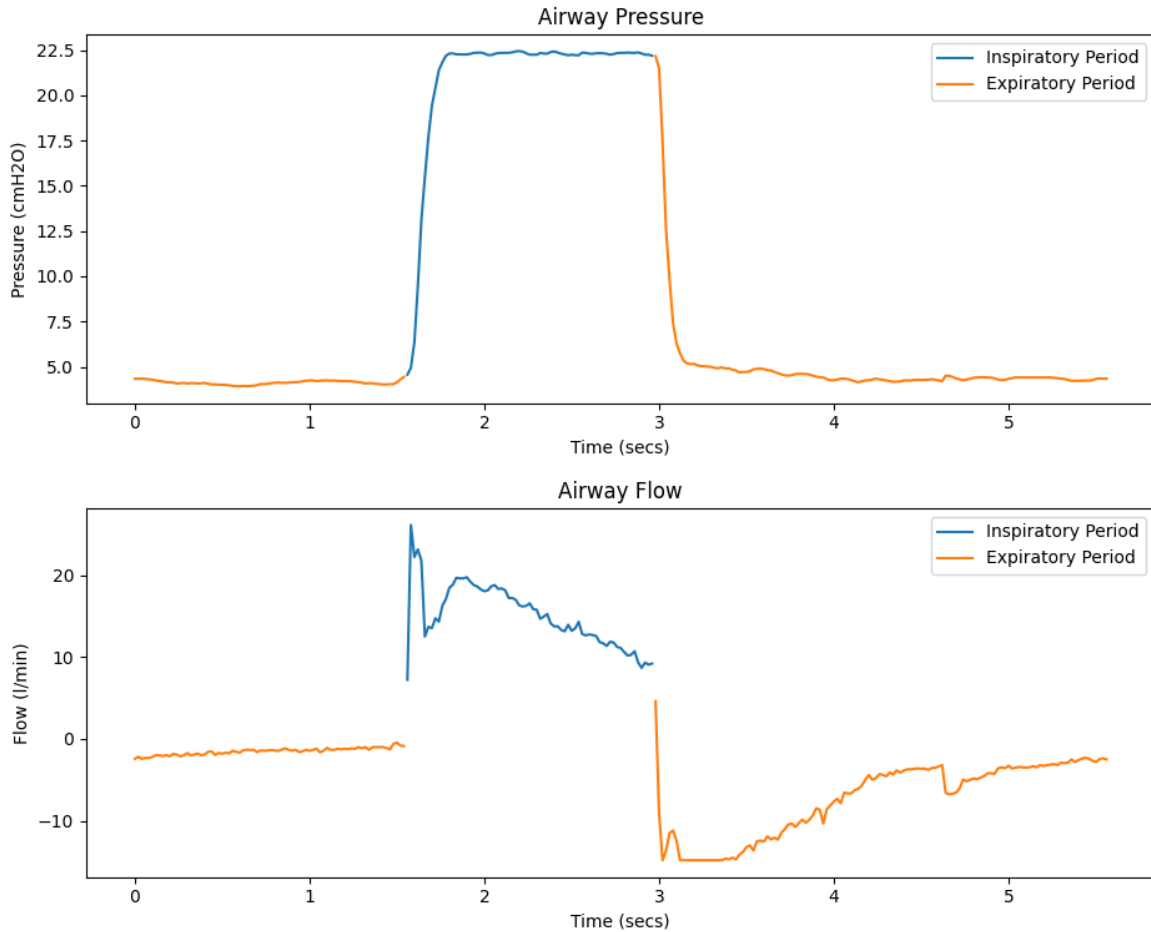


Figure 3.14: This figure was created using the *finding inspiration and expiration periods* function. Inspiration and expiration periods of the signals have been extracted for individual analysis.

3.4.3 Respiratory Cycle Features

These are features that can be extracted from each respiratory cycle. The features that can be extracted from a respiratory cycle signal differ depending on the type of ventilation mode used.

In this section only methods for PCV signals will be shown but methods for VCV signals can be found in the Appendix.

3.4.3.1 *Peak inspiratory pressure*

Peak inspiratory pressure is the maximum pressure applied by the ventilator during ventilation. During PCV ventilation inspiratory pressure is a critical parameter in mechanical ventilation as it directly affects the volume of air delivered to the lungs and helps in maintaining adequate ventilation and oxygenation. It is crucial for ensuring that sufficient air is provided to the patient without causing barotrauma (see: Lung Protective Ventilation). In most cases it is trivial to extract the peak pressure as the maximum value of the signal. In some cases, it is more appropriate to use an averaging technique.

In PCV ventilation the pressure remains at peak inspiratory pressure for the majority of inspiration phases. Therefore, we can use averaging techniques to reduce the effect of artifacts and get a better estimate of the peak pressure applied. Using the “*constant pressure periods function*” described above (3.4.2.1) we can extract the period where pressure is relatively constant during inspiration, and average the pressure over this period giving us a better estimate of the peak inspiratory pressure during that respiratory cycle, this is shown in Figure 3.15.

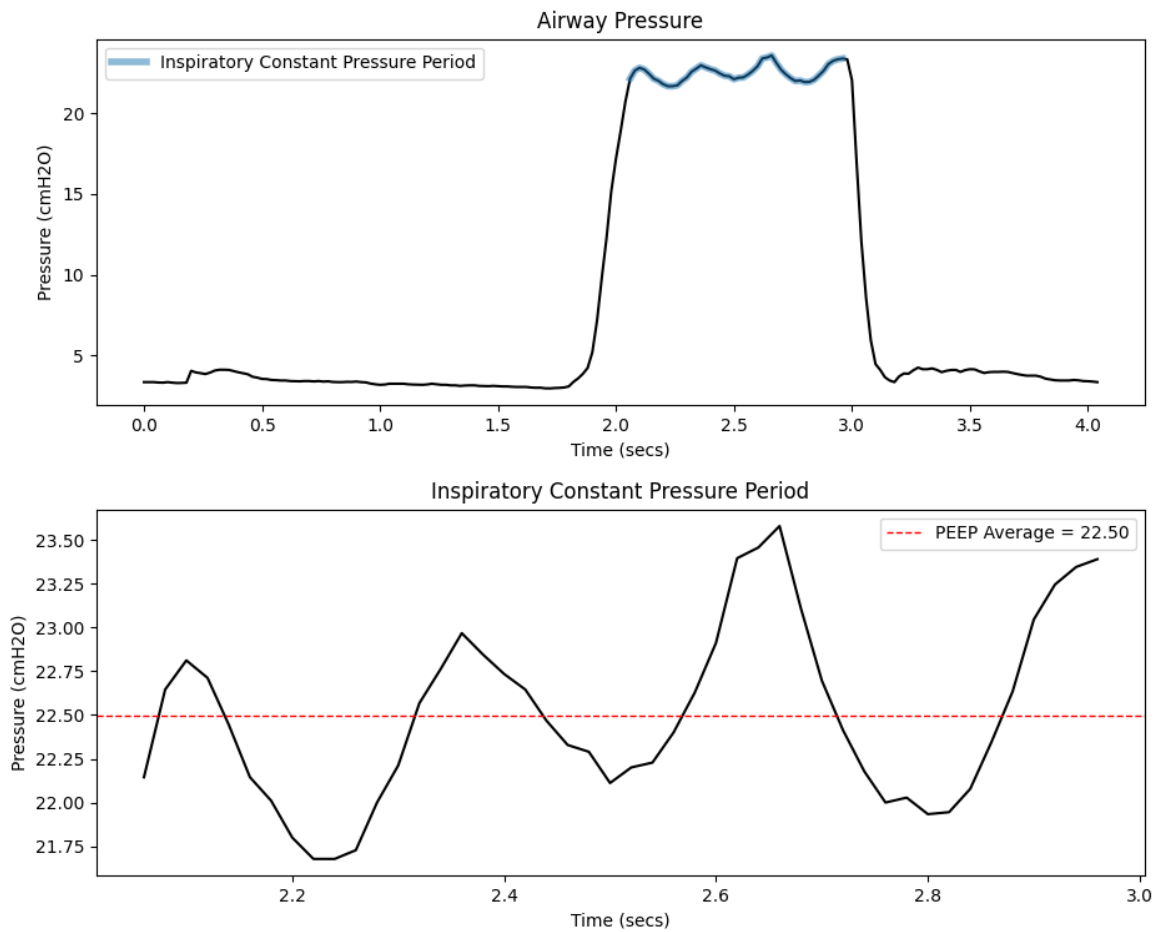


Figure 3.15: This figure depicts an AWP signal that has some noise during the high-pressure inspiration phase. The average PIP is extracted by isolating the inspiratory constant pressure period shown in blue (top) and isolated (bottom). PIP for this respiratory cycle is extracted as the average of the inspiratory constant pressure period.

3.4.3.2 Positive end expiratory pressure

Positive end expiratory pressure (PEEP) refers to the pressure in the lungs (alveolar pressure) above atmospheric pressure that is maintained at the end of expiration by the ventilator. PEEP has been advised during LPV as it helps keep the alveoli open, improving oxygenation and preventing atelectasis. This has been discussed in section 2.4.4.

PEEP set by the ventilator is observed in the constant expiratory pressure period of the AWP waveform. The pressure signal during this period can have variation due to noise and other artifacts. We can use the finding constant pressure periods function to extract the constant

pressure expiratory period and average along this period to obtain an estimate of the average PEEP actually applied. This can be seen in Figure 3.16.

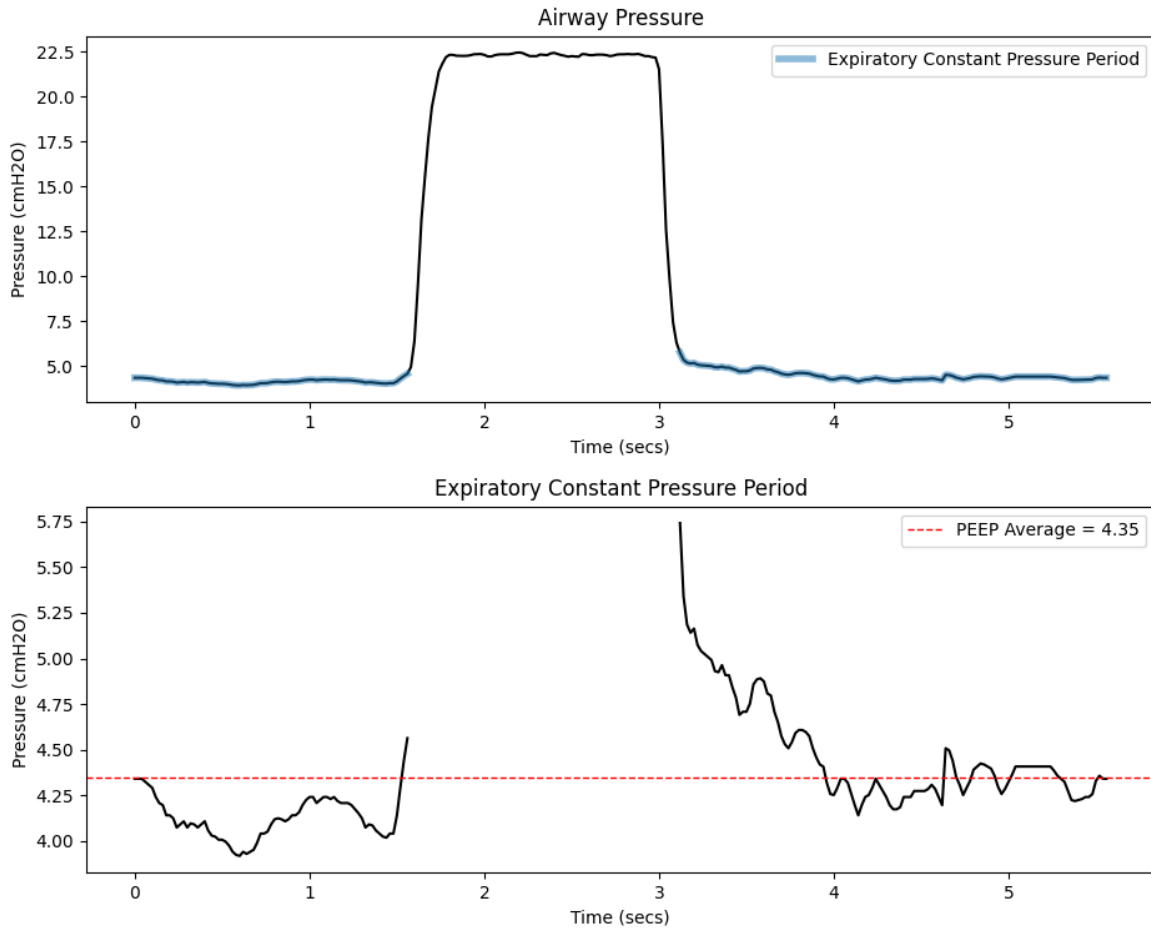


Figure 3.16: This figure depicts an AWP signal. The average PEEP is extracted by isolating the expiratory constant pressure period shown in blue (top) and isolated (bottom). PEEP for this respiratory cycle is extracted as the average of the expiratory constant pressure period.

3.4.3.3 Inspiratory time

Inspiratory time (TI) refers to the duration of the inhalation phase of the respiratory cycle during mechanical ventilation. It is the period from the start of the inhalation until the end of the inhalation, before the exhalation phase begins. TI is an important parameter determining the duration for which positive pressure and flow are applied to the lungs. TI is an important factor

contributing to tidal volume. Properly set inspiratory time ensures adequate air exchange and oxygen delivery to the alveoli.

This can be found by using the finding inspiration and expiration periods function. After extracting the inspiration period, we can check its length. Multiplying the length of the inspiration period by 20 gives us the inspiration time in milliseconds, since the sampling time is 20ms.

Unfortunately, this method for extracting inspiration time can be susceptible to noise, especially on the AWP signals. However, set inspiration time does not change often during the surgery. Averaging and filtering methods can be used on surgery wide signal to improve accuracy by referencing values extracted from the surrounding respiratory cycles.

3.4.3.4 Volume signal and tidal volume

The volume signal is a representation of the volume of air that the ventilator has pumped into the tubes, airways and lungs. Some portion of this volume will be in gas exchanging parts of the lung but some part of it will be in dead space. The volume signal is derived by integrating the airway flow signal (AWF), this was implemented as a function in python.

Tidal volume (TV) refers to the specific volume of air that is moved into and out of the patients' lungs during one respiratory cycle. It is a very important ventilatory parameter that has been the focus of many research works regarding protective practices, more information can be read in section 2.1.4.2.

TV is extracted from the volume signal as the maximum volume subtracted by the minimum. An assumption is made to ignore the effect of volume in the airway tubes. All volume is assumed to enter the lungs as an approximation for TV calculation.

TV can be normalized to predicted body weight (PBW). PBW is calculated in the following way for normalization [46].

$$\text{Male: } PBW = 50 + 0.91 (\text{centimeters of height} - 152.4)$$

$$\text{Female: } PBW = 45.5 + 0.91 (\text{centimeters of height} - 152.4)$$

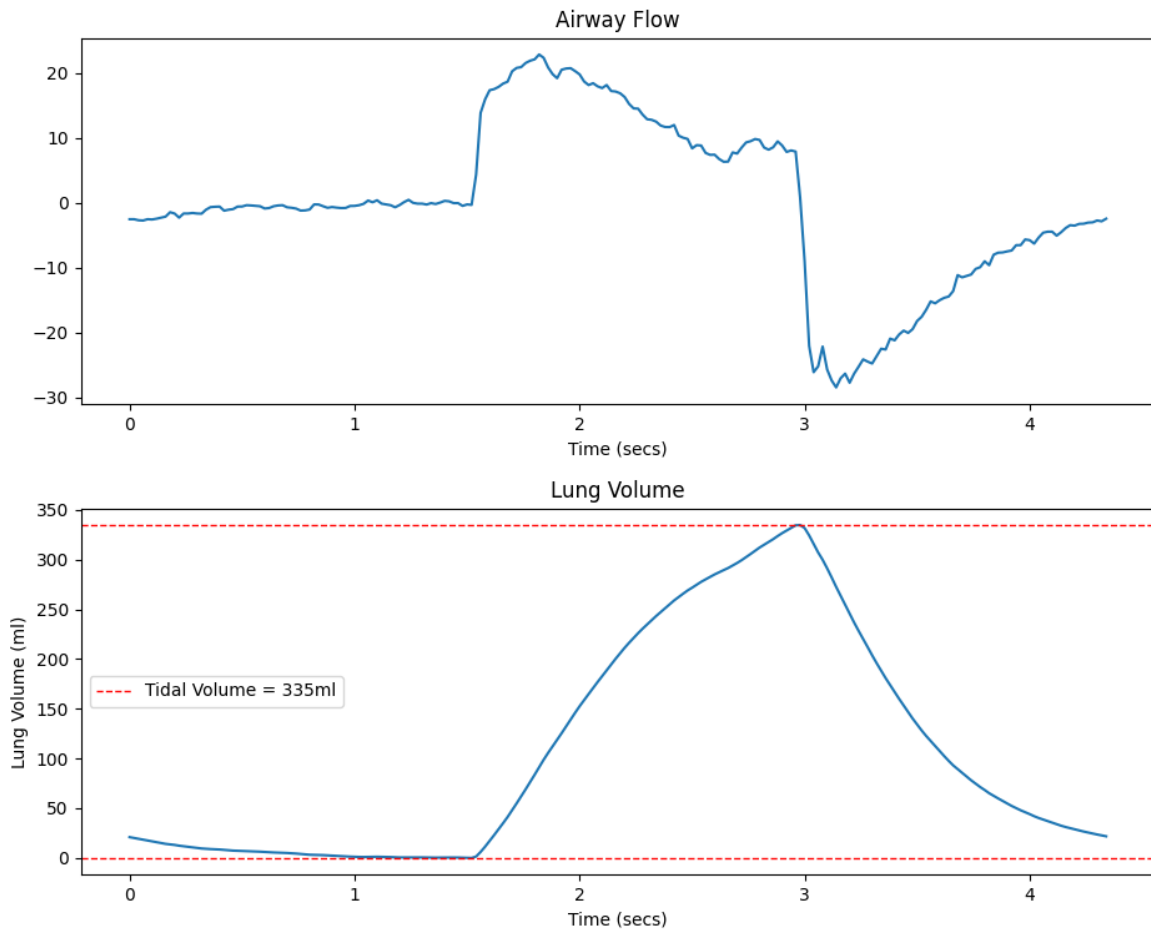


Figure 3.17: This figure depicts the AWF signal (top) and the integrated volume signal (bottom) for an individual respiratory cycle. Non-normalized tidal volume is extracted from the volume signal.

3.4.4 Surgery Wide Feature Processing Functions

Some functions were written in python to help with the extraction of multiple surgery wide features.

3.4.4.1 *Extract Unique Values*

This refers to extracting a unique set of values that a given ventilation parameter was set to during the surgery. The values throughout the surgery are extracted from the raw signal data, this is explained in section 3.4.3. This preprocessing step is used in the process to create several surgery wide features including Median Feature Value, Maximum Feature Value and Feature Range.

First, all values are quantized to integer values using:

$$q_{RC} = \lfloor f_{RC} + 0.5 \rfloor$$

$$f_{RC} = \text{Respiratory cycle feature}$$

$$q_{RC} = \text{Quantized respiratory cycle feature}$$

Values for f_{RC} are quantized from floating point to integers. When values are within 0.5 of one another they should be considered non-unique due to precision of extraction functions and noise. All q_{RC} values are added to a python set and occurrence frequencies are also recorded.

This allows filtering of the quantized set to determine values that had occurrences above a threshold which is by default set to 10. This means unique values that occurred in less than 10 respiratory cycles are not included. This threshold serves as protection against erroneous values from being included in the unique set.

3.4.4.2 *Determining static ventilation parameter periods*

During surgery, ventilator settings often need to be adjusted to meet changing clinical demands. Some ventilatory parameters are dependent on others, meaning that changes in one parameter can directly influence another. For example in PCV, TV is dependent upon setpoints for PIP, PEEP and TI. In this study, the analysis will include tracking trends in these dependent ventilatory parameters throughout the surgery to see if they vary with time. However, this

analysis becomes more complex if the independent ventilatory parameters they rely on are also changing, as it can be difficult to determine whether observed trends are due to time or the adjustments in related parameters. To isolate the effect of ventilatory parameters on the extracted features, some analyses were conducted on segments of the surgeries where the relevant ventilatory parameters remained static. During PCV, this means finding periods where PIP, PEEP and TI were constant.

Extraction of the static periods was done manually by inspection of plots showing the relevant features plotted against respiratory cycles. The largest static section was selected for analysis this can be seen in Figure 3.18.

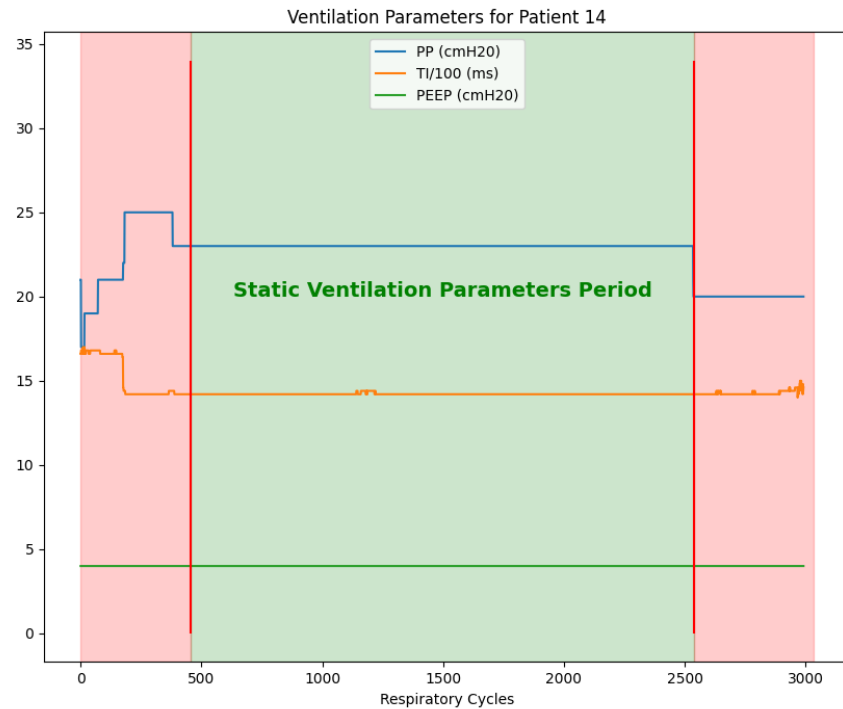


Figure 3.18: This figure shows PCV ventilatory parameters that have been extracted from individual respiratory cycles in a surgery. Plotted here is Peak Pressure (PP), Inspiratory time (TI) and Positive End Expiratory Pressure (PEEP). TI has been divided by 100 for ease of visualization. The largest consecutive period where these parameters do not change is selected.

In some surgeries with higher variation in the ventilation parameters the static periods were less than 50% of the size of the surgery this can be seen in Figure 3.19.

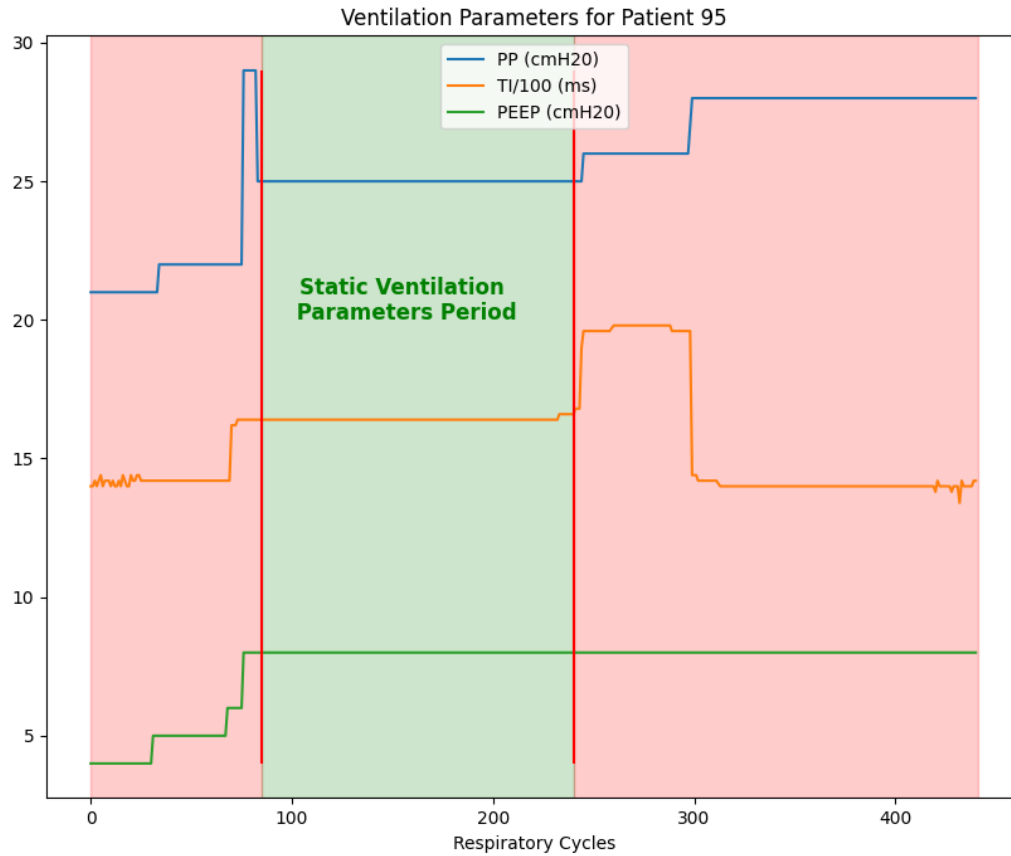


Figure 3.19: This figure shows PCV ventilatory parameters that have been extracted from individual respiratory cycles in a surgery. Plotted here is Peak Pressure (PP), Inspiratory time (TI) and Positive End Expiratory Pressure (PEEP). TI has been divided by 100 for ease of visualization. The largest consecutive period where these parameters do not change is selected.

3.4.5 Surgery Wide Features

Surgery wide features (F_{sw}) are features that are quantifiable for the whole surgery. These are computed from respiratory cycle features.

3.4.5.1 Median feature value

Median was calculated for respiratory cycle features to be used in statistical tests including peak inspiratory pressure and tidal volume. This was calculated by first obtaining the unique values

with frequencies (see: Extract Unique Values). An array is created from the unique values by inserting each unique value according to its frequency. We then take the median of this array representing the median feature value. This method is highly resistant to outliers by both using the unique values function and opting for median instead of mean.

3.4.5.2 Maximum feature value

The maximum was calculated for respiratory cycle features to be used in statistical tests including peak inspiratory pressure and tidal volume. This was calculated by first obtaining the unique values then taking the maximum value from this set.

3.4.5.3 Feature range

The range of values was calculated for respiratory cycle features to be used in statistical tests for heterogeneity. This was calculated by first finding unique values and frequencies, then calculating the interquartile range (IQR). A lower and upper bound were derived from the IQR.

$$IQR = Q_3 - Q_1$$

$$lower\ bound = Q_1 - 1.5 * IQR$$

$$upper\ bound = Q_3 + 1.5 * IQR$$

The range of values between the lower bound and upper bound was then found using NumPy library function `numpy.ptp` which finds the difference between the maximum and minimum.

3.4.5.4 Static TV Drift

Static TV-Drift is a not an established ventilation parameter, this feature was created to measure an observed pattern in the tidal volume signal. The first part of this chapter will explain the TV-Drift feature and how it was found during observations.

3.4.5.4.1 Development of observations

Upon observation of the ventilator signals we noticed that in some surgeries the shape of the AWF signal was changing throughout the course of the surgery despite similar AWP signal shapes. An example of this is shown in Figure 3.20.

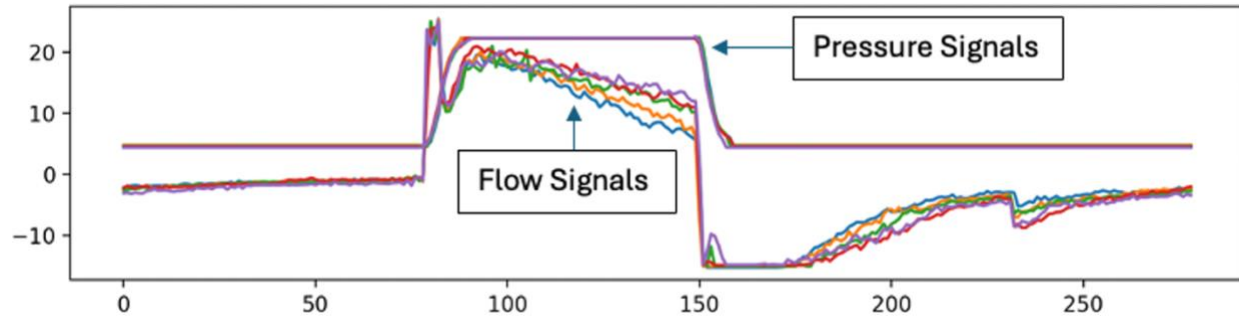


Figure 3.20: This figure depicts the AWP (Pressure) and AWF (Flow) signals from five respiratory cycles extracted from different time points in the same surgery. AWP and AWF signals from the same respiratory cycle are the same color. It is observed that the AWP signal remains consistent across these cycles, while the AWF signal varies between them.

During PCV ventilation the AWP signal is set by the ventilator and the flow signal is dependent on the ventilator settings and the lung properties. Past papers showed a change in the flow signal like this could indicate a change in resistance or compliance, this is explained in detail in section 2.2.3.1. Therefore, analysis of the changing flow signal during PCV ventilation could give insight into changing lung properties due to damage caused by ventilation. In order to gain better insight into what was causing this change in the flow signal a 4D plot was used for visualization. The tidal volume was used to assess the changing shape of the flow signal. Additionally, peak inspiratory pressure and PEEP were plotted to ensure comparison of similar AWP signals. Color was used to show the position in the surgery, an example of this plot is shown in Figure 3.21.

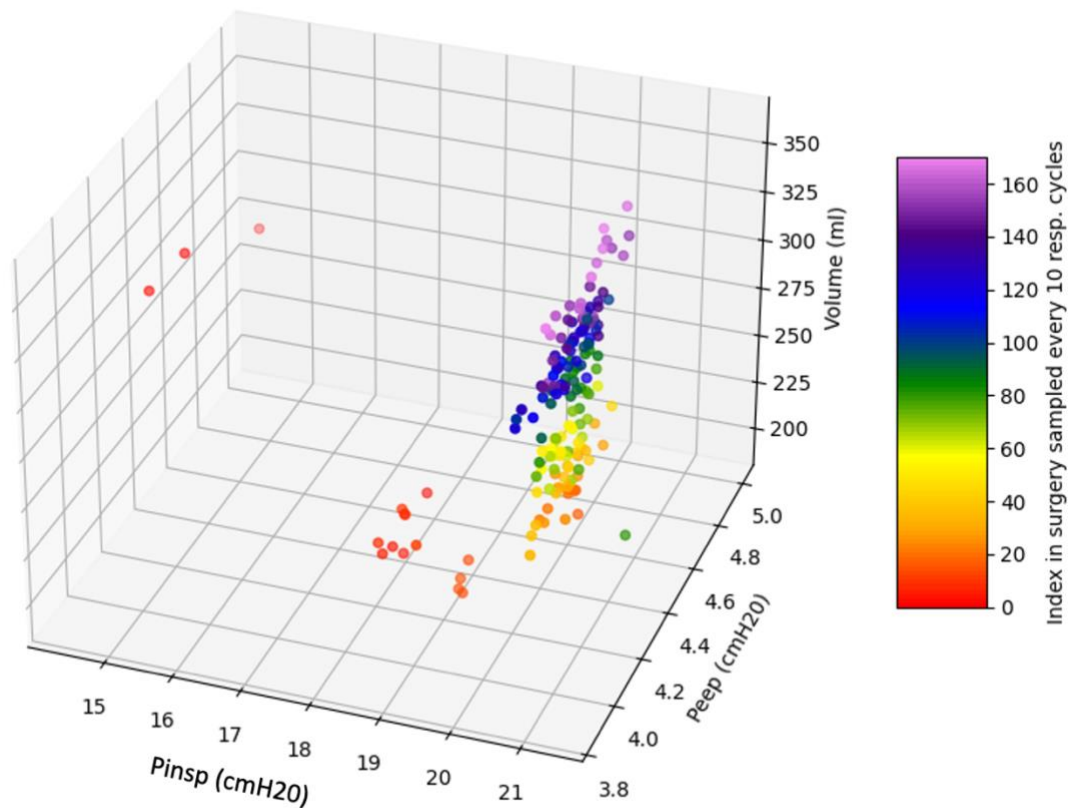


Figure 3.21: In this figure, each point represents an individual respiratory cycle, with peak inspiratory pressure (Pinsp or PIP), positive end-expiratory pressure (PEEP), tidal volume (TV), and the index in surgery (measured in respiratory cycles) plotted. The color gradient from red to purple indicates the progression of the surgery. It is observed that as the surgery progresses (red to green to blue to purple), TV increases even though PIP and PEEP remain relatively constant.

Observation suggested that tidal volume was increasing despite similar AWP signal characteristics in several of the surgeries.

3.4.5.4.2 Initial statistical testing

A test was devised to determine if TV was changing with respect to time, and if this change differed between groups of patients who had pulmonary complications and groups that did not. We conducted a retrospective analysis of mechanically ventilated patients to assess the impact of ventilatory settings on tidal volume, with a particular focus on the interaction between respiratory cycles and the presence of pulmonary complications. The relationship between

ventilatory settings and tidal volume was modeled using a mixed linear model (MixedLM) to account for the repeated measures nature of the data and the potential random effects due to variability among patients. The MixedLM approach allows for the modeling of both fixed effects (ventilatory settings and pulmonary complications) and random effects (inter-patient variability) on tidal volume. Tidal volume was normalized to facilitate comparisons by converting to TV/PBW (predicted body weight). Independent variables included ventilatory parameters (Driving Pressure, PEEP, Insp. Time), patient identifiers, a variable to measure time since start of surgery as '# Resp. Cycles' and clinical outcomes indicating the presence or absence of pulmonary complications (PulmComp), along with their interaction terms. Specifically, an interaction term between # Resp. Cycles and PulmComp was included to investigate whether the sensitivities of the lung to change in tidal volume differ based on the presence of pulmonary complications. The test was performed on 29 patients where 14 patients were matched to DLCO and type of surgery and one extra Pulmonary Complication patient was included that could not be adequately matched. Results of this test are shown in Figure 46 and suggest that the TV increases with respect to #Resp Cycles when controlling for other ventilation parameters.

Variable	Coefficient	Standard Error	z-value	P-value	95% CI
Intercept	0.694	0.057	12.115	<0.001	[0.582, 0.806]
# Respiratory Cycles	0.025	0.002	15.106	<0.001	[0.022, 0.028]
PIP-PEEP	0.008	0.002	3.600	<0.001	[0.004, 0.013]
PEEP	-0.023	0.002	-12.271	<0.001	[-0.026, -0.019]
Inspiratory Time	-0.014	0.002	-8.139	<0.001	[-0.017, -0.010]
Pulmonary Complications	-0.059	0.080	-0.740	0.459	[-0.215, 0.097]
Pulmonary Complications * # Resp. Cycles	0.031	0.002	15.323	<0.001	[0.027, 0.035]
Group Variance	0.046	0.067			

Figure 3.22: Results from mixed linear regression test showing that the tidal volume increases more as number of respiratory cycles (time since beginning of surgery) increases in presence of pulmonary complication.

The interaction between #Resp Cycles and presence of a pulmonary complication was also significant indicating that the amount of change in TV with respect to time changes depending on whether or not the patient had a pulmonary complication.

There were two limitations with this method, firstly presence of pulmonary complications is not used as the predicted variable and only as a predictor. Secondly, model fitting for ventilation parameters was inconsistent among different surgeries. Therefore, to solve both these problems it was determined that a feature called *Static TV Drift* should be derived in order to do further statistical testing.

3.4.5.4.3 Static TV Drift

In PCV the flow signal is highly dependent on the ventilation parameters and the effect of these ventilation parameters is hard to control for across many different surgeries. Therefore, only periods of static ventilation parameters should be assessed, extraction of static ventilation parameter periods was explained in section 3.4.4.2. Tidal Volume was used to describe the changes in the flow signal. TV was extracted from each respiratory cycle in the surgeries, explained in a previous section (3.4.3.4).

The TV drift represents the change in tidal volume during the largest static ventilation period in the surgery. To measure the drift in TV throughout the static period a linear trendline was utilized. First TV was estimated from respiratory cycles using linear regression.

$$\widehat{TV} = mx + b$$

$$\{0 \leq x < n | x \in \mathbb{Z}\}$$

Where:

$$\widehat{TV} = \text{Estimated TV from respiratory cycle}$$

$x = \text{Respiratory cycle}$

$n = \text{Number of respiratory cycles in period}$

$m = \text{Slope of trendline}$

$b = y - \text{intercept}$

From the linear trendline we can calculate the approximate change in TV across the static section. This is calculated using the following equation:

$$\Delta \widehat{TV} = \widehat{TV}(x = n) - \widehat{TV}(x = 0) = m \cdot n + b - b$$

$$\Delta \widehat{TV} = m \cdot n$$

The TV trendline can be seen in Figure 3.23.

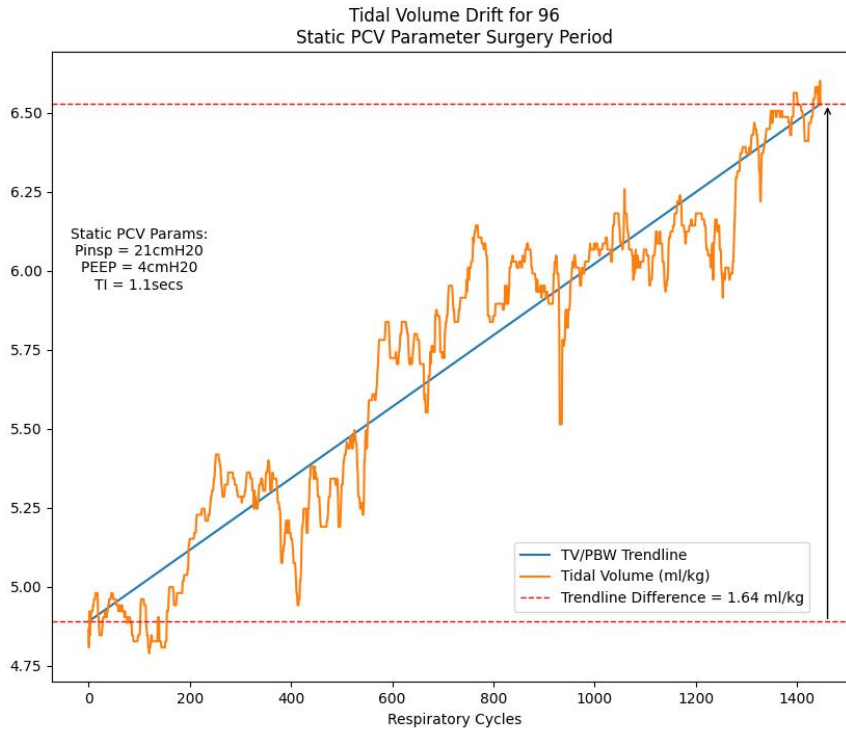


Figure 3.23: This figure depicts the method of finding tidal volume drift (TV-Drift) from a period of static ventilator parameters. The longest static period extracted from patient 96's surgery is shown. The tidal volume (TV) during this period is plotted along with the TV trendline used to calculate TV-Drift. The static pressure control ventilation (PCV) parameters for this period are shown in the top left.

3.5 Statistical Tests

This study will employ several statistical tests, including the Mann-Whitney U test, Wilcoxon Signed-Rank test, and Chi-Squared test. Additionally, models such as logistic regression, linear regression, and support vector machine will be used with the features discussed earlier in this chapter. Non-parametric tests were chosen, even in cases where the data is normally distributed, due to their increased reliability in handling outliers and small sample sizes. Specifics of statistical tests will be described in more detail in the results section.

Chapter 4: Results

4.1 Sequential Feature Selection with Perioperative Predictors

Sequential feature selection was used to determine the relative predictive power of the perioperative predictors of postoperative pulmonary complications in our dataset. In this test 8 features were selected to be included in the feature pool. The dataset is randomly split into a training set and a validation sets 100 times. This is done such that the ratio of Pulmonary Complication class to Non-Pulmonary Complication class is the same in the training and validation sets.

The training set is then used with the sequential feature selection (SFS) algorithm. A support vector machine (SVM) model was used during SFS. SVM was chosen for its robustness when handling multi-dimensional data, being effective in avoiding overfitting and handling class imbalances, linear kernel was used for easier interpretability.

The SFS algorithm searches over all possible combinations of features to determine the best combination of three features according to the metric. The metric chosen was the area under the receiver operator curve (ROC-AUC) this is due to its insensitivity to class imbalances. The SFS also used a 5-fold cross validation.

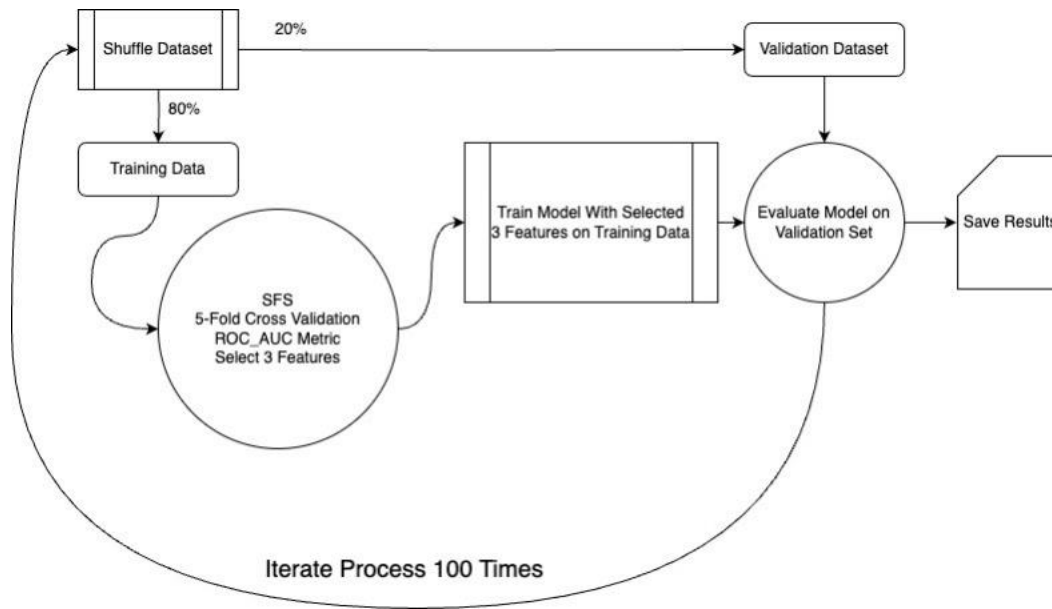


Figure 4.1: This figure shows outline of the statistical test in flow chart form.

After the selection of the three best features a model is trained on the training data using these features. This model is then evaluated on the validation set and the results are saved. This process is then repeated for 100 iterations. At the end of the 100 iterations the saved results were evaluated to determine which combinations of features were most often chosen and which features were most often found to be most important by the SFS.

4.1.1 Data

Since this statistical test was performed earlier in the project dataset one was used for this test dataset two was not received yet, see section 3.2.1. Dataset one includes 335 patients. The perioperative features in the selection pool were DLCO, FEV1, PBW, BMI, FVC, FEV1/FVC and Total Length of Surgery. OLV Length was also included to show patient exposure to possible dangers of one lung ventilation. Total length was used with OLV Length to control effect caused by relative surgery difficulty on patient outcome.

The outcome variable that is being predicted by the model is the presence of Pulmonary

Features Selected by SFS	Count	mean precision	mean sensitivity	mean specificity	mean accuracy	mean roc-auc
['DLCO', 'FEV1', 'OLV Length']	20	0.22	0.70	0.79	0.78	0.75
['DLCO', 'BMI', 'OLV Length']	18	0.23	0.81	0.78	0.78	0.79
['DLCO', 'PBW', 'OLV Length']	14	0.22	0.77	0.79	0.78	0.78
['DLCO', 'OLV Length', 'Total Length']	10	0.21	0.68	0.79	0.79	0.74
['DLCO', 'FEV1', 'Total Length']	6	0.22	0.83	0.76	0.76	0.80
['DLCO', 'FVC', 'OLV Length']	6	0.19	0.70	0.75	0.75	0.73
['DLCO', 'PBW', 'Total Length']	5	0.20	0.88	0.71	0.72	0.79
['DLCO', 'BMI', 'Total Length']	4	0.22	0.65	0.79	0.78	0.72
['DLCO', 'FEV1/FVC', 'OLV Length']	4	0.21	0.90	0.73	0.74	0.81
['FEV1', 'PBW', 'OLV Length']	4	0.22	0.70	0.81	0.80	0.76
['DLCO', 'FEV1/FVC', 'Total Length']	2	0.21	0.80	0.75	0.75	0.78
['FEV1', 'BMI', 'OLV Length']	2	0.22	0.90	0.75	0.76	0.83
['FEV1', 'BMI', 'Total Length']	2	0.16	0.60	0.75	0.74	0.68
['DLCO', 'FVC', 'Total Length']	1	0.31	1.00	0.82	0.84	0.91
['FEV1', 'FVC', 'OLV Length']	1	0.21	0.80	0.76	0.76	0.78
['FVC', 'PBW', 'OLV Length']	1	0.08	0.20	0.81	0.76	0.50

Complications.

4.1.2 Results

Feature	Selection Frequency
DLCO	93%
FEV1	34%
OLV Length	86%
Total Length	25%
BMI	26%
PBW	24%
FVC	10%
FEV1/FVC	60%

4.2 Distributions of Features

4.2.1 Perioperative

The distributions of perioperative features were plotted, and medians were compared between pulmonary complication patients and non-pulmonary complication patients using a non-parametric Mann Whitney U-test.

4.2.1.1 Results

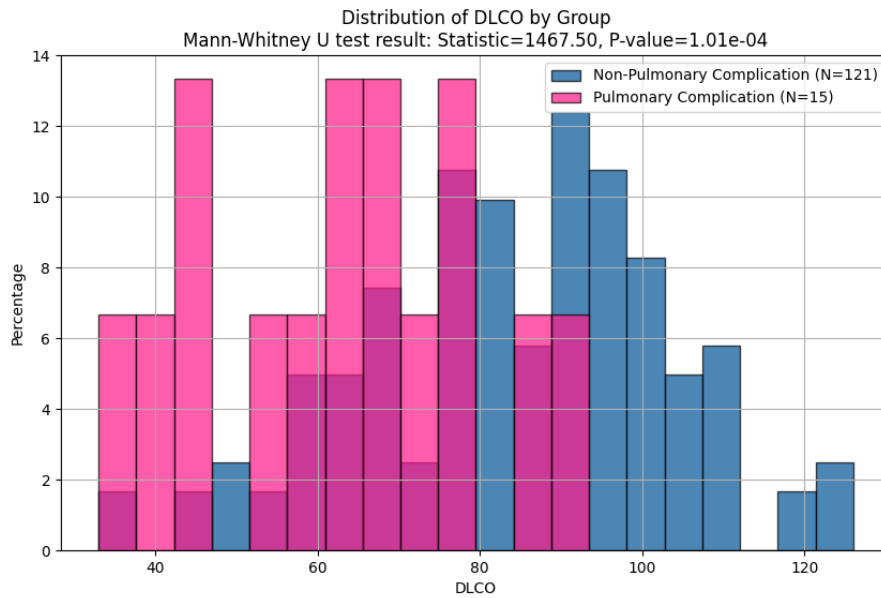


Figure 4.2: Histogram comparing the distribution of DLCO between patients with and without post-operative pulmonary complications (PPCs). The percentages represent the proportion of patients within each group falling into specific DLCO bins. The Mann-Whitney U test result indicates a statistically significant difference between the two groups (Statistic = 1467.00, P-value = 1.01e-04), with the Non-Pulmonary Complication group (N=121) shown in blue and the Pulmonary Complication group (N=15) in pink.

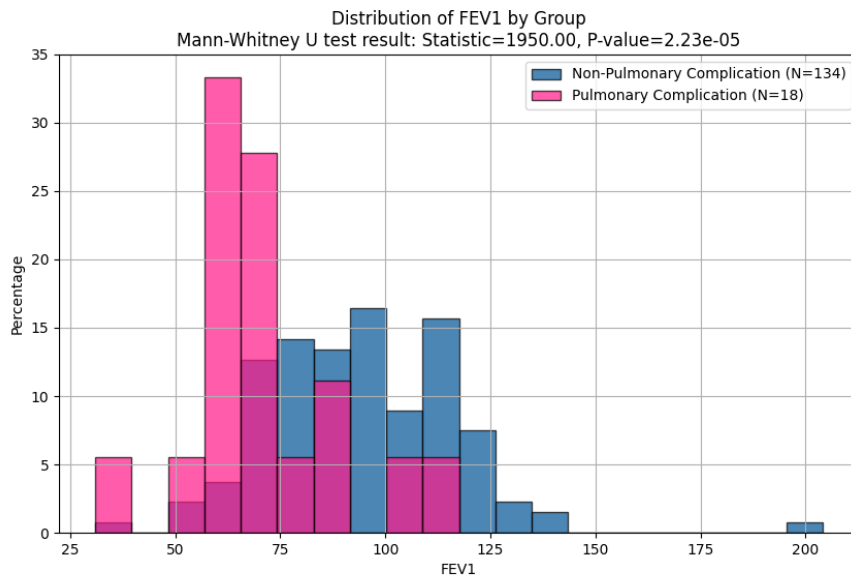


Figure 4.3: Histogram comparing the distribution of FEV1 between patients with and without post-operative pulmonary complications (PPCs). The percentages represent the proportion of patients within each group falling into specific FEV1 bins. The Mann-Whitney U test result indicates a statistically significant difference between the two groups (Statistic = 1950.00, P-value = 2.23e-05), with the Non-Pulmonary Complication group (N=134) shown in blue and the Pulmonary Complication group (N=18) in pink.

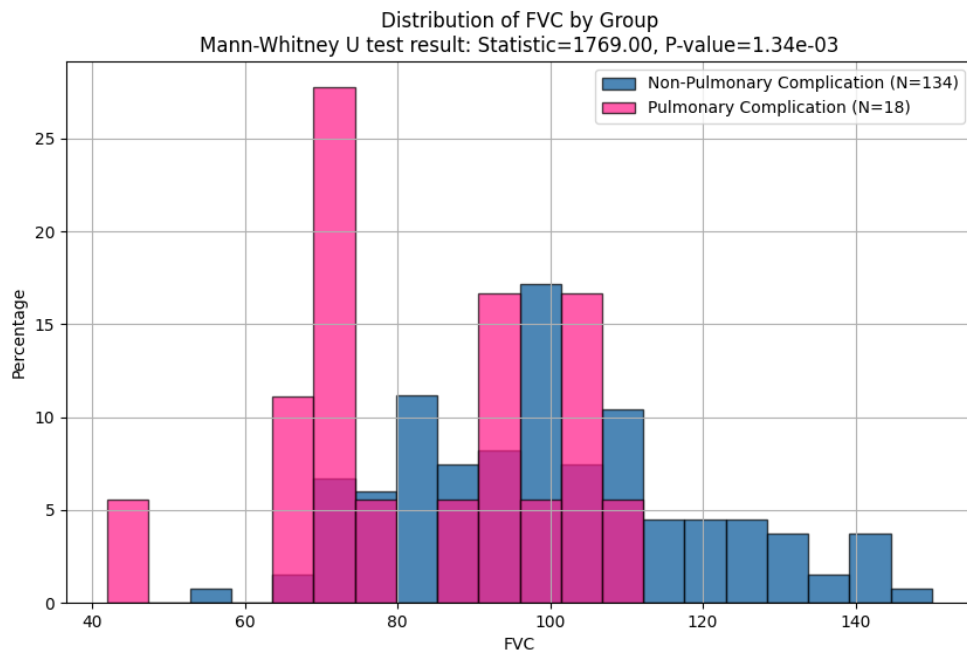


Figure 4.4: Histogram comparing the distribution of FVC between patients with and without post-operative pulmonary complications (PPCs). The percentages represent the proportion of patients within each group falling into specific FVC bins. The Mann-Whitney U test result indicates a statistically significant difference between the two groups (Statistic = 1769.00, P-value = 1.34e-03), with the Non-Pulmonary Complication group (N=134) shown in blue and the Pulmonary Complication group (N=18) in pink.

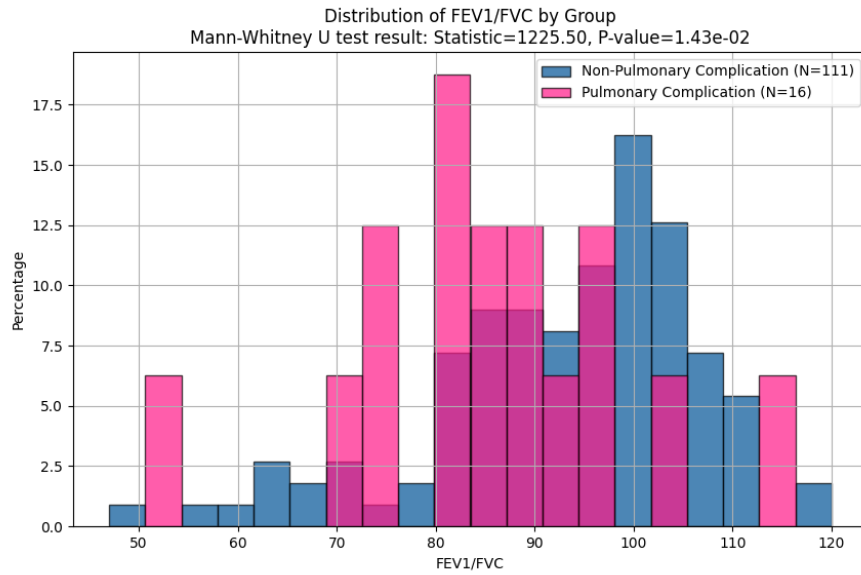


Figure 4.5: Histogram comparing the distribution of FEV1/FVC between patients with and without post-operative pulmonary complications (PPCs). The percentages represent the proportion of patients within each group falling into specific FEV1/FVC bins. The Mann-Whitney U test result indicates a statistically significant difference between the two groups (Statistic = 1225.00, P-value = 1.43e-02), with the Non-Pulmonary Complication group (N=111) shown in blue and the Pulmonary Complication group (N=16) in pink.

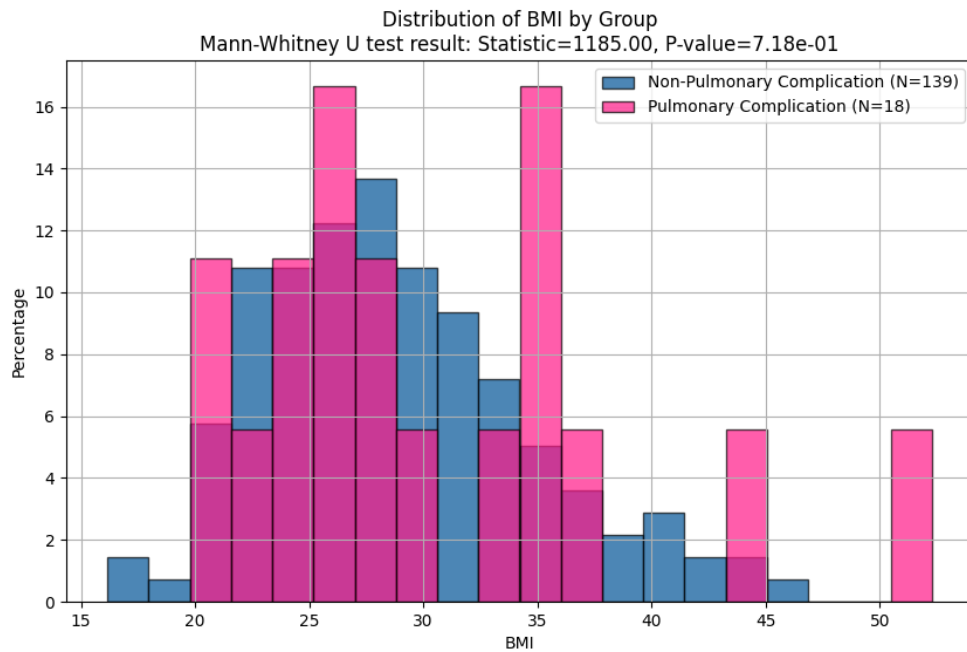


Figure 4.6: Histogram showing the distribution of BMI between patients with and without post-operative pulmonary complications (PPCs). The percentages represent the proportion of patients within each group that fall into specific BMI bins. The Mann-Whitney U test result indicates no statistically significant difference between the two groups (Statistic = 1185.00, P-value = 7.18e-01). The Non-Pulmonary Complication group (N=139) is represented in blue, while the Pulmonary Complication group (N=18) is shown in pink.

4.2.2 Intra-operative

The distributions of median intra-operative features were plotted, and medians were compared between pulmonary complication patients and non-pulmonary complication patients using a non-parametric Mann Whitney U-test.

4.2.2.1 Results

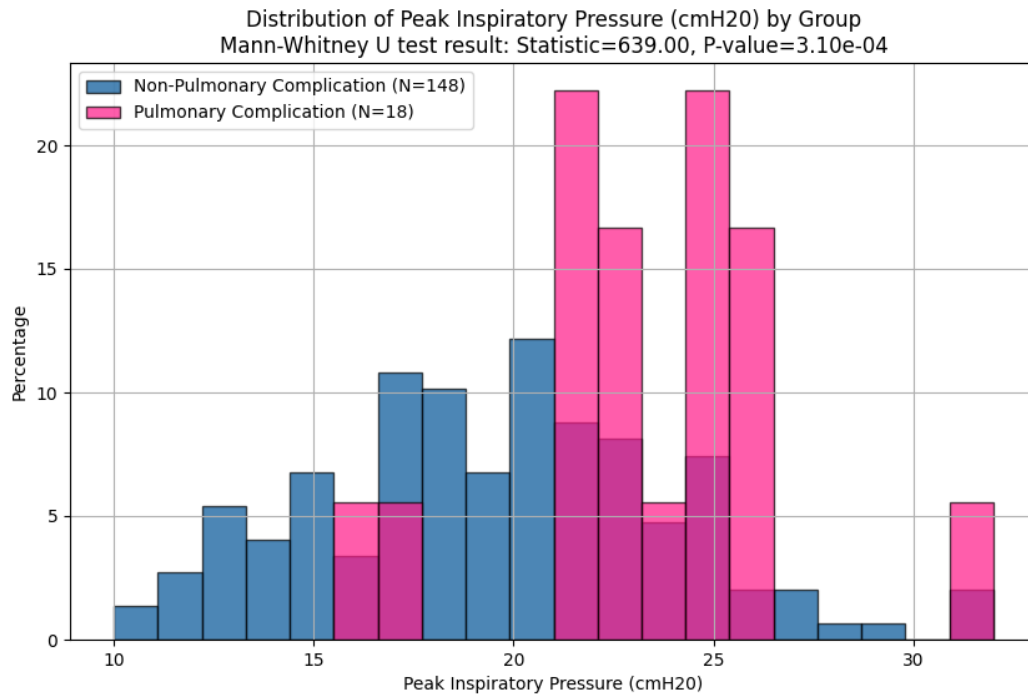


Figure 4.7: Histogram illustrating the distribution of Peak Inspiratory Pressure (PIP) in cmH2O between patients with and without post-operative pulmonary complications (PPCs). The percentages represent the proportion of patients within each group that fall into specific PIP bins. The Mann-Whitney U test result indicates a statistically significant difference between the two groups (Statistic = 639.00, P-value = 3.10e-04). The Non-Pulmonary Complication group (N=148) is shown in blue, while the Pulmonary Complication group (N=18) is depicted in pink.

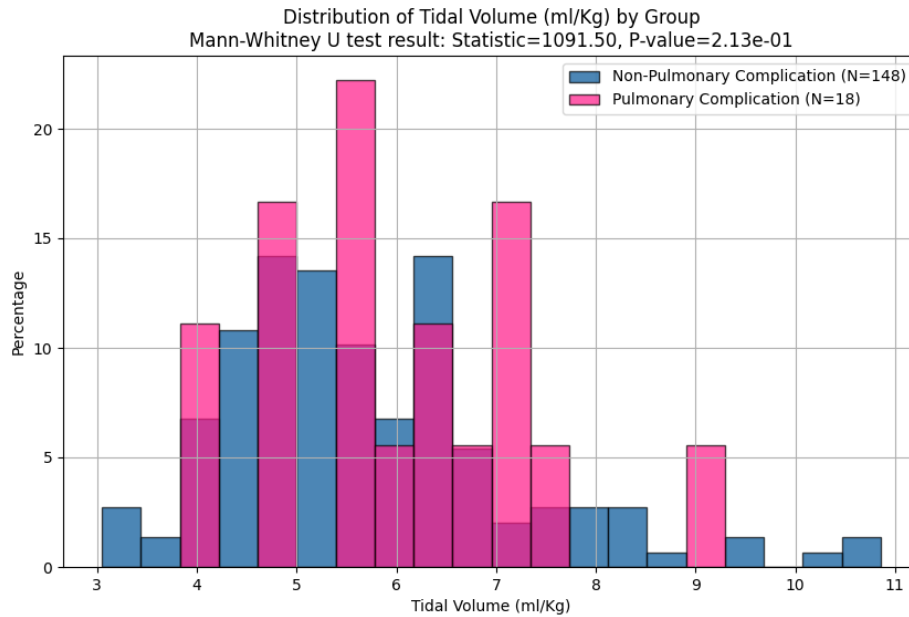


Figure 4.8: Histogram displaying the distribution of Tidal Volume (ml/kg) between patients with and without post-operative pulmonary complications (PPCs). The percentages represent the proportion of patients within each group that fall into specific tidal volume bins. The Mann-Whitney U test result indicates no statistically significant difference between the two groups (Statistic = 1091.50, P-value = 2.13e-01). The Non-Pulmonary Complication group (N=148) is represented in blue, and the Pulmonary Complication group (N=18) is shown in pink.

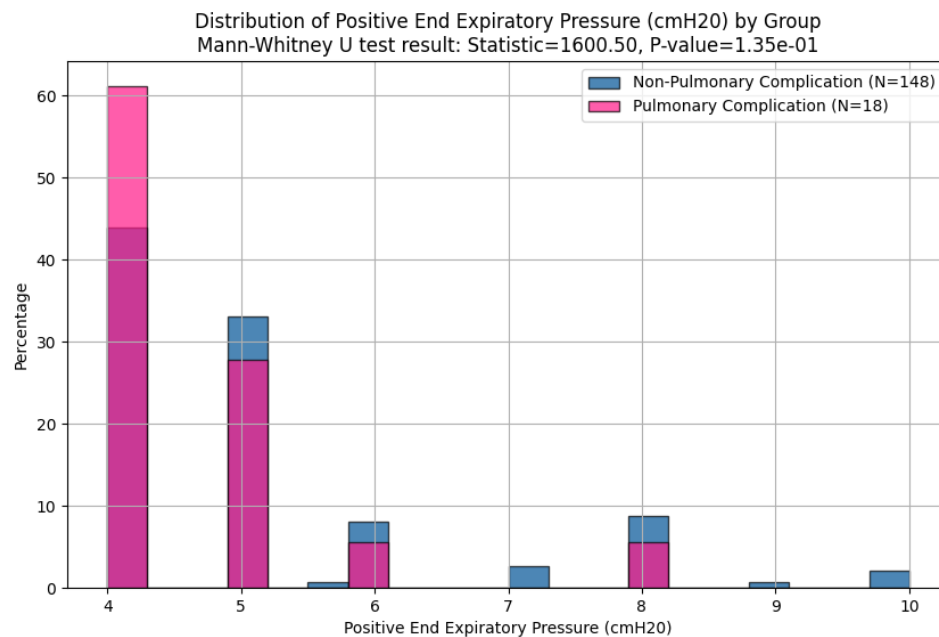


Figure 4.9: Histogram displaying the distribution of positive end expiratory pressure (PEEP) between patients with and without post-operative pulmonary complications (PPCs). The percentages represent the proportion of patients within each group that fall into specific tidal volume bins. The Mann-Whitney U test result indicates no statistically significant difference between the two groups (Statistic = 1600.50, P-value = 1.35e-01). The Non-Pulmonary Complication group (N=148) is represented in blue, and the Pulmonary Complication group (N=18) is shown in pink.

4.3 Testing Heterogeneity of Signals

4.3.1.1 *Rationale*

Using average or median summary metrics to describe and compare the ventilation for a patient during their surgery limits our ability to account for small periods of injurious ventilation. If damage caused by ventilation does not increase linearly with magnitude then this is not accounted for in a surgery wide summary metric like mean or median. In order to test whether the surgeries could be treated as homogenous ventilation parameter ranges were plotted on a set of histograms with cumulative density functions were created.

First the unique values and counts for the ventilation parameters were extracted from each surgery this was previously explained (see: Extract Unique Values). Next the range was calculated from the unique values as described in section 3.4.5.3. This was then plotted and inspected to determine how many patients could be considered homogenous. The distribution of the range of ventilation parameters for the patients was then compared using a Mann-Whitney U test between the pulmonary complication group and the non-pulmonary complication group. This test was done on the following ventilation metrics: peak inspiratory pressure, positive-end-expiratory-pressure, tidal volume and the number of unique PCV setpoints within a surgery.

4.3.1.2 Results

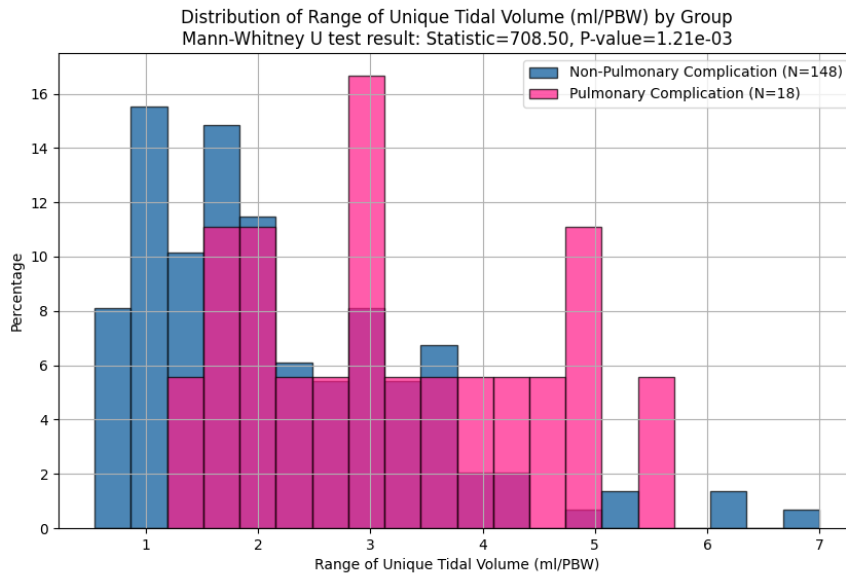


Figure 4.10: Histogram illustrating the distribution of the range of unique Tidal Volume (ml/PBW) that patients were exposed to during surgery, comparing those with and without post-operative pulmonary complications (PPCs). The percentages indicate the proportion of patients within each group across different ranges of unique tidal volumes experienced during surgery. The Mann-Whitney U test reveals a statistically significant difference between the two groups (Statistic = 708.50, P-value = 1.21e-03). The Non-Pulmonary Complication group (N=148) is represented in blue, and the Pulmonary Complication group (N=18) is shown in pink. Patients with PPCs were exposed to a larger range of Tidal Volumes.

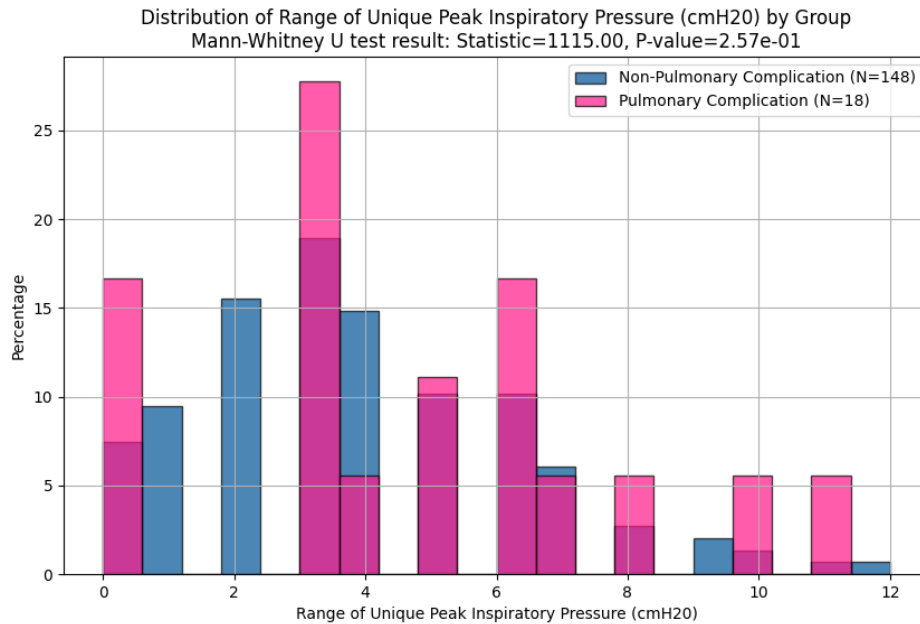


Figure 4.11: Histogram showing the distribution of the range of unique Peak Inspiratory Pressure (cmH2O) that patients were exposed to during surgery, comparing those with and without post-operative pulmonary complications (PPCs). The graph displays the percentage of patients within each group across different ranges of unique peak inspiratory pressures experienced during the surgery. The Mann-Whitney U test indicates no statistically significant difference between the two groups (Statistic = 1115.00, P-value = 2.57e-01). The Non-Pulmonary Complication group (N=148) is represented in blue, and the Pulmonary Complication group (N=18) is shown in pink.

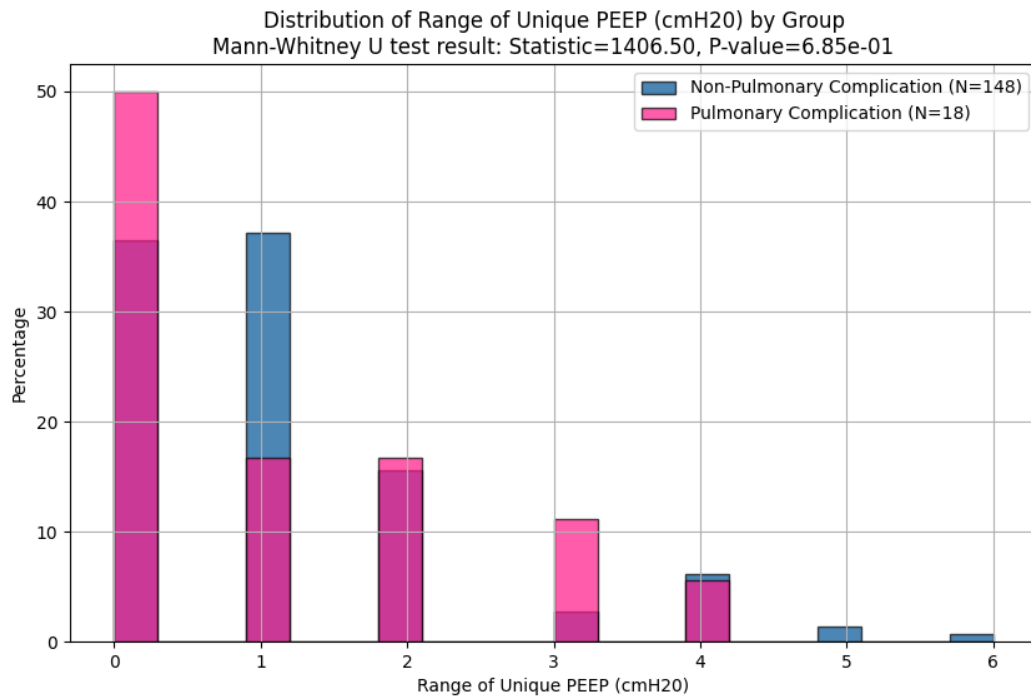


Figure 4.12: Histogram showing the distribution of the range of unique Positive End Expiratory Pressures (cmH2O) that patients were exposed to during surgery, comparing those with and without post-operative pulmonary complications (PPCs). The graph displays the percentage of patients within each group across different ranges of unique peak inspiratory pressures experienced during the surgery. The Mann-Whitney U test indicates no statistically significant difference between the two groups (Statistic = 1406.50, P-value = 6.85e-01). The Non-Pulmonary Complication group (N=148) is represented in blue, and the Pulmonary Complication group (N=18) is shown in pink.

4.4 Chi-Squared Tests for Protective Ventilation

4.4.1 Peak inspiratory pressure

4.4.1.1 Rationale

This statistical test groups patients by their peak inspiratory pressure (PIP) based on whether the PIP follows protective ventilation guidelines. Protective ventilation guidelines aim to minimize the negative effects of mechanical ventilation. The guidelines recommend ensuring plateau pressure is kept below 25cmH2O. Setting $PIP \leq 25\text{cmH2O}$ ensures that the plateau pressure will also be below 25cmH2O. The importance of protective ventilation and its impact on patient outcomes are discussed in more detail in section 2.4.4.

Previous results from this study showed that median peak inspiratory pressure differed between the pulmonary complication and non-pulmonary complication classes (see: Distributions of Features). However, PIP was also visibly inspected to be heterogenous throughout many of the recorded surgeries, with ~50% of the surgeries having PIP that have a range of values $>4\text{cmH2O}$ (see: Testing Heterogeneity of Signals). In surgeries with heterogenous ventilation parameters, it is possible that summary metrics like median do not accurately describe the damage caused by ventilation. For this reason, maximum PIP was selected to be used as a feature in addition to the median PIP.

This test has two aims:

Firstly, to determine if there is a difference in rate of pulmonary complications when the median/maximum PIP is below or above protective ventilation guidelines, using a Chi-square test.

Second it seeks to compare test results between using the median and maximum PIP.

This test does not control for other factors, focusing solely on the relationship between PIP and complications.

4.4.1.2 Data

The data for this test were derived from PIP measurements within the group 3 PCV dataset.

The median PIP value for each patient was calculated from the airway pressure signal recorded during the surgery.

The maximum PIP was found by first extracting unique PIP values with N=10 as detailed in a previous chapter. The maximum PIP is taken as the maximum value in this unique list of PIPs.

This dataset includes patients categorized into two classes, pulmonary complication and non-pulmonary complication.

4.4.1.3 Results

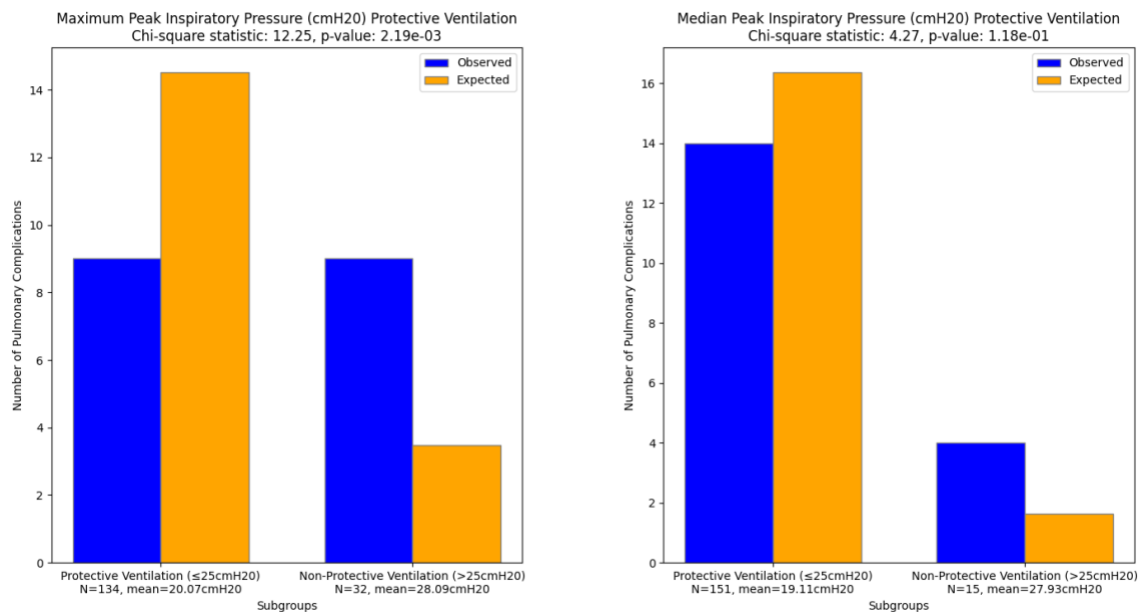


Figure 4.13: Comparison of pulmonary complications by ventilation strategy, using maximum (left) and median (right) Peak Inspiratory Pressure (PIP) values to define protective versus non-protective ventilation. The left panel shows the distribution of pulmonary complications based on the maximum PIP, with a significant difference between protective ventilation (≤ 25 cmH₂O) and non-protective ventilation (> 25 cmH₂O) groups (Chi-square statistic: 12.25, p-value: 2.19e-03). The right panel compares complications based on the median PIP, showing a less pronounced difference between the groups (Chi-square statistic: 4.27, p-value: 1.18e-01). Observed values (blue) and expected values (orange) are displayed for both protective and non-protective ventilation strategies.

4.4.2 Tidal volume

4.4.2.1 Rationale

This statistical test groups patients by their median tidal volume (TV) based on whether TV follows protective ventilation guidelines. Protective ventilation guidelines generally recommend TV to be ideally less than 6ml/kg however, in patients with COPD they allow for up to a maximum of 8ml/kg. These guidelines aim to minimize the negative effects of mechanical ventilation, by keeping the tidal volume high enough to provide adequate gas exchange while not damaging lungs through excessive volumes. Cutoff points of 6ml/kg and 8ml/kg were tested to determine if keeping TVs below either had an effect on complication rate. The importance of protective ventilation and its impact on patient outcomes are discussed in more detail in section 2.4.4.

TV was visibly inspected to be heterogenous throughout many of the recorded surgeries, with ~40% of the surgeries having PIP that have a range of values >2ml/kg. In surgeries with heterogenous ventilation parameters, it is possible that summary metrics like median do not accurately describe the damage caused by ventilation. For this reason, maximum TV was selected to be used as a feature in addition to the median TV.

This test has two aims:

Firstly, to determine if there is a difference in rate of pulmonary complications when the median/maximum TV for a surgery is below or above protective ventilation guidelines, using a Chi-square test.

Second it seeks to compare test results between using the median and maximum TV.

This test does not control for other factors, focusing solely on the relationship between TV and complications.

4.4.2.2 Data

The data for this test were derived from TV measurements within the group 3 PCV dataset. The TVs for each patient was calculated by integrating the airway flow signal recorded during the surgery.

The median was calculated from the list of TV measurements during a surgery.

The maximum TV was found by first extracting unique TV values with N=10 as detailed in a previous chapter. The maximum TV is taken as the maximum value in this unique list of TVs.

This dataset includes patients categorized into two classes, pulmonary complication and non-pulmonary complication.

4.4.2.3 Results

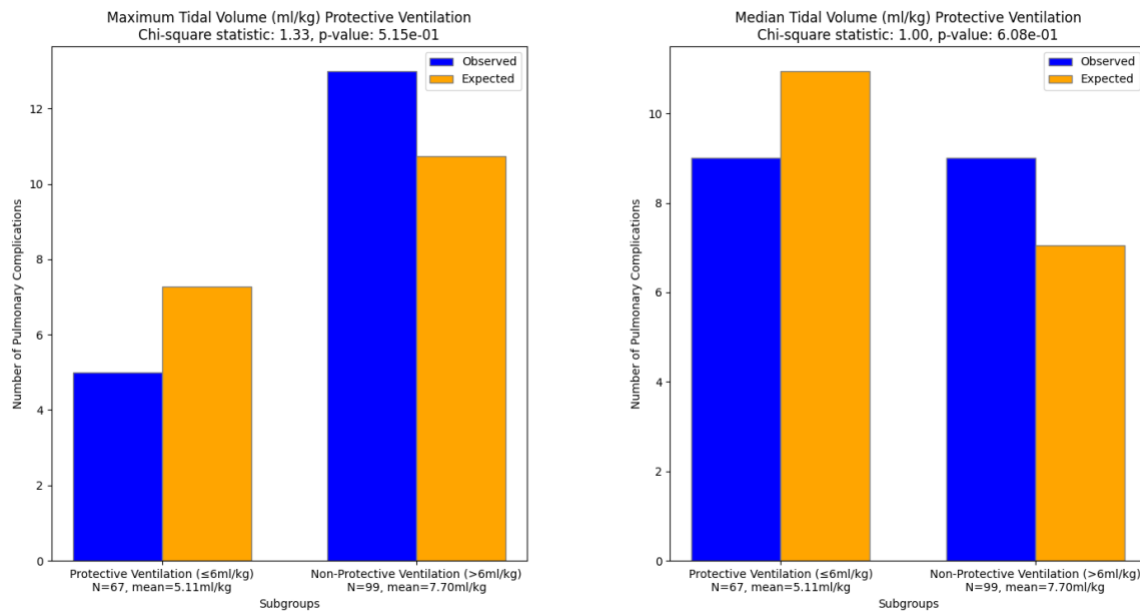


Figure 4.14: Comparison of pulmonary complications by ventilation strategy, using maximum (left) and median (right) Tidal Volume (TV) values to define protective versus non-protective ventilation. The left panel shows the distribution of pulmonary complications based on the maximum TV, with no significant difference between protective ventilation (≤ 6 ml/kg) and non-protective ventilation (> 6 ml/kg) groups (Chi-square statistic: 1.33, p-value: 5.15e-01). The right panel compares complications based on the median TV, also showing no significant difference between the groups (Chi-square statistic: 1.00, p-value: 6.08e-01). Observed values (blue) and expected values (orange) are displayed for both protective and non-protective ventilation strategies.

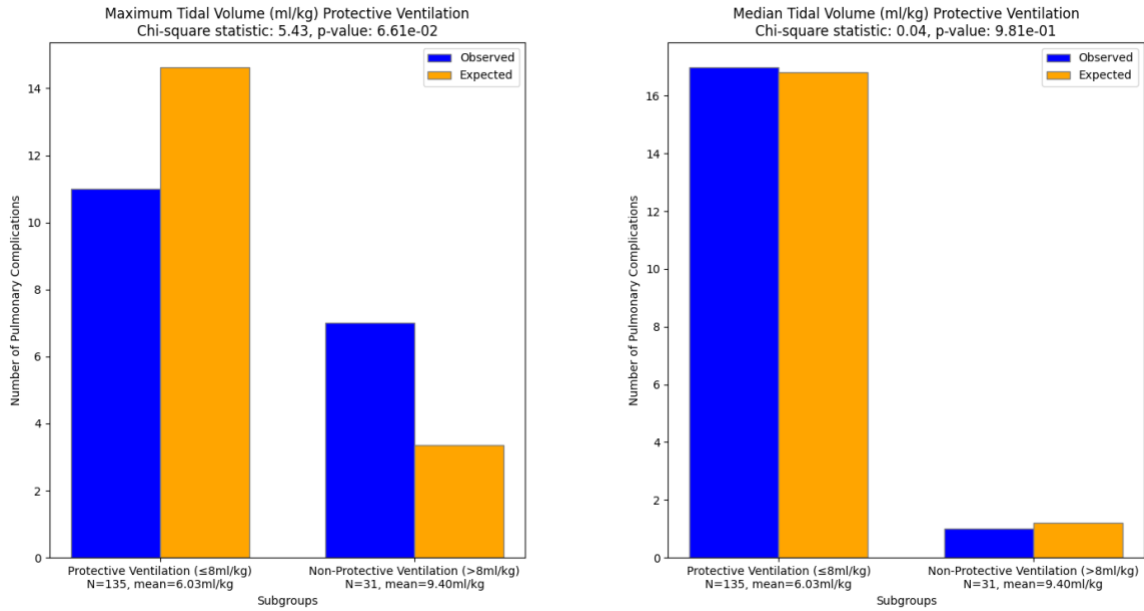


Figure 4.15: Comparison of pulmonary complications by ventilation strategy, using maximum (left) and median (right) Tidal Volume (TV) values to define protective versus non-protective ventilation. The left panel illustrates the distribution of pulmonary complications based on the maximum TV, showing a statistically significant difference between protective ventilation (≤ 8 ml/kg) and non-protective ventilation (> 8 ml/kg) groups (Chi-square statistic: 5.43, p-value: 6.61e-02). The right panel compares complications based on the median TV, with no significant difference observed between the groups (Chi-square statistic: 0.04, p-value: 9.81e-01). Observed values (blue) and expected values (orange) are displayed for both protective and non-protective ventilation strategies.

4.5 Logistic Regression to Predict Pulmonary Complications

4.5.1 Median inspiratory pressure

4.5.1.1 Rationale

This statistical analysis uses logistic regression to examine the relationship between median Peak Inspiratory Pressure (PIP) and the occurrence of pulmonary complications, while controlling for important covariates such as Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO) and the type of surgery performed. Peak inspiratory pressure was selected to be used in the test because during this study median peak inspiratory pressure was shown to differ between the pulmonary complication and non-pulmonary complication classes (see: Distributions of Features, Chi-Squared Tests for Protective Ventilation). Additionally, protective ventilation has often highlighted minimizing PIP as being important to minimizing the risk of pulmonary complications (see: Lung Protective Ventilation). Additionally results previous tests showed that

when stratifying groups by median PIP above the protective margin of 25cmH₂O there was a significant difference in rate of complications. This test seeks to better describe the relationship.

DLCO and type of surgery were included as co-variates as they have both been shown to correlate with Pulmonary Complications (see: DLCO, see: Sequential Feature Selection with Perioperative Predictors).

4.5.1.2 Data

The data for this test were derived from PIP measurements within the group 3 PCV dataset. The median PIP value for each patient was calculated from the airway pressure signal recorded during the surgery. This dataset includes patients categorized into two classes, pulmonary complication and non-pulmonary complication.

4.5.1.3 Results

Logit Regression Results						
Dep. Variable:	Pulmonary Complication	No. Observations:	136			
Model:	Logit	Df Residuals:	131			
Method:	MLE	Df Model:	4			
Date:	Wed, 31 Jul 2024	Pseudo R-squ:	0.3109			
Time:	14:10:21	Log-Likelihood:	-32.532			
converged:	True	LL-Null:	-47.210			
Covariance Type:	nonrobust	LLR p-value:	6.623e-06			

	coef	std err	z	P> z	[0.025	0.975]
const	-1.8871	2.314	-0.815	0.415	-6.423	2.648
Median Peak Inspiratory Pressure (cmH ₂ O)	0.1325	0.078	1.707	0.088	-0.020	0.285
Wedge Resection	0.6105	0.883	0.691	0.489	-1.121	2.342
Lobe Resection	2.3439	1.009	2.323	0.020	0.366	4.322
DLCO	-0.0657	0.019	-3.440	0.001	-0.103	-0.028

Figure 4.16: Logistic regression results for predicting pulmonary complications based on Median Peak Inspiratory Pressure (cmH₂O), Wedge Resection, Lobe Resection, and DLCO. When controlling for co-variates, median Peak Inspiratory Pressure is only marginally significant.

4.5.2 Maximum inspiratory pressure

4.5.2.1 Rationale

This statistical analysis uses logistic regression to examine the relationship between maximum Peak Inspiratory Pressure (PIP) and the occurrence of pulmonary complications, while controlling for important covariates such as Diffusing Capacity of the Lungs for Carbon

Monoxide (DLCO) and the type of surgery performed. Peak inspiratory pressure was selected to be used in the test because protective ventilation has often highlighted minimizing PIP as being important to minimizing the risk of pulmonary complications (see: Lung Protective Ventilation). PIP was also visibly inspected to be heterogenous throughout many of the recorded surgeries, with ~50% of the surgeries having PIP that have a range of values $>4\text{cmH}_2\text{O}$. In surgeries with heterogenous ventilation parameters, it is possible that summary metrics like median do not accurately describe the damage caused by ventilation. This is why logistic regression is being done with maximum PIP in addition to median PIP. Additionally results from previous tests showed that when stratifying groups by maximum PIP above the protective margin of $25\text{cmH}_2\text{O}$ there was a significant difference in rate of complications. This test seeks to better describe the relationship.

DLCO and type of surgery were included as co-variates as they have both been shown to correlate with Pulmonary Complications (see: DLCO, see: Sequential Feature Selection with Perioperative Predictors).

4.5.2.2 Data

The data for this test were derived from PIP measurements within the group 3 PCV dataset. The PIP was extracted from the airway pressure signal. Unique PIP values are then extracted with $N=10$ as detailed in a previous chapter and outliers were removed from the unique value set. Finally, the maximum is taken as the maximum value in this list of PIPs.

This dataset includes patients categorized into two classes, pulmonary complication and non-pulmonary complication.

4.5.2.3 Results

Logit Regression Results						
Dep. Variable:	Pulmonary Complication	No. Observations:	136			
Model:	Logit	Df Residuals:	131			
Method:	MLE	Df Model:	4			
Date:	Wed, 31 Jul 2024	Pseudo R-squ:	0.3275			
Time:	14:09:15	Log-Likelihood:	-31.750			
converged:	True	LL-Null:	-47.210			
Covariance Type:	nonrobust	LLR p-value:	3.180e-06			

	coef	std err	z	P> z	[0.025	0.975]
const	-2.7547	2.374	-1.160	0.246	-7.408	1.898
Maximum Peak Inspiratory Pressure (cmH ₂ O)	0.1627	0.077	2.120	0.034	0.012	0.313
Wedge Resection	0.6565	0.891	0.737	0.461	-1.090	2.403
Lobe Resection	2.1443	1.022	2.099	0.036	0.142	4.147
DLCO	-0.0659	0.020	-3.366	0.001	-0.104	-0.028

Figure 4.17: Logistic regression results for predicting pulmonary complications based on Maximum Peak Inspiratory Pressure (cmH₂O), Wedge Resection, Lobe Resection, and DLCO. When controlling for covariates, Maximum Peak Inspiratory Pressure is statistically significant.

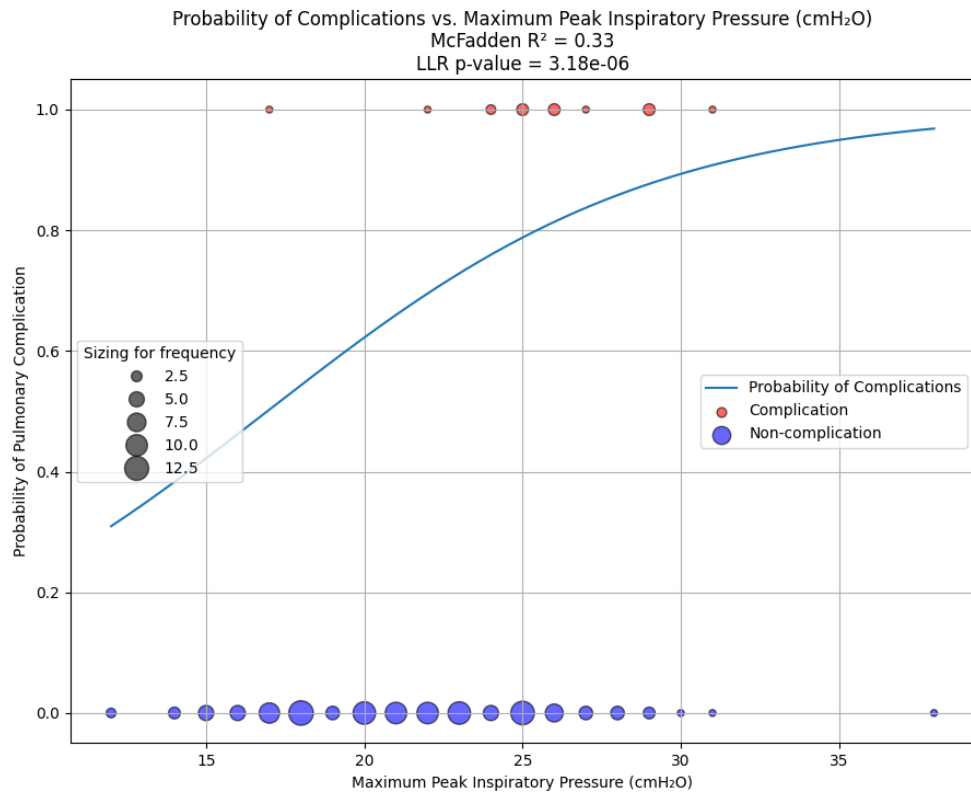


Figure 4.18: Plot of the predicted probability of pulmonary complications as a function of Maximum Peak Inspiratory Pressure (cmH₂O). The logistic regression model shows an increasing probability of complications with higher Maximum PIP values, as depicted by the blue curve. The size of the points represents the frequency of observations, with red circles indicating complications and blue circles indicating non-complications. The McFadden R-squared value of 0.33 and an LLR p-value of 3.18e-06 suggest a good fit for the model.

4.6 Modeling Pressure Damage Function

4.6.1.1 Rationale

Previous results from this study suggested that using the max PIP throughout the surgery better predicted pulmonary complications (PPC) than the median PIP. This result leaves a lot left unexplained, notably what is the relationship with time. It seems logical that both the magnitude of the pressure the patient was exposed to and the duration of their exposure would be important factors to consider. The rate at which exposure causes damage however is not known and would likely differ based on patient factors.

The goal of this test is to derive a model that predicts PPCs using all the PIPs the patient was exposed to and the times they were exposed to them.

4.6.1.2 Outline

First a formula was hypothesized to predict probability of PPCs. This formula assumes that the rate of damage or risk of PPCs changes as the pressure changes. It also assumes that this change is exponential in nature.

$$P(\phi) = \frac{1}{1 + e^{-\phi}}$$
$$\phi = b_0 + b_1 \sum_{n=1}^N \dot{D}_n r_n + b_3 * DLCO$$
$$\dot{D}_n = P_n^{b_2}$$

Where:

P = Probability of pulmonary complication

ϕ = Log odds of pulmonary complication

b_0 = Constant

b_1 = Coefficient for $(\dot{D} * r)$ term

$\dot{D}_n$ = Rate of damage per respiratory cycle at pressure P_n

$r_n = \text{Number of respiratory cycles at pressure } P_n$

$P_n = \text{nth pressure setpoint in patient exposure}$

$b_2 = \text{Exponential rate for increase in } \dot{V} \text{ per unit pressure}$

$N = \text{Number of unique pressure setpoints patient was exposed to}$

$b_3 = \text{DLCO coefficient}$

A function was created in python to represent this model. The minimize function from the SciPy library was then used to fit values for b_0 , b_1 , b_2 and b_3 minimizing the log likelihood function. This model takes into account every PIP a patient was exposed to during a surgery and the time for which they were exposed. It assumes a different rate of damage for each pressure level and that this rate of damage increases exponentially with respect to the number of respiratory cycles. Since the data is already matched on DLCO another model will be fit that does not include the $b_3 \cdot \text{DLCO}$ term.

4.6.1.3 Data

The data used to fit this model consists of data from 15 matched pairs of 29 patients. The 15 matched pairs were created by matching patients to DLCO and their type of surgery, two parameters shown to have predictive power in previous results (see: DLCO, see: Sequential Feature Selection with Perioperative Predictors). Three patients with a pulmonary complication did not have a recorded DLCO value (patients 100,279,472) they were not included. These patients were not included in both models (with and without $b_3 \cdot \text{DLCO}$ term) in order to directly compare their results.

PIP values and number of respiratory cycles for each PIP value was extracted using the Unique values function detailed in chapter 3.

4.6.1.4 Results

4.6.1.4.1 Model Optimization Results including $b_3 \cdot \text{DLCO}$ term

The logistic regression model was optimized using the L-BFGS-B algorithm. The optimized parameters are as follows:

Parameter	Value
Intercept (b_0)	-1.83
Damage estimation coefficient (b_1)	5.88E-6
Exponential pressure damage rate (b_2)	1.75E-3
DLCO coefficient (b_3)	-5.5E-3
Pseudo R-squared	0.22
Akaike Information Criterion (AIC)	39.41
Bayesian Information Criterion (BIC)	44.88
Log-Likelihood	-15.70
Likelihood Ratio Test Statistic	8.76
Degrees of Freedom	3
P-value	0.033

4.6.1.4.2 Model Optimization Results without $b_3 \cdot \text{DLCO}$ term

The logistic regression model was optimized using the L-BFGS-B algorithm. The optimized parameters are as follows:

Parameter	Value
Intercept (b_0)	-2.03
Damage estimation coefficient (b_1)	1.40E-6
Exponential pressure damage rate (b_2)	2.19
Pseudo R-squared	0.22
Akaike Information Criterion (AIC)	37.26
Bayesian Information Criterion (BIC)	41.36
Log-Likelihood	-15.63
Likelihood Ratio Test Statistic	8.91
Degrees of Freedom	2
P-value	0.011

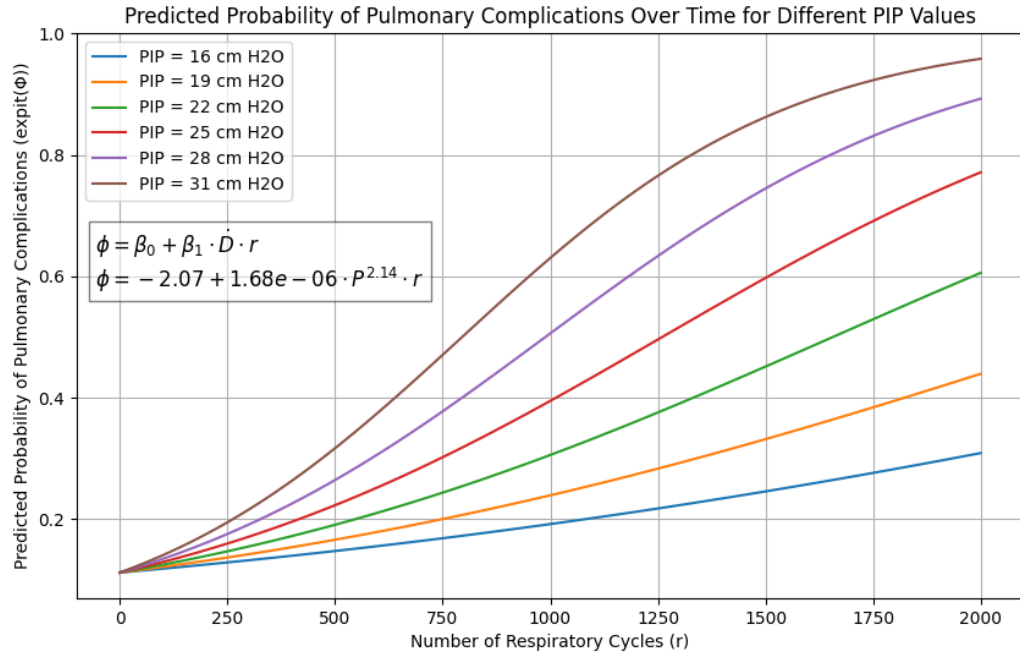


Figure 4.19: Predicted probability of pulmonary complications over time (number of respiratory cycles) for different Peak Inspiratory Pressure (PIP) values, ranging from 16 cmH2O to 31 cmH2O. The model incorporates all PIPs the patient was exposed to and the duration of exposure, assuming an exponential increase in the rate of damage with respect to the number of respiratory cycles at each pressure level. The probability of complications increases more rapidly with higher PIP values, as shown by the steeper curves for higher pressures. The equation inset represents the relationship used to model these probabilities, considering both the magnitude of pressure and the time of exposure.

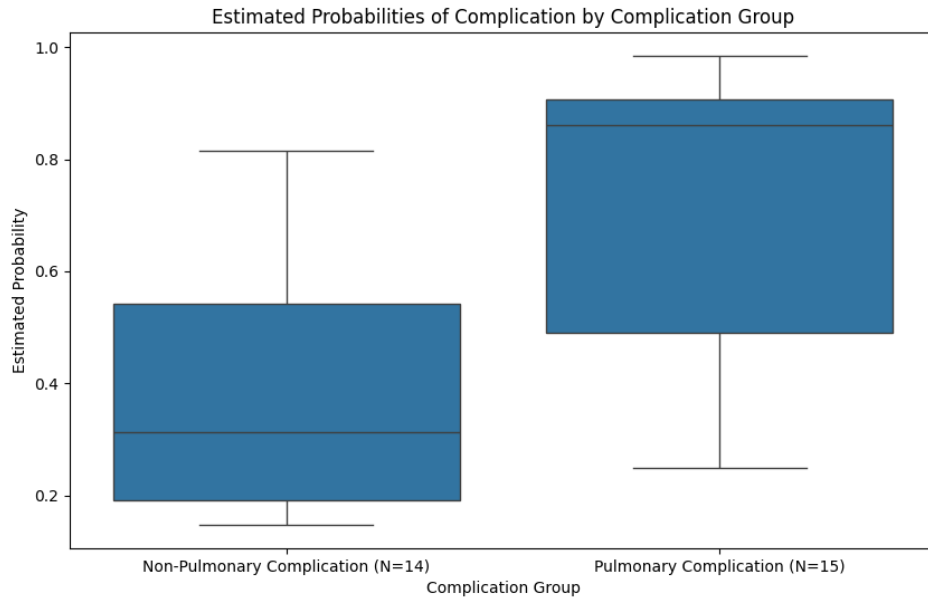


Figure 4.20: Box plot illustrating the estimated probabilities of pulmonary complications for the training data used in the model, grouped by complication status. The left box corresponds to patients without pulmonary complications ($N=14$), and the right box corresponds to patients with pulmonary complications ($N=15$). The plot shows that the model predicts higher probabilities of complications for the pulmonary complication group, with a greater median probability and narrower interquartile range compared to the non-pulmonary complication group. This differentiation in predicted probabilities reflects the model's ability to distinguish between the two groups based on the training data

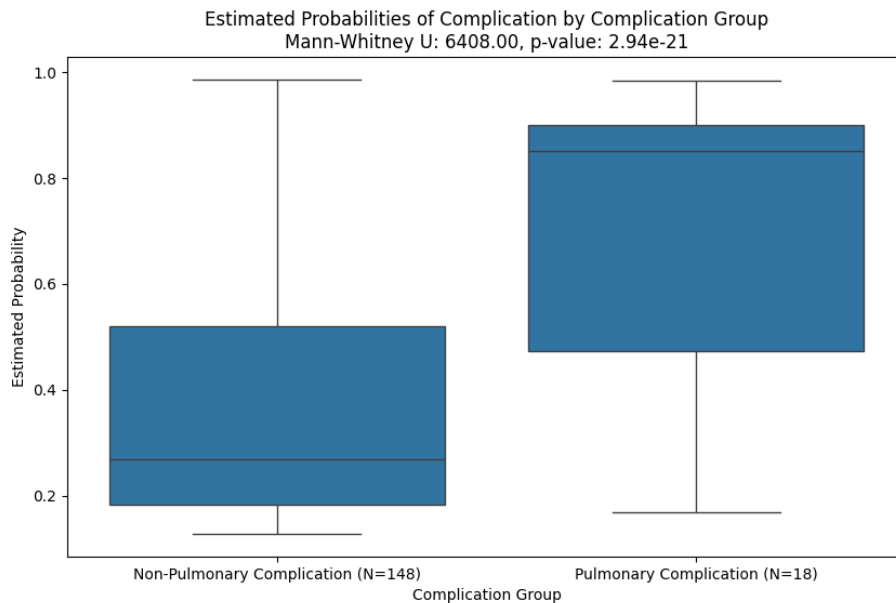


Figure 4.21: Box plot showing the estimated probabilities of pulmonary complications, grouped by complication status, including both the original training data and additional patients. The left box represents patients without pulmonary complications ($N=148$), while the right box represents patients with pulmonary complications ($N=18$). The plot demonstrates that the model continues to predict higher probabilities of complications for the pulmonary complication group. The Mann-Whitney U test result ($U = 6408.00$, $p\text{-value} = 2.94e-21$) indicates a statistically significant difference between the groups, supporting the model's robustness in distinguishing between patients with and without pulmonary complications, even with the inclusion of new data.

Dep. Variable:	PulmComp	No. Observations:	166
Model:	Logit	Df Residuals:	163
Method:	MLE	Df Model:	2
Date:	Sat, 17 Aug 2024	Pseudo R-squ.:	0.2071
Time:	14:38:18	Log-Likelihood:	-45.174
converged:	True	LL-Null:	-56.976
Covariance Type:	nonrobust	LLR p-value:	7.494e-06

	coef	std err	z	P> z	[0.025	0.975]
const	-6.5654	1.716	-3.827	0.000	-9.928	-3.203
Max PIP	0.1294	0.081	1.591	0.112	-0.030	0.289
Est. Prob. PComp	3.0595	1.324	2.311	0.021	0.464	5.655

Figure 4.22: Logistic regression results showing the relationship between Maximum Peak Inspiratory Pressure (Max PIP) and the estimated probability of post-operative pulmonary complications (PPCs) using the exponential model. The results indicate that while Max PIP alone approaches statistical significance ($p = 0.112$), its effect is overshadowed by the estimated probability from the exponential model, which is statistically significant ($p = 0.021$). This suggests that the exponential model's probability estimate provides a more robust predictor of PPCs, reducing the individual significance of Max PIP.

4.7 Wilcoxon Signed-Rank Tests for Matched Pairs

4.7.1 Tidal Volume Drift

4.7.1.1 Rationale

This test aims to determine if there is a significant difference in median tidal volume drift (TV Drift) between pulmonary complication matched pairs. Previous analysis indicated that the range of tidal volume (TV) differs between patients with and without pulmonary complications. Additionally, visual inspection suggested that TV increased more in surgeries with pulmonary complications, despite static pressure-controlled ventilation (PCV) settings. Tidal volume (TV) delivered to the patient is dependent upon the pressure settings during PCV ventilation and the properties of the lung. The TV Drift metric attempts to infer changing properties of the lung since it is extracting during periods of unchanging PCV ventilation settings. This is explained in more detail in a previous section (3.4.4.2)

The Wilcoxon Matched-Pairs Signed-Rank Test is employed to evaluate whether TV Drift is associated with the occurrence of pulmonary complications, while controlling for pre-operative factors through the matched pairs design.

4.7.1.2 *Data*

The data for this test were derived from a variety of ventilation parameter measurements within the group 3 PCV dataset.

Values for TV Drift were extracted for each patient in the manner detailed previously in this chapter. First the longest static period was found for each patient, then the TV Drift was extracted from this period.

This dataset includes patients categorized into two classes, pulmonary complication and non-pulmonary complication. The 18 matched pairs were created by matching patients to DLCO and their type of surgery, two parameters shown to have predictive power in previous results (see: DLCO, see: Sequential Feature Selection with Perioperative Predictors). In the case where a patient with a pulmonary complication did not have a recorded DLCO value (patients 100,279,472) they were matched to their FEV1 and type of surgery. Low FEV1 has also been shown to be correlated with pulmonary complications (see: FEV1, see: Sequential Feature Selection with Perioperative Predictors).

4.7.1.3 Results

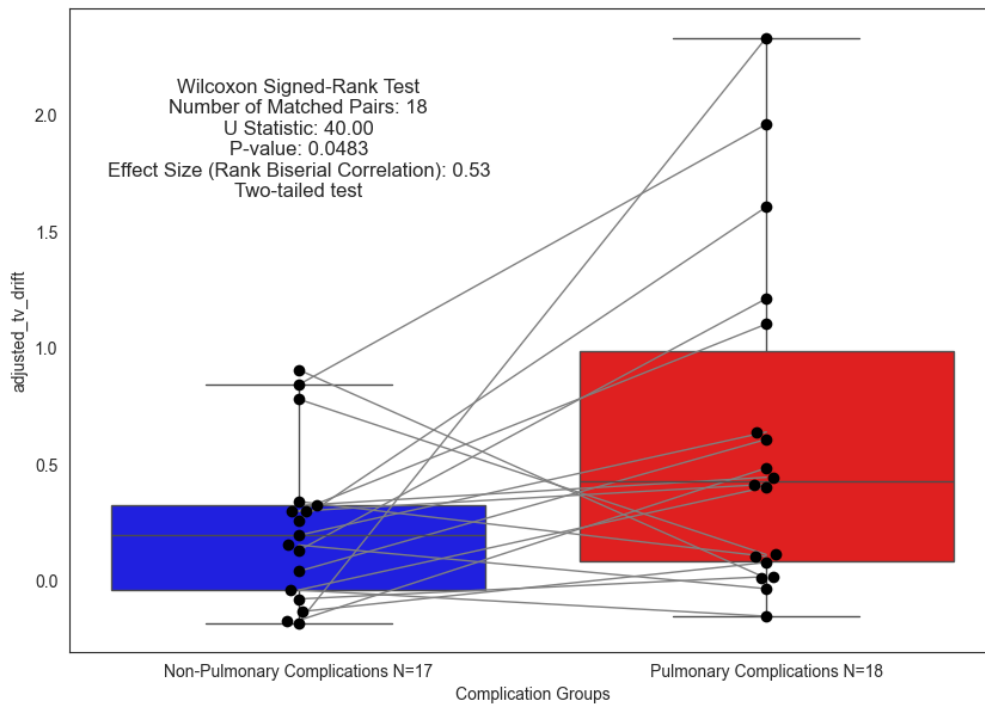


Figure 4.23: Box plot showing the difference in normalized Tidal Volume Drift (TV-Drift) between matched pairs of patients, comparing those with pulmonary complications (N=18) to those without (N=17). The Wilcoxon Signed-Rank Test was used to assess the difference between the two groups, yielding a U statistic of 40.00, a p-value of 0.0483, and an effect size (Rank Biserial Correlation) of 0.53. The significant p-value indicates a statistically meaningful difference in TV-Drift between the complication groups, with patients in the pulmonary complication group exhibiting greater normalized TV-Drift. The lines connecting points represent matched pairs.

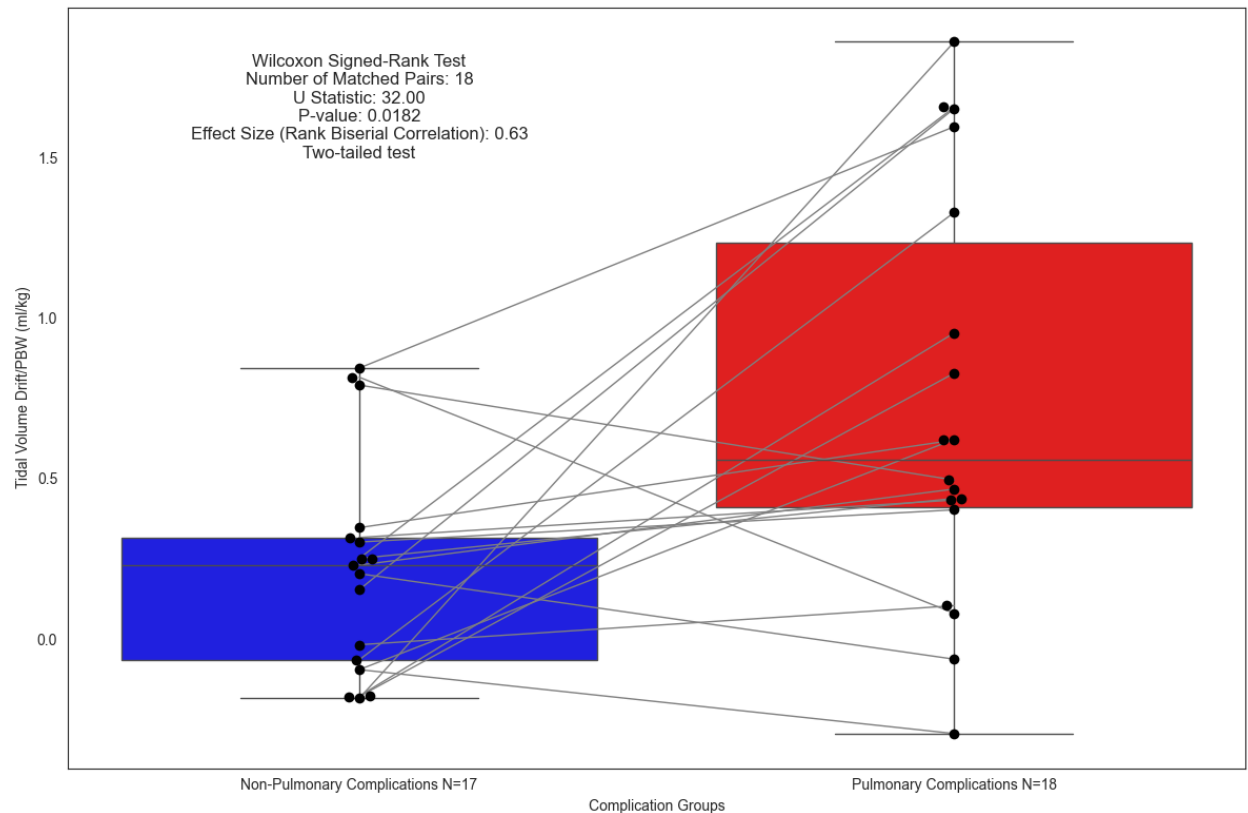


Figure 4.24: Box plot showing the difference in non-normalized Tidal Volume Drift (TV-Drift) between matched pairs of patients, comparing those with pulmonary complications (N=18) to those without (N=17). The Wilcoxon Signed-Rank Test was used to assess the difference between the two groups, yielding a U statistic of 32.00, a p-value of 0.0182, and an effect size (Rank Biserial Correlation) of 0.63. The significant p-value indicates a statistically meaningful difference in TV-Drift between the complication groups, with patients in the pulmonary complication group exhibiting greater TV-Drift. The lines connecting points represent matched pairs.

4.7.2 Peak inspiratory pressure

4.7.2.1 Rationale

After finding a difference in TV Drift for the matched pairs a test was performed to investigate the difference in ventilation techniques performed during these segments. Peak inspiratory pressure was selected to be compared between the groups since it was a significant predictor of pulmonary complications in other tests done in this study (see: Logistic Regression to Predict Pulmonary Complications) and has been described as an important ventilation variable in past research (see: Lung Protective Ventilation).

The Wilcoxon Matched-Pairs Signed-Rank Test is employed to evaluate whether PIP is

associated with the occurrence of pulmonary complications, while controlling for pre-operative factors through the matched pairs design.

4.7.2.2 Data

The matched pairs dataset for this test is the same as for the previous subsection Tidal Volume Drift. The PIP value used for each patient is the static PIP value during the static ventilation parameters period that was selected to measure TV Drift.

4.7.2.3 Results

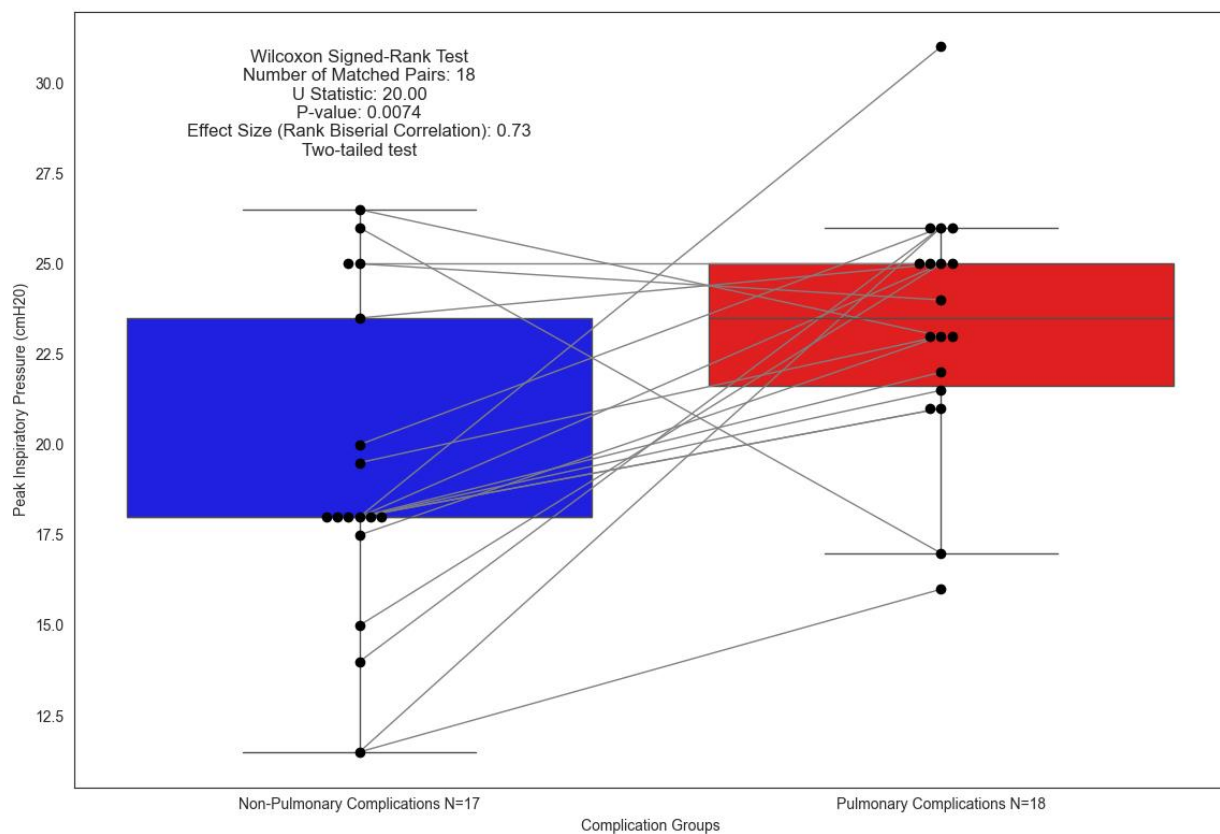


Figure 4.25: Box plot illustrating the differences in Peak Inspiratory Pressure (PIP) during the static period used to calculate TV-Drift. This was compared between matched pairs of patients, comparing those with pulmonary complications (N=18) to those without (N=17). The Wilcoxon Signed-Rank Test was used to evaluate the difference between the two groups, resulting in a U statistic of 20.00, a p-value of 0.0074, and an effect size (Rank Biserial Correlation) of 0.73. The significant p-value suggests a statistically meaningful difference in PIP between the groups, with higher PIP observed in the pulmonary complication group. The lines connecting points represent matched pairs.

4.8 Linear Regression to Predict TV-Drift

4.8.1.1 Rationale

After previous results indicated that both TV-Drift and PIP differed between matched pairs, we aimed to determine if the PIP level during the static period could predict TV-Drift. We tested

two approaches: the first approach considered only the pressure level, while the second approach considered both the pressure level and the duration of exposure. For the second method, we used the probability score derived from the model discussed in the previous section (4.6).

4.8.1.2 Data

The data for this test were derived from a variety of ventilation parameter measurements within the group 3 PCV dataset.

Values for TV Drift were extracted for each patient in the manner detailed previously in: Static TV Drift. First the longest static period was found for each patient, then the TV Drift was extracted from this period.

This dataset includes patients categorized into two classes, pulmonary complication and non-pulmonary complication. The 18 matched pairs were created by matching patients to DLCO and their type of surgery, two parameters shown to have predictive power in previous results (see: DLCO, see: Sequential Feature Selection with Perioperative Predictors). In the case where a patient with a pulmonary complication did not have a recorded DLCO value (patients 100,279,472) they were matched to their FEV1 and type of surgery. Low FEV1 has also been shown to be correlated with pulmonary complications (see: FEV1, see: Sequential Feature Selection with Perioperative Predictors).

4.8.1.3 Results

OLS Regression Results						
Dep. Variable:	TV Drift	R-squared:	0.052			
Model:	OLS	Adj. R-squared:	0.020			
Method:	Least Squares	F-statistic:	1.645			
Date:	Wed, 14 Aug 2024	Prob (F-statistic):	0.209			
Time:	12:30:12	Log-Likelihood:	-26.568			
No. Observations:	32	AIC:	57.14			
Df Residuals:	30	BIC:	60.07			
Df Model:	1					
Covariance Type:	nonrobust					
	coef	std err	t	P> t	[0.025	0.975]
const	-0.1786	0.508	-0.352	0.728	-1.217	0.859
PIP	0.0301	0.023	1.283	0.209	-0.018	0.078
Omnibus:	7.154	Durbin-Watson:	2.006			
Prob(Omnibus):	0.028	Jarque-Bera (JB):	5.985			
Skew:	1.042	Prob(JB):	0.0502			
Kurtosis:	3.377	Cond. No.	109.			

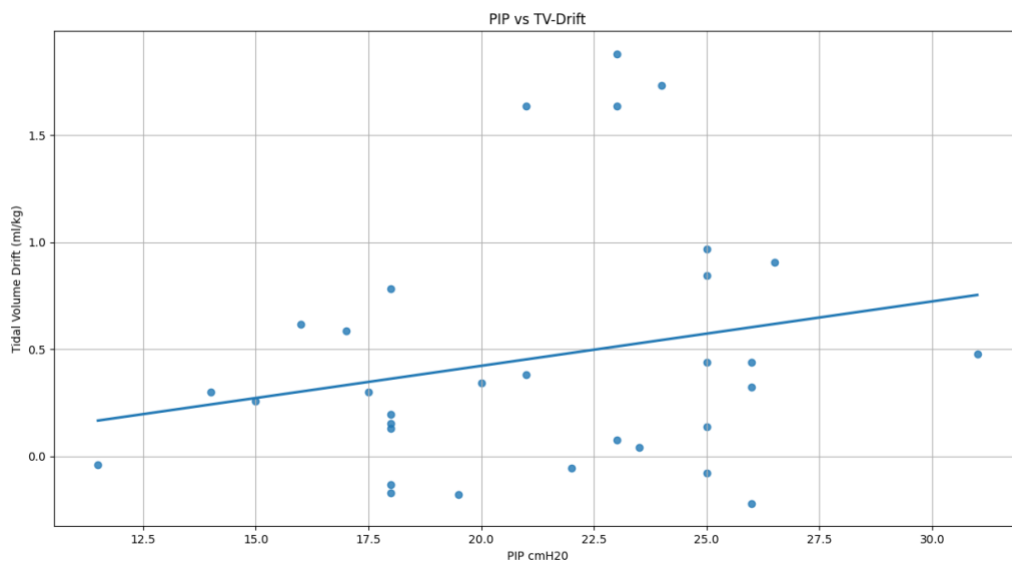


Figure 4.26: Ordinary Least Squares (OLS) regression analysis results examining the relationship between Peak Inspiratory Pressure (PIP) and Tidal Volume Drift (TV Drift). The regression model yielded an R-squared value of 0.052, indicating that approximately 5.2% of the variance in TV Drift can be explained by PIP. The coefficient for PIP was 0.0301, with a p-value of 0.209, suggesting that the relationship between PIP and TV Drift is not statistically significant at the 0.05 level.

OLS Regression Results						
Dep. Variable:	TV Drift	R-squared:	0.145			
Model:	OLS	Adj. R-squared:	0.116			
Method:	Least Squares	F-statistic:	5.076			
Date:	Wed, 14 Aug 2024	Prob (F-statistic):	0.0317			
Time:	12:21:14	Log-Likelihood:	-24.921			
No. Observations:	32	AIC:	53.84			
Df Residuals:	30	BIC:	56.77			
Df Model:	1					
Covariance Type:	nonrobust					
	coef	std err	t	P> t	[0.025	0.975]
const	0.0566	0.203	0.278	0.783	-0.359	0.472
Prob PCOMP	0.8578	0.381	2.253	0.032	0.080	1.635
Omnibus:	4.017	Durbin-Watson:	2.068			
Prob(Omnibus):	0.134	Jarque-Bera (JB):	3.335			
Skew:	0.789	Prob(JB):	0.189			
Kurtosis:	2.907	Cond. No.	4.88			

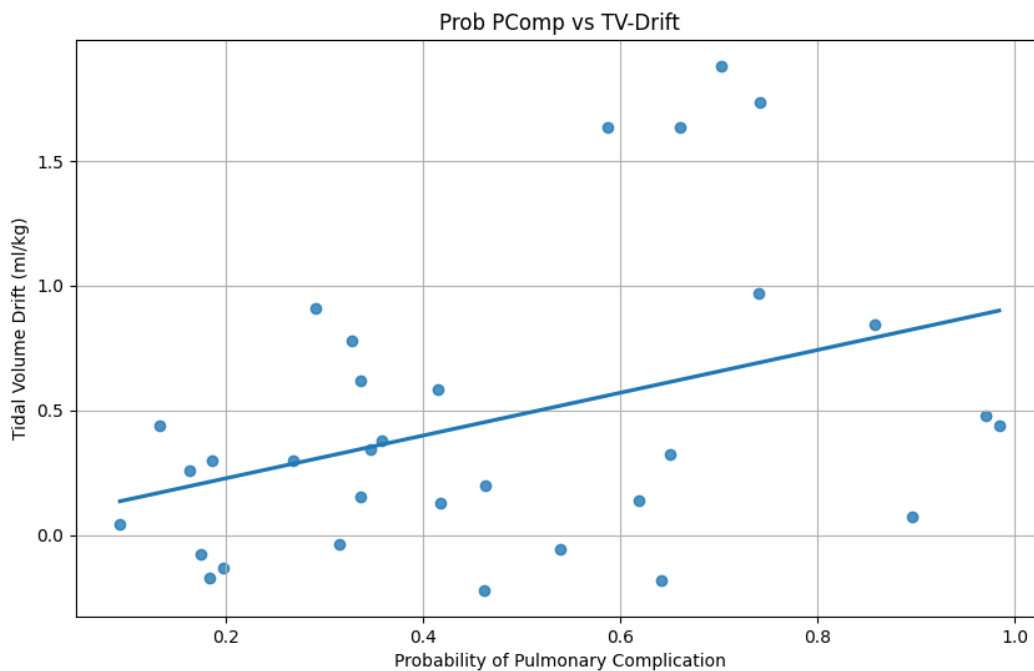


Figure 4.27: Ordinary Least Squares (OLS) regression analysis results examining the relationship between the probability of pulmonary complication (Prob PCOMP) and Tidal Volume Drift (TV Drift). Prob PCOMP is generated using the exponential pressure model. The regression model yielded an R-squared value of 0.145, indicating that approximately 14.5% of the variance in TV Drift can be explained by the probability of pulmonary complication. The coefficient for Prob PCOMP was 0.8578, with a p-value of 0.032, indicating a statistically significant positive relationship between the probability of pulmonary complication and TV Drift at the 0.05 level.

Chapter 5: Discussion

5.1 Sequential Feature Selection with Perioperative Predictors

In the results for this test we can see that variables like DLCO and total length of surgery were highlighted as being important predictors. Additionally, OLV Length was selected as a meaningful predictor even when controlling for total length of the surgery. This suggested that there was something happening during the OLV portion of the surgery that would predict pulmonary complications. It should be noted however, that the predictive power of most of the models was relatively low. In addition to this a potential confounding factor is that perhaps OLV length was a better predictor than total surgery length because this represents the active portion of the lung surgery. This may explain why it would have higher predictive power than total length without actually having anything to do with the damage induced by OLV.

Nevertheless, these results agree with previous work showing that DLCO is a strong predictor of Pulmonary Complications [32], [33], [36], [37].

5.2 Intraoperative Data Distributions and Heterogeneity

5.2.1 Comparing medians

Ventilator parameters investigated included: positive end expiratory pressure (PEEP), peak inspiratory pressure (PIP) and tidal volume (TV). Of these only PIP showed a difference in median value between patients with PPCs and those without. This agrees with previous studies finding driving pressure a more significant predictor of complications than tidal volumes [57], [58], [59], [60].

5.2.2 Range of setpoints

It was observed that some patients were exposed to a range of different ventilation parameters. Range of values for each ventilation parameter was extracted for each patient as explained in results section. Some notable findings were that the range of PIP experienced by roughly 50% of

patients was greater than 4cmH₂O. Additionally, the range of TV/PBW experienced for roughly 40% of patients was greater than 2ml/kg. It was also observed that the range for TV/PBW differed between patients who had pulmonary complications and those who do not. This along with other observations led to creation of the TV Drift parameter discussed in more detail in section 3.4.5.4.

5.2.3 Surgeries followed LPV guidelines for PEEP

The median PEEP did not significantly differ between groups, and the distribution for range of values indicates that PEEP was rarely adjusted throughout the surgery. However, this does not necessarily imply that PEEP levels are unimportant. All recorded data showed PEEP levels consistently within protective ventilation guidelines, with little variation. Due to this uniformity in PEEP settings, further statistical tests comparing PEEP were not conducted.

5.3 The Assumptions of Using Median/Mean

Observing the heterogeneity of ventilation parameter setpoints during the surgeries analyzed leads to some interesting considerations about using median or mean values to represent exposure. Let's assume that for a given pressure there is an associated risk of injury per respiratory cycle and that the risk of injury increases linearly with the magnitude of pressure. If we then collected measurements at each respiratory cycle throughout a surgery and averaged them, we could use this average to find our average risk of injury per respiratory cycle. Using this we could then determine our total risk of injury if we also know the length of the surgery. The assumption of linearity is critical here if we are going to use the mean. If the risk of injury does not increase linearly with the magnitude of pressure, then we do not have an accurate average risk of injury by taking the mean of the pressure observations.

This led to the idea of using “maximum PIP” and “maximum TV”. Using maximum values tells us the highest pressure or volume the patient was exposed to even if it was only for a short time. If this has more predictive power than the average PIP or TV then this suggests that increasing these values increase the risk of injury in a non-linear fashion.

5.4 Protective Ventilation Subgroups – comparing median and maximum

Protective ventilation its role in OLV and the guidelines for each parameter are still debated amongst leaders in the field however, recommendations to keep pressures in the lung below 25cmH2O and TV below 6-8ml/kg have been in discussion [46].

Results from the CHI-squared tests stratified patients based on median and maximum pressure above or below 25cmH2O. Results showed statistically significant differences in rate of complications between the two groups with higher rates of pulmonary complications in the group above 25cmH2O. This shows that increasing pressures above the 25cmH2O guideline may increase the chance of complications. Additionally, using maximum PIP instead of median PIP increased the CHI-squared test statistic suggesting that keeping the maximum pressure the patient is exposed to is perhaps more important than keeping the average pressure low.

The CHI-squared test did not yield significant results for median or maximum TV/PBW at the $\alpha = 0.05$ level. However, when using the maximum TV/PBW the results were marginally significant. This perhaps suggest a relationship with less strength than for PIP that requires a larger dataset for adequate demonstration. These results agree with past studies that have found no reduction in PPCs for patients with protective low tidal volume ventilation [60], [61].

5.5 PIP Investigation

5.5.1 Logistic regression of peak inspiratory pressure – comparing median and maximum

Since Chi-Square results showed that median and maximum measurements for peak inspiratory pressure (PIP) were associated with different rates of complications this was tested further with a logistic regression controlling for co-variables; DLCO, and type of surgery. The results showed again that using the maximum PIP is a better predictor of Pulmonary Complications than using the median PIP. This seems to confirm our hypothesis regarding heterogenous ventilation parameters. Using the median value on a heterogenous signal does not adequately summarize the potential damage done to the patient. Using the median assumes that risk of injury increases linearly with the magnitude of PIP, these results suggest this is not the case.

One of the limitations with the maximum PIP method was that there was no information regarding the length of time the patient was exposed to the maximum PIP except that it was for at least 10 respiratory cycles.

5.5.2 Modelling dose response curves for peak inspiratory pressure

This model was created in attempt to address the limitations of the maximum PIP methods.

These results showed that likely the risk of injury does not scale linearly with the magnitude of PIP. However, using only maximum PIP is not likely to be a good measurement due to the limitation of ignoring length of exposure.

Suppose that if two patients were exposed to the same high PIP, the first for only 10 respiratory cycles and the second for 500 respiratory cycles. It seems intuitive that the second would have a probability of having a pulmonary complication than the first. This introduces some challenging questions. At what rate does this risk of complications climb? If the rate of the increase in risk is different at different pressures, then how much does it change for each pressure unit change? The

general regression model that was fit to the data (see: Results) assumed that the rate of increase in pulmonary complications changes with the pressure. It also assumes this change is non-linear. This model shows how probability of complications increases at different levels of PIP for differing periods of time.

Two different models were created one including an additional coefficient, b_3 for DLCO. When adding the DLCO term the model performed worse in terms of pseudo-R squared, AIC and BIC. This is likely because the dataset contained patient pairs matched to DLCO. Therefore, the model without DLCO was used for further investigation. Predicted probabilities of PPCs were compared for dataset that the model was trained on. It was also compared for the complete dataset 3 including 3 more PPC patients and 131 more non-PPC patients. Results show separation on the boxplots and a Mann-Whitney U-test confirms a difference of means between these two groups. Additionally, a logistic regression was run of pulmonary complications using both predicted probabilities of PPCs and the max peak inspiratory pressure. This model showed that the max PIP was no longer a significant predictor when using the predicted probability from the exponential model. The exponential model's probability of pulmonary complications was a significant predictor. This suggests that the exponential model better describes how pressure and length of time interact to increase the probability of a pulmonary complication. This strengthens the argument that considering heterogeneity of the magnitude and time length of pressure exposure is important to prediction of PPCs. A limitation of this test is that some of the data in the logistic regression model was used as training data for the exponential model.

5.5.3 Placing PIP findings in context

Multiple observational studies in the operating room report that higher driving pressure (defined as plateau pressure – PEEP) is associated with worse postoperative pulmonary outcomes [58],

[59], [60], [62]. Because plateau pressure was unavailable in our dataset, our primary analyses used peak inspiratory pressure (PIP) as the exposure. However, when remodelling using a modified driving pressure calculated from peak inspiratory pressure in a sensitivity analysis, we observed a similar relationship which can be seen in the appendix.

Prior work typically summarizes ventilation with case-average metrics, for example, average DP throughout the surgery. As discussed earlier, averaging does not allow us to consider non-linear relationships and can dilute brief periods of high pressure that may be most injurious, which may help explain why randomized trials targeting lower average DP have not consistently reduced PPCs [61], [63]. In contrast, our results indicate a non-linear pressure–time relationship. Higher airway pressures confer disproportionately greater risk, and risk accumulates with the duration of exposure. Thus, while our findings align with prior literature in showing that increasing airway pressure increases PPC probability, they further suggest that how long a patient is exposed to a given pressure materially modifies that risk, with the marginal risk per unit time increasing at higher pressures.

5.5.4 Limitations of peak inspiratory pressure as a metric

From the results found in this study PIP appears to be a meaningful predictor of whether a patient undergoing one lung ventilation will have a pulmonary complication. This could be intuitively interpreted as high pressures causing stress or strain to the lungs through some barotrauma like action. However, there are some limitations to using PIP and difficulties with interpretation that will be discussed here. The first is a problem with cause and effect. It is possible that patients who were delivered respiratory cycles with higher PIP required this for adequate ventilation due to poor respiratory function. Therefore, a confounding variable is that

patients who had high PIP likely had poor respiratory function necessitating higher PIP and putting them at risk for pulmonary complications because of the poor respiratory function. On the other hand even when controlling for DLCO along matched pairs patients with pulmonary complications still had higher PIP.

Another major consideration and limitation of discussing PIP in this entire study is that during PCV we are not able to conclusively determine pressure exposure to the lung. This is because the PIP setpoint only sets a maximum pressure for the lung to inflate to, if the inspiratory time is not long enough the pressure in the lung will not reach the PIP setpoint. If the airway flow does not descend to zero by end of inspiration as discussed in a previous section (2.2.4.2), we know that the pressure in the lung (PLung) is less than PIP. The problem is that we don't know how much less PLung is, (a potential method of estimating lung pressure during PCV is discussed in the Appendix see: *Estimation of Plateau Pressure under nonzero flow conditions*). Therefore, when using PCV we can only say that PLung is less than or equal to PIP. Therefore, when comparing two patients at the same PIP setpoint we cannot be sure they had the same PLung and therefore we cannot be sure of their exposure.

5.6 Limitations of tracking Post-Operative Pulmonary Complications

One of the challenges of both practicing and determining safe ventilation practices is the absence of intraoperative signs of damage. Our primary outcome of interest indicating that damage has been done is the development of post-operative pulmonary complications (PPCs). However one of the limitations of this work is that PPCs were all treated equally. PPCs have several categories and levels of severity associated with them[27], [28]. However, due to low sample sizes this variation was not incorporated, it was instead treated as a binary outcome.

Determining a metric that represents damage done to the lung and could be tracked during the process of ventilation would be extremely beneficial to both clinicians and researchers trying to determine the cause of this damage. Some of the work during this thesis attempted to approach this problem both through drift in the K-factor which can be seen in the appendix and TV-Drift.

5.7 TV-Drift Investigation

5.7.1 Comparing tidal volume drift for matched pairs

Results from this study showed that the range of tidal volumes experienced by the patients differed whether they were complication patients or non-complication patients. In addition to this the flow signals of patients with pulmonary complications were visually inspected to change without changes made to PCV ventilation settings (PIP, PEEP, Ti). The observed changes in flow signals closely resembled those described in a study referenced in section 2.2.3.1. This similarity suggests that alterations in AWF may indicate a change in compliance. Consequently, it was hypothesized that these observations could reflect underlying changes in lung properties. The TV-Drift statistical test was then designed to test tidal volume change in these static ventilation parameter periods and compare them between matched pairs. These results suggest that the tidal volume tends to increase despite static ventilation parameters more often in the patients who had pulmonary complications than with those who did not.

If we infer this to mean that the compliance is increasing this seems to be a strange result. Increasing lung compliance or lung recruitment is generally considered to be a good thing, so it is strange that in these results tidal volume seems to increase more often in the patients with pulmonary complications. One explanation could be that what appears to be an increase in compliance or lung recruitment is instead some damage being caused to the lung that is causing it to accept higher tidal volumes. One may hypothesize of a stretch related injury that causes the

lung to only appear to increase its compliance. This cannot be determined from the results of this statistical test and should be explored further. This would require validation with assessment of tissue and blood based biomarkers of stretch-related injury in the tissues collected from these patients intra-operatively as well as cell based in vitro models and in vivo experimental animal models.

5.7.2 Normalized or magnitude TV-Drift

One thing that may be noticed about the results section for TV-Drift comparison is that two separate results are presented. These are the results when comparing “normalized TV-Drift” and “magnitude TV-Drift”. The reason for both being included is that it is difficult to determine which is the more appropriate testing metric.

5.7.3 Rationale for using normalized TV-Drift

Evaluation of TV-Drift involves extracting the longest period of static ventilation parameters from each of the surgeries. The periods that were able to be extracted from the surgeries with pulmonary complications were longer in matched pairs. Since TV-Drift is a parameter increasing with time it seems to add a confounding variable if we do not account for the different lengths somehow. To account for this the TV-Drift was normalized to the length difference in the matched pairs.

5.7.4 Rationale for using magnitude TV-Drift

A counter argument could be made that although it seems appropriate to normalize the TV-Drift we also know that time should have some effect. Assume that TV-Drift is a measure of some damage to the lung per unit time. If two patients were ventilated under conditions that caused TV to drift with respect to time at the same rate and that one patient were ventilated under these conditions for double the length. Interpretating this as a rate of damage we are more interested in

the total damage that was done rather than the rate of the damage when predicting pulmonary complications.

5.7.5 TV-Drift limitations

More limitations are related to the calculation of TV-Drift and the method of selection for the static periods. Since the ventilator parameters in these surgeries are heterogeneous some surgeries sometimes have only relatively small periods where they are all static. The static periods also differed in length along matched pairs. This could cause some confounding in the results, especially related to the discussion in a previous section about whether or not to normalize the TV-Drift. In addition to this the periods extracted and compared along matched pairs may come from different relative time points (beginning, middle, end) in the surgery.

5.7.6 PIP correlation with TV-Drift magnitude

To start to investigate the causation it was hypothesized that the PIP setpoint during the static period may have caused the hypothesized lung stretch and consequent tv-drift. It was shown that PIP during the extracted period was higher across matched pairs. However, the PIP during the extracted static ventilation period was not correlated with TV-drift.

However, in order to take into account not only the magnitude of the pressure but also the time the patient was exposed to this pressure and the patients' DLCO the exponential model proposed in a previous section was used. The magnitude of TV-drift was found to be correlated with this model's estimation for probability of PPCs. The probability estimate was used here to imply damage done. Therefore, according to these results, the damage estimation from the exponential model correlates with TV-Drift better than PIP magnitude alone. The exponential model again

seems that it is able to provide better explanation of the observations, albeit, with somewhat low explanation of the variance

5.7.7 Limitations of TV-Drift regression

We should take some caution when using this model because it has not been verified on a larger sample size. In addition to this, the exponential pressure model was trained on entire surgeries and not subsections. However, the output of the model should still represent the risk of complication posed by the period of surgery analyzed it only assumes that this is the entire surgery when making its prediction.

The R-squared value is also very low indicating low explanation of variance. In addition to this as discussed previously magnitude of TV-Drift is correlated with length of time. The exponential pressure model also uses length of time to calculate a probability of PPC. It is intuitive that damage should be linked to time

Chapter 6: Concluding Remarks

6.1 Conclusion

This thesis set out to explore the predictive power of various ventilatory parameters during one lung ventilation, with a particular focus on peak inspiratory pressure (PIP), tidal volume (TV) and drift in tidal volume (TV-Drift). It explored their relationship with post-operative pulmonary complications (PPCs) in patients undergoing lung surgery. Another focus of this thesis was highlighting the variability of ventilation parameters during surgeries. To fully understand relationships between ventilatory parameters and PPCs there must be consideration past just summary metrics such as median or mean. Because by using this metric the assumption made is that risk of damage increases linearly with time when this may not be the case.

Finding that the maximum PIP was a better predictor than the median suggests that high pressure portions of the surgeries were disproportionately more dangerous than lower pressure portions.

Following these results, the study introduced an exponential pressure damage model that incorporates both the magnitude of PIP and the duration of pressure exposure. This model had higher predictive power than just using the maximum PIP when predicting pulmonary complications and the observed tidal volume drift (TV-Drift). These results highlight the importance of considering both pressure intensity and exposure time in assessing the risk of lung injury during OLV.

These results underscore the need for careful management of ventilation settings during lung surgery, particularly in minimizing PIP to reduce the risk of PPCs.

TV-Drift emerged as a potential intraoperative indicator of lung injury. The study found that patients who developed PPCs often exhibited greater TV-Drift under static ventilation settings.

Increasing TV under static ventilatory parameters suggest underlying changes in lung compliance that could potentially be damaging. However, the exact nature of this relationship remains unclear and warrants further investigation.

Despite the promising results, there are limitations, including the small sample size and the challenges of accounting for variability in static ventilation periods across surgeries.

Additionally, the modest explanatory power of the models indicates that further research is needed to refine these findings and explore their clinical applications.

In conclusion, this thesis contributes to the field of perioperative care by highlighting the complexity of ventilatory exposure and its impact on lung injury. The insights gained from the analysis of PIP and TV-Drift offer potential avenues for developing more sophisticated and individualized lung-protective strategies during thoracic surgery. Further research should aim to

validate these findings and explore the use of TV-Drift as a real-time indicator of lung injury, ultimately improving patient outcomes and reducing the incidence of PPCs.

6.2 Future Works

The findings of this thesis open several avenues for future research, particularly in the areas of ventilatory management during thoracic surgery and the real-time monitoring of lung injury.

While this study has provided insights into the predictive power of peak inspiratory pressure (PIP) and the potential of tidal volume drift (TV-Drift) as an indicator of lung injury, further work is needed to validate and extend these findings.

6.2.1 Better Pressure Measure

As discussed in this paper, PIP only limits plateau pressures and is not a good measure of alveolar pressures. Further research working with either plateau pressure measurements or approximations for transpulmonary pressure through use of esophageal balloons would increase our ability to accurately describe exposure and likely the risk of PPCs.

6.2.2 Validation of the Exponential Pressure Model

The exponential pressure damage model introduced in this thesis has shown promise in predicting post operative pulmonary complications (PPCs) by incorporating both the magnitude and duration of PIP exposure. Future research should focus on validating this model with better pressure measurements as discussed above and with larger populations.

6.2.3 Further Exploration of TV-Drift as a Biomarker

TV-Drift has emerged as a potential intraoperative biomarker for lung injury, yet its precise role and significance require further investigation. Future research should aim to better understand the mechanisms underlying TV-Drift, particularly the relationship between TV-Drift and

changes in lung compliance. Research should be done to investigate possible lung-stretch related biomarkers in patients who experienced TV-Drift.

Future analysis of surgeries where ventilatory parameters are static for the entire duration would greatly increase interpretability by negating the difficulty of extracting and comparing partial static periods.

6.2.4 Exploration of Alternative Biomarkers

While TV-Drift shows potential, it is essential to continue exploring other biomarkers that may offer complementary or more sensitive indicators of lung injury. Drift in Bachofen-Hildebrandt K-Factor could be a robust method of tracking changes in lung properties. This was unable to be fully explored in this study due to difficulties in with interpretation of PV-Loops during PCV. However, still showed some results that would be beneficial to explore in more detail in a large population of patients ventilated in VCV mode where PV-Loops are more interpretable. It would be even more beneficial to collect data from patients ventilated with an esophageal balloon. This would allow assessment of PV-loops using transpulmonary pressures.

6.2.5 Development of Real-Time Monitoring Tools

The integration of TV-Drift and other dynamic ventilation parameters into real-time monitoring tools represents a significant area for future work. Such tools could enable clinicians to detect and respond to lung injury as it occurs, potentially preventing the progression of PPCs.

Developing algorithms that can continuously analyze ventilation data and provide actionable feedback during surgery would be a major advancement for intraoperative care.

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Appendix

Additional Features and Data Processing Functions

Plateau pressure from VCV AWP

Plateau pressure (PP) is the AWP measured when AWF is zero. The absence of flow eliminates the pressure drop due to resistance. This means that the AWP measurement represents the alveolar pressure. This has high clinical relevance as it is the pressure within the alveoli that has implications for damage.

During VCV plateau pressure is the pressure reached during the inspiratory pause at the end of inspiration. This gives the signal the characteristic plateau shape and can be found by processing an AWP signal with a python function. This is done using a similar algorithm to the alignment function in Methods chapter. The first and second derivative of the pressure signal are found and masked to only include values where the first derivative is negative. Then `find_closest_local_max` function is used to find the largest local max in the second derivative close to the most negative slope point in the first derivative. This represents the point on the pressure curve that is most concave down and closest to the point in the pressure curve with the most negative slope. The part of the pressure curve with highest negative slope should be halfway in-between the transition from end inspiration to beginning of expiration, therefore we cannot use this point as the pressure has already dropped too much. We need to find the point in the pressure curve where it is just starting to transition from end inspiration, this is the point of maximum concave down behaviour. The result of the plateau pressure finding function is demonstrated on a VCV signal in Figure 6.1.

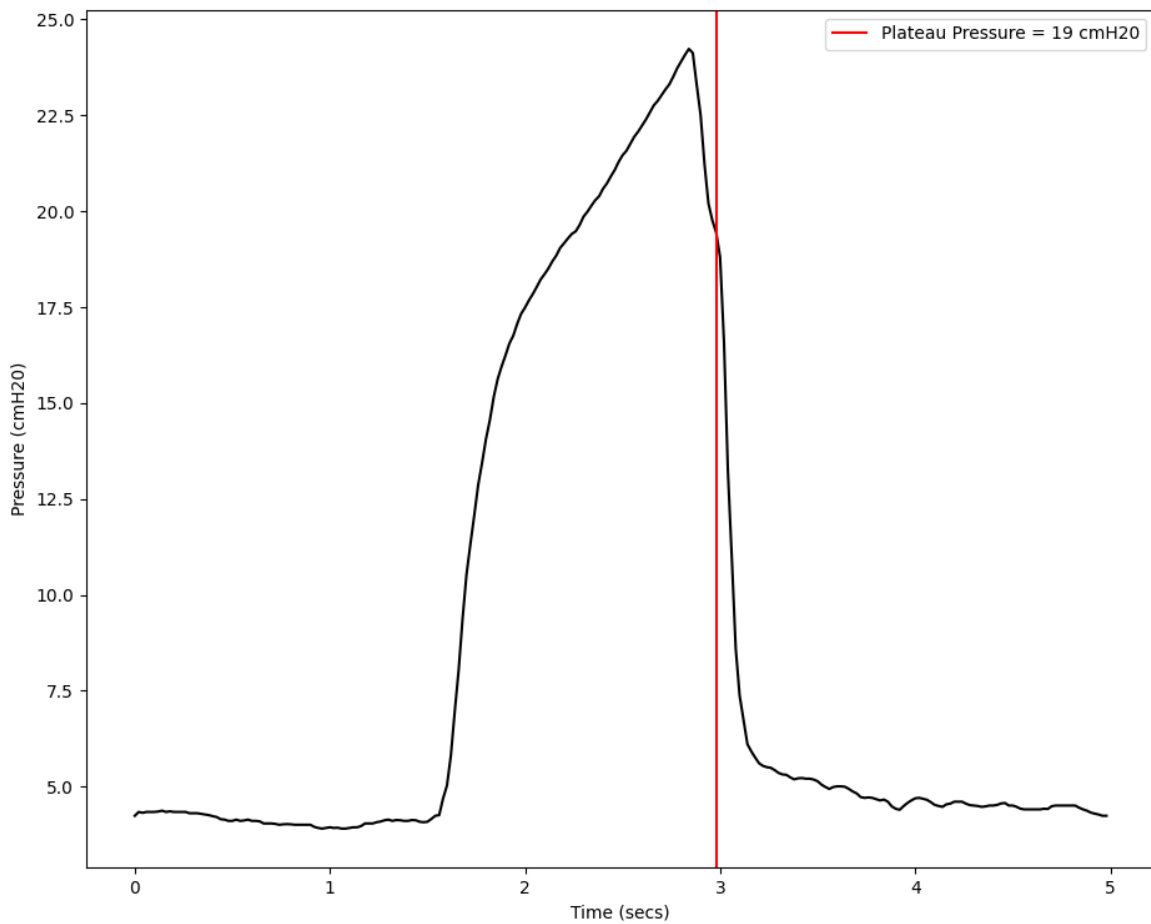


Figure 6.1: Figure shows the extraction of plateau pressure (PP) from an AWP signal during VCV. The red line indicates the position of the PP.

Start of expiration and end of inspiration flow

During PCV ventilation, if flow at the end of inspiration is zero then P_{insp} can be used as an approximation for the pressure within the lungs or P_{Plat} . However, if flow does not reach zero then TI was not sufficient for pressures to equalize, this was explained in detail in the background (see: Airway Pressure in PCV). Therefore, this is a meaningful feature to determine whether this approximation can be used.

Additionally, if TI is not sufficient it is hypothesized that the relative magnitudes of flow for last inspiration and start of expiration flow could be used to approximate the pressure within the lung during PCV under certain conditions.

These values are derived from the flow signal and the finding inspiration and expiration periods function is utilized. Once these periods are found the last inspiration flow value was found by averaging the last 100ms of the inspiration period as shown Figure 6.2.

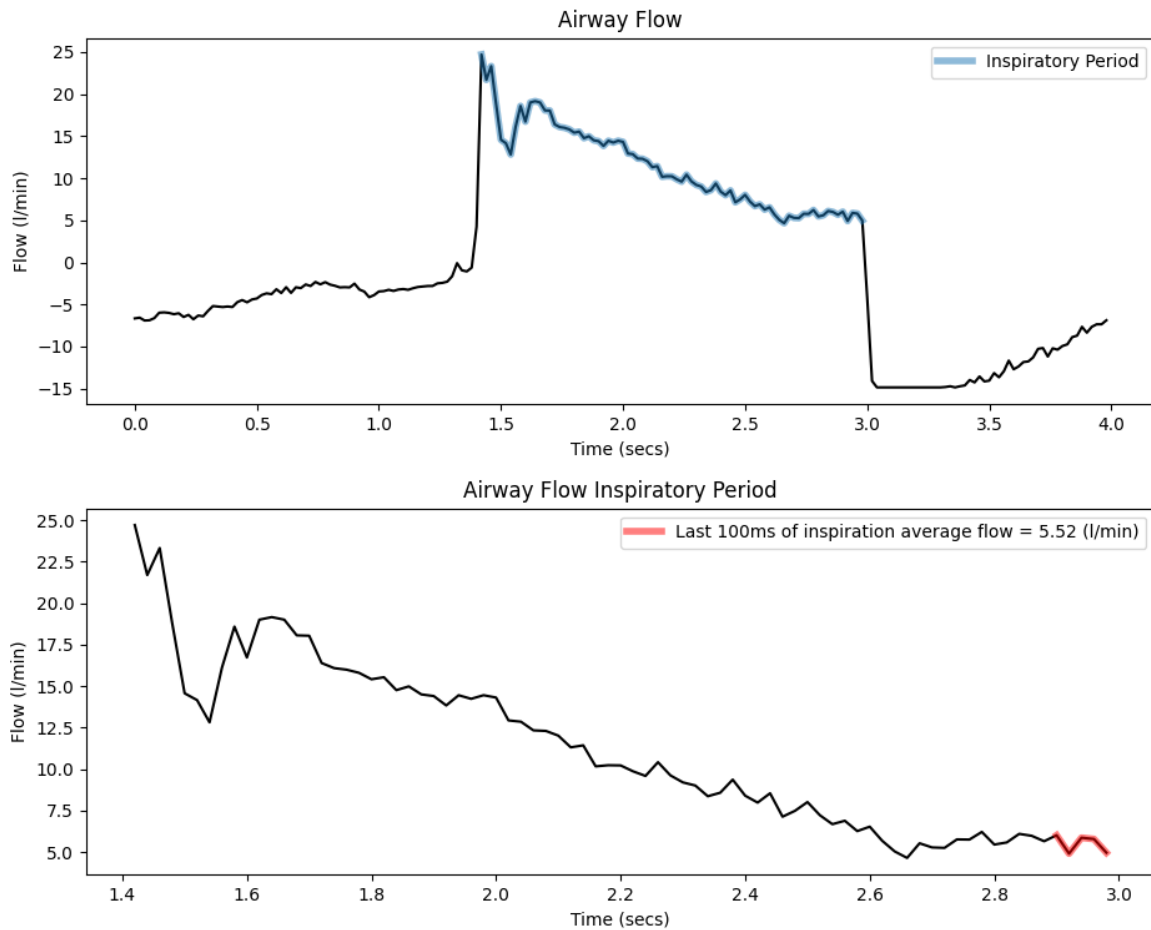


Figure 6.2

The first expiratory flow value was found by averaging the 5 lowest flow values since expiration is a passive process with naturally descending flow pattern the lowest values should correspond to the values at the start of expiration, this is shown in Figure 6.3.

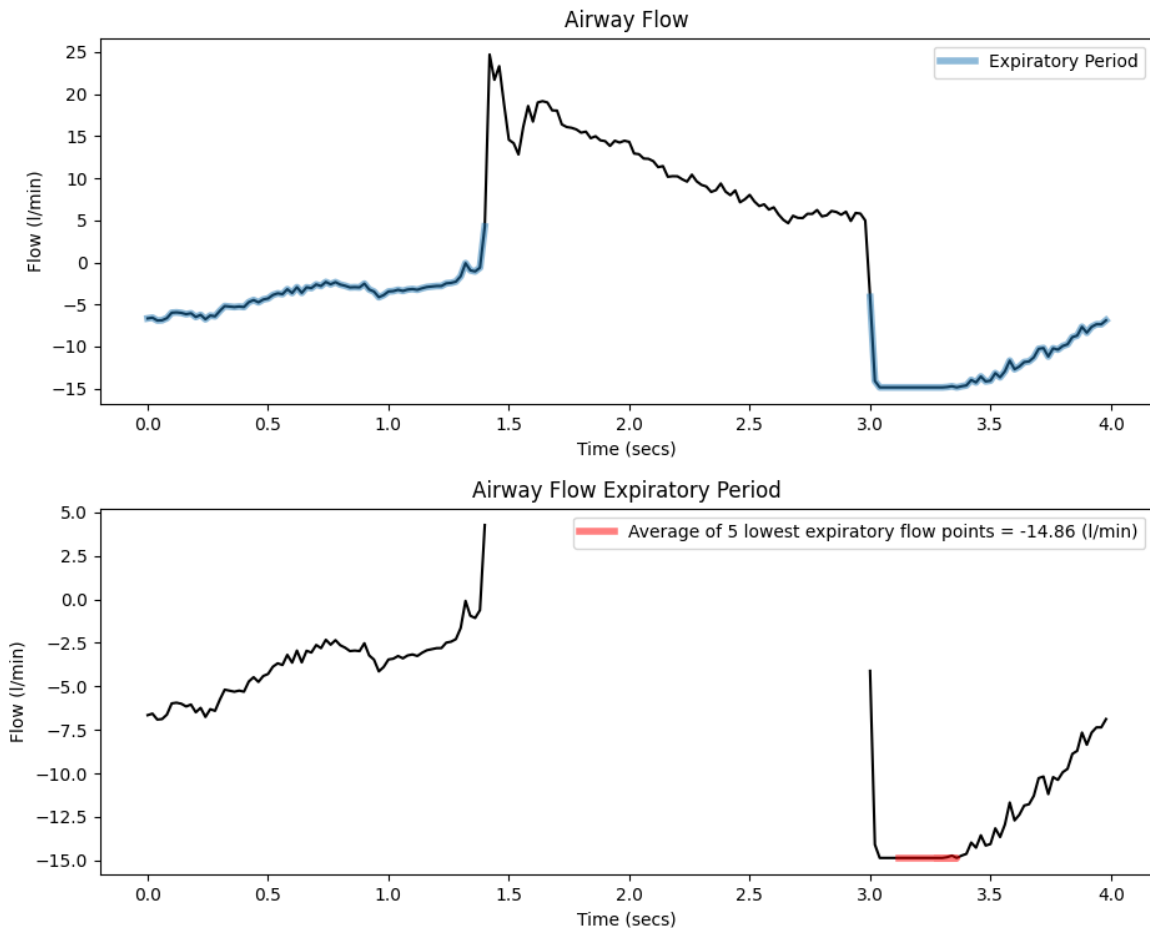


Figure 6.3

Estimation of Plateau Pressure under nonzero flow conditions

If flow does not descend to zero at the end of inspiration during PCV we cannot obtain a plateau pressure value in the standard manner. We may be able to still obtain an estimate for plateau pressure if we assume that instantaneous change in airway resistance is small between the last instant of inspiration and the first instant of expiration.

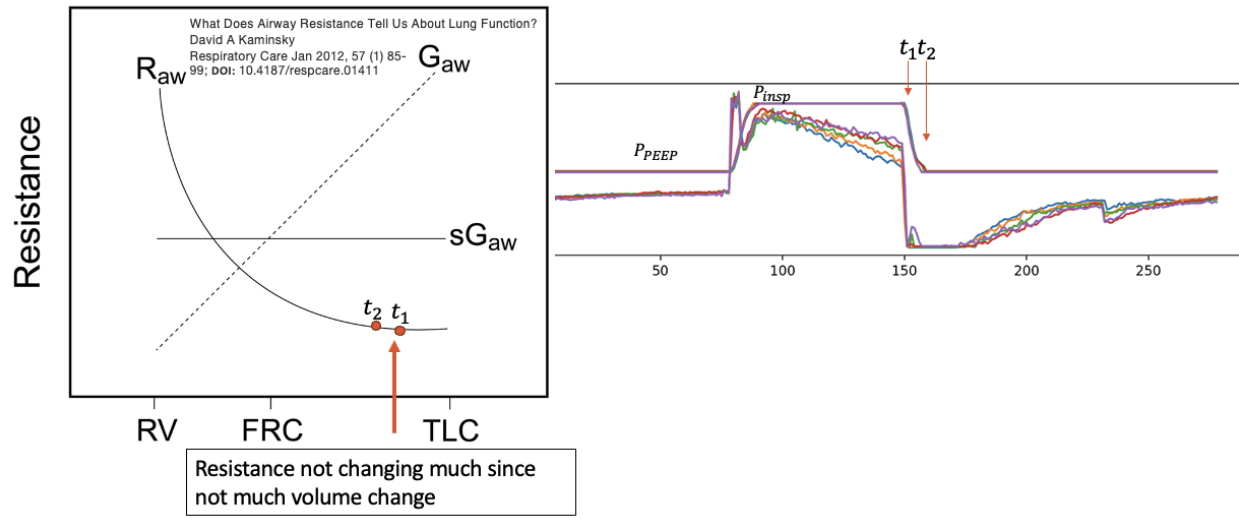


Figure 6.4

Referencing Figure 78 we can see that although resistance is variable with lung volume it may not drastically change between two points of very similar volume. Note that counter to this we know that patients with COPD have very different resistances to inspiratory and expiratory flow. However, perhaps this difference is less drastic at this specific point between t_1 and t_2 in the figure. It is proposed that through the following equation substitution you could obtain an estimate for P_{Lung} .

$$@t_1 - R_1 = \frac{P_{insp} - P_{Lung}}{f_1}$$

$$@t_2 - R_2 = \frac{P_{PEEP} - P_{Lung}}{f_2}$$

Assuming $R_1 \cong R_2$ and solve:

$$P_{Lung} \cong \frac{P_{PEEP}f_1 - P_{insp}f_2}{f_1 - f_2}$$

Since during PCV ventilation the generated flow is dependent upon the pressure difference between AWP and lung pressure the relative magnitudes of flow at the end of inspiration and

beginning of expiration could give some insight for how close lung pressure is to PIP setpoint during PCV.

Bachofen and Hildebrandt Shape Factor

The shape factor is defined as:

$$K = \frac{A}{\Delta P * V_T}$$

Area A is the area bounded by the lungs PV loop during a respiratory cycle, this is the work imparted on the system due to the elasticity of the lungs some of the energy imparted during inhalation is returned during exhalation. Area ($\Delta P * V_T$) represents the maximum possible energy dissipation assuming an entirely plastic system, a system with no elasticity. Therefore, “K is the fraction of that maximum that is actually dissipated. As such, K is bounded such that $0 \leq K \leq 1$, with the lower bound corresponding to a conservative perfectly elastic system and the upper to a dissipative perfectly plastic system.” [64], [65]

“This constant changes very little with lung volume, lung size, tidal volume, or animal species. It also approximates dynamic data obtained in humans.” [64], [65]

K constant appears to be a robust measure of energy dissipation properties of lung tissue. It is hypothesized that as damage is done to lung tissue, this may be reflected in the K constant for the ventilated lung. K should be calculated from a PV loop with transpulmonary pressure and lung volume.

K was calculated for matched pairs who were ventilated with PCV. Trends in K were compared between matched pairs and patients with PPCs were shown to have K fraction increase more than patients without PPCs, results shown in Figure 79. These results should be heavily scrutinized and were not included in the main results section because K constant was shown to be calculated using PV loops with transpulmonary pressures. In this test it was calculated using

AWP measurements during PCV. PV-loops have troublesome interpretation during PCV ventilation because the AWP measurement is controlled by the ventilator and not as a result of lung properties.

Nevertheless, it is possible that the K factor is detecting variations rise time as the ventilator pressurizes the system.

Whether or not the K factor results from this PCV statistical test are meaningless it does not disprove the theory. It is recommended that changes in K factor be investigated with proper AWP measurements estimating transpulmonary pressures such as using an esophageal balloon. If unable to obtain esophageal balloon AWP during VCV ventilation may provide better approximations for K factor as well.

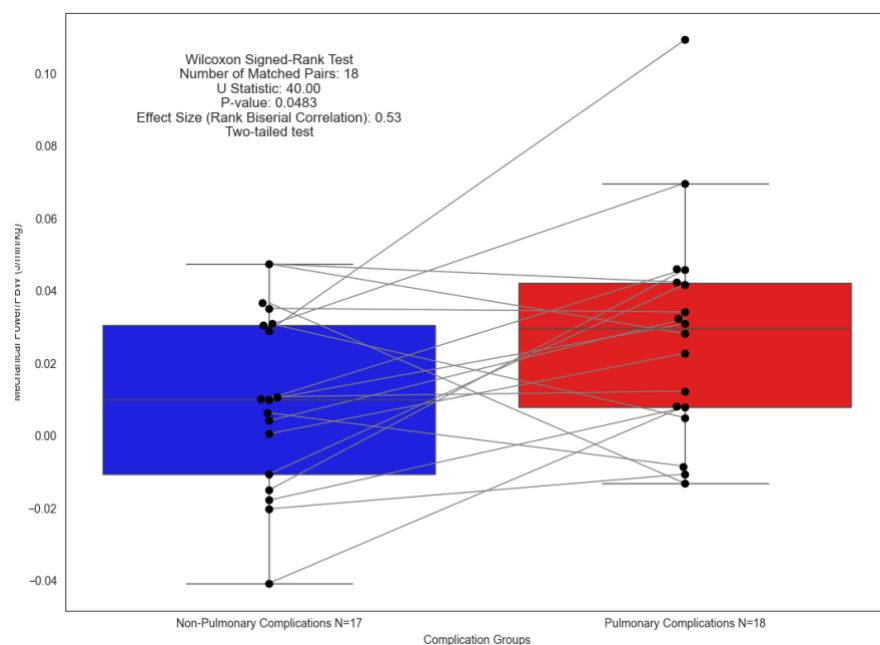


Figure 6.5

Exponential pressure modelling with modified driving pressure

Modified driving pressure calculated as (PIP-PEEP) has been shown to highly correlate with actual driving pressures [57], [58], [59], [60]. An exponential pressure model was derived in the same fashion as done for PIP but using modified driving pressure.

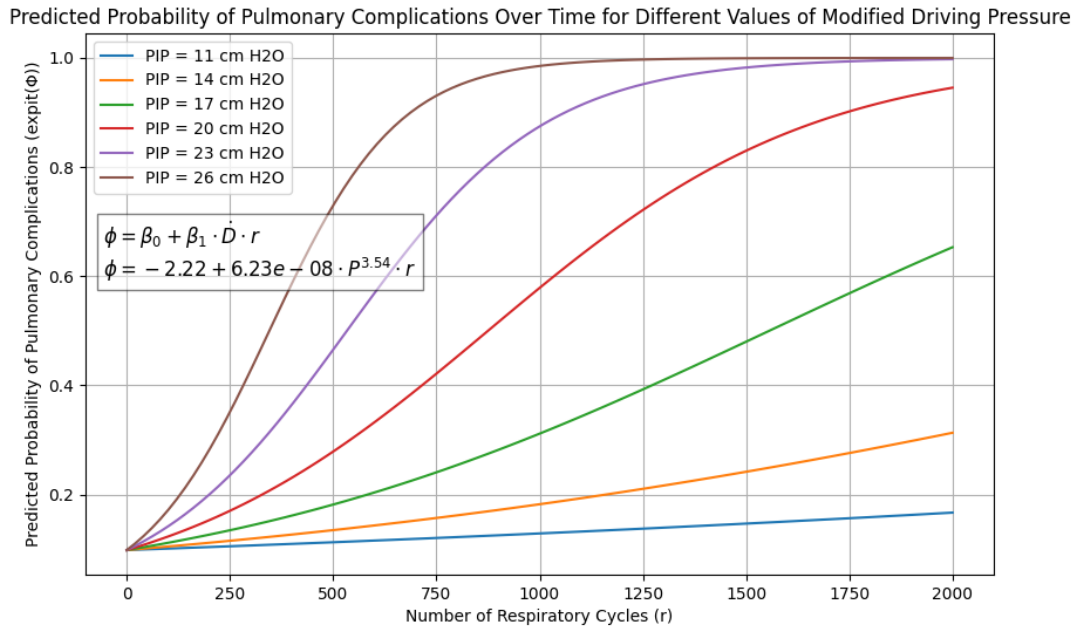


Figure 6.6 Predicted probability of pulmonary complications over time (number of respiratory cycles) for different modified driving pressure (DP) values, ranging from 11 cmH2O to 26 cmH2O. The model incorporates all DPs the patient was exposed to and the duration of exposure, assuming an exponential increase in the rate of damage with respect to the number of respiratory cycles at each pressure level. The probability of complications increases more rapidly with higher DP values, as shown by the steeper curves for higher pressures. The equation inset represents the relationship used to model these probabilities, considering both the magnitude of pressure and the time of exposure.

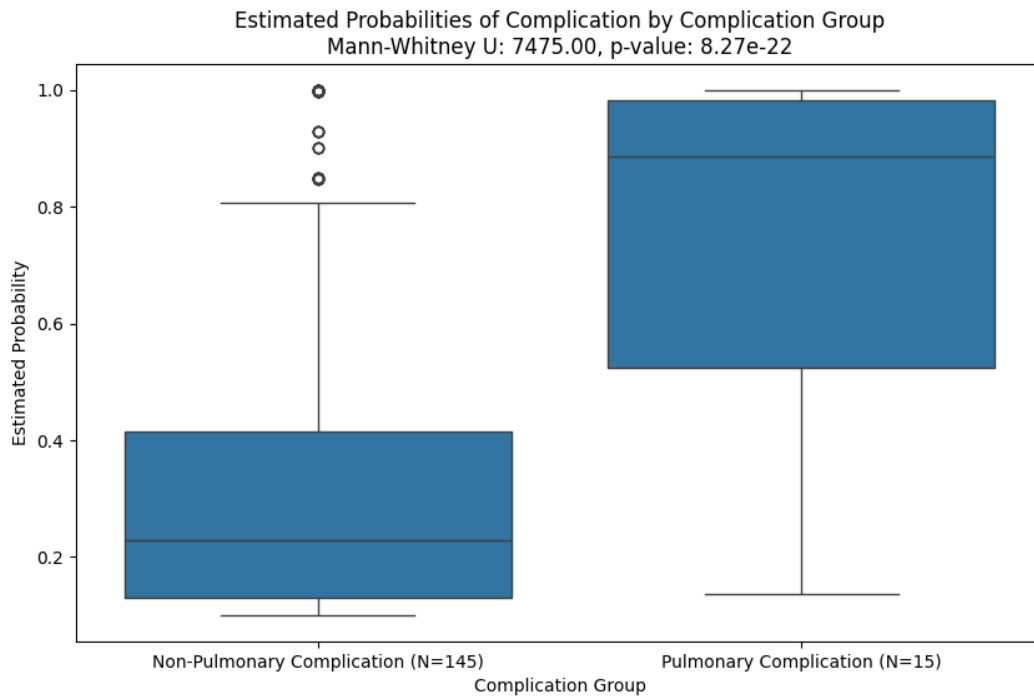


Figure 6.7 Box plot showing the estimated probabilities of pulmonary complications, grouped by complication status, including both the original training data and additional patients. The left box represents patients without pulmonary complications ($N=148$), while the right box represents patients with pulmonary complications ($N=18$). The plot demonstrates that the model continues to predict higher probabilities of complications for the pulmonary complication group. The Mann-Whitney U test result ($U = 6408.00$, $p\text{-value} = 2.94e-21$) indicates a statistically significant difference between the groups, supporting the model's robustness in distinguishing between patients with and without pulmonary complications, even with the inclusion of new data.