A new system for real-time monitoring of respiratory mechanics parameters in mechanically ventilated patients

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Summary

The respiratory system is one of the most important systems of human body. Its main function is the gas exchange between the organism and the external environment. This phenomenon is made possible by the activity of the respiratory muscles, which generate a pressure gradient between inside and outside of the body, allowing movement of air flows. This work, in particular, focuses on the study of respiratory mechanics. Starting from the well-known models present in literature, an analysis about the methods able to estimate the mechanical parameters (resistance and elastance) which characterize the models is executed. The R and E estimations are performed using different methods such as: least squares, Mead-Whittenberger and other analyses derived from motion equation. These models have been evaluated under mechanical ventilation conditions in which the activity of respiratory muscles is replaced or integrated in case of pathological conditions such as "Acute Respiratory Distress Syndrome" (ARDS). One of the possible complications induced by mechanical ventilation is the ventilator-induced lung injury (VILI). It has been evaluated during various ventilation techniques, which differ in the degree of collaboration required by the patient or in the ventilator control setting. This because the study and monitoring of patient conditions can help in identifying the most appropriate ventilation mode so as to reduce its induced damage and guide doctors in weaning practice. This procedure consists of a continuous decrease of the ventilation support until detached from the ventilator. For this purpose, in multiple scientific studies, different parameters have been evaluated such as cardiac variability, sleep quality, diaphragmatic dysfunctions, etc. Instead, an experimental method consists in the monitoring of the mechanical power index, defined as the amount of power to which the lung is subjected during ventilation. It is
important in this sense, to distinguish the work done by the ventilator to that one performed by the patient. The purpose of this thesis is therefore the development of a real-time monitoring system of the mechanical power index starting from the acquisition of airway pressure, esophageal pressure and flow signals for patients in mechanical ventilation. This device is able to evaluate the stress to which the lung is subjected trying to subdivide the work executed by the ventilator from that of the patient. In addition to a preliminary real-time analysis, the device saves data for an offline processing. Its design is splitted in two parts: Hardware and Software. The first part consists in the acquisition system for pressure and flow signals through the sensors connected to the ventilator. The airway pressure sensor and flowmeter are applied directly to the patient’s mask (or endotracheal tube), while the esophageal pressure sensor is connected to a balloon catheter inserted into the esophagus. All three sensors are connected to a principal box, containing the front-end electronic circuit, an Arduino for data acquisition and a Bluetooth module for transmission to PC. The system is powered by a rechargeable battery, so as to make it will completely stand alone. The Software is subdivided into two processes: real-time and offline analysis. In the first part, the acquired signals are displayed in real time on PC in two different modalities, using the Processing software: in the first mode, the traces of pressures, flow and the values of inspiratory and expiratory volumes are shown; while in the second one, the P-V loops for each breath, both with airways pressure and transpulmonary pressure are displayed. In addition, the calculation of the mechanical power index is performed using the acquired signals and the values obtained are displayed on screen. The offline analysis is implemented using MatLab, which, given the input data file, allows to review the acquired traces and extract the elastance and resistance parameters through different models. Then, the obtained values are used to estimate the airway pressure. Each model is therefore compared to the real measurement. This process allows to obtain a determination coefficient (CD) that evaluates the reliability of each estimation. Subsequently, the measured mechanical power index is compared with a value obtained through an experimental formula that uses the mechanical parameters previously extracted. After that, in order to separate the patient’s respiratory muscles contribution one case has been analyzed comparing the difference of mechanical power developed by a breath during controlled ventilation with breaths in which the subject’s effort is present. Once the Hardware and Software design has been completed, the accuracy and correct functioning.
of the sensors has been verified through calibration procedures. The pressure sensors have been calibrated through a U-pressure gauge, while a super-syringe has been used to evaluate flowmeter response to different volumes. Verified the reliability of the sensors, the device has been connected to a ventilator, in order to evaluate the operation of the whole system in terms of acquisition, transmission, treatment of data and battery life. This test has been performed by setting the ventilator in different modalities, and changing several parameters during the monitoring. The instrument has turned out to be reliable and able to correctly represent the traces and changes of the ventilator parameters, as well as a good Bluetooth data transmission quality, for all the three hours of test. During in-vivo analysis, the system has been used to monitor one patient at Istanbul's Sureyyapasa Education and Research Hospital and six patients at the Intensive Care Unit at San Paolo Hospital in Milan, all undergoing mechanical ventilation for different pathologies. The system has been designed in order to minimize the size and avoid obstructions of the work space in ICU room. Once the sensors are connected, the computer for displaying the data can be positioned at an adequate distance from the patient's bed. For each subject, the monitoring has taken different duration, from a few minutes to one hour. Furthermore, for problems related to patient conditions, only for some of them it has been possible to acquire esophageal pressure. Finally, after the offline data analysis, a statistical study has been performed about the mathematical models used to estimate the elastance and resistance parameters. Although the system has demonstrated good operational skills and reliability of measures, both from Hardware and Software point of view, there are several possible future implementations that would make the device even more efficient. An hardware upgrade could involve designing a compact system equipped with a screen, so as to represent in real time the traces, avoiding the use of the PC in the room. Additionally, concerning parameters extraction, it would be interesting in being able to extract elastance and resistance in real-time for each breath, displaying the values on screen. Regarding, the accuracy of the mechanical power and inspiratory muscles effort indexes, it would be important to have further researches about, so as to study in detail their impact on patient conditions. Once gained this knowledge, the system could be used as a continuous monitoring of ICU patients, allowing clinicians to define the most appropriate ventilation modalities depending on the condition of each treated subject.
The following thesis is divided into five chapters:

**Chapter 1: Respiratory system.** In this chapter, the basic knowledge about the anatomy and the physiology of the respiratory system with the related pathologies are presented. Mechanical ventilation is then introduced and described in detail, presenting the various operating modalities and the practice of weaning, aimed at the patient's detachment from the ventilator.

**Chapter 2: Respiratory mechanics:** In the detailed description of the respiratory mechanics for both healthy and ventilated subjects is presented. In particular the most significant mechanical parameters with the relative estimation methods and the various mathematical models that best describe the respiratory system behavior are discussed. The concepts of work of breathing and mechanical power are also introduced. For each of these, possible estimation methods are proposed. Finally, the last paragraph presents the objectives of the thesis.

**Chapter 3: Development of the system.** The third chapter describes the hardware, firmware, and software structure of the system developed. The hardware section presents the used sensors, the front-end electronic circuit, the project specifications in terms of Bluetooth signal transmission and system power supply. Subsequently, the firmware, which allows signals reading from the sensors, is described. Finally, there is a detailed description of the Software used to visualize and process acquired signals, subdivided into a first real-time part and a second offline part.

**Chapter 4: Test.** The fourth chapter describes the calibration procedures adopted for the sensors and for the whole system, in order to evaluate the reliability of the acquired data and the correct functioning for a long period of monitoring. Then, the ventilation conditions of monitored patients during the in-vivo phase and the type of data analysis performed, are described.

**Chapter 5: Results and Conclusions.** In the last chapter, results about the data analysis performed on each patient are reported, evaluating the outcomes of the studies and suggesting future system developments.
Sommario

Il sistema respiratorio è uno dei più importanti sistemi del corpo umano. La sua principale funzione è lo scambio di gas tra organismo ed ambiente esterno. Questo fenomeno è reso possibile dall’attività dei muscoli respiratori, i quali generano un gradiente di pressione tra l’interno e l’esterno dell’organismo, consentendo il movimento di flussi d’aria.

Questo lavoro, in particolare si concenra sullo studio della meccanica respiratoria. Partendo dai più noti modelli presenti in letteratura è stata effettuata un’analisi sui metodi in grado di stimare i parametri meccanici, resistenza ed elastanza, che caratterizzano i modelli in esame. Le stime di R ed E sono state eseguite utilizzando i metodi di: minimi quadrati, Mead-Whittenberger ed altre analisi derivanti dall’equazione di moto. Questi modelli sono stati valutati in condizioni di ventilazione meccanica in cui si sostituisce o si integra l’attività dei muscoli respiratori nel caso in cui siano presenti condizioni patologiche, come ad esempio “Acute Respiratory Distress Syndorme” (ARDS). Una delle possibili complicazioni dovute alla ventilazione meccanica è il danno polmonare indotto da ventilazione (VILI). Questo è stato valutato durante le diverse modalità di ventilazione, che si differenziano per il grado di collaborazione richiesta dal paziente o per la modalità di controllo del ventilatore. Questo poiché lo studio e il monitoraggio approfondito delle condizioni del paziente può aiutare nell’identificazione del tipo di ventilazione più adeguata, in modo da ridurre i relativi danni indotti e guidare i medici nella pratica di svezzamento. Questa procedura consiste in una continua diminuzione del supporto di ventilazione fino al distaccamento dal ventilatore. Per questo scopo, in molteplici ricerche scientifiche, sono stati valutati differenti parametri come ad esempio variabilità cardiaca, qualità del sonno, disfunzioni diaframmatiche, ecc.
Un metodo sperimentale per lo studio di questa pratica è il monitoraggio dell’indice di potenza meccanica cioè la potenza a cui viene sottoposto il polmone durante la ventilazione. Questa viene definita come l’energia che deve essere applicata al polmone per incrementare il proprio volume, nell’unità di tempo. Per avere una risposta più completa, inoltre, è importante cercare di distinguere il lavoro svolto dal solo ventilatore rispetto a quello svolto dal paziente.

Lo scopo di questa tesi, pertanto è lo sviluppo di un sistema di monitoraggio real-time di parametri relativi alla meccanica respiratoria, in particolare, l’indice di potenza meccanica, partendo dall’acquisizione dei segnali di pressione delle vie aeree, pressione esofagea e flusso di pazienti in ventilazione meccanica. Questo dispositivo, inoltre, valuta lo sforzo a cui è sottoposto il polmone provando a separare il lavoro sviluppato dal ventilatore da quello del paziente. Oltre ad un’analisi preliminare in real-time, il dispositivo consente il salvataggio dei dati per un’elaborazione offline. La progettazione si scompone in due parti: Hardware e Software. La prima è composta dall’acquisizione dei segnali di pressione e di flusso che avvengono tramite dei sensori collegati al ventilatore. Il sensore di pressione delle vie aeree e flussimetro vengono applicati direttamente a livello della maschera del paziente (o tubo endotracheale) mentre il sensore della pressione esofagea viene connesso ad un catetere a palloncino inserito nell’esofago. Tutti e tre sono connessi tramite cavi ad una scatola di dimensioni compatte, contenente il circuito elettronico per il condizionamento del segnale, una scheda Arduino per la lettura dei segnali ed un modulo Bluetooth per la trasmissione al PC. Il sistema è alimentato attraverso una batteria portatile, ricaricabile tramite presa a muro, in modo da renderlo completamente stand alone. La parte Software si suddivide a sua volta in due sottoprocessi: analisi real-time e offline. Nella prima, i segnali acquisiti ed inviati al PC, vengono mostrati in tempo reale attraverso il software Processing, il quale permette la visualizzazione in due modalità: una in cui vengono rappresentate le tracce delle pressioni e del flusso ed i valori dei volumi inspiratori ed espiratori ed una seconda invece, in cui vengono visualizzati i grafici P-V loop per ogni respiro, sia con la pressione delle vie aeree che con la pressione transpulmonare. In aggiunta, partendo proprio da questi ultimi, avviene il calcolo dell’indice di potenza meccanica, il cui valore viene mostrato su schermo. L’analisi offline è implementata tramite il software MatLab, il quale, dato in ingresso il file di dati precedentemente salvato, permette di visualizzare le tracce acquisite ed estrarre i parametri...
di elastanza e resistenza con diversi modelli. I valori ottenuti vengono utilizzati per eseguire una stima della pressione delle vie aeree. Ogni modello viene pertanto confrontato con la misura reale e permette di ottenere un coefficiente di determinazione (CD) che valuta l'affidabilità di ciascuna stima. Successivamente l'indice di potenza meccanica misurato, viene confrontato con un valore ottenuto attraverso una formula sperimentale che utilizza i parametri meccanici estratti precedentemente. Infine, per separare il contributo del lavoro dei muscoli respiratori del paziente è stato analizzato un caso andando a confrontare la differenza di potenza meccanica sviluppata tra un respiro completamente controllato dal ventilatore con respiri in cui è presente lo sforzo del soggetto. Una volta terminata la progettazione Hardware e Software, si è verificata l'accuratezza ed il corretto funzionamento dei sensori, attraverso delle procedure di calibrazione. I sensori di pressione sono stati calibrati attraverso un manometro ad U, mentre per il sensore di flusso si è utilizzata una super-siringa andando a valutare la risposta di questo a diversi volumi. Verificata l'affidabilità dei sensori, il dispositivo è stato connesso ad un ventilatore, il quale insufflava aria in un palloncino elastico per valutare il funzionamento dell'intero sistema, in termini di acquisizione, trasmissione e valutazione dati e durata della batteria. Questo test è stato eseguito impostando il ventilatore a diverse modalità, e cambiando i diversi parametri durante il monitoraggio. Lo strumento ha mostrato una buona affidabilità e capacità di rappresentare in modo corretto le tracce ed i cambiamenti dei parametri del ventilatore, oltre ad una buona qualità di trasmissione Bluetooth dei dati, per le tre ore in cui è stato eseguito il test. Nelle analisi in-vivo, il sistema è stato utilizzato per monitorare un paziente presso l'ospedale “Sureyyapasa Education and Research Hospital” di Istanbul e sei pazienti presso il reparto di terapia intensiva dell’ospedale “San Paolo” di Milano, tutti sottoposti a ventilazione meccanica per diverse patologie. Lo sviluppo del sistema è stato pensato per ridurre il più possibile l’ingombro in sala di rianimazione e consentirne l’utilizzo senza ostruire lo spazio di lavoro. Una volta connessi i sensori, il computer per la visualizzazione dei dati, può essere posizionato ad una distanza adeguata dal letto del paziente. Per ognuno dei soggetti è stato effettuato un monitoraggio di durata differente, da qualche minuto fino ad un’ora. Inoltre, per problemi legati alle condizioni dei pazienti, solo per alcuni di essi è stato possibile acquisire la pressione esofagea. Infine, dopo aver eseguito l’analisi offline dei dati, è stato effettuato uno studio statistico relativo ai modelli matematici utilizzati per la stima dei parametri di elasticità e resistenza. Seppur il sistema
sviluppato abbia dimostrato una buona operatività ed affidabilità sia dal punto di vista Hardware che Software, diverse sono le possibili implementazioni future, che servirebbero a rendere il dispositivo ancor più efficiente. Un miglioramento dell’hardware potrebbe riguardare la progettazione di un sistema dotato di schermo sul quale rappresentare direttamente le tracce acquisite, evitando così l’utilizzo del PC in sala. Inoltre, dal punto di vista dell’estrazione dei parametri, sarebbe interessante riuscire ad estrarre in real-time elastanza e resistenza ad ogni respiro, visualizzandone a schermo i valori. Per quanto riguarda invece, l’accuratezza degli indici di potenza meccanica e lavoro compiuto dai muscoli inspiratori, sarebbe importante avere a disposizione ulteriori ricerche in merito, in modo da studiare nel dettaglio il loro impatto sulle condizioni dei pazienti. Una volta ottenute queste conoscenze, il sistema potrebbe essere utilizzato come monitoraggio continuo dei pazienti in rianimazione, permettendo ai medici di definire le modalità più adeguate di ventilazione a seconda dello stato di ognuno dei soggetti in cura.

La seguente tesi è suddivisa in cinque capitoli:

**Capitolo 1: Sistema respiratorio.** In questo capitolo vengono inizialmente presentate le conoscenze fondamentali riguardanti l’anatomia e la fisiologia del sistema respiratorio con le relative patologie. Viene quindi introdotta e descritta in dettaglio la ventilazione meccanica, presentando le varie modalità di funzionamento e la pratica di weaning, rivolta al distaccamento del paziente dal ventilatore.

**Capitolo 2: Meccanica respiratoria.** Nel secondo capitolo viene presentata una descrizione dettagliata sia della meccanica respiratoria sia per soggetti sani che ventilati. In particolare vengono discussi i parametri più significativi con i relativi metodi di stima ed i diversi modelli matematici che meglio descrivono il comportamento del sistema respiratorio. Viene inoltre introdotto il concetto di lavoro respiratorio e di indice di potenza meccanica. Per entrambi vengono quindi presentati dei possibili metodi di stima. Infine, l’ultimo paragrafo presenta gli obiettivi della tesi.

**Capitolo 3: Sviluppo del sistema.** Il terzo capitolo descrive la struttura Hardware, Firmware e Software del sistema sviluppato. Nella parte Hardware vengono descritti i sensori utilizzati, il circuito elettronico per il front-end dei segnali oltre alle specifiche di progetto in termini di trasmissione Bluetooth dei segnali ed alimentazione del sistema.
Sommario

Successivamente, viene descritto il Firmware che consente la lettura dei segnali dai sensori. Segue una descrizione dettagliata del Software utilizzato per la visualizzazione dei segnali acquisiti ed elaborazione dei dati, suddivisa in una prima parte real-time ed una seconda parte offline.


Capitolo 5: Risultati e Conclusioni. Nell'ultimo capitolo vengono riportati i risultati in merito all'analisi dei dati eseguita su ogni paziente, valutando gli esiti degli studi e proponendo eventuali sviluppi futuri del sistema.
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Chapter 1

1. Respiratory System

1.1 Principles of Breathing

1.1.1 Anatomy

The respiratory system is an anatomical structure which functioning allows gas exchange between environment and body, through respiratory airways. It is responsible for oxygen assumption and carbon dioxide ejection during two phases called inspiration and expiration.

As we already know, every cell in our body needs oxygen to accomplish its functions.

The apparatus is made by different structures:

- **Nose/Mouth**: This part allows air to flow inside and outside the body. It contributes in warming, humidifying and filtering air.

- **Pharynx**: It is the part behind the mouth and nose, its function is to warm, humidify and filter air.

- **Larynx**: It is situated just below the Pharynx. One its aim is the prevention of foreign objects from entering the lungs by coughing and other reflexive actions.
• Trachea: It is a cartilaginous tube that connects the pharynx and larynx to the lungs, allowing the passage of air.

• Bronchi: They are two airways in the respiratory tract that conduct air into the lungs. There is a right bronchus and a left bronchus and these bronchi branch into smaller secondary and tertiary bronchi which branch into smaller tubes, known as bronchioles.

• Lungs: Organs in which the gas exchange take place through passive diffusion between the alveoli and the blood vessels that surround their external structure. These are made by elastic tissues which allows inflation and deflation movements, in order to take and eject air. Actually, being lungs a pure elastic structure, they normally tend to collapse. This phenomenon is impeded by the opposite nature of the chest wall, to which the lungs are pasted through pleura, which tend to expand.

• Pleura: It is a membrane that covers both lungs and attaches them to the chest wall. This structure is fundamental in order to assure a negative pressure outside the lungs, allowing their expansion during inhalation.

Composition of inhaled air is roughly 78% Nitrogen, 20% Oxygen and the last 2% is made by Argon, Carbon dioxide and water vapor.

Exhaled air is slightly different, due to the gas exchange that occurs at lungs level. In detail, it is made by 78% Nitrogen, 16% Oxygen, 5% Carbon dioxide and 1% by Argon.

Gas transfer between respiratory system airways and blood vessel occurs by passive diffusion at lung level, thanks to gradient of gasses partial pressures.
In fact, at alveolar level, oxygen and carbon dioxide have respectively a partial pressure of about 100mmHg and 40mmHg, while at venous level their pressures are around 40mmHg and 46mmHg. These differences allow the diffusion of O₂ from alveolar space to venous one and in opposite direction for CO₂. This process leads to partial pressure values of 95mmHg for O₂ and 40mmHg for CO₂ in arteries, which then supply the entire body with oxygen. Breathing is a process that requires the collaboration of different structures and apparatus in addition to the one described above, as the respiratory muscles and intercostal muscles. Respiratory muscles are contracted during inspiration which is an active process, while are relaxed during expiration which is a passive movement. The most important inspiratory muscle is the diaphragm, a dome shape muscle, placed immediately underneath the lungs. During inspiration, the diaphragm contracts and acquires a flat shape, provoking the expansion of both lungs. The execution of an inspiration and expiration is called respiratory cycle and the mean number of respiratory cycle is 12-18 in healthy humans.

The basis of breath lies on the generation of pressure difference inside the respiratory system’s structures, in order to generate flow and thus gas volume movements. In way to assure this continuously variation of pressure, different dynamic forces are applied by all the unit involved. If some of these structures stop to work correctly, the forces applied may not be able to allow a correct respiration. For this purpose, the study, comprehension and monitoring of respiratory mechanics, is essential to evaluate the functioning of the different structures involved, how their fail would affect the system and how they could be recovered or supported by mechanical ventilation.

1.1.2 Physiology

For a better understanding about how the respiratory system achieves its tasks, a full description of its physiological characteristics is necessary. As said previously, the main events that allows breathing, consist of changes in volume due to pressure differences among structures. The drop of pressure between airway opening and the inside of the system generates an air movement according to the Poiseuille law:

\[ \Delta P = R \times \dot{V} \]  

(1.1)
Assuming to be in stationary condition with Newtonian fluid in laminar flow flowing in a cylindrical duct with constant section, this law states that that a pressure difference ($\Delta P$) between two points of the conduit generates a flow ($V$) in the opposite direction to the pressure drop, which is inversely proportional to a resistance ($R$) which depends on the fluid characteristics and the duct dimensions. Pressure ($P$) and volume ($V$) are also related between them through the Boyle law for gases, which states that in constant temperature condition, the gas pressure is inversely proportional to its volume.

$$P \times V = K$$

(1.2)

According to this, during inspiration, the inspiratory muscles produce a decrease of the inside pressure, followed by an inspiratory flow and consequently an increase of lungs volume as total effect. Instead, the relaxation of respiratory muscles increase the pressure, inducing an expiratory flow and then a decrease in lungs volume.

During each inspiration phase, the air taken into the lungs is called tidal volume and in a normal breath usually count up roughly to 500mL. The tidal volume sum up to the volume of air remained at the end of each normal expiration, called Functional residual capacity (FRC). The total volume, which can be forcibly expired after a maximal inspiration, is called vital capacity and in a healthy man is approximately 4.8L. The vital capacity can be also expressed as the difference between the total lung capacity and the residual volume, which is the volume of air that rests in lungs after a maximum expiration.

►Figure 1.2: Pulmonary Volumes
In order to better understand the real functioning of the system, the pressure $P$ can be decomposed in different terms, describing the drop of pressure among the different compartments. Their measuring is essential for the assessment of the system’s mechanical properties. The pressures acting in the system are: the airway opening Pressure ($P_{AO}$), which refers to the pressure at the mouth, the alveolar Pressure ($P_{AL}$), pleural Pressure ($P_{PL}$), abdominal Pressure ($P_{AB}$) and body surface Pressure ($P_{BS}$) (usually taken as the atmospheric pressure).

The total pressure applied ($P_{RS}$) is the difference between $P_{AO}$ and $P_{BS}$, while in a ventilated patient is given by the sum of the pressure generated by the mechanical ventilator ($P_{VENT}$) and the pressure developed by the respiratory muscles ($P_{MUS}$):

$$P_{RS} = P_{AO} - P_{BS} = P_{VENT} \pm P_{MUS} \quad (1.3)$$

These sequence of pressures can be schematized as follow:

![Figure 1.3: Model of the entire respiratory system](image)

Other pressures, which represents as well specific characteristic of respiration, can be determined as differences among those previously described.

The elastic recoil pressure ($P_{EL}$), is defined as difference between $P_{AL}$ and $P_{PL}$, and it represents the rebound of the stretched lung after inhalation. Pressure drop due to airways flow resistance ($P_{AW}$) is defined as $P_{AO} - P_{AL}$.
Chapter 1: Respiratory System

1.1 Principles of Breathing

It is also possible to define the transpulmonary pressure \( P_{TP} \), as difference between \( P_{AO} \) and \( P_{PL} \). \( P_{TP} \) is usually positive during normal breathing, because \( P_{PL} \) is always negative, while \( P_{AW} \) rests between slightly negative and slightly positive values. Transdiaphragmatic pressure is given by \( P_{PL} \) minus \( P_{AB} \), it is used to assess the force executed by the diaphragm and so, it is used during clinical check to evaluate pathologic condition (as paralysis or weakness). Instead, chest wall pressure \( P_{CW} \) is defined as the pressure drop between \( P_{PL} \) and \( P_{BS} \).

Consequently, \( P_{RS} \) may be expressed as summation of the two terms \( P_{TP} \) and \( P_{CW} \), as stated in the following equation:

\[
P_{RS} = P_{AO} - P_{BS} = (P_{AO} - P_{PL}) + (P_{PL} - P_{BS}) = P_{TP} + P_{CW}
\]  

(1.4)

Pleural pressure plays an important role in avoiding lungs collapse at end expiration. This pressure always has negative value and so it induces a positive transpulmonary pressure and a consequent lung expansion.

1.1.3 Measurement of variables

In order to further design a model for respiratory mechanics, the experimental data of pressure, volume and flow are of fundamental importance.

Pressure is measured by pressure transducers, the most common sensors detect a deformation of a mechanical element due to pressure forces, and convert it in an electric signal. The most important pressures that can be measured in a low-invasive way in clinical application are the airway opening pressure and the esophageal pressure.

The \( P_{AO} \) is measured by inserting a perpendicular tap into the tube in which the patient is breathing (as the endotracheal tube in a mechanical ventilated patient or face masks for healthy subjects), disregarding the Bernoulli Effect for the driving pressure.

Esophageal pressure \( P_{ES} \) and gastric pressure \( P_{GA} \) are used to approximate respectively \( P_{PL} \) and \( P_{AB} \), that can’t be clinically measurable. \( P_{ES} \) is measured by means of a thin catheter with a 10-cm balloon at the tip, filled with 0.5mL of air and inserted in the lower third of the esophagus, while the distal part of it is connected to a pressure transducer. The position of the catheter is crucial to have a good approximation of \( P_{PL} \) and because of this, there are different test to check it. One of those is the Baydur’s occlusion test [1], used for
spontaneously breathing patients. This method is performed during end-expiratory occlusion maneuver with a simultaneous measure of airway and esophageal pressure during an inspiratory effort. Then, if the ratio $\Delta P_{AO}/\Delta P_{ES}$ is close to unity (deviation lower than $\pm 10\%$) the position of the catheter is acceptable. A similar system is used to assess the correct position of the catheter which measures $P_{GA}$, evaluating the ratio $\Delta P_{AO}/\Delta P_{GA}$. Flow is measured using sensors called flowmeters, which lies on various physical principles. Most common used are differential pressure sensors (also known as pneumotacographs), in which a drop of pressure over a resistive element is induced when flow is passing through it. Given the previously described Poiseuille law, the measurement of the pressure drop allows to obtain the relative flow.

A second type of flowmeters are based on thermic principle, in which a sensitive element changes its temperature when crossed by flow. This temperature variation is transduced in electrical signal proportional to the flow.

Volumes are obtained as integral of flow during time.

The integration can be made in two different methods:

- Rectangle method: Volume is obtained as the area under the flow signal curve during time. This area is subdivided in different rectangles whose height is determined by the flow signal value, and the width depends on the time interval between the consecutive flow data points. The summation of the each single rectangle area represents the total volume.

![Figure 1.4: Rectangle method](image)

- Trapezoidal method: Volume is obtained approximating the region under the flow signal curve in time as a trapezoid, and calculating its area.
Chapter 1: Respiratory System

1.1 Principles of Breathing

For a real lung, the assumption that the flow is the time derivative of volume is not always true. The inspired air becomes warmed and humidified when it pass through the airways, in order to adapt to the lungs conditions. This event implies a mismatch between the integrated mouth flow and the thoracic expansion. The rate of change at which oxygen moves from lungs into the pulmonary blood in generally slightly greater than the rate at which carbon dioxide is excreted from the blood into the lungs.

Then, this problem implies a drift in volume calculation. The drift is observed as a slightly greater inspired volume than the one expired, one of the main cause is the different gas composition and temperature.

1.1.4 Diseases

Different pathologies can be related to malfunctioning of the respiratory system. Being a complex structure, every failure in one of its components can then lead to an insufficient work of the entire block. Diseases can be classified basing on the tract of the system that is affected. For example, pathologies for airway tract are asthma, chronic obstructive pulmonary disease, emphysema and so on, while at lungs level the most diffused are pneumonia, tuberculosis, edema, ARDS (acute respiratory distress syndrome) and cancer.

Thanks to technological development in clinical field, now part of those disease can be treated by mechanical ventilation, in which a machine is used to assist or substitute spontaneous breathing. Clinical states that are treated with mechanical ventilation can be divided basing on the organ affected in pulmonary or non-pulmonary conditions.
1.1.4.1 Acute respiratory distress syndrome (ARDS)

The acute respiratory distress syndrome (ARDS) is a hypoxemic respiratory failure characterized by severe inflammatory damage to the alveolar–capillary barrier. This damage can be triggered by primary injury to the epithelium (pulmonary ARDS), as in cases of pneumonia or bronchial aspiration, or to the endothelium (extrapulmonary ARDS), as in cases of nonpulmonary sepsis.

Its definition has evolved in a significant way over the time. ARDS was first described by Ashbaugh and colleagues in 1967 [2] in a case series of 12 ICU patients who shared the common features of unusually persistent tachypnea and hypoxemia accompanied by opacification on chest radiographs and poor lung compliance. In 1971, Petty and Ashbaugh [3] described principles of management of ARDS based mainly on mechanical ventilation using high FiO$_2$ and positive end-expiratory pressure (PEEP).

For more than 20 years, there was no common definition of ARDS so, in 1994, an international American–European Consensus Conference (AECC) laid the foundations for the first clinical definition of ARDS. This consensus conference aimed to bring uniformity to the definition of ARDS for research, epidemiologic studies, and individual patient care. ARDS was consequently defined using the following four criteria:

- the acute onset of hypoxemia
- a PaO$_2$ to FiO$_2$ ratio ≤ 200 mmHg regardless of PEEP level
- the presence of bilateral infiltrates on chest X-ray
- the pulmonary artery wedge pressure ≤18 mmHg or no clinical sign of left atrial hypertension.

Patients meeting all these criteria but having less severe hypoxemia with a PaO$_2$/FiO$_2$ between 201 and 300 mmHg were considered as having acute lung injury (ALI) and not ARDS. This clinical definition has been criticized leading to the establishment of a new statement in 2012, the Berlin definition [4]. This last aimed to provide a better clinical definition and to classify patients according to severity. The changes proposed in this document in order to address the major limitations of AECC definition are the following:

1) The “acute onset” of ARDS has been specified, and respiratory symptoms have to be present within 7 days after a clinical insult.
2) Patients have been stratified according to their severity in terms of hypoxemia and classified as mild, moderate, and severe ARDS when PaO$_2$/FiO$_2$ ratio is between 201 and 300, between 101 and 200, and equal to or below 100 mmHg, respectively.

3) The AECC definition considered that pulmonary arterial wedge pressure should not exceed 18 mmHg in ARDS.

4) The Berlin definition considered radiological findings as bilateral opacities on chest X-ray but also on CT scan, which were not fully explained by effusions, lobar or lung collapse, or nodules.

Four ancillary variables were assessed for severe ARDS, including more extensive opacities on chest radiograph, i.e., at least three quadrants, a high PEEP level $\geq$10 cmH$_2$O, low respiratory system compliance $\leq$40 ml/cm H$_2$O, and a corrected expired volume $\geq$10 L/min. However, these criteria were not included in the Berlin definition because they did not help to discriminate patients with severe ARDS.
1.2 Mechanical Ventilation

1.2.1 Different types of mechanical ventilation

As stated in formula 1.3, the combination of ventilator and muscle pressure can drive the total pressure developed on the system. From this relationship different situations may occur. For example, when the patient’s respiratory muscles are not functioning ($P_{MUS}=0$), the ventilator must generate all the pressure for inspiration. In the opposite situations, when ventilator is not needed all the pressure is developed by respiratory muscles, as happen during a spontaneous breathing. Between these two conditions, different combinations of muscles and ventilator contributes are possible, depending on patient condition, identifying a condition of ventilator support.

Different ventilation techniques are available nowadays, depending on the controlled variables, the type of breathing or the variable set on ventilator.

1.2.1.1 Control Variables

The classification made on the controlled variables identifies two main modalities:

- **Pressure Control**: Pressure is the independent variable, and may take a specific waveform, while volume and flow waveforms depend on it. Pressure ventilation can be classified as positive if the airway pressure is raised above a threshold, or negative whether the body surface pressure is lowered below a baseline. Negative pressure ventilation requires a sub-atmospheric pressure applied outside the body, in order to expand the chest wall during inspiration, while allows passive patient exhalation when no negative pressure is present. During positive pressure inspiration a pressure greater than atmospheric is applied inside the chest to expand it. Expiration occurs passively, due to pressure difference between lungs and atmosphere and due to lungs’ elastic recoil. The main advantage of this modality is that the lungs can be protected from excessive pressures. A typical waveform of positive pressure ventilation is shown below:


- **Volume Control**: The shape of volume waveform is specified, making flow and pressure dependent variables. This type of ventilation results in a more stable minute ventilation. A typical waveform of volume ventilation is shown below:

![Volume-controlled mode](image1)

Flow controlled ventilation may be not considered, because when the ventilator controls volume directly, flow is controlled indirectly and vice versa.

### 1.2.1.2 Breath Sequence

Ventilations may be distinguished also basing on the type of breaths which come in succession. A breath is defined as a positive airway flow relative to baseline, paired with a negative airway flow, both associated with ventilation of the lungs. Different type of
breathing may be discussed, depending on who generates it, between the patients or the ventilator.

- **Spontaneous breath**: The patient determines both breath timing and size, defining the start and the end of inspiration.

- **Assisted breath**: The breath is assisted by the ventilator, as for example increasing airway pressure above a baseline. Each breath is also spontaneous because the patient both triggers and cycles the breath.

- **Mandatory breath**: The patient has no control on timing and size of breath. The start and end of inspiration are both determined by the ventilator. The machines triggers and cycles each breath.

Then, having defined the various types of breaths, there are several possibility of breath sequences to be used during mechanical ventilation:

- **Assist control (AC)**: the ventilator assist patient’s breathing with a specific number of breathing act during time.

- **Continuous positive airway pressure (CPAP)**: continuous pressure is given to the patients, improving oxygenation and reducing workload.

- **Intermittent mandatory ventilation (IMV)**: Spontaneous breaths are permitted between mandatory one. An example of IMV breaths sequence is depicted in Fig. 1.9
1.2.1.3 Targeting schemes

Targeting schemes are feedback control systems used by mechanical ventilators to deliver specific ventilatory patterns. The targeting scheme is a key component of a mode classification system. Feedback signals are used in order to deliver specific ventilatory patterns. Ventilators use closed loop control circuit in order to maintain consistent pressure and flow waveforms. The output of the variable is compared to its set input values, the difference is used to drive the system towards the desired output. For example, during pressure control mode, airway pressure is used as feedback signal, to control gas flow from the ventilator. A schematic representation of a closed loop control circuit is in Fig. 1.10.

![Figure 1.10: Close loop control circuit](image)

The controller convert the error signal into a signal that can drive the effector, in order to change the manipulated variable. The plant refers to the process under control, which is the patient. The transfer function which relates the input and the output of the controller is the targeting scheme. Several types of targeting schemes can be identified, mainly based on increasing levels of autonomy. Some of these schemes are:

- **Continuous mandatory ventilation (CMV):** The intent of this type of ventilation is to provide a mandatory breath for every patient inspiratory effort, thus spontaneous breaths are not permitted.
• **Set Point:** The operator sets specific target values and the ventilator attempt to deliver them. As example, in volume controlled mode, the tidal volume and inspiratory flow are set while in pressure mode, the operator may set the PIP or the inspiratory time.

• **Servo:** This control mechanism is capable of a high degree of synchrony with patient breathing effort. Then, ventilator work output can be made to match patient work demand with a high degree of fidelity. In this scheme, the ventilator’s output automatically follows a varying input.

![Figure 1.11: Servo control circuit](image1)

• **Adaptive:** In this targeting schemes, the transfer function between input and output is modified according to the varying patient conditions.

![Figure 1.12: Adaptive control circuit](image2)

• **Optimal:** It is an advanced form of adaptive targeting. The ventilator controller automatically adjust the targets of the ventilatory pattern, to either minimize or maximize some overall performance characteristic. An example of target to minimize is the work of rate of breathing.
• **Intelligent:** This scheme is useful for weaning procedures. The controller sets values of breathing frequency, tidal volume, and end tidal CO\(_2\) in an acceptable range for spontaneous breathing, automatically adjusting inspiratory pressure. The control process is divided into three steps. In the first one, the patient is stabilized in a “zone of respiratory comfort”. The second step is to progressively decrease the inspiratory pressure while making sure the patient remains in the “zone”. The third step tests readiness for extubation by maintaining the patient at the lowest level of inspiratory pressure. Once the lowest level of inspiratory pressure is reached, the patient’s breathing frequency, tidal volume, and end-tidal CO\(_2\) are monitored for 1-hour. After success of this step, the ventilator suggests to the clinician to consider the separation of the patient from the ventilator.
1.2.2 Operator Inputs

The operator input refers to the parameters of the ventilator setting by the operator. Each mode of ventilation has particular features, some of which can be adjusted by the operator. The effect of each parameter on the lung is better understood knowing the equation of motion (chapter 2). This explains that a change of one parameter will lead to changes in others (i.e., in volume control, for the same respiratory characteristics changing the tidal volume will cause a change in peak airway pressure).

The operator can control different types of variables during the ventilation:

1) Inspired Gas Concentration

A mechanical ventilator has the capacity of delivering different mixtures of gas. Most of ventilators allow the administration of specific concentrations of oxygen, while only a few allow the administration of helium, nitric oxide, or anesthesia gases

- Oxygen

Oxygen is the most common gas administered to patients undergoing mechanical ventilation. The oxygen percentage in the inspired gas (F_{\text{I O}_2}) can be regulated in most ventilators by means of a direct adjustment of a specific control (21% to 100%). The following formula can calculate the flow of oxygen to achieve a desired oxygen concentration:

\[
O_2 \text{ required} = \frac{RR \times V_t \times (\text{desired } F_{\text{I O}_2} \times 0.21)}{0.79}
\]

where O_2 required is 100% oxygen flow in L/min, RR is the respiratory rate in breaths/min, V_t is the tidal volume in liters and the F_{\text{I O}_2} is the patient O_2 concentration desired in decimal format (i.e., 30% = 0.3). An oxygen analyzer should be used to confirm the measurements. Changes in oxygen flow, breathing rate, or tidal volume brings a change in the F_{\text{I O}_2}.

- Heliox

Mixtures of helium and oxygen (heliox, HeO_2) instead of air and oxygen are occasionally used to help patients on mechanical ventilation with obstructive airway diseases. Helium is
less dense than air so, the decrease in density interferes with flow measurements, inspiratory and expiratory valve accuracy, and gas mixing.

- **Nitric Oxide**

  Inhaled nitric oxide (NO) is used as selective pulmonary vasodilator for patients with pulmonary hypertension, life-threatening hypoxia, or right-heart failure. Most of devices to deliver NO are custom made and required the use of mixing chambers, stand-alone NO/nitric dioxide monitors, and manual titration of the gas flow.

2) **Trigger Variables**

A ventilator-assisted breath can be triggered by the machine or the patient. A machine-triggered breath is defined by the start of the inspiratory phase, independent of any signal from the patient. The operator typically sets a breath frequency for machine-triggered breaths. A patient triggered breath is one for which inspiration is started solely by a signal from the patient. The key variable for patient triggering is sensitivity, or the magnitude of the patient signal required to initiate inspiratory flow. The patient signal can be obtained from measuring the airway pressure, flow, volume, electromyogram (EMG), abdominal motion, etc.

- **Time**

  Time is measured by the internal ventilator processor. The next breath is time triggered (in the absence of a patient trigger event) when the expiratory time has reached the threshold to maintain a set respiratory rate (e.g., if the set rate is 10 breaths per minute and the inspiratory time is set at 1 second, then the expiratory time is 5 seconds).

- **Pressure**

  The patient inspiratory effort causes a drop in pressure in the airway and the circuit. Inspiration starts when pressure falls below the preset “sensitivity” threshold. The site of measurement will have an impact on the performance of the device. The farther the sensor is from the signal source, the longer the potential time delay.

- **Flow**

  Flow triggering is based on the detection of a change in a constant, small, baseline (bias) flow through the patient circuit. The operator sets a flow sensitivity threshold. When the change in flow reaches the threshold, a breath is delivered. The changes in flow are
detected at the expiratory valves or by a flow sensor in the patient circuit. The ventilator measures the flow from the ventilator and from the patient. In a closed circuit, the two flow values should remain equal in the absence of patient effort.

- **Volume**
  A breath may be triggered when a preset volume is detected as the result of a patient inspiratory effort. This is similar to flow triggering but using volume has the theoretical advantage of being less susceptible to signal noise (i.e., integrating flow to get volume cancels out some noise because of flow oscillations).

3) **Target Variables**
During inspiration, the variable limiting the magnitude of any parameter is called the target variable. A target is a predetermined goal of ventilator output. Within-breath targets are the parameters of the pressure, volume, or flow waveform

- **Peak Inspiratory Pressure (PIP)**
The term inspiratory pressure is defined as the set change in airway pressure during inspiration relative to set end-expiratory airway pressure during pressure-control modes. The ventilator allows to the operator to set the PIP that can be achieved during the delivery of a mandatory breath. The goal is to prevent pressure peaks while maintaining the set tidal volume.

- **Positive End-Expiratory Pressure (PEEP)**
PEEP is define as the elevation of the baseline pressure during any mode of ventilation and is generally a setting for a mode. The PEEP is established by the ventilator exhalation valve. Until recently, the selection of PEEP has been a relatively arbitrary process and the meaning of “optimum PEEP” is debatable, in the last years, Hamilton Medical has developed the INTELLiVENT system for the G5 ventilator that uses an algorithm for automatic targeting of PEEP. A closed-loop algorithm based on expert rules defines the response of the ventilator to measured ventilation variables, end-tidal carbon dioxide and pulse oximetry.

- **Rise Time**
The speed with which the airway pressure reaches the set inspiratory pressure is called rise time. The rise time may be set by the operator or automatically adjusted based on a
computer algorithm. The name used to indicate pressure rise time varies by ventilator brand (e.g., inspiratory slope, P-ramp, plateau%, and slope rise time). Adjusting the rise time influences the synchronization between the patient and the ventilator secondary to changes in the initial inspiratory flow rate. The lower the rise time, the faster the pressurization rate and the higher the peak inspiratory flow. A higher initial inspiratory flow rate may decrease the work of breathing but can lead to patient discomfort and worse patient–ventilator synchrony.

- **Tidal Volume**

  The operator is required to enter a tidal volume in any volume-control mode. This may be a direct setting or an indirect one by setting frequency or minute ventilation. The ventilator will control the tidal volume and the pressure will be the dependent variable. A tidal volume target, however, may also be set when the mode uses adaptive targeting in pressure control. In such a case, inspiratory pressure is automatically adjusted between breaths by the ventilator to achieve an average measured tidal volume equal to the operator set target.

- **Minute Ventilation**

  In volume-control modes, the minimum minute ventilation is set by entering the tidal volume and respiratory rate. This assures that the patient receives a minimum amount of ventilatory support. The operator presets the target minute ventilation by setting tidal volume and frequency. The ventilator then monitors the total minute ventilation as the sum of the minute ventilations generated by mandatory and spontaneous breaths. If the total minute ventilation is below the target value, the mandatory breath frequency will increase.

**4) Cycles Variables**

The inspiratory phase of a mechanical breath ends (cycles off) when a threshold value for a measured variable is reached. This variable is called the cycle variable, and it ends the inspiratory time. Cycling is characterized by the initiation of expiratory flow. The cycle variable may be preset (by the operator or the ventilator manufacturer), or automatically defined by the ventilator.

- **Inspiratory Time**

  Inspiratory time is defined as the period from the start of inspiratory flow to the start of expiratory flow. Inspiratory time has two components; inspiratory flow time (period when inspiratory flow is above zero) and inspiratory pause time (period when flow is zero). In
pressure-controlled or volume-controlled breaths, the inspiration is cycled (terminated) when the set inspiratory time elapses. Inspiratory time is usually an operator-entered input but some modes of ventilation can automatically set it and change it based on expert rules and closed-loop feedback algorithms.

- **Inspiratory Pause**
  The inspiratory pause is the period during which flow ceases but expiration has not begun. The expiratory valves are closed during this period. The inspiratory pause time is part of the inspiratory time. When set directly, pause time may be entered in seconds or as a percentage of the inspiratory time. When it is activated, most ventilators display a plateau pressure (i.e., static inspiratory hold pressure). Increasing the inspiratory pause time increase the mean airway pressure and thus the time the lung is exposed to volume and pressure. This may have a positive effect on oxygenation and ventilation by increasing mixing time and decreasing dead space.

- **I:E Ratio and Duty cycle**
  I:E is the ratio of inspiratory time to expiratory time.

\[
I:E = T_I; T_E = \frac{T_I}{T_E}
\]  

(1.6)

The I:E can also be described as the duty cycle or percent inspiration. In engineering, the duty cycle is defined as the time spent in active state as a fraction of the total time. In mechanical ventilation, the active state is the inspiratory time, and the total time is the sum of the inspiratory and expiratory times. It is expressed as a percentage. The larger the percentage, the longer the inspiratory time in relation to the total cycle time.
1.2.3 Ventilator-Induced Lung Injury (VILI)

The mechanical ventilation (MV) by itself has been established as a factor that induces lung damage. It has been demonstrated that the MV could aggravate the lung effects of a ‘first inflammatory hit’, a concept known as ventilator-induced lung injury (VILI).

It was, for years, synonymous with clinical barotrauma, the leakage of air due to disruption of the airspace wall. This type of injury is now a major preoccupation of most physicians caring for patients needing ventilatory support. VILI causes lung damage, which is the result of the sum of local lung impairment with a heterogeneous distribution due to local lung susceptibility. These local events promote an anisotropic alveolar inflation in the opening phase and collapse at the end of the expiratory phase, which promotes greater damage. This initial anisotropic distribution promotes a local inflammatory response in areas that receive the higher trauma, but subsequently these areas trigger a generalized inflammatory response in the lung tissue. The pathophysiological basis of VILI are complex and characterized by different overlapping interactions: initially after the ARDS Network clinical trial, VILI was primarily linked to two phenomena: the first phenomenon occurs at the end of inspiratory cycle and is associated with the use of a high inspiratory pressure of tidal volume that promotes an alveolar over-distension, a process related to the risk of rupture of the airway and alveolar walls in the non-dependent lung regions.

The second phenomenon unfolds in dependent lung regions, which are exposed to significant stress when the airway and alveoli open on inspiration and collapse on expiration. The two phenomena may overlap, since an unnecessarily high PEEP may lead to over-distension and an excessive tidal volume drop, it can increase the effects caused by the cyclic alveolar collapse and reopening. Moreover, some experimental studies have confirmed that the collapse of the airspace and the cyclical recruitment in lungs affected by a previous inflammatory conditions are crucial in the development of VILI. The pathophysiological principles of VILI are complex and characterized by different interactions of multiple factors. These interactions include:

1) high VT causing over distension;
2) cyclic closing and opening of peripheral airways during tidal breath resulting in damage of both the bronchiolar epithelium and the parenchyma (lung strain), mainly at the alveolar-bronchiolar junctions;
3) lung stress by increased transpulmonary pressure;
4) low lung volume associated with recruitment and de-recruitment of unstable lung units (atelectrauma);

5) inactivation of surfactant by large alveolar surface area oscillations associated with surfactant aggregate conversion, which increases surface tension;

6) local and systemic release of lung-borne inflammatory mediators, namely biotrauma.

Multiple ventilation strategies have been evaluated with the purpose to reduce lung injury, for example: low tidal volumes to limit over-distention, higher PEEPs to prevent injury at low lung volumes and recruitment maneuvers (procedures used to reinflate collapsed lung units) through the sustained application of an P_AO higher than approximately 35 cmH_2O, which if achieved inflating atelectatic regions, than minimizes the ventilation heterogeneity.

In the presence of spontaneous breathing efforts, while receiving mechanical ventilation, direct measurement of the level of effort may help the clinician to better adjust the ventilator settings and/or the sedation level.

Furthermore a recent study [5], executed on animals, has shown that, during ventilation, spontaneous breathing with inspiratory muscles activity (as diaphragm) can improve ventilation distribution. It has been observed that their activation has positive impact on oxygenation and decreases lung injury scores mostly by producing a negative pleural pressure and transpulmonary pressure. Instead, the activation of expiratory muscles (as abdominal muscles) has contrary effects, possibly being determinant for VILI. Their work, during ventilation, can increase positive pleural pressure and intra-abdominal pressure, decreasing transpulmonary pressure and leading to more alveolar collapse. This research has inferred that the expiratory muscles activity worsen oxygenation, enhancing work of breathing, oxygen consumption, atelectasis and dead-space.
1.2.4 Weaning

The term "weaning" is used to describe the entire process of decreasing ventilator support that ends with the liberation of the patient from mechanical ventilation and from the endotracheal tube. It is estimated that 40% of the duration of mechanical ventilation is dedicated to this process [6]. Delayed weaning can lead to complications such as ventilator induced lung injury (VILI), ventilator associated pneumonia (VAP), and ventilator induced diaphragmatic dysfunction [7]. On the other hand, premature weaning can lead to complications like loss of the airway, defective gas exchange, aspiration and respiratory muscle fatigue [8]. There is uncertainty about the best methods for conducting this process, which will generally require the cooperation of the patient during the phase of recovery from critical illness. In April 2005, a two-day International Consensus Conference in Intensive Care Medicine sponsored by five scientific societies was held in Budapest, Hungary, on the subject of weaning from mechanical ventilation. During this Conference the professor Laurent Brochard defined 3 types of weaning, according to the difficulty and length of the process:

- **Simple**: referring to patients who are solved without difficulty at first attempt.
- **Difficult**: referring to patients requiring a time equal to or less than 7 days from the first spontaneous breathing test, or they need to repeat it up to 3 times
- **Prolonged**: which includes patients who need a longer time than 7 days of experimentation from the first spontaneous respiratory test or requiring the repeat the test for more than 3 times

Most international weaning researchers have attempted to find better indexes or parameters which can predict the weaning outcome in the best possible way. Among them:

1) **Heart rate variability**: the process of weaning leads to changes in the hemodynamic and autonomic nervous systems. Acrementales et al. [9] found that spectral coherence between heart rate variability and respiratory flow signals could predict extubation failure with good sensitivity and specificity. However, all these results still need validation in larger groups of patients

2) **Sleep quality**: poor quality of sleep may affect the function of the respiratory muscles and weaning outcome. In a cross sectional study, Chen et al. [10] assessed the quality of sleep using the Verran and Snyder-Halpern Sleep Scale and found that poor quality of sleep was significantly associated with weaning failure.
3) *Hand grip strength:* muscle weakness can negatively affect the weaning outcome. Cottereau et al. [11] assessed handgrip strength by a handheld dynamometer and found that handgrip strength was significantly associated with difficult or prolonged weaning but not with extubation failure.

4) *Diaphragmatic dysfunction:* the acquired diaphragmatic dysfunction following prolonged mechanical ventilation can affect the weaning outcome. Di Nino et al. [12] assessed diaphragmatic dysfunction by measuring the difference between diaphragm thickness at the end of inspiration and expiration using ultrasonography to view the diaphragm in the zone of apposition. They found that a difference of 30% or more could predict extubation failure with a sensitivity of 88% and a specificity of 71%.

5) *Oxidative stress markers:* oxidative stress is a key mechanism involved in ventilator-induced respiratory muscle dysfunction. Verona et al. [13] estimated the plasma levels of oxidative stress markers before and after SBT. They found higher plasma concentration of malondialdehyde and vitamin C, and lower level of nitric oxide in plasma were significantly associated with SBT failure.
Chapter 2

2. Respiratory Mechanics

The respiratory mechanics represents the set of forces that effects on the respiratory system, both in static and dynamic conditions. The study of respiratory mechanics involves finding the relationships among the variables as pressures, flow and volumes which drive the respiration mechanisms. During the years, several studies have been executed with the aim of explaining the behavior of the system through more or less complex models, characterized by parameter closely related to the mechanical breathing.

In this chapter in addition to the description of these models, the methods proposed by various researches for the computation of the parameters are described. After discussing the main forces acting on the system, the work that they perform on it is presented. Then, a mechanical power index, related to the energy induced to the lung, during mechanical ventilation is discussed.

Starting from the researches treated, the objectives of this work are presented.
2.1 Respiratory System Modeling

A simple way to study respiratory mechanics is to build mathematical models which represent the system in an easy and reliable way. The models are then described by the so-called equation of motion. This equation states how the flow, pressure and volume are related to each other through parameters, as expressed in formula 2.1. Volume is linked to pressure by an elastance term, while flow is related to it by a resistance parameter. Depending on the complexity of the model, these two parameters may be split into more components, introducing non-linear relationships. The value of these parameters should be fixed in order to characterize the behavior of the system.

\[ P = \text{Resistance} \times V + \text{Elastance} \times V \] (2.1)

2.1.1 Parameter of the System

As already stated, the system parameters considered are resistance and elastance. Total resistance \( (R_{RS}) \) is usually made by two components, one from the airway resistance \( (R_{AW}) \) and one from lung tissues \( (R_T) \).

\[ R_{RS} = R_{AW} + R_T \] (2.2)

Airway resistance is due to the transition of gas along a conduit with a circular cross section, in which the opposition to the flowing depends mostly on conduit length \( (l) \) and radius \( (r) \) and gas viscosity \( (\mu) \) as expressed in the Poiseuille formula:

\[ R_{AW} = \frac{8\mu l}{\pi r^4} \] (2.3)

Total airway resistance can be considered as the sum of all the resistances exerted by the single branches of the airway tree. \( R_T \) instead, depends on lung tissues characteristics. When tissues are stretched, as during changes in volumes, their constituent fibers move against each other producing friction and heat. These resistances may be influenced by pathological conditions involving alteration in tissues structure and composition. Elastance \( (E) \), reflects the rheological properties of the lung tissues. It represents how difficult is to stretch the tissues in order to expand volume. So it strongly depends on
tissues composition and on the lung size. Due to these dependences, E is highly modified in pathological situations which may block air flow in some lungs area. This process is called derecruitment of alveoli. E can be also expressed as its inverse, called pulmonary compliance. This is defined like the slope of the pressure-volume graph.

The total relaxation pressure curve ($P_{EL}^{TOT}$) records the pressure in the alveoli at any lung volume when the respiratory muscles are relaxed.

![Figure 2.1: Relaxation Pressure curve](image)

The relaxation pressure curve crosses the zero axis at the functional residual capacity (FRC), which is defined as the volume of air in the lungs when the muscles of breathing are relaxed and when the pressure in the air passages is atmospheric. As it can be seen in Fig. 2.1 the total curve can be considered fairly linear over a range about FRC. Furthermore in this figure it’s shown like the $P_{EL}^{TOT}$ can be broken down into its component: the relaxation pressure curve of the lungs ($P_{EL}^{L}$) and the relaxation curve of the chest wall ($P_{EL}^{CW}$). The $P_{EL}^{L}$ is to the right of $P_{EL}^{CW}$ implying that the lungs are always tending to collapse and that at any given pressure the volume of the lungs alone would be less than the volume of the thoracic cage alone.
To obtain the $P_{EL}^{TOT}$ both static and dynamic method can be used. Dynamic compliance, however, will always be lower than static compliance, because the former includes resistive pressure components, and therefore the term is incorrect.

For each of these curves different techniques are implemented:

**Static methods**:

- *Super-Syringe Technique*: In this technique [14] increments of gas volume up to a total volume of 1.5–3 liters are applied to the patient. After each step, the static airway pressure is measured during a pause of a few seconds where there is no flow, and the pressure is the same in the entire system from the super syringe to the alveoli. The lung is then deflated in a similar way, and the inflation and deflation $P$–$V$ curve is plotted (Fig. 2.2). In ARDS patients, alveolar recruitment taking place during the stepwise inflation to a high pressure will also cause hysteresis.

- *Inspiration Occlusion Technique*: it was developed in the late 1980s and was initially described by Levy et al [15]. It consist of sequence of different-sized volume-controlled inflations with an end-inspiratory pause to allow semi-static pressure measurements (Fig. 2.3). Intrinsic PEEP is determined before each inflation to ensure that the lung volume and the end-expiratory pressure are stable. Pressure and volume are plotted for each end-inspiratory pause to form a static $P$–$V$ curve. The inspiratory
occlusion technique offers the advantage of avoiding disconnection of the patient from the ventilator, and it allows measurements from any level of PEEP.

![Figure 2.3: Inspiration Occlusion Technique](image)

- **Low-Flow Inflation Technique**: It’s a method\[16\] in which a very low constant inspiratory flow is provided to the patient to generate a large total volume. The low flow causes a pressure decrease over the endotracheal tube, which means that the pressure–volume curve obtained under this “quasi-static” condition is shifted to the right with respect to a “true” static P–V curve (Figure 2.4).

![Figure 2.4: Low-Flow Inflation Technique](image)
Dynamic methods:
Unlike static or quasi-static procedures, dynamic methods are continuous and can be used during ventilator treatment. The term “dynamic compliance” refers to the computation of compliance under mechanical ventilation and is calculated by dividing the tidal volume by the peak airway pressure (minus PEEP). Among these techniques, the SLICE method is one of the most used (or the gliding-SLICE method [17], evolution of this)

- **SLICE method**: in this procedure the tidal volume of each breath is divided into different volume slices of equal size: six in classical SLICE method while much more in gliding-SLICE. A slice along the volume axis of the pressure–volume loop indicated as consecutive rectangles with a distance in volume indicated as step size (SS). The difference between this two studies is the vertical step size. This is smaller in the second case, in order to achieve a better intratidal resolution.

![Figure 2.5: Slice Method](image)

2.1.2 Description of the Models

The initial point in modeling a physiological system is the choice of the structure of the model in terms of the number of its components, their relationships and what they represent. Usually, the models adopted for the respiratory system are rather simple, involving only a single compartment and few independent components and parameters. A general representation of the entire system may be schematized as follow:
Chapter 2: Respiratory Mechanics

2.1 Respiratory System Modeling

Basing on this general representation, different models can be inferred:

- **The linear single-compartment model**

This model lies on two main assumptions:

- All the flow-resistive airways are represented only by one duct
- The lungs are homogeneously ventilated so as all the alveoli have the same pressure

The lung is viewed like a balloon inflated by a pipe through a single conduit. This model has both an anatomical analogy, as the balloon represents the elastic parenchymal tissue, and a functional analogy as the balloon can be inflated and deflated through the pipe as during a real breathing. A schematic representation of this model follows:
Air flows through a single conduit from outside to inside and vice versa. This process requires a certain pressure drop as in real breathing. The conduit exerts a certain resistance to flow, which is directly proportional to the conduit length and inversely proportional to its radius. The elastic behavior of the balloon is represented by an ideal spring which connects the two alveolar compartments, having $E$ as spring constant. The spring becomes stretched when compartment volume increases, generating an elastic pressure $P_{EL}$ inside the balloon, which is responsible for the return of the balloon to its original volume, when inflating pressure ceases.

This model has a single degree of freedom, because its state is uniquely identified at each time by a single variable: the volume of the elastic compartment. This representation can be described by a simple equation called motion equation. This last, needs certain assumption about the elastic properties of the spring and flow resistance, called constitutive properties. First assumption relates linearly the elastic pressure $P_{EL}$ with volume, through the slope $E$ (elastance):

$$P_{EL} = E \times V$$ \hspace{1cm} (2.4)

Second assumption is about drop of pressure ($\Delta P$) between proximal and distal ends of the conduit, which is linearly related to the flow ($V'$) through slope $R$ (resistance).

$$\Delta P = R \times V'$$ \hspace{1cm} (2.5)

Ideal relationships are shown below:

▶Figure 2.8: Relationship between: Elastance-Volume (A); Resistance – Flow (B)
So, the total pressure across the system is the sum of these two components:

\[ P = P_{EL} + \Delta P = E \times V + R \times V \]  
\[ (2.6) \]

This is a simple model and this equation doesn’t represent exactly the behavior of the real system. Then, it requires a modification before being applied to it.

- **Multiple compartment model**

In the real case, the lungs are encased in the thorax and are surrounded by the pleural space, having a certain pleural pressure \( P_{PL} \). The total pressure may be subdivided in two components, the transpulmonary pressure \( P_{TP} \) and the chest-wall pressure \( P_{CW} \) as already defined in formula 1.4.

![Figure 2.9: Multiple compartment model](image)

The pleural pressure has a significant role in determining lung expansion. Due to measurement problems, \( P_{ES} \) is often used as a surrogate for \( P_{PL} \) [18]. The transpulmonary pressure has been defined as the pressure drop across airways and lung:

\[ P_{TP} = P_{AO} - P_{PL} \]  
\[ (2.7) \]

Then, substituting \( P_{PL} \) with \( P_{ES} \):

\[ P_{TP} = P_{AO} - P_{ES} \]  
\[ (2.8) \]
Subdividing $P_{RS}$ in $P_{TP}$ and $P_{CW}$, the parameters $R$ and $E$ must be subdivided as well, in two components pertain to lungs tissues and chest wall. So, Elastance and Resistance become equal to:

$$E_{RS} = E_L + E_{CW} = \frac{C_L + C_{CW}}{C_L \times C_{CW}} \quad (2.9)$$

$$R_{RS} = R_{t,L} + R_{t,CW} + R_{AW} \quad (2.10)$$

The transpulmonary pressure can be expressed in terms of resistance and elastance, taking into account only the lungs section contribute:

$$P_{TP} = E_L \times V + (R_{t,L} + R_{AW}) \times \dot{V} + P_0 \quad (2.11)$$

Where $P_0$ is added as an offset pressure to account for the fact that $P_{TP}$ is non-zero when $V$ and $V'$ both are zero and the term $E_L$ and $R_L$ ($R_{t,L} + R_{AW}$) specifically denote the elastance and resistance of the lung. In a ventilated patient $P_0$ assumes the values of PEEP and $V$ is defined as being zero at the end of an expiration.

- **Nonlinear single-compartment model**

The linear model described above, explains the behaviour of healthy lung during breathing or mechanical ventilation. However, this model doesn’t fix well when the lung is forced to operate in pathological conditions. These cases require the extension of the model through the addition of extra features that make the system to be nonlinear. As an example, the model extents the relationship between $\Delta P$ and $V'$, adding a second resistance parameter that relates pressure to a quadratic term of flow

$$\Delta P = R_1 \times \dot{V} + R_2 \times \dot{V} \times |\dot{V}| \quad (2.12)$$

Known as Rhorer’s equation, usable when flow is turbulent.

$$P_{RS} = E_{RS} \times V + R_1 \times \dot{V} + R_2 \times \dot{V} \times |\dot{V}| + P_0 \quad (2.13)$$

$R_1$ and $R_2$ should be considered as a pair of parameters that describe a quadratic dependence of resistive pressure on flow.
Another nonlinear modeling consider a quadratic relationship between elastance and volume.

\[ P_{EL} = E_1 \times V + E_2 \times V^2 \]  
(2.14)

\[ P_{RS} = R \times \dot{V} + E_1 \times V + E_2 \times V^2 + P_0 \]  
(2.15)

This model seems to be a good representation when the lungs are ventilated over a large volume range or in pathological situations where lung elasticity is abnormally high. Clearly, both nonlinearities could be present at the same time, as:

\[ P_{RS} = R_1 \times \dot{V} + R_2 \times \dot{V} \times |\dot{V}| + E_1 \times V + E_2 \times V^2 + P_0 \]  
(2.16)

### 2.1.3 Parameter estimation

There are different approaches in order to estimate the resistance and elastance parameters present in the equations previously described.

- **Least Square Method**

A reliable method is called “Least square estimation” [19], in which the total respiratory system pressure which has been measured is compared to pressure obtained by the equation of motion, using the volume and flow values. In this approach, the predicted pressure can never be exactly the same as the measured one, due to models approximations. Then, the least square model provides the R and E values as the one that minimizes the sum of the squared residuals, defined as:

\[ SSR = \sum_{i=1}^{N} [P_i - P'_i]^2 \]  
(2.17)

Where P is the measured pressure and P’ is its prediction. When R is held fixed and E is varying, the SSR will reach the minimum when its derivative respect to E is zero. Then:

\[ \frac{\partial SSR}{\partial E} = -2 \times \sum_{i=1}^{N} V_i \times [P_i - E \times V_i - R \times \dot{V}_i] = 0 \]  
(2.18)
Rearranging:

\[ \sum_{i=1}^{N} V_i \times P_i = E \times \sum_{i=1}^{N} V_i^2 + R \times \sum_{i=1}^{N} V_i \dot{V}_i \]  

(2.19)

If the same assumption is taken reversing \( E \) and \( R \), then:

\[ \sum_{i=1}^{N} \dot{V}_i \times P_i = E \times \sum_{i=1}^{N} V \times \dot{V}_i + R \times \sum_{i=1}^{N} \dot{V}_i^2 \]  

(2.20)

The equations give the values of \( R \) and \( E \):

\[
R = \frac{\sum_{i=1}^{N} V_i^2 \times \sum_{i=1}^{N} \dot{V}_i \times P_i - \sum_{i=1}^{N} V_i \times \dot{V}_i \times \sum_{i=1}^{N} V_i \times P_i}{\sum_{i=1}^{N} V_i^2 \times \sum_{i=1}^{N} \dot{V}_i^2 - (\sum_{i=1}^{N} V_i \times \dot{V}_i)^2}
\]

(2.21)

\[
E = \frac{\sum_{i=1}^{N} V_i \times P_i - R \times \sum_{i=1}^{N} V_i \times \dot{V}_i}{\sum_{i=1}^{N} V_i^2}
\]

(2.22)

These equations can be represented in a more suitable way using matrices:

\[ P = \begin{bmatrix} P_1 \\ P_2 \\ \vdots \\ P_n \end{bmatrix} \]

(2.23)

Which represents the column vector of the dependent variable \( P \).

The parameters of the model are written as the vector:

\[ A = \begin{bmatrix} E \\ R \\ P_0 \end{bmatrix} \]

(2.25)
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The final equation results:

\[ P = X \times A \]  \hspace{1cm} (2.26)

As the aim is to find the values of the elements in the vector \( A \), it is simple reachable by pre-multiplying both sides of the previous equation by the transpose of \( X \), as the number of parameter is always less than \( n \) and \( X \) has no inverse.

The solution turn to be:

\[ A = \left( X^T X \right)^{-1} \times X^T \times P \]  \hspace{1cm} (2.27)

This model can be extended for an arbitrary number of parameters, so as to be used also in the case of nonlinear representation. As example, for the nonlinear model with two resistances and two elastances terms and \( n \) sequential measurements, the problem can be represented as:

\[ X = \begin{bmatrix} V_1 & V_1^2 & \dot{V}_1 & \dot{V}_1^2 & 1 \\ V_2 & V_2^2 & \dot{V}_2 & \dot{V}_2^2 & 1 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ V_n & V_n^2 & \dot{V}_n & \dot{V}_n^2 & 1 \end{bmatrix} \]  \hspace{1cm} (2.28)

\[ A = \begin{bmatrix} E_1 \\ E_2 \\ R_1 \\ R_2 \\ 1 \end{bmatrix} \]  \hspace{1cm} (2.29)

A measure of the goodness of fit for these models is provided by the coefficient of determination \( \text{CD} \), which express the fraction of the variation in the data accounted for by the model according to:

\[ \text{CD} = 1 - \frac{SSR}{\Sigma_i \left( P_i - \overline{P} \right)^2} \]  \hspace{1cm} (2.30)

Where \( \overline{P} \) is the mean value of measured Pressures. \( \text{CD} \) can take a value anywhere from 1 to 0, where a high value means that the model has a good fit to the data.
• **Estimation during Volume-controlled mode**

This method can be used only during volume controlled mode and paralyzed patients, in which occlusion maneuver are executed to rapid interrupt airflow at the airway opening during standard breath. The traces obtained in this modality are:

![Figure 2.10: Traces obtained in Volume-controlled ventilation with an occlusion maneuver](image)

The values of R and E can be expressed as:

\[
R_{RS} = \frac{P_{RES}}{V_{INSP}}
\]  

(2.31)

\[
E_{RS} = \frac{P_{EL}}{\Delta V}
\]  

(2.32)

In this model the total pressure considered is the drop of pressure between airway opening and body surface. Subdividing \(P_{RS}\) in \(P_{TP}\) and \(P_{CW}\), as described in the previous paragraph, the chest wall compliance can be obtained from \(P_{ES}\) dynamics, as represented in the following figure:

![Figure 2.11: Estimation of chest wall Compliance](image)
Chest wall compliance is calculated as:

\[
C_{CW} = \frac{\Delta V}{P_{EL_{CW}}} = \frac{\Delta V}{P_{ES,plat} - P_{ES,end-exp}}
\]  

(2.33)

Where \(P_{ES,plat}\) is the plateau esophageal pressure value and \(P_{ES,end-exp}\) is the esophageal pressure value at end expiration.

Then, lung compliance can be obtained as:

\[
\frac{1}{C_{CW}} = \frac{1}{C_{RS}} - \frac{1}{C_{L}}
\]  

(2.34)

- **Estimation during Pressure-controlled mode**

The computation of mechanical parameters during pressure controlled can be obtained considering two different time instant of the breath. As can be seen in Fig. 2.12 at the start of the breath (\(t_1\)), indicated by the dashed line, the volume is around zero while pressure and flow increase. In this condition, the elastic contributes can be assumed null, and then only the resistive one is responsible for the total pressure developing (formula 2.35). The elastic contribute can be estimated in a similar way. At end expiration in fact (\(t_2\)), indicated by the dotted, the flow reaches zero value while pressure is non zero and volume reaches its maximum values. In this case, the resistive contribute is null and consequently the elastance is obtained as in formula 2.36.
\[
R = \frac{P(t_1)}{\dot{V}(t_1)} \quad (2.35)
\]

\[
E = \frac{P(t_2)}{V(t_2)} \quad (2.36)
\]

- **Mead-Whittenberger Method**

With this technique [20] pressure and flow are displayed graphically to make a loop. Then a signal proportional to volume \((E \times V)\) is subtracted from \(P\), so a narrower loop is obtained. The slope of this loop is taken as an estimate of \(R\) (formula 2.37). An example of this method is shown in figure:

\[
R = \frac{\Delta(P - E \times V)}{\Delta V} \quad (2.37)
\]

The elastance is obtained through formula 2.32 for a volume-controlled ventilated patient, and through the formula 2.36 for a pressure controlled ventilated patient. The advantage of this technique is that all of acquired data are used for the \(R\) computation.
• **Recursive Algorithm**

In the previous methods, it is assumed that R and E do not change in time. However, in real situations the lungs are not in a mechanical steady state, then R and E are not constant. The implementation of the recursive method [21] allows to deal with this situation, fitting the data within a small time window which moves along the data acquired. R and E stay constant over the duration of the window, but they can change from one to another. Depending on the window size, the system can be able to resolve better or not the values of R and E. Shorter windows are able to follow the rapid parameters trend, but at the same time they are more sensitive to noise, while larger windows have slower dynamics but they are more robust to the noise. The main feature of recursive formula is the fading memory. This term called forgetting factor ($\lambda$) allows to influence the data in the moving window, by the past values or the latest one. $\lambda$ is a fixed value between 0 and 1. If it is close to 1 the algorithm has a long memory, while making $\lambda$ close to 0 reduces the memory length and improves the algorithm ability to follow rapid changes of data. Then, the implementation of a multiple linear regression as a recursive algorithm, allow to track changing values of R and E starting from P, V and V'.

The recursive algorithm is:

$$\tilde{A}_{k+1} = \tilde{A}_k + \frac{M_k \times X_{k+1} \times (y_{k+1} - X^T_{k+1} \times \tilde{A}_k)}{\lambda + X^T_{k+1} \times M_k \times X_{k+1}}$$

(2.38)

Where

$$M_{k+1} = \frac{1}{\lambda} \times \left[ M_k + \frac{M_k \times X_{k+1} \times X^T_{k+1} \times M_k}{\lambda + X^T_{k+1} \times M_k \times X_{k+1}} \right]$$

(2.39)

$A_k$ is the vector of parameters determined from the first k sets of measurements, $A_{k+1}$ is its update with the new set of data, $X_{k+1}$ is the vector of k+1 set of measurements and $M_k$ is the information matrix equal to $\left[ X^T \times X \right]^{-1}$ and $y_{k+1}$ is the measured $P_{AO}$.

The parameters, estimated at each time step, are given by those found at the previous time step plus a correction term, which is proportional to the difference between the model prediction and the measurement at the current step. The initial parameter values are estimated through conventional multiple linear regression using the first few sets of data.
2.2  Work of breathing

The term “work of breathing” is generally understood to relate to patient effort during breathing activity. Otis [22] pointed out that there are two different but complementary approaches of quantifying the work of breathing:

1) Estimation of the mechanical work from measurements of the pressures developed and the volumes displaced by the respiratory muscles

2) Estimation of the energy cost by measuring the oxygen consumption of the muscles of breathing

During mechanical ventilation or spontaneous breathing investigators are often interested in quantifying not only the total work performed by the respiratory muscles but also the subcomponent performed by a group of respiratory muscles during different ventilator modes or the work performed by the patient during assisted mechanical ventilation.

Work is usually measured in Joule (1 J represents the work needs to move a volume of 1 L of gas through pressure gradient of 10 cmH₂O). In a physical sense, work (W) is defined as force-length product. When a pressure gradient (Pₜₛ) is applied in an area (A) to inflate a distensible structure, the applied force equals pressure multiplied by area. Since the product area and distance equals volume, the mechanical work performed can be estimated by the following formula:

\[ W = \int P_{TS} \times dV \]  

(2.40)

Similar principles are applied in the computation of mechanical work during expiration, although expiratory work of breathing is usually not taken into consideration since exhalation is normally passive. The measurement of work can be splitted in two components: the work performed across the lung (W_L) and the chest wall (W_CW):

\[ W = W_L + W_{CW} = \int (P_{AW} - P_{ES}) \times dV + \int (P_{ES} - P_{AT}) \times dV \]  

(2.41)

Where P_{AW} is airway pressure, P_{ES} is esophageal pressure and P_{AT} is atmospheric pressure. During mechanical ventilation, the W and W_{CW} can be measured respectively from the area enclosed in the plot P_{AW} and P_{ES} against inspired volume.

W_L, instead, can be divided in other two components, the resistive and the elastic work:
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2.2 Work of breathing

Resistive work = \((P_{AW} - P_A) \times \text{inflated volume}\) \hspace{1cm} (2.42)

Elastic work = \((P_A - P_{pl}) \times \text{inflated volume}\) \hspace{1cm} (2.43)

Where \(P_A\) is alveolar pressure.

The resistive work represent the work performed across the airways, while the elastic is the work performed across the lung parenchyma. During spontaneous breathing, the total \(W_{CW}\) can be quantified by using the equation of motion [23], as the product between the average distending pressure \(P_{AVG}\) and the tidal volume:

\[
P_{AVG} = \frac{V_T}{(2 \times C_{CW})} \hspace{1cm} (2.44)
\]

\[
W_{CW} = \frac{V_T^2}{(2 \times C_{CW})} \hspace{1cm} (2.45)
\]

While the \(W_L\), can be measured from a plot of \(P_{ES}\) against inspired volume.

A reliable representation of respiratory muscles activity is given by Campbell [24] (Fig. 2.14).

![Campbell Diagram](image)

**Figure 2.14: Campbell Diagram**

This graph has been obtained representing the chest wall and lung Compliance in pressure-volume diagram. The white area concerns the total work done by the inspiratory muscles against the non-elastic resistance of the lung and airways (Resistive work). The stippled area is the total work done by the inspiratory muscles against the elastic resistance of the
Chapter 2: Respiratory Mechanics

2.2 Work of breathing

The hatched area is the total work by the relaxation pressure of the thoracic cage against the elastic resistance of the lungs (Stored Energy of chest wall). Respiratory muscle effort has also been treated by Akoumianaki et al. [25], calculating the work of breathing (WOB) as in formula 2.47. WOB is expressed as a function of \( P_{\text{MUS}} \), which can be viewed as the difference between the static recoil pressure of the relaxed chest wall \( P_{\text{CW}, \text{rel}} \) and the esophageal pressure \( P_{\text{ES}} \).

\[
P_{\text{MUS}} = P_{\text{CW}, \text{rel}} - P_{\text{ES}} \tag{2.46}
\]

Then WOB is:

\[
W_{\text{mus}} = \int P_{\text{MUS}} \times dV \tag{2.47}
\]

Where \( dV \) represents lung volume distensions. It was commonly believed that mechanically ventilated patients are spared the majority of the energy cost of breathing, but studies did not confirm this. Instead, it has been shown that many ventilated patients without sedation perform expiratory work or share inspiratory work with their ventilator. This is more evident when a partial support ventilation mode is used, as SIMV or CPAP. In fact, during assisted controlled mechanical ventilation, the patient triggers inflation by lowering airway pressure. His work is related only to the effort involved in triggering. Patients may perform inspiratory work when there is a delay between the onset of the patient’s inspiratory effort and the moment that full machine support is achieved, and because the flow provided by the ventilator does not match the patient’s needs. The patient’s contribution to the work of breathing during assisted mechanical ventilation, may be estimated by plotting the \( P_{\text{AW}} \) against volume, during assisted and controlled cycles, and measuring the difference in the areas included in the plots. Sassoon et al. [26] demonstrated that inspiratory work performed by healthy subjects during ACMV is a function of the tidal volume and of the inspiratory flow delivered by the ventilator. Ward et al. [27] compared the plots of inflation against volume during controlled cycles and passive inflation (Fig. 2.15).
The patient’s contribution to the work of breathing during CMV can be estimated by plotting inflation pressure ($P_{RS}$) against volume during completely passive inflation (A) and during CMV cycle (B). The difference of the area included in such plots (C) yields the inspiratory work performed by the patient during each mode of ventilatory support.
2.2.1 Mechanical Power Index

In the last years, different parameters which are involved in mechanical ventilation have been included in a single variable called mechanical power, which seems to be related to the ventilation-induced lung injury (VILI). The amount of Energy applied at each breath with a certain frequency (power) may be seen as a sort of “fatigue” of the lung extracellular matrix [28]. When the lung is subject to an “excess” of energy, the unrecovered energy may be expected to be sufficient to break the molecular bonds of the polymers of the extracellular matrix, to detach endothelial and epithelial cells from the basement membrane, and to fracture the capillary walls. Alteration of the extracellular matrix, combined with capillary micro-fractures, may then activate an inflammatory reaction and micro-hemorrhage, leading to the extracellular edema typical of VILI. The main factors that are considered as possible triggers for VILI are tidal volume (TV) and plateau pressure. The TV is related to the strain induced due to lung size changes during ventilation while the plateau pressure concern the stress induced to the lung when a force is applied. Other factor as temperature, respiratory rate and flow are cofactors for VILI. All these factors together constitute the energy applied to the respiratory system, while the mechanical power express this energy per minute. A recent research on piglets [29] has demonstrated that when this index exceeds a certain threshold VILI is induced.

For this reason, a reliable and complete quantification and analysis of the mechanical power may be useful in order to select the better setting for a mechanical ventilation. The energy load to the respiratory system (Fig. 2.16) is composed of a static component, due to PEEP and PEEP volume (conceptually equivalent to potential energy), and a dynamic cyclic component, due to driving pressure and tidal volume above PEEP (conceptually equivalent to kinetic energy), plus the additional, resistive and inertial component generated by the pressure spent for gas movement, the surface tension forces, and tissue resistances to motion. Once PEEP is applied, no further cyclic energy load is imposed on the system, as the volume is constant. PEEP plays a complex role in the context of the energy provided by the ventilator, as it provides increased continuous tension to the extracellular matrix which then accumulates potential energy. Further energy is added when cyclic tidal ventilation is superimposed to reach a given end-inspiratory volume.

The quantification of the mechanical power requires the calculation of energy, from the P-V loop diagram, as shown in the following image:
The left cathetus of large triangle (green plus azure) represents the total volume (TV+PEEP volume) while the upper one represents the plateau pressure. The slope is the compliance of the system. The area of this triangle represents the total elastic energy. The yellow area stand for a resistive component of breathing. The energy is the product of the absolute value of pressure times the variation of volume. Then, the energy is multiplied by the respiratory rate and by 0.098 in order to obtain a value expressed in Joule/minute.

A research [30] proposed a new method for mechanical power computation. In this paper, the mechanical index is calculated from its components: tidal volume (TV), driving pressure ($\Delta P$), flow, positive-end expiratory pressure (PEEP) and respiratory rate. This computation starts from the classical equation of motion, where the total pressure of the respiratory system is:

$$ P = E \times \Delta V \times R_{AO} \times \dot{V} + PEEP $$

(2.48)

Then the energy computed from this equation becomes:

$$ E_{breath} = \Delta V \times \Delta V \times E_{RS} \times \frac{1}{2} + \Delta V \times R_{AO} \times \dot{V} + \Delta V \times PEEP $$

(2.49)

Which can be expressed in function of the respiratory rate as:

$$ E_{breath} = \Delta V \times \Delta V \times E_{RS} \times \frac{1}{2} + \Delta V \times R_{AO} \times \dot{V} + \Delta V \times PEEP $$

(2.49)
\[ E_{\text{breath}} = \Delta V^2 \times \left( E_{lRS} \times \frac{1}{2} + RR \times \frac{(1 + I:E)}{60 \times I:E} \times R_{AO} \right) + \Delta V \times PEEP \] (2.50)

So, the mechanical power is obtained as:

\[ Power_{rs} = 0.098 \times RR \times \left\{ \Delta V^2 \times \left[ \frac{1}{2} \times E_{lRS} + RR \times \frac{(1 + I:E)}{60 \times I:E} \times R_{AO} \right] + \Delta V \times PEEP \right\} \] (2.51)

From this formula, it is possible to assess the effects of changing whatever variable on the mechanical power.

Mechanical power obtained as the methods previously described represents both the efforts induced by the ventilator and respiratory muscles activity.

During ventilation and active conditions (with respiratory muscles activity), the \( P_{\text{MUS}} \) has important effects in distending of lung tissues.
2.3 Objectives

The aim of this thesis is the development of an instrument capable of monitoring breathing parameters of a patient during mechanical ventilation. The main features of this device are its low invasivity, low physical obstruction to clinicians and the possibility of displaying in real time the monitored variables. Not only device’s hardware has been developed, but also firmware and software. The real time monitored variables are: airway opening pressure, esophageal pressure and flow through sensors directly applied to the patient. Starting from this variables, the real time values of transpulmonary pressure, volume and mechanical power index are calculated. This last has been obtained, breath by breath, by the P-V loop as described in the previous chapter. As early stated, this index might be correlated to VILI, then its monitoring under different ventilation and patient conditions may help clinicians in setting ventilator parameters in order to improve patient treatment.

Besides, in a post processing analysis, the mechanical index is obtained also using the formula (2.51), in which the elastance and resistance parameters are estimated using different techniques, and then compared with the real-time calculated index, so as to find the best evaluation method for R and E.

Another important task performed, is the separation of the mechanical contribute deriving from patient in respect of ventilator in each breathing cycle. This separation, made in post processing, may be useful in order to understand how much effort is done by respiratory muscles of patient during breathing. Results from this study could be analyzed in order to drive a weaning procedure.
Chapter 3

3. Development of the System

This chapter describes the whole acquisition, processing, transmission and post-processing system of the data.

The first part explains the Hardware of the device, which is used to acquire from the patient and transmit to the computer the signals of flow, airway pressure and esophageal pressure using Bluetooth connection or USB.

The second section describes the Firmware of Arduino. The indicated code is necessary to start the data acquisition from the sensors and set the sampling frequency of the signals. It permits also to establish the connection between device and laptop.

In the third part, the software tools for the computation of all parameters is explained. The first one is Processing, a free available program, in which an algorithm has been implemented in order to receive data from the device, show them in real time on the monitor, compute Mechanical Power index and save data for a post-processing analysis.

The second one is Matlab, which has been used to review and analyse collected data.
3.1 Hardware

The Hardware of the system that has been built to perform the analysis is shown in Fig 3.1.

Starting with the assumption that, for this study, the patients are connected to mechanical ventilator, it was attempted to develop a compact and non-bulky system so as not to hinder operators in intensive care unit.

The system records three signals: airway opening pressure, esophageal pressure and flow. For the acquisition of these signals a pressure sensor and a flow sensor are located at patient’s mouth opening, while another pressure sensor is connected at the esophageal catheter. Each of them is connected through a cable at the board of Arduino situated in a compact case. The board allows to convert the analog signals in digital. Successively, the communication with the laptop can be realized via Bluetooth or via USB and at the end these data are shown on the monitor.
3.1.1 Flowmeter

For measuring the flow of inspired and exhaled air, the SFM3300-AW sensor (Fig 3.2) is used.

![Figure 3.2: SFM3300-AW Flowmeter](image)

The SFM3300-AW sensor is a digital flow meter made by Sensirion (Staefa ZH, Switzerland) designed for medical applications. It’s used for measuring the flow rate of air, oxygen and other non-aggressive gases with very high accuracy. It features medical cones for pneumatic connection to standard breathing circuits and a mechanical interface for easy and reliable electrical reconnection. A very small dead space combined with its ability to withstand autoclave procedures make the SFM3300-AW extremely suitable for proximal flow measurements in medical ventilation and other respiratory applications.

The sensor element, signal processing and digital calibration are on a single microchip assuring very fast signal processing time. This sensor, like many other Sensirion’s sensors, is based on CMOSens® Technology which enables to combine the sensor component with signal-processing circuitry on a tiny CMOS silicon chip. The flow is determined using a thermal measurement principle more evolved than the hot-wire anemometer. An adjustable heating element is positioned at the center of a pressure-stabilized membrane, with a temperature sensor both upstream and downstream of the membrane in the direction of gas flow (Fig 3.3). If no gas flows over the sensor surface, the symmetric temperature sensors measure the same rise in temperature, resulting in the same output. If a non-zero gas flows from the inlet to the outlet of the flowmeter, the velocity of a air flow unbalances the temperature profile around the heater and heat is transferred from upstream sensor to the downstream one, causing a change in the voltages of the thermopiles. Larger gas flow rates result in larger asymmetry in the temperature profile.

Ideally, sensors are thermally isolated so only heat transfer due to flow can occur.
Chapter 3: Development of the System

3.1 Hardware

These gas-flow sensors are a pressure-stabilized membrane, with a glass-passivation layer, closed from the front and etched into the silicon chip from below. Settling of contaminants is prevented by the flat glass surface. Simultaneously, the rear air cushion allows the pressure-tight membrane to be used even if there are strong vibrations. The CMOSens® Technology integrates this miniaturized sensor together with the entire high-precision processing circuitry on a tiny CMOS microchip.

On the same chip, not even a millimeter away from the sensor component, can be found: an analog-to-digital converter and a signal amplifier, which both contribute to the precision of the measurement, a temperature sensor, which emits a signal that compensates for any arising temperature effects and an EEPROM memory cell to store calibration data (Fig. 3.4). As a result, the signal received by the sensor chip is always fully calibrated, linearized and temperature-compensated. Furthermore, Sensirion's microthermal gas meter modules are equipped with integrated gas recognition. An innovative, high-tech algorithm recognizes various gas mixtures and compensates for them.
Chapter 3: Development of the System

3.1 Hardware

Its technical characteristics are:
- Flow Range: ±250 slm
- Dead space: < 10ml
- Update time: 0.5ms
- Resolution: 14 bit
- Accuracy: 1% Measured Value
- Media Compatibility: Air (non-condensing), N₂, O₂, other non-aggressive gases
- Operating Temperature Range (Temperature compensated): 5÷50 °C
- Cleanable and autoclavable

The signal processing circuitry on the chip also includes the digital communication interface. It uses an I²C protocol, the standard for communication between the various components on the circuit board. In addition to the 4 pin of the communication protocol (DATA, CLOCK, VDD, GND), the sensor has two additional pins: HEAT and HEAT_GND (Fig. 3.5). These two pins are used in case it wants to adjust the heated element. This is possible by applying a voltage to their heads not exceeding 5V. This is done because between them a R = 50 Ω is present and according to the datasheet the maximum power to be delivered is 0.5 W (V_{MAX} = √{Power * R}).

► Figure 3.4: Schematic representation of signal processing

► Figure 3.5: SFM3300-AW flowmeter pins
Chapter 3: Development of the System

3.1 Hardware

One of the advantages of this sensor is the possibility to wash and autoclave it. Sensirion tested one standard method for autoclave sterilization and one standard cleaning method using a liquid agent with its SFM3300-AW flow meter. Sixty sensors were tested by autoclave process following these steps:

1) 135 °C and -0.8…+2.15 bar gauge pressure for 5 min
2) Drying through evacuation for 5 min
3) Cool down to 50 °C

The results obtained after the autoclave procedure are the following:

![Figure 3.6: Results after SFM-3300 autoclave procedure](image)

Instead, the stability of the sensor against cleaning in a liquid solution has been tested by repeatedly cycling 8 sensor units in CIDEX® Activated Dialdehyde solution for 10 cycles and an extended immersion, using the following steps:

1) Complete immersion of clean and dry sensor in CIDEX® for 15 minutes at ambient temperature (~21 °C)
2) All cavities were brought in contact with CIDEX®
3) Sensor was removed and thoroughly rinsed with distilled water. This procedure was repeated twice, for a total of three rinses. Each rinse was carried out for approx. 5 minutes in duration and a large volume of fresh distilled water.
4) Subsequent rinsing in isopropanol in order to facilitate the drying process.
5) Sensor was entirely dried before re-connection and re-use.

After these 10 cycles, test measurements were performed for each sensor. The sensors were then re-immersed for a prolonged period of >25 hours in CIDEX, which is equivalent to 100 cycles of 15 minutes. Due to unavailability of the CIDEX solution the sensor has been cleaned with GIOFTAL, a solution composed by ortho-phthalaldehyde often used in clinical field. This method didn’t affect sensor characteristics.
3.1.2 Pressure Sensors

Two sensors are necessary to record pressure signals at airway opening and at the esophagus. The sensors used are SSCSNBN001PDAA5 (Fig. 3.7), made by Honeywell (Morris Plains, New Jersey, USA).

They are a piezoresistive silicon pressure sensors offering a ratiometric analog output for reading pressure. The SSC Series is fully calibrated and temperature compensated for sensor offset, sensitivity, temperature effects, and non-linearity using an on-board Application Specific Integrated Circuit (ASIC).

Calibrated output values for pressure are updated at approximately 1 kHz. The TruStability® pressure sensors are intended for use with non-corrosive, non-ionic gases, such as air and other dry gases.

Its technical characteristics are:

- Pressure Range: ±1 PSI (1 PSI ≈ 70.307 cmH₂O)
- Accuracy: ±0.25% of the Full Scale Span (FSS)
- Compensated Temperature Range: -20 ÷ 80 °C
- Ratiometric Analog output
- Extremely low power consumption
- High resolution (min. 0.03 %FSS)
- RoHS compliant

These sensors are mainly employed in medical environment for different applications: airflow monitors, anesthesia machines, blood analysis machines, gas flow instrumentation, oxygen concentrators, etc.
Since these sensors are already amplified for the stage of Front-End, only a filter without amplification has been developed.

In particular, for this application a Sallen-Key low pass filter has been designed (Fig 3.8).

![Figure 3.8: Sallen-Key LP filter](image)

The cut-off frequency used for good measurements is approximately 25 Hz. It can be obtained from the following expression:

$$f_c = \frac{1}{2\pi \sqrt{R_1 \times R_2 \times C_1 \times C_2}}$$  \hspace{1cm} (3.1)

The chosen components values are:

- $R_1 = 22 \, \text{K}\Omega$
- $R_2 = 47 \, \text{K}\Omega$
- $C_1 = 0.12 \, \mu\text{F}$
- $C_2 = 0.27 \, \mu\text{F}$

It is important to underline that sensors used are totally independent of each other, then the use of one of them does not imply the use of the other and reversal.

In order to stabilize and protect the sensors, they are placed in proper boxes, on which M8 4-Pin connectors are mounted. Then the sensors communicate with Arduino board placed in bigger case through M8 4-Pin cable (Fig. 3.9).

![Figure 3.9: M8 4-Pin Connector and Cable](image)
3.1.3 Arduino Board

All these sensors are connected and interfaced with an Arduino UNO Board (Fig. 3.10). It is a microcontroller board based on the ATmega328P made by Arduino (Ivrea, Italy).

It has 14 digital input/output pins (of which 6 can be used as PWM outputs), 6 analog inputs, each of which provides 10 bits of resolution between GND and 5V, a 16 MHz quartz crystal, a USB connection, a power jack, an ICSP header and a reset button. The Arduino UNO can be programmed through the Arduino software, with an adequate firmware as shown in the section 3.2. Its specifications are shown below:

<table>
<thead>
<tr>
<th>Specifications</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcontroller</td>
<td>ATmega328P</td>
</tr>
<tr>
<td>Operating Voltage</td>
<td>5V</td>
</tr>
<tr>
<td>Input Voltage (recommended)</td>
<td>7-12V</td>
</tr>
<tr>
<td>Input Voltage (limit)</td>
<td>6-20V</td>
</tr>
<tr>
<td>Digital I/O Pins</td>
<td>14 (of which 6 provide PWM output)</td>
</tr>
<tr>
<td>PWM Digital I/O Pins</td>
<td>6</td>
</tr>
<tr>
<td>Analog Input Pins</td>
<td>6</td>
</tr>
<tr>
<td>DC Current per I/O Pin</td>
<td>20 mA</td>
</tr>
<tr>
<td>DC Current for 3.3V Pin</td>
<td>50 mA</td>
</tr>
</tbody>
</table>
Chapter 3: Development of the System

### 3.1 Hardware

<table>
<thead>
<tr>
<th>Component</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flash Memory</td>
<td>32 KB (ATmega328P)</td>
</tr>
<tr>
<td></td>
<td>of which 0.5 KB used by bootloader</td>
</tr>
<tr>
<td>SRAM</td>
<td>2 KB (ATmega328P)</td>
</tr>
<tr>
<td>EEPROM</td>
<td>1 KB (ATmega328P)</td>
</tr>
<tr>
<td>Clock Speed</td>
<td>16 MHz</td>
</tr>
<tr>
<td>LED_BUILTIN</td>
<td>13</td>
</tr>
<tr>
<td>Length</td>
<td>68.6 mm</td>
</tr>
<tr>
<td>Width</td>
<td>53.4 mm</td>
</tr>
<tr>
<td>Weight</td>
<td>25 g</td>
</tr>
</tbody>
</table>

*Table 3-1: Arduino UNO specifications*

The principal functions of the board are to sample signals coming from the three sensors and, in case of analog ones, convert them into digital. Furthermore, Arduino UNO is connected to Bluetooth Module through the serial communication available on digital pins 0 and 1 (RX and TX respectively), so as to send data to PC. The last role of this board is that of turn on a LED which indicates that the system is running.

#### 3.1.4 Bluetooth

To transmit data from device to PC a RN-42 Bluetooth Module (Figure 3.11) has been used.

![Figure 3.11: RN-42 Bluetooth Module](image.png)
The RN-42 is a small form factor, low power Bluetooth radio for designer’s who want to add wireless capability to their products. It supports multiple interface protocols, it is simple to design in, and it is fully certified. Furthermore, its capability to deliver up to a 3 Mbps data rate for distances up to 20 meters makes the global instrument completely stand-alone.

Since not all the PC are able to perform a Bluetooth communication, a USB Bluetooth dongle (Fig. 3.12) can overcome this problem.

Once the dongle has been installed a simple software named Bluesoleil allows to establish a reliable connection with RN-42 Bluetooth Module.

### 3.1.5 Power Supply

In principle, in order to power the device, a battery holder with 6 AA alkaline batteries, each of 1.5 Volts, was used and connected to a 2.1 mm center-positive socket. This allowed to power the board from which it takes out the 5 Volt needed to power all the components. From the table 3.1 it is noteworthy that Arduino UNO requires a power supply between 7 and 12 Volts in input. Using batteries with a capacity of 1500 mAh, knowing that the device consumes about 100 mA and using a correction factor of 1.2 it got a possible use up to 12 hours.

\[
Battery life [h] = \frac{Capacity \ [mAh]}{Consumption \ [mA] \times Correction \ Factor} \quad (3.2)
\]
Subsequently to increase the life of the device, the battery holders have been replaced with an Anker power bank (Shenzhen, China) with a capacity of 10’000 mAh (Fig 3.13).

This power bank has a system of led which indicated its battery life. Since the power bank provides only a 5 Volt output, a particular cable has been used (Fig 3.14).

This cable has an integrated boost converter, so it can plugged into any USB port (from a computer, battery pack, etc) and it will give a higher DC voltage. It's a handy way to supply 9V powered devices with a center-positive 2.1 mm DC barrel jack from a USB port. This cable has also been equipped with a button so that the device can be easily switched on and off.
Therefore the final system is the following:

![Diagram of the system connections]

►Figure 3.15: Schematic representation of the whole system connections

![Picture of the real encased system]

►Figure 3.16: Picture of the real encased system


3.2 Firmware

The Arduino board, to work properly, must be programmed using the IDE provided by Arduino. The software programming language, Wiring, is simple and intuitive as it is derived from C and C++ and is freely downloadable and modifiable. The firmware is cyclically executed by the μProcessor and it is developed in parallel with the software to show and save data. The functions done by the code are few and quite simple: read the data, send them to the pc and turn on a led to inform that the device is running. The firmware is composed by two main functions: a setup() function in which initialization operations appear and which is executed only once, when the firmware is loaded on the board, and a loop() function which is continuously cycled. The setup() function defines:

- the transmission baud rate (115k in this case)
- the frequency with which an Interrupt Service Routine (ISR) for reading and sending data is generated
- input port for signals acquisition
- output port for LED activation

The function allows also digital data reading which come from the flowmeter via I²C protocol. This is possible by writing a certain address from Arduino to the sensor, using the "Wire.h" library downloaded from the Arduino site (https://www.arduino.cc), as an initialization process. Once the setup is completed, the program begins to execute the loop function. To achieve greater efficiency, data reading is not performed in the loop, but with a frequency of 100Hz, where an ISR is generated. This Interrupt allows reading of the two analog ports of pressure and the flowmeter digital port. Then 10-bit ADC of Arduino converts the two analog signals in digital. Furthermore the Interrupt, after reading, prints the acquired data on the serial port which is connected to the Bluetooth Module, which send them to the PC. In serial printing, flow and pressure signals are separated by the character “|” a font that will then be used in the software to separate the data. At the end of the line with the sending data a ‘\n’ is printed to create a new line for the next data. When the Interrupt is called up, a counter is incremented. When this counter reaches 1000 (every 10 seconds) it allows the sampling and printing on serial output of an analog signal coming from a cable connected to the power bank. In this way the percentage of charge of the battery can be calculated.
Chapter 3: Development of the System

3.2 Firmware

![Figure 3.17: Arduino Firmware Flow chart]

`Figure 3.17: Arduino Firmware Flow chart`
3.3 Software

Once the signals are sent to the PC, the system allows a real-time graphical representation and the possibility to review the collected data after the acquisition.

In Fig. 3.18 a flow chart with the summary of all data analysis step is shown:

The software used to calculate the mechanical power and represent the real-time signals is completely implemented in Processing. This is an open source computer programming language developed at the MIT Media Lab starting from 2001. This software is very well-known for creating interactive and visual work. Furthermore, the integrated development environment (IDE) is very similar to the Arduino one and then they can well interact between them.

The goals of this sketch are essentially three:
1) Real-time representation of acquired data
2) Real-time calculation of the Mechanical Power index
3) Saving text files of the data for post-processing analysis

After the text file has obtained the data elaboration is done using MatLab (matrix laboratory), which is a multi-paradigm numerical computing environment and fourth-generation programming language. Post-processing analysis has been performed for the following aims:
1) Display the acquired traces
2) Evaluation of different lung mechanical models for parameters extraction
3) Comparison of different techniques for Mechanical Power index estimation
3.3.1 Real-time Analysis

As mentioned earlier, the real-time study is made using Processing software. The first thing to begin data transmission is to initialize the communication between hardware system and PC software through bluetooth. This procedure must be done only once. The operator has to identify the COM port connected to the Bluetooth dongle and write its number in the Processing sketch. As the devices are associated, it will no longer be necessary to perform this action.

3.3.1.1 Data Receiving

To make a proper analysis, first of all, it has to read correctly the data sent by Arduino. This is possible with the Processing function `Serialevent(Serialport)` that is called whenever new data are available. Within this function different tasks are executed in the following order: the `readStringUntil(\n')` function that saves a string containing flow, sampled pressures data and, if present, the signal coming from the battery. Subsequently, to subdivide the string and update the data, these two functions are needed: `split("|")` and `trim("string")`. The first one is necessary to separate the string in substrings whenever it finds the character "|", while the second one allows to remove blank spaces. Then, these data are converted from string to float to analyze them. In order to use the data, these must be reported into their units using the input-output relationships of the sensors.

In addition to the acquired data, further parameters can be derived:

1) Transpulmonary pressure defined as the difference between airway pressure and esophageal pressure \( P_{TP}=P_{AO}-P_{ES} \)

2) Inspiratory and expiratory volume calculated as the integral of the flow \( \Phi \) over time using the rectangle method \( \int \Phi \, dt \) 

3) Respiratory Rate computed at each breath

4) Mechanical Power obtained as the integral of the pressure over volume \( \int P \, dV \)
Figure 3.19: Real-Time Analysis flow chart
3.3.1.2 Display Modes

Three display modes have been developed in the Processing script that are interchangeable during the acquisition.

The first screen that shows when the program starts is:

![Figure 3.20: M4 Display Mode](image)

As can be seen, this is the representation of the traces of flow, airway opening pressure, esophageal pressure and transpulmonary pressure signals over time, thus called M4. At left of the Y-axes of each graph there are the zoom buttons to improve visualization in amplitude and other buttons with arrows which are necessary to shift the X-axis of ± 10 cmH$_2$O to allow a better reading of waves variation in a certain range of amplitude. On the top right, there are the following buttons:

1) TIME INTERVAL: for changing the time interval scale choosing between 1 or 5 seconds
2) PAUSE: that locks the image during the acquisition,
3) M4, M2 or POWER: allow to switch among display modes by continuing recording without losing any data.

The options in use are also marked by a second contour around the button. (Fig. 3.21)
In the center at the top, furthermore, whenever there is a non-zero flow, the corresponding amount of inspired or expired air volume (expressed in liter) is represented, depending on the positive or negative flow.

The M2 mode is almost the same as the one shown above with the only difference that only flow and airway opening pressure graphs are shown.

The third mode is the POWER (Fig 3.22).

In this case, two Pressure-Volume loops are displayed. The one on the left shows the volume (expressed in ml) in ordinate and the airway opening pressure in abscissa while the second one has the transpulmonary pressure in abscissa. As in the other modes, there are zoom buttons for the various graphics for better viewing. The various powers calculated, whose algorithms are explained in the next section, and the Respiratory Rate (RR) are
represented. In addition to the classical Power during inspiration phase (POWER insp.) calculated breath by breath, there are also:

- **POWER mean**: the mean Power, calculated like average over twenty breath
- **POWER exp**: the Power calculated during expiration phase
- **POWER hyst**: the difference between inspiration Power and expiration Power

For all these modes, it is also possible to save the data, as explained in the following flow chart (Fig 3.23).

Once the program is started, pressing the “s” button is created a text file in a known folder and data saving starts. There is also a data backup system: once program is started, every other half hour after the start, a new file is created so that data are not lost in case of problems.

During saving, the process can be temporarily stopped pressing the “Enter” button and restarted repressing “s”.

A saving frequency of 50 Hz (1 data every 20 ms) is used. An higher frequency can be chosen because the data are analysed at 100 Hz. This is done in order to not overload the text file because of too much data. With this frequency an average memory consumption of about 15 Mbyte/hour is measured.
This is an example of a part of a registration:

![Figure 3.24: Extract from the text file saved by Processing](image)

The saved data are:

- Day
- Month
- Year
- Hour
- Minute
- Second
- Millisecond
- Flow
- \( P_{AO} \)
- \( P_{ES} \)
- \( P_{TP} \)
- Inspiratory Volume
- Expiratory Volume
- Actual Volume
- Inspiratory Power
- Expiratory Power
- RR
- Inspiratory Power (using \( P_{TP} \))
- Expiratory Power (using \( P_{TP} \))
- Hysteresis Power
- Hysteresis Power (using \( P_{TP} \))
- Breath Number

All these parameters are then used for further post-processing.
3.3.1.3 Power Calculation

Another algorithm is applied in Processing for the calculation of the mechanical power. This consists in the computation of the integral of the pressure curve on the volume. Just as the method for calculating the volume, explained in 1.1.3 section, also in this case the rectangle method is used. However, it is necessary to distinguish the classical power and the transpulmonary power depending on if it has been computed using airway opening pressure or transpulmonary pressure. The temporal diagram of this algorithm is shown in Figure 3.25. During the inspiration phase ($t_1 < t < t_2$) the mechanical ventilator produces a positive pressure that generates a positive flow in the patient's direction, thus giving him a certain amount of volume, represented by the blue area. At this first stage, the flow is positive and it remains so throughout all the inspiratory phase. Going to check that the flow data at the present time ($F_i$) and the one at the previous time ($F_{i-1}$) are concordant, the consumed energy is calculated as the product between the pressure at the present time ($P_i$) and the delta of volume ($V_i - V_{i-1}$). The summation of energy produced over time constitutes a certain amount of work ($W_{\text{INSP}}$). When at time $t = t_2$ the flow changes its sign, becoming negative, and the product between two subsequent flows changes its sign too, the power, expressed in J/min, is computed by multiplying the $W_{\text{INSP}}$ for 0.098 and the respiratory rate (RR). During the expiration phase ($t_2 < t < t_3$) the pressure decreases until the value of PEEP. In this case $F_i$ is negative but the product between two successive flows ($F_i * F_{i-1}$) is greater than zero. The expiratory work ($W_{\text{EXP}}$) is then calculated as done during the inspiratory phase, with the only difference that the delta of volume is negative the absolute is considered. At time $t = t_3$ the flow returns to be positive so, in this moment, the product between the two subsequent flows is negative. This time represents the end of the expiration and the beginning of a new inspiration. Therefore in addition to the computation of the expiratory power, a time counter starts and continues until the beginning of the subsequent inspiratory phase. This counter indicates the duration of the breath.
Chapter 3: Development of the System

3.3 Software

$$F_i > 0 \quad F_i < 0$$

$$F_i * F_{i-1} > 0 \quad F_i * F_{i-1} > 0$$

$$W_{\text{INS}} \uparrow \quad W_{\text{EXP}} \uparrow$$

$$F_i < 0 \quad F_i > 0$$

$$F_i * F_{i-1} < 0 \quad F_i * F_{i-1} < 0$$

print (Power _INS) \quad print (Power _EXP)

print (RR) \quad RR_{\text{NEW}}$$

Figure 3.25: Temporal diagram of Power Calculation
3.3.2 Offline Analysis

The data saved during monitoring are analyzed at a later time using MatLab, in order to observe traces, calculate resistance and elastance and estimate the mechanical power. The power is obtained through the formula 2.51, using E and R calculated with the several methods considered. Then, the values obtained are compared with those from the pressure-volume loop in real time.

The first part of the code allows to the user to select the file .txt with the traces to be analyzed. Data are then extracted into a matrix in which each columns represent the different acquired parameter, as:

\[ A = \begin{bmatrix} V_1 & P_{ao1} & P_{es1} & \ldots & RR_1 \\ V_2 & P_{ao2} & P_{es2} & \ldots & RR_2 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ V_n & P_{aom} & P_{esm} & \ldots & RR_n \end{bmatrix} \]

Then a dialog box, ask the user if he wants to analyze a specific time interval of the trace.

In case of positive answer, the analysis is done about data included between the starting minute and ending minute inserted, while in case of negative answer all the data are considered.

Then in both cases a subplot of airway pressure, esophageal pressure and flow against time (basing on time interval chosen), is shown.
3.3.2.1 Algorithm for parameter extraction

Successively, the data are elaborated for the mechanical parameter extraction, in different methods:

- **Least square method**

The method used is the same explained in chapter 2. For its implementation, a training set containing n number of data has been used. Firstly, a \([n \times m+1]\) matrix \(X\) is defined as a matrix, in which \(n\) is the training set dimension, arbitrarily chosen during implementation, and \(m\) represent the number of variables considered depending on the model (ranging from 2 to 4).

As stated in formula 2.24, in the simplest model, the first \(X\) column contain the volume variables, the second one contain the flows and the third column is made by ones. Instead in the most complex model, \(X\) contains two variable linked to volume, other two columns linked to flow and the last column made by ones.

Then, a matrix \(P\) is defined as a column vector, containing \(n\) values of pressure measured. The calculated parameters are stored in a column vector named \(Sol\) of dimension \([m, 1]\).

For example, for the simplest model, the first element of \(Sol\) is the elastance parameter, the second one is the resistance and the third represent the PEEP pressure.
• **Estimation during Pressure-controlled mode**

In this modality, the PEEP value for each breath is calculated as the value of pressure reached at end expiration. The value of maximal flow, maximal volume, pressures, resistance and elastance are initialized at zero.

During the same breath, represented by an equal RR value (A(i,17)), the maximum value of flow and volume are obtained, taking also the relative pressure values at the same time instant. At the start of a new breath, identified by an RR change, the value of elastance and resistance are obtained.

```matlab
Sol=(X'*X)^(-1) * X' * P;
Elastanza_matrice=Sol(1);
Resistenza_matrice=Sol(2);
PEEP_matrice=Sol(3);

Figure 3.28: Least square Method Algorithm
```

```plaintext
flow_max(1)=0; volume_max(1)=0;
Pressure_in(1)=0; Pressure_out(1)=0;
R(1)=0; E(1)=0;
k=1;
for i=1:(size(A,1)-1)
    if(A(i,17)==A(i+1,17))
        if(flow_max(k)<A(i,8))
            flow_max(k)=A(i,8);
            Pressure_in(k)=A(i,9);
        end
        if(volume_max(k)<A(i,12))
            volume_max(k)=A(i,12);
            Pressure_out(k)=A(i,9);
        end
    else
        E(k)=Pressure_out(k)/volume_max(k);
        R(k)=Pressure_in(k)/flow_max(k);
        k=k+1;
    end

Figure 3.29: Pressure controlled Mode Algorithm
```
Estimation during Volume-controlled mode

The first step consists in the extrapolation of PIP (peak-inspiratory-pressure), plateau pressure and flow (at PIP) values. This process is computed for each breath. PIP is the maximum value of pressure reached during inspiration, while plateau pressure are the values of pressure reached during inspiratory pause phase. When plateau is occurring, the flow is zero. This condition has to be distinguished from the end expiration where flow is also zero, but pressure is around PEEP. Then, in order to recognize plateau pressure, the data of pressure has to be higher than a threshold (slightly greater than PEEP). At the same time, in real measurements, flow is not exactly zero, but it takes small values around it, due to noise factor. The threshold parameters (soglia_F, soglia_F2) define the range around zero in which the flow remains.

The airway resistance is computed as the ratio between the difference PIP-Pplateau and flow (at PIP). Later, through similar condition on volume and pressure, the maximum volume, and PEEP are obtained. Elastance is computed as the ratio between the difference Pplateau-PEEP and max. volume.

```
PIF(1)=0;
Flow_max(1)=0;
f=1;k=1;
for i=1:size(A,1)-1
    if A(1,17)==A(i+1,17))
        if (A(i,9)>soglia_F && A(i,8)<soglia_F && A(i,8)>soglia_F2)
            Pplat(i)=A(i,9);
            f=f+1;
        end
        if (PIP(k)<A(i,9))
            PIP(k)=A(i,9);
            Flow_max(k)=A(i,8);
        end
    else
        Pplateau(k)=mean(Pplat(:));
        Pplat=[];
        f=1;
        Pplat(1)=0;
        k=k+1;
        PIP(k)=0;
    end
end
```

►Figure 3.30: Plateau Pressure computation
• **Mead-Whittenberger Method**

This method is used only for the computation of the airway resistance value. A vector named \( Y_{\text{regression}} \) containing pressure values is defined. These values are calculated as in formula 2.37 in which the elastance used is the one obtained from volume controlled mode or pressure controlled mode, depending on patient ventilatory condition. Subsequently, the coefficient for the regression (\( \text{REGRESSION} \)) are obtained using \textit{polyfit} function, in which 1 represents the polynomial coefficient, in order to obtain a straight line. \textit{Polyval} function allows to obtain the values of the pressure through the polynomial \( \text{REGRESSION} \) evaluated at flow values. The resistance is then calculated as the slope of it. This procedure is done for each breath which is determined by \( i_p \) value.

```matlab
for i=1:size(1_p,2)
  Y_regression(1_p_old(1),1)=(A(1_p_old;1_p(1),9)-Elastance(1)*A(1_p_old;1_p(1),16));
  REGRESSION=polyfit(A(1_p_old;1_p(1),8),Y_regression(1_p_old;1_p(1)),1);
  REGRESSION_Y=polyval(REGRESSION,A(1_p_old;1_p(1),8));
  R_mead(1,1)=(REGRESSION_Y(3,1)-REGRESSION_Y(1,1))/(A(1_p_old+2,8)-A(1_p_old,8));
  i_p_old=i_p(1);
end
```

►Figure 3.31: Mead-Whittenberger Algorithm

• **Recursive method**

This method requires the definition of a parameter matrix (\( A_r \)), its update (\( A_r_n \)), the measurements matrix (\( X_r \)), the \( i \)-th row of the matrix \( X_r \) (\( X_r_n \)), the information matrix (\( M_r \)), its update (\( M_r_n \)) and the forgetting factor (\( \text{lambda} \)). \( A_r \) is a column vector, in which the first element is the elastance, the second is resistance and the third is PEEP. For its initialization, the first breath values of elastance, resistance and PEEP obtained using volume controlled or pressure controlled mode are used. \( X_r \) is defined as a 3-column matrix in which the first one includes volumes, the second includes flows and the third is made by ones. Then, in a “\textbf{for}” cycle at each iteration (\( i \)), a different row of \( X_r \) is chosen and it is used first to obtain \( M_r_n \) and then \( A_r_n \), respectively as in formula 2.39 and 2.38. The \( A_r_n \) trend gives the parameters estimation time by time.
3.3 Software

Then, the elastance and resistance parameters obtained from “Least square method” and “Recursive algorithm”, are used in the equation of motion in order to reconstruct the pressure curve for each model.

3.3.2.2 Mechanical Power Algorithm

In order to evaluate the most reliable estimation with further test, the relative sum of squares residual and coefficient of determination are calculated.

\begin{verbatim}
lambda=exp(-0.02/0.05);
A_r(1, 1)=E(1, 2);
A_r(2, 1)=R(1, 2);
A_r(3, 1)=PEEP(1, 2);
j=1;
n=3;
X_r=ones(size(A, 1), 3);
X_r(:, 1)=A(:, 28);
X_r(:, 2)=A(:, 3);
M_r=inv(X_r(1:n, :)'*X_r(1:n, :));
for i=1:size(A, 1)-n
    X_r_n=X_r(i+1, :);
    M_r_n=1/lambda*(M_r*(M_r*X_r_n'*X_r_n'*M_r)/((lambda*X_r_n'*M_r*X_r_n));
    R_r_n(:, j)=A_r+(X_r_n'*X_r_n'*A_r(i+1, :)-X_r_n'*R_r)/((lambda*X_r_n'*X_r_n'*X_r_n';
    R_r=R_r(:, j);
    M_r=inv(X_r(1:i+n, :)'*X_r(1:n+i, :));
end
end
\end{verbatim}

Figure 3.32: Recursive Algorithm

Figure 3.33: Pressure curves Algorithm

3.3.2.2 Mechanical Power Algorithm

The mechanical power index, computed in Processing, is stored in a column of matrix A. Then, an estimation of this index is computed through the formula 2.51, using the values of resistance and elastance obtained through pressure/volume controlled mode, Mead-
Wittenberger method and Least Square method with single elastance and resistance ($t$ is the inspiration time at each breath $i$).

```matlab
%% PRESSURE/VOLUME POWER
for i=1:size(RR,1)
    POWER(i)=RR(i)*0.098*(y_max(i)^2*(E(i)*0.5+ (R(i)/t(i)))+(y_max(i)*PEEP(i)));
end

% MEAD POWER
POWER_m(i)=RR(i)*0.098*(y_max(i)^2*(E(i)*0.5+ (R_mead(i)/t(i)))+(y_max(i)*PEEP(i)));

% LEAST SQUARE POWER
POWER_ls(i)=RR(i)*0.098*(y_max(i)^2*(R_2*0.5+ (R_2/t(i)))+(y_max(i)*PEEP(i)));
end
```

► Figure 3.34: Power Algorithm

The obtained values are then compared and the absolute errors are calculated.
Chapter 4

4. Tests

In this chapter the experimental protocol adopted for monitoring is described. In the first part the sensors calibration procedure and coherence with ventilator data are treated. The pressure sensors have been calibrated with a differential U-tube manometer, while for the flowmeter a super-syringe has been used. The aim of this trial is to check the accuracy of the data transmitted by the system in respect of those set on the ventilator. The second part explains the procedure for the in vivo monitoring. This regards the positioning of the system on the patient in a correct way. After that, a brief description of the patient conditions and their ventilation characteristics are discussed. At the end of the chapter, an accurate characterization of the data analysis obtained both in real-time and offline.
4.1 Functioning Test

The aim of these tests is to firstly assess the correct functioning of the sensors through standard calibration procedure and then to check the data coherence between data coming from sensors and the variables set on the ventilator.

4.1.1 Sensors Calibration

Calibration are the set of operations that establishes the relationship between values of quantities indicated by a measuring sensor and the corresponding values of a reference system. The purpose of calibration is to improve the accuracy measure obtained by the sensors.

The calibration procedures are different depending on the type of the sensor, but they often follow the same workflow:
1) Generation of the reference value through a reference tool
2) Acquisition of the data from the sensor
3) Evaluation of the accuracy error
4) Correction of the sensor calibration curve
5) Correction check

The reference tool used depends on the sensor type and on the physical variable measured. Calibration should be done before each new acquisition, in order to assure the correct functioning and values reliability, especially after each lavage and sterilization procedure, which may modify the sensors functioning.

Both pressure sensors and flowmeter have been calibrated before using them in vivo test. The procedures adopted for each sensor are described below:

- Flowmeter Calibration

Flowmeter calibration is based on a comparison of mass or volume produced by the reference tool and the one measured by the sensor. The flowmeter is inflated using a super syringe (Fig. 4.1). This instrument is able to blow a known quantity of air across the flowmeter to which it is connected, avoiding any leaks. The quantity of air moved at each
inflation is controlled by the user having as reference a graduation scale printed on the syringe. The air passes through the flowmeter, which return a certain values of flow. The time integration of measured flow allows to obtain the volume of air, which should be coincident to the volume moved by the super syringe.

SFM-3300 AW is a pre-calibrated sensor, which means that it doesn’t require a calibration procedure by the user. However, after a sterilization procedure, it is recommended to verify the correct functioning. The experimental procedure for this purpose has been executed by inflating and suctioning air to the sensor with the syringe, moving different quantity of air at different blowing speed. As expected the sensor has shown high accuracy feature, with an error lower than 3%.

- Pressure Calibration

The reference tool used for pressure calibration is a U-tube manometer, which is a U-shaped glass tube partially filled with water (Fig. 4.2).

When both ends of the manometer are at atmospheric pressure, the height of liquid in the two columns is equal and it has been set at the value of 0 cmH₂O, indicated by a graduated
scale printed on it. One of the column ends has been connected through a tube to a three-way valve, in which the three ends can be connected as it can be seen in Fig 4.3:

![Three-way valve diagram]

Once the connection are made, starting from a reference situation, a specific series of passages are executed, selecting the connection of the three-way valve, in order to apply different known values of pressure to the sensor under calibration.

1) Connection manometer (1) – sensor (2) in order to read the pressure value at reference situation (0 cmH₂O) for setting the offset
2) Connection manometer (1) - syringe (3) in order to aspire or inflate, respectively decreasing or increasing pressure (Fig. 4.4)
3) Connection manometer (1) – sensor (2) in order to read the new pressure value

![Pressure sensors calibration procedure diagram]

**Figure 4.3: Three-ways valve**

**Figure 4.4: Pressure sensors calibration procedure**
Chapter 4: Tests

4.1 Functioning Test

Then the procedure can be repeated in cycle from point 2, valuating the accuracy at different pressure values. The difference between the value on the graduation scale and that measured by the sensor represent the error in measuring necessary for setting the calibration curve.

The Honeywell pressure sensors used in this thesis have the following input-output relationship:

![Figure 4.5: Pressure sensors Input-Output Relationship](image)

After calibration, the Total Error Band of ±1% indicated on datasheet has been verified.

4.1.2 Data Acquisition Check

Before using the system in vivo monitoring, it has been tested by directly connecting the sensors to a Siemens 300A Servo Ventilator, kindly provided by Intensive Care Unit of “Ospedale San Paolo Milano”. This test has been useful in order to assure the correct functioning of the device and the coherence between the data acquired and the one developed by the ventilator.

The flowmeter has been connected to the ventilator on one side and to a reservoir bag on the other part so as to simulate the lung behaviour. In order to acquire the ventilator pressure signal, which represents pressure applied at airways, only one sensor has been used, attaching it immediately after the flowmeter, through a connector. It has not been possible to perform a procedure to simulate esophageal pressure.
Chapter 4: Tests

4.1 Functioning Test

The whole system for this test is represented in figure:

![Data acquisition check](figure4_6.png)

Pressure-controlled and volume-controlled modalities have been used, modifying the different ventilator settings.

For example, in pressure-controlled mode, different values of PIP have been selected, changing also different RR and inspiratory time. Each value of peak pressure developed has been correctly measured by the pressure sensor verifying the accuracy obtained in calibration phase.

During volume-controlled mode, different tidal volumes have been tested. They are measured by the integration in time of the airflow that passed through the flowmeter, both during inspiration and expiration, obtaining values consistent with the accuracy indicated in the sensor datasheet.

Also the changes of the respiratory rate have been correctly measured by the device, while the reliability of inspiratory rising time changes and inspiratory/expiratory duration changes have been observed graphically by real-time changes of waveform as expected.
Chapter 4: Tests

4.1 Functioning Test

This test have also checked the ability of the system to sustain a long term monitoring, both in terms of battery life and in terms of communication holdings. The device has been left in operation for 3 hours and all the data have been saved and made available for a post processing with a battery consumption of about 5%.

► Figure 4.7: Comparison between Ventilator and System Measurements
4.2 In Vivo Test

Once the device has been tested in the condition previously described, it has been used for the patient monitoring. In this section, after an explanation about how the system has been positioned during the acquisitions, the different patients, analyzed in this research, are presented. Then, in the last section all the analysis, executed on the collected data, are described in details.

4.2.1 System Positioning in Recovery Room

This device has been developed and designed in order to reduce as much as possible the physical obstruction to clinical operator, when it is applied to monitor patient’s conditions. Its compact size feature and the possibility to send data via Bluetooth have been planned in this sense. In fact, the absence of cable for data delivery, allows clinicians to be free to choose where to put the computer on which visualize waveforms and data, up to a distance of 15 meters. Although device and computer are physically independent, the sensors are directly connected to the device via cable. This, in part, limits the maximum distance feasible between device and patient bed, even though the cables length allows a comfortable positioning of the instrument. Each sensor have to be positioned in a specific part of the system patient-ventilator, in order to allow the best and reliable measurement of the physical variables of interest. The flowmeter is inserted in the tract between the ventilator tube and the patient mask (or endotracheal tube), putting an antibacterial filter on the patient side. The airway pressure transducer is attached to a specific connector placed among the flowmeter and the filter, as depicted in the following figure:

![Figure 4.8: System Positioning](image)
The acquisition of the esophageal pressure, instead, turns out to be the most problematic. Although the physical structure and size of the sensor is the same as the one used for the airway pressure, the achievement of the esophagus requires the insertion of a specific balloon catheter. The distal part of it (the one with the balloon), has to be inserted through the nasal ways until the lower third of the esophagus as described in section 1.1.3, while the other part is connected to the pressure transducer. The ventilators used in this case are provided by a system for warming air flows.

An example of system positioning during a real acquisition is shown below:
Figure 4.10: Real-time Monitoring at Sureyyapasa Education and Research Hospital
4.2.2 Patients

The experimental test have been executed on subjects affected by respiratory diseases and underwent to mechanical ventilation. The pathological conditions which brought patients to hospitalization, were different for most of them. For certain patient’s clinical states, it was not possible to measure the esophageal pressure, due to the invasiveness implied by the insertion of the balloon catheter in the esophagus. Consequently, in this cases, it has been unworkable the calculation of transpulmonary pressure and both the estimation of its relative mechanical power and the power related to patients effort. Seven patients have been monitored, each with its most suitable type and ventilation settings. Six of them were hospitalized at Intensive Care Unit of “San Paolo” Hospital of Milano, while one has been monitored at “Sureyyapasa Education and Research” Hospital of Istanbul.

The patient’s conditions are described below:

- **PATIENT 1**
  This patient was hospitalized at “Sureyyapasa Education and Research Hospital” for a pulmonary carcinoma. He was completely sedated because of a high dose of medicines drugged to him. He was treated with pressure-controlled ventilation, setting PEEP at 8 cmH\textsubscript{2}O and inserting the intra-esophageal balloon catheter for esophageal pressure acquisition. The monitoring has lasted approximately 30 minutes, in which RR and PIP and tidal volume parameters were modified to see the response of patient.

<table>
<thead>
<tr>
<th>Ventilator setting</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>8 [cmH\textsubscript{2}O]</td>
</tr>
<tr>
<td>PIP</td>
<td>36-22-28-24 [cmH\textsubscript{2}O]</td>
</tr>
<tr>
<td>VOLUME\textsubscript{TIDAL}</td>
<td>600-400-470-420 [mL]</td>
</tr>
<tr>
<td>TIME\textsubscript{INSPI}</td>
<td>1.2-2.5-1.3-1.3 [sec]</td>
</tr>
<tr>
<td>RR</td>
<td>16-8-15-14 [bpm]</td>
</tr>
</tbody>
</table>

*Table 4.1: Ventilator settings for Patient 1*

- **PATIENT 2**
  Patient hospitalized at “San Paolo” Hospital (as the next five patients). He has been recovered in ICU as preparation for a vascular surgery and also at the end of the operation.
At the beginning of the hospitalization, the subject showed regular respiratory and circulatory traces. Patient treated with volume-controlled ventilation, in passive conditions, with PEEP set at 11 cmH2O. He has been monitored for 10 minutes, acquiring also esophageal pressure.

<table>
<thead>
<tr>
<th>Ventilator setting</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>9 [cmH2O]</td>
</tr>
<tr>
<td>PIP</td>
<td>27 [cmH2O]</td>
</tr>
<tr>
<td>VOLUME TIDAL</td>
<td>390 [mL]</td>
</tr>
<tr>
<td>TIME INSF.</td>
<td>0.9 [sec]</td>
</tr>
<tr>
<td>RR</td>
<td>16 [bpm]</td>
</tr>
</tbody>
</table>

*Table 4.2: Ventilator settings for Patient 2*

- **PATIENT 3**
  
  This subject was awake and treated with pressure-controlled ventilation, setting PEEP at 8 cmH2O and PIP at 20 cmH2O. Monitoring has been carried out for about 9 minutes.

<table>
<thead>
<tr>
<th>Ventilator setting</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>8 [cmH2O]</td>
</tr>
<tr>
<td>PIP</td>
<td>18 [cmH2O]</td>
</tr>
<tr>
<td>VOLUME TIDAL</td>
<td>400 [mL]</td>
</tr>
<tr>
<td>TIME INSF.</td>
<td>1.3 [sec]</td>
</tr>
<tr>
<td>RR</td>
<td>12 [bpm]</td>
</tr>
</tbody>
</table>

*Table 4.3: Ventilator settings for Patient 3*

- **PATIENT 4**

  Patient hospitalized in ICU due to respiratory failure, after right femoral fracture surgery. Monitored in two different modalities. Firstly treated in pressure-controlled ventilation with PEEP set at 4 cmH2O. Initially he was awake and monitored for about 1 minute, whereupon he has been sedated and monitored in this condition for 1 minute more. After that, ventilation modality has been switched to volume-controlled mode with PEEP still set at 4 cmH2O, while tidal volume was changed from approximately 400 mL to 800 mL. In both modalities, esophageal pressure has been acquired.
4.2 In Vivo Test

Rapid patient weaning during intensive care, with extubation at a few hours after surgery.

- **PATIENT 5**
  This patient, a smoker, was hospitalized for heart diseases and for chronic obstructive bronchopneumopathy (BPCO). Ventilator modalities were set to pressure-controlled ventilation with PEEP 7 cmH2O and PIP at 15 cmH2O. Patient was awake for all the monitoring, lasted 5 minutes, and it has been impossible to acquire esophageal pressure.
• PATIENT 6
This subject has been treated in volume-controlled ventilation with PEEP 10 cmH2O, acquiring esophageal pressure. The monitoring followed for approximately 5 minutes during which patient was awake.

<table>
<thead>
<tr>
<th>Ventilator setting</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>10 [cmH2O]</td>
</tr>
<tr>
<td>PIP</td>
<td>24 [cmH2O]</td>
</tr>
<tr>
<td>VOLUME TIDAL</td>
<td>460 [mL]</td>
</tr>
<tr>
<td>TIME INSP.</td>
<td>1.4 [sec]</td>
</tr>
<tr>
<td>RR</td>
<td>16 [bpm]</td>
</tr>
</tbody>
</table>

Table 4-7: Ventilator settings for Patient 6

• PATIENT 7
This patient has been hospitalized for respiratory failure due to pneumococcal pneumonia. He has been followed in three different days, during a wining procedure. During the first acquisition, volume-controlled modality were applied, with PEEP 8 cmH2O, VT 436 mL, RR 17 breath/min, with esophageal catheter inserted. This monitoring lasted about 17 minutes. The second acquisition has been done the day after. In this case, patient has been treated in pressure-controlled ventilation with PEEP 8 cmH2O, PIP 19 cmH2O, RR 5 breath/min and has been monitored for 5 minutes. The last acquisition has been done two days after the second monitoring. The ventilator was set in pressure-controlled ventilation with PEEP 8 cmH2O, PIP 19 cmH2O and a pressure support of 10 cmH2O. Monitoring followed for 8 minutes. In these two last acquisition the esophageal catheter was removed.

<table>
<thead>
<tr>
<th>Ventilator setting</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>8 [cmH2O]</td>
</tr>
<tr>
<td>PIP</td>
<td>19 [cmH2O]</td>
</tr>
<tr>
<td>VOLUME TIDAL</td>
<td>430 [mL]</td>
</tr>
<tr>
<td>TIME INSP.</td>
<td>1.35 [sec]</td>
</tr>
<tr>
<td>RR</td>
<td>17 [bpm]</td>
</tr>
</tbody>
</table>

Table 4-8: Ventilator settings for Patient 7 (1 acquisition)
### Table 4-9: Ventilator settings for Patient 7 (2 acquisition)

<table>
<thead>
<tr>
<th>Ventilator setting</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PEEP</strong></td>
<td>8 [cmH$$_2$$O]</td>
</tr>
<tr>
<td><strong>PIP</strong></td>
<td>19 [cmH$$_2$$O]</td>
</tr>
<tr>
<td><strong>VOLUME_TIDAL</strong></td>
<td>500 [mL]</td>
</tr>
<tr>
<td><strong>TIME_INSPIR.</strong></td>
<td>1.4 [sec]</td>
</tr>
<tr>
<td><strong>RR</strong></td>
<td>15 [bpm]</td>
</tr>
</tbody>
</table>

### Table 4-10: Ventilator settings for Patient 7 (3 acquisition)

<table>
<thead>
<tr>
<th>Ventilator setting</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PEEP</strong></td>
<td>8 [cmH$$_2$$O]</td>
</tr>
<tr>
<td><strong>PIP</strong></td>
<td>19 [cmH$$_2$$O]</td>
</tr>
<tr>
<td><strong>VOLUME_TIDAL</strong></td>
<td>470 [mL]</td>
</tr>
<tr>
<td><strong>TIME_INSPIR.</strong></td>
<td>1 [sec]</td>
</tr>
<tr>
<td><strong>RR</strong></td>
<td>23 [bpm]</td>
</tr>
</tbody>
</table>
4.2.3 Data Analysis

For the study of the whole system, different types of data analysis have been considered. For each patient, in fact, the device is used in way to execute both a long term real time monitoring and a post processing data treatment, where saved file are exported on MatLab. The assessment of correct measuring in real-time is performed, not following a defined procedure, but only comparing the consistency of the parameters setting on the ventilator with those calculated and displayed on the PC video by the device. The accuracy of the displayed values has been verified, except for the inspiratory and expiratory volumes, in which there was a certain difference between inhaled and exhaled air (5-10%). It has been hypothesized that this phenomenon is due to the variation in gas composition, linked to the FIO₂ value set on the ventilator, and that for obvious reasons is not observed during the test phase as described in section 4.1.2.

The data saved during monitoring, which are used for a post-processing analysis, are stored in a .txt file. Tests made in this phase are described below:

- Parameter Estimation

  The aim of this elaboration is the evaluation of the mechanical model for elastance which best fits the lung mechanics. The different models that can be used for the estimation of the respiratory parameters, as already described in the section 2.1.3. This analysis has been executed using the Least Square Error method, subdividing the input dataset in two parts: training set and test set. The training dataset is composed by the values of volume, flow and airway pressure of the first 40 seconds of registration. These data are used for the estimation of resistance and elastance. Depending on the estimation model used, the calculated parameter may be:

  1) E and R: both parameters are linearly related to pressure
  2) R₁, R₂ and E: resistance is split in two terms, in a non-linear relation with pressure
  3) R, E₁ and E₂: elastance is split in two terms, in a non-linear relation with pressure
  4) E₁, E₂, R₁ and R₂: both elastance and resistance are split in two terms, becoming non-linearly related to pressure
  5) E(t) and R(t) as function of time
The test dataset, instead, uses 80 seconds of flow and volume recorded data. These values are used in the equation of motion, with the values of elastance and resistance found previously for each method, in order to reconstruct the airway pressure curve. The equation used for airway pressure calculation is modified depending on the numbers of parameters (as stated in paragraph 2.1.3) An evaluation of the reliability of the parameters extracted by the different models is made, comparing the estimated curve of pressure with the airway pressure curve acquired during monitoring. The relative sum of squares residual is used to obtain a parameter called CD (already described in paragraph 2.1.3), ranging from 0 to 1, where 1 indicates that the technique used has done a perfect parameter estimation, while values around 0 stays for the worst estimation. Subsequently, in order to evaluate the presence of a significant difference among the models, the two-way Analysis of Variance (ANOVA) test is performed. Starting from the assumption of this test, that is the normal distributions of the residuals, the analysis of the absolute errors has been made both evaluating the responses of different models in respect to the patient and vice versa.

- **Mechanical Power Estimation**
  Another outcome of post data analysis is the extrapolation of the mechanical power index. Even in this case, different methods are used and compared, in order to identify the most appropriate. In fact, as already stated in chapter 2, the mechanical power is initially calculated as integral of the pressure-volume diagram and secondly obtained through the formula 2.51 and, basing on the type of ventilation (pressure or volume controlled), using in turn the resistance and elastance values estimated by the Least square method, Mead-Whittenberger and Volume-controlled modality. Then, the mechanical power curves obtained with these techniques are compared with the one calculated by the P-V loop, and the absolute error is used as index of estimation accuracy.

- **Patient Effort Index**
  Various researches have looked for a reliable index able to represent as much as possible the level of patient contribute during external ventilation. As stated in paragraph 1.2.3, the patient activity during treatment, may be one of the principal causes of VILI, then it might be seriously useful to find a variable able to quantify the patient work. For the computation
of patient effort only one subject has been analyzed. This estimation is a hardly obtainable task since two hypothesis must be verified:

1) Same conditions of ventilation during all the acquisitions of the patient
2) In the same analysis, pressure traces both in passive and active conditions must be available

The effort index is therefore calculated as the difference between power when the subject is completely passive, with power while performing effort.
Chapter 5

5. Results and Conclusions

This last chapter presents the results of the patients tests, the conclusions derived from them and possible future developments of the system. In particular, in the first section of the results, the differences in accuracy of the various respiratory mechanics models are evaluated. In the second section, the index of mechanical power is analyzed and compared with the one proposed by prof. Gattinoni (formula 2.51). In the third section, the evaluation of mechanical power about the respiratory effort made by the subject is treated. The last part of the chapter focuses on evaluation of the system reliability with suggestions about possible evolutions of the system, both for its software/hardware and data analysis.
5.1 Pressure Model Evaluation

Given that the number of breaths for each patient is different, the same quantity of samples have been chosen as common reference for an equal data evaluation. Then, for this analysis a registration of 80 seconds sampled at 50Hz has been used as test set for the computation of pressure for each subject. The seven registrations shown below, are relative to patients in passive condition, without noticeable effort during breathing. For each patient, two images are shown: in the first one, an image of 20 seconds has been extracted, showing the pressure trend obtained through the considered methods. The legend at the top-right of the figure indicates the color assigned for the plot of each modeled pressure. The second figure, represents the absolute error of each model in respect to the measured pressure, rescaled in order to compare them with the same amplitude scale. Then, in order to evaluate the best reliable model, the coefficient of determination, has been calculated. It is obtained for each of those, from the sum of squared residual between the reconstructed pressures and the measured one. A more detailed analysis, can be executed by statistical test. Two-ways Anova (Analysis of variance), is a statistical technique, which allows to analyze the differences among groups means and their variances. The null hypothesis states that the data of all the groups have the same stochastic distribution, and that the differences observed between the groups are due only to the case. It is then useful for comparing groups of variables for assess their statistical significance. This test requires the observance of three hypothesis:

- Groups of data considered must have normal distribution
- Homogeneity of variances
- Independence of observations

In this study, the aim of the analysis is to check the presence of significant differences between the different models for each patient.
• **PATIENT 1**

**PRESSURE MODELS**

![Figure 5.1: Pressure Models (Patient 1)](image)

**ABSOLUTE ERROR**

![Figure 5.2: Models Error (Patient 1)](image)
5.1 Pressure Mode Evaluation

- **PATIENT 2**

**PRESSURE MODELS**

![Figure 5.3: Pressure Models (Patient 2)]

**ABSOLUTE ERROR**

![Figure 5.4: Models Error (Patient 2)]
5.1 Pressure Model Evaluation

- **PATIENT 3**

**PRESSURE MODELS**

![Figure 5.5: Pressure Models (Patient 3)]

**ABSOLUTE ERROR**

![Figure 5.6: Models Error (Patient 3)]
Chapter 5: Results and Conclusions

5.1 Pressure Model Evaluation

- **PATIENT 4**

PRESSURE MODELS

![Pressure Models (Patient 4)](image)

► Figure 5.7: Pressure Models (Patient 4)

ABSOLUTE ERROR

![Models Error (Patient 4)](image)

► Figure 5.8: Models Error (Patient 4)
Chapter 5: Results and Conclusions

5.1 Pressure Model Evaluation

• PATIENT 5

PRESSURE MODELS

ABSOLUTE ERROR

Figure 5.9: Pressure Models (Patient 5)

Figure 5.10: Models Error (Patient 5)
Chapter 5: Results and Conclusions

5.1 Pressure Model Evaluation

- **PATIENT 6**

**PRESSURE MODELS**

![Pressure Models Graph](image1)

*Figure 5.11: Pressure Models (Patient 6)*

**ABSOLUTE ERROR**

![Absolute Error Graph](image2)

*Figure 5.12: Models Error (Patient 6)*

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Chapter 5: Results and Conclusions

5.1 Pressure Model Evaluation

- **PATIENT 7**

**PRESSURE MODELS**

![Image of pressure models](image)

*Figure 5.13: Pressure Models (Patient 7)*

**ABSOLUTE ERROR**

![Image of absolute error](image)

*Figure 5.14: Models Error (Patient 7)*
As can be seen from the first figure of each patient, the models follow the pressure trend with different accuracy. From a first qualitative evaluation all the models perform a good reconstruction of the real pressure. For pressure-controlled ventilated subjects the worst reconstruction is during inspiration phase, while volume-controlled one it is during inspiratory pause. The observation of the error trend is useful in order to assess this behavior. In fact, from the evaluation of the second figures, it can be seen that the error, for each model, reaches its maximum values in correspondence of those time instants. Furthermore, from the analysis on patient 5 it can be seen that at start of inspiration the models do not fit the real pressure, which decreases due to patient respiratory muscles activation. The quantification of the coefficient of determination, allows to understand which is the best reliable model. As introduced in chapter 2, this coefficient takes values in a range between 0 and 1. Higher the value is, better is the ability of the model in prediction of the observed data. Lower the value is, worst is the reconstruction obtained. Then, CD has been calculated for every model as in formula 2.30, obtaining the following results:

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time [s]</th>
<th>N Breaths</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>R E</td>
</tr>
<tr>
<td>PATIENT 1</td>
<td>40</td>
<td>10</td>
<td>90.67%</td>
</tr>
<tr>
<td>PATIENT 2</td>
<td>40</td>
<td>10</td>
<td>97.42%</td>
</tr>
<tr>
<td>PATIENT 3</td>
<td>40</td>
<td>8</td>
<td>94.26%</td>
</tr>
<tr>
<td>PATIENT 4</td>
<td>40</td>
<td>10</td>
<td>97.75%</td>
</tr>
<tr>
<td>PATIENT 5</td>
<td>40</td>
<td>20</td>
<td>87.42%</td>
</tr>
<tr>
<td>PATIENT 6</td>
<td>40</td>
<td>10</td>
<td>92.92%</td>
</tr>
<tr>
<td>PATIENT 7</td>
<td>40</td>
<td>10</td>
<td>98.12%</td>
</tr>
</tbody>
</table>

*Table 5-1: Models Results*
Chapter 5: Results and Conclusions

5.1 Pressure Model Evaluation

For simplicity reasons, from now on, the models are named as shown in this legend:

<table>
<thead>
<tr>
<th>Model</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>( P = E \times V + R \times \dot{V} + P_0 )</td>
</tr>
<tr>
<td>M2</td>
<td>( P = E \times V + R_1 \times \dot{V} + R_2 \times \dot{V} \times</td>
</tr>
<tr>
<td>M3</td>
<td>( P = E_1 \times V + E_2 \times V^2 + R \times \dot{V} + P_0 )</td>
</tr>
<tr>
<td>M4</td>
<td>( P = E_1 \times V + E_2 \times V^2 + R_1 \times \dot{V} + R_2 \times \dot{V} \times</td>
</tr>
<tr>
<td>M5</td>
<td>( P = E(t) \times V + R(t) \times \dot{V} + P_0 )</td>
</tr>
</tbody>
</table>

Given that the CD does not respect the Anova’s hypothesis, the absolute error calculated previously has been used for this test. The aim of the test is to verify if there are any statistically significant differences among the means of the models. The error distribution does not satisfy the normality test required by Anova, however as can be seen in Fig. 5.15 it is close to it and then it has been used anyway.

![Figure 5.15: Error Distribution (M1)](image)

The Anova test refused the null hypothesis of groups homogeneity, this means that at least one of the model used is significantly different from the others. In order to better understand this relationship between the models, a Tukey post-hoc test has been performed [31].
The results obtained are shown in the following table:

<table>
<thead>
<tr>
<th></th>
<th>PAZ.1</th>
<th>PAZ.2</th>
<th>PAZ.3</th>
<th>PAZ.4</th>
<th>PAZ.5</th>
<th>PAZ.6</th>
<th>PAZ.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1-M2</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>M1-M3</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>M1-M4</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>M2-M3</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>M2-M4</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>M3-M4</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>M1-M5</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>M2-M5</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>M3-M5</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>M4-M5</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>

Table 5-2: Tukey test results

The test checks for each patient, which of the five models have significant differences. The result “NO” means that no significant difference has been found for those models, while “YES” means there is. As can be seen, the time-varying model (M5) is the one that mostly deviates from the others, while in the other cases there’s no significant differences except for patient 1 and 5. In the first one all the models are not equivalent, while in patient 5 the M4 model is dissimilar from the others.
5.2 Mechanical Power Analysis

In this section, the results about the study of the mechanical power index are presented. The values obtained through the equation 2.51, using different estimated of R and E have been compared with the value obtained during real-time acquisition. This analysis is carried out as an extension of the research of prof. Gattinoni where the system had been tested only under passive behavior of the patient and controlled-volume ventilation. The methods considered for the estimation in this analysis are:

1) Least square method with one R and one E
2) Pressure / volume method according to the ventilation mode
3) Mead Whittenberger method by modifying only R and using E obtained by method 2)

For each of the methods, Bland-Altman plot [32] has been used to illustrate if the two measurement techniques are comparable.

The dispersion diagram represents on the ordinates the difference between the two measurements and on the abscissa the measure of reference. The horizontal solid line indicates the mean of the differences, while the two dashed lines represent the mean difference of ±1.96×SD (standard deviation). The mean of the differences allows to estimate if one of the two methods underestimates or overrides the index with respect to the other, while the other two lines constitute the confidence interval.

The seven analyzed patients have the following characteristics, in terms of ventilation mode and on the basis of respiratory effort:

<table>
<thead>
<tr>
<th>Patient</th>
<th>N Breaths</th>
<th>Ventilation Mode</th>
<th>Effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENT 1</td>
<td>263</td>
<td>Pressure</td>
<td>No</td>
</tr>
<tr>
<td>PATIENT 2</td>
<td>151</td>
<td>Volume</td>
<td>No</td>
</tr>
<tr>
<td>PATIENT 3</td>
<td>142</td>
<td>Pressure</td>
<td>Yes</td>
</tr>
<tr>
<td>PATIENT 4</td>
<td>29</td>
<td>Pressure</td>
<td>No</td>
</tr>
<tr>
<td>PATIENT 5</td>
<td>123</td>
<td>Pressure</td>
<td>Yes</td>
</tr>
<tr>
<td>PATIENT 6</td>
<td>296</td>
<td>Volume</td>
<td>Yes</td>
</tr>
<tr>
<td>PATIENT 7</td>
<td>256</td>
<td>Volume</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 5-3: Patients Characteristics
PATIENT 1

Figure 5.16: Power-error Relationship (Patient 1)
PATIENT 2

Figure 5.17: Power-error Relationship (Patient 2)
PATIENT 3

Figure 5.18: Power-error Relationship (Patient 3)
- **PATIENT 4**

**Figure 5.19: Power-error Relationship (Patient 4)**
PATIENT 5

Figure 5.20: Power-error Relationship (Patient 5)
• PATIENT 6

> Figure 5.21: Power-error Relationship (Patient 6)
- **PATIENT 7**

Figure 5.22: Power-error Relationship (Patient 7)
The power-absolute error trend, for each ventilation modality, has also been plotted:

► Figure 5.23: Power-error Relationship for Pressure-mode
Figure 5.24: Power-error Relationship for Volume-mode
The results of the previous graphs are represented in the following table. The reported values indicate the mean power for each patient with confidential interval:

<table>
<thead>
<tr>
<th>PATIENT 1</th>
<th>Pressure-Volume</th>
<th>Mead-Whitt.</th>
<th>Least square</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2.63 ± 3.93</td>
<td>-0.50 ± 1.18</td>
<td>2.63 ± 2.43</td>
<td></td>
</tr>
<tr>
<td>PATIENT 2</td>
<td>-0.02 ± 0.67</td>
<td>-0.60 ± 0.33</td>
<td>-0.06 ± 0.32</td>
</tr>
<tr>
<td>PATIENT 3</td>
<td>-3.37 ± 4.68</td>
<td>-0.55 ± 2.47</td>
<td>-0.29 ± 3.42</td>
</tr>
<tr>
<td>PATIENT 4</td>
<td>-0.71 ± 0.31</td>
<td>-0.20 ± 0.18</td>
<td>0.49 ± 0.29</td>
</tr>
<tr>
<td>PATIENT 5</td>
<td>-2.26 ± 1.70</td>
<td>-0.75 ± 1.55</td>
<td>-0.36 ± 1.72</td>
</tr>
<tr>
<td>PATIENT 6</td>
<td>2.69 ± 2.65</td>
<td>3.01 ± 1.88</td>
<td>2.37 ± 2.67</td>
</tr>
<tr>
<td>PATIENT 7</td>
<td>0.17 ± 0.54</td>
<td>-0.38 ± 0.51</td>
<td>0.26 ± 0.37</td>
</tr>
</tbody>
</table>

*Table 5-4: Absolute Error values*

From this study it can be seen:
1) An increase in error both in terms of mean and variability in patients who perform respiratory effort
2) A very low error in patients 2 and 7 using the volume-controlled mode
3) A small error using the Mead-Whittenberger method for patients ventilated in pressure-controlled mode

These results suggest that in volume-controlled mode, the error remains small for the different power amplitude, except for one patient who shows respiratory muscles activity. In this case, the mean error obtained is still zero, while the variability is much greater than the others two cases. This is in coherence with the results obtained from the study [30]. Also the Mead-Whittenberger and Least Square methods, used in volume-controlled ventilation allow a good computation of parameters, maintaining the power error to small values. Then, the formula 2.51 used in this modality seems to be accurate for the mechanical power estimation.

Indeed, in pressure-controlled mode, the error is clearly related to the power amplitude, for each subject. As can be seen in Fig. 5.23, an increment in power amplitude corresponds to an increment of the error. This means that the computed power, assumes values much greater than the one measured, from this result, it can be hypothesized that probably the parameters used for computing power involves a kind of overestimation of it.
The error does not seem to be influenced by power amplitude with Mead-Whittenberger, this is probably due to the use of the dynamic compliance in power computation. Then, the resistance obtained in this method and the dynamic compliance, seem to be a more suitable parameters for the computation of mechanical power during pressure controlled ventilation. Instead, with Least Square, the behavior seems to be different for each patient.
5.3 Index Effort Estimation

As last analysis, an index able to represent the patient effort exerted during mechanical ventilation has been estimated. This analysis requires to satisfy two conditions:

1) maintaining of the same ventilatory setting for all the acquisition
2) availability of an airway pressure waveform with and without patient effort.

Due to the fact that these two conditions are difficult to be reached at every registration, only one subject has been studied for this analysis. The patient considered is the sixth one. The index has been obtained as the difference in pressure-volume loop integral, for a breath without effort (controlled only by the ventilator) and one developed with patient inspiratory muscles activity. In presence of patient effort, the pressure waveform is modified assuming an “M” shape, clearly visible by plotting the pressure signal. Then, the reference pressure waveform has been chosen from the several waves acquired, assessing its regularity shape, symptom of the absence of relevant patient inspiratory muscles activity. This breath has been replicated and compared to the whole trace. An extract of the two overlapped pressures is shown in Fig. 5.25, where the difference in shape is clearly visible:

![Figure 5.25: Pressure wave with and without effort](image-url)
The power developed for the different breaths is calculated as integral of their relative pressure-volume loop. As can be seen in Fig. 5.26, in case of patient activity the power developed is the sum of orange and pink area. Indeed power developed without effort is the sum of the orange, pink and blue area. The difference of these two measurements, represented by azure area, is a reliable indicator of the power developed by the patient respiratory muscles at that specific breath considered.

►Figure 5.26: P-V loop with and without effort

The trend of patient’s effort is then analyzed for all the trace by calculating this index breath-to-breath.

►Figure 5.27: Patient effort
From the previous figure it is possible to observe the evolution of the respiratory effort both in single breaths (red line) and in its mean value (black line).

By observing the trend in Fig. 5.27, periodic fluctuations of the signals may be noticed. Then, in order to assess the presence of auto-correlation, a Detrended Fluctuation Analysis (DFA) [33] has been performed. This method computes the fluctuation function as the root-mean-square of the integrated and detrended time series $y(k)$ as follows:

$$F(n) = \sqrt{\frac{1}{N} \sum_{k=1}^{N} [y(k) - y_n(k)]^2}$$  \hspace{1cm} (5.1)

The time series $y(k)$, containing $N$ data points, is obtained by integrating the original time series:

$$y(k) = \sum_{i=1}^{k} (x(i) - \bar{x})$$  \hspace{1cm} (5.2)

where $x(i)$ is the $i$th value of time series value of patient effort and $\bar{x}$ is the corresponding average of the time series. The time series $y(k)$ is then divided into non-overlapping windows of equal length ($n$). A linear regression line is fit through the data points of $y(k)$ in each window. The regression line $y_n(k)$ represents the local trend in that window.

The time series $y(k)$ is then detrended by subtracting the local trend, $y_n(k)$, from the data in each window. The calculation of $F(n)$ has been repeated for different $n$ and plotted as a function of $n$ on a log-log plot. When $F(n)$ shows a linear increase on the log-log plot, then $F(n)$ is said to follow a power-law functional form:

$$F(n) \sim n^\alpha$$  \hspace{1cm} (5.3)

Where $\alpha$ is the scaling exponent and it is calculated as the slope of a straight line fit to the log-log graph of $n$ against $F(n)$ using least-squares.

$\alpha$ can assume different values with specific meaning for self-affinity of the signal:

- $\alpha < 1/2$: anti-correlated
- $\alpha = 1/2$: random process, white noise
- $\alpha > 1/2$: correlated
To verify that the correlations in breath-to-breath fluctuations of the parameters are real, the order of the original breath-to-breath time series has been rearranged (shuffled), obtaining an uncorrelated time series (Fig 5.28). Thus, although this procedure does not alter the distribution of the amplitudes in the time series, the correlated ordering should disappear, and hence $\alpha$ of the shuffled time series should be 0.5, allowing to establish the existence of long-range correlations for a given variable if the value of $\alpha$ is significantly different from that after shuffling.

► Figure 5.28: Original and Shuffled time series
For this study a signal of 800 breaths has been analysed. The DFA plots that correspond to the two time series in Fig. 5.28 are shown below:

As result of the analysis, the $\alpha$ exponent assumes the following values:
- $\alpha = 0.9196$ for original time series
- $\alpha = 0.4825$ for shuffled time series

These outcome suggest that the patient effort signal has a long-term correlation, because the $\alpha$ value is included between 0.5 and 1.

The robustness of this procedure is also confirmed by the value obtained for the shuffled time series, which is around 0.5 as for a white noise signal.

The results indicate that the patient effort is characterized by a cyclical trend repeated over time. Furthermore in order to a better interpretation of these data, it would be useful having more in-depth studies, proposing models which describe in detail how the effort can be related to the mechanical properties of the respiratory system or to the activation of specific neural circuit for breath control.

In this sense neural networks may be used to represent the control system performed on the respiratory muscles, as done in the study of Dellacà et al. [34].
Concerning the computation of the mechanical power through the method represented in Fig. 5.26, an important problem is that the pressure decrease occurring between the end of inspiration and the start of expiration, is not considered.

This is due to the fact that in this situation the volume remains constant, and then its power doesn’t change. However, this effort should not be neglected, because it represents an isovolumetric contraction whose developed work is different from zero. A method that may be used for its computation is the pressure-time product, also used by Grinnan et al. [35]. As shown in Fig. 5.30, this contribute represented by azure area is equivalent to the one computed previously, while the green area is the one neglected but actually it is a relevant factor in effort executed.

![Image: Contributions of patient effort](image_url)
5.4 Future Developments

The system developed in this thesis, has been designed in order to satisfy specific requirements. The first of these, was the optimization of the device size, in order to reduce as much as possible the physical obstruction to clinician inside the intensive care room. In this sense, it was decided to use the connection Bluetooth to send data to be processed on PC. The second main feature, was the reliability of the system in variables monitoring and post-elaboration. The tests and use of the system on real treated patients, have assessed that all the characteristics initially supposed, have been effectively met. Nevertheless, various system improvements may still be made, on several aspects. In fact, both Hardware and Software may be improved.

As explained previously, the data acquired by the device, are sent to a PC both to show the traces in real time and for the post-processing elaboration. This obviously, requires the presence of an additive instrument (the PC) in the ICU room, in addition to the system. Even if the Bluetooth communication allows to keep the PC far from the patient bed, sometimes it may be cause of obstruction and discomfort. Then, it may be useful in terms of Hardware improvement, the design of a single instrument equipped with a screen and an appropriate elaboration software, in order to directly plot the traces and the main indexes extracted, on its screen. This system would not require the presence of the PC in room for the data display. From the Software point of view, a useful implementation may be related to the elastance and resistance parameters extraction. Indeed, currently the estimation of R and E is made only by post-processing, when monitoring is terminated. Instead a more suitable solution, may be the possibility to extract these values in real-time, in order to directly communicate these information to clinicians. Improvements may be also realized in terms of patient effort estimation. Even in this case, it may be useful the extraction of this index in real-time, in order to directly assess the patient activity breath by breath. However, the knowledge about this index and its interpretation is strictly related to the researches made about it, which nowadays are not exhaustive. The direct computation of patient effort together with the awareness about its influence on patient during mechanical ventilation, may be used in order to study appropriate weaning procedure, properly designed basing on each patient condition. In this sense it may be useful the computation of the mechanical power in respect to the FRC.
Bibliography


