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Automated Detection of Incomplete Exhalation as an Indirect Detection of Auto-PEEP on Mechanically Ventilated Adults

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AUTOMATED DETECTION OF INCOMPLETE EXHALATION AS AN INDIRECT DETECTION OF AUTO-PEEP ON MECHANICALLY VENTILATED ADULTS

A Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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Abstract

AUTOMATED DETECTION OF INCOMPLETE EXHALATION AS AN INDIRECT DETECTION OF AUTO-PEEP ON MECHANICALLY VENTILATED ADULTS

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Auto-PEEP is auto positive end-expiratory pressure due to excessive amounts of alveolar gas produced by sustained recurrent incomplete exhalation. Incomplete exhalation occurs when the exhaled breath never reaches a flow rate of 0 L/min. The objective of this dissertation is to develop an automated detection system of auto-PEEP through incomplete exhalation as revealed by ventilator graphics for mechanically ventilated adults. Auto-PEEP can cause adverse effects if allowed to linger and if not quickly identified. An automated detection system will be instrumental in helping to quickly identify auto-PEEP. A computerized algorithm was developed to detect incomplete exhalation based on the following three parameters:1) F_{oi}, was used to represent the value of the flow at the onset of inhalation, 2) ΔT, was used to represent the value

of time difference between onset inhalation to the 0 L/min mark, and 3) slope threshold, a value set for the slope of change of flow over ΔT. Optimum parameters of the algorithm were achieved for F_{oi} = -3 L/min, ΔT = 0.2 s, and slope threshold = 90 L-s/min. A novel data set was introduced to validate the algorithm, yielding no significant difference in true positive rates (t = 1.5, df = 12.402, p-value = 0.1408) and false positive rates (t = 1.9, df = 16.765, p-value = 0.0725) as outcomes for two-tailed t-tests comparing the novel and old data set. To determine the relationship between auto-PEEP and detection of sustained incomplete exhalation, a correlation of a linear model of the novel data set between auto-PEEP and the percentage of incomplete exhalation detection out of the existing breaths (index) was investigated. A linear model should interpret the index value that corresponds to significant auto-PEEP presence; unfortunately, no significant linear model was found between incomplete exhalation index and auto-PEEP ($F_{1,62}$ = 1.67, p-value = 0.2010). However, there was a relationship between the intrinsic PEEP values and the incomplete exhalation index as functions of time. The automated detection algorithm produced by this work provides a non-invasive method of automatically detecting auto-PEEP.

Chapter 1 Concerning Lungs and Artificial Ventilation

Overview

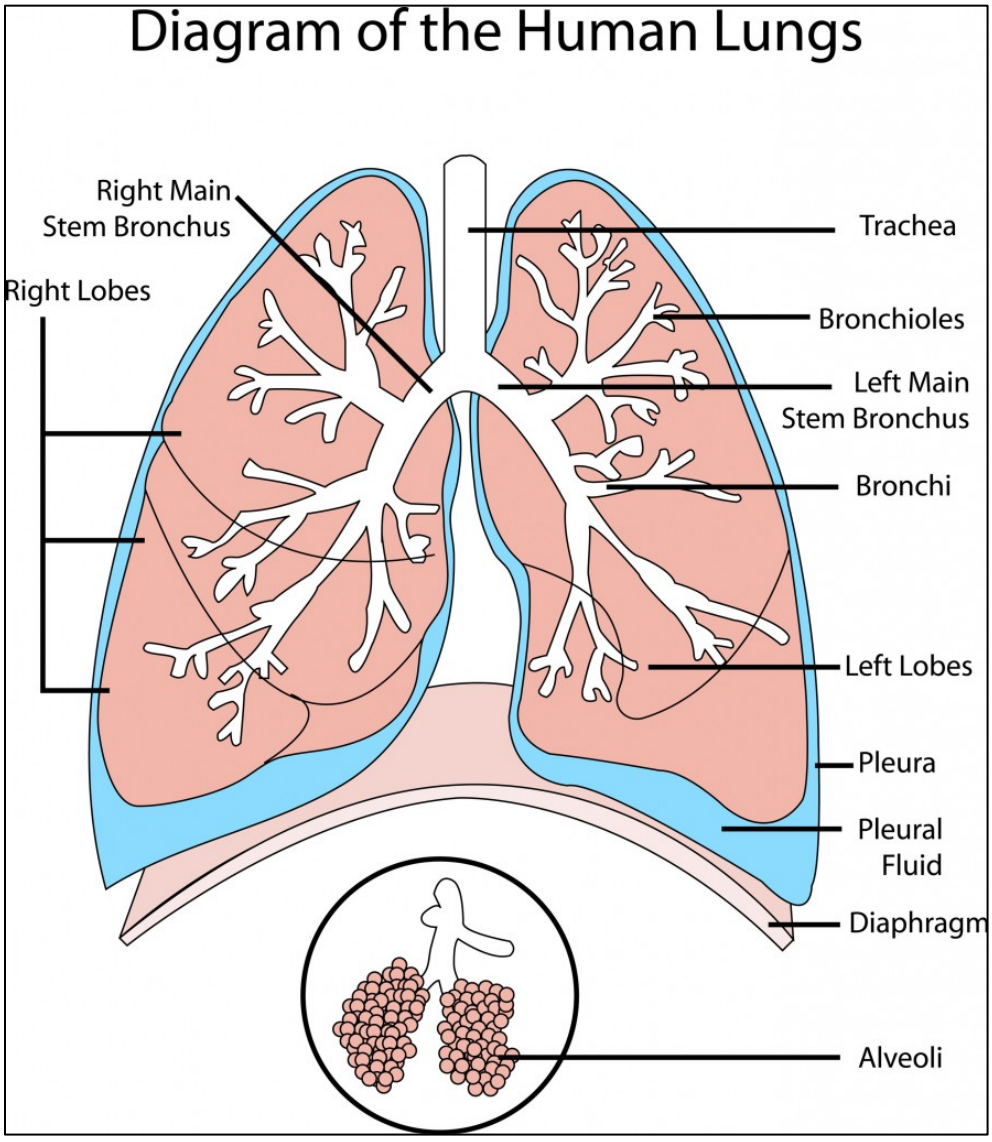
This chapter provides an overview of relevant material pertaining to lung anatomy and physiology. Physiological measurements such as respiratory rate, functional residual capacity, and compliance will be introduced with relevant information pertaining to artificial ventilation included. The function of an invasive mechanical ventilator requiring intubation will be explained along with modes of ventilators and how breath is triggered, delivered and terminated in each different type. The chapter will also cover how asynchrony between patient and a mechanical ventilator occurs and finally auto-PEEP and its adverse effects will be defined.

Anatomy and Physiology of the Lung

Lungs are an essential respiratory organ in humans whose primary function are to deliver oxygen to the blood and removes carbon dioxide. Air is delivered through the trachea into the lungs. Air passes through the trachea then divides into two bronchi that lead to the left lung and the right lung (see figure 1-1). On each side of the lungs, the bronchi divides further into branches of bronchioles and terminal bronchioles branching further into the respiratory zones of respiratory bronchioles, alveolar ducts, and alveoli. Gas exchange with blood occurs only in the respiratory zone. There is no gas exchange with blood in the conducting zone that includes the

trachea, the two bronchi and branches of bronchi. Any space in the lungs with no gas exchange is called the dead space.[1]

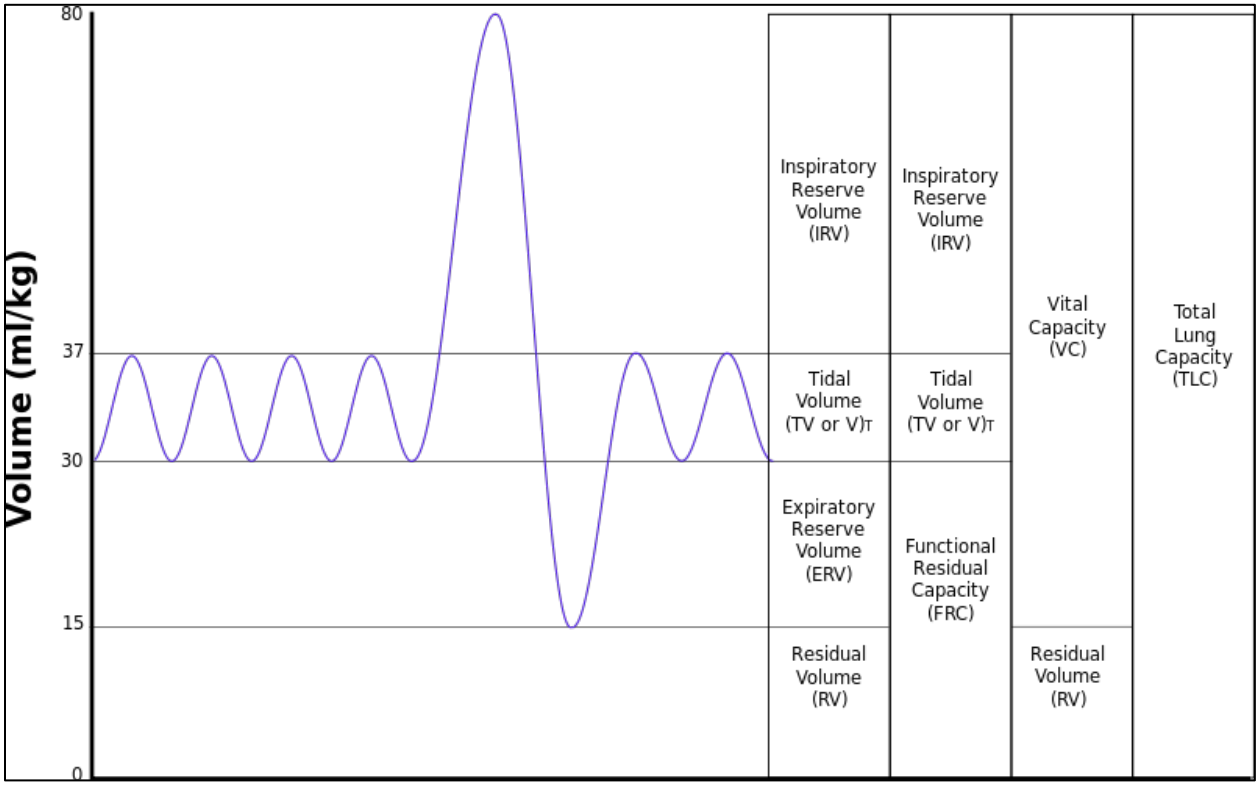
Figure 1-1: Diagram of the human lungs[2]



Lung volume and lung capacity describe the different volumes of a given space in the lungs for a particular function (see figure 1-2). Lung volume can be directly measured but lung capacity must be derived. Lung volume includes tidal volume (TV), inspiratory reserve volume (IRV), expiratory reserve volume (ERV), and residual volume (RV). Lung capacity includes

total lung capacity (TLC), vital capacity (VC), and functional residual capacity (FRC). Tidal volume is the amount of air that is normally inhaled and exhaled without extra effort Inspiratory reserve volume is the maximum amount of air that can be inhaled beyond tidal volume inhalation. Expiratory reserve volume is the maximum amount of air that can be exhaled beyond tidal volume exhalation. Residual volume is the amount of air in the lungs left over after expiratory reserve volume is exhaled. Total lung capacity is the entire amount of air in the lungs when no more air can be inhaled (all lung volumes added together). Vital capacity is the volume of air exhaled when no more air can be exhaled (TLC – RV). Functional residual capacity is the volume of air in the lungs at the end of a tidal volume exhalation (IRV + RV).[1]

Figure 1-2: Lung volumes and capacities[3]



The lungs are a dynamic organ that uses diaphragm muscle contraction to produce enough pressure for air to flow into the lungs for inspiration. Expiration is usually a passive

process, although forced expiration can occur by contraction of the diaphragm muscles – this is how ERV is produced. The pressure and volume relationship is much like a hydraulic equivalent of Ohm's Law, where flow is equal to the change in pressure over the equivalent resistance of gas flow through the airways.[1]

$$F = \frac{\Delta P}{R}$$

The measure of ease in expanding the lungs is called compliance and is equal to the change in volume over the change in pressure.[1]

$$C = \frac{\Delta V}{\Delta P}$$

Elastance is the inverse of compliance. Flow is the change in volume over time, or the first derivative of volume.[1]

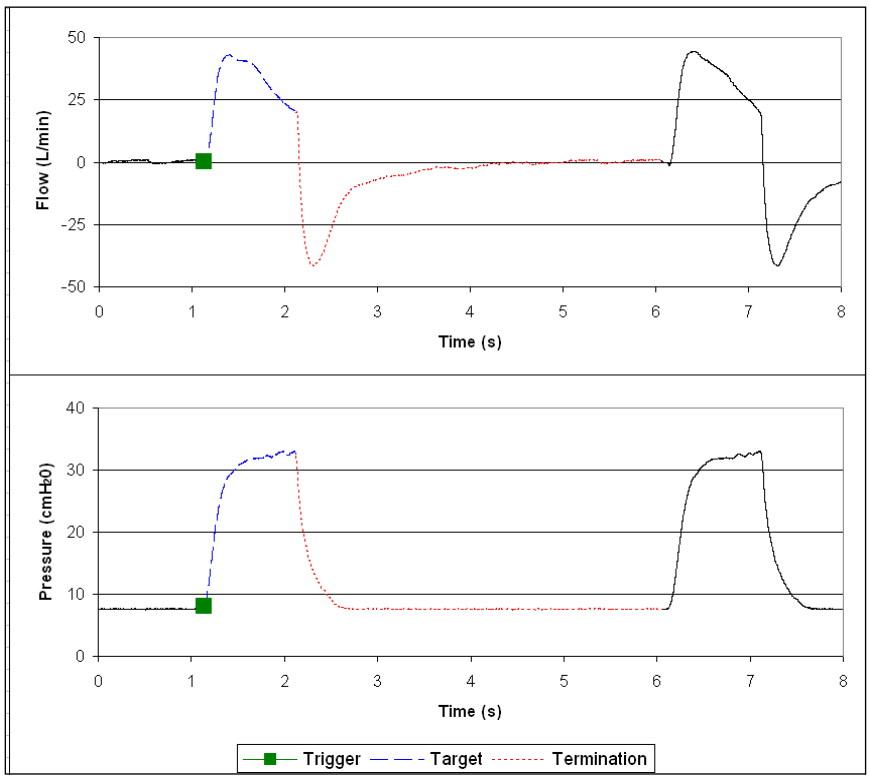
Pathologies such as asthma and chronic obstructive pulmonary disease (COPD) present obstruction in the airway passages. When asthma or COPD exacerbation worsens it may be necessary to provide respiratory support via artificial ventilation. Other serious conditions that may require artificial ventilation include acute respiratory distress syndrome (ARDS) which is a life-threatening reaction to an infection or injury of the lung.[4]

Invasive Mechanical Ventilator

In most cases involving the critically ill, artificial ventilation is delivered using a positive pressure ventilation machine since approximately 40% of patients in critical care units are on mechanical ventilators. There are two types of positive-pressure mechanical ventilators, a mask delivery system that is noninvasive, and an intubation system that is orally or nasally attached via an endotracheal tube and is very invasive. This dissertation focuses on the invasive mechanical ventilator with an endotracheal tube. Patients require artificial ventilation for many reasons such

as respiratory support during and after a surgical procedure/operation or as a result of a traumatic injury. Respiratory support is often required due to pathologies such as asthma exacerbation and respiratory distress. Artificial ventilation provides adequate oxygenation, steady respiratory rate (amount of breaths per minute), and steady tidal volume.[5,6]

Figure 1-3: Trigger, target, and termination sections of ventilator waveform



Because there are many different types of invasive mechanical ventilator with each operating differently, understanding their functions can be simplified by classifying them into the 3T's of breath; trigger, target, and termination (see figure 1-3). The first of the 3T's, trigger, can be defined as a breath that is initiated by patient (utilizing a flow or pressure threshold) or machine (timed). The second of the 3T's, target, can be defined as air supply that can either be volume controlled or pressure controlled. The third of the 3T's, termination can be defined as a breath that is ended by the machine setting or at the patient's demand. Three different ventilator

settings can be used to demonstrate how each of the 3T's can be varied: assist/control (A/C) also known as mandatory breath, pressure support (PSV) also known as spontaneous breath, and synchronous intermittent mandatory ventilation (SIMV). Table 1-1 gives a further understanding of the different mechanical ventilator settings with hypothetical examples. [7]

Table 1-1: Hypothetical Examples of Varying the Drive to Breath, the Number of Patient Inspiratory Efforts, and Clinician-Selected Parameters on Breath Types and Characteristics in Principle Modes of Ventilation. Five examples of ventilator modes are presented. The rate is set at 10 breaths/min for all except the spontaneous mode. Five scenarios are presented in which different numbers of patient inspiratory efforts are made (A, B, and C), there is a reduction in the set rate to 2 breaths/min (D), or pulmonary edema develops €. For the first four scenarios, the expected effect on mandatory and spontaneous breaths is depicted. In scenario E, the effect on tidal volume, V_T and peak airway pressure is illustrated.[7]

Scenarios	Parameters					
	Mode Set Frequency	AC mode (10 breaths/min)/ Pressure	AC mode (10 breaths/min)/Volume	SIMV (10 breaths/min)/ Mandatory PS	SIMV (10 breaths/min)/ Mandatory Volume Support	Spontaneous breathing/PSV
A. Baseline (12 inspiratory efforts/min)						
Mandatory breaths		12 breaths total; mix of controlled and assisted	12 breaths total; mix of controlled and assisted	10 breaths total; mix of controlled and assisted	10 breaths total; mix of controlled and assisted	0
Spontaneous breaths		0 breaths	0 breaths	2 breaths	2 breaths	12 breaths
B. Apnea						
Mandatory breaths		10 controlled breaths; 0 assisted breaths	10 controlled breaths; 0 assisted breaths	10 controlled breaths; 0 assisted breaths	10 controlled breaths; 0 assisted breaths	0 breaths
Spontaneous breaths		0 breaths	0 breaths	0 breaths	0 breaths	0 breaths
C. 30 patient inspiratory efforts/min						
Mandatory breaths		30 total breaths; most assisted since tachypneic	30 total breaths; most assisted since tachypneic	10 total breaths; 0-10 breaths controlled, the rest assisted	10 total breaths; 0-10 breaths controlled, the rest assisted	0 breaths
Spontaneous breaths		0 breaths	0 breaths	20 breaths	20 breaths	30 breaths
D.i set f to 2/min; there are 12 patient inspiratory efforts/min						
Mandatory breaths		12 total breaths, 2 controlled breaths; 10 assisted breaths	12 total breaths, 2 controlled breaths; 10 assisted breaths	2 total breaths; probably all controlled breaths	2 total breaths; probably all controlled breaths	0 breaths
Spontaneous breaths		0 breaths	0 breaths	10 breaths	10 breaths	12 breaths
E. Pulmonary edema develops						
V_T		Decreases	No change	Decreases	No change	Decreases
Peak airway pressure		No change	Decreases	No change	Decreases	No change

A/C mode consists of two types of breath delivery: 1) an assisted breath in which the patient initiates the effort to draw a breath and a machine assists the patient by delivering a breath, and 2) a controlled breath in which a machine delivers the breath without patient effort while being determined by a minimum respiratory that is sey by a clinician or ventilator technician. The assisted portion of an A/C setting is patient triggered, volume or pressure targeted, and machine terminated. While the control portion of an A/C is setting is the same

except for the trigger which is machine triggered (time triggered). A/C setting is mainly used for stabilization of patient. A disadvantage of this setting is when a patient is tachypnic, as this can cause air trapping and respiratory alkalosis.[7]

In the PSV setting the breath is triggered by a patient, air volume is targeted by pressure control and termination is controlled by the patient. This is known as the "comfortable" setting because the patient dictates initiation and termination; however, it is primarily used as an intermediate stage during the weaning of the patient from the ventilator since it requires a stable patient effort. PSV can be harmful to the patient if apnea or lung weakness is present.[7]

The SIMV setting is a combination of both PSV and A/C. The 3T's control for the PSV or A/C in SIMV was mentioned above. A/C setting is set at a minimum respiratory rate with any additional breaths provided by PSV setting. This setting has many options for the patient to breathe but the non-regularity of the breathing pattern can cause discomfort.[7]

Patient-Ventilator Asynchrony

Patient-ventilator asynchrony occurs when any phase of breath is not perfectly matched between the pulmonary system of the patient and the ventilator mechanics of the machine. Asynchrony can occur in any of the 3 T's. Adverse effects of patient-ventilator asynchrony includes the following: patient fighting the ventilator, increase in sedation, greater effort in breathing, muscle damage, ventilation-perfusion mismatching, dynamic hyperinflation, delayed or prolonged weaning, longer ICU stay, or higher healthcare costs. Forty percent of patients requiring intensive care in the US also require mechanical ventilation and nearly a quarter of them experience asynchrony in greater than 10% of respiratory efforts.[6,8,9] The two types of

asynchrony that are the focus of this dissertation are trigger asynchrony and termination asynchrony.[8,10]

Figure 1-4: Ineffective trigger[8]

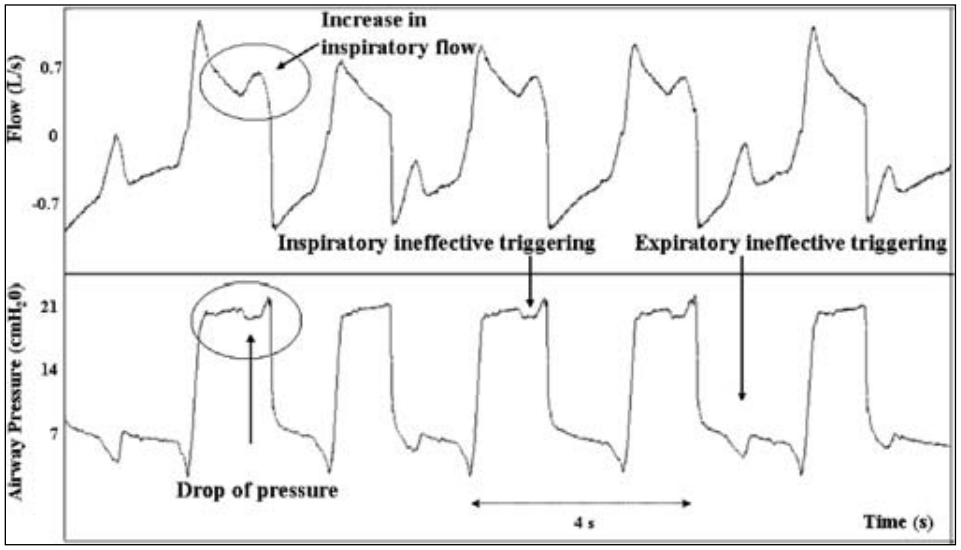


Figure 1-5: Double triggering[11]

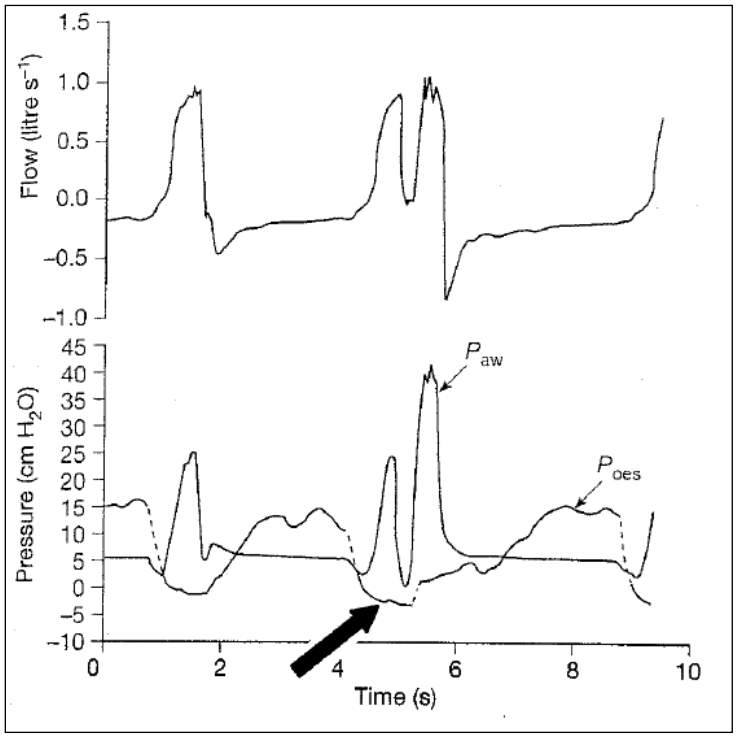
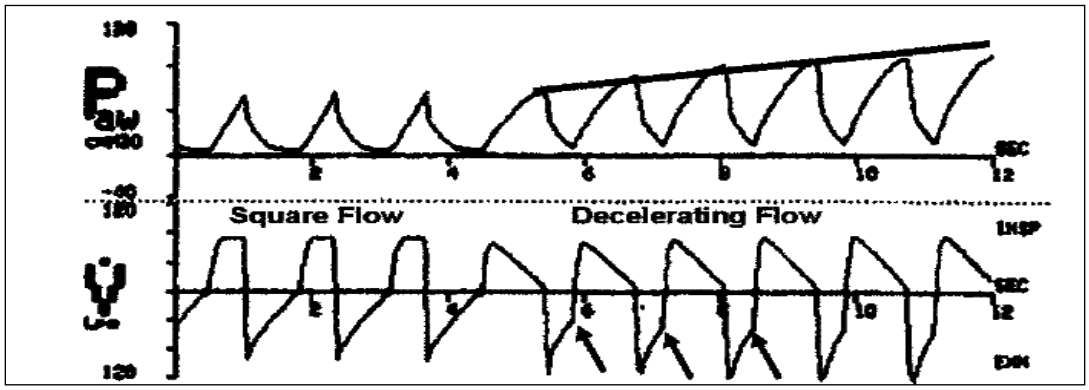


Figure 1-6: Auto-PEEP detection due to premature termination asynchrony. Buildup of pressure (auto-PEEP) is depicted in the pressure waveform (P_{aw}). Incomplete exhalation is detected in the flow waveform indicated by the black arrows ($\dot{V}$). [10]



Trigger asynchrony occurs more frequently than any other type of asynchrony and is easier to identify. Two types of trigger asynchrony are ineffective triggering or failure to trigger and double triggering. Ineffective triggering occurs when a muscular effort to breathe is not followed by a ventilator trigger. This is traditionally shown by a convex flow wave form paired with a concave pressure waveform, as seen in figure 1-4. In double triggering (see figure 1-5) as the name suggests; two breaths that are triggered by the ventilator in close proximity with expiratory time between the two triggered breaths in less than one half of the inspiratory time.[8,11]

One type of termination asynchrony discussed here is premature termination asynchrony. Premature termination asynchrony occurs when the inspiratory time is ended prematurely and breath is not allowed to passively, fully exhale; in other words, there is incomplete exhalation (IE). When incomplete exhalation occurs successively and is sustained, a buildup of pressure called auto-PEEP emerges (see figure 1-6).[10,12]

Origins of Auto-PEEP

The phenomenon of auto-PEEP was recorded as early as 1972 in the form of air trapping in the lungs during mechanical ventilation at rapid frequencies. Air trapping occurs when

inadequate time is given for exhalation due to rapid respirations. Increases in thoracic pressure compensate for the incomplete exhalation to permit expiration of larger volumes in a short time. These are followed by an increase in end-expiratory lung volume. This dynamic hyperinflation of lung volume leads to a pressurization of the alveoli that exceed the atmospheric pressure and hence the advent of auto-PEEP. Auto-PEEP is also known as intrinsic PEEP (PEEPi), and occult PEEP. Auto-PEEP is different from applied PEEP, which is a minimum PEEP value set by mechanical ventilation to open up airway passages. Auto-PEEP is different from total PEEP or global PEEP, which is the total value of applied PEEP and auto-PEEP. [12-14]

Auto-PEEP can occur in the presence or absence of dynamic hyperinflation of the lungs.[14] Blanch et. al suggest that auto-PEEP from dynamic hyperinflation originates from the sequential emptying of slow hypercapnic units since there is a significant correlation between expired carbon dioxide slope, respiratory-system resistance, and auto-PEEP. In the presence of dynamic hyperinflation, auto-PEEP can occur with intrinsic or external factors.[15]

Auto-PEEP caused by intrinsic factor is when expiratory flow limitations/ compressions occur in smaller airways with air-trapping occurring deeper in the lungs. This is most often occurred in patients with chronic obstructive pulmonary disease (COPD). For patients experiencing COPD exacerbations from airflow obstruction and/or anatomical abnormalities, when expiratory effort increases, the results are increases in pleural and alveolar pressure without improving the exhalation flow. This can occur for both flow limitation and passive deflation. An applied PEEP delivered by the ventilator to the patient that matched the auto-PEEP value, as opposed to the usual default value of zero cmH_20, allowed the patient to breathe without increasing the work of breathing. COPD patients are likely to develop auto-PEEP because they

are inclined to have increases in expiratory effort, but they are not the only sufferers from auto-PEEP.[12,14] Bernasconi et al. demonstrated that even for patients without COPD unexpected auto-PEEP occurs up to 35%.[16]

Auto-PEEP caused by extrinsic factor occurs when high respiratory rate or a form of expiratory resistance from the mechanical ventilator equipment such as narrowing of endotracheal tube due to mucus thickening restricts exhalation. An applied PEEP by the ventilator would not help in this case because it would only add more pressure to the expiratory airflow, cascading pressure increase to the airway, thorax, and alveoli. [12,14]

In the absence of dynamic hyperinflation, Mughal et al show that auto-PEEP occurs when there is strong expiratory muscle activity, often with normal or even low lung volumes. This was demonstrated by patients who were actively exhaling and causing pressure gradient between alveolar and central airway. It produced an auto-PEEP without lung distention. [14,17]

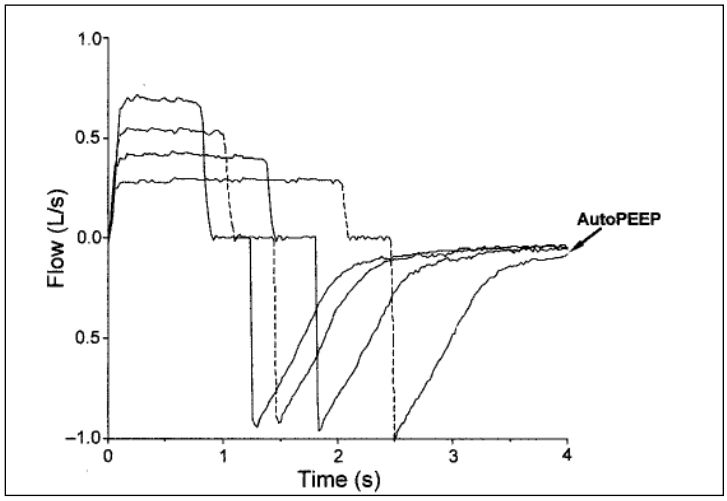
Even though auto-PEEP arising in the absence of dynamic hyperinflation can occur, it is only auto-PEEP arising from dynamic hyperinflation that has been associated with adverse effects. [4,12,14,17] Auto-PEEP that arises from dynamic hyperinflation produces traces of incomplete exhalation that can be detected non-invasively using a mechanical ventilator monitor (ventilator graphic).[12,14,18] On the other hand, auto-PEEP without dynamic hyperinflation would require detection beyond looking at ventilator graphic.[14,17] For this reason, this dissertation will narrow its focus on auto-PEEP with the presence of dynamic hyperinflation.

Auto-PEEP and Incomplete Exhalation

Incomplete exhalation occurs when an exhaled breath is not fully emptied; leaving excess air volume above functional residual capacity that is trapped. On a flow waveform, this can be

seen as the airway flow of exhaled breath not returning to its 0 L/min equilibrium. If incomplete exhalation occurs often and sustains a high percentage (index) of incomplete exhalation breaths during a ventilation treatment, auto-PEEP will occur. Figure 1-7 shows the ventilator graphic for auto-PEEP occurring from incomplete exhalation. Bedside clinicians are typically not aware of the ventilator graphic characteristics that identify incomplete exhalation. Because they could not recognize incomplete exhalation, they cannot perform interventions to fix the incomplete exhalation before adverse effects from auto-PEEP significantly harm the patient. Automatic monitoring and detection of incomplete exhalation can help inform clinicians quickly before adverse effects take place.[12]

Figure 1-7: Auto-PEEP occurring from incomplete exhalation. [12]



Auto-PEEP's Adverse Effects

There are many adverse effects of auto-PEEP. These include increase in work of breathing, failure to wean from mechanical ventilation, worsening of alveolar gas exchange, hemodynamic compromise, and inappropriate treatment.[12,14,19] Applied PEEP has been shown to reduce patient effort in place of auto-PEEP, which indicates that auto-PEEP unnecessarily

increases patient's work of breathing. [20,21] The discomfort caused by increase in the work of breathing leads to patient-ventilator asynchrony and failure to wean a patient from a mechanical ventilator. [4,10,12,14]

Those with auto-PEEP would need to generate more negative intrapleural pressure than those without auto-PEEP and this eventually causes ineffective trigger. [18] An auto-PEEP sufferer who doesn't have applied PEEP to compensate for the extra pressure would have to overcome a larger threshold to trigger the ventilator sensitivity level. When inspiratory effort cannot reach that threshold, the ventilator will not deliver a breath. If auto-PEEP is not recognized or is even mistaken for something else, the patient will continually have discomfort from ineffective trigger and adverse effects from the auto-PEEP. [18,21,22]

Patients experiencing auto-PEEP have been shown to have lower oxygen tension, suggesting that auto-PEEP contributes to the worsening of gas exchange due to an uneven distribution of inspired gases.[23] The increase in intrathoracic pressure due to auto-PEEP reduces venous return which reduces preload to the right and left ventricles. Due to high pulmonary vascular resistance, decreases left ventricular compliance can lead to increase in right ventricular afterload. The inadequate venous return becomes a primary cause of low cardiac output which may cause hypotension in patients with auto-PEEP and can lead to subsequent administration of potent vasopressors.[12,14] Auto-PEEP's adverse hemodynamic effect is also considered the cause of cardiac electromechanical dissociation.[24,25] Additionally, auto-PEEP manifests asynchronous breaths and is the underlying cause of respiratory function impairment related to patient-ventilator asynchrony.[12,18,26,27]

Having determined the numerous potential adverse effects of auto-PEEP, it is important that an automated detection system of auto-PEEP through ventilator graphics for adults requiring mechanical ventilation be created. Using the experiential lessons and data from existing research on automated detection, the remainder of this dissertation will describe the development of a process for automated detection of auto-PEEP that may improve clinical outcomes of mechanically ventilated patients.

Chapter 2 Automated Detection and Calculation Derived from Ventilator Graphics

Introduction

Auto-PEEP can be identified in ventilator graphics where the ventilated adults exhibit an incomplete exhalation in the flow waveform; however, such knowledge is not commonly used in daily clinical care. Furthermore, since the incomplete exhalation detection requires continuous or frequent observation of real-time ventilator graphics, it is not pragmatic for clinicians to standby at all time at the patient's bedside to continually evaluate ventilator graphics. Automated detection of incomplete exhalation would contribute greatly to the monitoring of ventilated patients and the prevention of ventilator related injuries or even death.[10,12,18,28,29]

Combing through the literature review, the following questions are kept in mind: 1) Can an automated detection of auto-PEEP through the readily available ventilator graphics be developed? 2) Can the expertise of the clinician's detection of patient's incomplete exhalation be translated into a task that a machine can perform? 3) How strong does the presence of sustained incomplete exhalation (index) need to be to alarm the presence of auto-PEEP? Answers to these questions are obtained by fulfilling the objective, which is to create an automated detection of auto-PEEP through ventilator graphics for mechanically ventilated adults.

Through literature review it was discovered that respiratory measurand detections from ventilator graphics coupled with clinician's expertise formed plentiful automated detection of

various respiratory measurands. It can be seen that the path others took to automatically delineate breaths, calculate total PEEP, and automatically detect asynchrony, can be used to automatically detect incomplete exhalation and auto-PEEP.

Literature Review

Since the 2005 release of Nilsestuen and Hargett's paper "Using ventilator graphics to identify patient-ventilator asynchrony"[10] there has been interest in creating a method for the automated detection of patient-ventilator asynchrony. Since the first automatic asynchrony publications of Mulqueeny et al.and Chen et al., more authors have described various ways to automatically detect asynchrony.[30,31] However , automation of detection and calculation of respiratory measurands from mechanical ventilation, prior to asynchrony, are just as varied.

The progression of instrumentation for measuring and recording of ventilator graphics from the original pen and ink pneumotachometer to the modern mechanical ventilator's digital waveform have been essential in shaping the technology for artificial ventilation. Threshold based detection of airway pressure or volume has enabled the automation of breath triggers, volume targets, and many other ventilator related markings. Close-loop systems that govern the settings and modes of the ventilator use automatic detection of the waveform values based on set thresholds. Detecting when a waveform has reached or has not reached a threshold value for pressure, flow, or volume dictates whether the ventilator is to deliver more or less air.[5] Similarities in the early developments of automated detection from ventilator graphics and in the creation of automated detection methods of patient-ventilator asynchrony are described. Automated detection and calculation of respiratory measurands from mechanical ventilation have undergone complex and creative evolution of ventilator graphics.

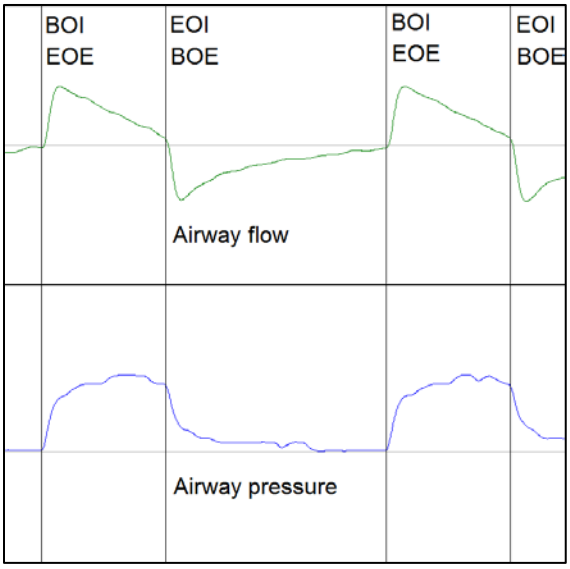
The original intent of automated detection of ventilator graphics was to make artificial ventilation easier and more effective than its manual data recording counterpart. Prior to the advent of automated detection of asynchronous breaths, automated detection of ventilator graphics of other respiratory measurand excluding asynchrony was used as part of mechanical ventilation control. Early development of computerized controls detected when a breath started and stopped. This detection occurred specifically at the starting and endpoints of inspiration, expiration, and end expiratory pause. This detection process led to the automation of reporting respiratory rate (numbers of breaths per minute) and is utilized in the more complex algorithms that have been developed since. [32]

Another value derived from waveforms is volume. Since pressure and flow are the signals acquired from sensors [33], to obtain volume information, the flow waveform is integrated over time through computerized automation and provides tidal and minute volumes. Automated detection is also applied to the airway pressure waveform to automatically obtain pressure information such as end-inspiratory pressure, end-expiratory pressure, the peak pressure and the mean.[32] From the flow and pressure sensors along with an infrared CO_2 analyzer, more variables of respiratory mechanics are automatically calculated. These provide instant information of PEEP, total compliance, inspiratory airway resistance, CO_2 partial pressures, CO_2 production, and airway dead space.[32]

Govindarajan and Prakash concisely describe their algorithm for computerized automated detection of breath delineation as a form of choreographed dance of checking status of the rise and fall of the waveforms for flow and pressure. The beginning of inspiration is noted when flow becomes a positive value while the same time the pressure waveform is rising. Start of expiration

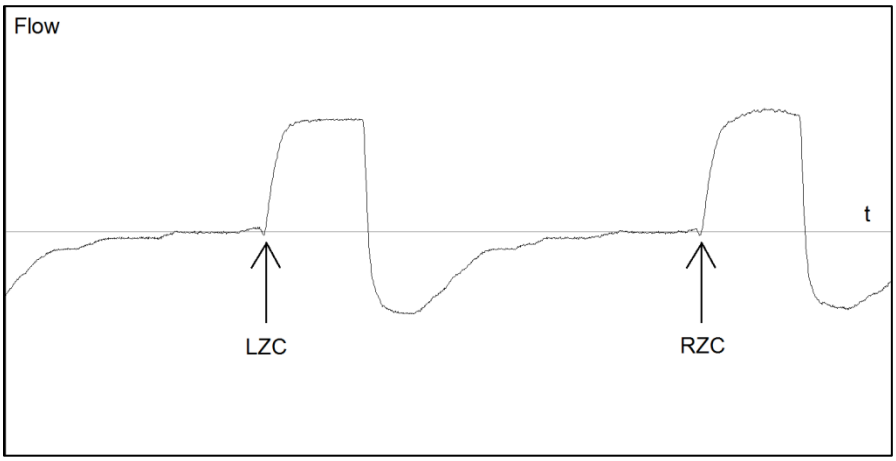
is defined as when flow waveform begins to fall at the same time pressure begins to drop (see figure 2-1).[34]

Figure 2-1: Example of breath delineation. As proposed by Govindarajan and Prakash, delineation is marked by beginning of inhalation (BOI) or end of exhalation (EOE) and end of inhalation (EOI) or beginning of exhalation (BOE).[34]



Baconnier et al. were able to automatically calculate global PEEP, resistance, elastance, and expiratory time constant from ventilator graphics. This is done by detecting one breath based on a left zero crossing (LZC) and right zero crossing (RZC) on the flow waveform (figure 2-2).[35]

Figure 2-2: Example of breath delineation based on flow waveform alone using right and left zero crossings.



Baconnier et al. used every part or aspect, characteristic or distinguishing feature of the flow and pressure waveform of the ventilator graphics to calculate global PEEP, resistance, elastance, and expiratory time constant. They segmented each breath into three phases; inflation, pause, and expiration. The inflation phase occurs when the inspiratory valve starts to open until it begins to close, allowing a constant flow for inflation. Elastance is obtained during the inflation phase when flow is constant, by calculating the derivative of pressure divided by the value of flow. The pause phase is between the beginning of the inspiratory valve closing until the beginning of the expiratory valve opening. The immediate pressure drop of the inspiratory valve closure is used to calculate resistance by dividing it with the flow value before the valve closes. The pressure value during this pause phase is used to calculate global PEEP along with the maximum pressure during inflation and the pressure at the left zero crossing. The last phase, deflation, starts once the inspiratory valve is closed and the expiratory valve is opened. Expiratory time constant is calculated from this phase. [35]

The automated calculations for ventilator mechanics are not without their limitations. For example, the global PEEP resulting from the algorithmic method employed by Baconnier et al. is valid only for waveforms with constant flow.[35] Whereas Govindarajan and Prakash's method of automated detection from ventilator graphics produces only breath delineation, which works more robustly for more types of settings including volume control, pressure control, and SIMV. [34]

So far multiple types of automated detection and calculations to acquire various ventilator measurands have been seen. These are reflected in the various ventilator modes with the different ways to trigger breaths, deliver, and terminate them.[5]

Some forms of detections of breath trigger (trigger detection) are products of threshold based automated detection algorithms that evaluate ventilator pressure, flow, and volume waveforms. Breath trigger based on pressure (pressure trigger) starts inspiration via computerized algorithm that automatically delivers a breath when a preset pressure value is detected at the end of expiration. Flow and volume control, where a preset value is also automatically detected for breath trigger can be described the same way. A unique type of breath trigger using ventilator graphics without a threshold value would be flow waveform triggering. In this situation, the ventilator creates a shadow flow waveform 300 ms after the patient's flow waveform that is offset by 15 L/min. When the shadow and original flow waveform cross each other, it would either cycle to expiration, or triggers inspiration. [5,11]

The determination of a breath's adequacy is based on an automated detection of the ventilator's waveform value. This in turn allows for immediate automatic adjustments to maintain preset parameter. For example on a dual control mode, when a breath does not reach a preset tidal volume during pressure control the mode would change to volume control to deliver the needed volume. Inversely, if a breath does not reach preset pressure value during volume control, the mode would change to pressure control to deliver the needed pressure. [5]

The termination of inspiration, or the trigger of expiration, is controlled by automated detection of a preset threshold. This is a very similar threshold method to the one that is used for trigger of inspiration. For each pressure, volume, and flow, a preset value would be detected on the waveform to switch the breath to an expiratory phase from an inspiratory phase.

Ventilator based automated breath event detection is so prevalent today in respiratory care that it can easily be taken for granted unless the method of the development of this existing

technology is reviewed. The development of ventilator based automated breath detection started from trying to figure out how to automatically delineate breaths and evolved into deriving simple calculations from the waveforms, like an automatic respiratory rate report, eventually leading to more complex endeavors, such as detecting/calculating global PEEP value. Learning what different asynchronies look like on ventilator graphics is undergoing the same evolution.

In the days of the pneumotachometer, when the ink gave life to paper in terms of the sinusoidal waveforms of lung volumes showing tidal volume, what translates as inspiration and expiration is learned. As the artificial ventilator evolved, flow and pressure waveforms and how to understand them are learned from the outputs that evolved from printed paper to electronic graphs. Inspiration and expiration from those waveforms along with the pauses, points, and phases in between became distinguishable. No longer sinusoidal, the waveforms took on more distinct shapes such as rectangular, ramp, and exponential waveforms. Today, hidden information to better respiratory care in terms of detecting asynchronous breaths are embedded in these waveforms.

Before physicians assign a set tidal volume for a patient, they identify an acceptable range. Before respiratory therapists set an applied PEEP, they must know what value of pressure would be too much. They know the ranges, the means, the modes, and standard deviations of the values that are important in respiratory treatment. In terms of automated detection of trigger asynchrony, Chen et al. explored the characteristics of asynchrony to see whether it is feasible to automatically detect it using a computer algorithm. Chen et al. familiarized themselves to asynchrony characteristics much like physicians and respiratory therapists would do.[31]

Thille et al. and Nilsestuen and Hargett previously defined ineffective triggering, when a patient triggers a breath that is not delivered by the ventilator. This is commonly viewed on the ventilator graphics as a convex flow waveform paired with a concave pressure waveform. Using this definition, Chen et. al compartmentalized the ineffective trigger data into a form that can be used in an algorithm for automated detection.[8,10,31] They obtained 14 patients from the ICU who were on mechanical ventilator and exhibited ineffective triggering during the expiratory phase. They defined ineffective triggering as a drop in airway pressure and/or a change in flow with no inspiratory trigger coupled with an esophageal pressure drop of greater than 1 cmH_2O. From this definition they recorded the deflection values of changes in the waveform of flow and pressure that would quantify the ineffective trigger. With 1,831 ineffectively triggered breaths from the 14 patients, the deflection values for pressure had a mean of 1.91 ± 0.97 cmH_20 and for pressure had a mean of 13.94 ± 8.0 L/min. [31]

Chen et al. used the Youden index to optimize the receiver operating characteristics curve (ROC). ROC graph is a graph of true positive rates (sensitivity) vs. false positive rates (1 – specificity). It is used for selecting classifiers based on performance.[36] The Youden index works by equally weighing the importance of sensitivity and specificity.[37] The index that yields the highest value using the following formula yields the optimal condition:

Youden index = sensitivity + specificity - 1

They found that the optimal value for detecting ineffective trigger for pressure deflection is 0.45 cmH_2O and for flow deflection 5.45 L/min. These values correspond to a sensitivity of 93.3% and a specificity of 92.9%. [31]

What Chen et al. effectively demonstrated is that waveform graphics of ineffective trigger can be described quantitatively based on the deflection values of the flow and pressure waveform. In these quantitative studies, optimum threshold values for detecting ineffective trigger are also established. This is not the only way of creating pathways of automatic detection of certain features of ventilator graphics. Just as Govindarajan and Prakash along with Klingstedt et al. show various ways of automatically obtaining respiratory rates, Younes et al. and Mulqueeny et al. show a different way of automatically detecting ineffective trigger. [30,32,34,38]

Younes et al. created a method for both monitoring and improving breath trigger for mechanically ventilated patient that would detect and prevent ineffective trigger. They did this by estimating when a patient wanted to trigger a breath by generating a signal representing muscle pressure output. A signal was produced in real time using equation of motion depicted as follows: [38]

$$P_{mus} = F*R + V*E - P_{aw} + PEEP$$

In this equation P_{mus} is muscle pressure output, F is flow, R is passive respiratory resistance, V is volume, E is passive respiratory system elastance, and PEEP is positive end-expiratory pressure.

P_{signal} is generated to estimate the timing of P_{mus}, where the magnitude does not have to be precise, because P_{signal} is used to look at trigger effort timing E and R change to become coefficients of flow and volume (K_F and K_V) for the P_{signal} equation. They are derived from two equations of P_{signal} from two safe points, points a and b, where they are a safe distance away from negative flow transients in the expiratory phase of a qualifying breath and are separated by at least 40% of the exhaled volume, depicted by the following formulas:

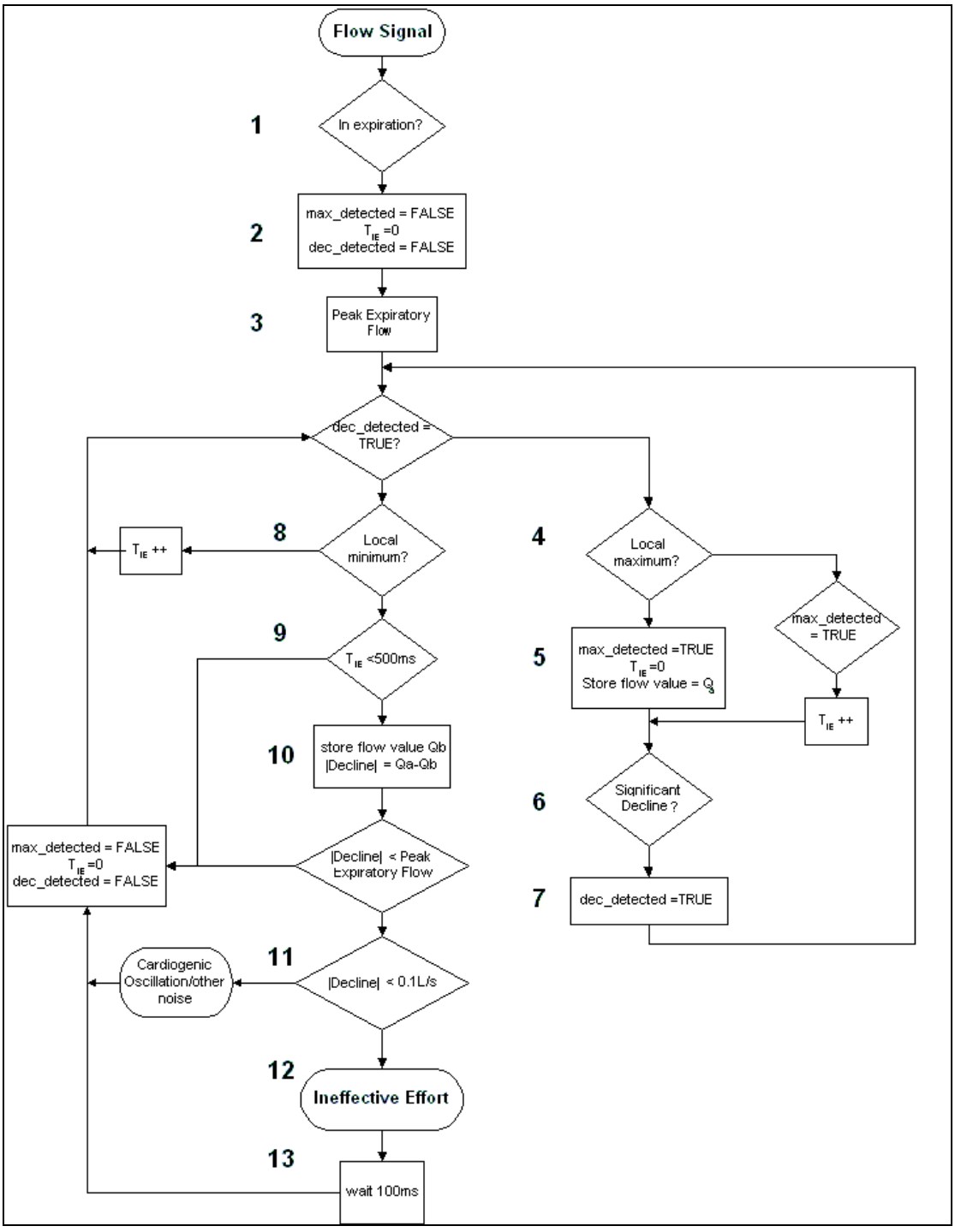
$$P_{signal(a)} = F_{(a)}* K_F + V_{(a)}* K_V - P_{aw(a)} + PEEP$$

$$P_{signal(b)} = F_{(b)} * K_F + V_{(b)} * K_V - P_{aw(b)} + PEEP$$

K_F and K_V are determined in the immediately preceding 10 qualifying breaths to generate P_{signal} in current breaths. Breath efforts are determined by P_{signal} and are confirmed with diaphragmatic pressure, although the generation of P_{signal} itself does not require diaphragmatic pressure. The automatic monitoring device using P_{signal}, identifies 80% of ineffective trigger from the ones identified via diaphragmatic pressure.[38]

Mulqueeny et al in 2007 created an automated detection for ineffective trigger and double triggering. A flowchart of the algorithm is shown in figure 2-3. For ineffective trigger, they calculated the first and second derivatives in the expiratory phase of flow to detect the deflections that are signature of the convex of flow indicative of ineffective trigger. The first derivative of flow, Q', is used to find a local maximum. It is defined by having $Q'_i < 0$ with having $Q'_{i-1} > 0$, or when $Q'_i = 0$. The flow at the local maximum is stored as Q_a. The algorithm loops to establish the local maximum until a decline is detected. A significant decline is noted when the second derivate of flow, or Q", shows a slowing down of the change of flow, denoted by Q" = 0 and if the value of Q' is greater than a negative threshold. The negative threshold is determined from $\alpha = -1/3$ of the standard deviation of Q' evaluated over a 10 second window. The local minimum is then determined by the following condition $Q'_i > 0$ and $Q'_{i-1} < 0$. If the local minimum occurs less than 500 ms after the local maximum, the local minimum is stored as Q_b. Otherwise the feature set is not considered to be ineffective trigger.[30]

Figure 2-3: Mulqueeny's flowchart for automated detection of ineffective effort.[30]



To differentiate between ineffective trigger deflections as oppose to cardiogenic oscillations, secretions, leaks, or other noises, a threshold of 0.1 L/s was used so that if the

difference between Q_a and Q_b is less than this, it will be considered noise. Furthermore, a minimum time of 100 ms is mandated between each affirmed ineffective trigger. As for double triggering, pressure waveform was used to determine this. When a breath cycle occurs less than 500 ms after another occurs, and when the expired volume is less than 40% of the average expired tidal volume of the past five breaths, this breath cycle is considered a double trigger.[30]

So far Chen et al., Younes et al. and Mulqueeny et al. have looked at deflections to determine trigger asynchrony. Chen et al. used an algorithm on both pressure and flow deflections to determine ineffective trigger.[31] Mulqueeny et al. uses a set of algorithm on flow alone to determine ineffective trigger and a different set of algorithm on pressure to determine double triggering.[30] Younes et al. looked at the changes of a derived P_{signal} waveform.[38] Shortly after this, a 2009 publication of Mulqueeny et al. embarked on a different pathway of solving automated detection of ineffective trigger. [39]

Mulqueeny et al. used Parzen Window Estimation, which is a classifier model for a morphologically based feature approach. They took data from 23 patients and had a physician determine ineffective trigger and breath demarcation to compare with their classifier model's detection. From these 23 subjects they also extracted features from expiratory flow that correspond to normal and asynchronous breaths based on identification by a physician specialized in mechanical ventilation. Features from 22 subjects were used to train the classifier model. The withheld subject was used to test the features for the classifier. Overall specificity for the model was high, 98.7%, but sensitivity was low, 58.7 %. The low sensitivity is speculated to be caused from having training data where the mode of pressure support breaths is a common occurrence. Pressure support mode ignores normal efforts by patient, preferring timed trigger,

causing flow swings with no pressure support. The authors excused this classification of ineffective trigger since it was not one influenced by intrinsic PEEP.[39]

Gutierrez et al. also came up with a detection method beyond measuring deflections. They created the automatic detection of asynchrony by spectral analysis of airflow. The idea behind this methodology is that a waveform can be displayed in the time domain, where values of airway flow and pressure are presented with dependence to time (as displayed on ventilator graphics), or in the frequency domain which partitions the waveforms into the different cyclical by their frequency. Smooth waveforms are dense with low frequency signal, whereas the sharp turns and changes on waveforms contain high frequency content. The frequency spectrum of the waveforms shows as peaks of varying amplitudes at different frequencies. The amplitude shown at zero frequency is called the DC value, after that there's amplitude at first harmonic frequency, second harmonic, and so on depending on the frequency content of the signal. Gutierrez et al. looked at the frequency spectrum of the expiratory phase of a flow waveform that was calculated with the Cooley-Tukey Fast Fourier Transform. Gutierrez et al. used Lorentzian Peak Analysis in their algorithm to find the first harmonic peak. A ratio of the amplitudes of first harmonic and the DC component of the spectra was calculated. They discovered that a ratio of less than 43% represented an asynchrony index greater than 10%. This ratio threshold was the optimum detection value that yielded sensitivity and specificity of 83%. The algorithm was tested against three trained, blinded observers on 110 adult subjects.[40]

Looking at a different population, Cuvelier et al. developed ineffective trigger automated detection for children receiving noninvasive ventilation.[41] Based on nonlinear dynamical system theory, they traced the trajectory of flow at time t, Q(t), and flow at a delayed time, $Q(t + \tau)$. The

curve shapes representing flow would be different depending on the patient-ventilator interaction. Normal expiratory phase produced larger loops than those of ineffective trigger. The tracings were analyzed by an algorithm that detected ineffective trigger from the rate of change of flow which corresponded to maximal airway pressure. The use of esophageal pressure was for confirmation only by visual observers for the presence of ineffective trigger and not part of the algorithm. From 14 subjects, the algorithm was successful in detecting 53 ineffective triggering out of 56 that were identified by the visual observers.

The most recent ineffective triggering automated detection system came from Blanch et al. who used continuous monitoring of airway flow and pressure to compare the expiratory phases of regular breaths and ineffective triggering breaths by calculating the deviations between the two.[42] They developed a software system, BetterCare®, to detect ineffective trigger efforts during expiratory phase. Theoretical expiratory flow curves are estimated by the software, where no ineffective trigger occurs. These curves are averaged to produce an ideal curve. This ideal curve is then compared with a patient's actual flow curve that has ineffective trigger. Four deviations between the ideal and the ineffective effort are weighed and converted into a percentage deviation. The authors find that the optimum cutoff percentage deviation is 42%, meaning if the level of deviation is equal or greater than that value ineffective effort is detected. Comparing the system's detection to five experts who independently analyzed the breaths, the software has a sensitivity of 91.5% and specificity of 91.7%. Comparing the software with diaphragm electrical activity, it yields 65.2% sensitivity and 99.3% specificity.

The only known publication that claims a working algorithm for automated detection of auto-PEEP is by Nguyen and Pastor. This paper bases the concept of auto-PEEP presence due to

the non-equilibration of flow at end of exhalation, in other words, during an incomplete exhalation. The automated detection uses the Signal Norm Testing, SNT, on the flow signal to detect said incomplete exhalation. Though the authors have demonstrated the effectiveness of the application of SNT to automatically detect incomplete exhalation, they prematurely established the relationship between incomplete exhalation and auto-PEEP as being the same. Although they are related, they are in fact not the same. The detection that Nguyen and Pastor use and claim to be auto-PEEP is being done in flow waveform in flow units, when in fact auto-PEEP is a pressure measurand. This effort is to be applauded for being the first of its kind; however the authors shouldn't jump to conclusion that they have in fact detected auto-PEEP. [43]

It is definitely fascinating to explore all the available methodologies in terms of utilizing ventilator waveform to further detect different measurement technique for improved ventilated patients. This dissertation will certainly draw conclusions from the past and examine the results of others to further its potential.

Research Objectives

In creating an automated detection of auto-PEEP through ventilator graphics for mechanically ventilated adults, several specific aims have been developed:

1. Develop an algorithm for the automatic detection on incomplete exhalation.
2. Validate the robustness of the algorithm for automated detection of incomplete exhalation.
3. Analyze the relationship between the index of incomplete exhalation with quantitative values of auto-PEEP.

The approach to fulfill the specific aims was inspired from the literature review. The first specific aim of developing automated detection of incomplete exhalation was fulfilled by studying flow and pressure waveform curves of incomplete exhalation just as Baconnier et al. and Govindarajan & Prakash developed an automated detection of various ventilator measurand.[34,35] Statistical tools like the Youden index employed by Chen et al. were used to optimize the algorithm that fulfilled the first specific aim.[31]The second specific aim explored the validation of incomplete exhalation automated detection algorithm just as past researchers have done validation, such as the validation Blanch et al. did with BetterCare®.[42] Unlike Nguyen and Pastor, the third specific aim made the connection between incomplete exhalation and auto-PEEP presence by comparing incomplete exhalation occurrence and pressure values of auto-PEEP.[43]

Chapter 3 Auto-PEEP Breath Signal Characteristics and How it is Acquired and Modeled

Overview

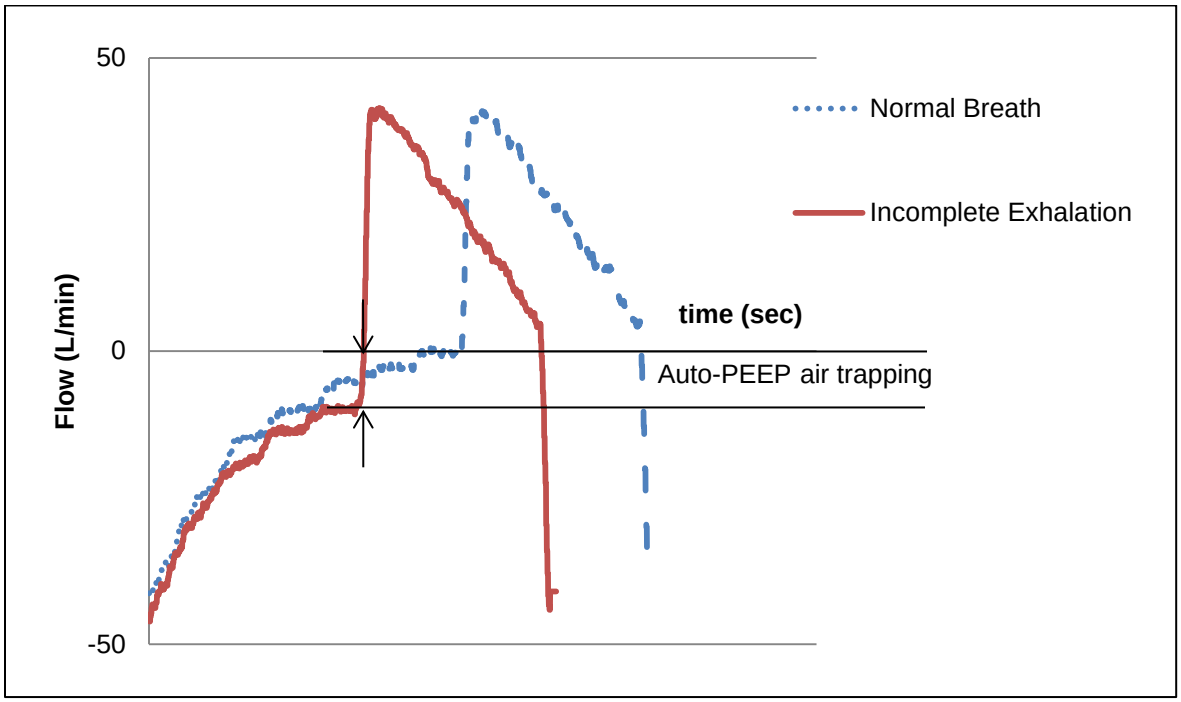
This chapter is a compilation of the technical details pertaining to the acquisition of breath signals and preliminary studies of the breath signals toward achieving the dissertation's objective. The hardware and software used in this study will be described including a description of the signal characteristics of the breath waveform for both normal and incomplete exhalation will be explored both in time and frequency domains. This will result in modeling of the breath signals and the development of the automated detection algorithm.

Signal Characteristics of Incomplete Exhalation

Incomplete exhalation (IE) occurs when an exhaled breath is not fully emptied, resulting in excess air volume above the normal functional residual capacity. On the flow waveform, this can be seen as exhaled breath not returning to its 0 L/min equilibrium (figure 3-1).

Digital recording of airway flow and pressure waveform from ventilators are pseudo-periodic signals with respiratory rates ranging from 10 – 30 breaths per minute, yielding a breath period of 1.5 – 6 seconds. Frequencies associated with breath signals are mostly in the 0 to 5 Hz range.

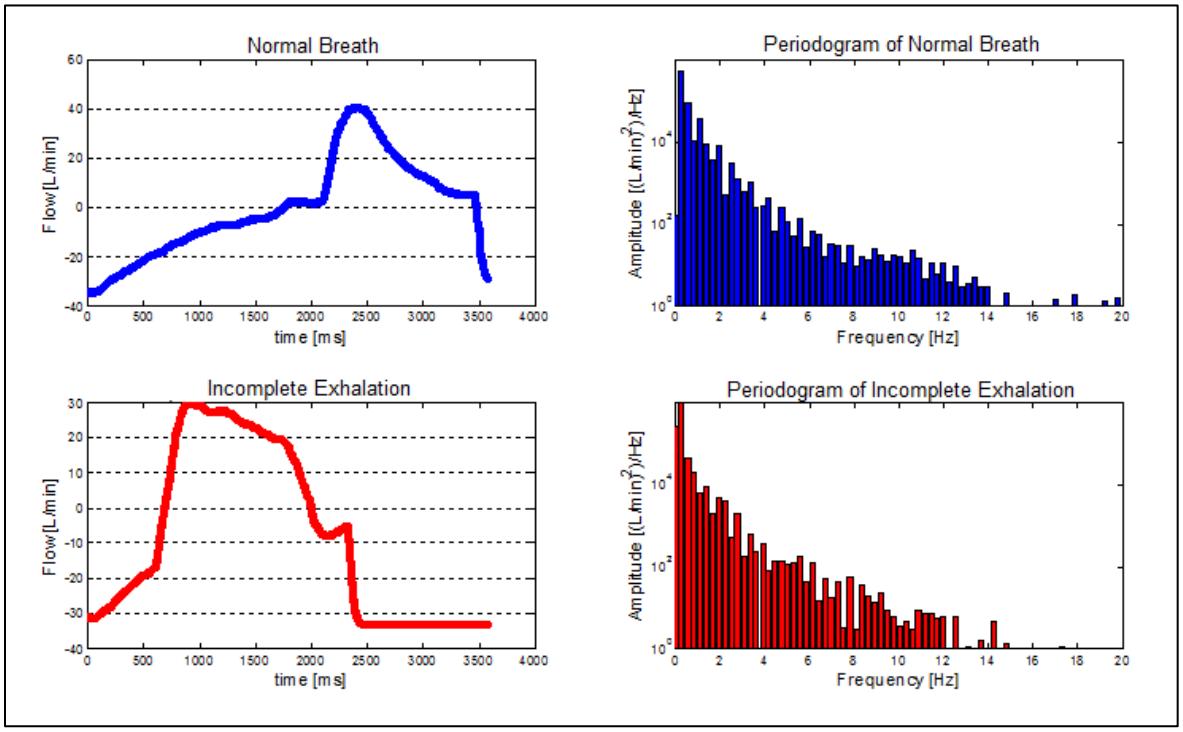
Figure 3-1: Auto-PEEP air trapping



Incomplete exhalation breaths are embedded in a series of normal, synchronous breath signals. Both signals have characteristics in frequency domain and time domain. Figure 3-1 shows the clear distinction between normal breath and incomplete breath in the time domain.

In the frequency domain, signals generated by normal breaths and incompletely exhaled breaths are dense in low frequencies. Figure 3-2 shows periodograms of the discrete Fourier transform (DFT) using fast Fourier transform (FFT) algorithm via MatLab. The frequency spectrum of the bad breath to be detected overlaps with the normal breath. Visual inspection of the periodogram reveals no clear distinguisher in frequency content between incomplete and normal breath. This shows that detecting IE breaths for auto-PEEP based on frequency domain will be challenging. So far, differences between the two types of breath are more obvious in the time domain.

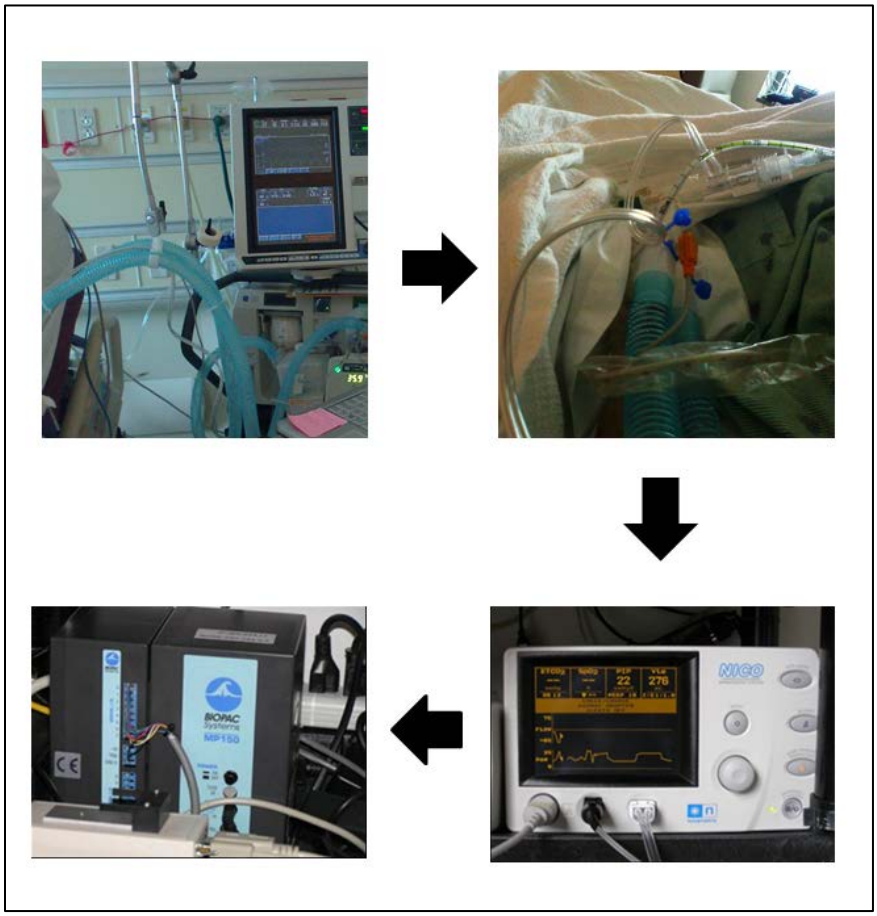
Figure 3-2: Periodogram of normal and incomplete exhalation breaths



Ventilator Waveform Acquisition

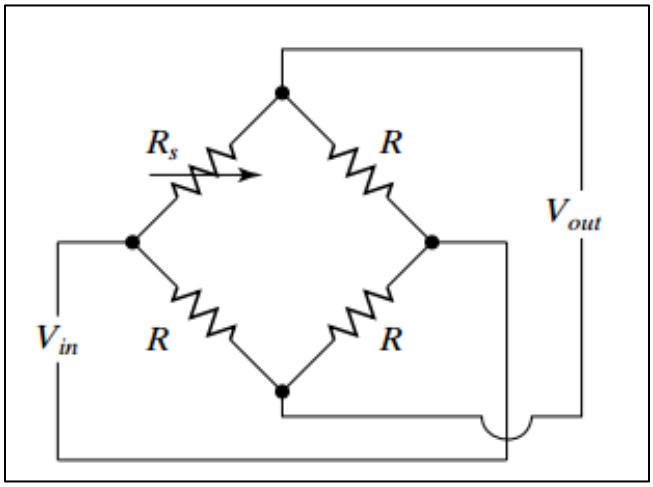
The waveform data were acquired using NICO® cardiopulmonary management system, an FDA approved medical monitoring device by Philips Respironics, Carlsbad, CA. Airway flow and pressure were measured from inline pressure and airflow sensors of the NICO® device connected to the patient ventilator line through medical grade tubing. Continuous analog voltage signals corresponding to pressure and flow values from the patient ventilator were sampled at a rate of 250 samples per second or every 4 milliseconds and stored on a notebook computer via AcqKnowledge® BIOPAC Systems (Goleta, CA) data acquisition system. Frequency content from the periodogram shows amplitude tapering off past 20 Hz. Sampling the breath signal at 250 Hz is well above the assumed Nyquist Rate of 40 Hz. Figure 3-3 shows the data acquisition setup.

Figure 3-3: Data acquisition setup



The sensor used to acquire the signal is very much like a Fleisch or Lily type pneumotachometer that is made up of a piezoresistive material. A piezoresistive material is an electrical resistor that changes its resistance due to stress, strain, and/or deformation. Piezoresistive materials are known to be used for pressure and flow sensors. [44-46] The most common method of acquiring voltage signals from piezoresistor is with a Wheatstone bridge circuit, shown in figure 3-4.[47]

Figure 3-4: Wheatstone bridge circuit



Where

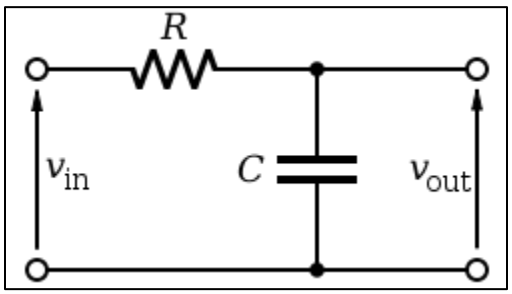
$$R_s = R + \Delta R$$

and

$$V_{out} = \left(\frac{-\Delta R}{2R + \Delta R}\right) V_{in}$$

The pneumotachometer from the NICO® monitor converts air pressure and air flow derived from the pressure into an electrical signal. The electrical signal is then fed into the BIOPAC system. If the signal is too noisy, an intermediate low-pass filter can be used between the NICO®'s output and the input to the BIOPAC system. Figure 3-5 shows a circuit schematic for a passive 1st order low pass filter.

Figure 3-5: Passive low-pass filter



Where the cutoff frequency f_c is determined as follows:

$$f_c = \frac{1}{2\pi RC}$$

After the BIOPAC receives inputs from the NICO® device, they are displayed through the AcqKnowledge™ software. The NICO®'s manual provides the specification for flow and pressure as follows: airway flow has a range of –125 L/min to 125 L/min at a conversion ratio of 4 mV per L/min, and airway pressure has a range of – 20 cmH_2O to 105 cmH_2O at a ratio of 8 mV per cmH_2O. Assuming linearity, conversion from voltage to units of ventilator measurand, the following conversion equations can be used to convert flow and pressure back into L/min and cmH_2O

$$Flow_{L/min} = 250Flow_V - 125$$

$$Pressure_{cmH_2O} = 125Pressure_V - 20$$

To adjust for the changes in gain, G, the following set of equations can be used:

$$Flow_{L/min} = \frac{250Flow_V}{G} - 125$$

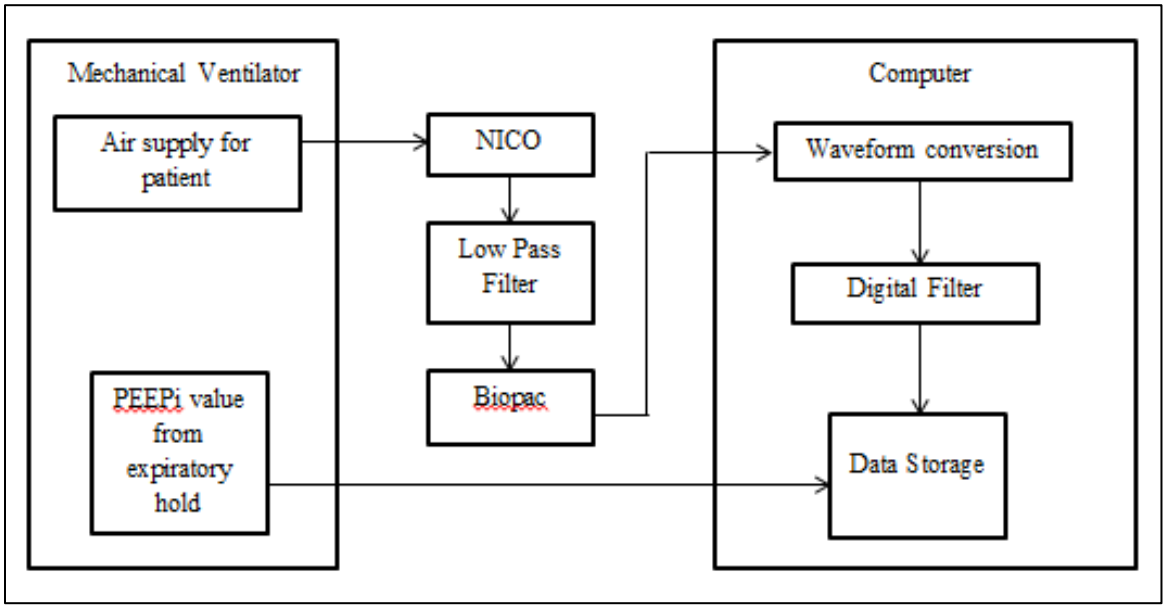
$$Pressure_{cmH_2O} = \frac{125Pressure_V}{G} - 20$$

After the storage and conversion of the voltage signal into the proper units they originally reflect, certain oscillatory noises still made through that did not reflect the original signal as first reported by Baconnier et al.[35] To further refine the data a digital infinite impulse response (IIR) low-pass filter with a cutoff frequency of 5 Hz were applied to each input via a function provided by the AcqKnowledge™ program.

For determining the auto-PEEP values, expiratory hold maneuver is the best option being that it is readily available, fairly reliable, and does not impose extra invasive procedures. In this

method end-expiratory occlusion is applied allowing equilibration of alveolar and airway pressure. The static auto-PEEP is measured by subtracting the applied PEEP (or previous airway pressure before occlusion) from the total PEEP (or the airway pressure at end-expiratory occlusion).[4,12,14,48] The Puritan Bennet 840 mechanical ventilator was the most commonly used ventilator in the Virginia Commonwealth University Health System's Intensive Care Units where data were collected. This ventilator has a button for expiratory hold maneuver that result in the display of the output value of intrinsic PEEP (auto-PEEP) and the total PEEP. Figure 3-6 shows the chart of data acquisition.

Figure 3-6. Chart of Data Acquisition



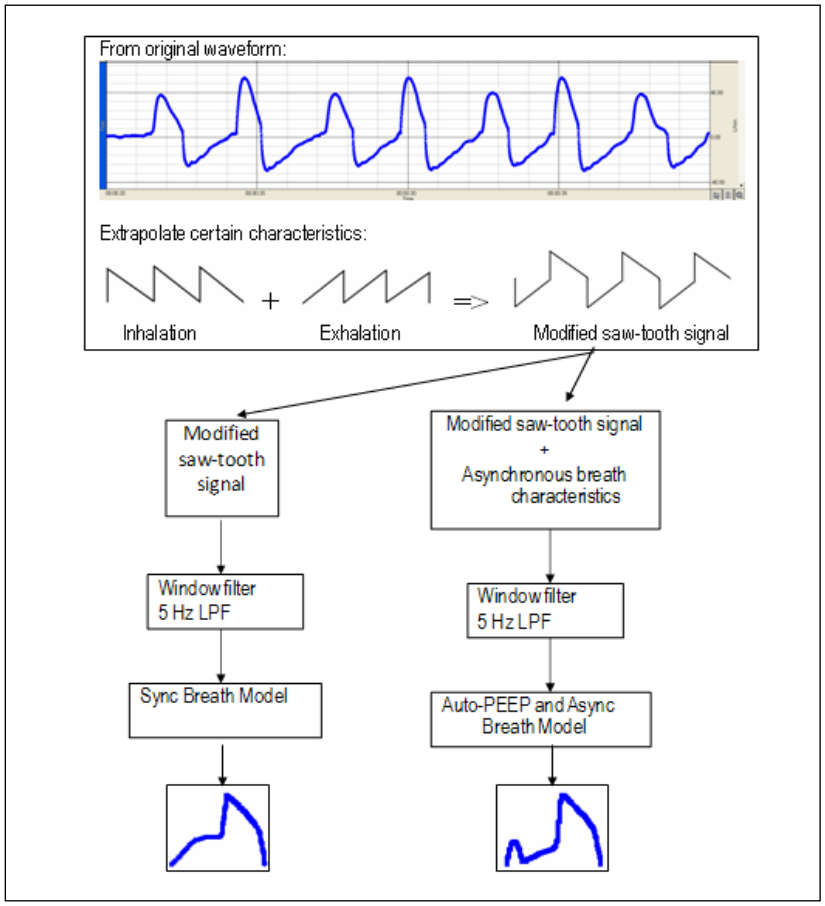
Modeling Ventilator Waveform Breaths

Signal estimation has been used to isolate the signal that is desired to be detected. The reason for this is if a signal can be estimated, then the estimation, or model, can be used as template for detection.

Respiratory experts observe waveforms of breath signal in the time domain to identify breaths that are not normal. Partitioning the signal into trigger, target, and termination identifies incomplete breaths from normal breaths, depending on the region of origin (see figure 1-3).[7] From the published literature, normal breaths and incompletely exhaled breaths are distinguishable based on incomplete exhalation breath not reaching equilibrium at the trigger region (see figure 3-1).[12,14,18]

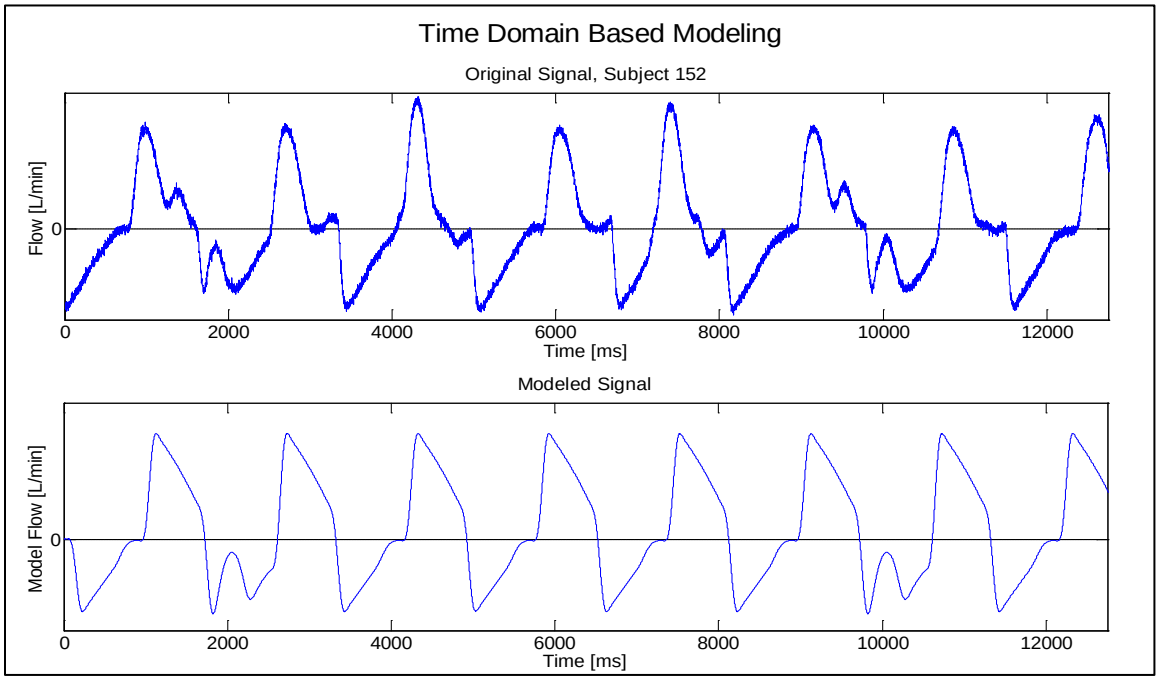
The combination of trigger, target, and termination, along with a priori information about the breath signal forms the basis for time-domain modeling as depicted in figure 3-7.

Figure 3-7: Flowchart for the process of modeling synchronous and asynchronous or auto-PEEP breaths based on time-domain signal characteristics



In ventilated patients, parts of their flow waveform resemble sawtooth-like waveform characteristics, which can be combined as a base model. Inhalation waveform (trigger and target) usually appears as a sharp intake of breath, which then decelerates, resembling the inverse sawtooth signal. The exhalation waveform (termination) appears as a fast breath exit that also decelerates, resembling a sawtooth signal. Both signals combined to represent one breath period consisting of an inhalation and an exhalation. They are then filtered through a low pass filter to attenuate the sharp characteristics. Breath models to depict any incomplete exhalation, auto-PEEP, and trigger asynchrony, would have those characteristics added to the modified saw-tooth signal before filtering. The resulting model as well as the original signal is shown in figure 3-8.

Figure 3-8: Excerpt of original signal (top) and its model (bottom) based on characteristics visible in the time domain



In terms of frequency domain-based modeling, parametric power spectral density (PSD) estimation is a popular method for estimating signals with a priori characteristics like breath waveforms. Since ventilator graphics are pseudo-periodic signals that are considered to be

composed of sinusoidal harmonics, use of a complex sinusoidal parametric PSD estimator rather than autoregressive (AR), moving average (MA), or autoregressive moving average (ARMA) parametric PSD estimator is appropriate. Pisarenko harmonic decomposition, as a complex sinusoidal parametric PSD estimator was employed in an attempt to model the signal. The Pisarenko method works by using the harmonic decomposition of an assumed signal $x(n)$ consisting of p complex exponentials (harmonics) in the presence of white noise. It estimates an autocorrelation matrix R of dimension (p+1) by (p+1) and evaluates the minimum eigenvalue, λ, of R and its eigenvector v. The resulting frequencies are the minima of the discrete-time Fourier transform, DTFT(v). Equations relating to Pisarenko harmonic decomposition are presented as follows:

The overall equation for the power density:

$$\hat{P}(e^{j\omega}) = \frac{1}{\left|\mathbf{e}^{H} V\right|^{2}}$$

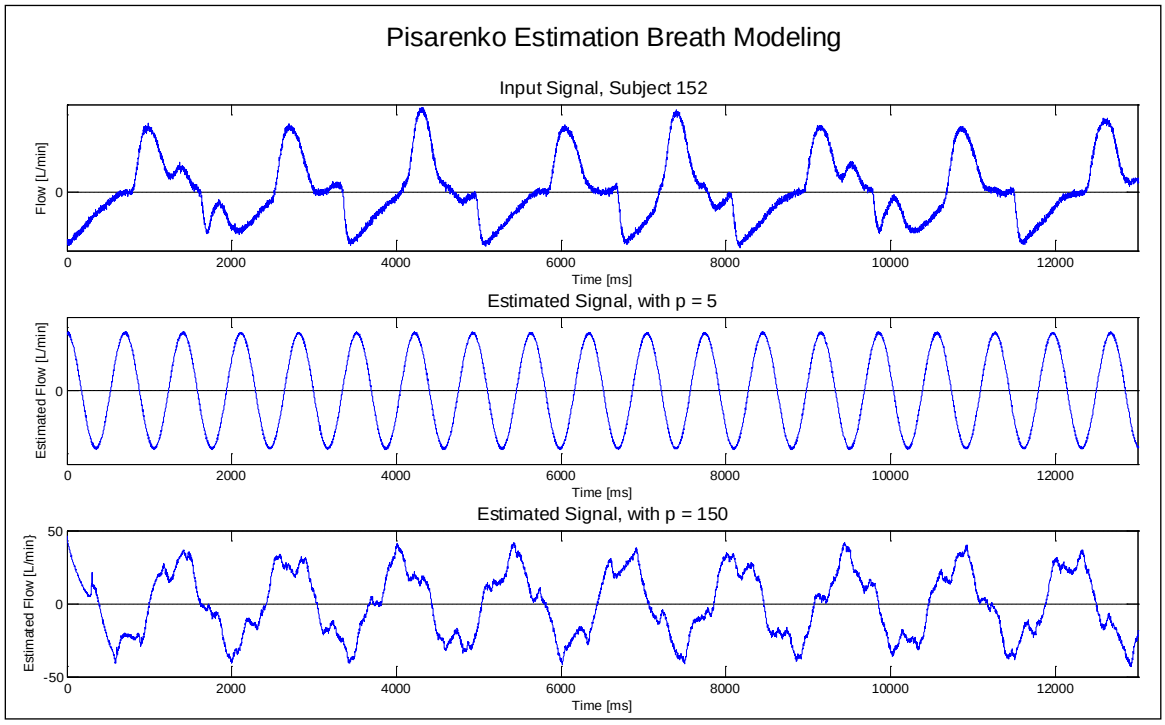
Where $\boldsymbol{V}$ is the noise eigenvector:

$$V(z) = \sum_{k=0}^{p} v(k) z^{-k}$$

Where $\mathbf{e}$ is the complex sinusoid vector:

$$\mathbf{e} = [1 \quad e^{j\omega} \quad e^{2j\omega} \quad \cdots \quad e^{j(p)\omega}]^{T}$$

Figure 3-9: Pisarenko estimation of a set of breathing cycles involving good and bad breaths with the top model having 5 harmonics and the bottom having 150 harmonics



From MatLab's `pisar.m` function, the airway flow waveform is estimated, and the models are presented in figure 3-9. For the purposes of detecting incomplete exhalation, modeling using Pisarenko estimation is unreliable. When $p = 5$ harmonic compositions were assigned to the Pisarenko estimation, the resulting signal only resembled a sinusoidal waveform. When $p = 150$ harmonic compositions were assigned to the Pisarenko estimation, it closely modeled the original signal, but all of the characteristics that would distinguish abnormal breaths from normal breaths from the original signal had been lost. The trend of increasing harmonic compositions shows when larger p is assigned then more breath attributions would appear in the model, but the model is still inadequate for differentiating bad and good breath signal for the purpose of detecting incomplete exhalation or auto-PEEP. Furthermore, even if higher harmonic

composition would achieve this differentiation, assigning higher magnitudes of harmonics for the modeling and detection is computationally inefficient and consumes more processing time.

Modeling in the time domain, allows better differentiation between normal breaths and incomplete exhalation breaths. This is accomplished by applying an understanding of the basic characteristics of mechanical ventilator breaths consisting of trigger, target, and termination, as well as the characteristics of bad breaths during incomplete exhalation that leads to auto-PEEP. The logic in creating this model will be used to develop the algorithm for automated detection of incomplete exhalation. Although Pisarenko estimation was not completely successful for incomplete exhalation detection, it is not the end of the road for using frequency domain-based incomplete exhalation detection. Gutierrez et al. successfully used frequency domain analysis to automatically detect trigger asynchrony.[40]

Summary

This chapter has presented incomplete exhalation's signal characteristics and how they relate to auto-PEEP. It also explored incomplete exhalation's signal modeling and acquisition as well as acquiring auto-PEEP values via expiratory hold. Information that is important to develop research to create an automated detection of auto-PEEP via automatically detecting incomplete exhalation. The next three chapters will describe the technical description of the signal acquisition for acquiring data, the logic behind the signal characteristic and modeling for developing the algorithm of automated detection.

Chapter 4 Development of an Algorithm for Automated Detection of Incomplete Exhalation Events of Mechanically Ventilated Adults

Introduction/ Background

Adults on conventional, positive pressure-based, mechanical ventilators can experience incomplete exhalation. Which if undetected can lead to auto-PEEP. Auto-PEEP may cause harm to the mechanically ventilated resulting in increased work of breathing, poor gas exchange, compromised hemodynamics, cardiac electromechanical dissociation, increased administration of vasopressor and sedatives, and prolonged mechanical ventilation treatment. Having an automated system for detection of incomplete exhalation can minimize the likelihood of auto-PEEP and the potential harm to the patient. [12-14,21,24,25,29,49]

Incomplete exhalation is identified when the airway flow fails to reach a flow rate of 0 L/min before a new breath is initiated. While the current method to detect incomplete exhalation is based on visual detection of the graphical waveform display, an algorithm will be developed to detect incomplete exhalation during the breath cycle.[12,14,18]

To identify when incomplete exhalation has occur, the automated detection process must first identify the starting point of a new breath. Once this is established, the automated detection algorithm then reads whether the value of flow is less than 0 L/min. If flow is less than zero, then incomplete exhalation is identified, if not, exhalation is complete.

Method

Examination of the Incomplete Exhalation Characteristics

Before starting the algorithm design, examples during incompletely exhaled breaths were examined at the onset of inhalation. Onset of inhalation is generally marked by a sharp slope increase with an obvious turn angle from the exhaled line. During a normal breath with complete exhalation, this sharp turn would occur at 0 L/min when onset of inhalation occurs after exhalation has properly ceases (see figure 4-1). Incomplete exhalation breath is marked by an onset of inhalation of similar sharp slope increase but the turn angle occurring below 0 L/min (see figure 4-2). However, the turn angle is not always sharp and obvious (see figure 4-3).

Figure 4-1. Breaths with complete exhalation

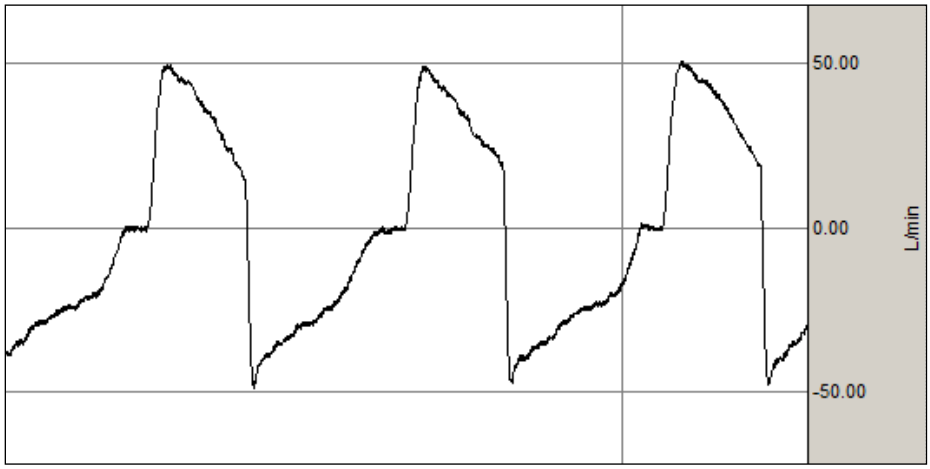


Figure 4-2: Breaths with incomplete exhalation

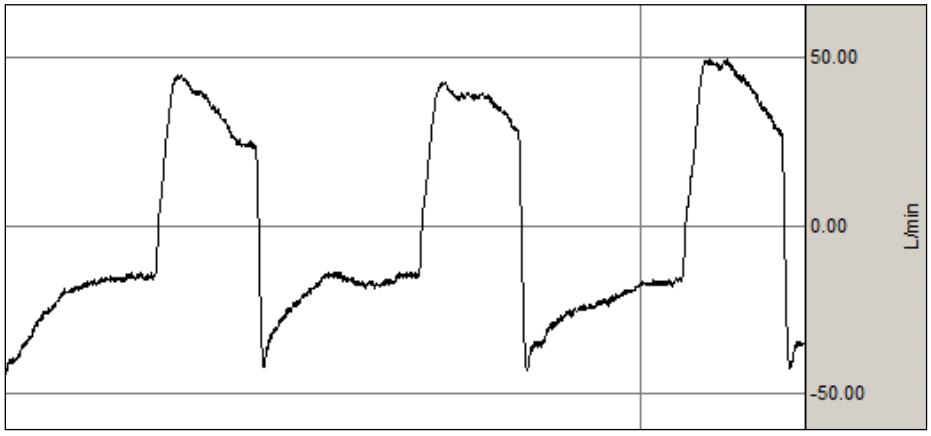
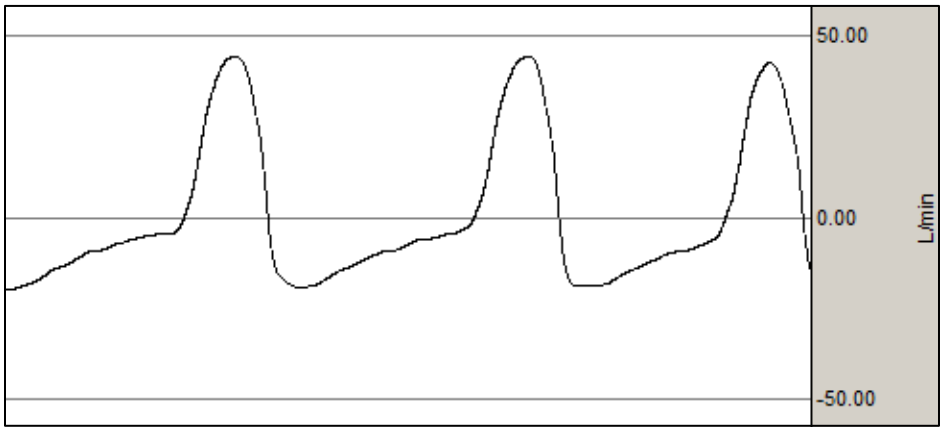


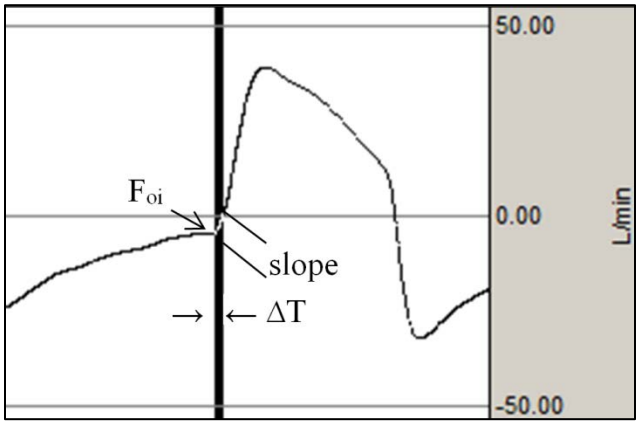
Figure 4-3: Breaths with ambiguous incomplete exhalation



A total of 203 examples of incomplete exhalation were found among 22 subjects who participated in an IRB approved (Virginia Commonwealth University IRB # HM 10466) Sedation and Ventilation Effects (SAVE) study (NIH R01 NR009506, M.J. Grap, PI).[50] Ventilator waveform data were obtained from the flow sensor of a NICO® cardiopulmonary management system, an FDA approved medical monitoring device manufactured by Philips Respironics (Carlsbad, CA). The flow sensor tube is attached to the subjects' ventilator airway tube with the NICO® outputting electrical signal ventilator waveform from an analog output port which then sampled at 250 Hz through AcqKnowledge® BIOPAC Systems (Goleta, CA) data

acquisition system then stored into a PC. The data were examined for the following 3 values: time difference, ΔT, from the onset inhalation turn angle to the 0 L/min mark, slope of change of flow over ΔT , and value of flow during onset inhalation, F_{oi} (see figure 4-4). The time difference, ΔT, had an average of 0.113 s, a minimum of 0.024 s, and a maximum of 0.320 s. Slope had an average value of 159 L/min/s, a minimum value of 34 L/min/s and, and a maximum value of 434 L/min/s. F_{oi} had an average value of -15 L/min, a minimum of -38 L/min, and a maximum of -3 L/min. These measures will be used to provide a basis for development of the detection algorithm.

Figure 4-4: Depiction of F_{oi}, ΔT, and slope



The Algorithm Design

There are three main parts to the incomplete exhalation detection algorithm. The primary part is to identify the onset of inhalation. The second part is to prevent double triggering as part of incomplete exhalation. The final and third part is to use inspiration from pressure waveform to prevent ineffective trigger to be identified as onset of inhalation.

The onset of inhalation algorithm identifies when a new breath starts. Since inhalation happens when there is an intake of air flow, this is indicated by the positive flow direction. In

contrast, exhalation has negative flow direction. It is logical then to say if a positive flow occurs after a negative exhalation flow, a new breath has started. ΔT is used as a distance barrier between past and present events. If the past flow value is negative, and the present flow value, which is ΔT seconds away, is positive, then onset of inhalation have occurred.

```
if flow(t) <= 1 && flow(t+△T) > 1
     OnsetInhalation = t;
end
```

Note that to further distinguish the onset of inhalation 1 L/min is used instead of 0 L/min to denote onset of inhalation because 0 L/min has no quantitative breath flow for inhalation.

Incomplete exhalation detection would occur during onset of inhalation detection, given the sharp turn of slope increase indicative of a new breath happening during negative flow value. This algorithm is written as thus:

```
slope = (flow(t+△T) - flow(t))/ △T;
if slope > slopethreshold && flow(t) <= F_oi
     IncompleteExhalation = t;
end
```

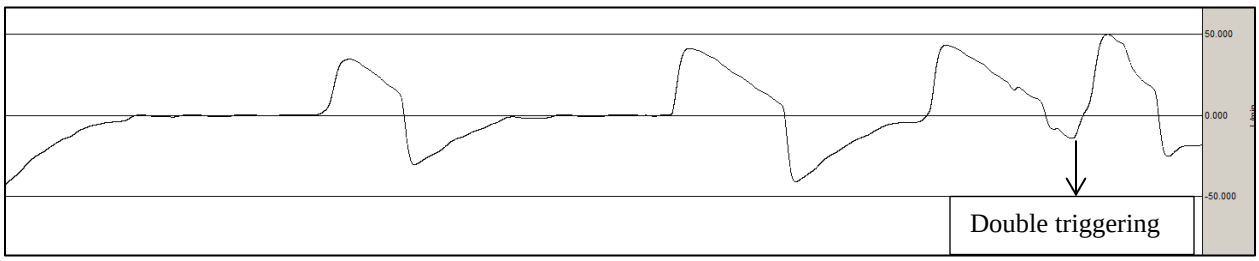
Here the variable slope threshold is introduced which is not yet defined. Also not defined by a value is the variable F_{oi}. F_{oi} , slope threshold, and ΔT remain as variables in the algorithm because the value assigned to them fell in the range based on the examination of the incomplete exhalation characteristics. Some values will be highly sensitive to detect incomplete exhalation that it would yield many false positive presence of incomplete exhalation and other values will be so restrictive and would yield false negative presence of incomplete exhalation.

Determination of the most optimum value for F_{oi} , slope threshold and ΔT will be attained through analysis of the receiver operating characteristic (ROC) curve.

Double triggering is noted on flow or pressure graphs as a breath followed shortly by another breath, where the time between them is very short, less than half the expected expiratory time (see figure 4-5).[8,30,51] The algorithm takes the average breath period for the last 5 breaths to determine expected expiratory time. If the current onset of inhalation breath fulfills the criteria of double triggering, it will not be considered for incomplete exhalation detection.

```
if (t-OnsetInhalation) > 0.5*meanLast5BrthPeriod
     if slope > slopethreshold && flow(t) <= -1
          IncompleteExhalation = t;
     end
end
```

Figure 4-5: Example of double triggering

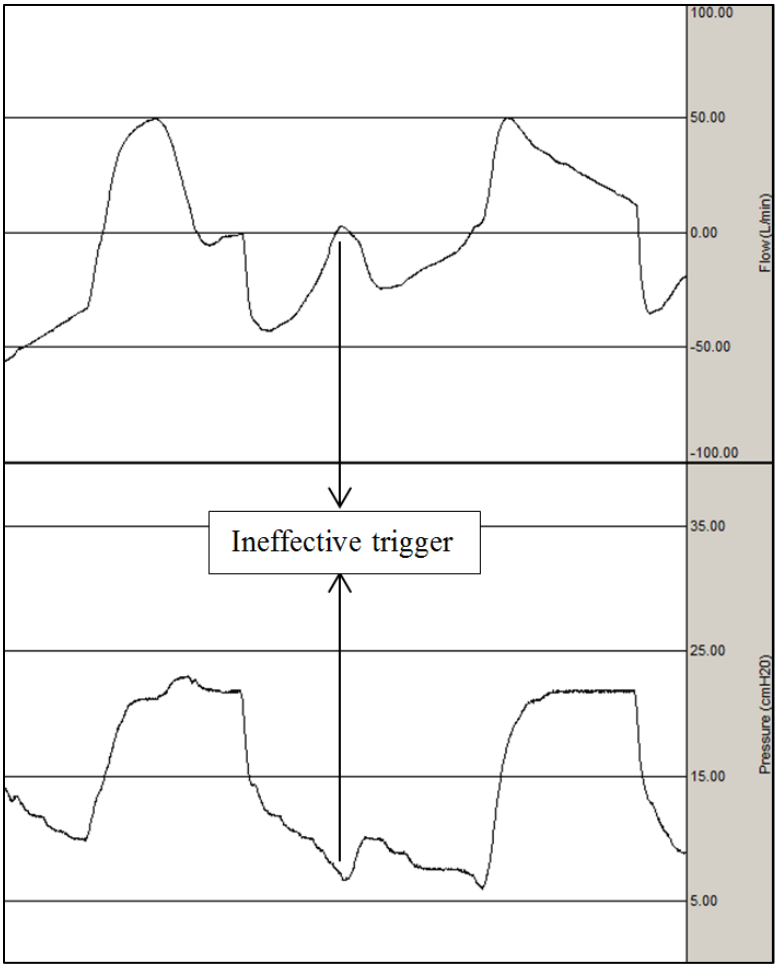


Ineffective trigger occurs when a ventilated patient initiates a breath trigger but the ventilator did not deliver the breath. This is shown on the waveform as a convex bump on the flow waveform usually accompanied by a concave dip on the pressure waveform (see figure 4-6).[8,30,31,52] Not wanting the detection algorithm to consider the ineffective trigger for incomplete exhalation the pressure waveform is used as an inhalation marker. Only incomplete exhalation

that occurs with a typical pressure waveform would be confirmed as a detection of incomplete exhalation.

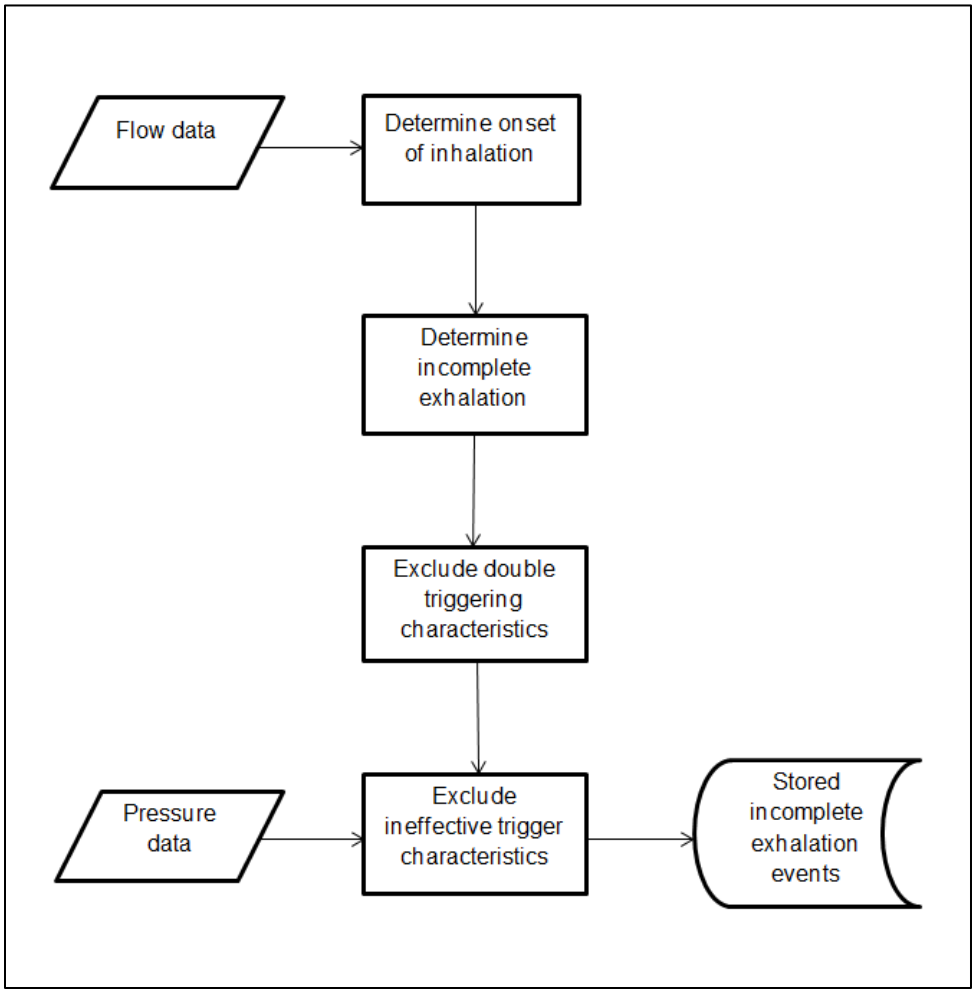
```
if match(IncompleteExhalation, InhalationMarker) = 1
     IEDetect = IncompleteExhalation;
End
```

Figure 4-6: Example of ineffective trigger



A summary of how the algorithm works, is shown in figure 4-7 and it depicts how the four codes discussed above relates to flow and pressure waveform.

Figure 4-7: Flowchart of algorithm



Testing the Algorithm

Out of 60 subjects from the SAVE study that were not involved in the examination of the incomplete exhalation characteristics, 13 were identified to have had at least one breath that exhibited incomplete exhalation characteristics by an observer during a sample of two minutes. These two minute samples of 13 subjects were not used as part of the incomplete exhalation characteristics examination to develop the algorithm. However, they were used to test the algorithm and identify optimum variable values for slope threshold and ΔT.

Table 4-1: Values of parameters used for classifier

F_{oi} (L/min)	ΔT (s)	slope threshold (L-s/min)
0	0.025	30
-1	0.050	60
-2	0.075	90
-3	0.100	120
-4	0.125	150
-5	0.150	180
-6	0.175	210
	0.200	240
	0.225	270
	0.250	300
	0.275	330
	0.300	360
	0.325	390
		420
		450

Three observers identifying incomplete exhalation from the data samples were used to test the algorithm detection. The three observers have expertise in mechanical ventilator waveform. The three observers were comprised of a critical care physician, a nursing educator experienced with ventilated patients, and a biomedical engineer specializing in ventilator waveform analysis. All three observers performed independent examination of waveform data for detection of incomplete exhalation. All three independently detected incomplete exhalation for the two minute data sets for each of the 13 subjects. Fleiss Kappa statistical measure was used to assess the inter-rater agreement, which is a modified version of Cohen's Kappa that can be used for more than two observers.[53,54] The incomplete exhalation events that were not initially agreed upon were given forced agreement unanimously by the three observers post independent detection. This agreed upon data therefore became the golden standard for testing the algorithm. Table 4-1 shows the parameter values of five different F_{oi}, thirteen different ΔT, and fifteen different slope thresholds. These values are within the range described in the "*Examination of the*

Incomplete Exhalation Characteristics" section and yielded 1365 discrete classifier points on a Receiver Operating Characteristics (ROC) curve.

Optimizing the Algorithm

A Youden index was used to find the set variables values that would optimize the algorithm's output by weighing sensitivity and specificity equally.[37] The Youden index finds the point on the ROC curve closest to the (0,1) point that satisfies the following:

$$max[Sensitivity(c) + Specificity(c) - 1]$$

Where c corresponds to the point on the ROC curve and max means the "maximum of."

Results

Fleiss kappa index from the three observers yielded 0.81 for agreement.

The discrete ROC curve shows the overall result of the mean values of sensitivity and specificity across the subjects for the 1365 classifier points (figure 4-8). The maximum value of the Youden index of 0.75 yielded a sensitivity of 0.91 and specificity of 0.84 and occur when results are set to F_{oi} = -3 L/min, ΔT = 0.2 s, and slope threshold = 90 L-s/min.

Youden values for F_{oi} parameters 0,-1,-5,and -6 L/min never reaches 0.7. Only F_{oi} values -2, -3, and -4 L/min yield Youden index values higher than 0.7.

Figure 4-8: ROC graph. Large point represents the optimal point based on Youden index.

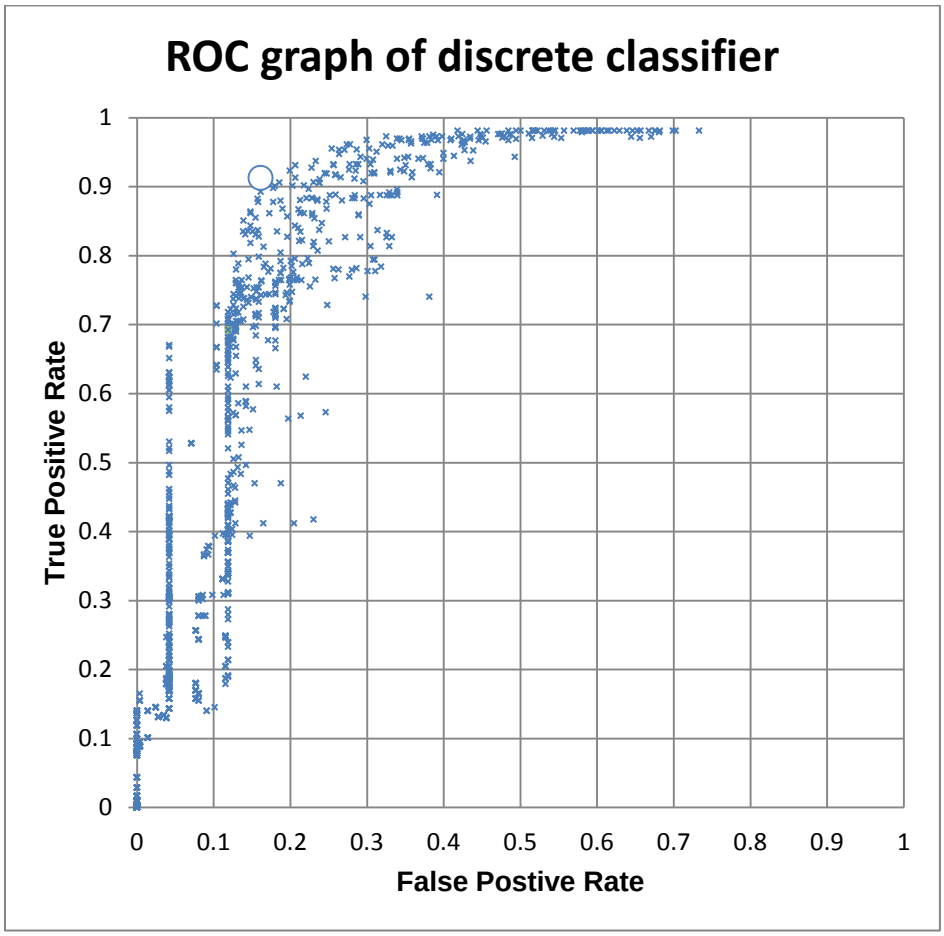


Figure 4-9: Contour plot for Youden values with F_{oi} = -2

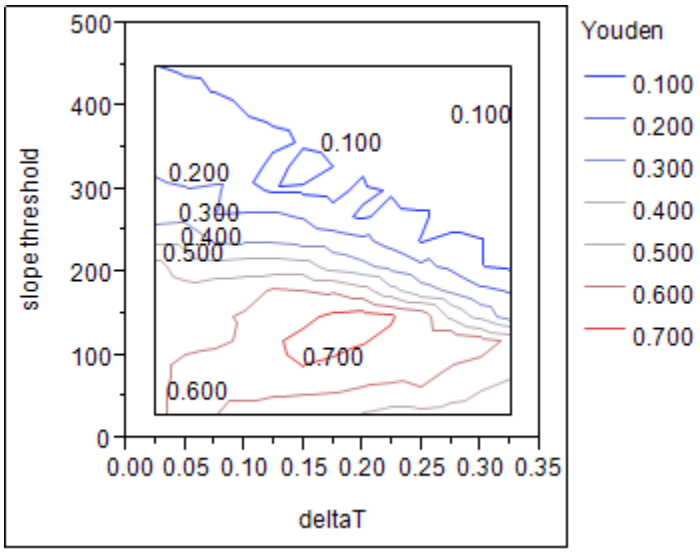


Figure 4-10: Contour plot for Youden values with F_{oi} = -3

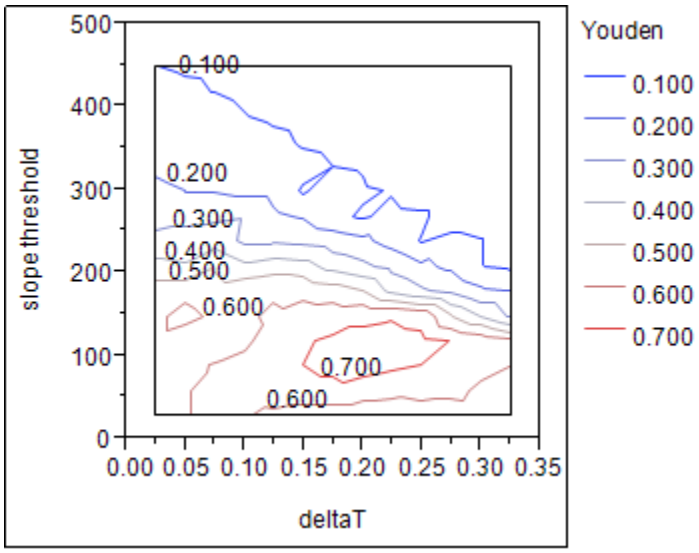


Figure 4-11: Contour plot for Youden values with F_{oi} = -4

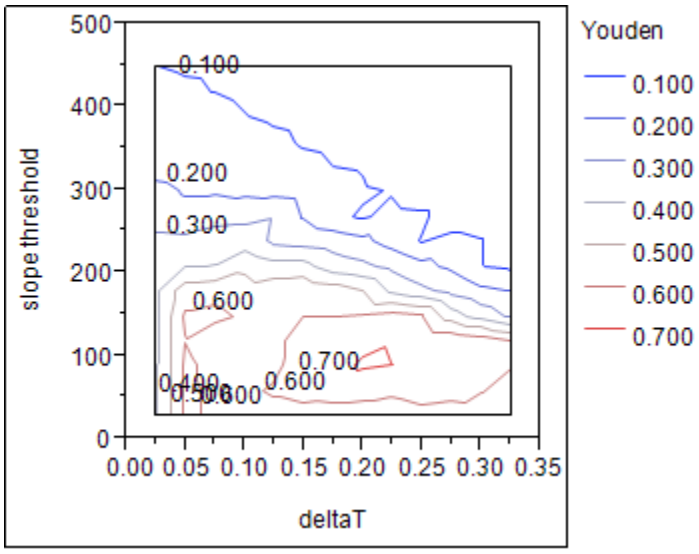
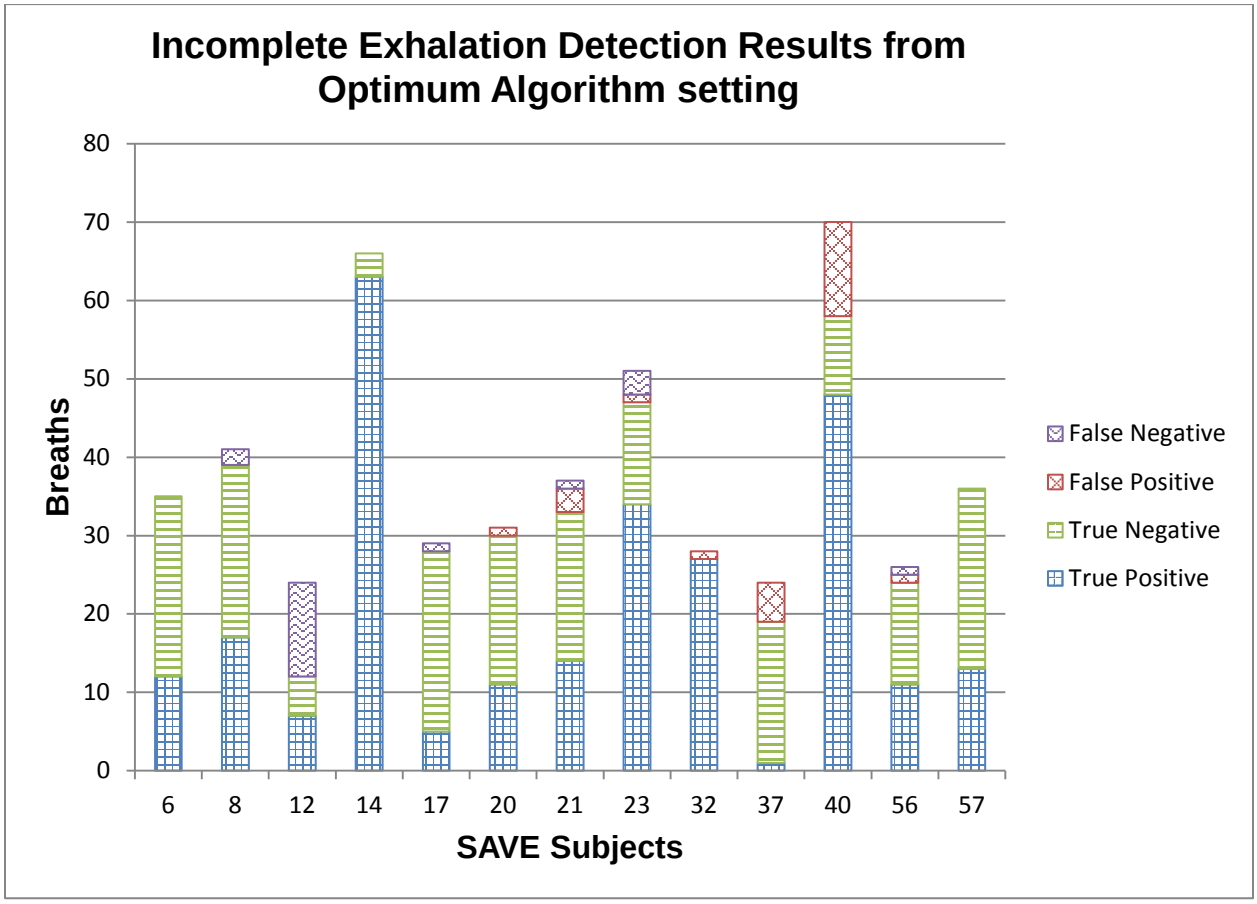


Figure 4-12: Incomplete exhalation detection with algorithm setting F_{oi} = -3, ΔT = 0.2, and slope threshold = 90



Discussion/ Conclusion

The high value of the Fleiss kappa index (0.81) validates strong agreement between the three observers in terms of identifying incomplete exhalation during their independent analysis. Any breath that were not agreed upon were discussed by all observers during a joint identification session. The breath identifications from the joint session were used to test the algorithm and the results are given by the ROC curve. The ROC curve shows that the algorithm performs better than random chance.[36] The clusters of points closest to (0,1) point represents the best performance of the algorithm in detecting incomplete exhalation when compared to observer's detection. As stated in the results, the maximum value of the Youden index yielded a

sensitivity of 0.91 and specificity of 0.84 corresponding to parameter values F_{oi} = -3 L/min, ΔT = 0.2 s, and slope threshold = 90 L-s/min. The sensitivity values shows a true positive rate of 91 % and a false positive rate of 16 %. This results in an accuracy of 0.89 and precision of 0.88. Given these values, it is acceptable to use these parameter as default values for the algorithm.

Figures 4-9 to 4-11 shows contour plots of the Youden values which give a comprehensive view of the contribution of each parameter to the peak of the Youden index value. The Youden index contour plots when F_{oi} is set to -2, -3, and -4 L/min are shown because they yielded higher Youden plateau (reaching 0.7). The contour plots shows Youden index values plateuing on the middle range of ΔT and the lower range of slope threshold. These ranges for F_{oi}, ΔT, and slope threshold contributed towards the peak of the Youden index. Though there are no other plateau reaching Youden index of 0.7, there is a hint of a second plateau emerging when looking at contour plots set to F_{oi} = -3 (figure 4-10) and -4 L/min (figure 4-11). This second plateau corresponds to lower values of slope threshold and lower values of ΔT. This suggests that the area has the potential to yield high sensitivity and specificity. The idea for the automated detection algorithm is to have a default parameter setting that can be adjusted within a range. These contour plots can serve as starting point of where that range should lie. Anywhere near the 0.7 plateau is a start.

Figure 4-12 shows the amount of breaths classified as true positive, true negative, false positive, or false negative from the two minute ventilator breath data when the optimum algorithm setting is used. The results show acceptable distribution of true positive and true negative values for the optimum setting. The algorithm was tested against observers and yielded

high sensitivity and specificity with optimum parameter values. This automated detection of incomplete exhalation using this algorithmic method shows much promise for future clinical use.

There are several limitations to this study that need to be addressed and should be the focus of future work. The data that was used to develop the algorithm was generously provided from another study focusing on mechanical ventilation effects but with no focus on detecting incomplete exhalation or auto-PEEP. As a result, many of the breaths were not easily categorized as either incomplete exhalation or not (i.e. yes or no). The observers raised concerns that some of the breaths were difficult to categorize in a binary fashion between yes for incomplete exhalation or no incomplete exhalation. In addition, the complete absence of auto-PEEP values is also a limitation. There is no way to confirm whether high occurrences of incomplete exhalation yield positive presence of auto-PEEP. One way to address this limitation is to conduct a study with new data sets with the specific focus on looking at incomplete exhalation detection and its link to auto-PEEP. Testing the performance of the algorithm with a new data set provides an opportunity to confirm or deny the robustness of the algorithm. Coupling the data with quantitative auto-PEEP values will provide insights about the relationship between the two.

Chapter 5 Testing the Robustness of Incomplete Exhalation Automated Detection Algorithm for Validation by Introducing Novel Data

Introduction/Background

Occult positive-end expiratory pressure (PEEP), also known as intrinsic PEEP (PEEPi) and auto-PEEP, is a condition that occurs when excessive air-pressure is present in the lungs at the end of expiration. For patients who are sedated on invasive mechanical ventilators, the presence of auto-PEEP could go unnoticed and result in severe consequences. Such as barotrauma, low cardiac output, hypotension, excessive sedation, cardiac electromechanical dissociation, and death. [12-14,21,24,25,29,49]

Fortunately, there are noninvasive ways to indicate the presence of auto-PEEP. From the mechanical ventilator waveform, examples of recurring incomplete exhalation have been noted as an indicator of auto-PEEP. [12,14,18] Unfortunately, the current method to detect this is by visual inspection by those with the knowledge of ventilator graphics. Such personnel are very few and certainly cannot monitor all patients all the time. An automated detection algorithm would be the better choice of monitor and detection of incomplete exhalation. In the previous chapter, an algorithm-based automated detection for incomplete exhalation was developed and tested for optimal parameter setting. This chapter tests the algorithm's robustness with novel data to determine whether there is any significant change in the performance of the algorithm.

Method

Virginia Commonwealth University (VCU) Institutional Review Board (IRB) approved a biomedical research study involving human subjects for the validation of incomplete exhalation automatic detection algorithm (IRB # HM 13962). Data collection conducted over a year enrolled 15 subjects from VCU Health System's (VCUHS) Medical Respiratory Intensive Care Unit (MRICU). Informed consents were obtained from the legally authorized representative of the ventilated and sedated adult patients of VCUHS's MRICU prior to subject enrollment and data collection. Prior to recruitment, potential subjects were screened for the following inclusion criteria: sedated and intubated on mechanical ventilation (excluding tracheal intubation with a collar), exhibition of incomplete exhalation of alveolar gas via ventilator graphics identification as defined by published works of non-zeroing of flow prior to new breath, and the presence of any known risk factors such as asthma, chronic obstructive pulmonary disease (COPD), or acute respiratory distress syndrome (ARDS). [12,14,18] Table 5-1 shows the subject demographic including age, gender, race, reason for ICU admission, ventilator setting, and Sequential Organ Failure Assessment (SOFA) score during the time of data collection.

Each subject's airway flow and pressure waveform were recorded up to 90 minutes via the NICO® cardiopulmonary management system, an FDA approved medical monitoring device by Philips Respironics, Carlsbad, CA. Airway flow and pressure were measured from inline pressure and airflow sensors of the NICO® device connected to the patient ventilator line through medical grade tubing. Continuous analog voltage signals that corresponded to pressure and flow values from the patient ventilator were sampled at a rate of 250 samples per second or every 4

milliseconds and stored on a notebook computer via the AcqKnowledge® BIOPAC Systems data acquisition system (BIOPAC Systems, Inc., Goleta, CA).

Table 5-1: Subject Demographic Novel Data

AA = African American, W- White, A/C = Assist/Control, SIMV = Synchronized Intermittent Mandatory Ventilation

Subject Number	Age	Gender	Race	Reason for ICU Admission	Ventilator setting	SOFA score
1	59	F	AA	Unresponsive with low O_2	A/C	10
2	27	F	W	Tylenol toxicity with hepatic injury	SIMV	15
3	54	F	W	Respiratory failure	A/C	6
4	57	M	W	Shortness of Breath	SIMV	12
5	62	M	W	Fever and sepsis	Spontaneous	5
6	50	M	W	Asthma exacerbation	A/C	6
7	46	F	AA	Asthma exacerbation	A/C	9
9	59	F	W	Fever and rash	A/C	9
10	63	M	W	Chronic obstructive pulmonary disease	A/C	4
11	48	M	W	Acute respiratory failure	A/C	13
12	54	F	Asian	Liver failure	Spontaneous	10
13	28	M	AA	Pleural effusion and chronic respiratory failure	BiLevel	7
14	54	F	W	Graft vs host disease, cunninghamella pneumania, & respiratory distress	A/C	4
15	59	M	AA	Shortness of breath and atrial fibrillation	A/C	8
16	60	M	W	Ascites	A/C	7

Once data was collected, two minute samples of each subject's ventilator graphics were presented to three observers for incomplete exhalation detection. The three observers have expertise in mechanical ventilator waveform. The first is a critical care physician, the second is a nursing educator with experience in ventilated patients, and the last is a biomedical engineer who specializes in ventilator waveform analysis. All three observers performed independent detection of incomplete exhalation. Fleiss Kappa statistical measure was used to quantify the inter-rater agreement, a modified version of Cohen's Kappa.[53,54] The incomplete exhalation events that were not initially agreed upon were given forced agreement unanimously by the three observers

post independent detection. The unanimous detection data are then used to validate the algorithm.

To look at whether there were significant difference in performance, the algorithm used the default parameter as follows: F_{oi} = -3 L/min, ΔT = 0.2 s, and slope threshold = 90 L-s/min. F_{oi} is the value of flow at the onset of inhalation. ΔT is the time difference between onset inhalation to the 0 L/min mark. Slope threshold is set for the slope of change of flow over ΔT. This default parameter came from an optimization from the highest Youden index from the old data that yielded sensitivity of 0.91 and specificity of 0.84. Data sets of both the old study population versus the novel population were compared for their true and false positive rates. Equal variance tests were performed and their subsequent results were used to perform a two-tailed t-test between the two population to determine whether there were any significant difference in the algorithm's performance for the two populations.

Results

Fleiss kappa index from the three observers yielded 0.88 for agreement.

Discrete ROC curve from novel data showed the overall result of the mean values of sensitivity and specificity across the subjects for the 1365 classifier points (figure 5-2). The default parameter yielded Youden index of 0.70 with sensitivity of 0.97 and specificity of 0.72 for the novel data.

Results from testing the algorithm with the default parameters yielded equal variance for true positive rate (TPR) values according to Brown-Forsythe test (p –value = 0.1408). A subsequent two tailed t-test assuming equal variances showed no significant difference (t = 1.5,

df = 12.402, *p*-value = 0.1408) for the algorithm's true positive rates between the old subjects data and the novel subjects data (see table 5-2).

Results from testing the algorithm with default parameter on both data sets yielded unequal variance for false positive rate (FPR) values according to Brown-Forsythe test (*p* –value = 0.0398). Subsequent two tailed t-test assuming unequal variances showed no significant difference (*t* = 1.9, *df* = 16.765, *p*-value = 0.0725) for the algorithm's false positive rates between the old subjects data and the novel subjects data (see table 5-2).

Table 5-2: Comparing Novel and Old Data

				TPR			FPR		
Parameter	F_{oi}	ΔT	slope threshold	Novel	Old	t-test p-value	Novel	Old	t-test p-value
Default/ Old max Youden	-3	0.2	90	0.97	0.91	0.1408	0.28	0.16	0.0725
Novel max Youden	-2	0.025	150	0.93			0.08		

The novel data's maximum Youden index yielded a different parameter set from the default parameter set. Youden index value for novel data is 0.85 at sensitivity of 0.93 and specificity of 0.91. Which yielded parameter settings of F_{oi} = -2 L/min, ΔT = 0.025 s, and slope threshold = 150 L-s/min.

Figure 5-1: ROC graph of old data. The large O represents the point with highest Youden index for old data resulting from inputting default optimum parameter set.

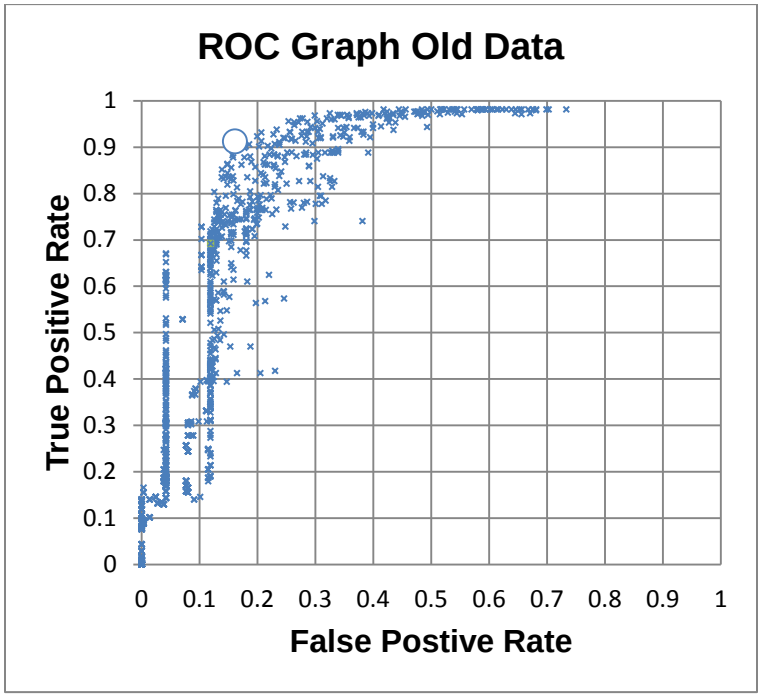


Figure 5-2: ROC graph of novel data. The large O represents the point resulting from inputting default optimum parameter set from the old data. The large diamond (◊) represents the point with highest Youden index for novel data.

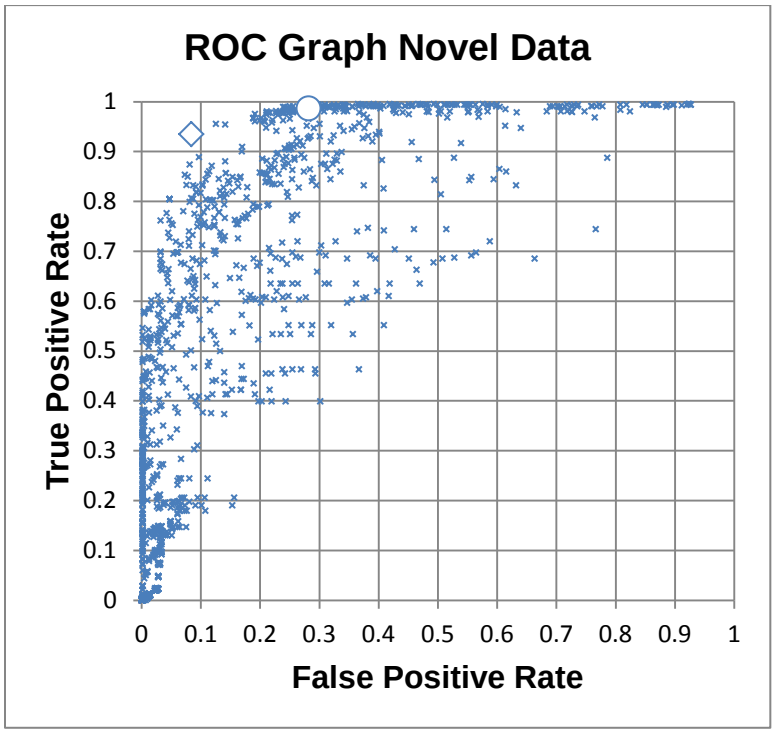


Figure 5-3: Old data's Youden index contour plot

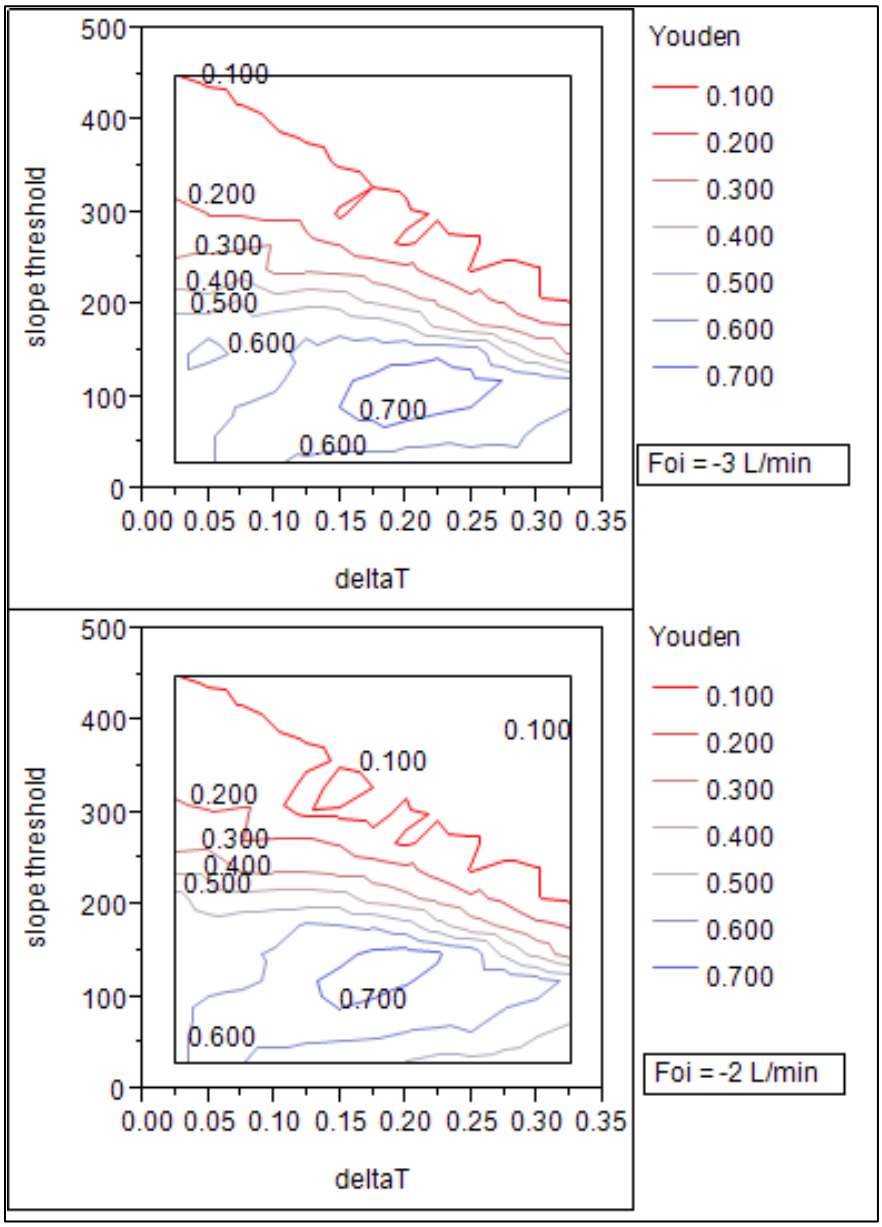


Figure 5-4: Novel data's Youden index contour plot

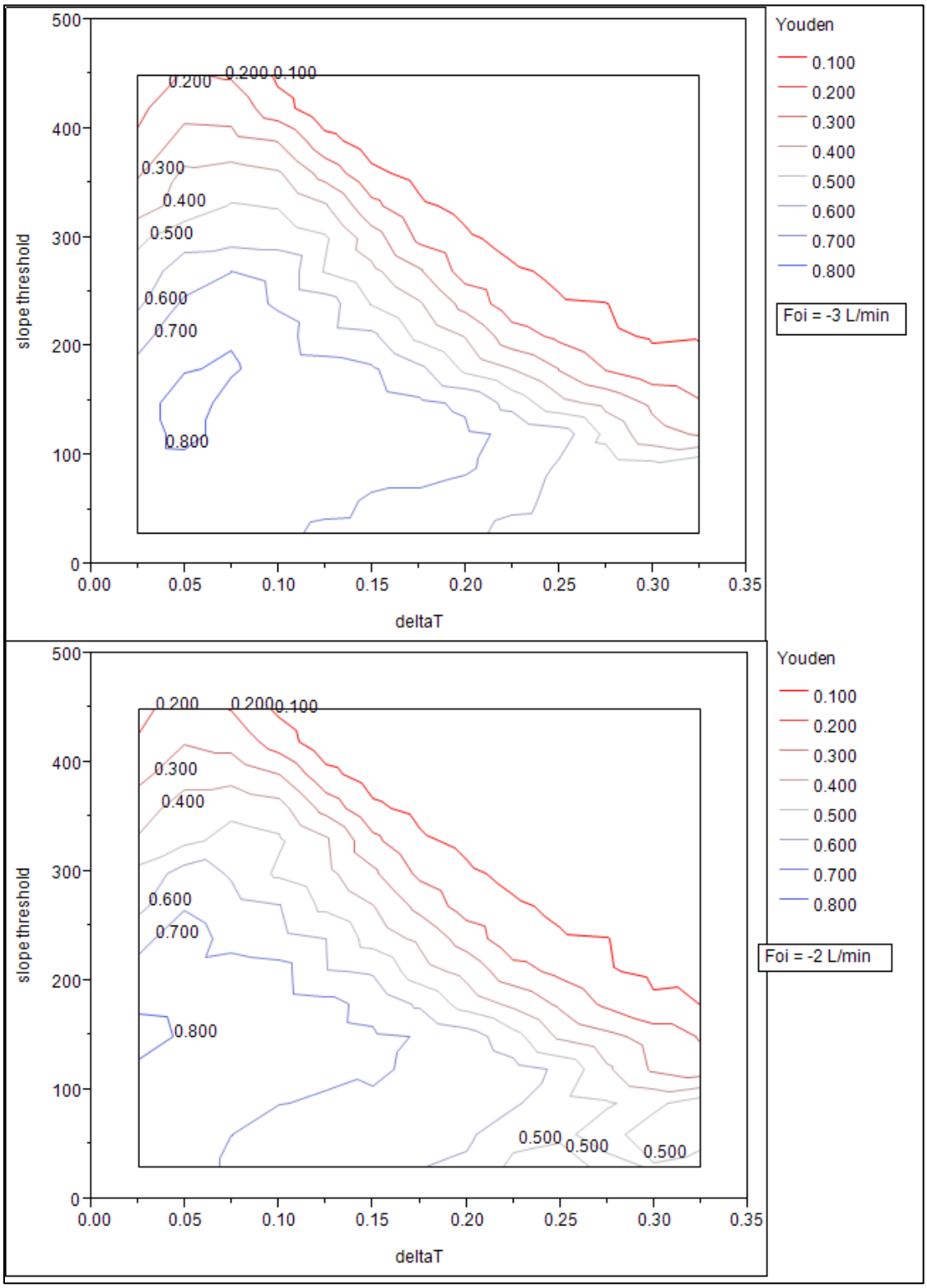
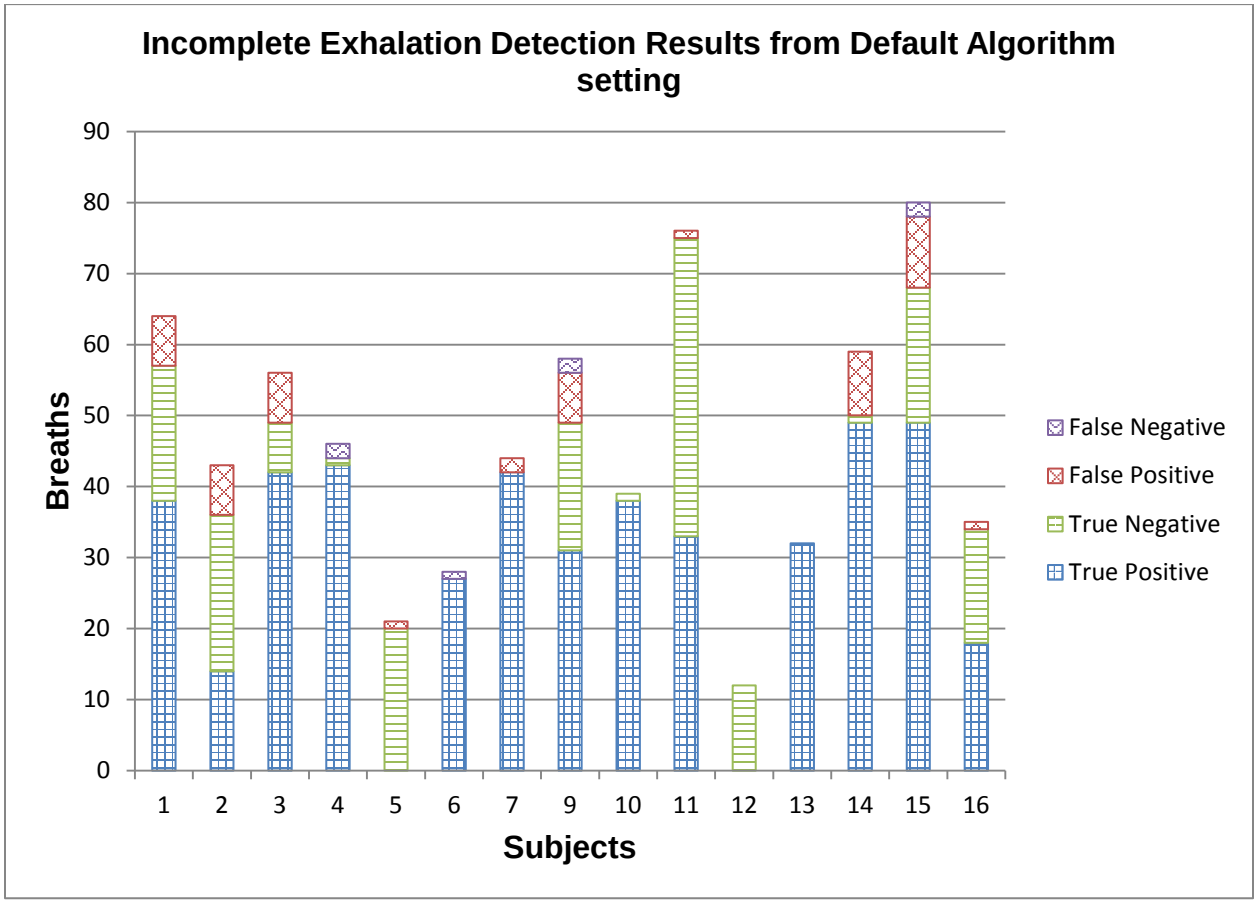


Figure 5-5: Novel data incomplete exhalation detection with algorithm setting F_{oi} = -3, ΔT = 0.2, and slope threshold = 90



Discussion/ Conclusion

The purpose of testing the algorithm with the default parameters on the novel data was to see whether the performance of the algorithm changed for a new set of data. Two tailed t-tests for both true positive rates and false positive rates mathematically showed that the algorithm's performance was not statistically different. Although the *p*-values were not high, the novel data did show a higher sensitivity value (0.97) than the old data (0.91). The novel data's specificity is acceptable (0.72) given that the novel data yielded high accuracy of 0.93 and high precision of

0.84. These numbers support the t-tests' results that the algorithm's performance was not significantly different between the two populations.

The novel data yielded a different maximum Youden index point than the old data, but this was to be expected since the novel data were made up of completely different subjects (see figures 5-1 and 5-2). The fact that the algorithm's default parameter did not yield statistically different performance between the old and novel data outweighs the concern of the novel data having a different maximum Youden index. It is conclusive that evidence points toward the algorithm's robust performance. Furthermore, the validation of the functionality of the algorithm to automatically detect incomplete exhalation is present because the algorithm's default setting yielded high accuracy and precision values for a set of untested, novel data.

In the previous chapter, one of the limitations of the study pointed towards grey categories of incomplete exhalation as expressed by the observers. Such complaints were not as prevalent for the novel data, and the higher Fleiss Kappa value (old = 0.81versus novel = 0.88) supports this notion. This is due to the fact that the novel data were screened for the positive presence of incomplete exhalation, whereas the old data was not. The changes in the Youden plateau between the old and novel data were presented in figures 5-3 and 5-4. The Youden plateau moved from the middle ΔT range to the lower ΔT range. Definitive incomplete exhalation detection by observers had shorter ΔT, due to a higher slope, when compared against ambiguous incomplete exhalation. Interestingly enough, the old data contour plot showed an emerging second plateau right around the area of the novel data's plateau. This suggested that within the old data set, incomplete exhalations with short ΔT were present indicating unambiguous incomplete exhalation. Figure 5-5 showed true positive, true negative, false

positive, and false negative resulted from testing the algorithm's default parameter for each subject. Note that subjects 5 and 12 actually had no incomplete exhalation even though they were screened to have them. This is because both subjects' ventilator settings were changed immediately before data collection that eliminated instances of incomplete exhalation.

It is reasonable to pick ranges for the default setting parameters based on the contour plots of both data sets. F_{oi} will be between -2 and -3 L/min. Slope thresholds will be between 80 and 160 L-s/min. ΔT will have the widest range from 0.025 to 0.225 s. The range for ΔT could be narrower if there is a consensus from respiratory healthcare providers as to the definite boundaries for incomplete exhalation detection. This can be achieved by recruiting more qualified observers to rate various incomplete exhalation waveforms and deliberate on their decisions.

Ultimately, the dissertation objective is to establish an automated detection algorithm of auto-PEEP. Now that there is a detection algorithm established for incomplete exhalation, the next task to quantitatively link between frequencies of incomplete exhalation (index) with pressure values of auto-PEEP. How many incomplete exhalations need to occur before auto-PEEP is significantly present? Would using an index of 50% of a person's breaths in a minute enough for auto-PEEP to emerge? Or would the index have to be 60%, 70%, or 80%? These are the questions that can be answered by collecting auto-PEEP values in tandem with incomplete exhalation detection.

Chapter 6 Analyzing Relationship of Incomplete Exhalation with Auto-PEEP

Introduction/ Background

Auto-PEEP, short for auto positive end-expiratory pressure, is an excessive pressure in the alveolar lungs. This auto-PEEP, also known as intrinsic PEEP (PEEPi), is caused by an accumulation of an air volume that is trapped by incomplete exhalation (IE) at the end of a breath. Air which is not allowed to exit can lead to excessive pressure. For those who are on mechanical ventilation, the lingering effect of this excessive pressure, or auto-PEEP, can cause increased work of breathing, failure to wean from mechanical ventilator, worsening of alveolar gas exchange, hemodynamic compromise, hypotension, inappropriate treatment, cardiac electromechanical dissociation, and even death. Hence it is important to be able to detect it quickly and change the mechanical ventilator treatment of the patient to avoid any of these adverse effects. [12-14,21,24,25,29,49]

Previous chapters have involved the description and validation of an algorithm for automatically detecting the incomplete exhalation that contributes to auto-PEEP. This chapter further investigates the quantitative relationship between the rates of occurrence of incomplete exhalation with the auto-PEEP values that are present. The algorithm developed for automated incomplete exhalation detection will be used to sweep through the waveform data for any incomplete exhalation and calculate the percentage of it occurring every minute (index).

Method

Data from 13 subjects were collected from the patients of Virginia Commonwealth University Health System (VCUHS) Medical Respiratory Intensive Care Unit (MRICU). Human subject research was approved by VCU Institutional Review Board (IRB # HM 13962), and consents were obtained from subjects' legally authorized representatives given the sedated condition of the subjects. Inclusion criteria for subject enrollment were adult patients who were sedated and intubated with mechanical ventilators, not including tracheal intubation with a collar. Further, ventilators must be in a setting where expiratory hold maneuver was allowed to take place. This excluded spontaneous setting. Additional inclusion criteria included patients with any known risk factors for developing auto-PEEP such as asthma, chronic obstructive pulmonary disease (COPD), or acute respiratory distress syndrome (ARDS). [12,14,18] Table 6-1 shows the subject demographic including age, gender, race, reason for ICU admission, ventilator setting, and Sequential Organ Failure Assessment (SOFA) score during the time of data collection.

For each participating subject the airway flow and pressure waveform were recorded up to 90 minutes using NICO® cardiopulmonary management system, an FDA approved medical monitoring device by Philips Respironics, Carlsbad, CA. Airway flow and pressure were measured from inline pressure and airflow sensors of the NICO® device connected to the patient ventilator line through medical grade tubing. Continuous analog voltage signals that corresponded to pressure and flow values from the patient ventilator were sampled at a rate of 250 samples per second or every 4 milliseconds and stored on a notebook computer via the AcqKnowledge® BIOPAC Systems data acquisition system (BIOPAC Systems, Inc., Goleta,

CA). Expiratory hold maneuvers were conducted every 10 minutes during data collection to record the quantitative value of auto-PEEP.[12,48]

Table 6-1: Subject Demographic

AA = African American, W- White, A/C = Assist/Control, SIMV = Synchronized Intermittent Mandatory Ventilation

Subject Number	Age	Gender	Race	Reason for ICU Admission	Ventilator setting	SOFA score
1	59	F	AA	Unresponsive with low O_2	A/C	10
2	27	F	W	Tylenol toxicity w/ hepatic injury	SIMV	15
3	54	F	W	Respiratory failure	A/C	6
4	57	M	W	Shortness of breath	SIMV	12
6	50	M	W	Asthma exacerbation	A/C	6
7	46	F	AA	Asthma exacerbation	A/C	9
9	59	F	W	Fever and rash	A/C	9
10	63	M	W	Chronic obstructive pulmonary disease	A/C	4
11	48	M	W	Acute respiratory failure	A/C	13
13	28	M	AA	Pleural effusion and chronic respiratory failure	BiLevel	7
14	54	F	W	Graft vs host disease, cunninghamella pneumania, & respiratory distress	A/C	4
15	59	M	AA	Shortness of breath and atrial fibrillation	A/C	8
16	60	M	W	Ascites	A/C	7

Once waveform data and auto-PEEP values from the expiratory hold maneuver were collected, index of incomplete exhalation was determined for every minute. A mean value of the index during the time range between expiratory hold was performed and paired with the auto-PEEP value.

Results

Based on statistical analysis, no significant linear model was found that described the relationship between IE index and auto-PEEP ($F_{1,62} = 1.67$, p-value = 0.2010). Figure 6-1 shows scatterplot of intrinsic PEEP and IE index.

Table 6-2 displays the correlation between IE index and intrinsic PEEP per subject. Subjects 1, 2, 3, 4, 6, 7, 10, and 13all showed positive correlation whereas subject 10 produced a

significant linear model ($F_{1,4}$= 12.53, *p*-value = 0.024). Subjects 9, 11, 15, and 16 showed a negative correlation while only subject 16 producing significant linear model ($F_{1,4}$= 49.55, *p*-value = 0.0021).

Table 6-2: Correlation of IE Index with PEEPi by Subject and Overall

	IE index			PEEPi				
Subject	Mean	Std Dev	N	Mean	Std Dev	Correlation	R^2	p-value
1	0.7692	0.0298	7	3.2286	2.2246	0.53	0.29	0.2127
2	0.7668	0.2319	9	0.9889	0.8313	0.55	0.3	0.1271
3	0.8543	0.0656	4	13	2.1602	0.49	0.26	0.4901
4	0.9777	0.0187	5	1.76	1.2361	0.62	0.38	0.2679
6	0.7479	0.2503	3	1.5667	0.2082	0.8	0.63	0.4144
7	0.614	0.317	6	2.65	0.5925	0.6	0.36	0.2071
9	0.7072	0.029	6	5.9333	4.1428	-0.7	0.5	0.1153
10	0.8682	0.2088	6	1.4333	0.5574	0.87	0.76	0.024
11	0.4884	0.0207	3	19.6667	1.1547	-0.2334	0.05	0.8497
13	0.791	0.1473	4	3.975	1.0404	0.79	0.62	0.2107
14	0.9899		1	1.8		0		
15	0.6589	0.0475	4	2.725	1.258	-0.2	0.04	0.804
16	0.6389	0.0238	6	2	0.8832	-0.96	0.93	0.0021
Overall	0.7509	0.1896	64	4.0109	4.8079	-0.16	0.03	0.201

Figure 6-1: Scatterplot of intrinsic PEEP with IE index

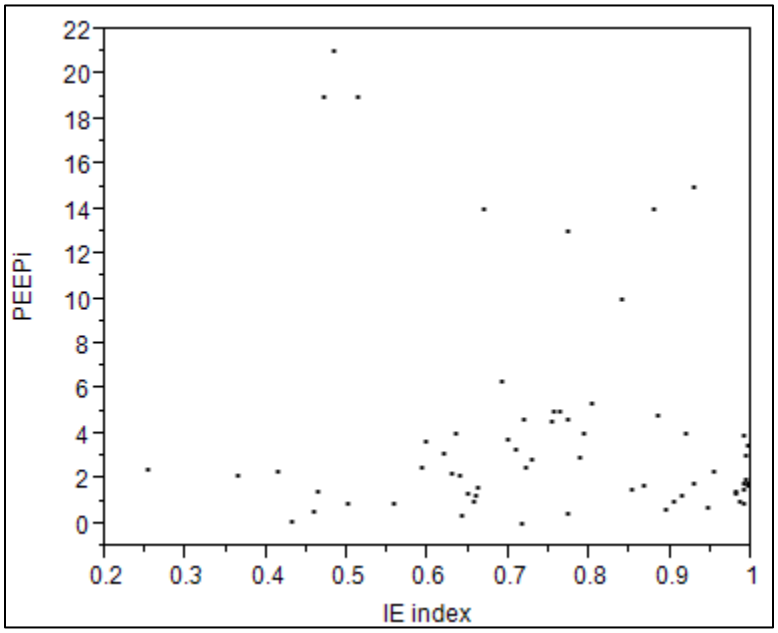


Figure 6-2: PEEPi values along with IE index vs time for subject 2

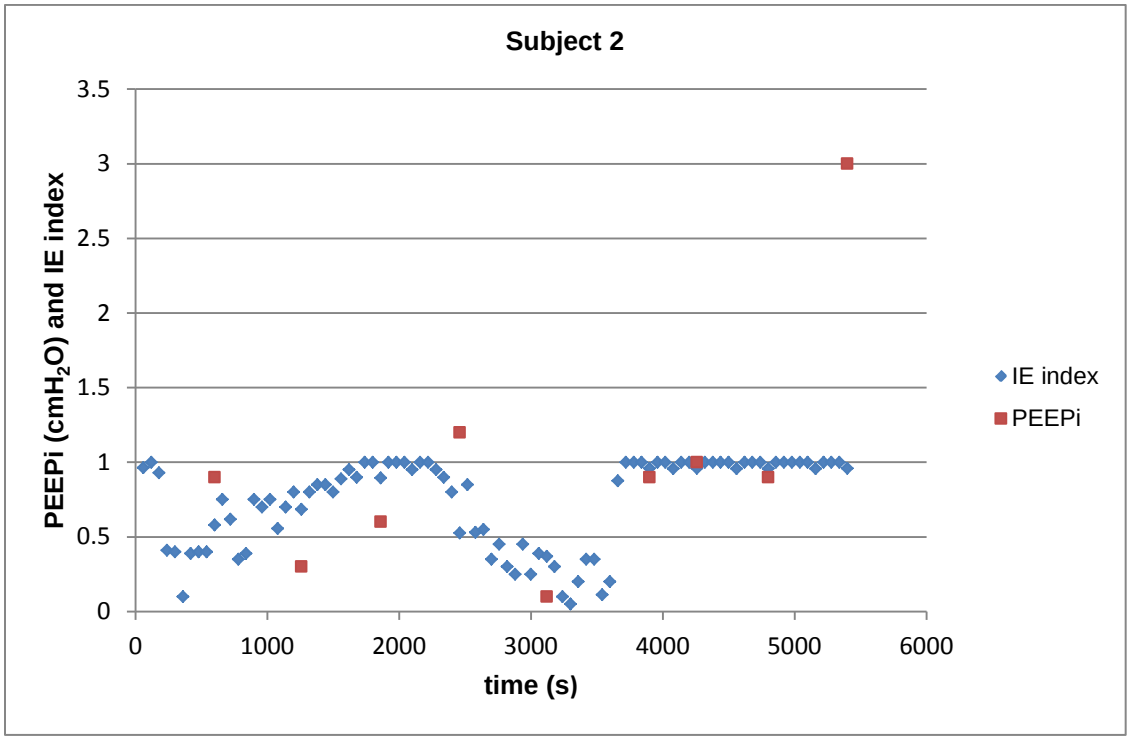


Figure 6-3: PEEPi values along with IE index vs time for subject 7

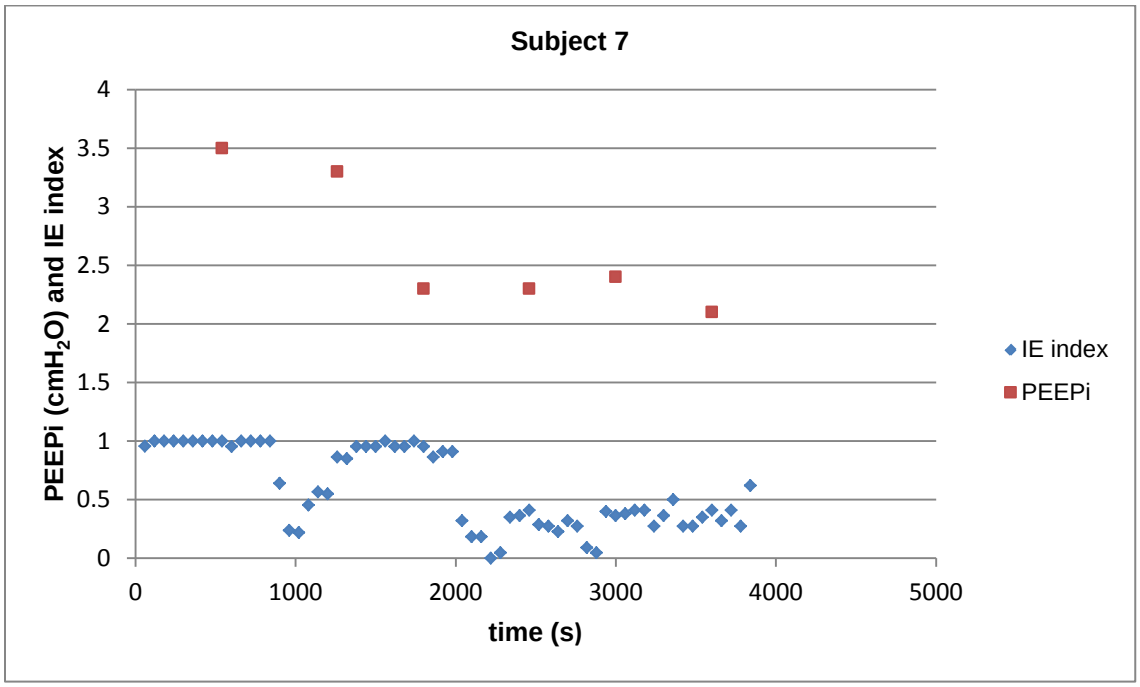
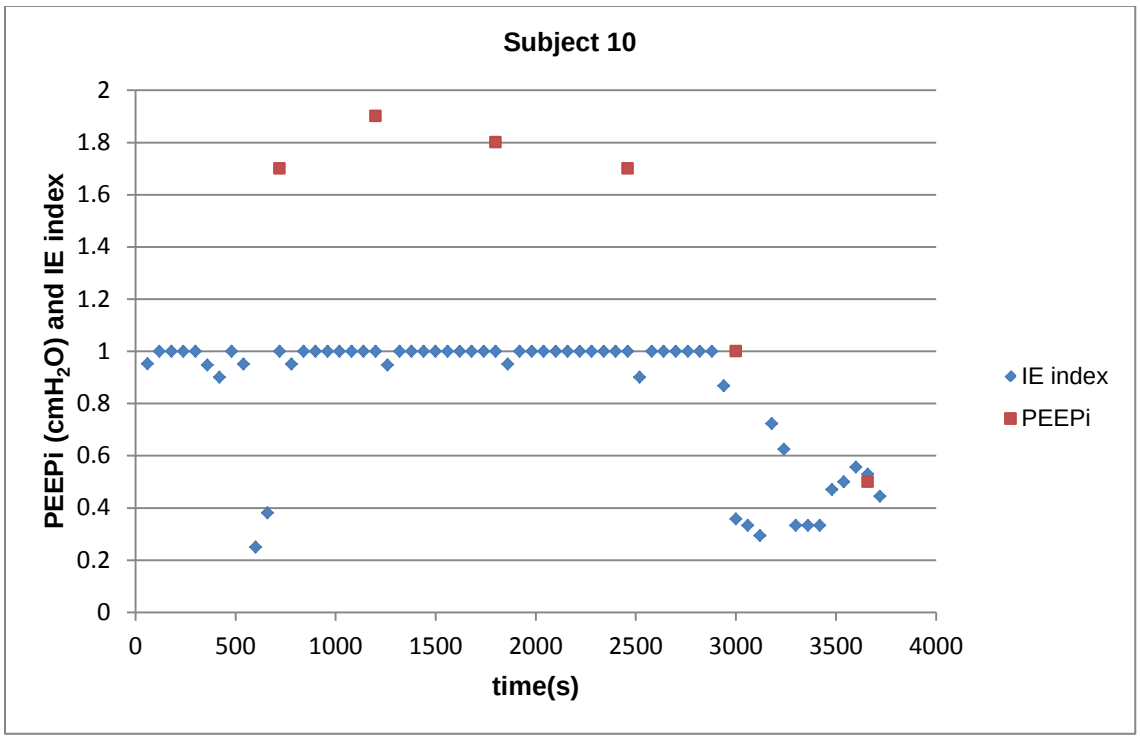


Figure 6-4. PEEPi values along with IE index vs time for subject 10



Discussion and Conclusion

Data showed no significant linear relationship for the overall correlation of incomplete exhalation index and intrinsic PEEP value during the expiratory hold maneuver and is counter to what the literature has suggested. One reason could be because different patient lungs have different compliance and stiffness causing higher or lower PEEPi values for the same IE index. Logic then infers to looking at the IE index and PEEPi values per subject. Even upon doing so, no definitive relationship was present (see table 6-2).

A pattern emerged when IE index and PEEPi values were both viewed as functions of time. Figures 6-2 to 6-4 showed subject 2, 7, and 10's IE index and PEEPi value with relation to time. These figures present a clear picture of the rise and fall of PEEPi values that corresponded to the rise and fall of IE index. With more data, there can be a better picture of how the time dependency influences the relationship of IE index and PEEPi. Speculation can be made that certain IE index need to be sustained for a period of time before a PEEPi value rises to a significant number, but that delay time is still unknown. Furthermore, how often expiratory hold maneuver should be performed for accurate PEEPi value is unknown. PEEPi taken in between long time period will yield lower sampling. PEEPi taken too often can cause significant air release from the incomplete exhalation air-trapping, thereby tainting the PEEPi measurement.

Two conclusions emerge from this chapter. The first being there is no conclusive significant linear relationship between IE index and auto-PEEP for this population. The second is that there is a time dependency that needs to be factored in when relationship between IE index and PEEPi are observed.

Chapter 7 Future Work

Auto-PEEP Cutoff for Incomplete Exhalation Index

The next step in the research for an automated detection of auto-PEEP is to establish a threshold for incomplete exhalation (IE) index. In theory, it is understood that when repeated incomplete exhalation occurs without allowing flow equlibriation for the trapped gas to escape, pressure builds up leading to an eventual auto-PEEP. The threshold of how many repetitive IE needs to occur for it to be significant enough to be warranted as auto-PEEP has yet to be established. Also, the threshold of what quantity of auto-PEEP is high enough that measures are necessary to be enacted to avoid impending negative has yet to be established as well. Is it 2 cmH_2O, 5 cmH_2O, 10 cmH_2O, or some other value?

A preliminary plan to progress the automated detection of auto-PEEP would be as follows: establishing an internal alarm when IE index reach a threshold and execute automatic expiratory hold maneuver to obtain auto-PEEP value; if auto-PEEP value passes a threshold, then the external alarm would be sound. If the auto-PEEP is not significantly high enough to sound the external alarm, but the IE index is high enough to warrant an expiratory hold maneuver, provisions for reasonable periodic frequency of performing expiratory hold maneuver would be in place. This frequency could be every half hour, every hour, or more depending how clinicians would deem it best for the patient.

Incomplete Exhalation Relationship with Asynchrony

Research has tied in the relationship between auto-PEEP and some forms of asynchrony.[4,20,21] It would be very interesting to see what relationship, if any exists between IE index and asynchrony. Can we predict event of asynchrony based on IE? With the algorithm provided in this dissertation combined with the numerous automated ways of detection trigger asynchrony mentioned in Chapter 2, it is conceivable to analyze very large ventilator data sets that can span days and weeks. Machines will do the detection work, where previously no observer could spare the time to do.

Real-Time Application

The automated detection cannot be incorporated into clinical use unless performed in real time. During the course of developing, optimizing, and analyzing the automated detection for IE, the algorithmic detection had always been done post data collection. It is a necessary goal to have a real-time automated detection.

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APPENDIX A

MatLab Code for Detection Algorithm

```
function [Result] = PEEPiDetectVER5(observerIE, subjMfile, sampling,
FlowChannel, PressureChannel, FlowThresh, deltaT, slopethreshold, Pthresh)

% This is a function to detect Auto-PEEP from Flow waveform,FPthresh
% after data is acquired.

% Creator: Nyimas Y. Isti Arief
%          ariefny@vcu.edu
%          Biomedical Engineering, VCU, Richmond, VA, USA
%          January 14, 2013

% VER5 update: include input of observer IE values and output true positive
% and true negative values, but data read cycle section is taken from VER3
% not VER4
% VER4 update: Combine with codes from AutoPEEPdetect for breath inhalation
% marker
%

% Inital concept of how it works
% 1. Read flow data bit by bit
% 2. Once data value is below FlowThresh, simultaneously read future data
deltaT
% bits ahead.
% 3. If future data is positive and fulfill slopethreshold (IE for slope
bigger than, eg 0.150 s: value of delta flow/delta t in seconds), then
% incomplete exhalation is detected.

% Other notes:
% --> addtnl notes, if BiLevel use Pthresh PEEPHI-1 ? - yes, works for
subj020
% - place a filtering window ahead of algorithm to smooth out Pressure
% waveform as well as Flow for phase shift continuity (recommend filter IIR
% LPF 5 Hz, delay about 40-50 ms)
%
% Criteria for use: Pressure must be in units of cmH20 and Flow in units of
% L/min, not volts
```

```
% and
% HAVE TO MAKE SURE DATA STARTS and STOPS BEFORE onset of INHALATION
% Notes 2/5/2013: FlowThresh should be fixed at -1 or int < 0, which would be
at -1. This is the theoretical definition of flow being and incomplete
exhalation, that is flow not reaching zero at the start of a new breath.


% Acquiring flow data
acqdata = load(subjMfile);
flow = acqdata.data(:, FlowChannel);
% Acquiring pressure data
pressure = acqdata.data(:, PressureChannel);
% Acquiring observer data
if ~isempty(observerIE)
    fid = fopen(observerIE);
    IE_Obs = [];
    while 1
        tline = fgetl(fid);
        if ~ischar(tline),   break,   end
        numtline = str2num(tline);
        IE_Obs = [IE_Obs; numtline];
    end
    fclose(fid);
else
    IE_Obs = [];
end

% Portion taken from AutoPEEPdetect
% Detection of Onset of Inhalation via Pressure waveform
if isempty(Pthresh)
    Pthresh = round(mean(pressure)); % for real-time coding, change this to
"mean pressure of last 5 breaths"
end
Pinhale = []; Pmin = pressure(1,:);
tinhale = []; t = 1;
i = 1;
while i < length(pressure)
    if Pmin < pressure(i,:)
        if pressure(i,:) < pressure(i+1)
            i = i+1;
        elseif pressure(i,:) > pressure(i+1,:)
            Pmin = pressure(i,:);
            t = i;
            i = i+1;
        else
            i = i+1;
        end
    elseif Pmin >= pressure(i,:)
        Pmin = pressure(i,:);
        t = i;
        i = i+1;
    end
```

```
    if pressure(i,:) > Pthresh % when data read, i, crosses over pressure
threshold to indicate inhalation,
        Pinhale = [Pinhale; Pmin]; % then store the latest Pmin
        tinhale = [tinhale; t];
        while (pressure(i,:) > Pthresh-1) && (i < length(pressure)) % while
data read, i, is on inhalation (indicated by Pthresh),
            i = i+1;                                                % then do
not record any i as Pmin, just keep on going
        end                                                         % Until i
fall below Pthresh - 1, the 1 value is a hysteresis buffer
        Pmin = pressure(i,:);                                       % Once
fall well below Pthresh line (Pthresh - 1), new Pmin indices can resume
        t = i;
    end
end
% rid of first value as a low pressure value for onset inhalation
if tinhale(1) == 1 % 1 being the first sample, if sampling is 1000 Hz, 1
corresponds to 0.001s, if sampling is 250 Hz, 1 corresponds to 0.004s
    tinhale = tinhale(2:end);
    Pinhale = Pinhale(2:end);
end

InhalationMarker = [tinhale/sampling, flow(tinhale,:),Pinhale];% div by
sampling to match seconds
[rowInhalationMarker, colInhalationMarker] = size(InhalationMarker);
% End portion from AutoPEEPdetect

% Replacing IE_Obs points to the corresponding points of InhalationMarker
if ~isempty(IE_Obs)
    for i = 1 : rowInhalationMarker
        for j = 1 : length(IE_Obs)
            if abs(IE_Obs(j) - InhalationMarker(i,1)) < 0.5
                InhalationMarker(i,1) = IE_Obs(j);
% 0.5 can be any number but it has to be the same cutoff value for comparing
IE_Obs to InhalationMarker, IE_Alg to InhalationMarker, and IE_Alg to IE_Obs.
% IE_Obs value is in InhalationMarker
% Only IEDetect that are on same breath as InhalationMarker are recorded as
IE_Alg
% Only IE_Alg that are on same breath as IE_Obs(values in InhalationMarker)
are valTruePositive
% IE_Alg that are not on same breath as IE_Obs are still on same breath as
InhalationMarker, and are recorded as valFalsePositive
            end
        end
    end
end
% End Replacing IE_Obs points to the corresponding points of InhalationMarker

% Calibrating deltaT based on sampling frequency
deltaValue = deltaT;
deltaT = deltaT * sampling;
if isinteger(deltaT) == 0
    deltaT = round(deltaT);
end
```

```
% Initializations
IEdetect = []; % Assigning IEdetect variable
OnsetInhalation = []; % Assigning Onset of Inhalation variable

% Commence data read cycle
for i = 1 :1: length(flow)- deltaT;
    % Check if flow is negative
    if flow(i,:) <= 1 % breath flow (negative) is exhaling before onset of
inhalation, choose value 1 because 0 value fluctuates during exhalation
        if flow(i+deltaT,:) > 1 % Read deltaT bits ahead to see if flow is
inhaling (positive), indicative of onset of inhalation
            % Calculate slope between present i and deltaT+i
            deltaflow = flow(i+deltaT,:) - flow(i,:);
            slope = deltaflow/(deltaValue);

            % Begin IE detection and Onset of Inhalation detection --> Flow-
dependent detection
                % Checking IE detection against Onset of Inhalation being
                % more than half (0.5) of meanLast5brthOnset time distance
                % away from the last onset should deter from any
                % double-trigger as IE detection (matching definition of
                % double trigger: a trigger occurring in less than half the
                % normal exhalation time)

            if isempty(OnsetInhalation)% Onset inhalation data is empty
                % Mark Onset of breath inhalation
                OnsetInhalation = [OnsetInhalation; i]; % i is in samples,
not seconds
                if (abs(slope) > slopethreshold) && (flow(i,:) <= FlowThresh)
% test slope threshold and flow threshold for conditions of IE
                    IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)]; % Record IE event; this is deltaT based on sampling, not
actual sec time
                end

            elseif max(size(OnsetInhalation)) == 1 % When there's only 1
onset inhalation recorded
                % check distance from last onset of inhalation
                if (i-OnsetInhalation)  > sampling*0.5 % Prevent redundancy
and trigger asynchrony (double triggering) detection during exhalation phase:
Write IE/onset inhalation detection only if enough time passes, ie 75% of
mean of last Breath Periods, or greater than 0.5 sec.
                    OnsetInhalation = [OnsetInhalation; i];
                    if (abs(slope) > slopethreshold) && (flow(i,:) <=
FlowThresh) % test slope threshold and flow threshold for conditions of IE
                        IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)]; % Record IE event
                    end
                elseif (i-OnsetInhalation(end)) < deltaT % for the case when
IE is detected after a non IE onset inhalation is detected that is within the
same onset point (IE-last Onset is within deltaT time)
```

```
                    if (abs(slope) > slopethreshold) && (flow(i,:) <=
FlowThresh) % test slope threshold and flow threshold for conditions of IE
                        if isempty(IEdetect)% for the case that there's no
previous IE detection
                            OnsetInhalation(end,1) = i ;
                            IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)];
                        elseif (i - IEdetect(end,1)) > sampling*.5
                            OnsetInhalation(end,1) = i ;
                            IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)];
                        end
                    end
                end

            elseif max(size(OnsetInhalation)) == 2 % When there's 2 onset
inhalation recorded
                % get mean values of latest breath periods
                Last5BrthOnset = OnsetInhalation(end)-OnsetInhalation(end-1);
                meanLast5BrthOnset = Last5BrthOnset;
                if (i-OnsetInhalation(end)) > 0.5*meanLast5BrthOnset %
Prevent redundancy and trigger asycnhrony (double triggering) detection
during exhalation phase: Write IE/onset inhalation detection only if enough
time passes, ie 75% of mean of last Breath Periods, or greater than 0.5 sec.
                    OnsetInhalation = [OnsetInhalation; i];
                    if (abs(slope) > slopethreshold) && (flow(i,:) <=
FlowThresh) % test slope threshold and flow threshold for conditions of IE
                        IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)];
                    end
                elseif (i-OnsetInhalation(end)) < deltaT % for the case when
IE is detected after a non IE onset inhalation is detected that is within the
same onset point (ie deltaT)
                    if (abs(slope) > slopethreshold) && (flow(i,:) <=
FlowThresh) % test slope threshold and flow threshold for conditions of IE
                        if isempty(IEdetect)% for the case that there's no
previous IE detection
                            OnsetInhalation(end,1) = i ;
                            IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)];
                        elseif (i - IEdetect(end,1)) > 0.5*meanLast5BrthOnset
                            OnsetInhalation(end,1) = i ;
                            IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)];
                        end
                    end
                end

            elseif max(size(OnsetInhalation)) == 3 % When there's 3 onset
inhalation recorded
                Last5BrthOnset = [OnsetInhalation(end)-OnsetInhalation(end-
1),OnsetInhalation(end-1)-OnsetInhalation(end-2)];
                meanLast5BrthOnset = mean(Last5BrthOnset);
```

```
                if (i-OnsetInhalation(end)) > 0.5*meanLast5BrthOnset %
Prevent redundancy and trigger asycnhrony (double triggering) detection
during exhalation phase: Write IE/onset inhalation detection only if enough
time passes, ie 75% of mean of last Breath Periods, or greater than 0.5 sec.
                    OnsetInhalation = [OnsetInhalation; i];
                    if (abs(slope) > slopethreshold) && (flow(i,:) <=
FlowThresh) % test slope threshold and flow threshold for conditions of IE
                        IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)];
                    end
                elseif (i-OnsetInhalation(end)) < deltaT % for the case when
IE is detected after a non IE onset inhalation is detected that is within the
same onset point (ie deltaT)
                    if (abs(slope) > slopethreshold) && (flow(i,:) <=
FlowThresh) % test slope threshold and flow threshold for conditions of IE
                        if isempty(IEdetect)% for the case that there's no
previous IE detection
                            OnsetInhalation(end,1) = i ;
                            IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)];
                        elseif (i - IEdetect(end,1)) > 0.5*meanLast5BrthOnset
                            OnsetInhalation(end,1) = i ;
                            IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)];
                        end
                    end
                end

            elseif max(size(OnsetInhalation)) == 4 % When there's 4 onset
inhalation recorded
                Last5BrthOnset = [OnsetInhalation(end)-OnsetInhalation(end-
1),OnsetInhalation(end-1)-OnsetInhalation(end-2), ...
                    OnsetInhalation(end-2)-OnsetInhalation(end-3)];
                meanLast5BrthOnset = mean(Last5BrthOnset);
                if (i-OnsetInhalation(end)) > 0.5*meanLast5BrthOnset %
Prevent redundancy and trigger asycnhrony (double triggering) detection
during exhalation phase: Write IE/onset inhalation detection only if enough
time passes, ie 75% of mean of last Breath Periods, or greater than 0.5 sec.
                    OnsetInhalation = [OnsetInhalation; i];
                    if (abs(slope) > slopethreshold) && (flow(i,:) <=
FlowThresh) % test slope threshold and flow threshold for conditions of IE
                        IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)];
                    end
                elseif (i-OnsetInhalation(end)) < deltaT % for the case when
IE is detected after a non IE onset inhalation is detected that is within the
same onset point (ie deltaT)
                    if (abs(slope) > slopethreshold) && (flow(i,:) <=
FlowThresh) % test slope threshold and flow threshold for conditions of IE
                        if isempty(IEdetect)% for the case that there's no
previous IE detection
                            OnsetInhalation(end,1) = i ;
                            IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)];
```

```
                        elseif (i - IEdetect(end,1)) > 0.5*meanLast5BrthOnset
                            OnsetInhalation(end,1) = i ;
                            IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)];
                        end
                    end
                end

            elseif max(size(OnsetInhalation)) == 5 % When there's 5 onset
inhalation recorded
                Last5BrthOnset = [OnsetInhalation(end)-OnsetInhalation(end-
1),OnsetInhalation(end-1)-OnsetInhalation(end-2), ...
                    OnsetInhalation(end-2)-OnsetInhalation(end-3),
OnsetInhalation(end-3)-OnsetInhalation(end-4)];
                meanLast5BrthOnset = mean(Last5BrthOnset);
                if (i-OnsetInhalation(end)) > 0.5*meanLast5BrthOnset %
Prevent redundancy and trigger asycnhrony (double triggering) detection
during exhalation phase: Write IE/onset inhalation detection only if enough
time passes, ie 75% of mean of last Breath Periods, or greater than 0.5 sec.
                    OnsetInhalation = [OnsetInhalation; i];
                    if (abs(slope) > slopethreshold) && (flow(i,:) <=
FlowThresh) % test slope threshold and flow threshold for conditions of IE
                        IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)];
                    end
                elseif (i-OnsetInhalation(end)) < deltaT % for the case when
IE is detected after a non IE onset inhalation is detected that is within the
same onset point (ie deltaT)
                    if (abs(slope) > slopethreshold) && (flow(i,:) <=
FlowThresh) % test slope threshold and flow threshold for conditions of IE
                        if isempty(IEdetect)% for the case that there's no
previous IE detection
                            OnsetInhalation(end,1) = i ;
                            IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)];
                        elseif (i - IEdetect(end,1)) > 0.5*meanLast5BrthOnset
                            OnsetInhalation(end,1) = i ;
                            IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)];
                        end
                    end
                end

            elseif max(size(OnsetInhalation)) > 5 % When there's more than 5
onset inhalation recorded
                Last5BrthOnset = [OnsetInhalation(end)-OnsetInhalation(end-
1),OnsetInhalation(end-1)-OnsetInhalation(end-2), ...
                    OnsetInhalation(end-2)-OnsetInhalation(end-3),
OnsetInhalation(end-3)-OnsetInhalation(end-4), OnsetInhalation(end-4)-
OnsetInhalation(end-5)];
                meanLast5BrthOnset = mean(Last5BrthOnset);
                if (i-OnsetInhalation(end)) > 0.5*meanLast5BrthOnset %
Prevent redundancy and trigger asycnhrony (double triggering) detection
```

```
during exhalation phase: Write IE/onset inhalation detection only if enough
time passes, ie 75% of mean of last Breath Periods, or greater than 0.5 sec.
                    OnsetInhalation = [OnsetInhalation; i];
                    if (abs(slope) > slopethreshold) && (flow(i,:) <=
FlowThresh) % test slope threshold and flow threshold for conditions of IE
                        IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)];
                    end
                elseif (i-OnsetInhalation(end)) < deltaT % for the case when
IE is detected after a non IE onset inhalation is detected that is within the
same onset point (ie deltaT)
                    if (abs(slope) > slopethreshold) && (flow(i,:) <=
FlowThresh) % test slope threshold and flow threshold for conditions of IE
                        if isempty(IEdetect)% for the case that there's no
previous IE detection
                            OnsetInhalation(end,1) = i ;
                            IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)];
                        elseif (i - IEdetect(end,1)) > 0.5*meanLast5BrthOnset
                            OnsetInhalation(end,1) = i ;
                            IEdetect = [IEdetect; i, flow(i,:), i+deltaT,
flow(i+deltaT,:)];
                        end
                    end
                end

            end % end of checking for IE and Onset Inhalation
        end % end of checking for inhalation flow (positive)
    end % end of checking for exhalation flow (negative)
end % end of reading flow data


% Rejecting IEdetect values that doesn't match InhalationMarker --> Pressure-
dependent detection
    % Rejecting IE detection that doesn't match inhalation marker taken
    % from pressure waveforms would prevent ineffective trigger as being
    % detected as IE
if ~isempty(IEdetect)
    IEDetect = [IEdetect(:,1)/sampling , IEdetect(:,2:end)]; % IEdetect
matching sampling units with InhalationMarker
    IEdtct = [];
    [rowIEDetect, colIEDetect] = size(IEDetect);
    for i = 1 : rowIEDetect
        match = [];
        for j = 1 : rowInhalationMarker
            if abs(IEDetect(i,1) - InhalationMarker(j,1)) < 0.5
                match = 1;
% 0.5 can be any number but it has to be the same cutoff value for comparing
IE_Obs to InhalationMarker, IE_Alg to InhalationMarker, and IE_Alg to IE_Obs.
% IE_Obs value is in InhalationMarker
% Only IEDetect that are on same breath as InhalationMarker are recorded as
IE_Alg
% Only IE_Alg that are on same breath as IE_Obs(values in InhalationMarker)
are valTruePositive
```

```
% IE_Alg that are not on same breath as IE_Obs are still on same breath as
% InhalationMarker, and are recorded as valFalsePositive
            end
        end
        if match == [1];
            IEdtct = [IEdtct; IEDetect(i,:)];
        end
    end
IEdetect = IEdtct;
end
% end Reject session

% Notes: if OnsetInhalation quantity > InhalationMarker quantity, this is a
sign of ineffective trigger presence
       % if InhalationMarker quantity > OnsetInhalation quantity, this is a
sign of double trigger presence
  OnsetInhalation = [OnsetInhalation,flow(OnsetInhalation)];

% adjust time for sampling
t = 1:length(flow);
t = t/sampling;
% making sure t array is same direction as flow
[m n] = size(flow);
[o p] = size(t);
if m==1, % is a row
    if p==1 % is a column
        t = t'; % transpose t
    end
elseif n==1 % is a column
    if o==1 % is a row
        t = t';
    end
end

% Validation
% Compare IE_Obs & IEdetect. InhalationMarker would be total breath
TotalBreath = length(InhalationMarker);

if ~isempty(IE_Obs)
    if ~isempty(IEdetect)
        length_IE_Obs = length(IE_Obs);
        IE_Alg = IEdetect(:,1);
        [rowIE_Alg,colIE_Alg] = size(IE_Alg);
        valTruePositive = [];
        plotTruePositive =[];
        for i = 1: rowIE_Alg
            for j = 1: length_IE_Obs
                if abs(IE_Alg(i)-IE_Obs(j)) < 0.5
                    valTruePositive = [valTruePositive; IE_Alg(i),
IEdetect(i,2)];
% 0.5 can be any number but it has to be the same cutoff value for comparing
IE_Obs to InhalationMarker, IE_Alg to InhalationMarker, and IE_Alg to IE_Obs.
% IE_Obs value is in InhalationMarker
```

```
% Only IEDetect that are on same breath as InhalationMarker are recorded as
IE_Alg
% Only IE_Alg that are on same breath as IE_Obs(values in InhalationMarker)
are valTruePositive
% IE_Alg that are not on same breath as IE_Obs are still on same breath as
% InhalationMarker, and are recorded as valFalsePositive
                end
            end
        end
        Nrml_Obs = TotalBreath - length_IE_Obs;
        Nrml_IE = TotalBreath - rowIE_Alg;
        [TruePositive, colvalTruePositive] = size(valTruePositive);
        FalsePositive = rowIE_Alg - TruePositive;
        TrueNegative = Nrml_Obs - FalsePositive;
        FalseNegative = Nrml_IE - TrueNegative;
    else
        rowIE_Alg = 0;
        length_valTruePositive = 0;
        valTruePositive = [];
        length_IE_Obs = length(IE_Obs);

        Nrml_Obs = TotalBreath - length_IE_Obs;
        Nrml_IE = TotalBreath - rowIE_Alg;
        TruePositive = length_valTruePositive;
        FalsePositive = rowIE_Alg - TruePositive;
        TrueNegative = Nrml_Obs - FalsePositive;
        FalseNegative = Nrml_IE - TrueNegative;
    end

else % IE_Obs is empty or non-existant
    length_IE_Obs = 0;
    if isempty(IEdetect)
        rowIE_Alg = 0;
    else
        IE_Alg = IEdetect(:,1);
        [rowIE_Alg,colIE_Alg] = size(IE_Alg);
    end
    length_valTruePositive = 0; % there's no true positive since observer see
no IE
    valTruePositive =[];

    Nrml_Obs = TotalBreath - length_IE_Obs;
    Nrml_IE = TotalBreath - rowIE_Alg;
    TruePositive = length_valTruePositive;
    FalsePositive = rowIE_Alg - TruePositive;
    TrueNegative = Nrml_Obs - FalsePositive;
    FalseNegative = Nrml_IE - TrueNegative;

end

Sensitivity = TruePositive/length_IE_Obs;
Specificity = 1 - (FalsePositive/Nrml_Obs);
FP_rate = FalsePositive/Nrml_Obs;
```

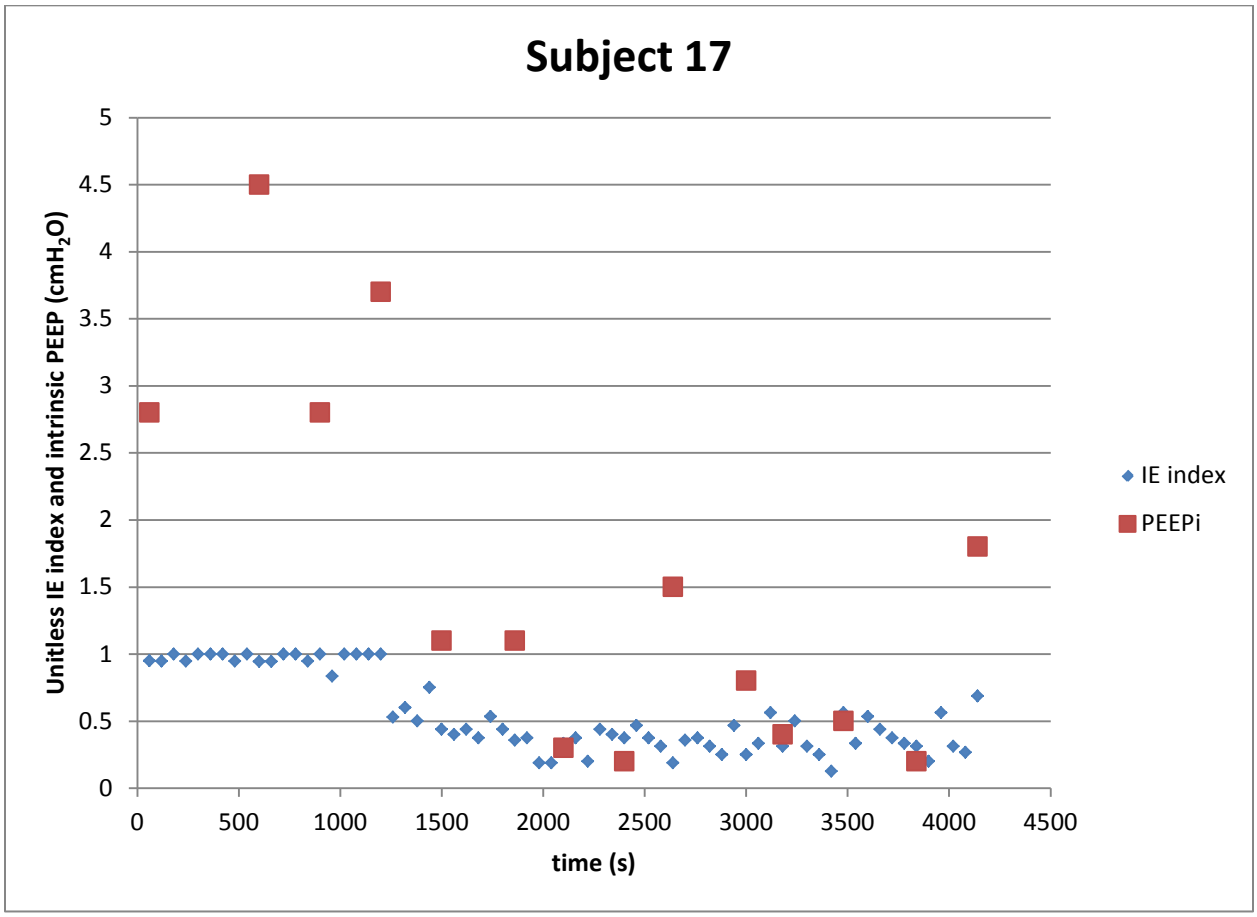
```
Result = [TotalBreath, length(IE_Obs), Nrml_Obs, rowIE_Alg, Nrml_IE,
TruePositive, FalsePositive, TrueNegative, FalseNegative, FP_rate,
Sensitivity, Specificity];

% Plot section start
% Plotting for No IE
if isempty(IEdetect)
    figure, plot(t, flow),hold,
    plot(InhalationMarker(:,1), InhalationMarker(:,2),'r+');
    plot(OnsetInhalation(:,1)/sampling, OnsetInhalation(:,2), 'bo');
    title([subjMfile, '; deltaT ', num2str(deltaT), '; slope threshold ',
num2str(slopethreshold),' - NO Detection']);
    ylabel('Airway Flow Waveform [L/min]'), xlabel('time [s]');
% Plotting if IE is present
else
    IEdetect(:,3) = IEdetect(:,3)/sampling; % converting sampled indices to
match time in seconds
    figure, subplot(2,1,1),plot(t, flow), hold,
    plot(IEdetect(:,1), IEdetect(:,2),'rx'),
    plot(InhalationMarker(:,1), InhalationMarker(:,2),'r+');
    plot(OnsetInhalation(:,1)/sampling, OnsetInhalation(:,2), 'bo');
    if ~isempty(valTruePositive)
        plot(valTruePositive(:,1), valTruePositive(:,2),'g+');
    end
    hold
    title([subjMfile, '; deltaT ', num2str(deltaT), '; slope threshold ',
num2str(slopethreshold), ' - Incomplete Exhalation Detection']);
    ylabel('Airway Flow Waveform [L/min]'), xlabel('time [s]');
    subplot(2,1,2), plot(t, pressure);
    title([subjMfile,': Pressure waveform']);
    ylabel('Pressure [cmH20]'), xlabel('time [s]');
end
% end Plot
```

APPENDIX B

Subject 17

Subject 17 was collected after the dissertation defense. Its chart is here as a supplement to chapter 6. It illustrates the IE index and PEEPi values as functions of time.

Figure B-1. PEEPi values along with IE index vs time for subject 17



VITA

Nyimas Yaumil Isti Arief was born on July 6, 1981 in Padang, West Sumatra, Indonesia and she is a citizen of the United States of America. Isti was raised both in Indonesia and United States. She had resided in the following towns in Indonesia; Padang, Jakarta, Surabaya, and Medan. She had resided in the following towns in United States; Philadelphia, New York, Blacksburg, and Richmond. Isti graduated from Blacksburg High School in Blacksburg, Virginia in 1999. She attended Virginia Tech the following fall. She subsequently transferred to Virginia Commonwealth University in 2002 after a sabbatical for the birth of her firstborn. She earned her Bachelor of Science degree in Biomedical Engineering from Virginia Commonwealth University in May 2005 with a perfect 4.0 GPA, earning her Summa Cum Laude. After graduation, Isti began working as a biomedical engineer researcher at Virginia Commonwealth University Health System's Cardiac Electrophysiology clinic under Dr. Kenneth Ellenbogen and the late Dr. Mark Wood. In 2007 Isti began pursuing a Doctor of Philosophy degree in Biomedical Engineering at Virginia Commonwealth University.

During Isti's time at Virginia Commonwealth University, she earned various honors and scholarships including Tau Beta Pi Engineering Honor Society, Alpha Eta Mu Beta Biomedical Engineering Honor Society, National Science Foundation's Science Technology Engineering and Math Scholarship, Who's Who among Students in American Universities & Colleges, Golden Key, and the Dean's List. Isti lectured in Human Factors Engineering and Radiology at Virginia

Commonwealth University, and she presented multiple times at Virginia Academy of Sciences meetings. At the beginning of graduate school, Isti was the sole engineering research assistant for the Sedation and Ventilation Effects study headed by Dr. Mary Jo Grap, Professor of School of Nursing, Virginia Commonwealth University. She acquired extensive methodology for research in the Intensive Care Unit that lead to her own Institutional Review Board approved study for human subject biomedical research that became the heart of her dissertation. Through her collaboration with the School of Nursing, Isti co-authored two published articles in American Journal of Critical Care and Heart & Lung. She is also the primary inventor for "Automated Detection of Incomplete Exhalation for Adults on Invasive Mechanical Ventilation" that is currently undergoing patent process through VCU Tech Transfer (docket VCU # 12-012).

Isti had also taught electronics to young engineers at Nubian Village Academy's National Society of Black Engineer Jr. Pre-College Initiative Program in Richmond, VA. United States Air Force Auxiliary Civil Air Patrol has recently approved her grant application for a robotics kit for Tawheed Prep School, an accredited college preparatory school in Richmond, VA, where she is currently tech master and adjunct robotics' lab instructor, as well as a candidate for board membership. She currently resides in Richmond with her husband and two children.