POLITECNICO DI MILANO
SCUOLA DI INGEGNERIA INDUSTRIALE E DELL'INFORMAZIONE
Dipartimento di Elettronica, Informazione e Bioingegneria
Corso di Laurea Magistrale in Ingegneria Biomedica

Oscillation mechanics during general anaesthesia: effect of lung recruitment manoeuvres and laparoscopic surgery

Relatore: **Prof. Raffaele Dellacà**
Correlatore: **Dr. Emanuela Zannin**

Tesi di Laurea Magistrale di:
Sara Vigevani
Matr. 877040

Anno Accademico 2019 – 2020

Sommario

L’elevato numero di chirurgie pediatriche annuali [1] e l’alta incidenza di complicanze polmonari postoperatorie [2] , che possono essere ricondotte alla ventilazione meccanica, rendono necessario un approccio su misura alla ventilazione. Per adattare la ventilazione ad ogni paziente, è necessario avere un metodo per misurare la funzionalità respiratoria durante la chirurgia, ma anche se vi sono molti metodi per misurare la funzionalità respiratoria, essi non sono appropriati all’ambiente chirurgico. La tecnica ad oscillazioni forzate è un’ottima soluzione per la misura delle proprietà meccaniche del sistema respiratorio durante la chirurgia in quanto può essere integrata al ventilatore anestetico. L'obiettivo di questo studio è lo sviluppo e la convalida di un set-up per implementare la tecnica ad oscillazioni forzate in ambiente intraoperatorio, che consente il monitoraggio della meccanica respiratoria durante la chirurgia. Le informazioni sulla meccanica respiratoria possono guidare i medici verso approcci più specifici e tempestivi alla ventilazione meccanica durante la chirurgia.

Il primo capitolo fornisce una panoramica della fisiologia e delle proprietà meccaniche del sistema respiratorio, evidenziando i meccanismi, le strutture e i muscoli coinvolti nella respirazione fisiologica e dando definizioni di pressioni e volumi coinvolti nella ventilazione. Le proprietà meccaniche del sistema respiratorio sono presentate prima nella più semplice condizione statica, che consente la definizione di compliance del sistema respiratorio come la pendenza della curva volume-pressione statica. In seguito, una rappresentazione dinamica dei cambiamenti di pressione e volume consente la definizione della pressione all'apertura delle vie aeree in funzione del volume, del flusso e dell'accelerazione, definendo così resistenza e inerzia del sistema respiratorio. Infine, particolare attenzione viene rivolta ai cambiamenti che si verificano nel sistema respiratorio attraverso l'infanzia e l'adolescenza.

Il secondo capitolo si concentra sugli effetti dell'anestesia generale sul sistema respiratorio che si traducono nella necessità di ventilare meccanicamente i pazienti. I farmaci anestetici influenzano il sistema respiratorio in diversi modi, tra cui la depressione dei centri respiratori del tronco encefalico, la perdita di tono dei muscoli respiratori e la riduzione della capacità residua funzionale, con conseguente riduzione dell’ossigenazione. Questa riduzione e la necessità di proteggere le vie aeree dal collasso utilizzando dispositivi per l’intubazione del

paziente, hanno portato ad un uso regolare della ventilazione meccanica. Nella seconda parte di questo capitolo viene descritto il ventilatore anestetico, evidenziando la funzione del ventilatore meccanico integrato e le principali modalità di ventilazione. Infine, l'attenzione viene rivolta ai rischi connessi all'anestesia generale pediatrica e alla ventilazione meccanica, presentando al contempo le principali strategie di protezione polmonare utilizzate nella pratica clinica. Particolare attenzione è rivolta alle strategie di reclutamento polmonare, che possono essere soluzioni efficaci per il reclutamento di regioni polmonari dereclutate a causa dell'anestesia generale. Mentre la ventilazione meccanica e le strategie di protezione polmonare vengono utilizzate regolarmente in ambiente chirurgico, nessuna strategia è chiaramente più efficace di altre, portando alla richiesta di un approccio personalizzato basato sulla misurazione della funzione respiratoria e della meccanica.

Il terzo capitolo fornisce una panoramica dei metodi utilizzati attualmente per valutare la funzione e la meccanica respiratoria e i loro vantaggi e svantaggi per quanto riguarda l’utilizzo nell’ambiente chirurgico. Infine, viene presentata la tecnica ad oscillazioni forzate, che rappresenta un'opzione adatta alla valutazione della meccanica respiratoria durante l'intervento chirurgico, dato che può essere integrata al ventilatore meccanico, non richiede l’attiva collaborazione del paziente e consente l'attività muscolare respiratoria.

Il quarto capitolo presenta l'obiettivo generale del lavoro che è lo sviluppo e la convalida di un set-up per implementare la tecnica ad oscillazioni forzate durante le chirurgie pediatriche, per valutare la meccanica respiratoria durante l'intervento chirurgico. Il set-up sviluppato viene utilizzato presso l'ospedale pediatrico di Perth in due studi clinici che utilizzano l'analisi dei cambiamenti nella meccanica respiratoria come mezzo per valutare l'efficacia di due diverse strategie di reclutamento e l’utilizzo di due diversi dispositivi per l’intubazione del paziente, e per valutare gli effetti sulla meccanica respiratoria dell'insufflazione addominale durante le appendicectomie laparoscopiche.

Il quinto capitolo fornisce una panoramica dei requisiti generali di un set-up per l’applicazione della FOT nell'ambiente pediatrico, come presentato da King et al. nello European Respiratory Journal [3], insieme a ulteriori requisiti introdotti dalla realtà chirurgica, che vengono utilizzati nello sviluppo del set-up utilizzato in questo studio. Il set-up sviluppato è costituito da un altoparlante, utilizzato per le oscillazioni forzate, sensori di pressione e di flusso e un software che controlla l'altoparlante, visualizza e salva i segnali di pressione e flusso. L'altoparlante genera oscillazioni di ampiezza contenuta a 5 Hz, che sono dirette all'apertura delle vie aeree del paziente creando una connessione al circuito respiratorio. La parte posteriore dell'altoparlante è racchiusa in una camera sigillata collegata alla valvola inspiratoria del ventilatore per resistere alle pressioni positive generate dal ventilatore. La pressione e il flusso vengono misurati il più vicino possibile all'apertura delle vie aeree posizionando un tubo per la pressione e un anemometro, tra la Y del circuito respiratorio e il filtro antibatterico. La linea di pressione è collegata a un trasduttore di pressione posto più lontano dal paziente, mentre l'anemometro è collegato a un monitor di respirazione neonatale (Florian). Entrambi i segnali vengono trasmessi a una scheda A/D-D/A che è responsabile per la trasmissione dei segnali a un computer portatile dove possono essere visualizzati e salvati. Ulteriori componenti permettono la corretta elaborazione del segnale analogico di flusso dal Florian. Il controllo delle oscillazioni, la visualizzazione e il salvataggio dei segnali di flusso e di pressione è effettuato tramite un software LabView, che consente anche la progettazione di un'interfaccia utente. I dati registrati vengono quindi elaborati offline in Matlab, attraverso due processi paralleli: il calcolo dell’impedenza tramite il metodo dei minimi quadrati applicato ai segnali di flusso e di pressione filtrati con un filtro passa-banda che isola la componente del segnale forzante e l'identificazione di fine espirazione. La resistenza e la reattanza sono calcolate per ogni registrazione come la media dei valori medi di R e X per ogni respiro identificato.

Il sesto capitolo descrive le fasi coinvolte nei test in vitro necessari per lo sviluppo e la convalida del set-up. Prima di tutto i test lung sono stati scelti per essere rappresentativi della popolazione pediatrica, con particolare attenzione ai pazienti con valori di compliance più bassi, che sono più facilmente rappresentati attraverso bottiglie di vetro di volume contenuto, e rappresentano anche una sfida più difficile nella misurazione della loro meccanica respiratoria. La resistenza del sistema respiratorio è stata modellata utilizzando tubi endotracheali. Inoltre, viene descritto il set-up di riferimento, costituito da uno pneumotacografo montato su un trasduttore di pressione e posto tra la Y del circuito respiratorio e il filtro del paziente. Anche se il set-up di riferimento è altamente preciso e assicura la sincronia tra pressione e flusso, non è appropriato per l’ambiente chirurgico data la dimensione e il peso che lo rendono inadatto ad essere posizionato vicino al paziente durante l'intervento chirurgico. Inoltre, il PNT aggiunge un significativo carico resistivo ed è altamente suscettibile alla condensazione dell'elemento resistivo, con conseguente perdita di linearità. I test lung sono stati misurati con il set-up di riferimento descritto per fornire valori di resistenza e reattanza rispetto ai quali è stato possibile testare l'accuratezza del set-up sviluppato. Sono stati effettuati ulteriori test per studiare l'effetto di una linea di pressione più lunga collegata al trasduttore di pressione e sono state effettuate modifiche nell'elaborazione del segnale di flusso analogico dal monitor Florian, con conseguenti valori di resistenza e reazione che sono contenuti all'interno dell'intervallo di errore relativo definito a ± 10% dai valori di riferimento. Sono stati effettuati ulteriori test per verificare l'accuratezza dell'algoritmo per l'analisi dei dati, confrontando i valori di resistenza e reattanza misurati durante le normali misurazioni dei test lung, che comportano l'utilizzo di una pressione positiva costante (in modalità CPAP), con valori calcolati applicando l'algoritmo alle registrazioni di pressione e flusso in modalità di controllo della pressione (PC) con una pressione di fine espirazione (PEEP) pari alla pressione applicata in CPAP. Infine, la ripetibilità della misura viene controllata periodicamente sia tra pazienti diversi sia tra misure successive dello stesso paziente, effettuando regolari misurazioni del test lung.

Il capitolo sette fornisce uno schema dettagliato degli studi clinici che utilizzano il set-up clinico sviluppato in questo studio. Entrambi gli studi si svolgono presso l'ospedale pediatrico di Perth grazie ad una collaborazione tra il Politecnico di Milano e Telethon Kid's Institute, e misurano la meccanica oscillatoria per monitorare gli effetti delle manovre di reclutamento polmonare (OASIS) e dell'insufflazione addominale (COMET) durante l'anestesia generale. Sono riportati i risultati basati sui dati disponibili fino ad oggi per entrambi gli studi; mentre è possibile un'analisi più approfondita dei dati dello studio OASIS, grazie al maggior numero di pazienti reclutati, viene effettuata solo un'analisi qualitativa dei dati dello studio COMET. I risultati preliminari suggeriscono che l'efficacia delle strategie di reclutamento polmonare dipenda dalla presenza di regioni polmonari dereclutate, mentre i loro effetti non permangono fino alla fine dell'intervento chirurgico. Inoltre, un'analisi preliminare dei pazienti che hanno beneficiato della RM suggerisce che la strategia di inflazioni ripetute è più efficace di un'unica inflazione sostenuta. Infine, l'osservazione delle registrazioni per i primi pazienti reclutati nello studio COMET non ha mostrato variazioni significative della meccanica respiratoria durante l'intervento chirurgico, probabilmente a causa delle basse pressioni di insufflazione intraddominale.

In conclusione, il set-up sviluppato può essere utilizzato in sala operatoria per monitorare i cambiamenti nella meccanica respiratoria durante l'intervento chirurgico. Inoltre, la correzione per i dispositivi di intubazione utilizzati contribuirà a definire linee guida e regole per indirizzare i medici nella scelta dei parametri di ventilazione e delle strategie di protezione polmonare in un approccio più specifico basato sulla meccanica respiratoria.

Summary

Given the volume of paediatric surgeries performed every year [1] and the higher incidence of postoperative pulmonary complications in children [2], linked to intraoperative mechanical ventilation, a patient-specific approach to mechanical ventilation is needed. In order to tailor ventilation a method to measure the patient's respiratory function during surgery is necessary; while many methods allow for measurement of respiratory function both during physiological and mechanical ventilation, they are not suited to the intraoperative setting. The forced oscillation technique is a method of measuring respiratory mechanics which can be integrated into the anaesthesia ventilator, making it the best solution for the surgical setting. The aim of the present study is the development and validation of a set-up to implement the forced oscillation technique in an intraoperative paediatric setting, which allows for the monitoring of respiratory mechanics throughout surgery. Information on respiratory mechanics can guide clinicians towards more patient specific and timed approaches to intraoperative mechanical ventilation.

Chapter one provides an overview of the physiology and mechanical properties of the respiratory system by highlighting the main mechanisms, structures and muscles involved in normal quiet breathing and providing definitions of pressures and volumes. Mechanical properties of the respiratory system are presented both in the simpler static condition, which allows for the definition of respiratory compliance as the slope of the static pressure-volume curve. Furthermore, a dynamic representation of changes in pressure and volume allows for the definition of pressure at the airway opening as a function of volume, flow and acceleration, thus defining resistance and inertance of the respiratory system. A particular focus is then directed towards the changes that occur in the respiratory system through childhood and adolescence.

Chapter two is focused on the effects of general anaesthesia on the respiratory system which result in the necessity of intraoperative mechanical ventilation. Anaesthetic drugs affect the respiratory system in multiple ways, which include the depression of brainstem respiratory centres, the loss of respiratory muscle tone and reduction of functional residual capacity, resulting ultimately in an oxygenation impairment. This impairment and the need to protect the airways from collapsing by means of airway devices have led to a regular use of controlled mechanical ventilation. In the second part of this chapter a description of the

anaesthesia ventilator is carried out, highlighting the function of the integrated mechanical ventilator and the main ventilation modes. Finally, the focus is shifted toward the increased risks involved in paediatric general anaesthesia and mechanical ventilation, while presenting the main lung protective strategies used in clinical practice. Particular attention is directed at lung recruitment strategies, which can be effective solutions in recruiting lung regions that have collapsed as a result of general anaesthesia. While mechanical ventilation and lung protective strategies are routinely used in the surgical setting, no strategy is clearly more effective than others, this observation has led to a call for a patient specific approach based on measurements of respiratory function and mechanics.

Chapter three provides an overview of current methods used to evaluate respiratory function and mechanics and their advantages and disadvantages with regards to their application to the surgical setting. Lastly, the forced oscillation technique is presented, which represents a suitable option for measuring respiratory mechanics throughout surgery, given that it can be integrated into ventilator, does not require patient collaboration, and allows for respiratory muscle activity.

Chapter four presents the general aim of this work which is the development and validation of a set-up to implement the forced oscillation technique in the intraoperative paediatric setting to measure respiratory mechanics during surgery. The developed set-up is being used at Perth Children’s Hospital in two clinical studies that use the analysis of changes in respiratory mechanics as means to evaluate the effectiveness of two different recruitment strategies and their delivery through two airway devices, and to evaluate the effects on respiratory mechanics of abdominal insufflation during laparoscopic appendectomies.

Chapter five gives an overview of the general requirements of a FOT set-up in the paediatric setting, as presented by King et al. in the European Respiratory Journal [3], together with additional requirements introduced by the surgical setting, which are used to develop the set-up used in this study. The developed set-up is made up of a loudspeaker, used to generate the forcing signal, pressure and flow sensors to measure pressure and flow and a software that controls the loudspeaker, while displaying and saving pressure and flow signals. The loudspeaker generates low-amplitude oscillations at 5 Hz, which are directed towards the patient’s airway opening by creating a connection to the breathing circuit. While the rear of the loudspeaker is enclosed in a sealed chamber connected to the inspiratory valve of the anaesthesia ventilator to withstand the positive pressures involved in mechanical ventilation.

Pressure and flow are measured as close as possible to the airway opening by placing a pressure sampling line and a hot-wire anemometer, between the Y of the breathing circuit and the antibacterial filter. The pressure sampling line is connected to a pressure transducer placed further away from the patient while the hot-wire anemometer is connected to a neonatal respiration monitor (Florian). Both signals are transmitted to an A/D-D/A board which is responsible for their transmission to a laptop where they can be displayed and saved. Further components are added to appropriately process the flow analog signal from the Florian monitor. The control of the generated oscillations, display and saving of flow and pressure signals is carried out by a LabView software, which also allows for the design of a graphic user interface. Recorded data are then processed offline in Matlab, through two parallel processes: impedance calculation through the least square method applied to flow and pressure signals filtered with a band-pass filter which isolates the forcing signals components, and the identification of end expiration. Resistance and reactance for each recording are then calculated as the average of the mean values of R and X for each identified breath.

Chapter six describes the steps involved in the in vitro testing necessary for the development and validation of the set-up. First of all test lungs were chosen to be representative of the paediatric population, with particular focus towards those with lower compliance values, that are more easily represented through glass bottles of contained volume, and also represent a harder challenge in the measurement of their respiratory mechanics. Respiratory resistance is represented by the resistance of the airway device used, so it was modelled using endotracheal tubes. Furthermore, the set-up used as reference is described, as made up a pneumotachograph mounted on a pressure transducer and placed between the Y of the breathing circuit and the patient filter. While this set-up is highly accurate and ensures synchrony between pressure and flow, it is not appropriate for the intraoperative setting given its dimension and weight which cannot be coupled to the need to be close to the patient during surgery. Furthermore, the PNT adds a significant resistive load and is highly susceptible to condensation of the resistive element, resulting in a loss of linearity. The test lungs were measured with the reference set-up described to provide values of resistance and reactance against which the accuracy of the developed set-up could be tested. Further tests were carried out to investigate the effect of a longer pressure line connected to the pressure transducer and adjustments in processing of the analog flow signal from the Florian monitor were made, resulting in values of resistance and reactance that are well within the relative error range defined as ±10% from the reference values. Additional test were carried out to check for the accuracy of the data analysis logarithm by comparing values of resistance and reactance measured during normal test lung measurements, that involves the application of a constant positive pressure (in CPAP mode), with values computed by applying the algorithm to recording of pressure and flow in pressure control mode (PC) with a positive end expiratory pressure (PEEP) equal to the pressure applied in CPAP. Finally the repeatability of the measure is periodically checked both between different patients and within the same patient, by carrying out regular repeated measurements of the test lung.

Chapter seven provides a detailed outline of the clinical studies which make use of the developed clinical set-up. Both studies are taking place at Perth Children's Hospital thanks to a collaboration between Politecnico of Milan and Telethon Kid Institute, and measure oscillation mechanics to monitor the effects of lung recruitment manoeuvres (OASIS) and abdominal insufflation (COMET) during general anaesthesia. Results based on data available to data are reported for both studies; while a more in depth analysis of data from the OASIS study is possible thanks to the higher number of patients recruited, only an initial, qualitative analysis of data from the COMET study is carried out. Preliminary results suggest that the effectiveness of lung recruitment strategies is dependent on the prior presence of derecruited lung regions, while their effects are not sustained until the end of surgery. Furthermore, a preliminary analysis of those patients which benefited from the RM suggests that the repeated inflation strategy is more effective than a single sustained inflation. Finally, observation of recordings for the first few patients recruited in the COMET study showed no significant variations in respiratory mechanics throughout surgery, possibly due to the low intrabdominal insufflation pressures.

Finally, the developed set-up can be used in the intraoperative setting to monitor changes in respiratory mechanics throughout surgery. Furthermore, correction for the airway devices used will help define evidence-based guidelines and policies to guide clinicians in choosing mechanical ventilation parameters and lung protective strategies in a more patient specific approach based on respiratory mechanics.

Introduction

The number of children undergoing surgery that requires general anaesthesia is very high (with an estimate of 450000 per year in the United States alone) [1], with laparoscopic surgery becoming the most sought out solution in case of abdominal surgery because of the advantages of this technology with respect to open surgery. Furthermore, the incidence of postoperative pulmonary complications, which can be linked to intraoperative mechanical ventilation, is higher in children than in adults [2] and can be reduced by a patient specific approach to mechanical ventilation.

The higher incidence of such complications in children, which decreases with age, is linked to the fact that children have lower functional residual capacity, closer to closing volume. The induction and maintenance of general anaesthesia in patient undergoing surgical procedures is achieved through the delivery of drugs which also affect the correct functioning of the respiratory system. Anaesthetic drugs cause a depression of the brainstem regions responsible for the control of breathing and a loss of tone of respiratory muscles which in turn reduce FRC. In addition, supine positioning of the patient further reduces end-expiratory lung volume. Children are particularly at risk of lung collapse as a result of general anaesthesia given that their physiological resting volume, which is closer to closing volume, is further reduced by supine positioning and diaphragmatic relaxation. Furthermore, the insufflation of the abdominal cavity during laparoscopic surgery causes an increase in intra-abdominal pressure, which in turn results in an ulterior reduction in resting volume of the lung.

Given that general anaesthesia causes a deterioration in pulmonary gas exchange, anaesthetised patients need some degree of mechanical ventilatory support, depending on the depth of anaesthesia and the presence or absence of total muscular blockade. Mechanical ventilation is aimed at delivering a breathing pattern able to overcome the elastic and resistive load of the patient’s respiratory system and reduce the work of breathing. Furthermore, given the increased collapsibility of the lung during general anaesthesia, protective ventilation strategies have become part of routine intraoperative mechanical ventilation. These strategies include recruitment manoeuvres (RM), which are aimed at opening collapsed lung regions by applying high pressures for a specific amount of time, and the application of a positive end-expiratory pressure (PEEP), which is aimed at preventing the repeated opening and closure of collapsed lung regions. While many studies have shown the effectiveness of lung protective strategies, there is no clear consensus on which RMs and which levels of PEEP are most effective, calling for a more patient-specific approach in the choice of lung protective strategies.

The evaluation and tailoring of mechanical ventilation are based on measures of lung function and mechanics, which can be achieved using different techniques. However, most techniques require either patient cooperation, which is not possible in case of anaesthetised patients, disconnection of the patient from the breathing circuit, interrupting the delivery of the breathing pattern, or total muscle blockade, which is not always deemed necessary during surgery.

The forced oscillation technique (FOT), first introduced by Dubois et al., is a method of measuring respiratory mechanics by superimposing external driving forces, such as small-amplitude oscillations, to the breathing pattern. The mechanical response of the respiratory system to the driving forces is represented by impedance (Z) which is the ratio between the applied pressure and the resulting airflow in the frequency domain. The impedance is a complex number whose real part represents the resistance of the respiratory system, while the imaginary part, called reactance, describes the elastic properties of the respiratory system. FOT is better suited to applications in the surgical setting, given that it is a simple, non-invasive technique that doesn’t require patient collaboration or total muscle blockade. Furthermore, the FOT set-up can be integrated into the anaesthesia ventilator without interrupting ventilation, allowing for a continuous monitoring of respiratory mechanics during surgery.

The aim of this work is to develop and validate a set-up to implement the forced oscillation technique in the intraoperative setting in accordance both with existing technical standards of the FOT and with clinical requirements during surgery. The set-up developed is then used in collaboration with Telethon Kids Institute in two clinical studies at Perth Children’s Hospital:

- Oscillation mechanics and sustained inflation study using FOT measurements of children under general anaesthesia (OASIS)
- Changes in oscillation mechanics evaluated by the forced oscillation technique and lung recruitment during mechanical ventilation in paediatric laparoscopic appendectomy (COMET)

The OASIS study is focused on evaluating the effectiveness of two different recruitment manoeuvres in recruiting the lung and their delivery using two different airway devices, by analysing variations in respiratory mechanics before and after the recruitment strategy.

The COMET study is focused on evaluating the effects of laparoscopic appendectomy on lung recruitment, by monitoring respiratory mechanics throughout surgery.

Both studies will help formulate evidence-based guidelines and policies to optimize ventilation strategies in children undergoing general anaesthesia and laparoscopic appendectomies.

1. Respiratory System

1.1 Physiology

The respiratory system, comprised of the lungs, airways and respiratory muscles, is responsible for providing oxygen to the organism and removing carbon dioxide and other waste gases. The gas interchange happens thanks to the movement of air into and out of the airways and lungs, alternating inspiration and expiration in a process called ventilation or breathing.

During inspiration in normal breathing the diaphragm contracts causing an increase in thoracic volume, which is stabilised or increased further by the action of intercostal muscles. Due to this enlargement intrathoracic pressure drops, expanding the lungs and allowing air to flow from the environment into the lungs (Figure 1).

Lung expansion is opposed by the elastic recoil of the lung tissue and the surface tension of the alveoli, both of which are responsible for expiration being passive in normal breathing.

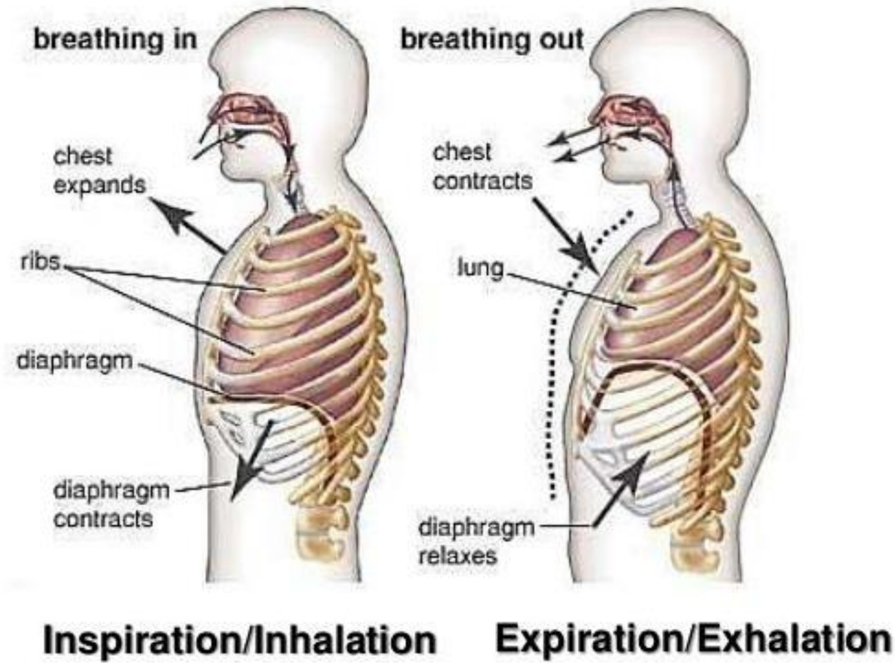


Figure 1 Diaphragm and rib cage movements during inspiration and expiration during quiet breathing.

The respiratory systems anatomical structures can be divided into:

- Upper respiratory structures: nasal cavity and nasal passages, paranasal sinuses, the pharynx and the upper portion of the larynx.
- Lower respiratory structures: lower portion of the larynx, trachea, bronchi and bronchioles.
- Lungs: respiratory bronchioles, alveolar ducts, alveolar sacs and alveoli.

The upper and lower airways, where air is filtered, humidified and warmed, can also be described as conducting airways as air flows through them to reach the respiratory zone, in particular the alveoli where the exchange of oxygen and carbon dioxide between air and blood happens. The alveoli are small cavities and they contain collagen, elastic fibres and two different types of alveolar cells. The elastic fibres allow the alveoli to stretch during inhalation and to spring back during exhalation, while type II pneumocytes secrete surfactant, creating a film of phospholipids inside the alveoli, that reduce surface tension preventing the collapse of the alveoli during expiration.

Air flows in and out of the lungs causing changes in lung volume. Traditionally lung function can be measured through spirometry, which also allows to define a number of characteristic lung volumes, associated to different phases of the respiratory cycle (Figure 2).

- Tidal volume (VT) is the amount of air inspired and expired in one cycle of quiet breathing.
- Inspiratory reserve volume (IRV) is the maximum amount of air that can be forcefully inspired with respect to end-tidal inspiratory volume.
- Expiratory reserve volume (ERV) is the maximum amount of air that can be forcefully expired with respect to end-tidal expiratory volume.
- Residual volume (RV) is the amount of air remaining in the lungs after maximal expiration

Furthermore, lung capacities can be inferred from lung volumes.

- Inspiratory capacity (IC) is the maximum amount of air that can be inspired with respect to end-tidal expiratory volume (IRV+VT).
- Total lung capacity (TLC) is the maximum amount of air the lungs and airways can accommodate (VT+IRV+ERV+RV).
- Vital capacity (VC) is the total amount of air expired after maximal inhalation (VT+IRV+ERV).

- Functional residual capacity (FRC) is the amount of air remaining in the lung with respect to end-tidal expiratory volume (RV+ERV).

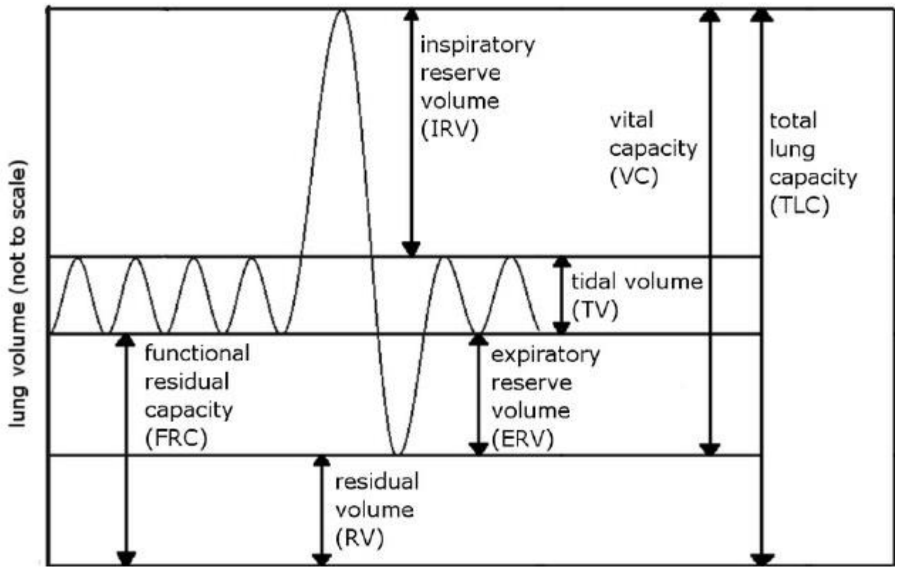


Figure 2 Lung volumes and capacities

Changes in volume are a result of the different pressures inside and outside the thorax that direct the flow of air through the respiratory tracts.

- External pressure (P_{EXT}) is the pressure outside the body.
- Airway opening pressure (P_{AO}) is the pressure measured at the mouth.
- Alveolar pressure (P_{ALV}) is the pressure inside the alveoli.
- Intrapleural pressure (P_{PL}) is the pressure inside the pleural cavity.
- Transpulmonary or lung pressure (P_L) is the difference between alveolar and intrapleural pressure, giving a measure of the elastic recoil that resist lung expansion.
- Chest wall pressure (P_{CW}) is the difference between intrapleural and external pressure.
- Airway pressure (P_{AW}) is the difference between airway opening and alveolar pressure.
- Respiratory Pressure (P_{RESP}) is the total pressure in the respiratory system, seen as the sum of airway, transpulmonary and chest wall pressures.

1.2 Mechanical Properties

The mechanics of the respiratory system can be characterized by studying its properties both in static and dynamic conditions and by using both mechanical and electrical models.

The main components of the respiratory system can be represented in an electrical equivalent model where pressure is represented by voltage, volume by electrical charge and flow by current, in particular the respiratory muscles are represented by a voltage generator given that there are able to exert a pressure that in turn changes pleural pressure (P_{pl}). In addition, a capacitance (C_g) can be introduced between airways and lungs to represent the compression and expansion of gas.

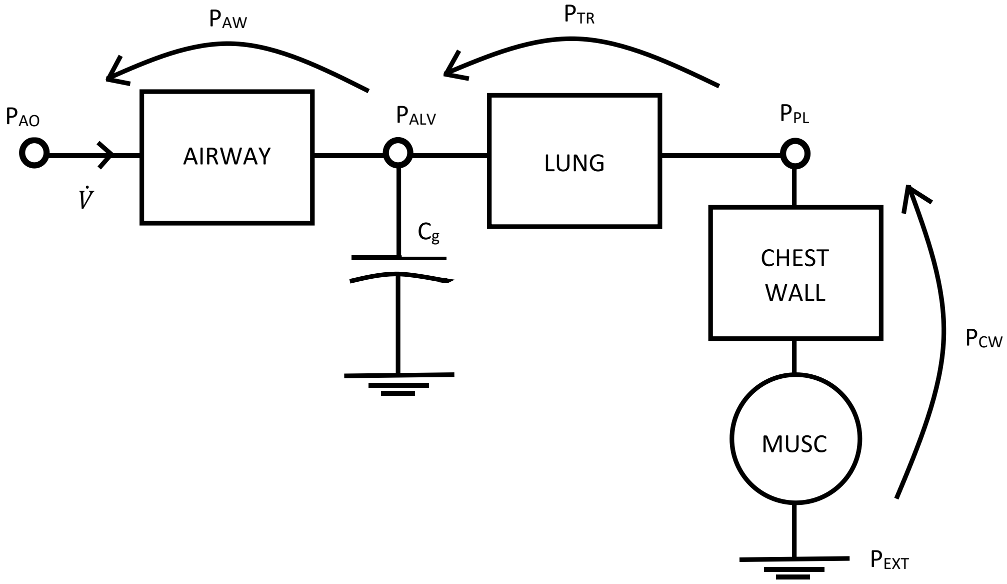


Figure 3 Electrical equivalent model of the respiratory system

The static behaviour has been studied by determining and analysing the volume-pressure relations during relaxation at different lung volumes. The volume-pressure curve obtained (Figure 4) allows the definition of the resting volume of the respiratory system, as the volume corresponding to a null airway pressure which corresponds to the FRC during quiet breathing. The curve also presents an almost linear region around the resting volume and its slope represents the distensibility, or compliance, of the respiratory system (C_{RS}).

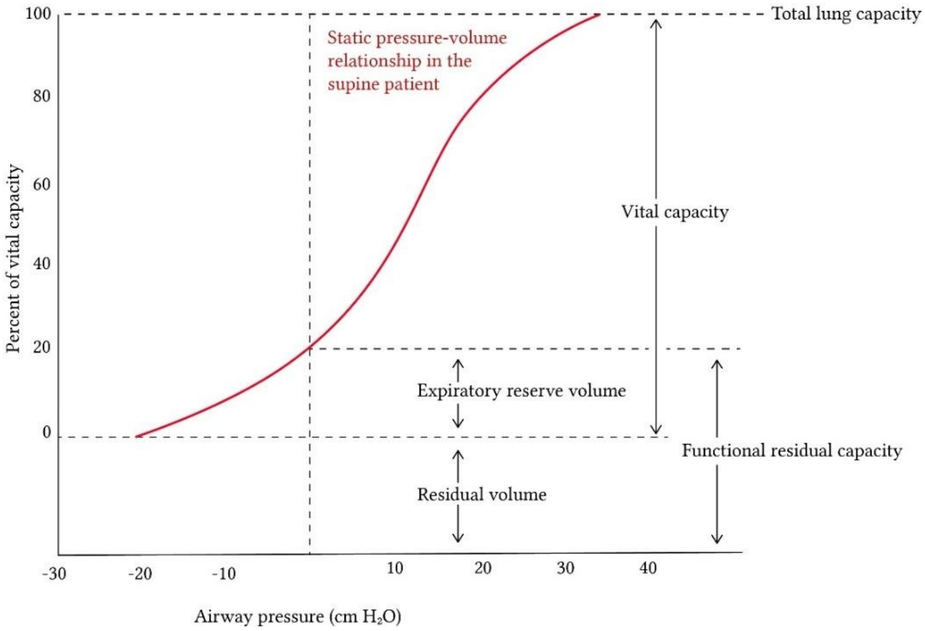


Figure 4 Static pressure-volume curve

In a condition of relaxation of the respiratory muscles the pressure developed by the respiratory system (P_{RS}) is the result of the pressures exerted by the elastic elements and is equal to the difference between alveolar pressure (P_{AL}), when the airways are closed, or airway opening pressure, when the glottis is open, and the external pressure, measured as the pressure at the body surface (P_{BS}). The pressure of the respiratory system, in this case, is also an indicator of the pressure that the respiratory muscles must exert to maintain the lung open. However, the pressure generated by the activation of the respiratory muscles (P_{MUSC}) causes a change in configuration, increasing the elastic pressure as a whole.

Given that the chest wall and the lung are placed in series, their changes in volume should be the same and equal to the changes in volume of the whole respiratory system, the pressure of the respiratory system can be seen as the sum of the pressures of the relaxed chest wall and of the lung ($P_{RS}=P_W+P_L$) and the compliances also sum in series ($\frac{1}{C_{RS}}=\frac{1}{C_W}+\frac{1}{C_L}$). Analysing the volume-pressure diagrams for P_W and P_L, it should be noted that while they are both curvilinear, the slope of the former drops at lower volumes, thus causing the drop in C_{RS} below the resting volume, while the slope of lung pressure drops for higher lung volumes, thus causing C_{RS} to decrease at volumes higher than the resting volume. This is representative of how chest wall and lung behave like opposing springs, at resting volume the chest wall recoils outward while the lung recoils inward by the same amount, while for higher volumes they both recoil inward and for lower volumes the outward recoil of the chest wall is greater than the inward recoil of the lungs (Figure 5).

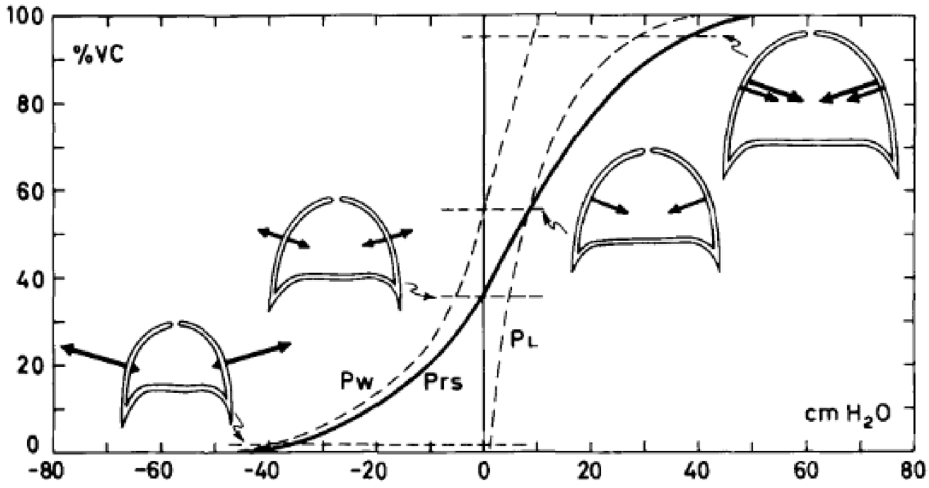


Figure 5 Chest wall and lung pressure

If we take into account the pressure actively exerted by the respiratory muscles at fixed volumes, adding it to the pressure of the respiratory system, we can define alveolar pressure (P_{AL}) as the sum of pressure of the chest wall ($P_{CW}=P_W+P_{MUSC}$) and the pressure of the lung.

While the static volume-pressure curves are represented as a single line, suggesting that pressure depends on volume alone, it actually also depends on volume history, as represented by hysteresis loops obtained by increasing lung volume from RV to TLC and then decreasing it, showing how pressures at the same volume are different during exhalation and inhalation. Hysteresis loops are a common characteristic among various elastic structures in the body and it occurs both in the lung, due to surface properties and alveolar recruitment or derecruitment, and in the chest wall, due to the elastic properties of its tissues.

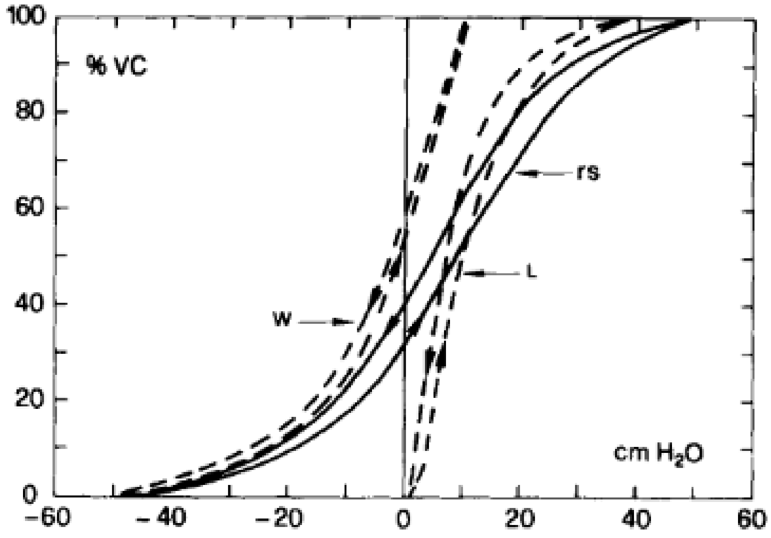


Figure 6 Hysteresis loop of pressure and volume

The respiratory muscles have to overcome not only the elastic recoil of chest wall and lung, but also the viscous friction of the air flowing through the airways, forces due to viscoelastic behaviour of the lungs and inertial forces. Given these properties the respiratory system can be represented using a mechanical model that can be described by its equation of motion (1) where pressure generated by respiratory muscles is also taken into account.

$$P_{AO} = \frac{V}{C} + R\dot{V} + I\ddot{V} - P_{MUSC} \tag{1}$$

This equation not only accounts for the pressure generated by the muscles, but also relates pressure to volume (V), through compliance (C), to flow ($\dot{V}$), through resistance opposed to it in the respiratory system (R), and to acceleration ($\ddot{V}$), through inertance (I).

If we consider breathing at normal tidal frequencies the contribution of inertance is negligible and the total pressure can be described as the sum of an elastic and a resistive contribution. The pressure needed to overcome the elastic forces exerted throughout the respiratory system is the only contribution when flow is null, and compliance can be defined as the ratio between volume and pressure variation (2). And, as seen previously, compliance of the respiratory system has contributions of both lung and chest wall.

$$C = \frac{\Delta V}{\Delta P} \tag{2}$$

Conversely the pressure needed to overcome resistive forces is the only contribution when volume variation is null, and resistance can be defined as the ratio between pressure variation and flow (3).

$$R = \frac{\Delta P}{\dot{V}} \tag{3}$$

Resistance is a measurement of the opposition to air flow through a structure, as airways, and depends on the length and diameter of the structure, the viscosity and density of the gas flowing through them, flow rate and whether the flow is laminar or turbulent. Air flow is predominantly laminar at the periphery given that the total cross-sectional area is large even if the diameter is small and the relation between pressure and flow is linear. On the other hand in the central airways the opposite is true and air flow is predominantly turbulent and the pressure is proportional to the square of flow. When both flow regimes are present the relation between pressure and flow is expressed by Rohrer's equation (4) that is used to represent the total resistance of the respiratory system which is the sum of the resistance of lung, airways and chest wall.

$$\Delta P = K_1\dot{V} + K_2\dot{V}^2 \tag{4}$$

1.3 Development through childhood and adolescence

The respiratory system in children and adolescents is structurally and mechanically affected by growth and development occurring throughout the years [4].

Structural changes happen throughout childhood together with changes in body size, mainly height. In fact children double in size from birth to 18 months of age, then again by the age of five, and finally they double to achieve their adult size; during this period they also go through two main growth spurts, one during infancy and early childhood and one during puberty, which represent peculiar and critical times in their development and also in that of the respiratory system. In the first two to three years of life the number of alveolar units rapidly increases and in the first few years of life the infant's more compliant rib cage progressively stiffens and changes its configuration, while the strength of the respiratory muscles increases, as does lung capacity [4]. Before and after puberty the relationship between lung function and stature is relatively linear, but during puberty, which starts between the ages of twelve and fourteen, the higher growth in stature causes and even more increased growth of the lungs [5].

The most important determinant of lung size in children is height, while a good amount of variance between children is accounted for by differences in thoracic dimensions and a smaller amount by differences in body composition [5].

It is important to note that the development of the lungs does not happen at a uniform rate compared to somatic growth or passage of time, but different compartments of the respiratory system have their own characteristic patterns that can also be perturbated by environmental exposure and growth spurts [5].

All the structural changes occurring during the years of childhood and adolescence are accompanied by changes in the mechanical properties of the respiratory system [4].

The static pressure-volume curves reveal that the resting volume is much lower in infants than in adults and so are the elastic recoil outward of the chest wall and the elastic recoil inward of the lungs, while the linear portion of the curve is relatively small in small children.

Compliance of the respiratory system, related to total volume, decreases with increasing height all trough childhood and adolescence. Total compliance of the respiratory system (C_{RS}) is made up of compliance of the lungs (C_L) and that of the chest wall (C_W); the latter is up to three times greater than that of the lungs during the first years of life, when the chest wall hasn't stiffened yet, while the two become equal in older children, with the stiffening of the chest wall and increase in lung volume, which determine respectively a decrease in C_W and an increase in C_L [6].The same decrease with increasing height is true for resistance of the respiratory system (R_{RS}) and of the airways (R_{AW}); in particular airway resistance is higher than in adults even if airways are relatively large in children, given the much smaller diameter [7].Furthermore in children up to two years of age the resistance of the peripheral airway account for up to 50% of the total airway resistance.

Throughout different studies it has been found that the best determinant for the mechanics of the respiratory system during childhood is height, while at different stages of growth other indices, as age, sex, weight and body composition, might explain further differences.

2. Mechanical ventilation during general anaesthesia

The first means used to anaesthetise patients for surgical procedures were inhalation devices, able to deliver different anaesthetic agents in spontaneously breathing subjects. However, the increasing complexity of surgical procedures, the introduction of neuromuscular blocking and intravenous anaesthetic agents, and the need to protect the airways resulted in the need for mechanical ventilation during general anaesthesia. Further advances in technology and understanding of respiratory physiology resulted in the development of modern anaesthesia ventilators able to meet the requirements of an intraoperative setting.

2.1 Effects of anaesthesia and surgery on the respiratory system

Most patients undergoing surgical procedures require general anaesthesia, which is achieved through the delivery of drugs that also cause the depression of brainstem respiratory centres, responsible for the control of breathing, and of respiratory muscles [8]. Furthermore, patient positioning during surgery, usually in the supine position, also affects the mechanics of the respiratory system. Surgical settings involving general anaesthesia affect the distribution in ventilation and perfusion, thus resulting in a deterioration in pulmonary gas exchange which calls for different degrees of mechanical ventilatory support.

2.1.1 Control of breathing

The control of breathing aims mainly at maintaining blood gases, especially arterial carbon dioxide, within a restricted range. Furthermore, it is involved in maintaining brain pH and optimizing breathing frequencies while maximizing the work output of respiratory muscles in order to maintain an adequate gas exchange.

Breathing control originates from the interaction of different neuronal networks along the nervous system, mainly situated in the respiratory centres in the brainstem, where three main areas can be recognized: inspiratory, pneumotaxic and expiratory.

Most drugs used to achieve analgesia and anaesthesia affect the control of breathing, through their action on peripheral and central chemoreceptors, behavioural control, respiratory muscles or respiratory centres, resulting in a reduction of alveolar ventilation [9].

2.1.2 Respiratory muscles

Most anaesthetics cause a loss of respiratory muscle tone and a possible change of position or shape of the diaphragm which influences the balance between the lung's inward elastic recoil and the chest wall's outward recoil.

2.1.3 Compliance and Resistance

Anaesthesia causes a reduction in total static compliance of the respiratory system, while resistance increases, probably as a result of reduced FRC [9].

2.1.4 Functional residual capacity

The functional residual capacity is the amount of air remaining in the lungs after an end-tidal expiration and it is the result of the balance between the inward recoil of the lung and the outward force of the chest wall. In normal conditions FRC is greater than the closing volume, but during intraoperative anaesthesia, given the supine position and the diaphragmatic relaxation, FRC is closer and could also fall below closing volume, thus resulting in airway closure. Closure of smaller airways and alveoli is also promoted by the fact that in the supine position intrapleural pressure is less negative in the basal region of the lung than at the apex because lung weight counteracts the elastic recoil in the lower area [10].

2.1.5 Dead space

Reduction of FRC causes a shift of all lung area toward the lower region of the pressure-volume curve, meaning that apex alveoli are best ventilated, but less perfused. These changes explain the increase in alveolar dead space which in turn reduces the effective elimination of carbon dioxide occurring during alveolar ventilation. Furthermore, in the more perfused, but less ventilated areas of the lung, gas uptake by the blood flow can exceed fresh gas inflow when using high inspired oxygen fractions, possibly resulting in absorption atelectasis [10].

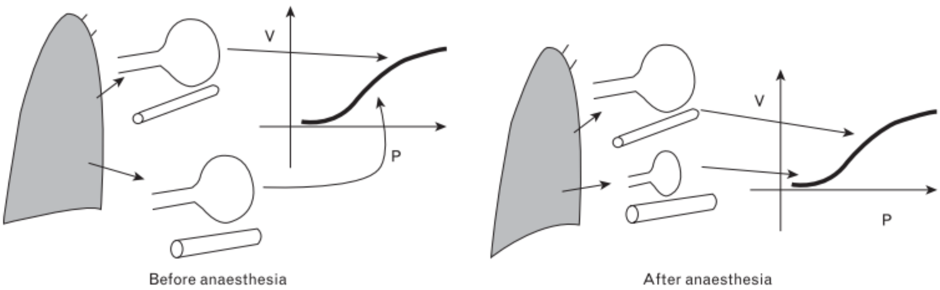


Figure 7 Effect of anaesthesia on alveoli

General anaesthesia has not historically required mechanical ventilation, but it has been associated to changes throughout the respiratory system resulting in an oxygenation impairment. These changes, together with the need to protect the airways using airway devices such as endotracheal tubes or laryngeal masks, have led to a regular use of controlled mechanical ventilation to maintain an adequate gas exchange.

2.2 Anaesthesia ventilator

Anaesthesia ventilators provide a mixture of anaesthetic gases and vapours in varying proportions to control the level of consciousness and analgesia during surgery. Additionally, the machine provides oxygen and enables patient ventilation while monitoring of various parameters [11].

The anaesthesia ventilator is made up of four main components: an anaesthesia machine, a ventilator, a breathing circuit and a waste gas scavenger system. Additionally, most of modern anaesthetic set ups also include patient monitoring and information management functions.

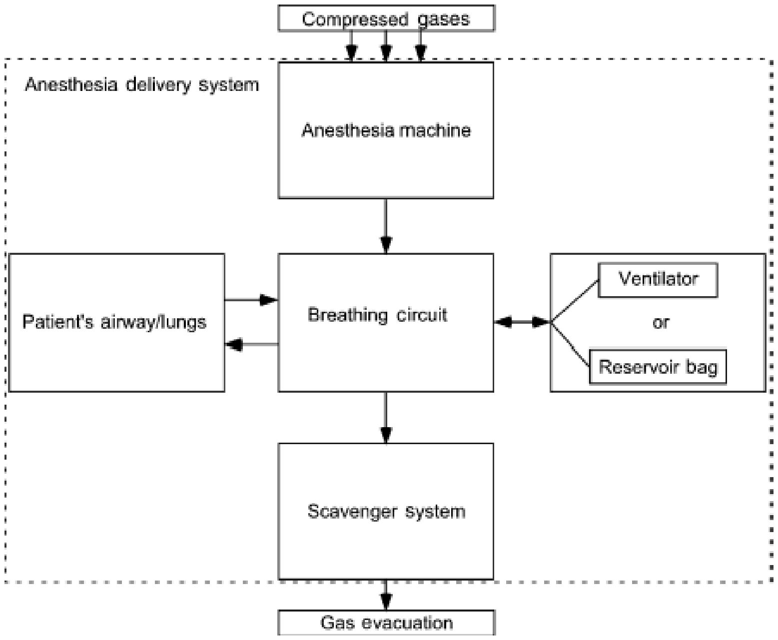


Figure 8 Block diagram of an anaesthesia ventilator

2.2.1 Anaesthesia machine

The anaesthesia machine is defined as the component which is responsible for creating a precise mixture of anaesthetic fresh gases and vapours that enable the control of the level of consciousness and analgesia during surgery.

2.2.2 Mechanical ventilator

The mechanical ventilator is a positive-pressure ventilator which is responsible for accurately delivering a defined ventilation strategy to the patient; this is possible thanks to the evolution of technology and understanding of respiratory physiology. Modern ventilators are made up of a control unit, a pneumatic unit and sensors.

The pneumatic unit replaces, or supports, the action of the respiratory muscles by delivering pressurised oxygen rich air through fast valves resulting in an inspiratory pressure able to overcome the elastic and resistive load imposed by the patient’s respiratory system while reducing their work of breathing. Passive expiration is then allowed through the opening of the expiratory valve.

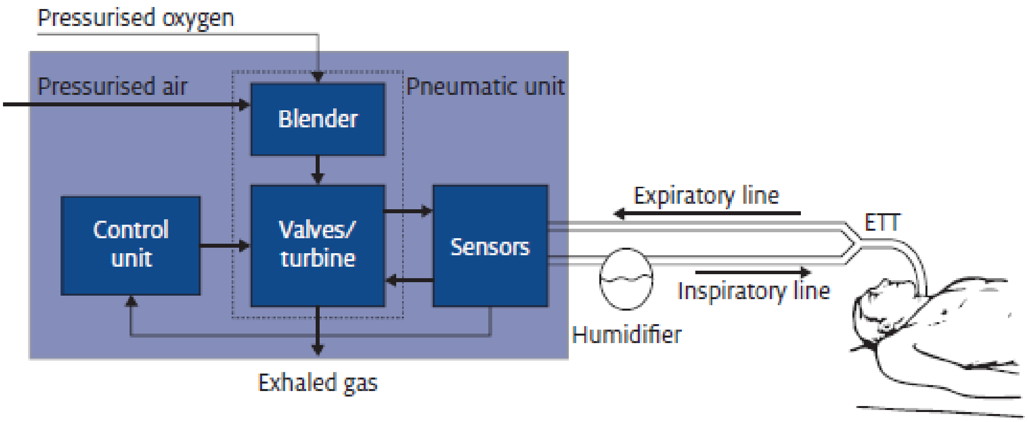


Figure 9 Schematic representation of a mechanical ventilator

The sensors measure relevant ventilation variables, communicating them to the control unit, that is thus able to adjust the valves in order to deliver the desired ventilation strategy.

Ventilation modes

The ventilation strategy is set by using a predetermined pattern of patient-ventilator interaction, or mechanical ventilation mode, and selecting the parameters accordingly.

Each mode of ventilation can be classified based on its three phase variables components: the trigger, the target and the cycle [12] [13].

The trigger variable can be set as time, flow, pressure or volume and it determines how and when the ventilator initiates and ends a breath. It also determines whether a ventilation mode is controlled or assisted by the ventilator.

The target variable defines the maximum value which certain parameters can achieve during inspiration.

The cycling variable defines the mechanism used to end inspiration and commence expiration.

The combinations are numerous and can determine complicated and refined ventilation modes, that can be understood starting from three basic modes of ventilation largely used in intraoperative settings: volume-controlled ventilation (VCV), pressure-controlled ventilation (PCV) and pressure-support ventilation.

- Volume-control ventilation (VCV)

  Volume-control ventilation is an assist-control mode, in which the patient-triggered component can be either pressure or flow and the ventilator-triggered component is set by selecting the respiratory rate. It is a time-cycled, volume-targeted ventilation mode where a desired tidal volume is delivered by means of a constant flow with a square waveform. Volume increases linearly until the desired tidal volume is achieved within an allowed inspiratory time; once V_T has been delivered the expiratory valve is opened allowing passive expiration [8].

- Pressure-control ventilation (PCV)

  Pressure-control ventilation is an assist-control pressure-targeted, time cycled ventilation mode, where the desired inspiratory pressure is delivered and maintained throughout inspiration. To achieve the pressure square wave the ventilator provides a high inspiratory flow, that then decreases over the course of inspiration to maintain the constant inspiratory pressure. Once the set inspiratory time has been reached, pressure the expiratory valve is opened to allow expiration [8].

  The main difference between VCV and PCV is that the former delivers a set amount of tidal volume, without controlling the inspiratory pressure, while the latter delivers a set amount of inspiratory pressure but does not assure a minimum tidal volume. Given the relationship described by the equation of motion between the three variables of volume, flow and pressure, the two modes wouldn’t be significantly different if there weren’t any changes in the respiratory system.

  In fact, if characteristic of the respiratory system, such as resistance and compliance, change during surgery, PVC and VCV modes respond differently. In VCV changes will be reflected in changes in pressure that could increase and reach possibly dangerous values. In PCV the same changes will influence the tidal volume, possibly shifting it from the safe range [12].

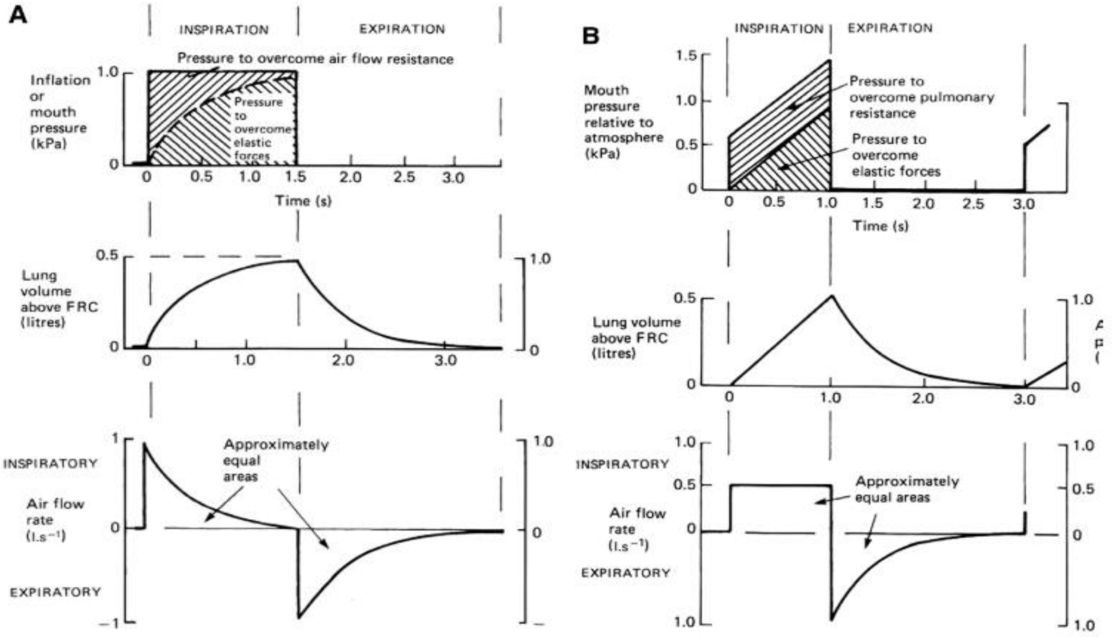


Figure 10 Pressure (A) and volume (B) control ventilation mode

- Pressure-support ventilation (PSV)

Pressure support ventilation is a pressure-targeted mode, that delivers and maintains a set amount of inspiratory pressure during inspiration. PSV differs from PCV because it is patient triggered only: the ventilator recognises an inspiratory effort initiated by the patient using a flow or pressure trigger and delivers flow to achieve the set pressure support during inspiration. Expiration is commenced once inspiratory flow drops below a set threshold, defined as a percentage of peak inspiratory flow, thus inspiratory time varies following changes in respiratory system resistance and compliance as well as patient respiratory effort [12].

During minor surgical procedures anaesthesia is not as deep and an adequate respiratory drive is maintained, thus mechanical ventilation aims at decreasing the work of breathing by assisting the spontaneously breathing patient. Furthermore, PSV allows for the definition of a backup rate, so that if the patients doesn’t trigger a spontaneous breath inside a limited time frame, the ventilator will trigger a breath. This feature takes into account changes in the respiratory drive resulting from the deepening of anaesthesia, also allowing to assess it together with the adequacy of analgesia by monitoring the changes in respiratory rate [13].

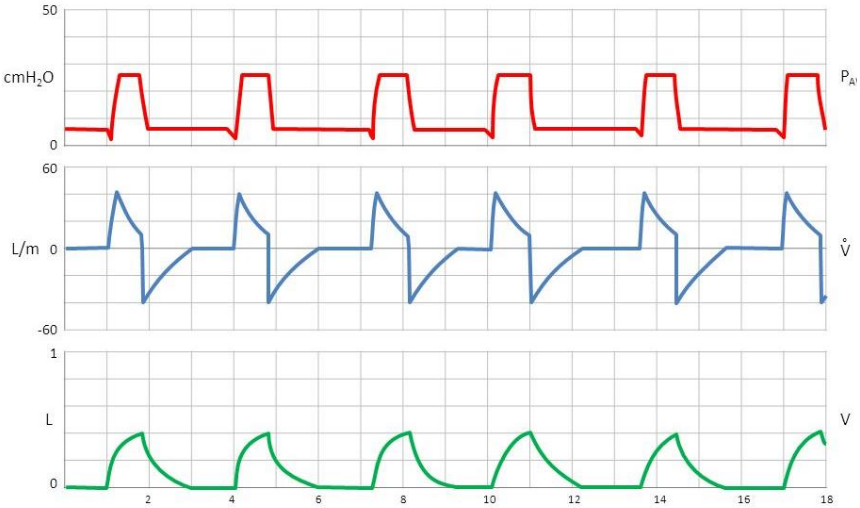


Figure 11 Pressure, flow and volume recordings in pressure support mode

Given that the number of ventilation modes has grown exponentially in the last three decades and that there is a multitude of different names identifying them on different ventilator brands, a novel classification system for modes of mechanical ventilation by identifying similar characteristics has been defined. This taxonomy is based 10 maxims that describe the theoretical framework of mechanical ventilation and three basic components: the ventilator breath control variable, the breath sequence and the targeting scheme [14]

Intraoperative protective mechanical ventilation

Postoperative pulmonary complications (PPC) affect approximately 5% of patients undergoing surgery and intraoperative mechanical ventilation plays an important role in their development. For this reason, the use of protective ventilation strategies such as low tidal volumes, positive end-expiratory pressures (PEEP) and recruitment manoeuvres (RM) has spread widely [15].

PPCs include a number both fatal and nonfatal respiratory events, such as respiratory failure and pneumonia, developed within 5 to 7 days after surgery. The prediction of such events is useful for planning perioperative strategies aimed at their prevention. Studies have led to determine that 50% of the risk factors for PPCs are associated to the patient’s health, while the remaining 50% are related to surgery and anaesthesia.

Furthermore, the presence of closed, recruitable and overdistended regions, induced by surgical conditions, make the lung more vulnerable to the negative effects of mechanical stress and strain induced by ventilation, that can result in ventilator-induced lung injuries and lung inflammation, partly depending on the duration of mechanical ventilation.

The majority of patients undergoing general anaesthesia develop atelectasis that can persist after surgery. Atelectasis is a result of a number of different mechanisms that develop during general anaesthesia, such as collapse of small airways and impairment of a correct alveolar function.

- Tidal volumes

  Perioperative protective ventilation strategies have been heavily influenced by those used during mechanical ventilation in patients suffering from acute respiratory distress syndrome. As a result, average tidal volumes used in intraoperative mechanical ventilation have been reduced to a range of 6 to 9 ml/kg of the patient's ideal body weight, aiming at reducing overdistension of the lung.

- Positive end expiratory pressure (PEEP)

  In numerous circumstances the application of a positive end-expiratory pressure is associated with reduced atelectasis and improved oxygenation, and it prevents the repeated opening and closure of small airways, avoiding the consequences of lung derecruitment associated with low tidal volumes thus protecting against ventilator-induced lung injury (VILI). However, there are several different approaches to setting PEEP, calling for a more patient-specific approach to its definition based on oxygenation, mechanical properties of the respiratory system and distribution of ventilation. Nonetheless a small level of PEEP, associated to low tidal volume, benefits most surgical patients because it improves gas-exchange and helps prevent VILIs.

- Lung recruitment manoeuvres (RM)

  Lung recruitment manoeuvres are ventilatory strategies that respond to the need for a mean to open collapsed lung areas without excessively increasing PEEP, who in turn counteracts alveolar derecruitment associated to low tidal volumes. Recruitment manoeuvres are based on the knowledge that applying high pressures at the airways opens the lungs, while PEEP allows to keep them open in time. The selected peak inspiratory pressure used to reopen collapsed area can be achieve either through a sustained inflation for up to 40 seconds or through stepwise increments in pressure.

Recruitment manoeuvres are routinely used at various stages during intraoperative mechanical ventilation and many studies show that they are effective in reducing the incidence of PPC, however it is not clear which RM is the best, given that the response to lung recruitment effectiveness also depends on patient specific characteristics [16].

2.2.3 Breathing circuit

The breathing pattern defined by a selected ventilatory mode is delivered to the patients through a breathing circuit. It represents the functional centre of the system since it is physically and functionally connected to each of the other components and to the patient's airway, there is a one-directional flow between the breathing circuit and both the anaesthesia machine and the scavenger system, and a bidirectional flow with both the patient and the ventilator [11].

During inhalation gas from the ventilator, or reservoir bag, flows to the patient's lung through the input line of the breathing circuit; during exhalation oxygen poor and carbon dioxide rich air flows through the expiratory line and is then rebreathed by the patient after going through a carbon dioxide absorbent. In the circle breathing system fresh gases, which contain zero water vapor, are humidified and heated by mixing with the rebreathed air.

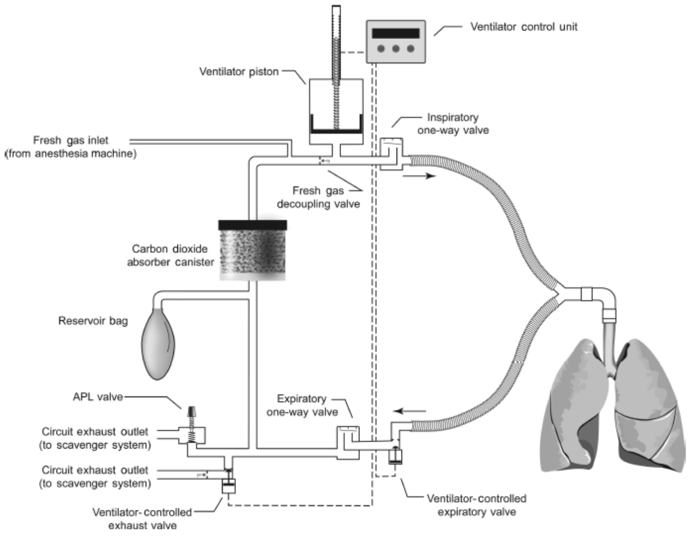


Figure 12 Anaesthesia breathing circuit

The semi closed circle system includes: two one way valves, a reservoir bag, a CO_2 absorption cannister, an adjustable pressure-limiting valve (APL) and tubes connecting to all the other components of the anaesthesia ventilator.

One-way valves

The one-way valves establish the direction of gas flow in the breathing circuit.

During inspiration the patient inspires fresh gas and gas stored in the reservoir bag which flow through the carbon dioxide absorption cannister first and then through the one-way inspiratory valve. During expiration the gas flows from the patient through the one-way expiratory valve to the reservoir bag.

The use of a fresh gas flow (FGF) decoupling valve channels the continuous fresh flow of gas away from ventilator-delivered gas. During inhalation gas dispensed from the ventilator travels directly through the inspiratory valve, while a passive decoupling valve blocks retrograde flow and fresh gas travels toward a non-pressurized portion of the breathing circuit. During exhalation the one-way expiratory valve opens and the ventilator piston withdraws to actively fill with a mix of fresh gas and gas from the reservoir bag, which fills and empties throughout the ventilator cycle. This allow for conservation of anaesthetic gases and vapours, allowing for very low fresh gas flows.

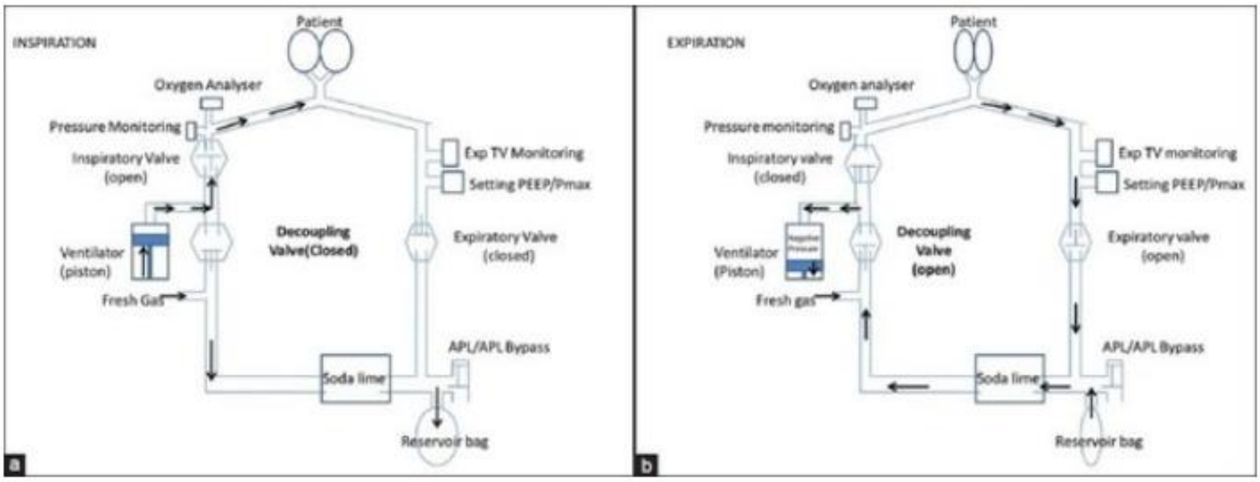


Figure 13 Inspiration and expiration in a ventilator with fresh gas flow decoupling valves

Adjustable pressure level valve (APL)

The adjustable pressure valve allows for the exhaustion of excess gas through the scavenger system. It is called adjustable because its opening pressure can be selected and changed by the operator. It is usually closed during inspiration and it opens during expiration to avoid over filling the reservoir bag.

2.2.4 Airway devices

The breathing circuit is connected to the patients via tubes that have an inspiratory and an expiratory limb, connected to the respective one-way vale, which meet at the patient end in a Y shape. A filter, either a simple bacterial filter or a humidity and moisture exchange filter (HME), is placed between the Y of the patient circuit and the selected airway device to avoid contamination.

Airway devices serve three main purposes:

1. Maintaining patency of the airway
2. Protecting the lungs from contamination such as gastric content and blood
3. Allowing ventilation of the lung

Endotracheal Tube (ETT)

The endotracheal tube is a PVC tube placed between the vocal cords and through the trachea. The tubes come in different sizes that are defined by their inner and outer diameter, the narrower the tube, the greater the resistance to airflow. Once the ETT is in the correct placement, the cuff placed at the distal end is inflated to produce a seal against the trachea wall, thus preventing contamination of the lung and facilitating positive pressure ventilation.

The ETT is the most effective and safe method for securing an airway, however it has a higher risk of airway trauma and its placement calls for a high level of anaesthesia, including muscle relaxation.

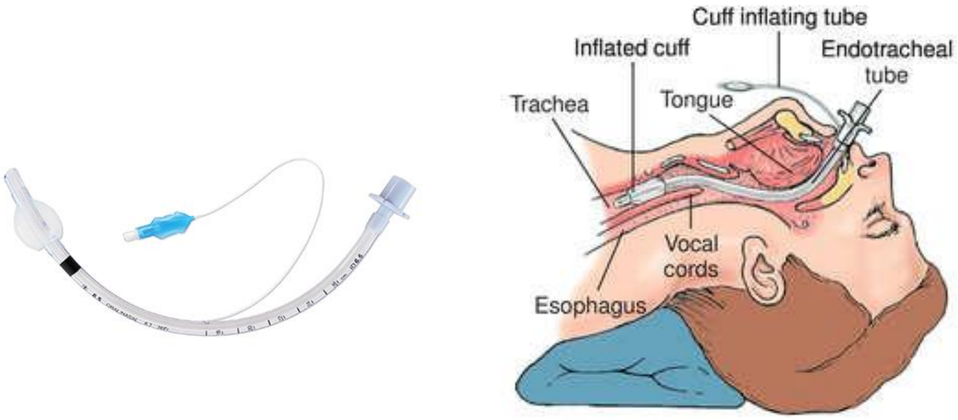


Figure 14 Endotracheal tube and positioning inside the airways

Laryngeal mask airway (LMA)

Supraglottic airway devices are less invasive than ETTs but still provide an effective seal of the upper airways, allowing for a correct ventilation of the lung.

Laryngeal mask airway is the most widely used supraglottic airway device and it is made up if a tube with an inflatable mask with an open front. When the mask is in the correct position the opening lies over the glottis and the distal part is placed against the upper portion of the oesophagus and inflation of the mask effectively seals off the trachea avoiding contamination and allowing ventilation.

The classic LMA has been modified throughout the years to provide an increasing effectiveness and control of the seal.

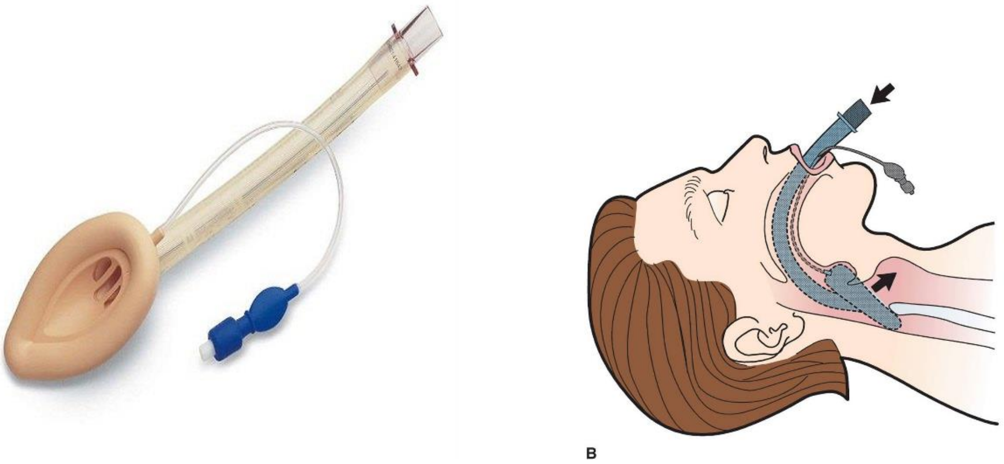


Figure 15 Laryngeal mask and positioning inside the airways

The laryngeal mask airway and the endotracheal tube both present advantages and disadvantages and are best suited to different intraoperative situations and patients.

The laryngeal mask is more easily placed and represents a valid solution to intubation of difficult airways, is better tolerated in less anaesthetized patients. However, it usually achieves a lower seal pressure and has a higher frequency of gastric insufflation than an endotracheal tube.

2.3 General anaesthesia and the paediatric patient

Many respiratory adverse events in paediatric anaesthesia are directly attributable to the effect it has on the respiratory system. In fact, anaesthesia, as in adults, has different adverse effects on respiratory drive, ventilation/perfusion mismatching and tidal breathing, that can lead to an impaired gas exchange in the lungs.

In the intraoperative setting all children which undergo general anaesthesia require some type of invasive mechanical ventilation, even though many of them present a normal pulmonary function.

Even though mechanical ventilation is a common and widespread practice in paediatric anaesthesia, it should be taken into account that the respiratory system of infants and young children present a number of age-related characteristic that put them more at risk of adverse events related to general anaesthesia and mechanical ventilation.

These age-related differences make a specific approach to paediatric necessary, rather than applying the same strategies used in adult patients.

A specific focus will be directed toward the use of recruitment manoeuvres in the intraoperative setting.

2.3.1 Differences between children and adults

Infants and children present a number of age-related characteristics of their respiratory physiology that put them at higher risk during general anaesthesia.

- Immaturity of the control of breathing

- Protective reflexes
- Smaller size and higher collapsibility of the upper and lower airways
- Lower efficiency of the respiratory muscles
- Lower surface area for gas exchange
- Altered balance between lung and chest wall compliance

While these differences are more prominent during the first two years of life, the development of the respiratory system is a gradual process that spans all throughout childhood and adolescence, hence specific age ranges are difficult to define and particular attention should be placed to all paediatric patients.

Most importantly infants and children are characterized by lower FRC, as a result of the fact that the outer recoil of the chest wall is lower than in adults, while the inward recoil of the lung is not significantly different from adult values. These differences result in a shift FRC toward the lower inflection point of the pressure-volume curve, placing children at a higher risk of derecruitment and atelectasis.

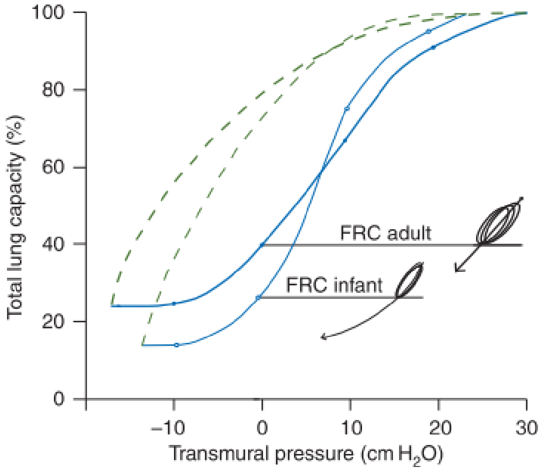


Figure 16 Adult and infant pressure-volume curve

In the awake and asleep state, the reduction of FRC is counterbalanced by a number of mechanisms actively elevating it; as in adults, the induction of general anaesthesia, together with the supine positioning, causes an ulterior reduction of FRC. However, paediatric patients are more at risk of atelectasis in dependent lung regions, since their FRC at rest is much closer to the lower portion of the pressure-volume curve.

Given that in children chest wall compliance is much larger than lung compliance, C_{RS} reflects primarily lung compliance. Airway closure and microatelectases cause the pressure-volume curve of the lung to be flattened and shifted to the right during anaesthesia, meaning that greater pressures are needed to maintain a given lung volume, while there is a decrease in compliance. Furthermore, the reduction in FRC decreases airway diameter, increasing airway resistance.

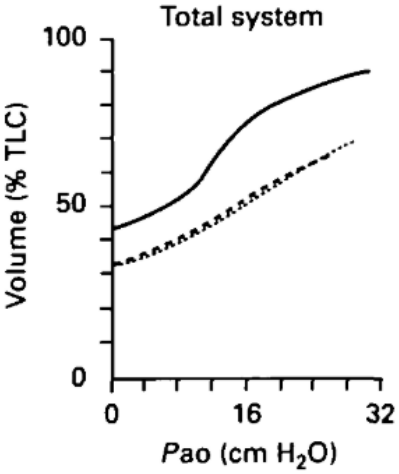


Figure 17 Pressure-volume curve in awake (solid line), anaesthetised (dashed line) and paralyzed (dotted line) patients

2.3.2 Intraoperative mechanical ventilation and lung protective strategies

Ventilation strategies used in adult patients are routinely applied in paediatrics, with adjustments that are mainly the result of personal experience, given the low number of scientific researches aimed at defining the best approach in paediatric anaesthesia.

Historically anaesthesia ventilators weren’t able to deliver precise tidal volumes due to the compliance of the breathing circuit, mainly due to gas compression and distensibility of the tubing, with increasing pressure during inspiration, compression of the gas results in a portion of the delivered volume to not reach the patient.

This represented an important drawback to volume controlled ventilation in paediatric, given that the lack of accuracy and precision in delivering the set amount of tidal volume has a greater impact the lower the tidal volumes. However, modern anaesthesia ventilators have implemented different methods to compensate for compliance of the breathing system, nonetheless pressure control ventilation modes remain the preferred setting in intraoperative mechanical ventilation [17].

In accordance with practice in the intraoperative setting with adult patients and clinical experience, lung protective ventilation strategies, typical of the ICU setting, are part of routine practice also in the paediatric setting.

Lung protective ventilation strategies, such as PEEP, the use of low tidal volumes and recruitment manoeuvres, are a crucial part of preventing atelectasis and postoperative pulmonary complications, however, hard evidence as to which values and strategies are the best is not available. Nonetheless there are recommendations in place which advocate for the use of tidal volumes between 6-8 ml/kg of ideal body weight and a PEEP of 5 cmH_2O during intraoperative mechanical ventilation.

2.3.3 Recruitment manoeuvres

Lung recruitment manoeuvres are characterized by a deliberate increase in transpulmonary pressure to maximise the number of alveoli participating in gas exchange by re-opening atelectatic regions of the lung, thus improving oxygenation and end-expiratory levels, and reducing the incidence of ventilator induced lung injuries.

Given the high incidence of atelectasis both in adults and even more so in children, recruitment manoeuvres are part of routine practice in the operating room, however there is no decisive consensus on which recruitment strategy is the most effective, furthermore especially in the paediatric patients the high pressures involved in most RMs could potentially lead to overdistension of proximal regions [16].

Throughout the years different recruitment manoeuvres have been used in the intraoperative setting; most of them can be subdivided into two main groups: sustained inflations and stepwise approaches.

The sustained inflation (SI) has been commonly used throughout the years and it consists in increasing inspiratory pressure up to 30-40 cmH_2O and holding it for 15-20 seconds, this can be achieved either automatically using the ventilator’s CPAP setting or manually by using the anaesthetic bag. The rationale behind the use of SI is to overcome the closing pressure of the alveoli, which are then kept open thanks to the use of an appropriate PEEP. Even though SI is predominant among the recruitment manoeuvres, several studies have shown that, if used without care and for too long period of times, does not succeed in its goal and could lead to complications. Furthermore, steep increases in inspiratory pressure are less tolerated than a graded rise in pressure [18]. However, it has been shown that SI represents an effective way of opening up the lung [19], thus further research is needed to determine the effectiveness of a recruitment manoeuvre, such as sustained inflation, and the optimal conditions for its practice.

Stepwise approaches respond to the issue of steep and prolonged increases in inspiratory pressure, that can lead to excessive increase in volume and overdistension. Stepwise approaches include the manipulation of PEEP and/or peak inspiratory pressure (PIP), while monitoring parameters such as oxygenation or by observation of changes in the pressure-volume curve, to determine the best combination of PEEP and PIP [20]. Another stepwise approach is the use of repeated inflations which consist in a set number of breaths between a higher level of PEEP and high inspiratory pressure, such as the ones reached in SI [21].

The effectiveness of recruitment manoeuvres can be assessed by comparing several outcomes measures before and after the RM.

Recruitment strategies are the object of numerous studies, both in healthy and non-healthy adults, as well as children (Table 1). However, the specific recruitment manoeuvres, the outcome measures, and the study population are often very different between studies, making it harder to compare the effectiveness of different recruitment strategies as a whole. Nonetheless these studies provide useful information on the effects of recruitment strategies in different settings and on the mean used to assess their effectiveness.

In particular, the optimal recruitment strategy in the intraoperative setting is likely to be different from the optimal one in the paediatric intensive care unit, given that the amount of derecruitment and the recruitability of healthy and diseased are different. In addition, in the intraoperative setting, paediatric patients are mostly connected to the breathing circuit using laryngeal mask airways (LMA) which offer less seal to high pressures than endotracheal tubes.

Study	Population	RM	Outcome measures	Results
Marcus et al. (2002) [22]	Age: < 2 years Healthy Intraoperative general anaesthesia	TRIM: 30 cmH_2O for 10 seconds	C_{DYN} R_{AW}	C_{DYN} increased by 30% No significant changes in R_{AW}
Tusman et al. (2003) [21]	Age: 6mo-6yrs Healthy General anaesthesia for cranial MRI	3 groups: ZEEP (no PEEP or RM) CPAP (PEEP of 5 cmH_2O) ARS (10 breaths between PEEP = 15 cmH_2O and PIP=40 cmH_2O)	% of atelectatic regions through lung MRI	Lower percentage of atelectatic regions in ARS group
Boriosi et al. (2012) [23]	Age: 0.1-15yrs Acute lung injury (ALI) Paediatric intensive care unit (PICU) Mechanical ventilation during CT	Incremental PEEP	% of aerated lung PaO_2/FiO_2 $PaCO_2$ Oxygenation index (OI)	Variable increase in % of aerated lung Increase in PaO_2/FiO_2 Decrease in $PaCO_2$ Decrease in OI
Boriosi et al. (2011) [24]	Age: 1-14yrs ALI and ARDS PICU	Incremental PEEP	PaO_2/FiO_2 $PaCO_2$ Peak inspiratory pressure (PIP)	Persisting increase in PaO_2/FiO_2 Significant decrease in the short term of $PaCO_2$ Persisting decrease in PIP
Duff et al. (2007) [19]	Age: 11 days – 14yrs Healthy and non-healthy PICU	Sustained inflation: 30-40 cmH_2O for 15-20 seconds Post circuit disconnection, hypoxia, suctioning or routinely every 12 hours	FiO_2	Decrease in FiO_2 requirements
Wolf et al. (2012) [25]	Age: 4.9-17.3yrs ALI PICU	SI: 40 cmH_2O for 40 seconds Stepwise RM: PEEP and P_{PLAT} increased by steps of 5 cmH_2O	Regional atelectasis C_L Regional overdistension PaO_2/ $PaCO_2$	Significant lung overdistension Stepwise RM more effective in improvement of oxygenation and reversal of atelectasis
Song et al. (2017) [26]	Age: 2-12 months Healthy General anaesthesia	2 groups: No RM Ultrasound guided stepwise RM: P_{AW} increased by steps of 5 cmH_2O	Lung ultrasound scores for atelectasis	Lower atelectasis in patients in RM group Negative correlation between atelectasis and age

Table 1 Studies investigating the effects of recruitment manoeuvres in children

3. Assessment of respiratory function

Measurements of lung function are necessary to determine whether therapy improves mechanical function and are essential in determining the natural history of many respiratory diseases.

In the intraoperative setting the mechanics of breathing helps understand the underlying issues involved in general anaesthesia and mechanical ventilation and assess the effectiveness of ventilation modes and strategies both in the healthy and non-healthy patient.

Classic methods of assessing respiratory function in awake patients involve the use of a spirometer or a pneumotachograph and require active participation of the subject [27], therefore they are not suitable for use in awake children or in the intraoperative setting were the patient is undergoing general anaesthesia.

Assessment of lung function in mechanically ventilated patients undergoing general anaesthesia is, by definition, not possible using methods which require active participation of the subject. With regards to anaesthetized and mechanically ventilated patients many different methods of assessing lung function and mechanics have been used: from simple monitoring of oxygenation, to imaging of the lungs and methods based on chest-wall motion.

However, many classical methods used to assess lung function and mechanics during mechanical ventilation in the intensive care unit are not suitable in the intraoperative setting, given that in the latter measurements have to take place in the operating room and without creating a disturbance to the surgical procedure.

A technique that is better suited to measure respiratory mechanics during surgery is the forced oscillation technique (FOT), given that it does not interfere with ventilation, allows continuous monitoring and it can be integrated inside the breathing circuit of an anaesthesia machine.

3.1 Plethysmography

Different types of techniques based on plethysmography are described in literature regarding the assessment of respiratory function both during the awake state and mechanical ventilation.

Whole body plethysmography has been regarded as the standard method for assessing FRC and airway resistance (R_{AW}) [28], but the fact that it has to be carried out in a sealed box is both a reason for non-compliance of paediatric patient and for it not being a suitable method in an intraoperative setting.

Respiratory inductive plethysmography (RIP) allows for the measurement of changes in the cross-section of the ribcage and abdomen through the use of two elastic bands around the chest and abdomen. These elastic bands contain a wire which is made up in a way that forms a coil, thus generating a weak magnetic field, that changes because of movement of the chest and abdomen, together with its inductance. Measurement of changes in inductance reflect changes in lung volume. While it’s a non-invasive technique that can measure lung volume and breathing pattern changes during mechanical ventilation, it is not suited for the intraoperative setting since the elastic bands could be a disturbance inside the surgical field. Furthermore, a patient-specific and positioning dependant calibration is needed, which is based on the assumption that the system has only two degrees of freedom, which could not be the case, especially in young children. It has also been shown that, compared to other lung volume assessment techniques, RIP is not as consistently precise and is affected by a high and unstable baseline drift [29].

Optoelectronic plethysmography (OEP) uses passive reflective markers placed on the patient’s skin to measure changes of shape and dimension of the chest wall, thus determining lung volume, by means of cameras and LEDs [30] . Although it is a non-invasive technique that allows for a more accurate estimation of lung volumes than RIP, it is not suitable for surgical setting because of the set up needed represents an obstacle in the operating room.

3.2 Tomography

Computed tomography (CT) and electrical impedance tomography (EIT) are imaging techniques that can be used to assess regional lung aeration.

Analysis of lung CT scans allow for a quantitative definition of differently aerated lung regions, making it a technique able to measure atelectasis, overdistension and it is used to assess the effectiveness of lung protective ventilation strategies such as different levels of PEEP and tidal volumes and recruitment manoeuvres [31] [32]. Although computed tomography is widely used in respiratory function assessment also during mechanical ventilation, it is not suitable for the intraoperative setting given that it is carried out using machinery that would take up space in the operating room. Furthermore, it does not allow for continuous monitoring.

The use of electrical impedance tomography in assessing lung aeration is based on the knowledge that changes in regional aeration modify the electrical properties of lung tissue [33]. These changes can thus be measured using surface electrodes and can be used to assess the effectiveness of recruitment manoeuvres, define optimal levels of PEEP and more generally evaluate the effects of mechanical ventilation [25]. However, it is not suitable to a wide range of surgical setting since the positioning of the surface electrodes and the leads could be in the way of the surgical procedure and movement of the patient during surgery can disturb the measurement. Furthermore, it only allows for imagining of one portion of the lung based on the positioning of the surface electrodes.

3.3 Respiratory mechanics measurement

While plethysmography and tomography are methods that allow for measurement of lung aeration and lung volume, they do not allow for direct measurement of the mechanical properties of the lung.

Techniques for the measurement of respiratory mechanics can be classified in two main groups: static or quasi-static and dynamic methods.

Static and quasi-static methods

Static and quasi-static techniques are used to determine the static pressure-volume (P-V) curve of the respiratory system that describes the mechanical behaviour of the lung and chest wall during inhalation and exhalation [34]. There are three main techniques used to acquire the data to construct the P-V curve: the supersyringe method, the constant-flow method, and the multiple occlusion method.

- Supersyringe method

The supersyringe method consist in disconnecting the patient from the ventilator and connecting a supersyringe to the end of the endotracheal tube. Starting from FRC the supersyringe is used to inflate the lung by regular volume steps (usually about 100 mL) while measuring airway pressure using a pressure transducer, then the same procedure is followed for deflation of the lung. Recorded pressure and volumes are used to construct the P-V curve and determine static compliance of the respiratory system (C_{RS}) and lower and upper inflection points [34]. The obvious drawback of the supersyringe method is that it requires a temporary disconnection of the patient from the mechanical ventilator.

- Constant-flow method

The constant flow method overcomes the main disadvantage of the supersyringe method by using the ventilator to deliver a constant flow to inflate the respiratory system [34]. However, it has been shown that the use of high flow determines a shift to the right of the P-V curve, which is particularly evident at higher volumes. Furthermore, the use of low flows increase the time needed to perform the measurement, causing an increase in hysteresis imputable to the effects of continuing gas exchange and oxygen consumption.

- Multiple occlusion technique

In the multiple occlusion technique tidal breathing is periodically interrupted at different volumes, which are plotted against the record pressure at the same instant to construct the P-V curve [34]. While it does not call for disconnection of the patient and it is not affected by continuing gas exchange and oxygen consumption, it is based on the assumption that end-expiratory levels are stable and muscle activity is totally absent. Furthermore, the fact that it uses multiple breaths in a periodic manner increases considerably the time needed to conduct the measurement.

Dynamic methods

Measurements of dynamic respiratory mechanics is better suited for the description of changes in the respiratory system during mechanical ventilation. The main methods used to measure compliance and resistance are multilinear regression analysis, single-occlusion technique, interrupter technique and forced oscillation technique.

- Multilinear regression analysis

Multilinear regression analysis is based on measurement of pressure and flow during mechanical ventilation and analysing the data by fitting the equation of motion of the respiratory system:

$$P_{AO} = \frac{V}{C_{RS,DYN}} + \dot{V}R_{RS} + EEP \tag{5}$$

Where P_{AO} is the pressure at the airway opening measured using a pressure transducer, $\dot{V}$ is the flow measured using a pneumotachograph (PNT), EEP is the end-expiratory pressure, and $C_{RS,DYN}$ and R_{RS} are respectively the dynamic compliance and resistance of the respiratory system [7] .

This method is non-invasive and does not interfere with the breathing pattern set by the ventilator, however it is strongly affected by the activity of respiratory muscles and it relies on a single compartment model of the respiratory system, which does not account for the viscoelastic properties of the lung tissue and chest wall.

- Single occlusion technique

Similarly to the multiple occlusion technique the single occlusion technique is based on the occlusion of the airway at the end-inspiratory part of tidal breathing and on the recording of pressure and flow to assess passive mechanics of the total respiratory system [35].

Assuming that expiration is passive the time constant can be calculated based on the flow-volume plot, while C_{RS} is calculated as the ratio between tidal volume and the difference between the plateau pressure reached and the applied PEEP. Finally, resistance of the respiratory system (R_{RS}) is the ratio between the compliance and the time constant of the respiratory system.

While SOT is a simple and non-invasive technique it relies on the assumption that the lung can be described by a single time constant and it calls for total relaxation of the respiratory muscles.

- Interrupter technique

In the interrupter technique airflow in interrupted and airway resistance is estimated as the ratio between change in mouth pressure occurring during the interruption and airflow measured right before the airflow interruption [36]. This technique is based on the assumption that if the airway is suddenly occluded during tidal breathing, the change in pressure at the mouth opening equals the resistive pressure drop across the airways. This technique is based on a simple single compartment model, which significantly simplifies the mechanics of the respiratory system, however, the same technique has been used with more refined models. These models can be used to further explain the fact that the very rapid drop in pressure is followed by damped pressure oscillation and then a slow rise, which can be reflective of the resistance of different parts of the airway.

- Forced oscillation technique

The forced oscillation technique (FOT), first introduced by Dubois et al. [37], is set apart from other methods used to measure respiratory mechanics not only by the fact that it is a non-invasive technique that does not require active participation of the subject, but also by the fact that it is based on the use of external driving forces which are superimposed to normal breathing and are used to investigate the mechanics of the respiratory system.

FOT relies on linear system analysis, meanwhile the respiratory system can be non-linear. The requirement of linearity calls for the use of small-amplitude oscillation (usually around 2 cmH_2O), while they should also guarantee a high enough signal to noise ratio and not cause discomfort in the patient.

The mechanical response of the respiratory system to the driving forces is studied by means of the impedance (Z), which is the ratio between the applied pressure (P) and the resulting airflow ($\dot{V}$) in the frequency domain (6).

$$Z(f) = \frac{P(f)}{\dot{V}(f)} \tag{6}$$

Z is a complex number that represents both the in phase and out of phase relationships between pressure and flow. Therefore, the impedance is usually characterized by means of oscillatory resistance (R) and reactance (X), which are respectively the in phase or and out of phase components of impedance (7).

$$Z = R + iX \tag{7}$$

Resistance is the real part of impedance and it describes the dissipative mechanical properties of the respiratory system and is interpreted as the resistance of both airway and tissue.

On the other hand, reactance is the imaginary part of impedance and it describes the energy storage capacity of the respiratory system and is determined by both the compliance (C) and inertance (I) of the respiratory system.

The respiratory system can be modelled by a two port system which has one port as the airway opening and the other as body surface. Depending on where pressure and flow are measured two different types of impedances can be found. When both pressure and flow are measured at the airway opening the impedance is called input impedance (Z_{IN}) while if they are measured at two different ports the impedance is called transfer impedance (Z_{TR}). If the forcing signals are sized in order to keep the system behaving linearly, the two transfer impedances are equivalent.

$$Z_{IN} = \frac{P_{AO}}{\dot{V}_{AO}} \quad ; \quad Z_{TR} = \frac{P_{AO}}{\dot{V}_{BS}} = \frac{P_{BS}}{\dot{V}_{AO}} \tag{8;9}$$

The internal connections between the two ports can be modelled using a T-network, with three different blocks that account for impedances of different components of the respiratory system and can be further modelled by lumped parameters using resistance capacitance and inductance.

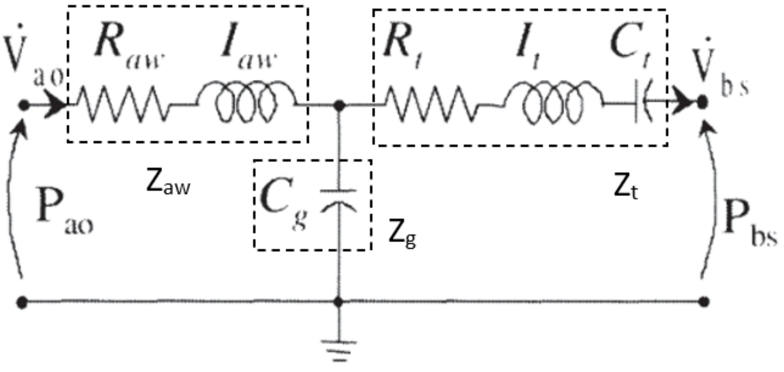


Figure 18 Two-port model of the respiratory system

If alveolar gas compressibility, represented by Z_g or C_g, is negligible, the model can be further simplified to a RIC model, where $R_{RS} = R_{AW} + R_T$, $I_{RS} = I_{AW} + I_T$ and $C_{RS} = C_T$. Pressure of the respiratory system corresponding to P_{AO} when P_{BS} is equal to atmospheric pressure, leading to the definition of the input impedance of the respiratory system as (10):

$$Z_{RS} = \frac{P_{AO}}{\dot{V}_{AO}} = R_{RS} + i\left(\omega I_{RS} - \frac{1}{\omega C_{RS}}\right) \tag{10}$$

The real part of the impedance of the respiratory system is the resistance of the total respiratory system (R_{RS}), both airway and tissue, and does not show a frequency dependence, while the imaginary part of the impedance, the reactance (X_{RS}), is dependent on frequency and accounts for the inertial and elastic properties of the respiratory system.

At lower frequencies reactance is dominated by compliance while at higher frequencies inertance is dominant.

It is apparent then that different frequencies of the forcing signal reveal different mechanical properties of the respiratory system, impedance calculated using lower frequencies is reflective of mechanical properties of tissue and lung periphery, while the use of higher frequencies provides information about the upper airways. Most commonly clinical application of FOT use a frequency higher than quiet breathing frequency, so that the measurement of respiratory impedance does not interfere with the breathing pattern. While much higher and lower frequencies can be used, they usually include components in the range of the breathing pattern and thus cannot be applied during spontaneous breathing.

A classical set-up used on spontaneously breathing patients is made up of a loudspeaker which generated the oscillations, a pneumotachograph and a pressure transducer which record flow and pressure [38].

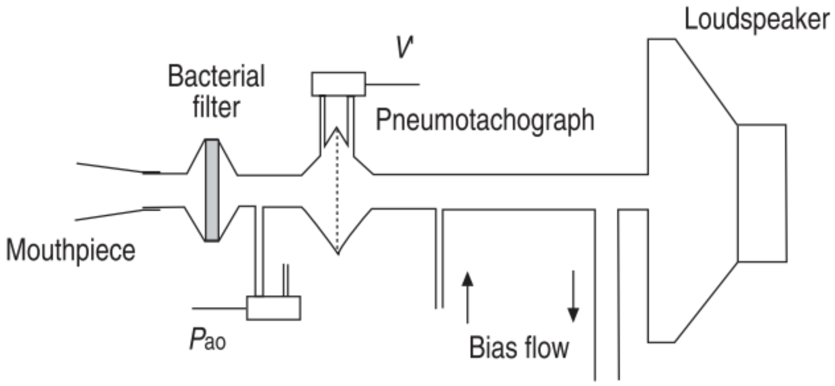


Figure 19 Traditional FOT set-up

Forced oscillation are delivered by means of a mouthpiece to the patient, who is also wearing a nose clip and can breathe spontaneously through the mouth. For tracking of rapid changes in impedance and continuous monitoring oscillations with an amplitude of around 2 cmH_2O and a frequency of 5 Hz are used.

Given that the forced oscillation technique does not require the active participation of the subject and that the use of frequencies higher than breathing frequencies render the activity of the muscle pump, which operates at breathing frequency and its first harmonics, negligible, FOT represents a valid technique to assess respiratory mechanics is artificially ventilated patients regardless of the degree of activity of the respiratory muscles [39]. This is particularly important under general anaesthesia, where the deepness of the level of anaesthesia and analgesia can vary, not only between different patient but also during surgery.

The setup used to apply FOT during mechanical ventilation must be modified with the respect to the setup used in awake patients [40]. First of all the loudspeaker is connected in parallel to the ventilator, in order to deliver the forcing signal at the inspiratory line of the breathing circuit and it must also be able to withstand the high positive pressures involved in mechanical ventilation. This can be accomplished by enclosing the rear part of the loudspeaker in a chamber and connect it to the inspiratory valve of the mechanical ventilator. Pressure and flow are measured as close as possible to the patient which receives the ventilator defined breathing pattern and the superimposed oscillation generated by the loudspeaker.

FOT has been used as a mean to measure respiratory mechanics both during spontaneous breathing and mechanical ventilation in different studies both in healthy and non-healthy adults and children. The main focus of studies is varied: from defining reference values for healthy subjects, investigating changes in respiratory mechanics with age or disease, assessing the effects of general anaesthesia, to studies aimed at giving the tools to tailor ventilation strategies for every patient.

In particular, it has been shown that measurements of reactance at 5 Hz are sensitive and specific to changes in peripheral lung mechanics and have been used for the evaluation of lung volume recruitment [41], thus making it a valuable tool to assess the effectiveness of lung protective ventilations strategies such as recruitment manoeuvres.

Technique	Measures	Advantages	Disadvantages
Whole-body plethysmography	• FRC • Airway Resistance	Standard method	• Patient cooperation • Sealed-off environment
Respiratory inductive plethysmography	Changes in lung volume	Continuous monitoring	• Patient-specific calibration • Baseline drift • Elastic bands around thorax
Optoelectronic plethysmography	Changes in lung volume	• No drift • No patient-specific calibration	Cumbersome set-up
Computed tomography	Lung aeration	Quantification of aeration	Need of specific cumbersome machine
Electrical impedance tomography	Lung aeration	Non cumbersome	Single portion image
Supersyringe method	Static P-V curve	No patient cooperation	Temporary disconnection of patient
Constant flow method	Static P-V curve	No disconnection	• Interruption of ventilation • Affected by continuing gas exchange
Multiple occlusion technique	Static P-V curve	• No disconnection • Not affected by continuing gas exchange	• Time consuming • Requires stable EELV
Multilinear regression analysis	Dynamic compliance Resistance	No interference with breathing pattern	• Strongly affected by muscles activity • Relies on single compartment model
Single occlusion technique	Passive mechanics	No patient cooperation	• Assumption of single time constant • Requires total relaxation of muscles
Interrupter technique	Resistance	No patient cooperation	Assumption of rapid pressure equilibration
Forced oscillation technique	Resistance Reactance	• No interference with breathing pattern • Not affected by muscle activity • Continuous monitoring	

Table 2 Methods for measuring respiratory function and mechanics

4. Aim

The aim of the present study is the development and validation of a set-up to implement the forced oscillation technique in an intraoperative paediatric setting, which allows for the measurement of respiratory mechanics during surgery, giving a quantifiable indication of lung recruitment through analysis of changes in resistance and reactance. Thus, it opens to the possibility of evaluating the effectiveness of different ventilation strategies and lung recruitment manoeuvres and the effects of invasive surgery on the respiratory system.

The development of a FOT setup needs to meet a set of technical requirements, which allow the achievement of the correct implementation of the technique and give reliable measure of the respiratory mechanics. In the present study, the setup is constructed in a way that allowed for its use in the surgical paediatric setting, thus an in-vitro validation is necessary.

The validated setup is then in use in two different research trials, OASIS and COMET, at Perth Children's Hospital thanks to a collaboration between Politecnico of Milan and Telethon Kids Institute. In both studies, recordings of pressure and flow, with the oscillations superimposed, are carried out during surgery to monitor the effects of different recruitment manoeuvres, in the case of OASIS, and to evaluate the effects of insufflation of the surgical cavity during laparoscopic appendectomies, in the case of COMET.

5. Methods

Forced oscillation technique (FOT) is a viable mean to assess respiratory mechanics during general anaesthesia in the intraoperative setting and the analysis of data recorded during surgery can be used to assess the effects of mechanical ventilation strategies and surgical procedures on the paediatric patient.

Forced oscillations are superimposed on the breathing pattern delivered by the mechanical ventilator through a loudspeaker which is placed in parallel to the breathing circuit, while flow and pressure are recorded close to the patient's airway opening using a pressure transducer and hot-wire anemometer flow sensor.

A printed board comprised of different electronic components, which is controlled via a custom software, allows for the simultaneous control of the loudspeaker and recording of numerous signals.

The recorded pressure and flow signals are then analysed in order to compute resistance and reactance, changes in which can be indicative of the effect of intraoperative procedures on respiratory mechanics.

5.1 Requirement specifications

A set-up for the implementation of FOT must meet a number of general specifications [3] :

- The amplitude of the input signal generated by the loudspeaker should be large enough to ensure an acceptable signal to noise ratio, but not so large that it could provoke discomfort in the subject, nonlinear behaviour of the respiratory system or synchronization with the breathing pattern. An optimal level of peak to peak amplitude of the forcing signal is between 1 cmH_2O and 3 cmH_2O.
- The frequency of the forcing signal depends on the application, and in the case of routine clinical applications it is usually set above the breathing rate, in order to allow an intra-breath tracking of impedance changes. The optimal value for frequency of the forcing signal is greater than 4 Hz.

- The forcing signal is to be applied as close as possible to the airway opening and delivered via the airway device used in the particular clinical setting, either a mouthpiece, a face mask, a laryngeal mask or an endotracheal tube.
- Pressure and flow are to be measured at the airway opening with sensors which are sensitive to small changes in amplitude, in order to correctly measure low-amplitude oscillations. A hot-wire anemometer paediatric flow sensor, is able to detect small variations in flow in the paediatric range.
- Furthermore, the range of the sensors must be consistent with the pressure and flow values expected in the application. When FOT is applied during mechanical ventilation, the range of the pressure sensor, most commonly a pressure transducer, and that of the flow sensor should account for the high pressures and flows developed during mechanical ventilation.
- To check the overall accuracy of the measurement set-up a reference impedance is to be used, the value of which is comparable to that of the highest impedance measurement expected in the population involved in the study. In children the expected value is between 15-25 $cmH_2O/L/s$ and, after proper calibration, the error must not exceed 10%.
- The addition of the loudspeaker, its connections to the breathing system and the sensors used determine an increase in both the resistance to breathing and in dead space. Resistance of the added set-up, without the bacterial filter, should be less than 1 $cmH_2O/L/s$ at 5 Hz. Furthermore, the measurement should be compensated for the known resistances of the added set-up and the filter. Dead space including the bacterial filter should be less than 70 ml in pre-school children.

Furthermore, the set-up must also meet requirements related to its use during mechanical ventilation of patients undergoing surgery:

- The set-up is modified in order to withstand the high positive pressures generated during mechanical ventilation by enclosing the loudspeaker and connecting the rear portion to the inspiratory valve.
- The set-up should not interfere with the practices involved in surgical procedures.

The intended use of such a set-up in the intraoperative setting adds regulatory requirements as defined by hospital guidelines:

- The set-up must undergo electrical safety control periodically.
- The set-up and the added components, such as connectors, tubing and sensors must be chosen and cleaned accordingly to infection control procedures.

Finally, some additional requirements arise from the intended use of the set-up to collect measurements for a clinical study:

- The set-up should allow for continuous monitoring of the pressure and flow signal, as to ensure that artefacts, leaks or any type of problem in the set-up can be identified by the operator, who can then act accordingly.
- The whole set-up should be easy to prepare and connect to the anaesthesia ventilator.
- The software should be simple to use and adaptable to different study protocols.
- Furthermore, it should ensure correct and reliable saving of measurements.

The developed set up is made up of:

- A loudspeaker used as a generator of oscillations
- Means to acquire pressure and flow signals
- Software to apply FOT and to display and save all signals and parameters of interest

The specific setup developed is further described in the following chapter, both in its hardware and software components, highlighting characteristics specific to the paediatric intraoperative setting.

5.2 Measurement set-up

The set-up implemented in this study is summarized in Figure in which the main components are highlighted as:

- An enclosed loudspeaker, used to generate sinusoidal pressure oscillations
- A flow sensor
- The Florian neonatal respiration monitor, used to acquire the flow signal from the sensor
- A pressure transducer
- A power amplifier, to drive the loudspeaker
- An A/D-D/A board that allows both for the control of the loudspeaker and the acquisition of the data
- A laptop which is connected via USB to the A/D-D/A board
- A LabView software that allows to control the loudspeaker while also displaying and saving the acquired data

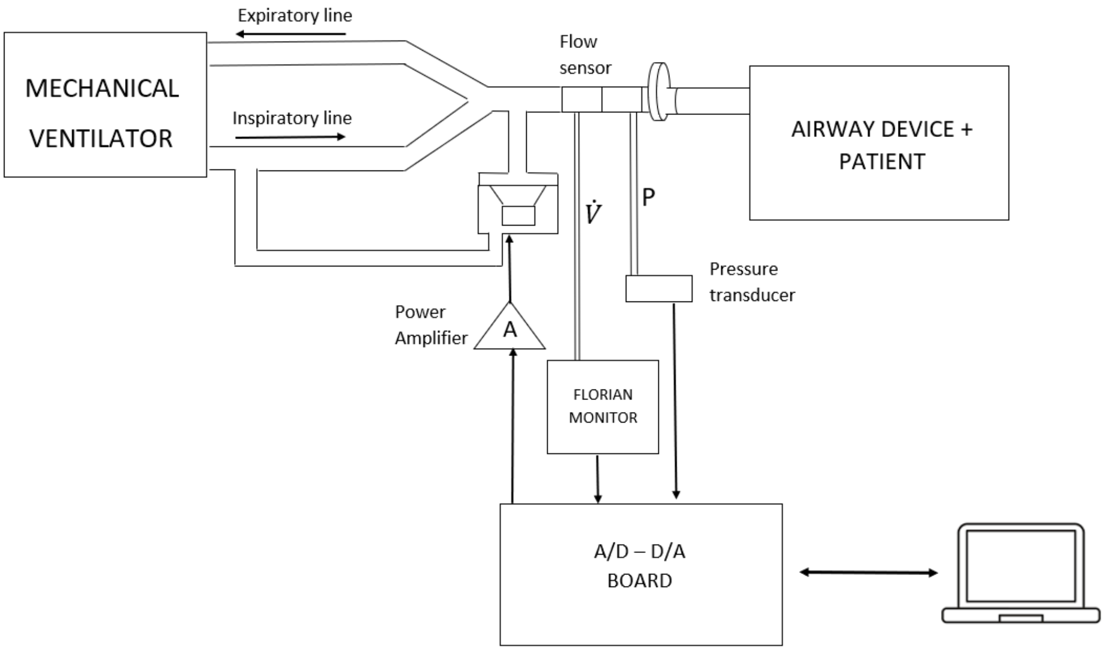


Figure 20 Schematic representation of the developed set-up

5.2.1 Hardware

The hardware set-up implemented is made up of:

- A loudspeaker (CW 170, Ciare)
- A power amplifier (XM-N502, Sony)
- A neonatal respiration monitor (FLORIAN, Acutronic)
- A paediatric flow sensor (ACUTRONIC Medical Systems AG)
- A pressure transducer
- An A/D- D/A board used to filter, acquire and transmit pressure and flow signals and to control the loudspeaker
- A laptop

Loudspeaker

The CW 170 loudspeaker is used to generate low amplitude sinusoidal oscillations at a set frequency, which are superimposed to the breathing pattern delivered by the mechanical ventilator. The oscillations are delivered by connecting the loudspeaker after the Y of the breathing circuit. The rear of the loudspeaker is enclosed in a chamber and connected to the inspiratory valve of the mechanical ventilator in order to allow it to withstand the positive pressures generated by the ventilator.

The connection of the loudspeaker to two different points of the breathing circuit is achieved by means of reusable smooth-bore tubing (15 mm ID, 1.8m length) and T connectors, which are connected to each other and to the loudspeaker by using appropriate connectors.

The loudspeaker, the gas enclosed in the box and the additional tubing represent an additional compliance to the breathing circuit, hence the tubing must be chosen accordingly and the circuit tested on the ventilator before applying it in a clinical setting.

The rear of the is connected between the inspiratory valve and the inspiratory line of the breathing circuit not only using a T connector, but also adding an antibacterial filter, while the oscillations are delivered by adding a T connector placed between the Y of the breathing circuit and the antibacterial filter on the patient side as in Figure.

Figure 21 Connection of the loudspeaker to the inspiratory line (left), and to the patient side (right)

The loudspeaker is connected to the power amplifier and controlled via the software installed on the laptop.

Flow and pressure sensor

Flow and pressure are measured between the Y of the breathing circuit and the patient filter by adding respectively a hot-wire anemometer flow sensor and an additional connector with a luer-lock to which a pressure sampling line is secured. Both are placed after the T connector, which was also chosen accordingly to the flow sensor's dimension. The addition of these connectors and the flow sensor result in an increase in dead space of less than 30 ml.

The flow sensor is connected to the Florian neonatal respiration monitor which displays flow and also is equipped with an analog output which can be used to transmit the analog signals to the A/D-D/A board.

The pressure sampling line is connected to a pressure transducer which transmits the pressure data to the A/D-D/A board via an Ethernet cable.

Figure 22 Hot-wire anemometer (left) and pressure transducer (right)

Florian neonatal respiration monitor

The Florian neonatal monitor is a stand-alone monitor that is used to measure and display flow, tidal volume and airway pressure in infants.

Figure 23 Front (left) and rear (right) of the Florian neonatal monitor

The front panel of the Florian monitor is equipped with LED alarm indicators and a number of controls used to modify the displayed graph, set alarm limits and start sensor calibration.

The rear panel is equipped with:

- A flow sensor cable connector
- A ventilator connector for external pressure input
- A serial port
- A parallel printer port
- A proximal pressure input
- An oxygen sensor input
- An analog output connector for recorder
- The power switch
- A power inlet

In the developed set-up the flow sensor cable is connected to the rear of the panel, allowing for the visualization of flow on the monitor, while a 6-pin DIN to 2 BNC cable is connected to the analog output on the rear panel and to two BNC connectors on the A/D-D/A board allowing for the transmission of flow and pressure signals.

Printed circuit board

The A/D-D/A board is comprised of a main board which generates the signal used to control the loudspeaker and acquires both analog and digital signals to transmit them to a laptop where they can be displayed and saved.

An additional printed circuit board (PCB) is added in order to amplify analog signals from the Florian monitor, accounting for differences between the output signals and shifting them accordingly to the ADC input range.

The outputs of the Florian monitor are transmitted using a custom-built cable to two BNC connectors on the PCB where they are amplified and shifted using a resistive trimmer and an operational amplifier. The outputs from the PCB are connected to the analog input pins of the main A/D-D/A board.

The BNC connector present on the board connects to the power amplifier allowing for its control in generating the driving forces used during FOT. While Ethernet cable connectors allow for communication of data from the pressure transducer to the board. The acquired signals are then sent to a laptop via serial communication.

At the heart of the A/D-D/A board is the CY8CKIT-059 PSoC 5LP, which is a highly integrated programmable SoC, allowing for the control of the loudspeaker, display of acquired signals and transmitting them to the laptop.

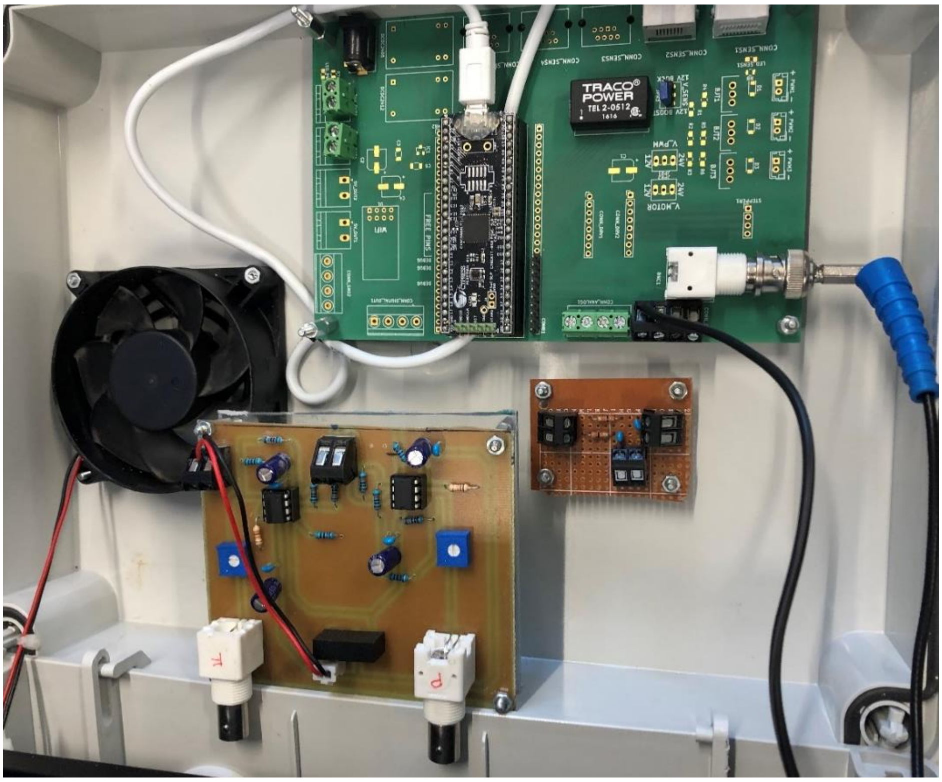


Figure 24 A/D-D/A board and PCB

5.2.2 Acquisition software

The whole set-up is controlled using a software that carries out a number of operations:

- Acquisition and plotting of flow and pressure signals
- Setting of the frequency and amplitude of oscillations
- Saving of data for offline processing

In order for these operations to be performed easily in a clinical setting a Graphical User Interface (GUI) was developed using LabView, which is a system design platform and a development environment using a visual programming language from National Instruments.

LabView allows for an immediate development of custom graphical interfaces creating virtual instruments while building block diagrams to construct the operations carried out by the software. Furthermore, the use of visual programming allows for simple modifications to be performed easily without affecting the rest of the program.

LabView can integrate easily with internal peripherals, such as the USB buffer, allowing for serial communication with the main A/D-D/A board.

A LabView program is made up of a front panel, which contains all the controls and indicators that make up the GUI, and a block diagram that contains the program source. In the clinical setting the program was developed and then used in its application form, which allows for the user to interact only with the front panel, to ensure that no unwanted changes to the program source can occur.

The LabView program developed ensures the saving of flow and pressure signals in binary form to then be processed offline.

While it can be easily adapted to different clinical protocols, the basic features remain both in the front panel and in the block diagram.

The front panel

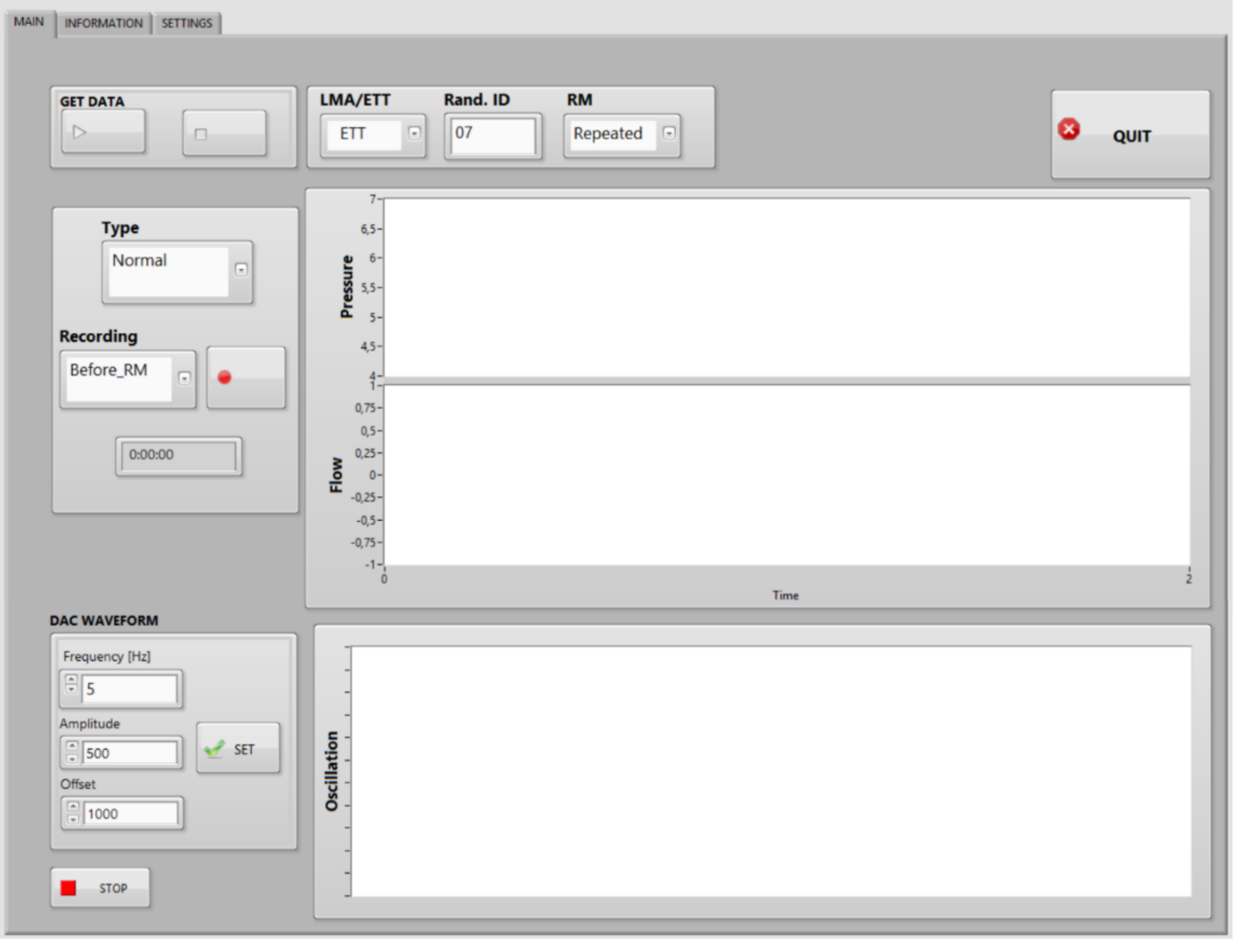
The GUI is made up of three different tabs:

- A Main tab where all the essential controls and indicators are placed

- An Info tab where relevant patient information can be typed in and is then saved as a .txt info file that can relay additional knowledge useful for data analysis
- A Settings tab where the correct COM port is set and calibration coefficients for flow and pressure can be set and are also save to the .txt info file

The Main tab can be divided into five main sections:

- Get data, in the top left corner which allows to start and stop communication between the laptop and the microprocessor on the A/D-D/A board.
- Patient identification section, at the top, which requires the operator to fill out a variable number of fields depending on how the patient data is going to be saved. In this case a folder is created for each patient using the LMA/ETT and Randomised ID, while the RM field is added to the name of each saved file as required by the protocol.
- A record data section, on the left side which is made up of two drop down menus from which the type and name of the recording is chosen, a button that starts and stops the recording and a display of the elapsed time since the current recording has started.
- A display section, where the pressure and flow signals are plotted in real-time.
- A FOT section, at the bottom, with controls that allow for the setting of frequency, amplitude and offset of the waveform used to control the loudspeaker in order to generate the oscillations and also gives a visual feedback of the generated oscillations.



LMA/ETT: ETT
Rand. ID: 07
RM: Repeated
Type: Normal
Recording: Before_RM
0:00:00
Frequency [Hz]: 5
Amplitude: 500
Offset: 1000

Figure 25 Front panel of the LabView acquisition software

The block diagram

The block diagram is made up of one block which is responsible for reading, displaying and saving the recorded signals, and another block that respond accordingly to the controls pressed by the user. When the patient identification fields are filled out and the recording type and name are selected the program creates a patient folder and a measurement file accordingly, which will then be open and written once the record button is pressed. On the other hand once the frequency, amplitude and offset fields have been filled out and the set button pressed then the FOT stimulus will be applied. With regards to the information page, it can be filled out at any moment during the procedure and will only be saved once all required recordings will have been saved.

Furthermore, given that the intraoperative setting can be a highly unstable setting some features have been included to allow for the quick interruption of oscillation, if so required by the clinician, while saving of the recordings is ensured even if the program is quit on accident. All controls give a quick visual feedback when they are pressed so that it is apparent to the operator whether the operations are being carried out correctly.

The signal are acquired via serial communication with the A/D-D/A board, thanks to an NI instrument driver that implements the Virtual Instruments Software Architecture (VISA) I/O standard, which is the standard for configuring, programming and troubleshooting instrumentation systems such as serial (RS232/RS482), Ethernet and USB interfaces. NI-VISA supports interaction both with parallel and serial ports, which are automatically detected and can be selected on the front panel.

In the developed software the data queue reference is generated as a queue of string elements, and this data queue allows for the acquisition and consumption loops to take place at the same time at different rates.

The acquisition loop is where, once the communication is initiated by pressing the GET DATA controls, the serial port is configured, and the notification of the serial character event is enabled. The serial port is specified by the *VISA resource name* that is selected by the operator in the Settings tab on the front panel, furthermore the baud rate, timeout, data bits and other specification are set accordingly to the desired initialization of the serial port. The initialized resource name is passed to the *VISA Enable Event VI* where the event type and mechanisms are defined.

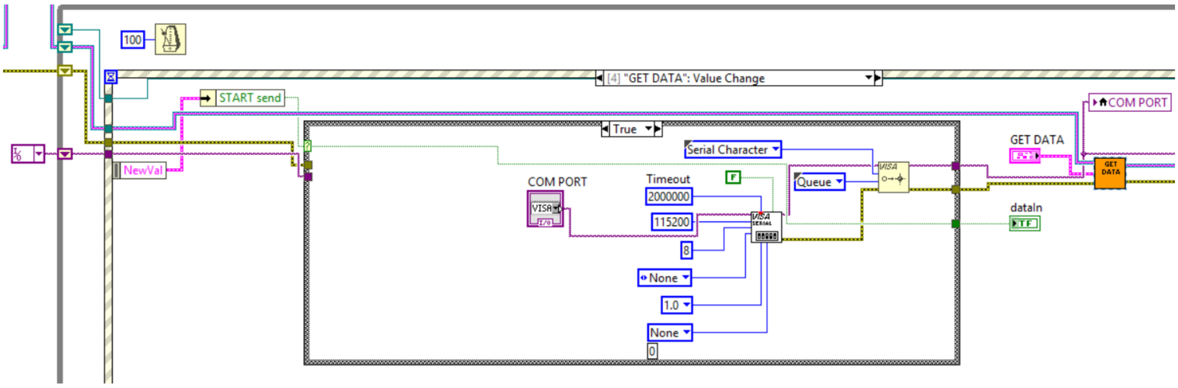


Figure 26 Acquisition loop in the block diagram

The consumption loop is where data is read and made ready to be displayed and written to a file during recording. This is achieved by dequeuing elements and through *VISA Write*, *Wait on Event and Read* VIs, where among other specification the acquisition rate is set at 200Hz and the data format is transformed from a string to a byte array. The calibrated byte array is used to write the data to a file when a recording is taking place and is displayed continuously on the front panel.

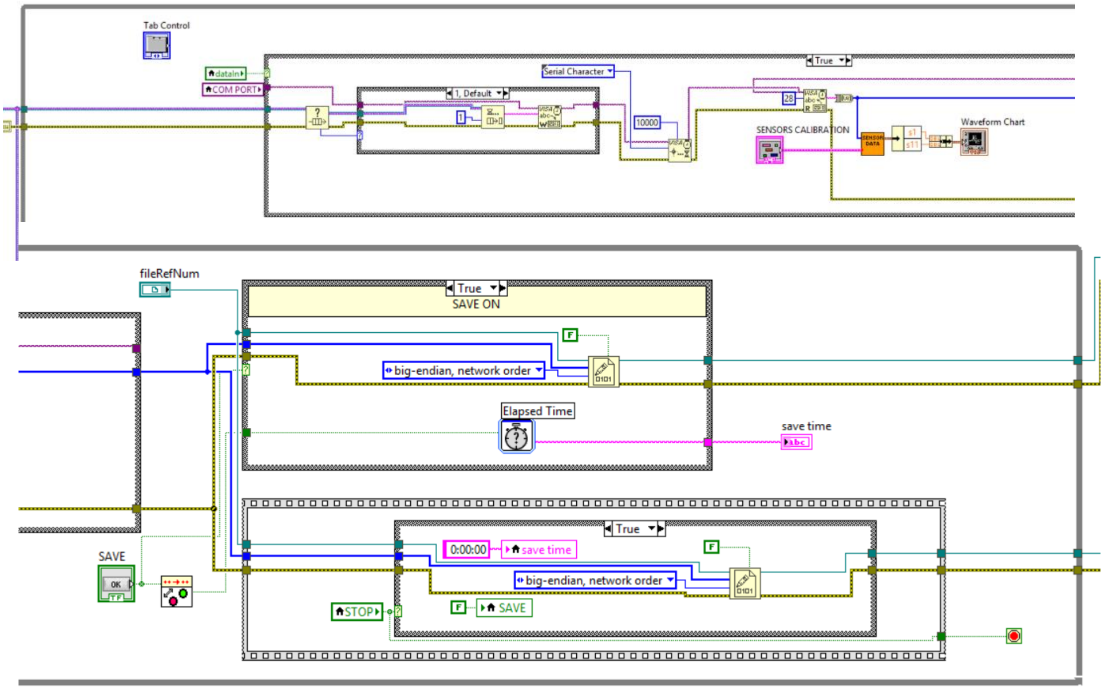


Figure 27 Consumption loop in the block diagram

5.3 Data analysis

Analysis of the recorded flow and pressure signals can be synthesised by the following flow chart:

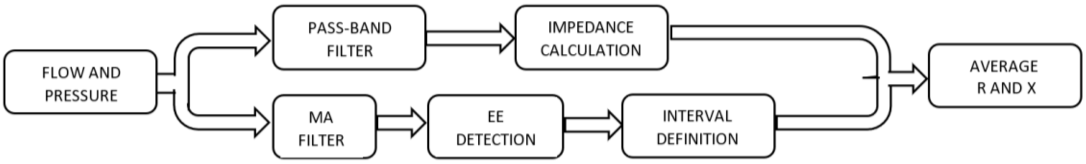


Figure 28 Block diagram for data analysis algorithm

The recordings of flow and pressure during mechanical ventilation under general anaesthesia are imported at a frequency of 200 Hz and saved for offline processing. The flow and pressure waveforms are reflective of the selected ventilation mode and of the patient’s effort, thus they are highly variable and need to be pre-processed before calculating impedance.

The saved binary files containing the recorded pressure and flow signal data are visualized and processed using appropriate Matlab functions. Given the single frequency forcing signal, impedance (Z_{RS}) is calculated using the least mean square method which allows the tracking of changes in impedance during the respiratory cycle.

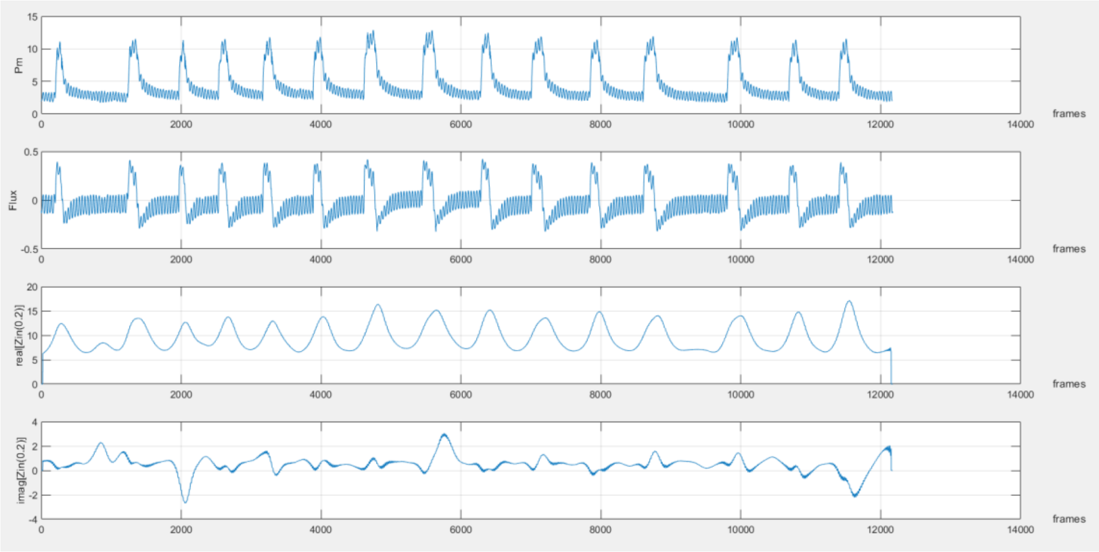


Figure 29 Pressure and flow recordings, with corresponding resistance and reactance tracings

First, the pressure and flow signals are filtered using a pass-band filter with a bandwidth of 1Hz centred around the frequency of the forcing signal (f_s) allowing for the isolation of the forcing signal components from the breathing pattern. The pass-band filter used is selected among different possible options, based on a visual comparison between the resulting tracings of reactance a resistance. Second order Bessel, Butterworth and Chebyshev filters are applied to a number of recordings and the tracings of the resulting resistance and reactance are plotted on the same graph allowing for the selection of a second order Butterworth filter based on the fact that the resulting R and X tracings during end of exhalation do not present significant oscillations.

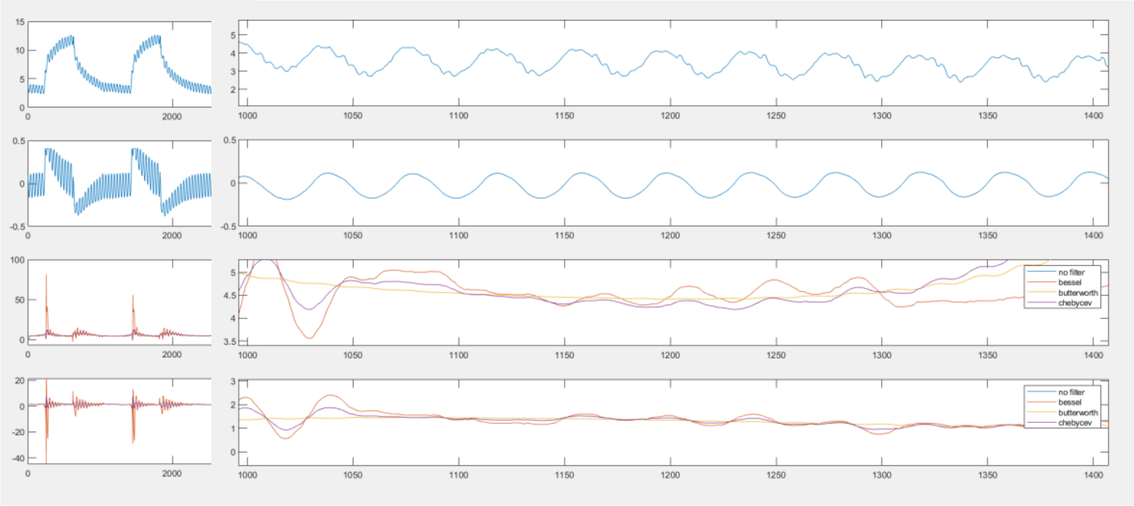


Figure 30 Comparison of different filter in the computation of resistance and reactance

The least square method consists in the comparison between a window of the forcing signal component containing a whole stimulus period and a sinusoidal function expressed as the weighted sum of sine and cosine at the stimulating frequency ($\omega = 2\pi f_s$) and takes into account the superimposed noise ($n(t)$) and offset (a_0) (11).

$$S(t) = a_0 + a_1 \cos(\omega t) - b_1 \sin(\omega t) + n(t) \tag{11}$$

The weights a_1 and b_1 are a measure of how much the reference sinusoidal function explains the recorded signal (S); in the case of discrete signal, the same relationship can be written in its matricial form (12):

$$S = AX + R \tag{12}$$

With

$$A = \begin{bmatrix} 1 & \cos(\omega t_1) & -\sin(\omega t_1) \\ \vdots & \vdots & \vdots \\ 1 & \cos(\omega t_N) & -\sin(\omega t_N) \end{bmatrix} \tag{13}$$

And X is a vector containing the coefficients that are estimated for each window as the product between the pseudoinverse of A and the recorded signal samples in the window. The window length is chosen according to the stimulus and sampling frequency (f_c) as the ratio between the two in order for the window to contain a whole stimulus period.

This operation is repeated sliding the window along the recorded signals of pressure and flow and returns a vector containing the estimated coefficients a_1 and b_1 for both pressure and flow. Therefore, impedance can be computed as:

$$Z_{RS} = \frac{P}{\dot{V}} = \frac{a_{P,1} + jb_{P,1}}{a_{\dot{V},1} + jb_{\dot{V},1}} \tag{14}$$

Finally, resistance (R_{RS}) and reactance (X_{RS}) are, respectively, the real and the imaginary part of the impedance, and by moving the window along they are computed for each sample and can be plotted as in Figure.

The computation of resistance and reactance instant by instant allows for the measurement of respiratory mechanics at different moments during the breathing cycle, in particular measuring R_{RS} and X_{RS} during inspiratory and expiratory pauses allows for the quantification of the dependence of respiratory mechanics on lung volume. Therefore, the end of exhalation is of particular interest, and, once it is identified for each breath in the recording, it can be used to determine the samples used to compute mean values of resistance and reactance. In order to identify end of exhalation, flow and pressure are filtered using a moving average filter in order to remove the component given by the oscillating forcing signal at 5 Hz and the filtered pressure signal is used to identify beginning and end of inspiration based on whether pressure is increasing or decreasing sample by sample, while end of exhalation is initially set to the sample immediately preceding the beginning of inhalation.

Given the variability of pressure recording in the clinical setting, some additional restraints are added to ensure the selection of samples appropriately representing end of exhalation:

- Exhalation should be long enough to ensure that a sufficient number of samples can be selected in the calculation of mean resistance and reactance.
- Incomplete breaths are identified based on volume variations which are not in a contained range around the median respiratory volume of the recording.
- In the event that the flow sensor saturates during inhalation, the sample representing end of exhalation is chosen accordingly so that the calculated impedance is not reflective of such as occurrence.

Once end of exhalation is correctly identified, then mean resistance (R) and reactance (X) are calculated on a window of 200 samples of the previously obtained R and X tracings over the whole recording, in order to average at least five periods of the sinusoidal forcing signal. Once mean values are obtained for all the identified breaths, they are averaged to obtain final values of resistance (R_{mean}) and reactance (X_{mean}) for each recording.

R_{mean} and X_{mean} are indicative of lung volumes during surgery and can be used to assess the effects of ventilation strategies and surgical procedures.

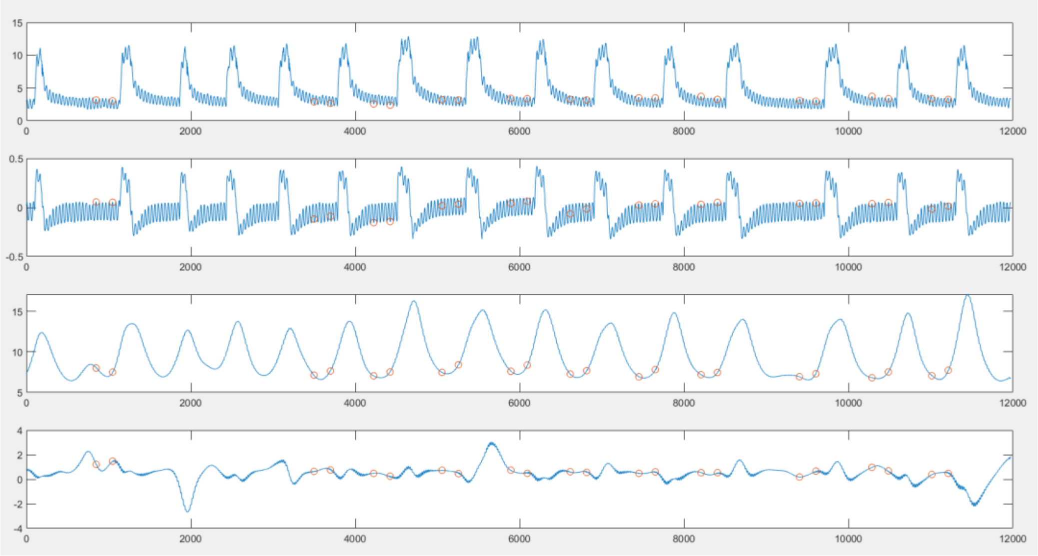


Figure 31 Recordings of pressure and flow, and resistance and reactance tracings with selected end expiratory time windows

6. In vitro testing

The developed set-up, described beforehand, had to undergo in-vitro testing before its use in a clinical setting. Testing was performed on models of the respiratory system representing the expected range of paediatric patients, while the developed set-up was validated against an already validated set-up, used as a reference. The clinical set-up has substantial physical differences from set-ups used routinely in FOT application, dictated by the intraoperative setting. Impedance measurements deriving from recordings of the novel set-up are compared to those resulting from the use of the reference set-up and eventual corrections are applied.

6.1 Test lungs

The in-vitro models used to represent the mechanical properties of paediatric patients between the age of 2 and 16 are made up of glass bottles and ETTs. This modelling of the respiratory system derives from a simple mechanical equivalent of the respiratory system represented by the series of a resistance (R), an inertance (I) and a compliance (C).

In the intraoperative paediatric setting the main contribute to respiratory resistance is represented by the resistance of the airway device used to deliver the breathing pattern from the anaesthesia ventilator, thus during in-vitro testing, resistance was modelled using ETTs. On the other hand, compliance of the respiratory system is modelled by the compressibility of gas contained in an inextensible glass bottle, while inertance can be considered negligible, as its contribution to the systems impedance is very little compared to that of resistance and compliance.

Modelling the respiratory system by means of endotracheal tubes of different diameter coupled with glass bottles of different volumes, various ranges of patients can be represented. An ideal resistance causes a pressure drop proportional to flow as:

$$\Delta P = R\dot{V}(t) \tag{15}$$

For fully laminar flows resistance varies, in accordance with Poiseuille's law (16), with the cross-section of the endotracheal tube (A), its length (L) and the viscosity of the fluid (μ).

$$R = \frac{8\pi\mu L}{A^2} \tag{16}$$

However, in case of turbulent flows the resistance is not only dependent on the characteristic of the tube and the fluid, but also on the frequency of the oscillations. As oscillations become more rapid the frequency dependent term increases, but in case of small-amplitude oscillations the oscillatory flow resistance can be approximated to the resistance of the linear model, constant and independent on frequency ($f = \omega/2\pi$) and cinematic viscosity of the fluid ($\nu = \mu/\rho$).

$$R = \frac{8\pi\mu L}{A^2} + \frac{\sqrt{2}}{\pi r^4}\mu \frac{(r^2\omega)^{1/2}}{\nu} L \tag{17}$$

According to Rohrer's equation the proportionality between pressure and flow is resistance described as:

$$R = k_1 + k_2\dot{V} \tag{18}$$

Which allows to consider resistance as constant for small oscillatory flows, while also representing an estimate of the oscillatory flow resistance in case of higher oscillatory flow, accounting for non-linearities. This determines pressure to be represented as a non-linear function of flow:

$$\Delta P = K_1\dot{V} + K_2\dot{V}^2 \tag{19}$$

On the other hand, compliance is strongly dependent on the volume of the bottle (V_{bott}), thus bottle volume have been chosen according to expected values of compliance in the paediatric population, while the compression is assumed to be adiabatic ($\beta = 1.4$) so that compliance can easily be calculated from the formula:

$$C = \frac{V_{bott}}{\beta P_{atm}} \tag{20}$$

While compliance for children between two and sixteen years of age covers a wide range, compliance of smaller children is much lower than that of older children, which would need very high volumes to be correctly modelled. Given the low feasibility of testing greater volumes, test lung volumes were chosen based on the lower end of expected values which would represent a harder challenge. The resulting chosen values of volumes for the bottles are 1 L and 2 L, where the smaller bottle is representative of smaller children with lower compliance (C=0.69 ml/cmH_2O), while the bigger children are represented by the bigger bottle (C=1.4 ml/cmH_2O).

6.2 Reference set-up

In-vitro validation of the clinical set-up requires the knowledge of reference values of resistance (R) and reactance (X). For this study the reference values adopted are those computed with recordings of pressure and flow employing an already validated set-up; such a choice represents a better option than computing theoretical reference values of R and X given the underlying assumptions involved, which are not reflective of the real respiratory system and are intrinsically different from real values.

The reference set-up is represented by a pneumotachograph (PNT) mounted on a pressure transducer, that is connected inside the breathing circuit between the Y and the antibacterial filter and communicates recorded pressure and flow data, via an Ethernet cable, directly to the A/D-D/A board. While the sensors used to measure the signals differ from the set-up described previously, the hardware generating the oscillations, the connections to the ventilator and the breathing circuit and the communication of data to a laptop for monitoring and recording, is not altered.

The use of a PNT mounted on a pressure transducer, allows for the measurement of both pressure and flow with a single device which ensures synchrony and accuracy of recorded data. Furthermore, mounting of the PNT by means of rigid and short tubes ensures an adequate recording of flow, given its flat frequency response.

However, the use of the PNT is not suitable for the intraoperative setting because of its excessive weight and the requirement of positioning the pressure transducer close, which would add additional weight on the breathing circuit proximally to the patient, risking the dislodgment of the airway device. Furthermore, the resistive load added by the PNT is non-negligible and humidity of the air flowing through the breathing circuit could lead to the condensation of the resistive element, causing the loss of linearity of the measure.

While the clinical set-up overcomes such limitations by substituting the PNT with a hot wire anemometer paediatric flow sensor and moving the pressure transducer farther away from the patient, it also introduces a number of possible errors in the measured resistance and reactance. Such errors are the result of the changes applied, particularly the introduction of a longer pressure sampling line can potentially introduce an additional compliance which affects pressure measurements. Furthermore, while the hot wire anemometer presents a flat frequency response, the conditioning of the signal applied inside the Florian monitor is unknown.

Reference values for resistance and reactance are computed for both test lungs in CPAP ventilation mode at 5 cmH_2O by superimposing a sinusoidal pressure oscillation of 2 cmH_2O at 5 Hz and reported in Table 3 as average ± SD of the recording. These values are taken as reference and values recorded via the developed set-up should differ no more than ±10% as stated in Technical standards for respiratory oscillometry by King et al.

Test Lung	R [$cmH_2O/L/s$]	X [$cmH_2O/L/s$]
1 L	12.61±0.29	-33.49±0.26
2 L	11.38±0.19	-16.05±0.17

Table 3 Reference values of resistance and reactance of the two test lungs. Values are represented as mean value and standard deviation within the same measurement.

To investigate the effect of two different longer pressure sampling lines, one more and one less rigid, resistance and reactance are computed for both test lungs, by connecting them to the pressure transducer and to the luer lock of a straight connector placed between the PNT and the bacterial filter. (Table 4)

Test Lung	Sampling line	R [$cmH_2O/L/s$]	Relative error (R) [%]	X [$cmH_2O/L/s$]	Relative error (X) [%]
1 L	More rigid	11.66±0.29	7.53	-34.28±0.30	2.36
2 L	More rigid	11.08±0.19	6.26	-16.65±0.19	3.74
1 L	Less rigid	11.82±0.29	3.87	-34.43±0.27	2.81
2 L	Less rigid	11.20±0.19	1.58	-16.62±0.17	3.55

Table 4 Reference values of resistance and reactance for both test lungs measured with different tubes for the pressure sampling lines.

Given that the relative error, introduced by the use of longer sampling lines is contained, a tube of the same diameter of less rigid sampling line, but with a higher external diameter is chosen due to the advantage of being less prone to kinking, which is an important requirement especially given the length required in order to reach the Y of the breathing circuit.

The same measurements are carried out using the clinical set-up (Table 5), which show the same behaviour with regard to the different sampling lines. However, clear and constant differences with the reference values of resistance and reactance are apparent.

Test Lung	R [$cmH_2O/L/s$]	X [$cmH_2O/L/s$]
1 L	13.51±0.23	-27.60±0.24
2 L	11.83±0.12	-12.34±0.11

Table 5 Initial resistance and reactance measured with the clinical set-up

Further modifications of the set-up, which included the application of a low-pass filtering and adjustment of a trimmer on the filtered flow analogic signal were performed and measurements of resistance and reactance with the present set-up were performed on the 1L test lung (Table 6). Relative error between impedance measured via reference set up and via clinical setup is 1.49%, which is well within the range mentioned earlier of ±10%.

Test lung	Set-up	R [$cmH_2O/L/s$]	X [$cmH_2O/L/s$]
1 L	Reference	12.61±0.29	-33.49±0.26
1 L	Clinical	13.97±0.37	-33.60±0.35

Table 6 Resistance and reactance measured with reference and clinical set-up.

The clinical set-up was then tested by computing the resistance and reactance of the 1 L test lung both by applying a breathing pattern with PEEP of 5 cmH_2O through the anaesthesia ventilator, by applying an algorithm to recognize end of expiration and the results are compared to the corrected measures of R and X (Table 7).

Mode	R [$cmH_2O/L/s$]	X [$cmH_2O/L/s$]
CPAP	13.97±0.37	-33.60±0.35
PC	14.18±0.21	-32.80±0.25

Table 7 Resistance and reactance from CPAP and PC pressure and flow recordings

Finally, the clinical set-up is periodically tested in order to check that compute values of impedance do not differ more than ±10% with respect to the reference impedance value (Table 10).

Test	R [$cmH_2O/L/s$]	X [$cmH_2O/L/s$]	Error[%]
1 - CPAP	15.49±0.30	-36.12±0.30	9%
1 - PC	15.95±0.26	-35.72 ±0.2	9.3%
2 - CPAP	13.13±0.37	-30.37±0.39	7.5%
2 - PC	13.95±0.31	-30.34±0.32	6.9%
3 - PC	11.74±0.23	-34.73±0.24	2.4%

Table 8 Periodical measures of resistance and reactance

Repeated measures were carried out during testing to check their consistency which is reflective of the consistency of measures throughout a surgical procedure.

Furthermore, recordings using both setups with and without the antibacterial filter showed a constant contribute of the antibacterial filter to the computed resistance. Further testing of filters before and after their use in the operating theatre determined that the contribute remained constant throughout surgery, hence the resulting resistance can simply be corrected by subtracting the contribute of the filter, together with that of airway devices used.

7. Clinical Studies

The developed FOT set-up is used in two research projects which investigate changes in respiratory mechanics in the intraoperative setting at Perth Children's Hospital:

- OASIS: Oscillation mechanics and sustained inflation study using FOT measurements of children under general anaesthesia.
- COMET: Changes in oscillation mechanics evaluated by the forced oscillation technique and lung recruitment during mechanical ventilation in paediatric laparoscopic appendectomy.

7.1 OASIS

The aim of this clinical study is to compare the effect on respiratory mechanics of two different recruitment strategies and their administration through two different airway devices in children undergoing general anaesthesia.

While recruitment manoeuvres are routinely used during surgery, it is not clear which strategy is the most effective in reopening collapsed lung regions. Recently several studies have been aimed at assessing the effectiveness of RMs on the diseased lung in the intensive care unit, however, in many cases, children undergoing surgery have healthy lungs which present with a different degree of derecruitment and recruitability . Furthermore, in the intraoperative setting mechanical ventilation is often delivered through LMAs, which do not guarantee an effective seal at pressures reached during RMs.

The recruitment manoeuvres compared are multiple repeated inflations and a single sustained inflation and both can be delivered either through a laryngeal mask (LMA) or an endotracheal tube (ETT). It can be hypothesized that one sustained inflation is more effective than multiple breaths with high inspiratory and expiratory pressure levels and that both RMs are less effective when applied via an LMA compared to an ETT.

This study will help formulate new evidence-based guidelines and policies in order to optimize ventilation strategies in children undergoing general anaesthesia.

7.1.1 Clinical study methods

The OASIS study is a single-centred randomised prospective study, in which recruited patients undergoing general anaesthesia are randomised to one of the two recruitment strategies under comparison. During surgery, FOT is applied using low amplitude sinusoidal pressure oscillations (2 cmH_2O) at 5 Hz generated by the aforementioned set-up and flow and pressure signals are recorded at selected time frames. These recordings are then processed offline to calculate resistance and reactance which are used to compare the effectiveness of the two recruitment strategies and administration through LMA or ETT.

Study Population

Recruitment is performed in children without major lung disease and who are undergoing surgery that requires general anaesthesia and ventilatory support, additional inclusion and exclusion criteria are applied.

Inclusion criteria:

- Children of any sex
- Age from 2 to 16 years
- Undergoing surgery with general anaesthesia through either laryngeal mask and tracheal tube

Exclusion criteria:

- Children with a known difficult airway and thoracic malformation
- Children with a known major lung and/or cardiopulmonary disease:
- Uncorrected congenital heart disease
- Primary/secondary pulmonary hypertension
- Cardiac/thoracic malformations or tumours
- Structural lung changes
- Uncontrolled asthma
- Cystic fibrosis

Any other less common cardiopulmonary conditions are assessed by the treating anaesthetist and accounted for in a more exhaustive exclusion criteria list.

Parents or guardians of children that meet the inclusion criteria are approached in order to obtain a written informed consent to their participation in the study if they so desire.

Furthermore, older children are also handed an information sheet in order for them to be aware of the proceedings involved in the study.

Experimental Protocol

After induction of anaesthesia the patient is transferred to the operating theatre where ventilation is started using the airway device and ventilation strategy considered appropriate by the attending anaesthetist.

The following guidelines are applied to minimise the confounding effect of the different ventilation approaches on lung recruitment and lung mechanics:

- PCV or PSV if the patient is breathing spontaneously
- FiO_2: 0.4 to maintain SpO_2 above 95%
- PEEP: 5 cmH_2O
- PCV: Peak inspiratory pressure (PIP): 10-25 cmH_2O above PEEP, to reach tidal volumes of 6-8 ml/kg
- PSV: Pressure support of 5-10 cmH_2O, to reach tidal volumes of 6-8 ml/kg
- Respiratory rate (RR): depends on the child's age and is adjusted to maintain $etCO_2$ between 35-45 mmHg

Once the airway device selected by the anaesthetist is in place children are randomised to one of the following recruitments manoeuvres:

- Repeated inflations (RI): 20 slow manual breaths with PIP = 40 cmH_2O and PEEP = 15 cmH_2O
- Sustained inflation (SI): a single inflation up to PIP = 40 cmH_2O for 20 seconds

Based on the airway device and the randomised recruitment manoeuvre, patients are grouped into 4 different groups:

1. Children receiving a SI via an LMA
2. Children receiving RI via an LMA
3. Children receiving a SI via ETT
4. Children receiving RI via ETT

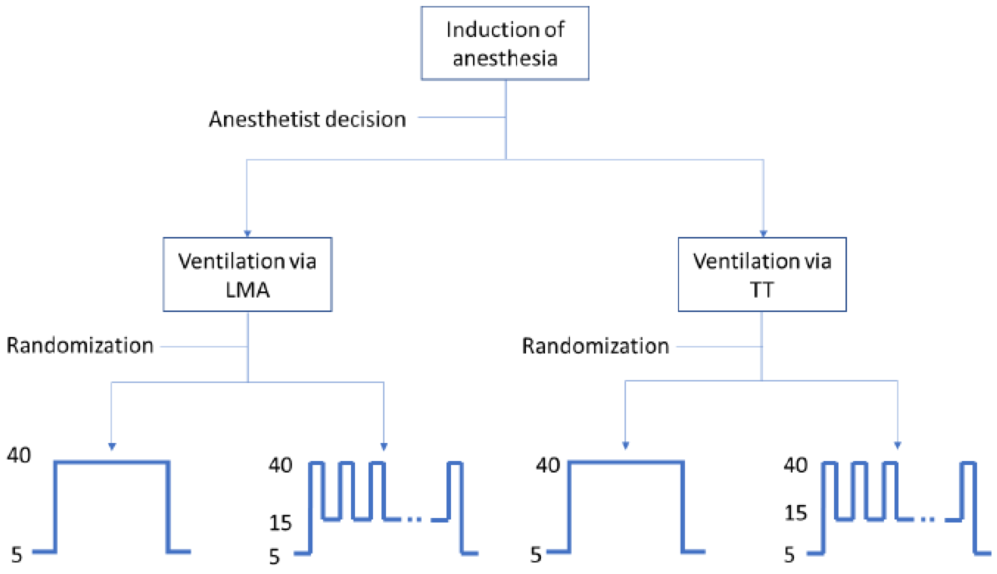


Figure 32 Schematic representation of randomisation process and the two different recruitment manoeuvres

The FOT set-up is connected to the anaesthesia ventilator prior to the transfer of the patient to the operating theatre in order to perform a leak test given the introduction of an additional circuit to the normal breathing circuit. Once the patient is connected to the anaesthesia ventilator and correctly ventilated the sinusoidal forcing signal at 5 Hz is applied and a visual check of its peak to peak amplitude is performed on the laptop, to ensure a peak to peak amplitude of approximately 2 cmH_2O. Throughout the surgery recordings are performed before and after the recruitment manoeuvre as well as at the end of surgery, resulting in a minimum of three recordings for each patient:

- Before RM
- After RM
- After Surgery

If any changes occur in the ventilation strategy at any point, the attending anaesthetist is asked to return to the initial ventilation strategy prior to recording.

In addition, pulse oximetry (SpO_2) and end-tidal carbon dioxide ($etCO_2$) are recorded both before and after the recruitment manoeuvre. Furthermore, additional recording can be performed:

- During RM, in order to have a quantifiable representation of the delivered recruitment strategy and the pressures reached

- Additional RM, in order to have the possibility to record before, after and during any necessary recruitment strategy
- Any extra recording if needed

All recordings are saved in the folder dedicated to the patient, which also includes any additional information provided by the operator, such as patient information, SpO_2, $etCO_2$ and calibration coefficients.

Statistical Analysis

The recordings saved are then processed offline to obtain resistance (R) and reactance (X) for each saved file and their magnitude changes before and after the recruitment manoeuvres are indicative of changes in lung recruitment. The comparison between the two recruitment strategies and the relative effectiveness of each strategy when administered through LMA or ETT can be evaluated using a two way Anova, in which one factor is the RM, with two levels (RI and SI), while the second factor is the airway device, with two levels (LMA and ETT).

Statistical analysis performed on the data available to date is:

- Two way Anova for repeated measures to compare variations in respiratory mechanics with regards to both recruitment strategy and protocol step.
- Linear regression between indicator of size of the patients and differences between respiratory mechanics before and after the recruitment manoeuvre.

7.1.2 Results and discussion

In accordance with the inclusion and exclusion criteria established for the OASIS study, thirty-two patients have been recruited to date. However, six have been excluded from analysis because of missing data, due either to researcher error or equipment failure, and unreliable data due to excessive mucus inside the airway device. The clinical FOT set-up proved to be easily tolerated from all patients throughout surgery and easily connected to the anaesthesia ventilator prior to the start of surgery. Patients recruited in the study were mostly ventilated as defined per protocol, however, the ventilatory strategy could be changed by the anaesthetist if deemed necessary. This resulted in eight of the patients being ventilated in spontaneous mode (SPONT), while the rest were either on pressure support (PS) or pressure control (PC) as defined in the protocol.

The population's demographics are reported both as a whole and divided into sub-populations based on the study protocol, which outlines four different groups characterized by different airway devices and recruitment manoeuvres:

- Laryngeal mask randomised to repeated inflation manoeuvre (LMA-RI)
- Laryngeal mask randomised to sustained inflation manoeuvre (LMA-SI)
- Endotracheal tube randomised to repeated inflation manoeuvre (ETT-RI)
- Endotracheal tube randomised to sustained inflation manoeuvre (ETT-SI)

Age [years] *range [years]*	10.05±3.24 [3.19-15]
Weight [kg] *range [kg]*	43.82±22.99 [19.1-100.2]
Height [cm] *range [cm]*	143.56±22.02 [101.6-180]
Sex [n] *Percentage of total [%]*	20 M [76.9%] 6 F [23.1%]
BMI [kg/m^2] *range [kg/m^2]*	20.07±4.86 [13.67-30.93]

Table 9 Demographics of study population

	LMA-RI	**LMA-SI**	**ETT-RI**	**ETT-SI**
Number [% of total]	46.15% [n=12]	42.3% [n=11]	3.85% [n=1]	7,7% [n=2]
Age [years] *range [years]*	10.31±3.62 [3.2-15.0]	10.43±3.1 [5.34-15.0]	6.47	8.28±1.57 [7.17-9.4]
Weight [kg] *range [kg]*	48.91±26.46 [19.35-100.2]	42.92±20.52 [21.7-84.65]	19.1	30.6±11.45 [22.5-38.7]
Height [cm] *range [cm]*	146.1±22.19 [101.6-180]	143.81±23.23 [117.0-177.6]	116.6	140.5±23.05 [124.2-156.8]
Sex	75% M 25% F	81.8% M 18.2% F	M	50% M 50% F
BMI [kg/m^2] *range [kg/m^2]*	21.27±5.35 [13.67-18.77]	18.62±3.98 [14.95-26.84]	14.05	15.16±0.81 [14.59-15.74]

Table 10 Demographics of study population divided into groups

From Table 10 a clear disproportion between LMA and ETT groups is evident, with almost 90% of patients belonging to either LMA-RI or LMA-SI. This can be explained by the fact that, while the recruitment manoeuvres are randomised, the choice of airway devices is left to the attending anaesthetist and the laryngeal mask is usually preferred to an endotracheal tube given that the latter is considered more invasive.

For this reason to this date no analysis can be carried out with regards to the effectiveness of the airways devices in delivering the recruitment manoeuvre given the small number of patients recruited in the ETT groups. However, recordings have been performed also during the recruitment manoeuvre in order to have a quantifible representation of the performed RM. Recordings of pressure signals during the recruitment manoeuvre (Figure 33) show significant differences, which have also been reported by the attending anaesthetist. In particular, delivery of the high pressures involved in both recruitment strategies through a LMA proves to be harder than with an ETT, due to leakege which could lead to the dislodgment of the airway device. This can be seen from the recordings where both during repeated inflations and sustained inflation the peak pressures reached are closer to the pressure of 40 cmH_2O, defined by the protocol. Furthermore, the recording of various RMs show difference not only due to the airway device used, but also due to the fact that they are performed manually by different clinicians.

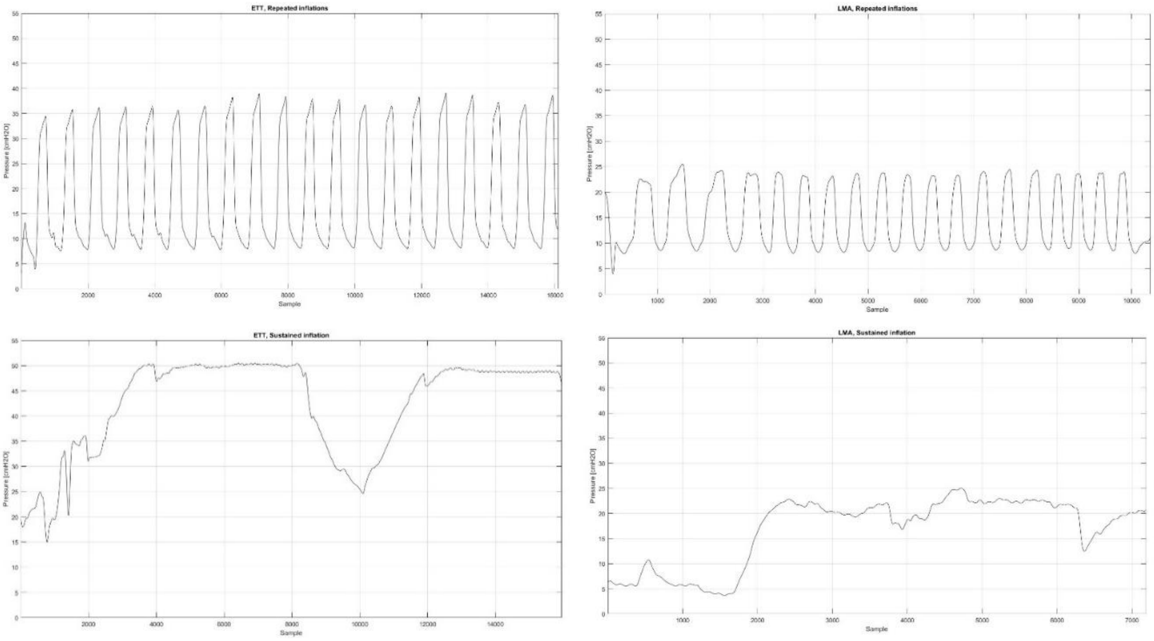


Figure 33 Recording of RI (top) and SI (bottom) recruitment manoeuvres delivered through an ETT (left) and a LMA (right)

Given the low number of patients in the ETT groups, only results regarding LMA groups will be presented.

Resistance (R) and reactance (X) were computed for each patient from three recordings as per protocol: before the recruitment manoeuvre (PRE-RM), after the recruitment manoeuvre (POST-RM) and at the end of surgery (POST-SURGERY). Absolute values of R and X at the three different protocol steps are represented in Figure 34 for the LMA-SI and LMA-RI groups.

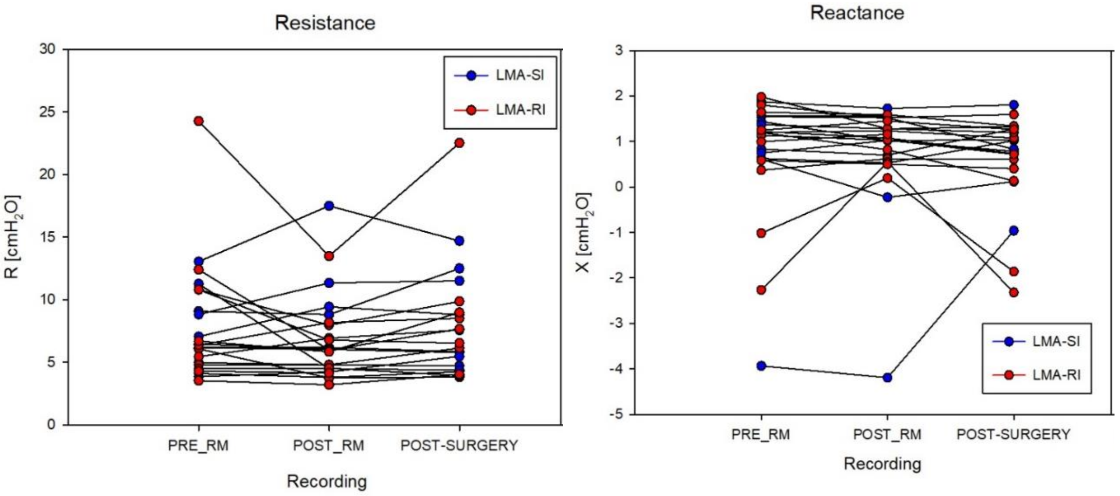


Figure 34 Absolute values of resistance and reactance for all patient in LMA-RI and LMA-SI groups at three protocol steps

Values of resistance and reactance for each group are reported for each recording in Table 11 as average ± SD of the group.

Group	**R [cmH$_2$O/L/s]**			**X [cmH$_2$O/L/s]**		
	PRE-RM	**POST-RM**	**POST-SURGERY**	**PRE-RM**	**POST-RM**	**POST-SURGERY**
LMA-RI	8.34±5.79	6.31±2.78	8.15±5.21	0.74±0.36	0.99±0.13	0.37±1.29
LMA-SI	7.37±2.91	7.56±4.08	7.80±3.82	0.71±1.6	0.54±1.66	0.78±0.76

Table 11 Mean resistance and reactance for each group at three different protocol steps

The computed values of R and X are analysed using a two way Anova for repeated measures, in which one factor is the recruitment strategy, either repeated inflations (RI) or sustained inflation (SI), while the second factor is represented by the protocol step. This structure of the two way Anova allows for a statistical analysis of differences both between groups and between successive recordings inside the same group. No statistically significant differences were found between different recordings inside the same group or between groups. However this could be due to the low power of the performed test, which is imputable to the low numerosity of both groups given that the number of recruited patients at this time is only half of the prospected number defined in the protocol.

Even if no statistically significant difference was found, the LMA-RI group mean resistance values do not show the same changes as in the LMA-SI group, where resistance decreases following the recruitment manoeuvre and then increases at the end of surgery. Furthermore, reactance following the recruitment manoeuvre increases in the LMA-SI group while it decreases in LMA-RI. On the other hand in both groups reactance at the end of surgery returns to values similar to or smaller then reactance prior to the recruitment manoeuvre.

Given that all measured resistance and reactance values also account for the mechanical properties of the airway devices used, which differ in size and brand between patients, they cannot be reported as z-scores, given that they will instrincally differ from normative data. To overcome the high observed variability for both R and X between patients, the evaluation of the effects of the recruitment manoeuvers is done by representing differences of POST-RM **(**ΔR_{RM} and ΔX_{RM}) and POST-SURGERY (ΔR_{SRG} and ΔX_{SRG}) values with regards to PRE-RM, taken as baseline. Mean differences from baseline are reported below and shown in Figure 35.

Group	**ΔR_{RM} [cmH_2O/L/s]**	**ΔX_{RM} [cmH_2O/L/s]**	**ΔR_{SRG} [cmH_2O/L/s]**	**ΔX_{SRG} [cmH_2O/L/s]**
LMA-RI	-2.03±3.61	0.26±0.93	-0.55±2.51	-0.34±0.40
LMA-SI	0.08±2.79	-0.17±0.28	0.13±3.06	0.14±1.01

Table 12 Average differences in resistance and reactance at three different protocol steps from baseline

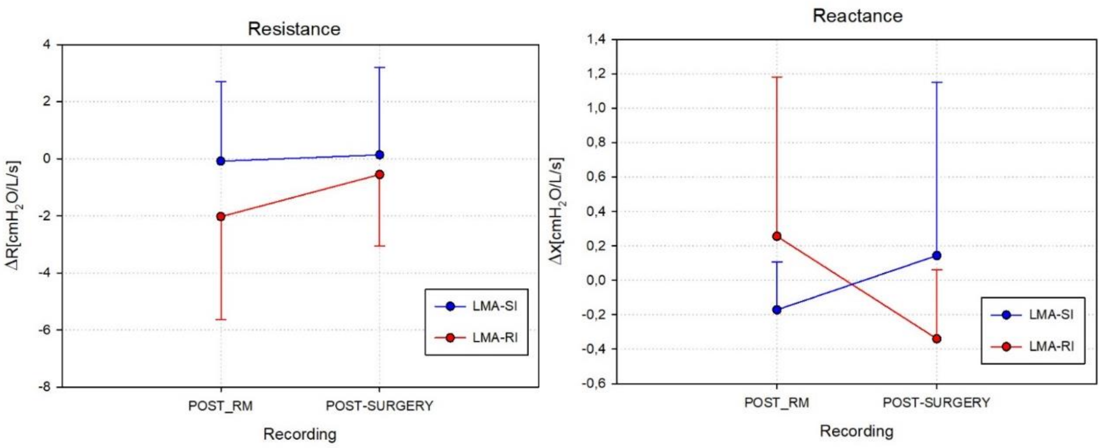


Figure 35 Mean differences in resistance and reactance from baseline for both groups.

Furthermore, oxygen saturation (SpO_2) and end tidal carbon dioxide ($etCO_2$), which are parameters used in clinical practice to monitor ventilation, have been reported before and after the recruitment manoeuvre and are shown in Figure 36. While oxygen saturation does not show significant variations, given that according to protocol the fraction of inspired oxygen (FiO$_2$) is adjusted by the anaesthetist to maintain SpO$_2$ above 95%. End tidal carbon dioxide decreases after the recruitment manoeuvre in the LMA-RI, while it increases in the LMA-SI group. These variations in etCO$_2$ are reflective of the changes in mechanical properties before and after the recruitment manoeuvre, where a decrease in resistance and increase in reactance are indicative of an increase in recruited lung regions, which in turn determines better gas exchange and carbon dioxide removal.

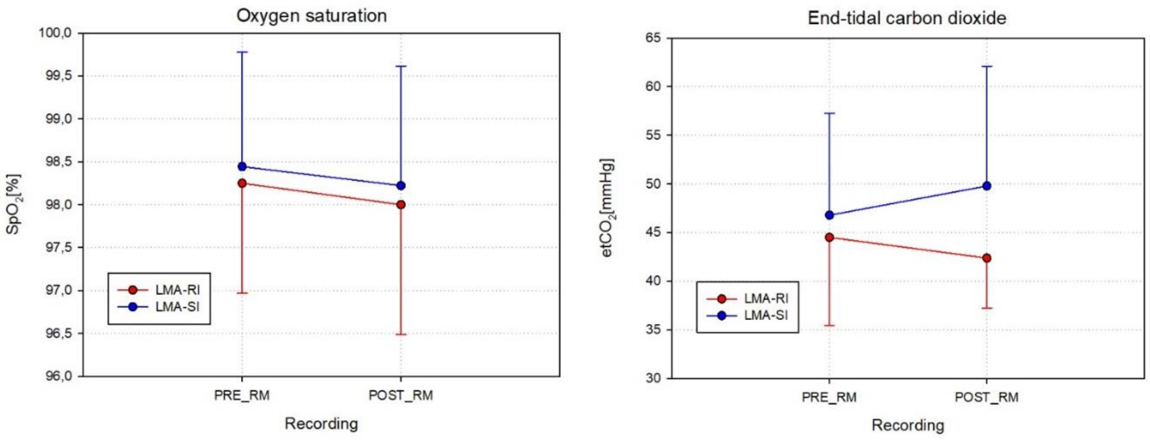


Figure 36 Mean values of oxygen saturation and end-tidal carbon dioxide before and after the recruitment manoeuvre

Changes in mechanics of the lung, reflected in changes of clinical parameters, suggest that the repeated inflation manoeuvre is more effective in recruiting the lung than a single sustained inflation. However, these positive changes in respiratory mechanics are not maintained in the long term, given that resistance increases back to values close to baseline and reactance decreases with respect to baseline values. Furthermore a more in depth analysis of the absolute values of resistance and reactance inside the groups, suggest that the repeated inflation manoeuvre performed after induction, results in significant improvements of respiratory mechanics only in those children which show derecruitment as a result of anaesthesia, however, the benefits are not sustained in the long term.

Given the high variability in age and size of the recruited patients in both groups and the fact that smaller children have a lower FRC making them more at risk of lung collapse and derecruitment as a result of intraoperative general anaesthesia, variations in resistance and reactance following the recruitment manoeuvre (ΔR_{RM} and ΔX_{RM}) are plotted against age, height and BMI (Figure 37) to invesigate whether smaller children show a higher effectivness of the recruitment manoeuvre.

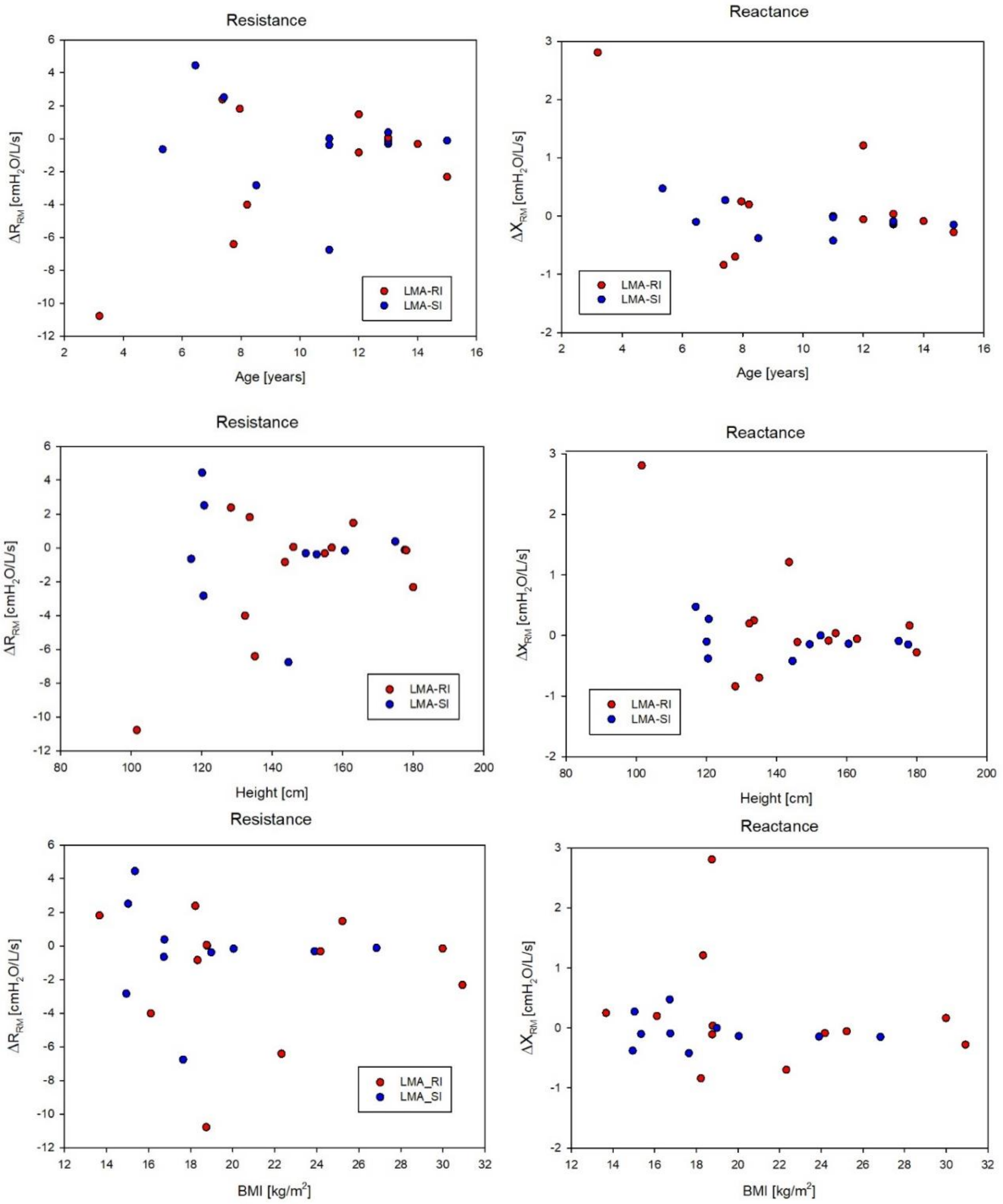


Figure 37 Plotting of difference in resistance (left) and reactance (right) before and after the recruitment manoeuvre, against age (top), height (middle) and BMI (bottom)

Simple linear regression was performed to check if variations in respiratory mechanics can be attributed to the size of the patient, indicated by both age and height. No statistically significant linear relationship was found between variations in resistance and reactance and either age, height or BMI (p-value > 0.05); however p-values for ΔX_{RM} and age and height, respectively 0.058 and 0.075, seem to suggest a higher relationship between the two variables than that between ΔR_{RM} and age and height. These preliminary results are to be further inspected with a higher number of patients in each group to achieve a higher power of the test which would lead to more representative conclusions.

Finally, while statistical analysis of the two groups by means of a two way Anova showed no significant statistical differences neither between the two groups nor between the different protocol steps, which is reflected by the plotted absolute values of resistance and reactance (Figure 34) where the majority of patients show no relevant changes in resistance or reactance, a further analysis of the few patients which show significant differences was carried out.

The patients which show significant changes are those whose respiratory mechanics at baseline differ significantly from the majority of the population, which is reflective of the fact that the effectiveness of the recruitment manoeuvres is determined by prior presence of derecruited alveolar units .Demographics for these patients are reported in Table 13 while absolute values of resistance and reactance are reported in Table 14 and ventilation parameters at the different protocol steps are reported in Table 15.

	LMA_O_02	**LMA_O_17**	**LMA_O_19**
Age [years]	8.52	3.19	12
Weight [kg]	21.7	19.35	37.8
Height [cm]	120.5	101.6	143.6
Sex	F	M	F
BMI [kg/m^2]	14.94	18.74	18.33

Table 13 Demographics

MODE

	PRE-RM	**POST-RM**	**POST-SURGERY**
LMA_O_02	PS	PS	PS
LMA_O_17	SPONT	PS	SPONT
LMA_O_19	PS	PS	PS
PEEP[cmH_2O]			
LMA_O_02	2	2	2
LMA_O_17	6	0	0
LMA_O_19	4	5	4
Δ P[cmH_2O]			
LMA_O_02	6	4.5	8
LMA_O_17	15	14	6
LMA_O_19	5	5	7

Table 14 Ventilation parameters

	R [cmH_2O/L/s]			**X [cmH_2O/L/s]**		
	PRE-RM	**POST-RM**	**POST-SURGERY**	**PRE-RM**	**POST-RM**	**POST-SURGERY**
LMA_O_02	9.08	8.82	12.5	-3.93	-4.19	-0.96
LMA_O_17	24.27	13.49	22.53	-2.26	0.54	-2.32
LMA_O_19	6.7	5.85	8.98	-1.02	0.19	-1.86

Table 15 Resistance and reactance

From the analysis of these patients it was found that two, which were randomised to repeated inflations, present different clinical parameters which suggest that their lungs were more derecruited than others at baseline:

- Patient LMA_O_17 randomised to repeated inflations, whose resistance decreases and reactance increases following the recruitment manoeuvre has baseline line values of resistance and reactance which are considerably different from mean baseline value (8.34 cmH_2O/L/s and 0.74 cmH_2O/L/s). While no clinically significant differences in SpO_2 or $etCO_2$ are present, this patient is one of the smallest in size and youngest in the group. Furthermore, ventilation parameters were changed before and after the recruitment manoeuvre, ventilation mode was changed from spontaneous to pressure support given that the patient was performing considerable effort. The difference from the mean of the group in baseline resistance and reactance suggest that, given the age and size, this patient was more susceptible to lung closure as a result of anaesthesia because smaller children have lower FRC, closer to closing volume. For this reason, the recruitment manoeuvre proved to be more effective than in the rest of recruited patients. However, after surgery, respiratory mechanics go back to baseline values, suggesting no long-term effect of the recruitment manoeuvre performed at the beginning of surgery.
- Patient LMA_O_19 randomised to repeated inflations whose resistance decreases and reactance increases following the recruitment manoeuvre has a baseline line value of reactance ,which differ from mean baseline values less considerably than the previous patient, who showed higher changes in respiratory mechanics. However, clinically significant differences were recorded in $etCO_2$ before and after the recruitment manoeuvre (from 59 mmHg to 35 mmHg), while SpO_2 is stable at 96%. No significant differences were recorded in the ventilation strategy. However, the significant change reactance is reflective of the significant change in $etCO_2$ which indicates a higher capability in the removal of carbon dioxide after the recruitment manoeuvre, suggesting the presence of a higher number of recruited alveolar units.
- Patient LMA_O_02 randomised to sustained inflation, whose resistance and reactance don’t show significant changes following the recruitment manoeuvre has baseline line values of resistance and reactance which are different from mean baseline values (7.37 cmH_2O/L/s and 0.71 cmH_2O/L/s). While the difference in size from other patients in the group could determine a more significant effect of anaesthesia on lung recruitment, the sustained inflations manoeuvre does not improve respiratory mechanics. Furthermore, significant

changes in reactance are observed at the end of surgery, which could be reflective of changes in ventilation parameters throughout surgery.

The analysis of data available to dare suggest that recruitment manoeuvres performed at the beginning of surgery do not introduce significant changes in respiratory mechanics, further suggesting no increase in recruited lung regions. However, patients with baseline values indicative of derecruitment following induction of anaesthesia showed improvements in respiratory mechanics following the recruitment manoeuvre. This difference suggests that patients for whom the induction of general anaesthesia generates a critical reduction of FRC, benefit from recruitment manoeuvres. While these patients do show an improvement in respiratory mechanics immediately following the recruitment manoeuvre, these effects are not sustained at the end of surgery.

Previous studies on the effectiveness of recruitment manoeuvres in reversing atelectasis have been carried out predominantly in children with lung disease in the paediatric intensive care unit. Wolf et al. [25] have studied the effects of a sustained inflation RM through electrical impedance tomography, finding that those who benefited from the recruitment strategy where the patients that showed more atelectatic regions to start with. Furthermore, Morrow et al. [42] found that there were no significant changes in dynamic compliance, airway resistance or SpO_2 following the recruitment manoeuvres both in the short and long term; while increases in tidal volume and respiratory rate were not sustained in the long term. Finally, Duff et al. [19] have found a significant and sustained decrease in required FiO_2 following a sustained inflation manoeuvre. With regards to the effects of lung recruitment during general anaesthesia, Marcus et al. [22] found that, in children under the age of two, compliance and airway resistance are respectively decreased and increased fifteen minutes after the induction of anaesthesia, while compliance increased significantly after a recruitment manoeuvre. Tusman et al. [21] found a lower percentage of atelectatic lung in patients randomised to the delivery of a recruitment manoeuvre with respect to patients ventilated with continuous positive pressure or with zero end expiratory pressure.

Preliminary results in this study are in accordance with previous results in the fact that recruitment strategies are effective only if atelectasis is present, while effects do not seem to be sustained in the long term. Studies have shown that younger children benefit from recruitment manoeuvres given that compliance decreases during general anaesthesia if the recruitment manoeuvres where performed fifteen minutes into surgery. This suggests that the correct timing of recruitment strategies based on the evaluation of atelectasis throughout surgery is also crucial to their effectiveness. While the developed set-up allows for the monitoring of respiratory mechanics throughout surgery, the correction for the airway devices would allow for the definition of absolute values of resistance and reactance. Normalized values of R and X would allow for the delivery of recruitment strategies based on the patient’s lung mechanics.

7.2 COMET

The aim of this study is to track changes in respiratory mechanics in mechanically ventilated children undergoing laparoscopic appendectomy, in particular possible changes due to the insufflation of the abdomen during surgery.

Laparoscopic appendectomy provides several advantages compared to open surgery, such as minimal incision, shorter hospital stays, less pain during surgery and early mobilization. However, the insufflation of the abdomen, which allows for the space needed to perform the surgery, causes an increase in abdominal pressure that can lead to an ulterior reduction in FRC. Such a reduction of the functional residual capacity, which can be critical in children, is reflected in changes in respiratory mechanics. It can be hypothesized that following insufflation reactance (X) decreases while resistance (R) increases, indicating lung derecruitment and that this effect is higher in younger children and in children with higher BMI. Furthermore, during surgery reactance decreases further and resistance does not change significantly until after exsufflation, when X increases and R decreases. Lung derecruitment can be counteracted by applying lung protective strategies, such as recruitment manoeuvres and PEEP, although it is not clear how to tailor them to the needs of the patient.

This study will help formulate new-evidence based ventilation guidelines and policies to ventilation strategy in children undergoing laparoscopic surgery.

7.2.1 Clinical study methods

The COMET study is a single-centred observational study. During surgery, FOT is applied using low amplitude sinusoidal pressure oscillations (2 cmH_2O) at 5 Hz and flow and pressure signals are recorded at selected time frames. These recordings are then processed offline to calculate resistance and reactance to evaluate changes in respiratory mechanics before, during and after laparoscopic surgery.

Study Population

Recruitment is performed in children without major lung disease and who are undergoing laparoscopic appendectomy, additional inclusion and exclusion criteria are applied.

Inclusion criteria:

- Children of any sex
- Age from 2 to 16 years
- Undergoing laparoscopic appendectomy

Exclusion criteria:

- Children with a known difficult airway and thoracic malformation
- Children with a known major lung and/or cardiopulmonary disease:
- Uncorrected congenital heart disease
- Primary/secondary pulmonary hypertension
- Cardiac/thoracic malformations or tumours
- Structural lung changes
- Uncontrolled asthma
- Cystic fibrosis

Any other less common cardiopulmonary conditions are assessed by the treating anaesthetist and accounted for in a more exhaustive exclusion criteria list.

Parents or guardians of children that meet the inclusion criteria are approached in order to obtain a written informed consent to their participation in the study if they so desire. Furthermore, older children are also handed an information sheet in order for them to be aware of the proceedings involved in the study.

Experimental Protocol

After induction of anaesthesia the patient is transferred to the operating theatre where ventilation is started and managed as deemed appropriate by the attending anaesthetist.

The following guidelines are applied to minimise the confounding effect of the different ventilation approaches on lung recruitment and lung mechanics:

- Pressure control mode
- FiO_2: 0.3-0.45 to maintain SpO_2 above 95%
- PEEP: 5 cmH_2O
- PCV: Peak inspiratory pressure (PIP): 10-25 cmH_2O above PEEP, to reach tidal volumes of 6-8 ml/kg
- Respiratory rate (RR): depends on the child's age and is adjusted to maintain $etCO_2$ between 35-45 mmHg

The FOT set-up is connected to the anaesthesia ventilator prior to the transfer of the patient to the operating theatre in order to perform a leak test given the introduction of an additional circuit to the normal breathing circuit. Once the patient is connected to the anaesthesia ventilator and correctly ventilated the sinusoidal forcing signal at 5 Hz is applied and a visual check of its peak to peak amplitude is performed on the laptop, to ensure a peak to peak amplitude of approximately 2 cmH_2O. Throughout the surgery recordings are performed at fixed times:

- After intubation, muscle relaxation and induction of anaesthesia
- After a recruitment manoeuvre
- After gas insufflation
- Every 15 minutes during surgery
- At the completion of surgery
- After exsufflation
- After a recruitment manoeuvre
- At the end of surgery

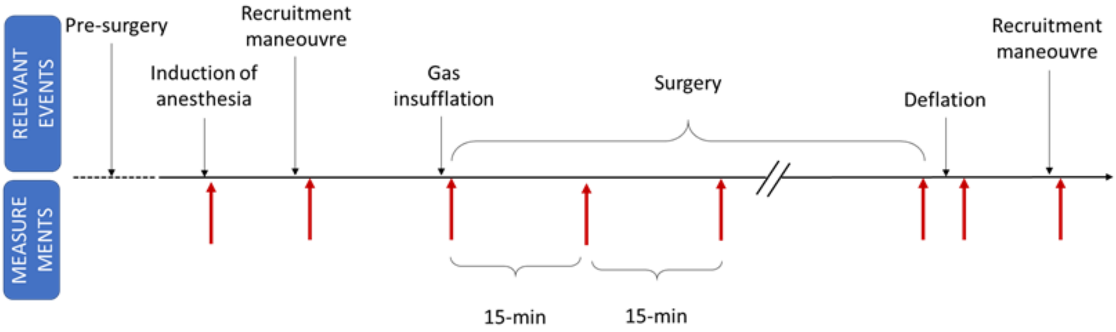


Figure 38 Protocol steps

Recruitment manoeuvres are performed manually ventilating the lungs with a peak airway pressure of 40 cmH_2O and a PEEP of 10-15 cmH_2O for 10 breaths to standardize lung volume history.

In addition, pulse oximetry (SpO_2), end-tidal carbon dioxide ($etCO_2$), fraction of inspired oxygen (FiO_2) and abdominal insufflation pressure are monitored at every step of the protocol. Furthermore, additional recordings can be performed.

- Additional RM, in order to have the possibility to record before, after and during any necessary recruitment strategy
- Any extra recording if needed

All recordings are saved in a folder dedicated to the patient.

Statistical Analysis

The recordings saved are then processed offline to obtain resistance (R) and reactance (X) for each saved file, which will be compared using one-way Anova for repeated measurements.

At this time very few patients have been recruited in this study, thus only a qualitative evaluation of the data can be carried out.

7.2.2 Results and discussion

In accordance with inclusion and exclusion criteria defined in the protocol, to date six patients have been recruited to the study. However, data was deemed acceptable for three of them, either because of missing recordings or failure of saving.

Age, weight and size of the ETT used are reported in Table 16 for each patient analysed. All patients were ventilated with PEEP=5 cmH_2O, PIP=15-20 cmH_2O and abdominal insufflation pressure of 12 cmH_2O.

	COMET_03	**COMET_04**	**COMET_05**
Age [years]	6.76	11	10
Weight [kg]	23.5	42.45	31.2
ETT size [mm]	5	6	5.5

Table 16 Age, weight and ETT size

Values of resistance (R) and reactance (X) were computed for the three patients for all recordings as per protocol, absolute values are plotted in Figure XX. While all patients have recordings for the first four and last three protocol steps (BEFORE_RM_1, AFTER_RM_1, AFTER_INSUFFLATION, SURGERY_1, BEFORE_DEFLATION, AFTER_DEFLATION, AFTER_RM_2), they differ in the number of recordings throughout the laparoscopic surgery depending on the length of the latter.

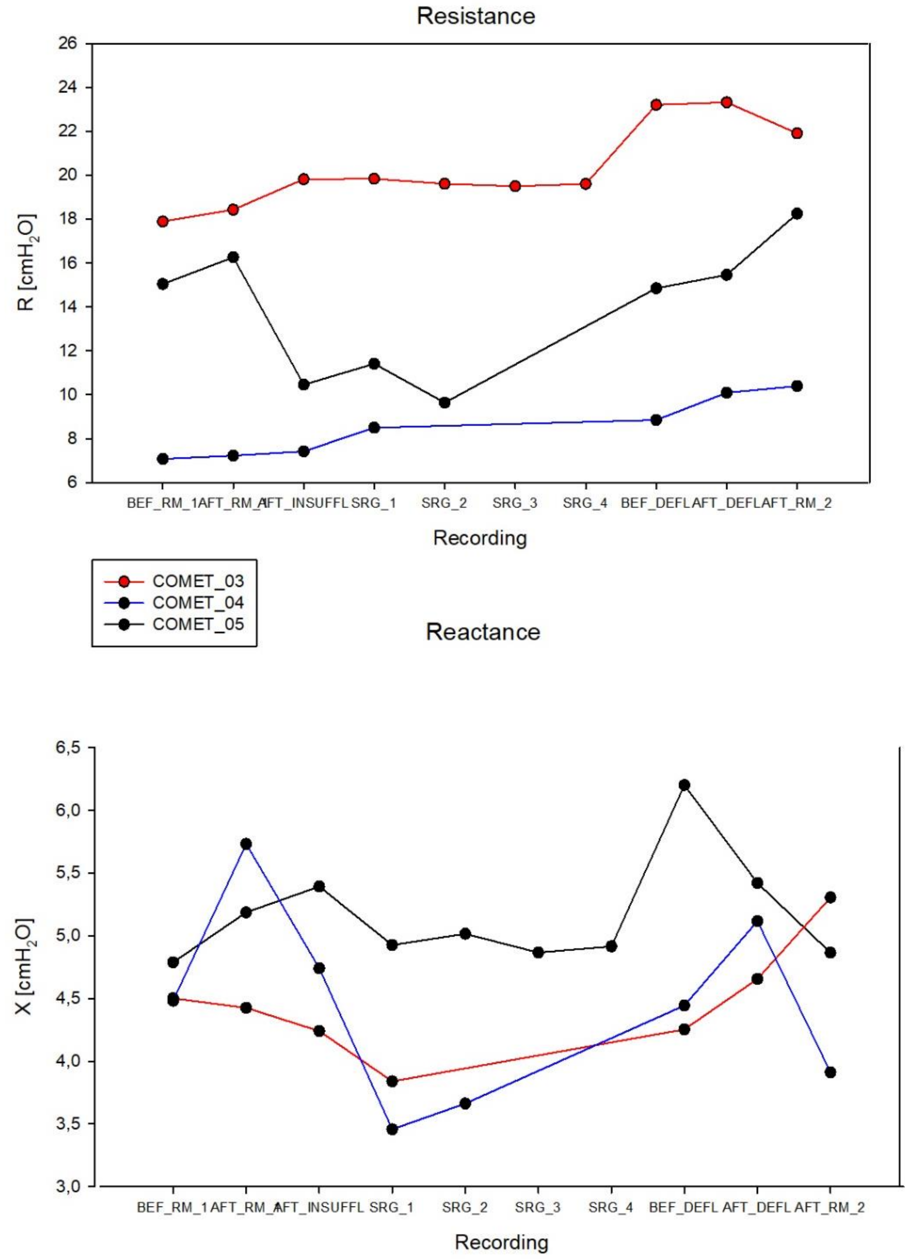


Figure 39 Absolute values of resistance (top) and reactance (bottom) for the different protocol steps

While plotted resistance and reactance seem to change significantly, they are actually contained within values that are not clinically significant. Furthermore, differences in absolute values of resistance between the three patients are reflective of different size endotracheal tubes: the patient with highest baseline resistance is intubated with a 4mm internal diameter ETT, while those with lower baseline values are intubated with ETTs with internal diameter of 5.5mm and 6 mm respectively. For this reason, correction for the tubes would further highlight the fact that the differences introduced by surgery are not clinically significant.

Furthermore, the fact that there seem to be no significative changes in respiratory mechanics can be due to the fact that intrabdominal insufflation pressures used during surgery are not high enough to cause such a reduction of FRC that results in closing of alveolar units.

8. Conclusions and future developments

Intraoperative mechanical ventilation strategies, such as the setting of positive end expiratory pressure levels and the delivery of recruitment strategies, which are part of routine practice in the paediatric setting need to be applied using a more patient-specific approach. While there are different methods to measure lung function and respiratory mechanics in children, most are not appropriate for the intraoperative setting given that they either require patient collaboration, disconnection from the breathing circuit or total muscle blockade. However, the forced oscillation technique represents a unique solution for the setting, since it allows for the measurement and monitoring of respiratory mechanics without the need for patient collaboration, allowing for activity of the respiratory muscles and it can be integrated into the breathing circuit of the anaesthesia ventilator.

Therefore, we developed a set-up to apply the FOT to the intraoperative setting in accordance with technical requirements defined by King et al. and clinical requirements dictated by the setting. The developed set-up was tested in vitro against a reference set-up to define the accuracy and repeatability of the measurements, both between two separate recordings from the same patient and between different patients. Resistance and reactance are computed from periodical measurements of a test lung, whose resistance and reactance are known, and the relative error with regards to reference values of impedance are checked to be within $\pm 10\%$. Furthermore, the algorithm implemented to compute resistance and reactance with a superimposed breathing pattern returns values of impedance with a relative error of less than 2% with regards to impedance measured during continuous positive pressure ventilation at a pressure equal to positive end expiratory pressure of the applied breathing pattern.

Resistance and reactance are measure of the resistive and elastic properties of the respiratory system, in particular end-expiratory reactance (X) at 5Hz has been proved to be indicative of the volume of aerated or non-aerated lung, thus it can be used to quantify the degree of derecruitment of the lung.

The developed set-up has been tested and is in use, thanks to a collaboration between Politecnico di Milano and Telethon Kids Institute, at Perth Children’s Hospital in two separate clinical studies aimed at defining evidence based guidelines for mechanical ventilation of children in the surgical setting.

In particular, the oscillation mechanics and sustained inflation study using FOT measurements of children under general anaesthesia (OASIS), is aimed at determining the effectiveness of two different recruitment strategies in re-opening collapsed lung regions, following the induction of anaesthesia, and their delivery through two different airway devices. Results of the analysis of data available to this date, which is predominantly made up of patients ventilated through laryngeal mask, show that there is no significant statistical difference in resistance or reactance before or after the recruitment manoeuvre and between patients randomised to a repeated or sustained inflation recruitment strategy. However, a further analysis of resistance and reactance changes showed that the repeated inflation manoeuvre seems to be effective in case of patients which show indications of derecruitment following the induction of anaesthesia. Furthermore, neither of the two recruitment strategies shows beneficial effects in the longer term.

The clinical study regarding changes in oscillation mechanics evaluated by the forced oscillation technique and lung recruitment during mechanical ventilation in paediatric laparoscopic appendectomy (COMET), is aimed at determining the effects of insufflation of the abdomen on respiratory mechanics. Only three patients have been studied to date and results suggest no significant variations in resistance or reactance throughout the procedure, possibly due to the low abdominal insufflation pressures used during appendectomies which does not produce a critical reduction of FRC in the children studied so far.

Thus, it is possible to say that the developed set-up represents a useful tool to monitor respiratory mechanics in order to customize the ventilation patterns and strategies to the needs of the patients.

To allow for such a solution values of resistance and reactance need to be corrected for the airway device used and represented as z-scores that give a clear indication as to whether the induction or maintenance of anaesthesia or the insufflation of the abdomen cause a critical reduction in FRC that can be resolved by the attending anaesthetist.

List of figures

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