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Design of a new function for mechanical ventilators to optimize PEEP in preterm infants

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Sommario

Un nuovo nato è definito come prematuro quando la sua età gestazionale è inferiore a 37 settimane complete. La prematurità può essere ulteriormente qualificata come tardiva (33-37 settimane), moderata (28-32 settimane) e grave (20-27 settimane). Un neonato prematuro, soprattutto quelli gravemente prematuri, soffrono di mancanza di surfactante. Inoltre, la loro parete toracica è scarsamente ossificata e loro muscoli intercostali non sono perfettamente funzionanti.
A causa di queste condizioni, può verificarsi insufficienza respiratoria. Inoltre, nelle prime ore dopo la nascita, questi neonati sono spesso soggetti a una malattia chiamata sindrome da distress infantile (IRDS), che è caratterizzata da un aumento della frequenza respiratoria, difficoltà nella respirazione, lamenti da fine espirazione e cianosi e, più importante , ampio volume polmonare dereclutamento compromettendo gli scambi gassosi.
Questa malattia è abbastanza comune nei neonati prematuri: infatti, il rischio di sviluppare RDS nei bambini nati prima di 30 settimane è di circa il 50% e può portare allo sviluppo di malattia polmonare cronica (CLD) compreso broncopneumo displasia (BPD).

Il trattamento più comune per IRDS a NICU (Unità di Terapia Intensiva Neonatale, terapia intensiva neonatale) è la ventilazione meccanica non invasiva o invasiva a pressione positiva (comprese pressione positiva continua Airways, CPAP, ventilazione meccanica non invasiva, NIV, e il supporto pressione invasiva o il volume garantito ventilazione meccanica), spesso associata a somministrazione di surfattante. Tuttavia, la ventilazione può provocare gravi lesioni al polmone, definite come danno polmonare indotto dal ventilatore (VILI). Il VILI aumenta la probabilità di sviluppare malattie respiratorie croniche come BPD, che è caratterizzato da un arresto dello sviluppo del polmone età gestazionale.
Poiché le caratteristiche del sistema respiratorio neonati li rendono più suscettibili al danno polmonare, la scelta della strategia corretta ventilazione è estremamente importante. Diverse strategie ventilatorie protettive sono state utilizzate nel periodo neonatale, con l'obiettivo di ridurre le malattie polmonari croniche.
Tuttavia, diversi randomized control trials hanno dimostrato che le modalità di ventilazione specifiche non sono differenti in termini di efficacia e sicurezza, al contrario, è sempre più evidente che un ruolo importante nel danno polmonare è dovuta alla errata impostazione di parametri di ventilazione. Pertanto, sempre maggiore attenzione è rivolta al miglioramento dei criteri per adattare la selezione di questi parametri di ciascun paziente e condizione. Tra tutti i parametri di ventilazione, quella che influenza di più il reclutamento volume polmonare è la PEEP (pressione positiva di fine espirazione). Infatti, il ruolo di PEEP è di impedire la chiusura degli alveoli di fine

espirazione. Nella pratica clinica, osservando di saturazione di ossigeno (SpO2) durante il trial crescente-decrescente di PEEP è il procedimento più diffuso per la selezione del valore ottimale della pressione di fine espirazione. Tuttavia, questo approccio non è strettamente legato alla condizione meccanica del polmone del paziente. In effetti, impostazione di valori troppo alti o troppo bassi di PEEP per un dato paziente può portare a VILI e malattie polmonari croniche.
Il legame importante tra la meccanica respiratoria e del volume polmonare reclutamento sottolinea l'urgente necessità di nuovi strumenti clinici per la valutazione al letto del paziente delle proprietà meccaniche del sistema respiratorio. Una soluzione promettente è l'uso della tecnica delle oscillazioni forzate (FOT), che consente la stima non invasiva della impedenza di ingresso del sistema respiratorio (Zin) applicando oscillazioni di pressione piccola ampiezza in apertura delle vie aeree e misurando la risposta di il sistema in termini di flusso. Zin è un numero complesso definito da una parte reale, detta resistenza (RR), e una parte immaginaria, denominata reattanza (Xrs). [9]
È stato recentemente dimostrato che l'impedenza respiratoria totale misurata ad una frequenza di 5 Hz è molto sensibile alle variazioni nella meccanica della periferia polmonare e che può fornire informazioni adeguate sul reclutamento e dereclutamento di volume polmonare. [1]
Inoltre, studi su modelli animali impoveriti di surfactante hanno dimostrato che le FOT applicate durante i trial di PEEP possono essere usati con successo per ottimizzare PEEP. In particolare, è stato dimostrato che il valore della pressione di fine espirazione che massimizza la reattanza duranti la fase decrescente del PEEP trial riduce il VILI. [2], [3] Inoltre, si è osservato che la stessa tecnica può essere applicata sia durante la ventilazione convenzionale e durante la ventilazione HFOV modalità. Mentre nel primo stimolo deve essere aggiunto in cima alla forma d'onda di ventilazione, in quest'ultimo l'uso delle oscillazioni di pressione ad alta frequenza in grado di fornire lo stimolo per sé. [4] - [6]
Infine, nel 2013 la possibilità di applicare le FOT durante i PEEP trial nei neonati è stato dimostrato con risultati promettenti. Tuttavia, al fine di approfondire il ruolo delle FOT nell'ottimizzare la PEEP nei neonati pretermine, è ancora necessario un set-up adeguato e clinicamente applicabile. [6] - [8]

Pertanto lo scopo di questa tesi è quello di sviluppare un dispositivo che può guidare il clinico nella scelta del PEEP nei neonati prematuri. In particolare, i risultati di recenti studi sulla utilità della misura della reattanza attraverso le FOT evidenzia la necessità di ulteriori studi sui neonati prematuri per rafforzare l'evidenza di utilità clinica di questa tecnica. A questo scopo è necessario un dispositivo in grado di fornire in tempo reale i valori medi di reattanza per ogni fase del PEEP durante un trial. Questo dispositivo deve essere facile da usare, sicuro ed affidabile ed in grado di fornire la ventilazione meccanica durante l'applicazione FOT. Al fine di soddisfare i requisiti di sicurezza della ventilazione di neonati prematuri, la metodologia dovrebbe essere integrata in un ventilatore meccanico che già garantisce la corretta gestione del trattamento ventilatore.

Inoltre, sono necessari anche un robusto algoritmo per la stima della media reattanza sistema respiratorio a fine espirazione per ogni fase del trial di PEEP. Pertanto, la progettazione di un algoritmo automatico per la selezione dei dati è di primaria importanza. Infatti, si deve verificare se le ipotesi di base sulla stima dell'impedenza sono soddisfatte e se tali dati sono alla fine dell'espirazione.

Nel primo capitolo, il background necessario per capire questo lavoro è presentato. In particolare, sono riportate l'analisi della meccanica del sistema respiratorio, la descrizione dello sviluppo del polmone durante la vita fetale e perinatale, diverse tecniche di ventilazione meccanica, danno polmonare indotto dal ventilatore e l'ottimizzazione dei parametri di ventilazione. La nascita non rappresenta la fine dello sviluppo del polmone, ma vi è un complesso processo di crescita dopo la nascita per cui il sistema respiratorio del bambino è in gran parte diverso da quello adulto. Le principali differenze tra neonato e sistema respiratorio dell'adulto sono che i neonati presentano una compliance della parete toracica superiore, un numero ridotto di alveoli e che il ritorno elastico può essere elevato a causa della tensione superficiale più alta dovuta alla mancanza del surfactance, un tensioattivo. I neonati prematuri sono caratterizzati da uno sviluppo strutturale incompleta, una minore capacità di assorbire il liquido polmone fetale, la mancanza di surfactante e maggiore spessore della membrana alveolo-capillare che interferisce con scambio di gas. Le principali patologie neonatali sono dovute ad alterazioni nel processo di rapido adattamento che deve avvenire alla nascita, come per esempio il fatto che i polmoni devono adeguarsi all’aria. In particolare, la carenza di surfattante è la causa principale dello sviluppo della Sindrome da distress respiratorio (RDS). L’RDS è una delle patologie più diffusa che è caratterizzata da un aumento della frequenza respiratoria, difficoltà nella respirazione, gemiti di fine espirazione e cianosi e, più importante, esteso dereclutamento polmonare portando ad egli scambi gassosi seriamente compromessi. Quest’ultimo effetto è principalmente dovuto alla mancanza del tensioattivo. Il trattamento più comune per RDS in NICU è ventilazione meccanica a pressione positiva, spesso associata alla somministrazione di tensioattivo. Tuttavia, la ventilazione può provocare gravi lesioni al polmone che vengono definite come danno polmonare indotto dal ventilatore (VILI), che aumenta il rischio di sviluppare malattie respiratorie croniche. Una qualche forma ibrida (SIPPV + VG, PSV-SIPPV) della ventilazione meccanica convenzionale e qualche strategia di ventilazione alternativa (BPAP, HFOV NR) sono stati sviluppati e confrontati con la ventilazione meccanica convenzionale (CMV). Tuttavia, non è stato dimostrato che una modalità di ventilazione è più efficace e più sicura rispetto alle altre per neonati. Perciò attenzione crescente è rivolta al miglioramento dei criteri per adattare la selezione di questi parametri di ciascun paziente e condizione.

Nella gestione clinica di neonati ventilati una sfida importante è quella di ottimizzare il volume polmonare applicando una pressione sufficiente a mantenere il polmone reclutati interamente senza aumentare la tensione applicata ai tessuti. Il parametro di ventilazione che maggiormente influenza il numero di unità alveolare che rimane aperto attraverso tutto il ciclo respiratorio è la pressione positiva di fine espirazione (PEEP).
Pertanto, una tecnica affidabile e non invasiva per la valutazione della funzione respiratoria al letto del paziente è necessaria per scegliere il valore di PEEP corretto per ciascun bambino, secondo il suo stato patologico.
Attualmente, l’impostazione della PEEP si basa principalmente sulla ossigenazione arteriosa e l’osservazione del volume polmonare attraverso delle radiografie del torace del paziente. Tuttavia, le strategie che sono guidate dal volume polmonare offrono vantaggi rispetto a quelli che si concentrano solo sugli scambi gassosi. Per determinare il volume polmonare reclutato, la CT è lo strumento diagnostico standard, ma non è disponibile al letto ed è associato ad un alto carico di radiazioni.
Diverse tecniche sono state proposte ed utilizzate su neonati, ma nessuno di queste viene utilizzata nella pratica clinica standard per l'ottimizzazione PEEP o perché sono inadatti per una unità di terapia intensiva o perché non forniscono informazioni complete.
Un approccio promettente per il monitoraggio non invasivo della meccanica respiratoria è la tecnica delle oscillazioni forzate (FOT) durante il quale uno stimulo sinosuidale di pressione viene applicato all'apertura vie aeree e la risposta meccanica del sistema respiratorio è misurata dalla resistenza e reattanza. In particolare, l'uso delle FOT durante un PEEP tiral sembra promettente per ottimizzare PEEP.

Nel secondo capitolo, il software e l'hardware di sviluppo è descritto. Le FOT in combinazione con PEEP trial offre risultati promettenti per l’ottimizzazione della PEEP in modelli animale. In effetti, la scelta migliore per sviluppare la metodologia dovrebbe essere quello di integrarla in un ventilatore meccanico che garantisce già la corretta gestione del trattamento ventilatore. Tuttavia, i costi umani ed economici di integrare tutto in un ventilatore meccanico non sarebbero giustificati in quanto non è ancora noto quanto l'ottimizzazione della PEEP basata su FOT è efficace nel ridurre gli effetti della RDS nei neonati.
Pertanto, si decide di utilizzare un approccio ibrido che consiste nello sviluppare la nuova metodologia di un dispositivo esterno che comunica con un ventilatore meccanico. In questo modo consente modifiche minime nel firmware del ventilatore, che sono: invio di dati tramite una comunicazione seriale e capacità di generare lo stimolo pressione necessaria per le FOT. Una società svizzera biomedica, Acutronics, ha implementato le modifiche di cui in uno dei loro dispositivi

commerciali, il Fabian HFO. Pertanto, nel contesto di questo lavoro di tesi, abbiamo scelto di sviluppare un'applicazione Android per tablet/smatphone che si interfaccia con il respiratore meccanico Fabian HFO.

Il Fabian HFO campiona i dati di pressione e flusso e invia questi dati con una frequenza di campionamento di 200 Hz attraverso una comunicazione seriale (RS232). Poiché il dispositivo esterno per la costruzione della curva di PEEP-reattanza è stato fatto in Android, abbiamo scelto di utilizzare un approccio wireless per semplificare l'uso da parte dei clinici. In particolare, è stato scelto il protocollo Bluetooth. Dato che il Fabian non fornisce i dati di uscita con protocollo Bluetooth, è stato costruito con la tecnica di Press 'n' Peel una scheda elettronica che potrebbe realizzare la conversione Bluetooth Sriale e viceversa.

L'applicazione Android gestisce l'acquisizione di flusso e la pressione dal ventilatore meccanico e calcola il valore di impedenza medio come descritto nel terzo capitolo. L'interfaccia utente sviluppata deve gestire le misure con le FOT sia durante CMV e HFOV. Mentre nella prima modalità lo stimolo può essere impostato, nella seconda lo stimolo è la stessa forma d'onda di ventilazione. Infatti, in CMV è possibile scegliere fra tre frequenze (5, 10, 17 Hz) e tre ampiezze (2,5, 5, 7,5 mbar). Dato che l'unica frequenza necessaria per l'applicazione corrente è di 5 Hz, abbiamo deciso di sviluppare due differenti UI: si scelto di farne una nella si è semplificato e velocizzato l'utilizzo del dispositivo preimpostando le FOT, e una seconda un cui fosse possibile all'utente di scegliere di utilizzare frequenze e ampiezze diverse di stimolo pressione.

Sia in HFOV e in CMV c'era la necessità di costruire una curva PEEP-reattanza durante un trial di PEEP. Per ogni step del trial, l'impedenza media del sistema respiratorio è calcolata negli ultimi 30 secondi. Al fine di costruire la PEEP-reattanza, nell'interfaccia utente è presente un pulsante che, quando premuto, inizia a memorizzare resistenza e reattanza selezionate per la valutazione del comportamento meccanico degli infanti. Pertanto, l'utente deve cambiare la PEEP sul ventilatore meccanico e quindi premere il pulsante sul app per avere uno step del tial di PEEP. In questo modo l'utente si costruisce la curva PEEP-reattanza passo dopo passo.

Nel terzo capitolo, il progetto di algoritmi per ottenere misure di impedenza accurate è presentato. In particolare, per l'applicazione corrente è necessario: selezionare il fine espirazione impedenza, rimuovere manufatto dalla selezione e correggere l'eventuale sfasamento tra flusso e pressione.

In primo luogo, abbiamo dovuto scegliere tra il LMSM e FFTM per calcolare l'impedenza. Mentre il primo è molto accurata e ha una risoluzione temporale superiore, il secondo può essere utilizzato quando è applicata più di una frequenza. Tuttavia, dato si impiega una sola frequenza, abbiamo scelto il LMSM che, inoltre, garantisce una risoluzione temporale migliore.

Per selezionare l'impedenza a fine espirazione scadenza e rimuovere eventuali artefatti, sono stati identificati 8 parametri i quali verificano la fine espirazione e la presenza di ipotesi sottese LMSM. Questi indici sono: Posizionare il volume minimo, il valore massimo del valor medio del flusso sul periodo di stimolo, Derivata del valore massimo del valor medio del flusso sul periodo di stimolo, Derivata del valore massimo del valor medio della pressione sul periodo di stimolo, Flow Shape Index, Pressione Shape Index, Differenza Shape Index e Indice di Linearità. Mentre i primi 4 indici sono utilizzati per identificare la fine di scadenza, gli ultimi 4 sono stati utilizzati per osservare se i segnali di flusso e pressione sono conformi alle ipotesi sottostanti il LMSM. L'algoritmo seleziona l'impedenza controllando che i parametri sia inferiore ad una soglia.
Dopo l'algoritmo di selezione, è stato necessario procedere alla eliminazione degli outliers che tiene conto della distribuzione congiunta dei dati di resistenza e di reattanza sul piano complesso di fine espirazione.
Tutti i parametri descritti devono essere ottimizzati per migliorare i risultati della selezione. Per fare ciò, si è proceduto ad una ricerca dei valori ottimali di soglie da utilizzare con i dati dallo studio di Dellaca R., Veneroni, C. et al. 2013.
Infine, al fine di essere certi della precisione delle misure, è importante verificare che i dati di pressione e di flusso campionati dalla Fabian HFO sono sincroni. Infatti, i sensori utilizzati sono un anemometro per flusso ed un manometro differenziale per la pressione che passano per una diversa elaborazione digitale e analogico. Pertanto, il flusso e la pressione devono essere allineati. Le misure sono state fatte confrontando i sensori Fabian con i sensori del Politecnico di Milano utilizzati come gold standard.
Queste misure hanno mostrato come i segnali del Fabian possono essere utilizzato per la stima delle proprietà meccaniche, con alcune limitazioni. In effetti, l'acquisizione ed elaborazione digitale porta con sé un ritardo tra il flusso e la pressione. Questo ritardo è stato valutato effettuando misure su test lung indeformabile, che sono le bottiglie con l'ingresso capillare. Pertanto, tali correzioni sono state applicate per la misurazione di impedenza.

Nel quarto capitolo, il sistema è stato valutato in vitro e su modelli animali per vedere se possa essere utilizzato per uno studio clinico.
In primo luogo, i test in vitro sono stati fatti durante IPPV ed è stata osservata la capacità dell'algoritmo sviluppato per fornire risultati simili a quelli in cui è presente solo la frequenza di stimolazione. Per queste misure si sceglie di utilizzare un test lung rigido, che è una bottiglia con i capillari che simulano l'effetto di una resistenza e una cedevolezza meccanica in serie.
Questi test hanno mostrato una somiglianza tra i dati selezionati e quelli con solo la frequenza di stimolazione. Il problema principale è quanto deve essere lungo il periodo di acquisizione al fine di

ottenere risultati accurati e la necessità di avere una ottimizzazione custom dell'algoritmo in funzione del tipo di analisi da fare.

Poi, è stata analizzata la capacità di fornire una curva di uscita di PEEP-reattanza e dell'errore generato in confronto con una selezione manuale. Al fine di costruire una curva PEEP-reattanza che non sia piatto, è necessario utilizzare il test lung deformabile, ad esempio un palloncino. I risultati hanno dimostrato che l'algoritmo è in grado di fornire risultati con differenze non significative rispetto alla selezione manuale (svolto da un operatore esperto) per ogni fase del PEEP trial su diversi test lung deformabile.

Infine, prove su modello animale sono stati effettuati per valutare le prestazioni dell'algoritmo in presenza di respirazione spontanea e la variabilità modello di respirazione. Dato che misure su bambini non sono possibili per motivi di sicurezza, sono stati utilizzati i dati di agnelli. In effetti, gli agnelli prematuri sono il modello animale più simile a neonati pretermine. Questi test sono stati effettuati utilizzando i dati di agnelli da University of Western Australia (Perth, Australia) e University of Utah (Salt Lake City, Utah). Su questi dati, è stato analizzata la capacità dell'algoritmo sviluppato di fornire gli stessi risultati rispetto al gold standard, che consiste in una selezione manuale eseguita da un operatore esperto.

Successivamente, i trial di PEEP sono stati analizzati per vedere la capacità dell'algoritmo e la metodologia per fornire risultati precisi sulla PEEP ottimale. I trial di PEEP sono stati analizzati prima con l'algoritmo di selezione automatica o poi con una selezione manuale effettuata da un operatore esperto. Anche in questo caso, i risultati erano equivalenti.

L'ultimo risultato significativo è che l'interfaccia grafica sviluppata si è dimostrata intuitiva e di facile utilizzo per l'uso in ambiente ospedaliero.

In conclusione, un nuovo sistema per l'ottimizzazione PEEP usando i trial di PEEP con FOT è stato sviluppato e validato su un modello animale. In seguito, saranno necessari studi sugli esseri umani, al fine di verificare l'efficacia di questa metodologia su neonati prematuri.

Summary

A new-born is defined as premature when his gestational age is less than 37 completed weeks. Prematurity can be further classified as late (33-37 weeks), moderate (28-32 weeks) and severe (20-27 weeks). Premature new-born, especially those severely premature, suffer from lack of surfactant. In addition, their chest wall is poorly ossified and their intercostal muscles are not fully functional. Because of these conditions, respiratory failure may occur. Moreover, in the first hours after birth, these infants are often subject to a disease called infant distress syndrome (IRDS), which is characterised by an increased respiratory rate, a difficulty in breathing, groans from end-expiration and cyanosis and, most important, extensive lung volume derecruitment leading to a seriously impaired gas exchange.

This disease is quite common in premature infants: indeed, the risk of developing RDS in babies born before 30 weeks is about 50% and can lead to the development of chronic lung disease (CLD) including broncopneumo dysplasia (BPD).

The most common treatment for IRDS in NICU (Neonatal Intensive Care Unit, NICU) is positive pressure non-invasive or invasive mechanical ventilation (including Continuous Positive Airways Pressure, CPAP, non-invasive mechanical ventilation, NIV, and invasive pressure support or volume guaranteed mechanical ventilation), often associated with administration of surfactant. However, ventilation can cause serious injury to the lung, defined as Ventilator-Induced lung injury (VILI). VILI increases the likelihood of developing chronic respiratory diseases such as BPD, which is characterized by a stoppage of the development of lung gestational age.

Since the characteristics of newborns respiratory system make them more susceptible to lung injury, the choice of the correct ventilation strategy is extremely important. Several protective ventilatory strategies have been used in the neonatal period, with the goal of reducing chronic lung diseases. However, several large randomized control trials demonstrated that specific ventilation modalities are not different in term of effectiveness and safety, conversely, there is increasing evidence that an important role in lung injury is due to the incorrect setting of ventilation parameters. Therefore, increasing attention is paid to the improvement of the criteria for tailoring the selection of these parameters on each patient and condition. Among all ventilation parameters, the one that influences more the lung volume recruitment is the PEEP (positive end-expiratory pressure). Indeed, the role of PEEP is to prevent the closure of the alveoli at the end of expiration. In clinical practice, observing of oxygen saturation (SpO2) during an increasing-decreasing PEEP trial is the most widely adopted procedure for selecting the optimal value of PEEP. However, this approach is not strictly related to the mechanical condition of the patient’s lung. Indeed, setting either too high or too low PEEP values for a given patient may lead to VILI and chronic lung diseases.

The important link between respiratory mechanics and lung volume recruitment underlines the urgent need for new clinical tools for the bedside evaluation of the mechanical properties of the respiratory system. A promising solution is the use of the forced oscillation technique (FOT), which allows the non-invasive estimation of the input impedance of the respiratory system (Z_{in}) by applying small-amplitude pressure oscillations at the airway opening and by measuring the response of the system in term of flow. Z_{in} is a complex number defined by a real part, called resistance (R_{rs}), and an imaginary part, called reactance (X_{rs}). [9]
It was recently shown that the total respiratory impedance measured at a frequency of 5 Hz is very sensitive to changes in the mechanics of the lung periphery and that it can provide adequate information on recruitment and derecruitment of lung volume. [1]
Furthermore, studies in surfactant-depleted animal models have demonstrated that FOT applied during PEEP trials can be successfully used to optimize PEEP. In particular, it was shown that the value of end-expiratory pressure that maximizes the reactance in the decreasing limb of the PEEP trial reduces VILI. [2], [3] Moreover, it was observed that the same technique can be applied both during conventional ventilation and during HFOV ventilation modality. While in the former the stimulus has to be added on top of the ventilation waveform, in the latter the use of high frequency pressure swings can provide the stimulus by itself. [4]–[6]
Finally, in 2013 the feasibility of applying the FOT during PEEP trial in newborns was demonstrated obtaining promising results. However, in order to further investigate the role of FOT in optimizing peep in preterm newborns, an appropriate clinically applicable set up is still needed. [6]–[8]

Therefore the purpose of this thesis is to develop a device which can guide the clinician in choosing the PEEP in premature infants. In particular, the results of recent studies on the usefulness of the measurement of reactance through the FOT highlights the need of further studies on preterm infants in order to strengthen the evidence of clinical usefulness of this technique. To this purpose a device able to provide in real time the mean values of reactance for each step of PEEP during a trial is needed. This device should be easy to use, safe and reliable and able to deliver mechanical ventilation while applying FOT. In order to meet the safety requirements of the ventilation of preterm infants, the methodology should be integrated in a mechanical ventilator that already guarantees the proper management of the ventilator treatment.
Moreover, a robust algorithms for the estimation of the mean respiratory system reactance at end-expiration for each step of a PEEP trial are also needed. Therefore, the design of an automatic algorithm for the selection of data was of primary importance. Indeed, it has to check if the underlying assumptions on the impedance estimation are satisfied and if those data are at the end of expiration.

In the first chapter, the background need to understand this work is presented. In particular, the analysis of respiratory system mechanics, the description of lung development during fetal and perinatal life, different techniques of mechanical ventilation, Ventilator-Induced lung injury and the ventilation parameter optimisation are reported. Birth does not represent the end of lung development, but there is a complex process of growth after birth so that the infant respiratory system is largely different from the adult one. The main differences between infant and adult respiratory system are that infants present higher chest wall compliance, a reduced number of alveoli and that the elastic recoil due to surface tension can be elevated by lack of surfactant. Preterm newborns are compounded by an incomplete structural development, a lower capacity to absorb fetal lung liquid, the lack of surfactant and increased thickness of the alveolar-capillary membrane that interferes with gas exchange. The major neonatal distresses are due to alterations in the principal change that have to occur at the birth as the lungs adjust to breathing air. In particular, the surfactant deficiency is the major cause of the development of RDS. Respiratory distress syndrome is one of the most diffuse pathology which is characterised by an increased respiratory rate, a difficulty in breathing, groans from end-expiration and cyanosis and, most important, extensive lung volume derecruitment leading to a seriously impaired gas exchange and is mainly due to lack of surfactant. The most common treatment for RDS in NICU is positive pressure non-invasive or invasive mechanical ventilation, often associated with administration of surfactant. However, ventilation can cause serious injury to the lung, defined as Ventilator-Induced lung injury (VILI) which increases the likelihood of developing chronic respiratory diseases. Some hybrid form (SIPPV+VG, PSV-SIPPV) of conventional mechanical ventilation and some alternative ventilation strategy (BPAP, HFOV, NIV) have been developed and opposed to conventional mechanical ventilation (CMV). However, it has not been proved that one ventilation mode is more effective and safer than the others for newborns while increasing attention is paid to the improvement of the criteria for tailoring the selection of these parameters on each patient and condition.

In the clinical management of ventilated infants a major challenge is to optimize lung volume applying sufficient pressure to keep the lung fully recruited without increasing the stress applied to the tissues. The ventilation parameter which most affects the number of alveolar unit that remains opened through all the respiratory cycle is the positive (PEEP).

Therefore, a reliable and non-invasive technique for the bedside assessment of respiratory function is necessary to choose the correct PEEP value for each infant, according to his pathological state. Currently, PEEP setting is based primarily on arterial oxygenation and on inflation of the lung on the patient's chest radiograph. However, lung volume-targeted strategies offer advantages over those

that focus only on gas exchange. To determine lung volume recruitment CT is the preferred diagnostic tool, but it is not available at bedside and is associated with radiation load.
Different techniques have been proposed and used on infants, but none of them is used in the standard clinical practice for PEEP optimization either because they are unsuitable for an intensive care unit or do not provide completed information.
One promising approach to non-invasive monitoring of respiratory mechanics is the forced oscillation technique (FOT) during which a pressure stimulus is applied at the airways opening and the mechanical response of the respiratory system is measured by resistance and reactance. In particular, the usage of FOT along with a PEEP trial seem promising in order to optimise PEEP.

In the second chapter, the software and hardware development is described. The FOT combined with PEEP trial provides promising results in optimising PEEP in animal model. Indeed, the best choice to develop the methodology should be to integrate it in a mechanical ventilator that already guarantees the proper management of the ventilator treatment. However, the human and economic costs to integrate everything into a mechanical ventilator is not justified as it is not yet known how much the optimization of PEEP based on FOT is effective in reducing the effects of RDS in infants.
Therefore, we decide to use a hybrid approach which consists in developing the new methodology of an external device which communicates with a mechanical ventilator. This way allows minimal changes within the firmware of the ventilator which are: sending data via a serial communication and ability to generate the pressure stimulus needed for FOT. A biomedical Swiss company, Acutronics, has implemented the changes mentioned in one of their commercial devices, the Fabian HFO. Therefore in the context of this thesis work, we chose to develop an Android application for tablet/smatphone which interfaces with the mechanical respirator Fabian HFO.
The Fabian HFO samples the data of pressure and flow and it sends those data with a sample rate of 200 Hz with a serial communication (RS232). In order to simplify the usage by clinicians, we decided to use a wireless communication between the mechanical ventilator anche the Android device. In particular, it was chosen the Bluetooth protocol. As the Fabian does not provide the output data with Bluetooth protocol, it was built with the technique of Press 'n' Peel an electronic board that could realize the Bluetooth to Serial conversion and vice versa.
The Android application manages the acquisition of flow and pressure from the mechanical ventilator and computes the mean impedance value as described in the third chapter. The developed UI has to manage FOT measurements both during CMV and HFOV. While in the former modality the stimulus can be set, in the latter the stimulus is the ventilation waveform itself. Indeed, in CMV it is possible to choose between three frequencies (5, 10, 17 Hz) and three amplitudes (2.5, 5, 7.5 mbar). As the only frequency needed for the current application is 5 Hz, we decided to develop two different UI: one is

done to simply the usage with pre-set FOT setting while the other allow the user to choose to use different frequency or different amplitude of the pressure stimulus.
Both in HFOV and in CMV there was the need to build a PEEP-Reactance curve during a PEEP trial. For each step of PEEP the mean impedance of the respiratory system is computed at end expiration in the last 30 seconds of the step.
In order to build the PEEP-Reactance, in the UI there is a button which, when pressed, starts to save resistance and reactance selected for the evaluation of the mechanical behaviour of the infants. Therefore, the user has to change the PEEP on the mechanical ventilator and then press this button on the app in order to have a step of the PEEP trial. That way allow the user to build the PEEP-Reactance curve step by step.

In the third chapter, the algorithm design for obtaining accurate impedance measurements is presented. In particular, for the current application is need to: select the end of expiration impedance, remove artefact from the selection and correcting the possible phase shift between flow and pressure.
Firstly, we had to choose between the LMSM and the FFTM for computing the impedance. As the former is very accurate and has a higher temporal resolution, the latter can be used when more than one frequency is applied. However, as only one frequency is employed, we choose the LMSM because of the better time resolution.
In order to select the end of expiration impedance and to remove artefact, 8 parameters has been identified to individuate the end-expiration and the occurrence of the assumptions underlying the LMSM. These indices are: Position the minimum volume, Maximum mean value of the flow on the stimulus period, Derivative of Maximum mean value of the flow on the stimulus period, Derivative of Maximum mean value of the pressure on the stimulus period, Shape Flow Index, Pressure Shape Index, Difference Shape Index and linearity Index. While the first 4 indexes are used to identify the end of expiration, the last 4 were used to observe whether the signals of flow and pressure comply with the assumptions underlying the LMSM. The algorithm selects the impedance by checking the identified parameter if their value is below a proper threshold.
After the selection algorithm, it was necessary to proceed at the outliers' elimination which takes into account the joint distribution of the data of resistance and reactance on the complex plane at the end of exhalation.
All the described parameters are to be optimized to improve the results of the selection. In order to do that, we proceeded to a search of the optimum values of thresholds to be used with the data from the study of Dellacà R., Veneroni, C. et al. 2013.

Finally, in order to be sure of the accuracy of the measurements it is important to verify that pressure and flow data sampled from the Fabian HFO are synchronous. In fact, the sensor used are an anemometer for flow and a differential manometer for the pressure which passes to different digital and analogical elaboration. Therefore, flow and pressure are to be aligned. Measures were done by comparing the Fabian sensors with the sensors of the Politecnico di Milano used as gold standard. These measurements have shown how the signals of the Fabian can be used for estimation of mechanical properties, with certain limitations. Indeed, their acquisition and digital elaboration brings along a delay between flow and pressure. This delay was evaluated by conducting measurements on non-deformable test lung, which are the bottles with the capillary entrance. Therefore, those corrections were applied at for measuring impedance.

In the fourth chapter, the system was evaluated both in vitro and on model animal in order to see if it could be used for a clinical study.
Firstly, In vitro test were made during IPPV and it was observed the ability of the algorithm developed to provide results similar to those in which only the frequency of stimulation is present. For these measures it is chosen to use a rigid test lung, which is a bottle with the capillaries that simulate the effect of a resistance and a mechanical compliance in series.
This test has shown a similarity between the selected data and those with only the stimulation frequency.
Then, it was analysed the ability of the application to provide an output curve of PEEP-reactance and of the error generated in comparison with a manual selection. In order to build a curve PEEP-reactance that is not flat it is necessary to use deformable test lung, for example a balloon. The results have shown that the algorithm is able to provide results with non-significant differences compared to manual selection (done by an experienced operator) for each step of PEEP on different deformable test lung.
Finally, tests on animal model were carried out to evaluate the performance of the algorithm in the presence of spontaneous breathing and breathing pattern variability. As measurements on infants are not possible for safety reasons, data from lambs were used. Indeed, preterm lambs are the most similar animal model to pre-term infants. These tests were made using data from lambs from University of Western Australia (Perth, Australia), and University of Utah (Salt Lake City, Utah). On these data, it was analysed the ability of the algorithm developed to provide the same results with respect to the gold standard, which consists of a manual selection performed by an experienced operator.
Subsequently, PEEP trial were analysed in order to see the ability of the algorithm and the methodology to provide accurate results on the optimal PEEP. The trial of PEEP were analysed before

with the algorithm of automatic selection or then with a manual selection by an experienced operator. Also in this case, the results were equivalent.
The last significant result is that the graphical interface developed proved intuitive and user friendly for use in a hospital setting.

In conclusion, a new system for PEEP optimisation using PEEP trial along with FOT was developed and validated on an animal model. Following, studies on humans are needed in order to see how effective this methodology on premature infants is.

Introduction

There are several physiological and anatomical reasons why infants are less able to cope with a given stress to the respiratory system than older children and adults. Birth represents a critical event associated with dramatic changes in the lung function: the new-born lung fluid which maintains the lungs in a distended state during fetal life needs to be absorbed, the lungs have to be filled with air, adequate gas-exchanging surface area has to be established, the pulmonary blood flow has to greatly increase and the surfactant system has to ensure the lungs remain expanded by decreasing the alveolar surface tension. Moreover preterm new-borns are compounded by an incomplete structural development, a lower capacity to reabsorb fetal lung liquid, the lack of surfactant and increased thickness of the alveolar-capillary membrane that interferes with gas exchange. All these features make infants and especially the preterm ones very exposed to respiratory system pathologies.
Respiratory distress syndrome (RDS) is the most severe form of acute lung injury and is responsible for high rates of neonatal morbidity and mortality. It affects about the 10% of all infants born prematurely, with an incidence that decreases with the degree of maturity at birth, and only rarely affects those born at term. RDS results from a deficiency of surfactant, a chemical substance essential for alveolar expansion, which is produced by the lung between the 34th and 37th week of gestation and is characterised by reduced functional residual capacity, decreased lung compliance and disordered gas exchange. These symptoms usually appear shortly after birth and become progressively more severe causing increasing difficulties in breathing. No effective drugs exist to treat RDS and therapy consists in surfactant administration and in supporting respiration by mechanical ventilation. Assisted ventilation aims at re-expanding atelectasis lung units and preventing the alveoli from collapsing, resulting in increased gas-exchange surface and in improved ventilation-perfusion matching. Although mechanical ventilation is lifesaving and critical to survival for most infants with RDS, its improper use can cause a secondary Ventilator-Induced lung injury (VILI), particularly in premature diseased lungs. VILI dramatically increases mortality in infants suffering from RDS and it is the main cause of the development of a chronic lung pathology called bronchopulmonary dysplasia (BPD). About 5,000 to 10,000 babies born in the United States each year developed BPD. Two type of BPD can be distinguished: the old and the new BPD. The main pathological features of the old BPD consist of squamous metaplasia of airway epithelium, smooth muscle hypertrophy, inhomogeneous lung ventilation, emphysema, fibrosis and a common inflammatory condition. The new BPD is characterized by simplified alveolar structures, dysmorphic capillary configuration and variable interstitial cellularity and/or fibro proliferation that indicate an arrest of lung development at the gestational age of birth.

More babies have BPD today than 30 years ago because more very premature babies survive. Although most children can come off supplemental oxygen by the end of their first year, a few with serious cases may need a mechanical ventilator support for several years or, in rare cases, their entire lives.

As the characteristics of new-borns' respiratory system make the infants' lung more exposed to injury, the choice of the correct ventilation strategy is crucial from the first moment of life. A number of strategies have been employed in the neonatal period with the aim of reducing chronic lung disease, including ventilation techniques designed to avoid pulmonary trauma.

There is evidence that a major role in lung injury is due to incorrect setting of ventilator parameters. Therefore crescent attention is paid on the choice of protective values for the ventilation parameters. Although the study of the characteristics of the respiratory system of each infants is indispensable for the definition of the optimal ventilation setting, until now there isn't a reliable and non-invasive technique suitable for the bedside assessment of respiratory mechanics in ventilated newborns.

One promising approach is provided by the forced oscillation technique (FOT). During forced oscillations, a small amplitude sinusoidal pressure stimulus is applied to the airway opening and the mechanical response of the respiratory system is studied by means of the total respiratory input impedance (Z_{in}). Z_{in} is a complex number that can be expressed as real part, called resistance (R_{rs}), and imaginary part, called reactance (X_{rs}). Particularly, it has been recently shown that X_{rs} measured at 5Hz is very sensible to changes in the mechanics of lung periphery and provides accurate information about lung volume recruitment and derecruitment, both then using FOT with conventional mechanic or in HFOV strategy of ventilation.

In 2011 Dellacà et al. has shown that, applying FOT during PEEP trial, might lead to find the optimal PEEP that permits to increase the lung recruitment minimising tissue distention. The study was performed on seven pigs which were prepared removing the surfactant doing lavage procedures. It was found that, during PEEP decremental, the reactance has a dome shape: the value of PEEP corresponding to the maximum reactance in the decremental phase can be used to asset the optimal PEEP.[6][8]

It was found that in a lavage model of lung injury a PEEP optimization strategy based on maximizing Xrs attenuated the signs of ventilator induced lung injury. Therefore the respiratory system reactance measured by FOT could thus be an important component in a strategy for delivering protective ventilation to patients with ARDS/acute lung injury. Moreover, the study underline that the new methodologies was significant better than standard ARDSNet protocol.[7]

Indeed, nowadays PEEP titration in clinical practice in new-borns relies on monitoring oxygen saturation, which is an indirect indicator of lung recruitment. Moreover, recent studies have provided evidence that PEEP can be successfully optimised by maximising dynamic compliance

during a decrement PEEP trial. The optimised PEEP level was defined as the minimum PEEP which can counteract lung volume de-recruitment without damaging the lungs.
As explained, one of the mayor issues in the infants is the lack of surfactant that, combined with the poor outward elastic recoil of the chest wall, makes premature infants susceptible to alveolar instability which usually results in not completed recruited lungs. It has been demonstrated that the recruitment of the lungs depends on the nCPAP, PEEP or CDP. Indeed, the application of PEEP is used to prevent the collapse of the alveoli. However, too high or too low pressure might results in the development of VILI (paragraph 1.4.1.2).
In 2013, Dellacà et al. evaluate the "the feasibility of forced oscillation technique (FOT) measurements at the bedside to describe the relationship between positive end-expiration pressure (PEEP) and lung mechanics in different groups of ventilated infants." [10]
In conclusion as there is the need of PEEP optimisation and as there are promising results in the usage of the FOT combined with the PEEP trial, it was chosen to implement this technique in order to do a clinic trial on infants. Indeed, the evidence on animal model does not mean that the method is suitable for the usage on men.
For this reason, the objective of the work is to develop a method which can be uses to generate automatically and in real time the PEEP Reactance curve in order to permits studies in infants and verify the clinical utility of this technique.
This new approach might be usefully in order to reduce the impact of new-born chronical pathologies which require a ventilation support. Moreover, it may decrease the frequency of VILI due to an incorrect setting of the ventilation parameters improving the wellness of millions of premature infants.

1 The infant respiratory system and respiratory treatments

1.1 Anatomy and function of the respiratory system

The respiratory system is in charge of the gas exchange between the alveoli and open air and between alveoli and blood. Therefore, its primary functions are: the ventilation, the diffusion of gases (oxygen and carbon dioxide) across the alveoli membrane and the perfusion of blood.
The ventilation aims to transport the atmospheric air, oxygen-rich, in the alveoli and to carry out alveoli air, which contain carbon dioxide coming from the blood. Therefore, a good perfusion is important in order to have the gas exchange across the alveoli membrane for diffusion.

Anatomically speaking the system is dived in upper airways, lower airways and, finally, lungs. The upper airways are composed of nose, pharynx and larynx which are in charge of conditioning the inspired air in term of purifying, humidifying and warming.
Through the nose, the air enters in our body and there, it is purified. Then it continues on its path towards the inside of the human body, through the pharynx where lies the epiglottis which, by closing the larynx, prevents food from entering the streets aerial. The air then passes from the pharynx to the larynx, organ shaped as an inverted funnel, which consists of five pieces of cartilage. In the larynx there are the vocal cords.

Once passed the larynx, the air get in the lower airways, made by the tree tracheobronchial which is structured over 23 levels including: trachea, bronchi, bronchioles, terminal bronchioles, respiratory bronchioles, alveolar ducts and alveolar sacs. The lungs tissue is called the parenchyma, and it is a very stretchable fibroelastic tissue containing elastin and collagen fibres. The lungs are wrapped in a membrane called pleura, which divides them into lobes: three in the right lung and two to the left.
The pleura is made up of two layers: the pulmonary pleura strictly wraps the lungs, while the parietal pleura constitutes the coiling inside of the chest cavity. The intrapleural space is characterized by a subatmospheric pressure (-2/3 mm Hg) and is filled by the intrapleural liquid, with excellent lubricating properties. Therefore, the pleura allows the lung, during ventilation, to follow the changes in volume of the thoracic cage, but at the same time lungs have the possibility of sliding with respect to this.

The lungs are within the ribcage, which consists of: the thoracic spine, the ribs with their costal cartilages and a bone median called sternum. The ribs posteriorly come out the vertebral body and in the front are connected with the sternum. These joints allow you to vary the anteroposterior and transverse diameters of the rib cage due to the contraction of the respiratory muscles.

These muscles, which act on the thoracoabdominal wall, are classified in inspiratory and expiratory, or principal (the diaphragm, which separates the chest and abdominal cavity, the external intercostal and scalene) and accessories (sternocleidomastoid, latissimus dorsi, serratus anterior and small and medium pectoral, abdominal, quadratus lumborum).
The diaphragm is a particular muscle skeletal, which has fibres that radiate from a central tendon structure and peripherally they fit in the lower ribs.

During the inhalation phase, the muscle fibres of the diaphragm are shortened, causing a lowering of the diaphragmatic dome (the structure of the central tendon) and an increase in intra-abdominal pressure. Therefore, a displacement towards the outside of the wall in that area is generated. At the same time, the pleural pressure lowers which causes a gas flow from the outside towards the inside of the lungs, causing the expansion. However, during the inhalation it must be observed that the diaphragm is not the only active muscle as the scalene and the external intercostal contribute to raising the coast and, consequently, the expansion of the rib cage.

On the contrary, the exhalation is generally a passive mechanism, determined by the recovery of the equilibrium point of the structure because of viscoelastic behaviour of the lung-chest well system. Nonetheless, in certain circumstances, it may happen that the expiratory muscles help the structure to get back in its equilibrium point. Indeed, if expiratory muscles contract, they move inward the abdominal wall, and thanks to the incompressibility of the abdominal contents, it results in a cranial displacement of the diaphragm. This action causes an increase in pleural pressure and the decrease in lung volume. [11]

1.2 Biomechanical modelling

1.2.1 Pressure

In a mechanical system, such as the respiratory system, the displacements may be described by volumetric changes, while the forces are expressible in terms of pressure.

The pressure applied at the entire respiratory system (Prs) is defined as the difference between the pressure at the opened airways (Pao) and the external pressure applied at the body surface (Pbs). On the contrary, the pressure at the ends of the whole thoracic-abdominal wall (Pcw) is defined as the difference between the pleural pressure (Ppl) and the outside. Finally the pressure applied at the lung (Pl) is the difference between Palv, alveolar pressure, and Ppl.

1.2.2 Volume

The state of the lungs can also be described by its state of inflation, expressed through the subdivision in volumes shown in Fig. 1**Errore. L'origine riferimento non è stata trovata.**.

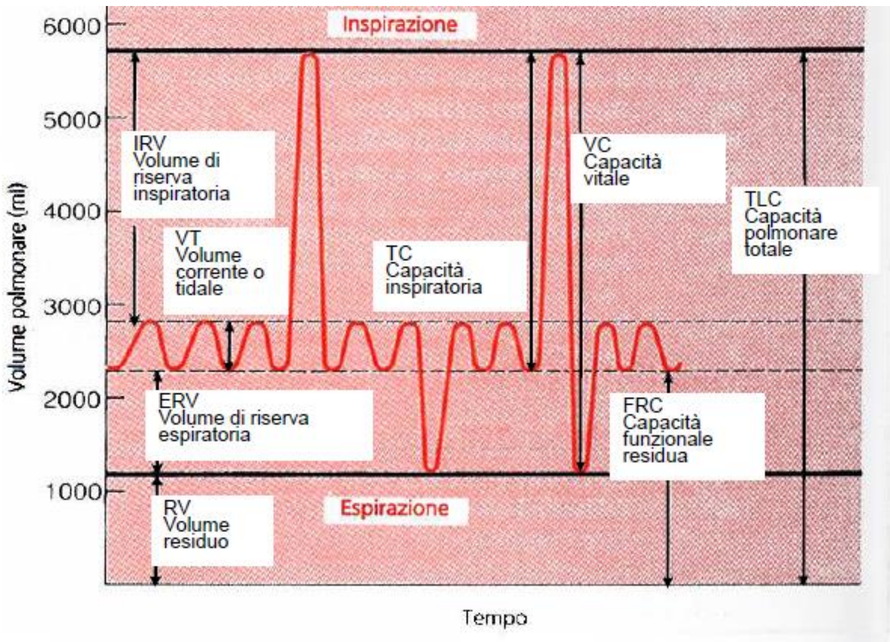


Fig. 1: Respiratory Volume

Following, there are the volume definition:

- The tidal volume (VT) is the volume of air breathed normally;
- The total lung capacity (TLC) is the maximum volume corresponding to the maximum possible inspiration;
- The remaining volume (RV) is the minimum volume reached a forced;
- Vital capacity (VC) is the volume between maximum inspiration and maximum exhalation;

- The functional residual capacity (FRC) is the volume at the end of a quiet exhalation. In this volume the system elastic lung-rib cage is in equilibrium and there is not any need of any muscular activity to maintain such volume;
- Inspiratory capacity (IC) is the volume of air inspirable starting from a condition of quiet exhalation;
- The forced inspiratory volume is air inspirable from the end of an inhalation quiet;
- The forced expiratory volume is the volume of air can blow out further at the end of an exhalation quiet. [12]

1.2.3 Static behaviour

The lung is an entirely passive structure, so external forces must be applied in order to change their volume. Normally respiratory muscles provide these forces, however, in case of disease, artificial respiration could be used to move the respiratory system.

In either case the impedance of the system determines the movement. This impedance is principally composed by the elastic and resistive characteristics of the lung and the chest wall.

The lung is an elastic structure and over a certain range obeys the Hooke's Law. There are different reasons for the elastic behaviour of the lung. One of this is that elastin and collagen fibres mainly compose the elastic tissue of the lung. Besides the tissue recoil is, probably, not explained by the elongation of these fibres, but it is due to their geometrical arrangement.

However surface tension of the liquid coating the alveoli is responsible for a large part of the elastic recoil pressure of the lung. Surface tension is the contractive tendency of the surface of a liquid and it originates from the cohesive force between the molecules. Each molecule is pulled equally in every direction by neighbouring molecule, except for the ones at the surface. The latter ones are in fact pulled inward because they aren't surrounded in every direction (Fig. 2).

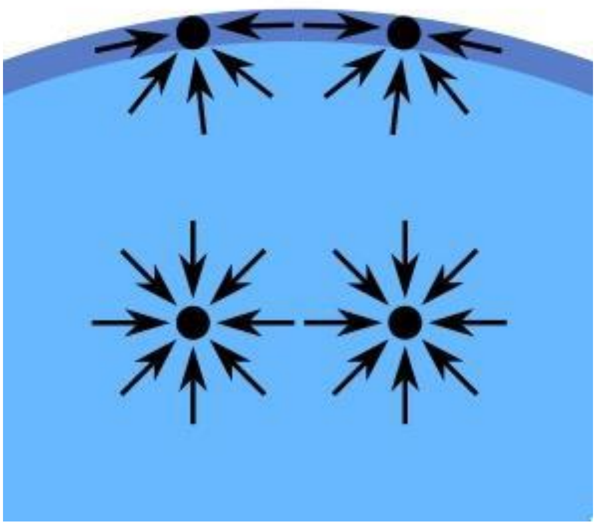


Fig. 2: Surface tension attraction forces in a liquid.

The alveolar surface tension is similar to the one it arises in a spherical cavity, so it can be computed thanks to the Laplace Law (Figure 1.3):

$$\boldsymbol{P = \frac{2\gamma}{R}} \qquad \textbf{Equation 1}$$

Where P is the pressure inside the sphere, γ is the surface tension and R is its radius.
The total pressure across the alveolar wall is the sum of the pressure gradient at liquid-air interface (P_{LF}–P_{EXT}) and the pressure between the alveolar wall and the liquid film (P_{ALV}–P_{LF}):

$$\boldsymbol{P = P_{ALV} - P_{EXT} = \frac{4\gamma}{R}} \qquad \textbf{Equation 2}$$

From this equation we can conclude that the alveolar stabilization pressure is directly proportional to surface tension (γ) and inversely proportional to the radius (R). The greater is the radius, the less pressure is needed to keep the alveolus open, and vice versa.

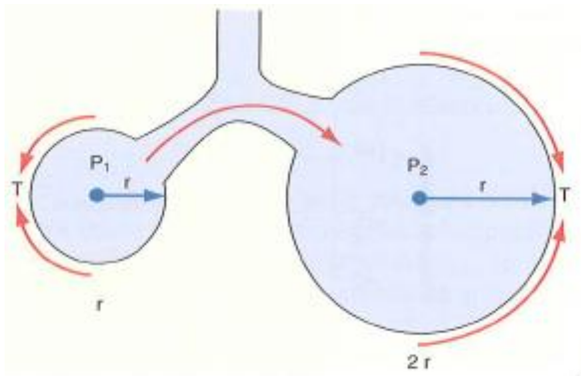


Fig. 3 Laplace law applied to alveoli

Actually the surface tension at air-alveolus interface is really lower than in presence of air-water surface.
This kind of behaviour is due to the presence of surfactant on the alveolar walls. Pulmonary surfactant is a surface-active lipoprotein formed by type II pulmonary cells, which are adsorbed to the alveolar interface.
The pulmonary surfactant cover many different function:

I. Thanks to his particular conformation, with a hydrophobic and a hydrophilic region, the surfactant can be embedded in the air-alveolus interface, lowering so the surface tension, increasing the compliance and reducing the work of pulmonary muscles.
II. As said before, the pressure across the alveolar wall depends on the alveolus radius. Therefore, if the surface tension were the same for all alveoli, the pressure in smaller alveoli would exceed the pressure in larger ones, determining a flow along this gradient. Pulmonary surfactant

makes the surface tension dependent on the alveolar diameter. Because in smaller alveoli the concentration of surfactant is higher, this effect is reduced.

III. It promotes the stability of alveoli during a respiration cycle. In effect thanks to his hysteretic behaviour, while the alveolar radii decrease during expiration, the efficacy of the surfactant increases in order to prevent further lung deflation.

IV. Prevent fluid accumulation and keeps airways dry reducing surface tension.

V. It has an immune function; it regulates inflammatory responses and interacts with adaptive immune response. [13]

The mechanical characteristics of the lung are resumed in the "Static elastic pressure-volume curve" (**Fig. 4: Static inflation and deflation pressure-volume curves**Fig. 4).

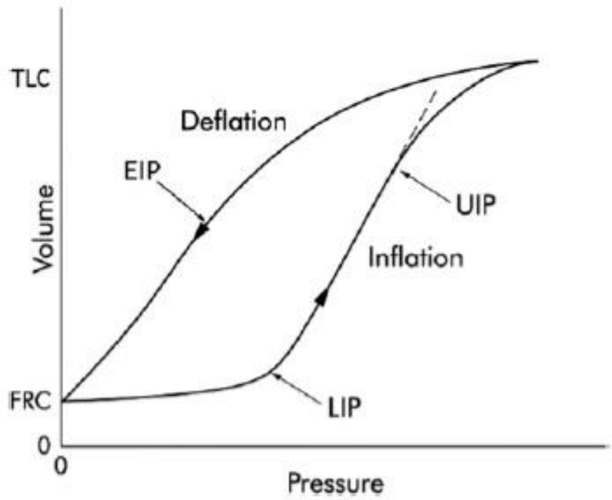


Fig. 4: Static inflation and deflation pressure-volume curves [14]

In physiological condition, this curve is composed of three main segments:

- An initial flat segment which represent collapse of peripheral airways and lung units
- A quite-linear segment with higher slope. The transition between the previous and the current segment is called lower inflection point (LIP).
- A flat segment at high pressures and large volumes, and its slope approaches zero when the system is over-distended. The point at which the slope starts decreasing is called upper inflection point (UIP).
- As with the inflation limb, an ideal deflation limb has an inflection, which is known as the expiratory inflection point (EIP) and which is said to represent the onset of alveolar collapse.

The region between LIP and UIP is the zone where in health the lung operates. The slope of this curve, or the volume change per unit pressure, is called compliance and it represents the insensibility of the lung:

$$C = \frac{\Delta V}{\Delta P}$$ **Equation 3**

However the lung is not an isolated system, and in vivo it is coupled with the thoracic wall. The chest wall consists of all the structure that moves during respiration (except for lungs), such as diaphragm and thorax, and, naturally, it exhibits elastic properties. Ribcage and lung are coupled together with the pleura and a thin liquid film (pleural liquid). In fact the pressure inside the pleural cavity is negative respect to the atmospheric one and so it keeps these structures close to each other. Therefore the volume variation is equal for both the structure and the total pressure exerted by the overall system (P_{L+T}) is the sum of the pressure exerted by the lung (P_L) and by the chest wall (P_T) alone, and:

$$P_L = P_{ALV} - P_{PL}$$ **Equation 4**

$$P_T = P_{PL} - P_B$$ **Equation 5**

$$P_{L+T} = P_L + P_T = P_A - P_B$$ **Equation 6**

where

From $\boldsymbol{PL{+}T} = P_L + P_T = P_A - P_B$ Equation 6 we can conclude that the overall pressure is equal to the one in the alveoli, which in static condition is the one measured at the mouth of the subject. [11]

Therefore, we can plot a pressure-volume curve of the mechanical interactions between the lung and the chest wall simply by asking a subject to breathe in to a spirometer and then relax the respiratory muscles while measuring the airway pressure **Fig. 5.** [13]

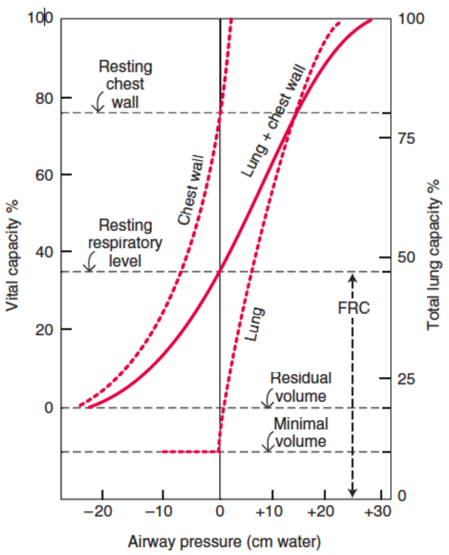


Fig. 5 Relaxation pressure-volume curve of the lung and chest wall.

As we can see the isolated lung tend to reduce its volume, instead the thoracic wall tend to spring out. Moreover, FRC is the volume where the system is at equilibrium, the tendency of lung to collapse at its minimum volume is perfectly counterbalanced by the tendency of the rib cage to bow out. The "two-spring mechanical model" can describe the interaction between ribcage and lung **Fig. 6.**

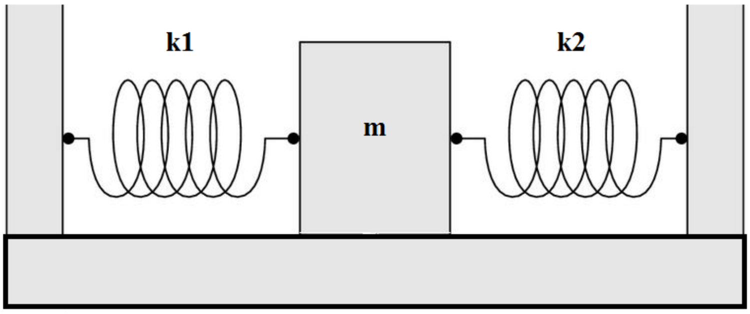


Fig. 6 Two-spring mechanical model

This model consists of two springs in parallel, which represent the elastic properties of the chest wall (E_T) and of the lung (E_L):

$$\boldsymbol{\Delta P_R = \Delta P_T + \Delta P_L = E_T \Delta V_T + E_L \Delta V_L = (E_T + E_T)\Delta V_R = E_R \Delta V_R} \qquad \textbf{Equation 7}$$

where ΔP_R and ΔV_R= ΔV_T = ΔV_L are the variation of pressure and of volume of the respiratory system, ΔP_T and ΔP_L are respectively the variation of pressure of the thorax and of the lung. E_R is the elastance of the respiratory system and it is equal to the sum of lung plus chest wall elastance.
Elastance is the reciprocal of compliance, therefore the respiratory-system compliance is:

$$\boldsymbol{\frac{1}{C_R} = \frac{1}{C_T} + \frac{1}{C_L}} \qquad \textbf{Equation 8}$$

[13]

1.2.4 Dynamic behaviour

During breathing we must consider not only the static force generated by the elastic properties of the respiratory system, but also the dynamic forces which arise in presence of an air flux.
These forces are due to viscous friction of air flowing in the airways, to the viscoelastic behaviour of the tissues and to inertia. The equation of motion of the respiratory system describes in a simplified way the balance of forces acting in the system:

$$\boldsymbol{P = \frac{1}{C}V + R\dot{V} + L\ddot{V}} \qquad \textbf{Equation 9}$$

C, R and L are respectively the compliance, the resistance, and the inertance of the system, which relates the volume (V), the flow ($\dot{V}$) and the acceleration ($\ddot{V}$) to the pressure (P) at the airway opening. However, during normal tidal breathing the inertial component is negligible because air acceleration is not very high.

1.2.4.1 *Dynamic compliance*

Dynamic compliance (C_{dyn}) is the compliance measured while air is flowing in the respiratory system, therefore it represents not only the lung and chest wall distensibility, but also the airway resistance against which distending forces act, thus it's always less than or equal to static compliance.

[15]

1.2.4.2 *Resistance*

The resistive component of the pressure is composed of two different contributes, the resistance opposed by the airways to the flow, and the resistance due to viscous properties of the lung and the chest wall.

The first one depends on the airflow in the lungs. In first approximation, to compute the pressure gradient arose because of the flow, we can apply the Poiseuille Law.

The Poiseuille Law states that in case of incompressible and Newtonian fluid, with laminar flow through a pipe of constant diameter with no acceleration, the pressure drop is directly proportional to the flow **Fig. 7**:

$$\boldsymbol{P = R\dot{V} = \frac{8\eta L}{\pi r^4}} \qquad \textbf{Equation 10}$$

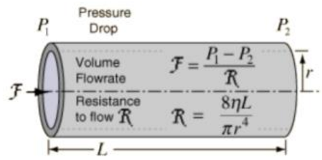


Fig. 7 Poiseuille law applied to a cylindrical pipe

where η is the dynamic viscosity and L and R are respectively the length and the radius of the pipe. As can be clearly seen, the radius of the pipe is the most significant term which determines airway resistance since it is raised to the power of 4: if the radius of the tube is halved, the resistance increases 16 times. The resistance is not homogenous along the airways, in fact descending along the tracheobronchial tree we have many ramification which increase the resulting transversal section (Fig. 8)

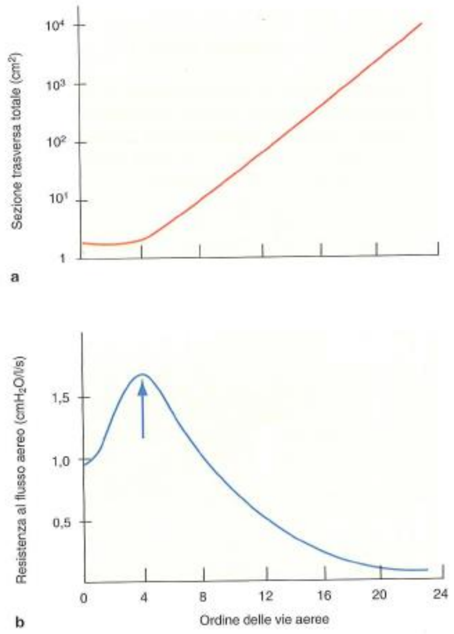


Fig. 8 Course of cross-sectional area and resistance with the increasing of airways generation.

In resting condition, approximately 70% of the total resistance resides in the upper airways, and of this 50% is due to nasal cavities. [13]

In fact, in nasal cavities the flow is turbulent because airflow is high. Random movement of gas molecule characterizes turbulent flow, thus under this condition the driving pressure required to maintain flow is larger than in laminar flow and it is proportional to the square of the flow:

$$\Delta P = k_2 \dot{V}^2 \qquad \textbf{Equation 11}$$

We can predict the flow pattern thanks to the Reynolds number (Re). This is a dimensionless quantity defined as the ratio of inertial force to viscous force in a fluid:

$$Re = \frac{\rho v D}{\eta} \qquad \textbf{Equation 12}$$

where ρ is the density of the fluid, v is its average velocity and D is the hydraulic diameter of the pipe. The flow in a cylindrical pipe is consider completely laminar when Re < 2300 and completely turbulent when Re > 4000. However, the tracheobronchial tree is a complicated system of tubes with many branching points where the flow is nor laminar, nor turbulent but it is transitional. In this case Rohrer's equation, in which resistive pressure is determined by flow and also by its square, should be employed:

$$\Delta P = k_1 V + k_2 \dot{V}^2 \qquad \textbf{Equation 13}$$

where $k1$ relates to laminar flow and $k2$ to the turbulent component. [16]

1.2.4.3 *Lumped element model*

In order to have a better understanding of the respiratory system, it is usually represented with simplified model. The most used is the lumped parameter models, which represents it through an electrical equivalent, consisting of a combination of active and passive elements. Regarding the passive ones, we have: resistors, which represent the dissipation due to friction, inertance, which model the accumulation of kinetic energy or the presence of moving masses, and compliances, which describe the accumulation of elastic potential energy though deformation. The active components that are used are the generators of current and voltage, which represent the flows and pressure differences applied to the terminal of the respiratory system. Through the combination of these components, what can be obtained is one of the most popular models: the so-called T model, Fig. 9.

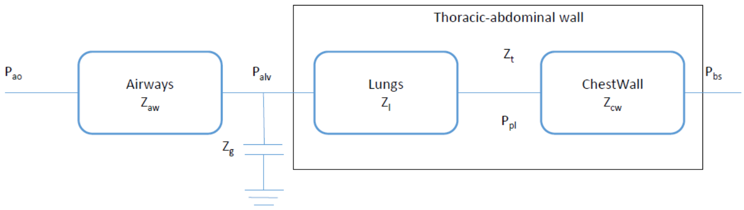


Fig. 9 T model of the respiratory system

Having presented the pulmonary system through the combination of some elements that concentrate the mechanical properties, it is evident that the study of the conditions of the respiratory system, as well as the diagnosis of any disease, can be addressed through the analysis of the alteration of these components. A parameter, very usefully to assess the mechanic behaviour of the respiratory system is the input impedance which consists in the impedance measured at the entrance of the respiratory system. In other word, it is the relationship between the pressure at the entrance of the air ways and the air flow generated.

$$Z_{in} = Z_{aw} + \frac{Z_g Z_t}{Z_g + Z_t} \qquad \textbf{Equation 14}$$

[16]

Therefore, the input impedance can be used to asset the mechanic behaviour of the respiratory system. An even easier model is the one showed in Fig. 10 which is an electric equivalent of the system with only three parameter.

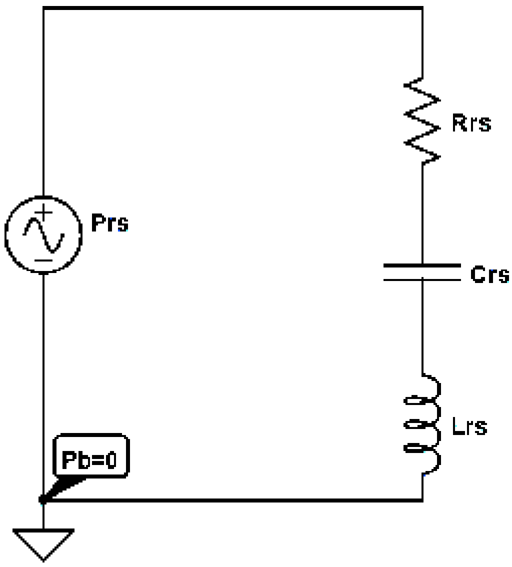


Fig. 10 Electrical model of the respiratory system.

Those three parameters represent the physical properties of the respiratory system: following the equations are reported.

- RESISTANCE: $\Delta P_R = R\dot{V}$ → $Z_R = R$
- COMPLIANCE: $\frac{d}{dt}P_R = \frac{1}{C}\dot{V}$ → $Z_C = -\frac{1}{j2\pi fC}$
- RESISTANCE: $P_R = \frac{d}{dt}\dot{V}$ → $Z_L = j2\pi fL$

Assuming that the barometric pressure P_b is null, the equation that describe the system is:

$$\boldsymbol{P_{rs} = \dot{V}_{rs}\left[R + j\left(2\pi fL - \frac{1}{j2\pi fC}\right)\right]}$$ **Equation 15**

therefore the impedance of the model is:

$$\boldsymbol{Z_{rs} = \frac{P_{rs}}{\dot{V}_{rs}} = \left[R + j\left(2\pi fL - \frac{1}{j2\pi fC}\right)\right] = R + jX}$$ **Equation 16**

Impedance is composed of a real term, called resistance, and of an imaginary part, which is called reactance and it is frequency dependent. At low frequency, the compliant term is predominant, while at high frequency it is negligible and the inductance term prevails.

Under hypothesis of time invariant linear system, we can estimate the transfer function of the system by stimulating it with a sinusoidal input. Because of the non-linearity of the relationship between pressure and flow in the respiratory system, to satisfy the linearity hypothesis the oscillation amplitude must be small.

Stimulating the system with a sinusoidal pressure input:

$$\boldsymbol{P_{rs} = P_0 e^{-i\omega t}}$$ **Equation 17**

according to the frequency response theorem, the flow will also be a sinusoid, shifted of a phase ϕ_{rs} and with a gain equal to $|Z_{rs}(\omega)|$:

$$\boldsymbol{Z_{rs}} = \frac{\boldsymbol{P_{rs}}}{\boldsymbol{\dot{V}_{rs}}} = \frac{\boldsymbol{P_0 e^{-i\omega t}}}{\boldsymbol{\dot{V}_0 e^{-i\omega t+\phi_{rs}}}} = \boldsymbol{|Z_{rs}| e^{-\phi_{rs}}}$$ **Equation 18**

Thanks to what said so far, the impedance can be seen as a generalised resistance: if the shifted of phase is null, then we impedance and the resistance are the same. While the resistance part describe the mechanical dissipation of energy, the reactance describe the accumulation of energy as kinetic energy or elastic energy.

1.3 Infants' respiratory system

At birth the baby has to face a dramatic and life dependent transition: he has to be able to adapt to air breathing within few minutes. In fact, his lung develops in a liquid environment, and, before birth, it is filled with liquid. So to establish adequate pulmonary exchange he must clear his lung from liquid. Moreover, immediately after birth, there is a major changing in the blood circulation. Only 8-10% of the foetus' total cardiac output flows through the pulmonary circulation.

The initial breath generates high negative inspiratory pressure (of up to 80 cmH2O) which permits the lung expansion. In fact, this overcomes airway resistance, inertia of fluid in the airways and surface tension.

Moreover, this sudden expansion of the lungs causes the traction on blood vessels from the interstitial lung tissue. This results in a drop of pulmonary arterial resistance and, therefore, in a redistribution of blood flow from the placental to pulmonary circulation.

These are just the first adaptations of the respiratory system, and it will continue to develop during infancy and childhood.

There are some major differences in the constitution and in the mechanics of the lung between new-borns and adults, which are resumed in the following Tables.

Table 1 Magnitude of lung development from fetal age to adulthood

	30 wk	Term	Adult	Increase*
Surface area (m^2)	0.3	4.0	100	23
Lung volume (mL)	25	200	5000	23
Lung weight (g)	25	50	800	16
Alveoli (no.)	Few	50 m	300 m	6
Alveolar diameter (μ)	32*	150	300	10
Airway branching (no.)	24	24	24	03

*Two-Fold increase after term postconceptional age.
m, million.

Table 2 Modification in respiratory system's mechanical parameters and their anatomical physiological basis

CHANGES IN MECHANICAL PARAMETER			CAUSES OF CHANGES
$C_{CW} \uparrow$			- higher ratio of cartilage to rib. - thinner cartilage. - softer bone due to incomplete mineralization.
C_L	absolute $\downarrow$		- smaller lung.
	specific $\downarrow$		healthy infants: - normalizes as fetal lung fluid is absorbed and normal functional residual capacity is established.
			premature infants: - due to persistent atelectasis and failure to achieve a normal FRC.
R_{RS}	absolute $\uparrow$	$\uparrow R_{viscous}$	- higher tissue density. - bigger amount of pulmonary interstitial fluid.
		$\uparrow R_{airways}$	- small cross-sectional aerea of airways.
	specific $\downarrow$		- shorter bronchial tree. - lower inspiratory flow velocities.

[17] At birth the lung has a small volume, but this is related to the low body weight of the infant. It has the same number of airway and the airway wall are composed of the same components of an adult.

The upper airways are very compliant, and so they would tend to collapse. However, thanks to the complex interaction of upper airways muscles that work in conjunction with diaphragm and chest-wall muscle, they are kept open and stable.

The quantity of alveoli present is about half of adults and they are relatively smaller, with a thicker blood-gas barrier. Pulmonary blood supply is complete except for the blood vessel that will furnish the enlarging alveolar region.

During infancy the lung volume increases as alveoli continue to multiply by septal division, providing more elastic recoil and decrease tendency of airway to collapse.

In full-term neonatal lung, alveolar pool size of surfactant has been estimated to be about 100mg/kg, which is ten times larger than in healthy adults. This high amount of surfactant is for preparing the baby for his first breath, whose lung is full of liquid that must be removed to leave space for gas exchange.

The compliance of the chest wall is very high, usually over 25 mL/cmH2O, because of the incomplete ossification of the ribs and stern. Upper ribs are shorter than the lower ones, giving a triangular shape to the thorax in contrast to the dome shaped ribcage of adults.

Although the very compliant behaviour, it is relatively stable thanks to the intercostal muscles, which seems to provide chest-wall rigidity rather than expansion on inspiration, and thanks to the horizontal position of the rib which tend to splint the rib cage open.

The diaphragm is less efficient in new-borns due both to its rather flat shape that reduces its excursion and to its histological characteristics. In fact, diaphragm, and generally the respiratory muscles, are composed only for the 25% of type I muscle fibres, so they are more prone to fatigue. In childhood they will be made of 55% of type I fibres.
Breathing in neonates is particularly irregular with a significant breath-to-breath variability, and it is alternated with apnea phases. In addition, major changes in breathing pattern were recorded during sleep.
In case of preterm birth the respiratory system characteristics are still different. Preterm birth is defined as a delivery at less than 37 completed weeks, and can be further divided in late preterm (33-37 weeks), moderate preterm (28-32 weeks) and severe preterm (20-27 weeks). In preterm infants, especially in case of severe preterm, the surfactant pool size is very low in comparison to a full term baby. Also the chest is subject to distortions due the very poor ossification of the ribs and sternum and because intercostal muscle are not fully functional. The result is an inward distortion of the chest during inspiration that force the diaphragm to do more work. This accelerate exhaustion, aggravated by the fact that the diaphragm is composed of only 10% of type I muscle fibres.
Prematurity is the main cause of low birth weight, perinatal mortality, and the most frequent determinant of neonatal and infant mortality and morbidity. The following diseases are frequently associated with prematurity: transient tachypnea of the new-born, respiratory distress syndrome, persistent pulmonary hypertension, respiratory failure, temperature instability, jaundice, feeding difficulties, interventricular haemorrhage, necrotizing enter colitis and brain damage. [18]

1.3.1 Neonatal respiratory disorders

The clinical presentation of respiratory distress in the new-born includes apnea, cyanosis, grunting, inspiratory stridor, nasal flaring, poor feeding, and tachypnea (more than 60 breaths per minute). There may also be retractions in the intercostal, subcostal, or supracostal spaces.
The major neonatal distresses are due to alterations in the principal change that have to occur at the birth as the lungs adjust to breathing air:

- An incomplete clearance of the fetal lung liquid leads to TTN (transient tachypnea of the new-born);
- Delayed or inadequate decrease in pulmonary vascular resistance, resulting inPPHN (Persistent pulmonary hypertension of the new-born)
- The deficiency of surfactant is the principal cause of IRDS (infant respiratory distress syndrome).

While the risk of incidence of IRDS and TTN is obviously more elevated in preterm infants PPHN is rare and occurs most often in full-term or post-term babies who have had a difficult birth, or

conditions such as infection or birth asphyxia, in which a baby receives an inadequate amount of oxygen during delivery. At these pathologies should be added the presence in many cases of pulmonary hypoplasia due to incomplete lung development.
Finally the MAS (meconium aspiration syndrome) must be cited in order to complete the list of the most common causes of infant respiratory distress. The clinical course of respiratory distress can be complicated because of a number of conditions, some closely linked to prematurity, other related to specific therapy or both. Possible complications are divided between chronic and acute and both may affect mainly the respiratory system or other physiological system.
Persistent respiratory distress syndrome leads to bronchopulmonary dysplasia, a chronic lung pathology that remains an important cause of mortality and morbidity in very low birth weight (VLBW) infants. [19]

1.3.1.1 Pulmonary hypoplasia

Pulmonary hypoplasia is incomplete development of the lung so that it is smaller in weight and volume, with a reduction in the number of airway branches, alveoli, arteries and veins.
Infants with pulmonary hypoplasia have small-volume, non-compliant lungs. The chest is disproportionately small with respect to the abdomen and sometimes the ribs appear crowded. The lung fields are clear unless there is coexisting RDS. Pneumothorax or other forms of air leak will often be seen on the chest radiograph. After delivery because of noncompliant lungs infants with pulmonary hypoplasia, are difficult to resuscitate, requiring high peak inflating pressures. This requirement for aggressive ventilation often persists into the neonatal period. [20]

1.3.1.2 Persistent pulmonary hypertension of the new-born (PPHN)

Persistent pulmonary hypertension of the new-born (PPHN) occurs when a new-born’s circulation system does not adapt to breathing air. Under normal circumstances, a progressive fall in pulmonary vascular resistance (PVR) accompanies the immediate rise in systemic vascular resistance (SVR) that occurs after birth.
The process of transition depends upon several factors. Factors that contribute to the postnatal increase in SVR include removal of the placenta, the catecholamine surge associated with birth, and the cold extra uterine environment. Factors that promote the postnatal decrease in PVR include expansion of the lung to normal resting volume, establishment of adequate alveolar ventilation and oxygenation, and successful clearance of fetal lung fluid. Conditions that interfere with the normal postnatal decline in the PVR/SVR ratio because the transitional circulation to persist, the pressure in the lungs remains high and the ductus arteriosus remains open, allowing blood to be directed away from the lungs and result in PPHN. [21]

1.3.1.3 Transient Tachypnea of the new-born (TTN)

TTN, also called wet lung or type II RDS, is attributed to the delay in fetal lung fluid clearance. Alveolar fluid normally has a very low protein content and thus can be absorbed into circulation. This protein content could be increased during an episode of asphyxia, either by alteration of the permeability of the lung capillaries or by inhalation of amniotic fluid and also surfactant deficiency may be important in the pathogenesis of transient tachypnea. The resultant fluid would have more difficulty passing into the pulmonary circulation. Affected infants are tachypnoetic with respiratory rates up to 100-200 bpm. In a large study of lung mechanics in babies with established TTN, Sandberg et al. found a reduced tidal volume. There were some air trapping and an increased FRC in severe cases with an increased total lung resistance. The dynamic lung compliance was reduced. This is probably due to lung liquid retained within the lung causing narrowing of the small airways. [22]

1.3.1.4 Meconium aspiration syndrome (MAS)

This illness follows the inhalation of meconium before, during or immediately after delivery. Meconium is composed of inspissated fetal intestinal secretion including bile, swallowed amniotic debris and the remains of desquamated fetal intestinal mucosal cells. When inhaled, it has deleterious effects on the neonatal lung. It blocks airways, creating a ball valve mechanism in which air can be sucked in past the plug, but can’t be exhaled. This causes an increase in airways resistance, particularly in expiration, gas trapping, and lung over distension and predisposes to pneumothorax. Secondly, it acts as a chemical irritant causing an exudative and inflammatory pneumonitis with alveolar collapse and cellular necrosis.

The respiratory failure and hypoxaemia in babies with MAS are due to stiff lungs, marked ventilation perfusion imbalance and pulmonary hypertension precipitating extra pulmonary right to left shunts. Babies with MAS have a reduced compliance and increased airway resistance; their tidal volume is low, but with the tachypnea the minute volume is increased to twice normal. FRC is increased in infants with MAS. [23]

1.3.1.5 The respiratory distress syndrome (RDS)

Respiratory distress syndrome of the new-born, also called hyaline membrane disease, is the most common cause of respiratory distress in premature infants, correlating with structural and functional lung immaturity. It is most common in infants born at fewer than 28 weeks’ gestation and affects one third of infants born at 28 to 34 weeks’ gestation, but occurs in less than 5 percent of those born after 34 weeks’ gestation.

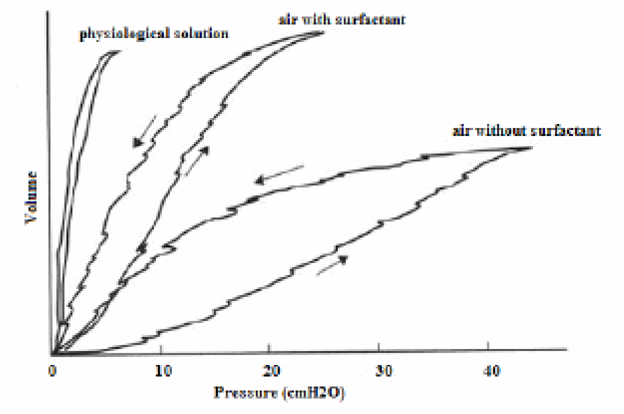


Fig. 11 Modification of pressure-volume curve in case of surfactant deficiency.

The pathophysiology is complex. Immature type II alveolar cells produce less surfactant, causing an increase in alveolar surface tension and a decrease in compliance (Fig. 11). The different curve results in higher required of energy to breath. Moreover, the resultant atelectasis, often also due to inadequate mechanical ventilation and oxygen toxicity, causes pulmonary vascular constriction, increases ventilation perfusion mismatch, hypo perfusion. In fact the alveoli which contain surfactant in nearly normal quantities tend to iperexpand when the surrounding surfactant-free alveoli collapse, creating a nonhomogeneous distribution of gas in the lung. The iperexpanded areas, tend to be poorly perfused due to the flattening of the pulmonary capillaries while hypo ventilated areas is, in contrast, iperperfused.

This situation results also in lung tissue injury which is mediated by a marked pulmonary inflammatory response. The expression of the acute injury is the production of hyaline membranes form through the combination of sloughed epithelium, protein, and edema which further hinder gas exchange.

In untreated RDS, each breath requires significant energy expenditure. If the infant cannot stand such a large work, he develops progressive respiratory failure. Once the diagnosis of RDS has been established, management is directed toward specific measures to replace surfactant and ensure adequate oxygenation and ventilation, as well as general supportive measures.

In order to prevent collapse and the development of atelectasis, positive end-expiratory pressure (PEEP), continuous positive airways pressure (CPAP) or continuous distending pressure (CDP) may be applied and relatively high ventilator pressures may be required.

An important consequence of RDS in infants is the reduction of lung gas volume because the lung has not yet developed sufficiently to hold much gas or because distal air spaces are uninflated. In infants with RDS assisted by mechanical ventilation, the volume loss may also be caused by alveolar edema, which is characterized by four variables: gestational age, positive end-expiratory pressure, tidal volume and surfactant treatment.

Without surfactant treatment, pulmonary edema can occur with relatively low tidal volume ventilation. The severity of surfactant deficiency also influences the development of pulmonary edema. [24]

1.3.1.6 Bronchopulmonary dysplasia (BPD)

The BPD or chronic lung disease (CLD) is the result of dynamic processes involving inflammation, injury, repair and maturation.

The cause of BPD is multifactorial with major factors being 1) prematurity and incomplete development of the lung, 2) pulmonary volutrauma/barotrauma, 3) oxygen toxicity, 4) pulmonary edema, and 5) airway inflammation.

There is no universally accepted definition of BPD. The criteria for diagnosis of BPD and its severity were different according the gestational age at birth (Fig. 12). Two type of BPD can be distinguish: the old and the new BPD.

The old BPD is mainly provoked by an acute insult to the neonatal lung following therapy with high concentrations of oxygen and mechanical ventilation with high positive pressures that result in inflammation, fibrosis, and smooth muscle hypertrophy in the airways (3, 4).

Before the era of surfactant, the main pathological features of BPD consisted of squamous metaplasia of airway epithelium, smooth muscle hypertrophy, and inhomogeneous lung ventilation alternating with emphysema and fibrosis, and a common inflammatory condition. With progress in neonatal care that includes antenatal glucocorticoids, surfactant treatments, and gentler ventilation strategies, large preterm infants seldom develop BPD and even more small infants survive.

Gestational Age	< 32 wk	> 32 wk
Time point of assessment	36 wk PMA or discharge to home*	> 28 d but < 56 d postnatal age or discharge to home*
Treatment with oxygen	> 21% for at least 28 d	> 21% for at least 28 d
Mild BPD	Breathing room air at 36 wk PMA or discharge*	Breathing room air by 56 d postnatal age or discharge*
Moderate BPD	Need for < 30% oxygen at 36 wk PMA or discharge*	Need for < 30% oxygen at 56 d postnatal age or discharge*
Severe BPD	Need for > 30% oxygen and/or positive pressure, (PPV or NCPAP) at 36 wk PMA or discharge*	Need for > 30% oxygen and/or positive pressure (PPV or NCPAP) at 56 d postnatal age or discharge*

Fig. 12 Diagnostic criteria for BPD * -whichever comes first

Histopathological features of the lungs of infants dying of BPD in recent years differ from the described old picture, the lungs are ventilated in a more uniform, the airway epithelial damage is minimal, shown less fibrosis, and the large and small airways are remarkably free of epithelial metaplasia, smooth-muscle hypertrophy and fibrosis. However, there are fewer and larger alveoli, indicating an interference with septation despite an increase in elastic tissue that is proportionate to

the severity and duration of the respiratory disease before death. Some specimens also have decreased pulmonary microvascular development.
These simplified alveolar structures, dysmorphic capillary configuration and variable interstitial cellularity and/or fibroproliferation characterized the new BPD as an arrest of lung development at the GA of birth while the traditional indicators of injury are less evident.
In recent years the important role of inflammation in the pathogenesis of lung injury and the development of chronic lung disease (CLD) has become evident. The factors that trigger this inflammatory reaction, mainly the baro-and volu-trauma, from oxygen toxicity, respiratory distress syndrome and infection are known causes of lung injury, to which the immature lung is more susceptible for a number of conditions, such as the lack of surfactant and the incomplete development of antioxidant enzyme systems.
Development of BPD results in significant alteration of lung mechanics. Pulmonary compliance is diminished by a combination of lung fibrosis and increase in lung water resulting from the disruption of the alveolar capillary interface. Decreased lung compliance and increased airway resistance because of fibrosis causes an increase in work of breathing, resulting in clinical findings of tachypnea, intercostal retractions and paradoxical breathing.
The alveolar and capillary hypoplasia of new BPD will require the development of specific therapies, but avoiding volutrauma, oxidant injury and inflammation/infection will improve lung morphology.
Outcomes of BPD are difficult to assess given the lack of a uniform definition, and changing modalities of management, including modes of ventilation. Infants with BPD have significant pulmonary sequelae during childhood and adolescence. [25]

1.4 Respiratory treatments

The most common pathology is the RDS which is usually threated with ventilation support, the usage of oxygen and surfactant administration. Therefore, in this thesis work the attention is focus on the RDS and, especially, on the ventilation support and how to optimize it.
When, for any reason, the respiratory muscles can't provide the necessary pressure for respiratory flow, the lung ventilation must be guaranteed by artificial ventilators. Although mechanical ventilation is indispensable for the survival of patients with acute or chronic lung injury, excessive tidal volumes and inadequate lung recruitment may contribute to mortality by causing Ventilator-Induced lung injury (paragraph 1.4.1.2). Therefore, finding a protective ventilation technique and providing the clinicians with a reliable method to correctly set ventilation parameters is of major importance.
There are several reasons why very preterm infants may have difficulty aerating their lungs and keeping them open:

- Deficiency of surfactant predisposes to higher surface tension within the alveoli resulting in atelectasis
- A marked imbalance exists between chest wall rigidity and elastic recoil of neonatal lungs. Highly compliant chest wall offers little support to the noncompliant lungs with immature elastic fibres leading to airway collapse
- A flatter diaphragm and more horizontal ribs limit inspiratory reserve volume. Hence the minute volume is achieved by increasing the rate of respiration
- Respiratory fatigue is common in neonates because the diaphragm and intercostal muscles lack type 1 oxidative fibres

In addition, the lungs of preterm infants are less responsive to mechanisms such as sodium reabsorption and so are less efficient at clearing lung liquid. Retention of lung liquid in the air spaces reduces lung gas volume, promotes non-uniform aeration and impairs the changes in cardiopulmonary physiology that are essential for postnatal survival. Understanding the underlying physiology and pathophysiological basis of new-born respiratory disease is essential for optimal respiratory management and thereby reduction of morbidity such as Bronchopulmonary dysplasia (BPD) which is a multifactorial disease, of which ventilator induced lung injury is considered as a major factor in its pathogenesis. As the knowledge of the particular characteristic of the respiratory system of each infant is indispensable to choose the best ventilation setting there is a need of an accurate, non-invasive technique for the bedside assessment of lung and chest wall mechanic.
The forced oscillation technique is a non-invasive, versatile method to assess respiratory mechanic without patient's cooperation that attempts to answer this necessity.

1.4.1 Mechanical ventilation

Assisted ventilation could be defined as the movement of gas into and out of lungs by an external source connected directly to the patient.

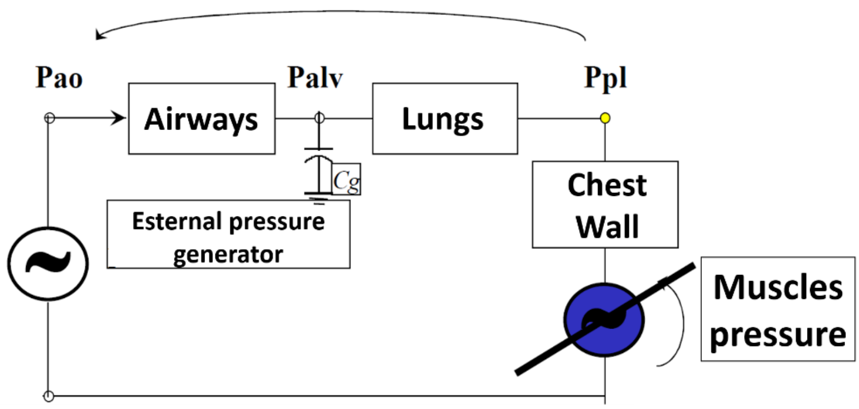


Fig. 13 Ventilators vs physiological pressure

A positive-pressure mechanical ventilator typically provides this (Fig. 13). The aim of mechanical ventilation would be to replicate normal physiologic process of delivering a tidal volume breath. Therefore, the expiration is passive. However, there is a major difference between the physiological and artificial ventilation: while the physiological ventilation generate a depression inside the lungs which allow air to enter, the artificial ventilation increased the external pressure pushing air inside. Moreover, mechanical ventilation of small neonates poses multiple technological challenges which are caused by the pathophysiology of the neonatal diseases and the small size of our patients. Furthermore, the infants usually shows a rapid respiratory rate, low and/or rapidly changing lung compliance, highly compliant chest wall, very short inspiratory time and very small tidal volumes (V_t). Another layer of complexity is added by the air leak associated with use of uncuffed endotracheal tubes (ETT), facial masks, nasal prongs or laryngeal mask airways (LMA) in neonates. Advances in microprocessor driven ventilators now compensate for the obligatory air leak, allow accurate volume, and flow measurements, essential for most ventilator modes. Combination of persistent air leak and small V_t, as small of 2-3 ml, makes flow detection and accurate measurement of inspiratory and expiratory V_t difficult. Introduction of additional flow and volume measuring equipment at the airway opening helps to partially alleviate these problems yet it comes at the expense of an increase in circuit dead space. [26]
Modern ventilators and the software accompanying them have become more complex and sophisticated with many of these ventilators certified for use in neonatal, paediatric and adult patients. Available modes of ventilation have exponentially increased, with many ventilators offering mixed modes of ventilation.

As explained in the paragraph 1.2.4.3, there are three variables that can be evaluated: volume, pressure and flow. Usually, one is chosen as independent (ant, therefore, control) variable and the other two are the dependents variables. Usually, positive-pressure mechanical ventilators can be classified based on chosen target variable:

- Volume Controlled (VC) ventilators deliver the same tidal volume of gas with each breath, regardless of the inflating pressure that is needed.
- Pressure controlled (PC) ventilators, in contrast, are designed to deliver a volume of gas with each breath until a pre-set limiting pressure designated by the physician is reached

For many years, an ongoing debate has persisted in neonatal respiratory care as to the relative merits of volume-controlled versus pressure-controlled mechanical ventilation for the neonate.
VC ventilators may occasionally over distend the “healthier” areas of the lung and promote air leaks. Areas of the lung that are atelectasis from collapsed or obstructed airways require a higher opening pressure, which can often be achieved with a volume-pre-set ventilator. Nonetheless, most of the

tidal volume will be preferentially delivered into segments of the lung that remain partially inflated and more compliant. The application of pressure-controlled ventilation results in better gas distribution and less distension of non-compliant lung units (**Errore. L'origine riferimento non è stata trovata.**).

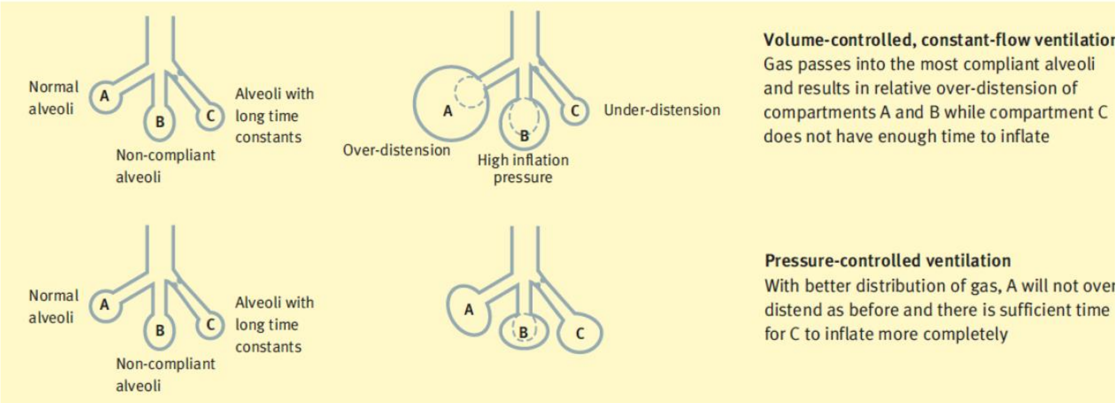


Fig. 14 Effects of volume- and pressure-controlled ventilation on alveoli with different compliance and time constants

[27] With a decrease in lung compliance (increased lung stiffness), the pre-set pressure is reached more rapidly during gas compression and delivery, and residual volume is released to the atmosphere. As a result, tidal volume decreases, and if ventilation is inadequate, the clinicians must compensate for this loss of volume by increasing the peak inspiratory pressure (PIP). An obvious shortcoming, therefore, with pressure-controlled ventilation is that in disease states in which compliance is frequently changing, the inability of the operator to vary the peak pre-set pressure with each breath may be problematic. With VC ventilation, changing compliance is compensated by terminating the delivery of a breath only when the desired volume has been delivered to the patient. A beneficial adjunct to volume ventilation, therefore, is that during weaning phases of ventilator support, as the lung compliance improves, the required pressure needed to ventilate the patient will automatically decrease.

In 2006, J. Singh et al. found that VC ventilation is both a safe and effective method of ventilating very preterm, extremely and very low birth weight new-borns with RDS. There were trends toward faster weaning, reduction in the duration of respiratory support, and an improvement in survival. These findings were even more noticeable in the subgroup of infants who weighed <1000 g at birth. These babies are most at risk for sustaining complications from mechanical ventilation and may benefit from VC ventilation with less Ventilator-Induced lung injury compared to PC ventilation.

[28] Another classification criteria is based on how transition between inspiration and expiration is performed:

- Time-cycle ventilation permits to define a specific inspiration/expiration ratio and a fixed respiration rate, irrespective of the spontaneous ventilation effort of the infant.

- In Patient-trigger ventilation (also referred to Synchronized ventilation, indicated with an S prefix) inspiration is initiated in association with patient breaths.

Patient-trigger ventilators may be triggered by changes in pressure or flow:

- Pressure: the ventilator delivers a breath when the baseline pressure decreases during the patient's inspiratory effort.
- Flow: some ICU ventilators deliver a constant background flow throughout the respiratory cycle (flow by). A change in this constant flow, caused by patient inspiration is detected at the flow sensor in the expiratory limb. This triggers the ventilator to increase the flow and a breath is delivered to the patient. Flow triggering reduces the work of breathing when compared with pressure triggering because there is always some background gas flow from the patient and no delay in inspiratory valve opening.

Asynchrony may result in several deleterious effects. Efficiency of gas exchange may be impaired when an infant attempts to exhale against positive pressure or, alternatively, when an infant attempts to inhale during the exhalation phase of the mechanical cycle. Asynchrony has been shown to contribute to air trapping and pneumothorax, thus increasing pulmonary morbidity and prolonging recovery. Even central nervous system function may be adversely impacted.
[29]
Especially in neonatal respiratory management, ventilation techniques are mostly non-invasive, which means that do not require the use of ETT but the ventilation is delivered through specialized face or nasal masks. This category can be defined as non-invasive ventilation (NIV), usually indicated by N prefix. When in NIV, all the modalities of ventilation that are described below might be employed. Even though there are large and variable leaks through the mouth that could make impossible the knowledge of the pressure transmitted to airways, the neonatal endotracheal intubation and ventilation are associated with increased pulmonary morbidity (subglottic stenosis, respiratory infection, VILI and increased risk of chronic lung disease (CLD)). Therefore, NIV is preferred.
Whether the ventilation strategy choice, the ventilator parameters are to be set in order to achieve adequate gas exchange without injuring the lung. This represents a difficult challenge for the clinicians and the following guidelines must be considered (Fig. 15).

Peak Inspiratory Pressure (PIP)

LOW (≤20 cm H_2O)		HIGH (≥20 cm H_2O)	
Advantages	**Adverse Effects**	**Advantages**	**Adverse Effects**
1. Fewer side effects, especially BPD, PAL 2. Normal lung development may proceed more rapidly	1. Insufficient ventilation; may not control $PaCO_2$ 2. $\downarrow$ PaO_2, if too low 3. Generalized atelectasis may occur (may be desirable in some cases of air leaks)	1. May help reexpand atelectasis 2. $\downarrow$ $PaCO_2$ 3. $\uparrow$ PaO_2 4. Decrease pulmonary vascular resistance	1. Associated with $\uparrow$ PAL, BPD 2. May impede venous return 3. May decrease cardiac output

Wave Forms in Neonatal Mechanical Ventilation

SINE WAVE		SQUARE WAVE	
Advantages	**Adverse Effects**	**Advantages**	**Adverse Effects**
1. Smoother increase of pressure 2. More like normal respiratory pattern	1. Lower mean airway pressure	1. Higher MAP for equivalent PIP 2. Longer time at PIP may open atelectatic areas of lung and improve distribution of ventilation	1. With high flow, the ventilation may be applying higher pressure to normal airways and alveoli 2. Impede venous return if longer T_I is used or I:E ratio is reversed

Continuous Positive Airway Pressure or Positive End-Expiratory Pressure (CPAP or PEEP)

LOW (2-3 cm H_2O)		MEDIUM (4-7 cm H_2O)		HIGH (>8 cm H_2O)	
Advantages	**Adverse Effects**	**Advantages**	**Adverse Effects**	**Advantages**	**Adverse Effects**
1. Used during late phases of weaning 2. Maintenance of lung volume in very premature infants with low FRC 3. Useful in some extremely LBW infants on A/C ventilation	1. May be too low to maintain adequate lung volume 2. CO_2 retention from $\dot{V}/\dot{Q}$ mismatch, as alveolar volume is inadequate	1. Recruit lung volume with surfactant deficiency states (e.g., RDS) 2. Stabilizes lung volume once recruited 3. Improve $\dot{V}/\dot{Q}$ matching	1. May overdistend lungs with normal compliance	1. Prevents alveolar collapse in surfactant deficiency states with severely decreased C_L 2. Improves distribution of ventilation	1. PAL 2. Decreases compliance if lung overdistends 3. May impede venous return to the heart 4. May increase PVR 5. CO_2 retention

Inspiratory: Expiratory (I:E) Ratio Control in Neonatal Mechanical Ventilation

INVERSE (>1:1)		NORMAL (1:1 to 1:3)		PROLONGED EXPIRATORY (<1:3)	
Advantages	**Adverse Effects**	**Advantages**	**Adverse Effects**	**Advantages**	**Adverse Effects**
1. $\uparrow$ MAP 2. $\uparrow$ PaO_2 in RDS 3. May enhance alveolar recruitment when atelectasis is present	1. May have insufficient emptying time and air trapping may result 2. May impede venous return to the heart 3. $\uparrow$ Pulmonary vascular resistance and worsens diseases such as PPHN and CHD 4. Worsens PAL	1. Mimics natural breathing pattern 2. May give best ratio at higher rates	1. Insufficient emptying at highest rates	1. Useful during weaning, when oxygenation is less of a problem 2. May be more useful in diseases such as MAS, when air trapping is a part of the disease process	1. Low T_I may decrease tidal volume 2. May have to use higher flow rates, which may not be optimal for distribution of ventilation 3. May ventilate more dead space

Neonatal Mechanical Ventilatory Rates (f)

SLOW (≤40 breaths/min)		MEDIUM (40-60 breaths/min)		RAPID (≥60 breaths/min)	
Advantages	**Adverse Effects**	**Advantages**	**Adverse Effects**	**Advantages**	**Adverse Effects**
1. $\uparrow$ PaO_2 with increased MAP 2. Useful in weaning 3. Used with square wave ventilation 4. Needed when I:E ratio is inverted	1. Must $\uparrow$ PIP to maintain minute ventilation 2. $\uparrow$ PIP may cause barotrauma 3. Patient may require paralysis	1. Mimics normal ventilatory rate 2. Will effectively treat most neonatal lung diseases 3. Usually does not exceed time constant of lung, so air trapping is unlikely	1. May not provide adequate ventilation in some cases 2. $\uparrow$ PIP may still be needed to maintain minute ventilation	1. Higher PaO_2 (may be the result of air trapping) 2. May allow $\uparrow$ PIP and V_T 3. Hyperventilation may be useful in PPHN 4. May reduce atelectasis (air trapping)	1. May exceed time constant and produce air trapping 2. May cause inadvertent PEEP 3. May result in change in compliance (frequency dependence of compliance) 4. Inadequate V_T and minute ventilation if only dead space is ventilated

Fig. 15 Guidelines for neonatal ventilations

1.4.1.1 *Common ventilation modes in Neonatal Intensive Care Unit (NICU)*

1.4.1.1.1 *Continuous positive airway pressure (CPAP)*

Continuous positive airway pressure (CPAP) was first used as a method of supporting the breathing of preterm infants in 1971. The purpose of nasal CPAP is to deliver a supporting positive pressure (5 cmH2O is traditionally used) to the upper airways and lungs.

It is established as an effective method of preventing extubation failure, is used in the management of apnea of prematurity, and is increasingly seen as an alternative to intubation and ventilation for the treatment of respiratory distress syndrome (RDS). [30]

1.4.1.1.2 *Bilevel positive airway pressure (BiPAP) (or intermittent positive pressure ventilation (IPPV)) and intermittent mandatory ventilation (IMV)*

Time cycled, pressure limited ventilation is usually referred to as conventional ventilation, as it has been the most frequently used ventilation mode for the new-born. These techniques differs from CPAP because rather than delivering a constant level of pressure through inspiration and expiration, two different pressure levels are cycled between the two. The pressure delivered during inspiration is higher than that during expiration, thereby providing a degree of assistance during inspiration. The inspiratory pressure (IPAP or PIP) and expiratory pressure (EPAP or PEEP) are programmed in the ventilator. BiPAP not only provides the benefits of CPAP by providing increased airway pressure during expiration, but the added inspiratory assist theoretically should further reduce the work of breathing and assist with augmenting ventilation in patients at risk for hypercapnia or with ventilator fatigue or failure.

IMV ventilation mode is a special case of IPPV. The patient is allowed the option of spontaneous breathing between the ventilation strokes. This means that the expiration time must be set (generally via the frequency) to allow an expiratory time greater than 1.5 seconds. The weaning is facilitated by progressively reduction in IMV rate which allowed the patient to gradually increase spontaneous breathing against distending pressure.

1.4.1.1.3 *Pressure support ventilation (PSV)*

Pressure support is a patient-triggered, pressure-limited, flow-cycled mode of ventilation designed to assist a patient’s spontaneous effort with an inspiratory pressure “boost”. Pressure support is generally applied during weaning to reduce the imposed work of breathing created by high-resistance endotracheal tubes, the ventilator circuit, and the demand valve in demand systems. At the highest level of pressure support, known as PSMAX, complete ventilator support (for example a full tidal volume breath) is provided and patient respiratory muscle work is reduced to almost zero. The lowest level of PSV (PSMIN) is the pressure necessary to overcome the imposed work of breathing. Intermediate levels can be used to provide partial support. [29]

1.4.1.1.4 Volume guaranteed (VG)

The VG ventilation ensures that at least a guaranteed volume is provided to the patient on each breath and the device automatically generates the necessary pressure to achieve this volume. The pre-set inspiratory time determines the duration of inflation. These modalities permit to obtain a stable and consistent tidal volume delivery and minute ventilation independent of pulmonary mechanics but may result in high pressure peaks when compliance is poor. To avoid this it is used combined with a pressure limited ventilation resulting in another hybrid form that attempts to combine the desirable features of both pressure-controlled and volume controlled breath in one mode.

1.4.1.1.5 High frequency oscillatory ventilation (HFOV)

A constant distending airways pressure (CDP) is applied, over which small tidal volumes are superimposed at a super physiologic rate to provide oxygenation and ventilation. While in conventional mechanical ventilation direct ventilation and bulk convection play a central role for the gas transport, in HFOV they contribute only marginally. However adequate gas exchange during HFOV is possible with extremely small tidal volumes, often less than the anatomic dead space because of other mechanisms as pendelluft (the movement of gas between adjacent lung units), asymmetrical velocity profiles and asymmetry between inspiratory and expiratory velocity profiles (that results in a convective transport of gas), Taylor's dispersion (diffusion, caused by the combination of axial asymmetric velocity vectors and radial concentration gradients) and molecular diffusion. CDP is the primary variable affecting lung volume and oxygenation: low CDP levels can promote alveolar collapse while excessive CDP levels can lead to alveolar over distention and barotrauma. [31]

1.4.1.2 Ventilator-Induced Lung Injury (VILI)

Vili is a disease that come along with not an optimal setting of the ventilation parameters. It can occur due to atelectrauma, volutrauma, barotrauma, and bio trauma, and respiratory management varies with each type of injury.

Atelectrauma is caused by mechanical shear stress to the lung tissue when the alveoli sacs are recruited but then collapse during the breathing cycle.

Volutrauma is excessive stretching of the lung tissue caused by aggressive positive pressure ventilation, whereas barotrauma is the combination of fluid overload, high ventilation pressures, and pulmonary air leak.

Bio trauma is the release of free radicals and cytokines that alter the interstitial tissue of the lung, thereby altering lung function.

Methods to reduce atelectrauma include recruitment manoeuvres (inspiratory hold and positive end-expiratory pressure), optimizing the functional residual capacity (FRC) of the lung, and high-frequency mechanical ventilation.

Volutrauma and barotrauma can be reduced by avoiding high airway pressures and large lung volumes. Ventilator methods that reduce volutrauma and barotrauma include opening the lungs with an inspiratory hold, providing continuous positive airway pressure (CPAP), maintaining low tidal volumes, and maintaining inspiratory pressures that adequately inflate the lungs without over distension but assist in the evacuation of lung fluid. These methods will optimize FRC and will reduce atelectrauma, volutrauma, and barotrauma.

Reduction of biotrauma can be achieved by any method that reduces the inflammatory markers, cytokines, and free radicals that alter lung function and includes the reduction of oxygen exposure.

1.4.2 Ventilator settings

Depending on the modality of ventilation there are different parameters to set. Oxygenation is directly related to the fraction of inspired oxygen (FiO2) and the mean airway pressure (MAP). MAP can be increased by changes in peak inspiratory pressure (PIP), positive end expiratory pressure (PEEP) or by changing the inspiratory-expiratory (I:E) ratio by prolonging the inspiratory time when the rate is kept constant. The most effective method to increase MAP is by increasing the PEEP level. A very high MAP, however, may cause over distension, and oxygen transport may decrease due to reduced cardiac output. CO2 elimination is proportional to minute ventilation, providing the tidal volume is greater than the dead space. Minute ventilation is determined by the product of tidal volume (minus dead space ventilation) and inflation rate. For the same minute ventilation, changes that alter tidal volume delivery rather than the inflation rate are usually more effective in changing CO2 elimination, because dead space ventilation remains constant. In the synchronized ventilation modes there is another parameter to be set that establishes a threshold for the trigger variable.

- Fraction of inspired oxygen (FiO2)

Inhalation of any gas with a fraction of inspired oxygen higher the FiO2 of room air can potentially be toxic. To minimize the risk of toxicity, the lowest FiO2 that achieves adequate oxygenation should be employed. [32]

- Tidal volume (Vt)

Large tidal volumes can induce overdistention of alveoli and lung damage (increased pulmonary microvascular permeability, pulmonary edema, and lung rupture). Low tidal volumes may lead to decreased ventilation and an elevated arterial partial pressure of carbon dioxide (PaCO2). A ventilation strategy referred to as permissive hypercapnia is focus on the pH, rather than the PaCO2. [33]

In pressure-control ventilation tidal volume delivery is determined by the difference in pressure between the peak and positive end expiratory pressure (ΔP=PIP-PEEP).

- Peak inspiratory pressure (PIP)

Changes in PIP affect oxygenation (by altering the MAP) and the $PaCO_2$ (by altering the tidal volume and alveolar ventilation). An increase in PIP decreases $PaCO_2$ and improves oxygenation. PIP requirements are determined by the compliance of the respiratory system; the stiffer the lungs the greater PIP required. The lowest PIP that adequately ventilates the patient, as assessed by the clinical examination (chest movement and breath sounds) and blood gas analysis, should be used. Inappropriately excessive PIP may cause lung over-distension and increase the risk of baro/volutrauma and hence air leak.

- Respiratory rate

For controlled ventilation, the rate equals the total number of ventilator breaths the patient will receive while for synchronized ventilation, the rate represents the minimal number of breaths; depending on the inspiratory sensitivity set, the patient may initiate more than the minimal amount.

- Inspiratory-expiratory time ratio (I:E)

Prolonging the inflation time will increase the MAP and hence improve oxygenation and is an alternative to other manoeuvres such as increasing PIP. A prolonged inflation time, however, will predispose to lung over-distension and gas trapping, as it is likely to reduce the expiratory time unless the rate is altered to account for the change. For these reasons the expiratory time usually exceeds the inspiratory one regardless of the rate strategy used in order to prevent inadvertent alveolar over-distension.

- Inspiratory flow rate

Higher flow rates allow the delivery of a tidal volume in a shorter period of time and leave a longer period of time for exhalation, which favours more complete lung emptying and less gas trapping. [34][33]

If high respiratory rates or short inspiratory times are used, high flow rates may be needed to ensure delivery of the intended volume. Moreover a high flow rate is more likely to produce a square waveform, which compared to a saw tooth waveform, will increase MAP and hence oxygenation. With higher flow rates, however, peak inspiratory pressure also increases and may exceed the ventilator safety limits, which reduces delivered tidal volume. If the inspiratory flow rate is too slow to meet the ventilatory requirements, the patient generates highly negative intrapleural pressure by inhaling against a closed inspiratory valve. The negative intrapleural pressure may lead to muscle fatigue and even pulmonary edema. [35]

- Positive end expiratory pressure (PEEP)

Positive end-expiration pressure is applied to airway opening to avoid the mouth pressure to fall to ambient one. When PEEP is applied, end-expiratory lung volume equals the applied PEEP level and FRC changes in accordance with the pressure volume curve of the respiratory system.

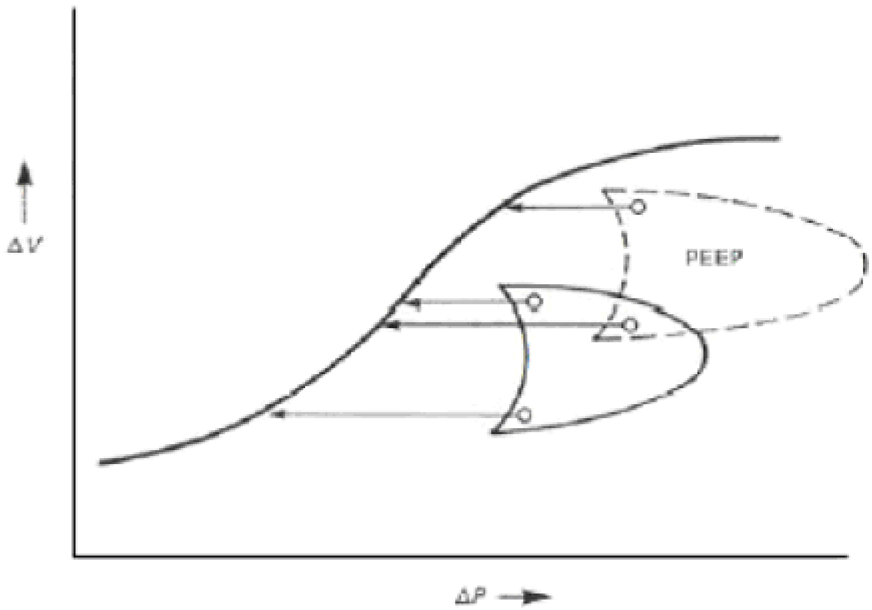


Fig. 16 How expiration is influenced by the use of positive end-expiration pressure

This has the advantage of opening closed lung units, preventing the collapse of alveoli and terminal airways during expiration. It also reduces airways resistance in accordance to the inverse relationship between lung volume and airways resistance and changes the relative compliance of the upper and lower parts of the lung, improving the ventilation of the dependant overperfused parts of the lung. Thus, gas exchange initially improves: pO_2 increases and pCO_2 decreases. However, if PEEP is increased too much the lung becomes overdistended and gas exchange worsens: pO_2 remains high but pCO_2 also begins to raise as dead volume to tidal volume ratio (VD/VT) increases. Excessive increases in PEEP may lead to serious consequences, such as air leak syndromes. Moreover, although low levels of PEEP decrease pulmonary edema and right-to-left cardiac shunting, high levels reduce venous return and hence reduce cardiac output and pulmonary perfusion and enhance ventilation-perfusion mismatching, resulting in a lower pO_2.

PEEP is used to treat neonates of both preterm and term gestation with respiratory distresses. Application of PEEP produces a more regular breathing pattern in preterm neonates thanks to chest wall stabilization and reduction of thoracic distortion.

Levels of 3 cm H_2O improve oxygenation in newborns with RDS without compromising lung mechanics, CO_2 elimination or haemodynamic stability. [36] [37] [38] [39]

- Sensitivity

If the trigger sensitivity is set too high the detection of patient effort can fail while with a low trigger sensitivity, the ventilator may deliver breaths too frequently (commonly referred to as auto-cycling) and produce severe respiratory alkalosis. [40] [41]

1.5 Optimization of Mechanical Ventilation

The combination of interdependent ventilation parameters can result in an adequate exchange of O2 and CO2 reducing all the possible damage. When treating RDS, special care is give in setting PEEP and CDP respectively during CMV and HFOV. In fact CDP keeps the lung opened during HFOV while PEEP prevents the collapse of alveoli at end-expiration protecting lungs from VILI (paragraph 1.4.1.2).

1.5.1 Ventilation parameters Optimisation

A lot of studies have been performed to find the most protective ventilatory strategy. Conventional ventilation (SIPPV, SIMV and their variations) have been compared with the alternative ventilation strategies (HFOV, NIV) on incidence of lung and hemodynamic complications. However it has not be proved that a particular ventilation mode is more effective and safer than the others for newborns. [42] [43]

Crescent attention is paid on the choice of protective values for the ventilatory parameters.

This need is more perceived for the setting of CDP during HFOV because it is the only way to recruit the lung, but the importance of correct parameters setting during conventional ventilation has become evident observing the outcome of the patients. [44] [45] [38]

The choice of CDP or PEEP setting may be based on arterial oxygenation, inflation of the lung on the patient's chest radiograph and subjective assessment of chest wall movement. The oxygenation index is an index that combines the goals to maximize arterial oxygenation and minimize CDP or PEEP and inspired oxygen concentration. However a lung volume-targeted strategy has the advantage to take into account not only the gas exchange but also respiratory mechanics. This is because the optimal end expiratory pressure value may result from a compromise between maximal lung recruitment and minimal overdistention. Several strategies have been suggested to determine the optimal CDP during HFOV and may be also apply to PEEP setting. Some of these techniques are based on the static pressure-volume curves, oscillatory pressure ratio, electrical impedance tomography or the inductive plethysmography. [46] [47] [48] [49] [50] [51] [52]

As the newborn lung condition is likely to be instable the ventilatory parameter are to be adjusted according to modifications in lung mechanic. Moreover any therapy, as the surfactant one, that rapidly changes lung mechanics by improving pulmonary compliance may also result in lung damage if there are not changes in the ventilatory management to reflect the altered characteristics.

Therefore the parameters setting is a dynamic process which lasts until the end of artificial ventilation.

In the clinical management of ventilated infants a major challenge is to optimize lung volume applying sufficient pressure to keep the lung fully recruited without either increasing the stress applied to the tissue that remains closed or overdistending alveoli through the tidal cycle.
In order to optimize lung volume it is essential to open atelectatic alveoli and rapidly find the maintenance value of ventilatory parameters that will keep them open. An important principle of lung recruitment is that the pressures required to open atelectatic alveoli are considerably higher than those required to keep them from closing again. So periodically recruitment manoeuvres may keep lungs open without repeated application of potentially damaging forces during tidal ventilation. [53] Recruitment depends not only on the magnitude of transpulmonary pressure but also on the duration of its application and because of viscoelastance and other time dependent force distribution phenomena. Therefore, the full volume change is realized only after multiple tidal cycles.
Alveolar re-expansion can be achieved either by brief increases in mean pressure, termed sustained inflations (SI) or by the use of progressive PEEP for brief periods.
However, lungs injured in different ways respond differently to recruitment manoeuvres and not all the lungs are recruitable. The optimal strategy to recruit lung has not be already defined.
Once recruited, a correct ventilatory strategy is necessary to avoid lung volume derecruitment. Currently, pressure setting is based primarily on arterial oxygenation, inflation of the lung on the patient's chest radiograph and subjective assessment of chest wall movement.
According to the open lung concept, the optimal CDP or PEEP is the lowest airways pressure necessary to achieve a fully recruited lung, at a physiological shunt fraction ($\frac{\dot{Q}_S}{\dot{Q}_T}$) below 0.1.
Physiological shunt fraction is the gold standard for assessment of pulmonary oxygen transfer; it is defined as the ratio between the flow of blood going to not ventilated districts ($\dot{Q}_S$) and the total cardiac output ($\dot{Q}_T$). Unfortunately its determination requires invasive access for mixed venous sampling, not commonly used in infants.
Moreover, a lung volume-targeted strategy offers advantages over those that focus only on gas exchange. The optimal CDP or PEEP value may result from a compromise between maximal lung recruitment and minimal overdistention.

1.5.2 Oscillatory mechanics: Forced Oscillation Technique (FOT)

[9]

This technique is a method for assessing respiratory mechanics based on the application of a small amplitude pressure oscillation at the respiratory system while recording pressure and flow signals.

The

From these measurements it is possible to obtain the respiratory system impedance (Z_{rs}) defined as the complex ratio between the applied pressure (P) and the resulting volumetric low rate ($\dot{V}$) at the frequencies contained in the forcing signal$\boldsymbol{Zrs}$= $\frac{P_{rs}}{\dot{V}_{rs}} = \frac{P_0 e^{-i\omega t}}{\dot{V}_0 e^{-i\omega t+\phi_{rs}}} = |Z_{rs}|e^{-\phi_{rs}}$

Equation 18).

The real part of Z is the resistance of the respiratory system (R_{rs}), and describes the dissipative mechanical properties of the respiratory system, whereas the imaginary part, or reactance (X_{rs}), is related to the energy storage capacity and, thus, determined jointly by the elastic and the inertness properties. [54]

The traditional set up (**Errore. L'origine riferimento non è stata trovata.** A) used to measure Z_{rs} consists in a loudspeaker to generate the forced oscillatory signal and two sensors to measure P and $\dot{V}$ at the mouth. To enable spontaneous breathing of the subject, a shunt pathway open to the atmosphere is necessary. This is usually a wide-bore side tube (with a high impedance to present a small leak for the high oscillatory frequencies and a low resistance against spontaneous breathing) placed in parallel to the loudspeaker. A mechanical resistor may also be used for this purpose. A bias flow to flush the dead space can be introduced between the loudspeaker and the pneumotachograph.

With the standard FOT technique, the motion of the upper airway walls affects Z_{rs}, especially at higher frequency. This upper airway shunt results in an artificial frequency dependency of R_{rs} while X_{rs} decreases when f_{res} increases, especially in the presence of a high Z_{rs}. Despite the elimination of the upper airway shunt during standard Z_{rs}, a firm and uniform support of the upper airway walls should be applied. More accurate Z_{rs} data can be obtained using the head generator technique (**Errore. L'origine riferimento non è stata trovata.** B), which minimizes the upper airway shunt. However, further studies are needed to identify the improvements offered by this method in terms of its sensitivity and specificity in clinical practice.

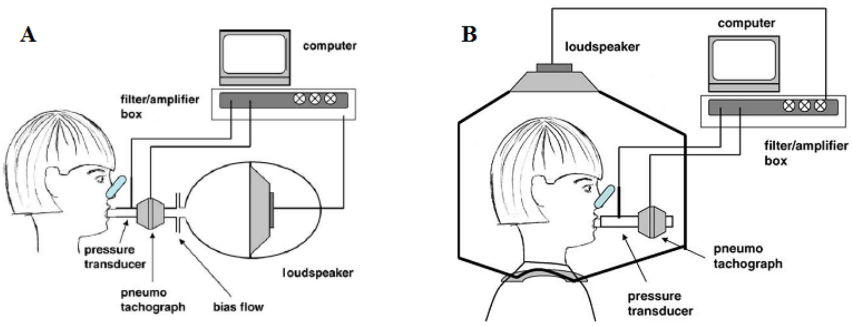


Fig. 17 Typical set-up of FOT measurement (A) and Head Generator Technique (B).

The response of the respiratory system depends on the frequency of the applied pressure oscillation (**Errore. L'origine riferimento non è stata trovata.**).

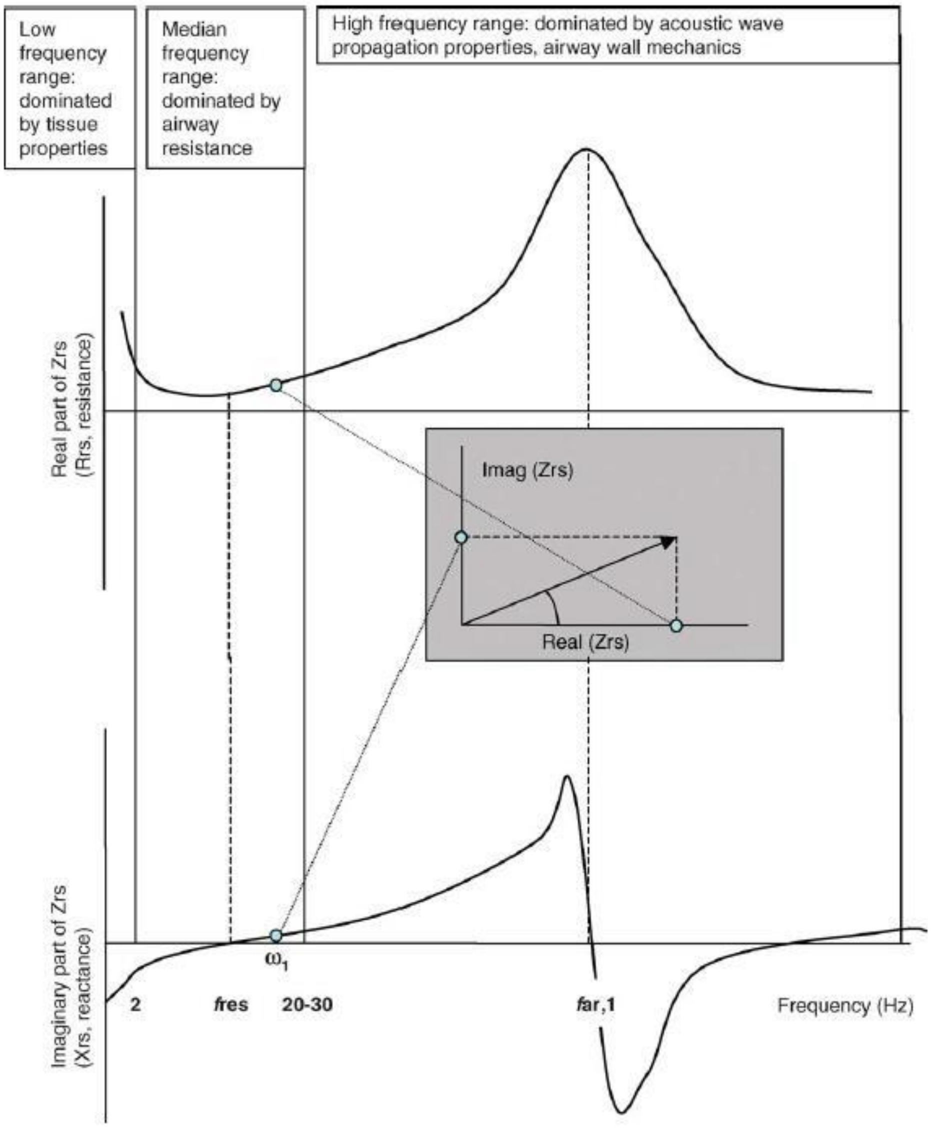


Fig. 18 Schematic representation of the human respiratory input impedance spectrum

[17]

Usually, for clinical FOT applications a range frequency range between 4 and 20 Hz is applied. In this range the healthy respiratory system exhibits a largely frequency-independent real part (R_{rs}) whose major component is dominated by airway resistance (R_{aw}). The real part of Z_{RS} at frequencies such as 4 or 6 Hz (R_{rs4}, R_{rs6}) is taken as a surrogate for airway resistance in many studies. The imaginary part of Z_{rs} (X_{rs}) is the balanced between inertial and compliant elements of the respiratory system. With increasing frequency, X_{rs} undergoes a transition from negative values (when elastic reactance dominates) to positive values where inertial properties dominate. At the zero crossing point, the so called resonant frequency (f_{res}), elastic and inertial components of the impedance are equal but opposite in magnitude thereby cancelling each other out.

The response to very slow pressure oscillations (<1–2 Hz) will contain information on lung tissue, however, the characteristics of the respiratory system below 2 Hz can only be revealed by

investigations during voluntarily apnea, in sedated infants after induction of the Hering Breuer reflex or after short interruption during spontaneous sleep. The advantage of investigating the low frequency range is that the different frequency dependences on the airway and tissue impedance allow the separate estimation of their parameters.
At very high frequencies (>100 Hz) Z_{rs} will contain information on the acoustic wave propagation phenomena in the airways which is dependent on airway length, on diameter and on airway wall compliance. Acoustic antiresonances (f_{ar}) comparable with the sound generation in a flute of the airway length occur at frequencies (f_{ar1}) around 150–250 Hz accompanied by higher harmonics around 600–800 Hz and higher (f_{ar} 2, 3. . .). These antiresonance phenomena contain information on airway wall mechanics. Moreover, those frequency are suitable to estimate the density of the lung parenchyma. [55] [56]
Respiratory system reactance (X_{rs}) measured at the oscillatory frequency of 5 Hz is sensitive and specific to changes in peripheral lung mechanics. Indeed, in 2009 Dellacà et al. has shown that the reactance at 5Hz can be used to estimate the recruitment/derecruitment on piglets before and after interventions to remove surfactant from the animals. [1]
The stimulus applied to the respiratory system induces very small lung volume changes (few ml) with a very short time period (only 0.2 s for a forcing frequency of 5 Hz). [57]
In this way the assessment of lung recruitment may be performed at a specific lung volume, minimizing the artefacts due to nonlinearities of the respiratory system.
Moreover it has been shown that FOT is applicable in ventilated new-borns and can provide useful information for tailoring the ventilator settings according to the patho-physiological characteristics of the patient. [10]

1.5.3 PEEP Optimisation

Nowadays, PEEP titration in clinical practice in newborns relies on monitoring oxygen saturation, which is an indirect indicator of lung recruitment. Moreover, recent study have provided evidence that PEEP can be successfully optimised by maximising dynamic compliance during a decremental PEEP trial [58].
Optimised PEEP level means to find the minimum PEEP which can counteract lung volume de-recruitment without damaging the lungs. The measure of dynamic compliance can be used to do this estimation, however, the measure is invasive and it provides an estimation of the mean compliance during a breath. Therefore, it is not suitable to do a customisation of the therapy which needs the monitoring of the physio-pathological changes of the mechanical property.
As explained, one of the mayor issues in the infants is the lack of surfactant combined with the poor elastic recoil of the chest wall which make premature infants susceptible to alveolar instability. This condition usually results in a not completed recruited lungs. However, it has been demonstrated that

the recruitment of the lungs depends on the nCPAP, PEEP or CDP. Indeed, the application of a distending pressure is used to prevent the collapse of the alveoli, but too high pressure might results in the development of VILI (paragraph 2.1.1.2).

In 2011 Dellacà et al. has shown that the usage of FOT during PEEP trial might lead to find the optimal PEEP that permits to increase the lung recruitment minimising tissue distention. The study was performed on seven pigs which were prepared removing the surfactant doing lavage procedures. It was found that, during PEEP decremental, the reactance has a dome shape: the value of PEEP corresponding to the maximum reactance in the decremental phase can be used to asset the optimal PEEP. [6] [8]

Last but not least, it was found that in a lavage model of lung injury a PEEP optimization strategy based on maximizing Xrs attenuated the signs of ventilator induced lung injury. Therefore the respiratory system reactance measured by FOT could thus be an important component in a strategy for delivering protective ventilation to patients with ARDS/acute lung injury. Moreover, the study underline that the new methodologies was significant better than standard ARDSNet protocol. [7]

Finally, in 2013, Dellacà et al. evaluate the "the feasibility of forced oscillation technique (FOT) measurements at the bedside to describe the relationship between positive end-expiration pressure (PEEP) and lung mechanics in different groups of ventilated infants." [10]

The study includes twenty-eight infants: 5 controls, 16 newborns with respiratory distress syndrome (RDS) and 7 chronically ventilated newborns that developed bronchopulmonary dysplasia.

An incremental/decremental PEEP trial was performed by changing PEEP in 1-min steps of 1 cmH2O between 2 and 10 cmH2O. During the trial the forced oscillations at 5 Hz, generated with a syringe, were superimposed on the ventilator waveform (Fig. 19).

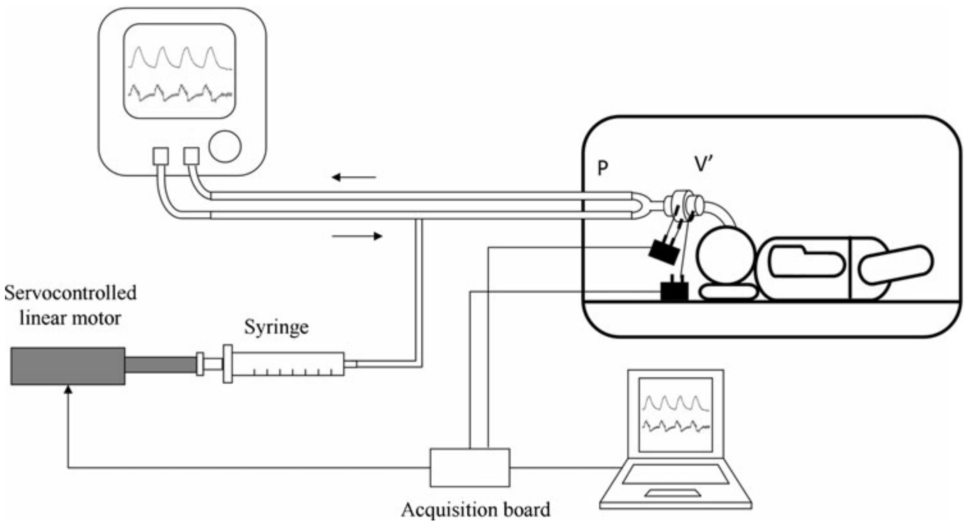


Fig. 19 Set up

From the pressure and flow measured at the inlet of the ETT, was possible to compute the impedance Z_{rs}. The choice of 5 Hz was guided by the evidence that is highly sensitive to peripheral phenomena, such as alveolar recruitment and distension, without being affected by the breathing rate. For each protocol step the last 2–4 breaths were selected, and their end-expiratory Rrs and Xrs values were averaged providing a single data point for each PEEP level.

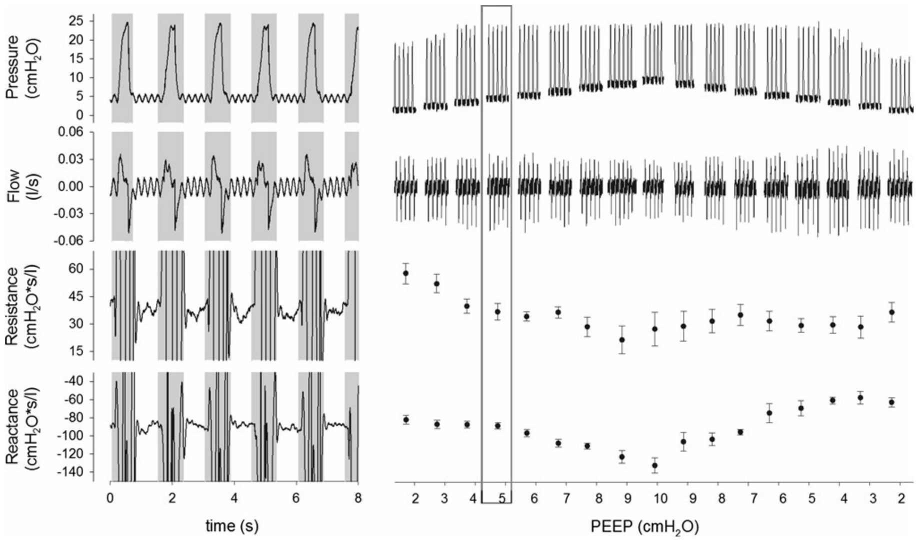


Fig. 20 Experimental tracings. Right panel: pressure, flow, resistance and reactance Left panel: For each PEEP step the last five breaths are reported. Resistance and reactance are reported as a mean and SD of these five breaths

The study concludes that it is possible to find the curve PEEP-X_{rs} which can be used to find recruitment of the lungs and, in particular, that the maximum value of reactance is related to the optimal PEEP setting. However, this study only proved that it was feasible: further studies are needed to see if the animal model reflects the actual behaviours of infant's respiratory system.

Other studies showed that the Z_{rs} at 5 Hz can be used to asset lung volume recruitment-derecruitment not only for conventional FOT, but also for high-frequency oscillatory ventilation. [2]

High-frequency oscillatory ventilation can be used to determinate the optimal PEEP using the same methodology. Indeed, the ventilation is done by imposing a sinusoidal pressure at high frequency. Therefore, although it does not satisfy the assumptions of linearity of the system because the amplitude of the signal is high, it has been showed that the reactance keep the same shape when it is measured in the PEEP trials. Therefore, it can still be used to asset the optimal level of PEEP. [3]

Therefore, the objective of the work is to develop a device which can be uses to generate automatically the PEEP-Reactance curve in real time to provide a tool for understanding the potentialities of this technique. Because of the need of using it in a hospital environment, it has to be easy to use, fast and automatic.

Finally, from a design point of view, this device has to perform an automatic selection of impedance at end of expiration, evaluated with the FOT both in HFOV and conventional ventilation strategies in order to build the PEEP-Reactance curve. Therefore, an automatic algorithm of selection is what it has to be implemented and tested.

2 System Overview

2.1 Objective and Requirements

The objective of the work is to develop a device which can create in real time the PEEP-Reactance curve which might be used in a clinical study to asset the effectiveness of the methodology. In order to do that the best choice is to implement this device in a mechanical ventilator as it is reliable in managing the ventilation and, because of its present in every hospital, it is easy to use for a clinician. However, as the effectiveness of this technique has still to be proven in premature infants, there are not enough evidences to justify the time and economical cost to modify a commercial ventilator. Therefore, a hybrid approach has been considered: it was decided to implement a software in a different board which communicate with a mechanical ventilator. This way allows to do minimal firmware change as the ventilator has to be able to send the data of pressure and flow a serial communication and to generate the FOT stimulus. As there is a collaboration between Acutronics and the TBM lab in order to implement the FOT technologies, the ventilator chosen is the Fabian HFO produced by Acutronics.

This device has to perform an automatic selection of impedance data, evaluated with the FOT, both in HFOV and conventional ventilation strategies in order to evaluate the reactance at the end of expiration. A good choice is to develop an Android application using a Tablet or a Smartphone. Indeed, this application will be used to evaluate the usage of FOT to find the optimal PEEP setting while the ventilator send the data of pressure and flow through a serial communication and it is able to generate the FOT stimulus. Therefore, the usage of Android is suitable to understand the effectiveness of this approach to find the optimal PEEP with FOT. Only after this has been proved, the methodology can be implemented completely in a mechanical ventilator.

Therefore, the system to develop consist in an application in Android that has to communicate with the Fabian HFO receiving the data of pressure and flow and sending the commands to enable the pressure stimulus at high frequency.

Fig. 21 System outline

The communication will be wireless and will take place with the Bluetooth protocol.

In order to do FOT measurement, there are some requirements in the signal acquisition to be respected. Indeed, in order to obtained accurate impedance measurements, the set-up for FOT measurements as to satisfy the following requirements:

- Adequate frequency response of the sensors in the frequency range used by the forcing waveform;
- Flow and pressure signals must be sampled synchronously;
- The pressure waveform used for FOT signal should be symmetrical and with frequency components limited to the frequencies of interest. In the case of single sinusoidal forcing, the pressure waveform should accurately resemble a sinusoidal shape with a peak to peak pressure independent by the ventilator settings and the mechanical load imposed by the patient.

2.2 Mechanical Ventilator – Fabian HFO

Because of the collaboration between the Switzerland Company and the Politecnico di Milano, a Fabian HFO was provided at the TBM lab. A preliminary analysis has confirmed that only software changes were needed to integrate this technology in the Fabian HFO device, as the modularity and flexibility of the device makes it possible to easily add the new functionalities. Some changes in the ventilators' software have already been made by Acutronics Medical System on Politecnico's requests:

- In order to send the digital measurements of airway opening flow and pressure signals to an external device by the serial port (RS232)

- In order to generate the oscillatory pressure overimposed to the ventilator waveform for measuring Z_{rs}.

It is required that the dynamic response of sensors let pass the stimulus frequency. Luckily, experimental data obtained during preliminary in-vitro bench tests by the ventilator have been analysed off-line and have shown that reliable Zrs measurements are possible under some ventilation modalities and settings after applying specific data processing procedures to the measurements. Indeed, in order to correctly compute the impedance, flow and pressure have to be perfectly aligned. The alignment of the signals is currently not gartered.

In paragraph **Errore. L'origine riferimento non è stata trovata.**, the requirements to obtain good impedance measurement are presented while the behaviour of the ventilator is presented below.

The ventilator uses a diaphragm manometer for evaluating pressure at the mouth and a hot-wire anemometer for the flow. While the former is very linear, the second presents some non-linarites. One of mayor impact for the evaluation of the impedance is the death zone, which means that some value of flow are zero as the device is not able to tell in which direction is air is going. Acutronics reduces the death zone to the minimum in order to reduce this problem.

Acutronics provided the front-end schematic and explain what kind of digital elaborations were performed.

They claim that for pressure the hardware-filtering has a τ = RC = 0,33 msec and that it is the only this filter applied in HFO-mode leading to a HW-time constant in HFO Mode of 0,33 msec. Then the signal is sampled at 1 kHz. The software-filter used leads to a time constant of 8 mses.

To what concern the Flow, the Hardware-Filtering leads to time constant of τ = RC = SQRT(0.12 + 0,032) = 0,104 mses. Again this is the only filter applied in HFO-mode. The signals is sampled at 1 kHz and the software-filter used leads to a time constant of 4 mses.

For both signals one sample each five is sent through the serial port obtaining a sample frequency of 200 Hz.

For those digital filter the bode diagram are showed below (**Errore. L'origine riferimento non è stata trovata.**, **Errore. L'origine riferimento non è stata trovata.**).

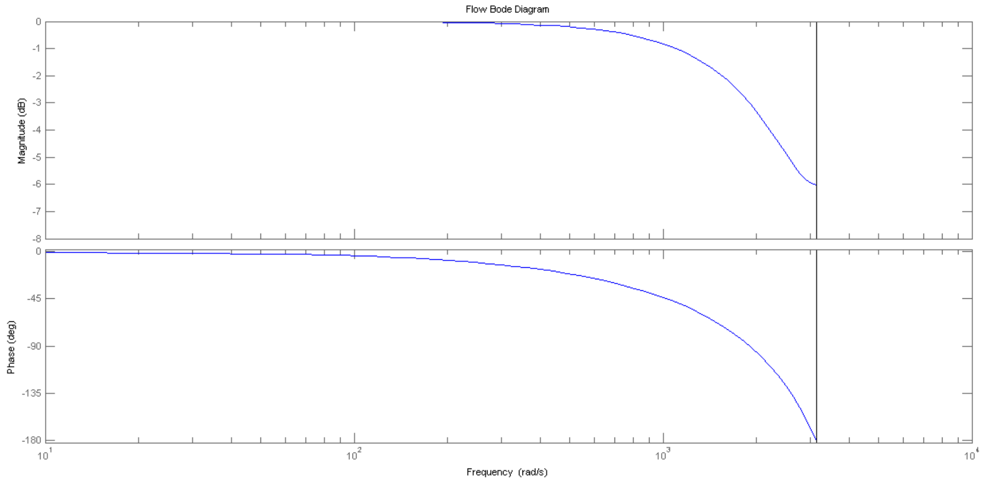


Fig. 22 Flow Bode Diagram

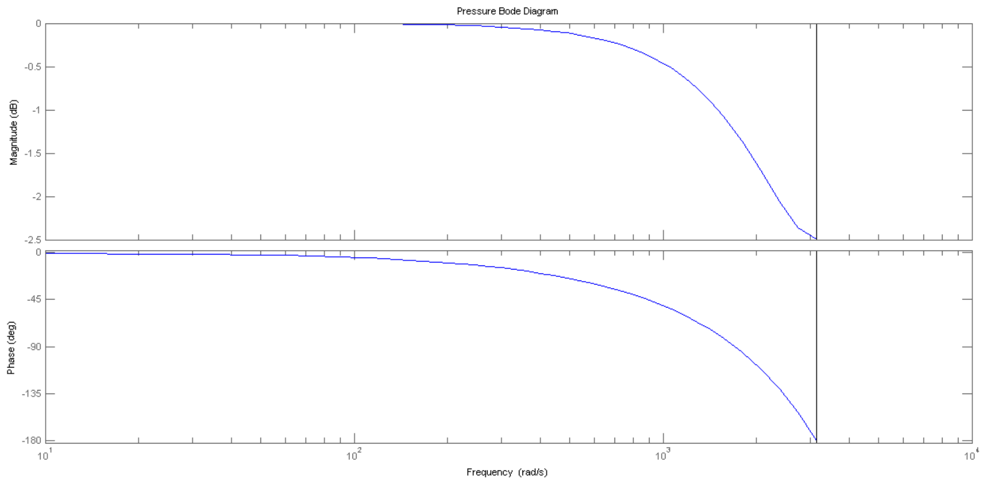


Fig. 23 Pressure Bode diagram

Even though they are FIR filter, as the impulse response is not symmetric (**Errore. L'origine riferimento non è stata trovata.**), the phase is not linear. However, in the band up to 20 Hz, the linearity of the phase is prevailing.

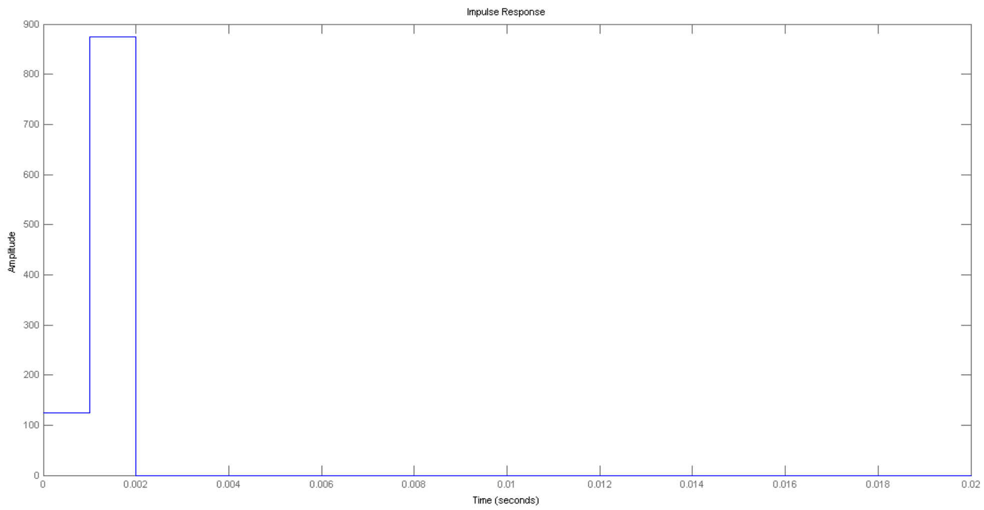


Fig. 24 Impulse response

As the two signals have to be aligned, the phase shift introduced by the filter is evaluated.

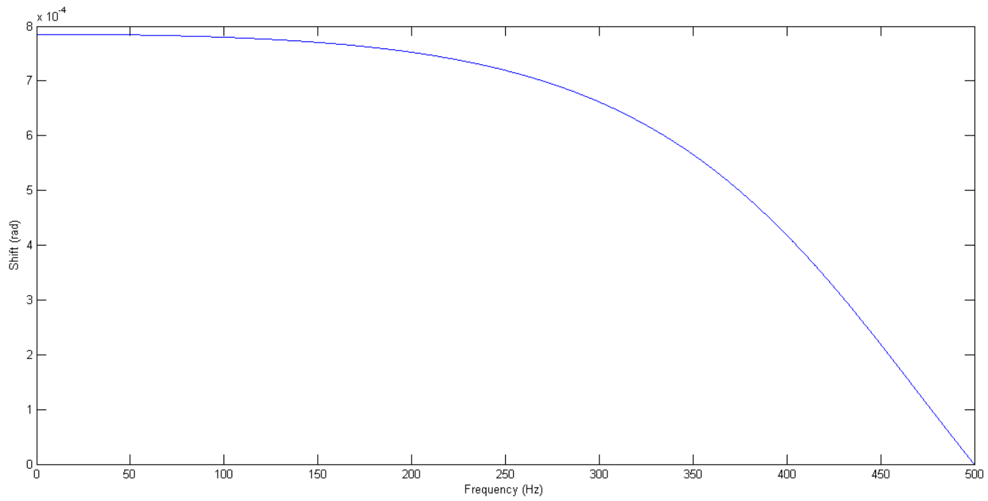


Fig. 25 Phase-shift

The frequencies of interest come up to 10 Hz, therefore we evaluated the shift between pressure and flow (**Errore. L'origine riferimento non è stata trovata.**).

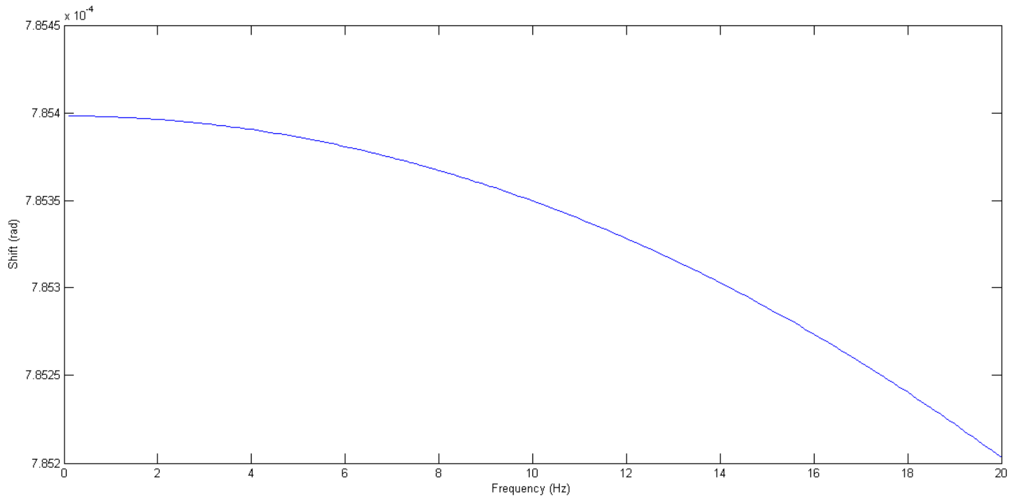


Fig. 26 Phase-shift up to 20 Hz

The shift evaluated in samples, when a sampling frequency of 200 Hz is used, is evaluated as follow:

$$\boldsymbol{samples} = \frac{\boldsymbol{fs}}{\boldsymbol{2\pi}}\alpha \qquad \textbf{Equation 19}$$

Table 3 Shitf introduced at CMV frequency

Frequencies	Phase-shift (rad)	Samples
5	7.8539e-04	0.0250
10	7.8535e-04	0.0250
17	7.8526e-04	0.0250

Therefore, the shift introduced by those filters appears to be constant and less than one sample.
In order to evaluate the actual displacement between flow and pressure, introduced by the sensor aswell, some in vitro tests were performed as described in paragraph 3.2.1.

2.3 Bluetooth Adapter

2.3.1 Communication protocol

The ventilator uses a RS232 interface and sends the data through the serial port placed on its back. In particular, the ventilator sends data with baud rate of 115200, with the following protocol:

…#P|F|P|F|P|F|P|F|P|F|P|F|P|F|P|F|P|F|P|F#…

Where P represent the Pressure and F the Flow. The data are sent in a string format: this is to say that for any data of pressure or flow is usually sent with more than one byte. Every time 10 flow and 10 pressure data are sent or at the beginning of any communication, the # character is sent. Within the range of two #, pressure data and flow are separated by |. The separator characters are used to synchronize the acquisition of the data, in particular # is used to resynchronize the acquisition in case of data loss.

Regarding the commands that can be sent to the ventilator, the following characters are interpreted as:

- M: starts the serial transmission of data.
- Q: stop transmitting serial data.
- a0, a1, a2, a3: to set the amplitude respectively to 0, 2.5, 5 or 7.5 mbar.
- f0, f1, f2: to set the frequency of the oscillation, respectively: 5, 10 and 15 Hz.

It is remarkable that the command for FOT are not recognised by the ventilator if the communication wasn't started before. Moreover, once the command character are sent, the ventilator will replay with the following acknowledge message:

1. The amplitude is set to OFF → a0
2. The amplitude is set to 2.5 mbar → a1
3. The amplitude is set to 5 mbar → a2
4. The amplitude is set to 7.5 mbar → a3
5. The frequency is set to 5 Hz → f0
6. The frequency is set to 10 Hz → f1
7. The frequency is set to 17 Hz → f2

2.3.2 Electronic board

As the Fabian HFO does not have Bluetooth module, a small hardware was realised in order to convert the RS232 communication in Bluetooth. The hardware structure is composed of a board that converts the output signals from the RS232 port of the ventilator into RF signals according to the Bluetooth protocol, in order to have a wireless connection with the Android device (**Errore. L'origine riferimento non è stata trovata.**).

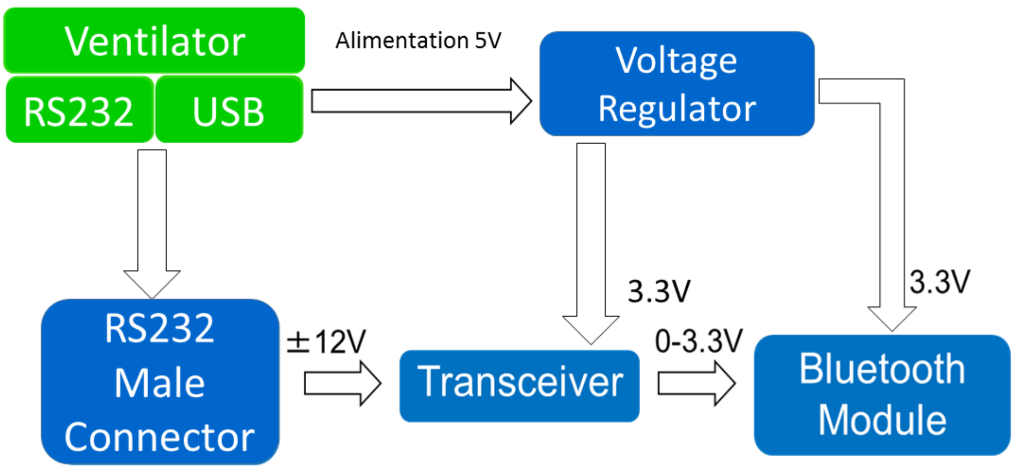


Fig. 27 Bluetooth Modulo scheme

The component chosen to reach blue box are listed below:

- Bluetooth: Roving Networks RN-42.

- Transceiver: Texas Instruments MAX2323.
- Regulator: Texas Instruments LM340s-05.
- Connector: SparkFun-Connectors DB9-male.

The alimentation was taken directly from the USB port and was given to the voltage regulator that give as output 3.3 V. The regulator was need because at the Bluetooth module can be applied tension up to 3.6 V. If, for the any reason, a constant high tension is applied at any pin, it will break down. For the same reason, the transceiver MAC2323 was chosen as it can give as output 3.3 volt if its alimentation is a 3.3 V.

The transceiver and the Bluetooth module can communicate though a simple UART (0-3.3V). Therefore, the first thing to be done is to convert the RS232 in UART. In order to do that, some condensers have to be applied as in **Errore. L'origine riferimento non è stata trovata.** so that the charge pump is realised.

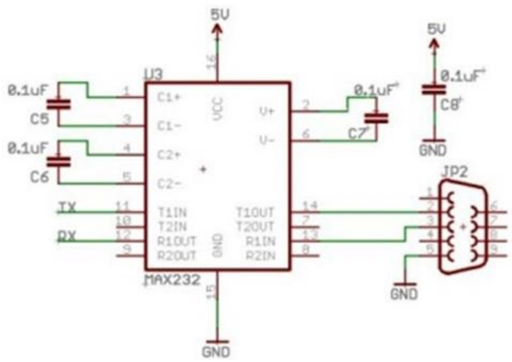


Fig. 28 Transceiver

In the datasheet it was suggested to use condensers higher that 100 nF in order to realise the pump change.

Once the components were decided, a schematic with the software Eagle was realised (**Errore. L'origine riferimento non è stata trovata.**).

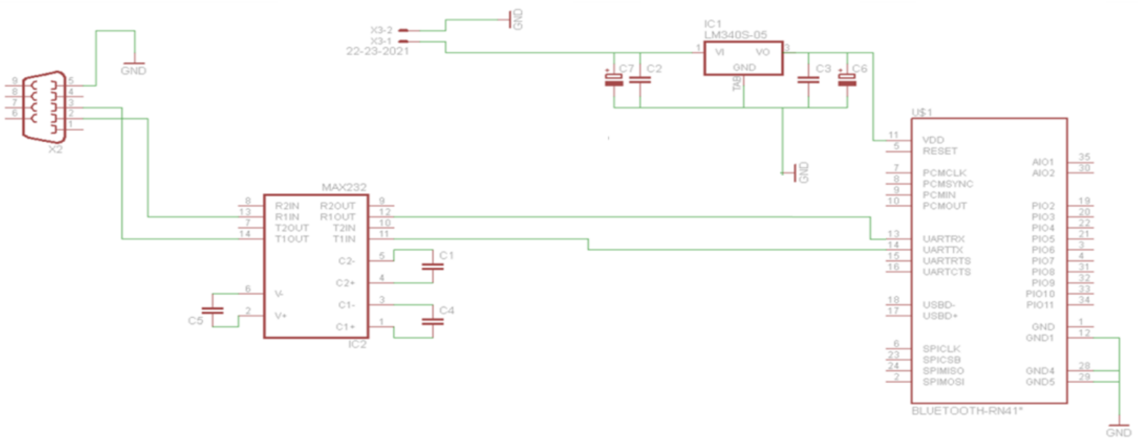


Fig. 29 Schematic Bluetooth module

When the schematic was realised, it followed the realisation of the board. Through Eagle the board was printed and therefore realised with the press 'n peel method. Finally, a case was draw using SketchUp (Fig. 30) and printed with the 3D-printer Makerbot Replicator 2X (Fig. 31).

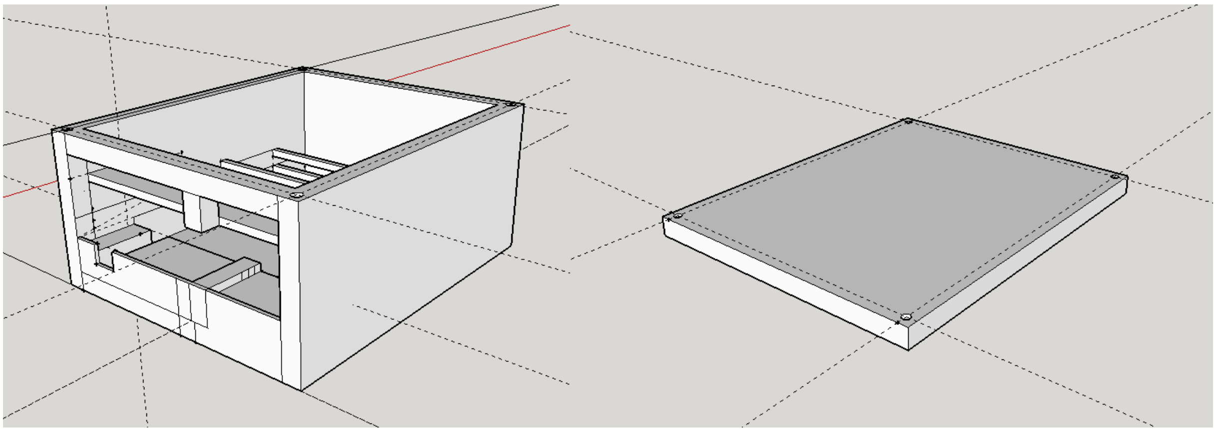


Fig. 30 SketchUp draw

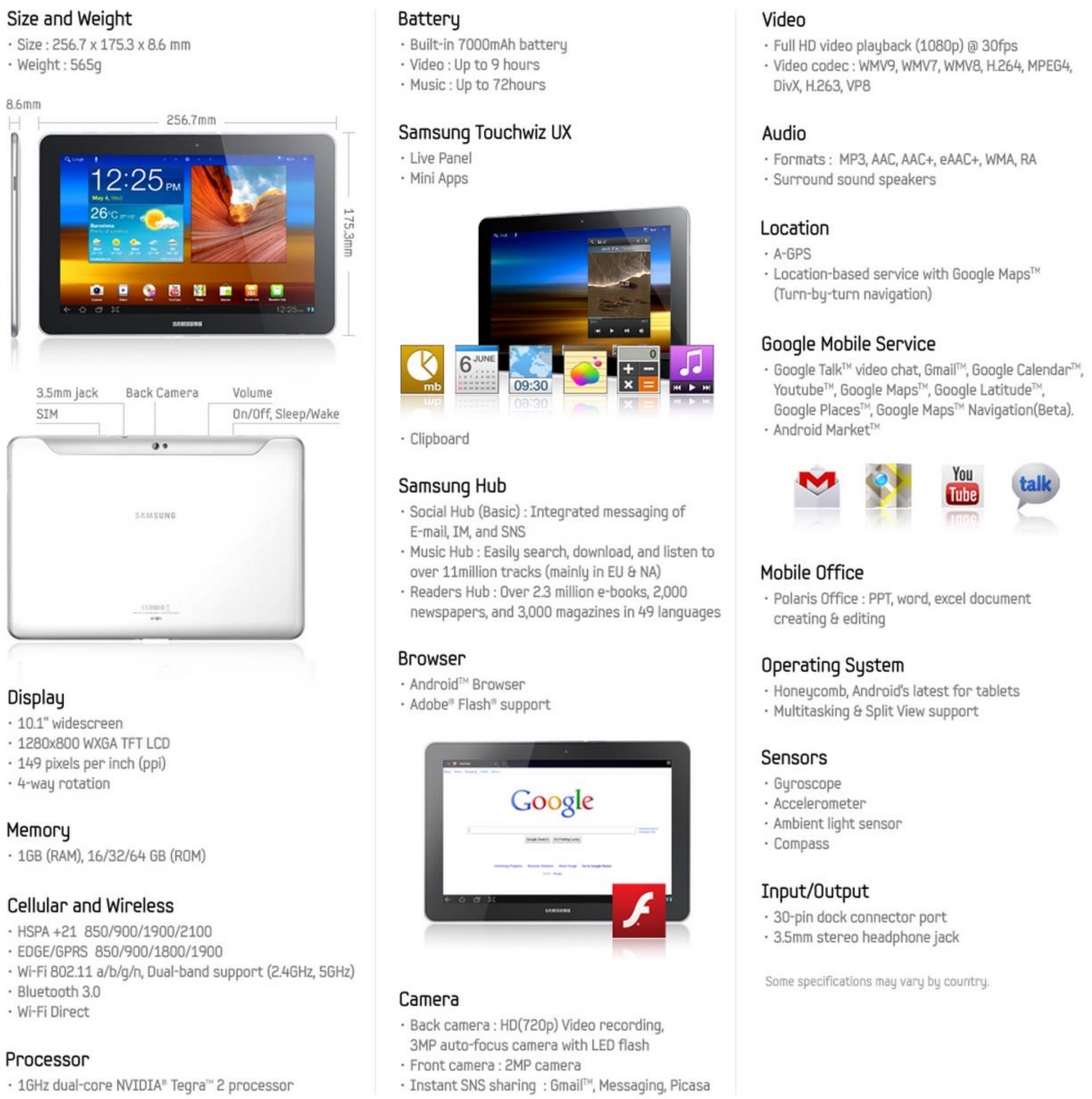
Fig. 31 Case printed

2.4 Tablet

In order to develop the device, it is suitable to use a tablet in order to manage the user interface and Bluetooth communication. The advantages of a device such as a tablet are its portability, it is easy to clean and it has an intuitive user interface.

Fig. 32 Tablet

The tablet used is the Samsung galaxy tab 2 10.1 shown in **Errore. L'origine riferimento non è stata trovata.** which has the following specification:



2.5 Software

The software has to acquire the signal of pressure and flow and has to compute the mechanical impedance using the LMSM. From those data has to perform the selection algorithm.

The Android application has to perform the function in Fig. 65.

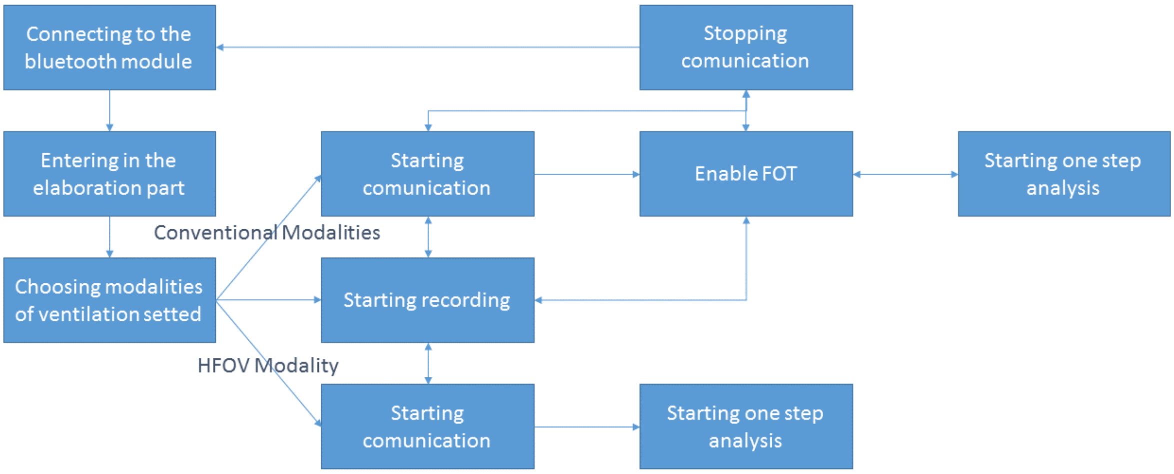


Fig. 33 Application function

In order to do that, it was organised in three activities and one service.

A Service is an application component that can perform long-running operations in the background and does not provide a user interface. Another application component can start a service and it will continue to run in the background even if the user switches to another application. An Activity is an application component that provides a screen with which users can interact in order to do something, such as dial the phone, take a photo, send an email, or view a map. Each activity is given a window in which to draw its user interface. The window typically fills the screen, but may be smaller than the screen and float on top of other windows.

An application usually consists of multiple activities that are loosely bound to each other.

The service is the BluetoothChatService which is describe in next paragraph.

The three activities are: MainActivity, DeviceListActivity and Grafici_Activity. Those are described in paragraph **Errore. L'origine riferimento non è stata trovata.**.

2.5.1 Bluetooth communication Android

Once the hardware for the ventilator is done, it is finally possible to start a Bluetooth communication between the two devices. Once the application is opened, the first thing to be checked is if the device has a Bluetooth module and, eventually, turn it on. To do this, it is convenient to use the 'BluetoothAdapter' which is unique for the whole system and the application can interact with the ventilator via this object. To get the BluetoothAdapter the method getDefaultAdapter() must invoked:

```
BluetoothAdapter mBluetoothAdapter = BluetoothAdapter.getDefaultAdapter();
if (mBluetoothAdapter == null) {
   // Device does not support Bluetooth
}
```

If the device does not have the Bluetooth, the method will return null. As it is discussed more in detail in the Appendix A, the application will be closed if no Bluetooth is available on the device.
Once checked if the device does have a Bluetooth, it will be checked if it is on. If the Bluetooth is not on, it will be requested to the user to turn it on. Again, for more detail read the Appendix A.

```
if (!mBluetoothAdapter.isEnabled()) {
   Intent enableBtIntent = new Intent(BluetoothAdapter.ACTION_REQUEST_ENABLE);
   startActivityForResult(enableBtIntent, REQUEST_ENABLE_BT);
}
```

Once the Bluetooth is on, it is possible to start searching any available devices if they are any in discoverable mode or have been paired with the device in use previously. In this case, they will share a variety of information such as their name, their classes and their MAC addresses. Using this MAC address, which is unique for each device, it is possible to start a connection.
It is important to note that there is a big difference between being coupled and being connected. Be coupled only means that two devices are aware of the existence of the other (that is, know their names, classes, and MAC addresses). However, be connected means that the two devices share a radio frequency RFCOMM channel and are able to exchange information through it.
To create a connection between two devices, some roles have to be decided: one act as server (keeping open a BluetoothServerSocket, so that it is listening to a possible connection request), while the other act as the client (who must try to initialize the connection by sending a connection request to the server). The BluetoothServerSocket return a connected BluetoothSocket when the connection will be accepted. The two devices, therefore, will be connected to one another when each of them will have a bluetoothSocket (i.e. a connection point) which refers to the same RFCOMM channel. At this point the transfer of data between the two devices can take place.
In this implementation the module RN-42 plays the role of the server. On a request sent from the application, it will be start to listen to any request for access (which means to open a BluetoothServerSocket) and subsequently, the application, acting as a client, try to start the connection.
The BluetoothServerSocket uses the *thelistenUsingRfcommWithServiceRecord (String, UUID)* in which the terms are respectively an arbitrary name, which is usually the application name, and the UUID (Universally Unique Identifier). The latter is a 128-bit ID which it is used to uniquely identify the Bluetooth service, in this case it was provided by the datasheet of the module RN-42.
In actual fact, the management of the Bluetooth connection is mainly entrusted to a class, the BluetoothChatService, which implements three threads that perform different functions useful to connect and communicate with one of the activity by a handler (a piece of code that is executed automatically when you receive one of the messages delivered by the thread, see Appendix A).

The threads implemented for the management of the Bluetooth are the following:

- AcceptThread: it is used to connect as a server. It is running while the system is waiting for an incoming connection and remains active until a connection is made:
  a) gets a BluetoothServerSocket using thelistenUsingRfcommWithServiceRecord (String, UUID);
  b) listens for a connection request by calling accept(). It returns a BluetoothSocket if it manages to connect;
  c) once it is called the close() function, it releases the server socket and all its resources, but does not close the connected BluetoothSocket returned by accept().
- ConnectThread: it is used to connect as a client. It is running while you are trying to create a new connection with a remote device:
  a) to initiate a connection must first get a BluetoothDevice object that represents the remote device with which the device has to connect;
  b) using the BluetoothDevice object, a BluetoothSocket is obtained by calling createRfcommSocketToServiceRecord (UUID);
  c) to initialize the connection connect() is used.
- ConnectedThread: it is running during a connection with a remote device and manages the transmissions of both incoming and outgoing data. Once two devices are successfully connected, each of them will have a connected BluetoothSocket through which it is possible to share data.
  a) Through the socket, invoking functions getInputStream () and getOutputStream (), you can get InputStream and OutputStream
  b) To read or send a stream of data using the functions read (byte []) and write (byte [])

Once the two devices are connected, the baud rate has to be set and, after, data can be sent. Therefore, the data flow has to be managed correctly in order to have the data of flow and pressure. Indeed, once the ConnectedThread receives the byte stream from the remote device, these bytes are first saved in a buffer and subsequently converted into the string. This data string are then sent to one activity of the application in order to be reorganized and, eventually, redirected to other activities.

The raw data received by the device are a string as follow:

…#P|F|P|F|P|F|P|F|P|F|P|F|P|F|P|F|P|F|P|F#…

In the string there is, then, the alternation of a value of pressure and a value of flow separated by the character "|". In addition, every 20 values of pressure and flow, there is the # character that divides the received stream into sub-blocks of 20 data. The purpose of this first step of elaboration is to divide the data of pressure and flow in order to be ready for any elaboration. Before that, it is important to distinguish between Pressure and Flow data and the acknowledge message. Therefore, it is enough to control if some letter arrives. If a letter arrives, the machine will start to save all the character is an array until it receive the # character. After that, the array will be showed to the user and the application will restart to recognize pressure and flow. See the finite state machine in **Errore. L'origine riferimento non è stata trovata.**.

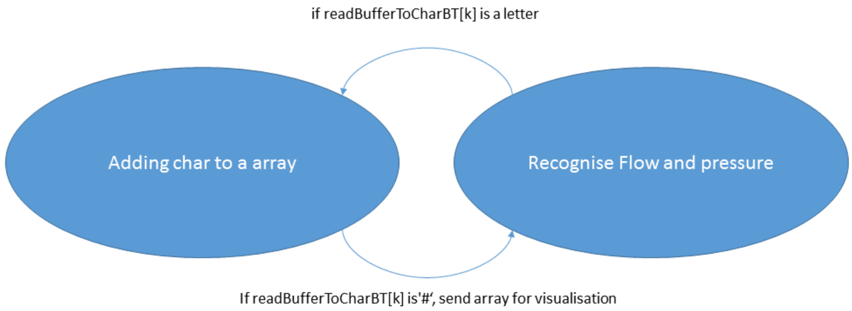


Fig. 34 Finite state machine to handle acknowledge message

Once the acknowledge message are managed, the recognition of flow and pressure is doing implementing another finite state machine (**Errore. L'origine riferimento non è stata trovata.**).

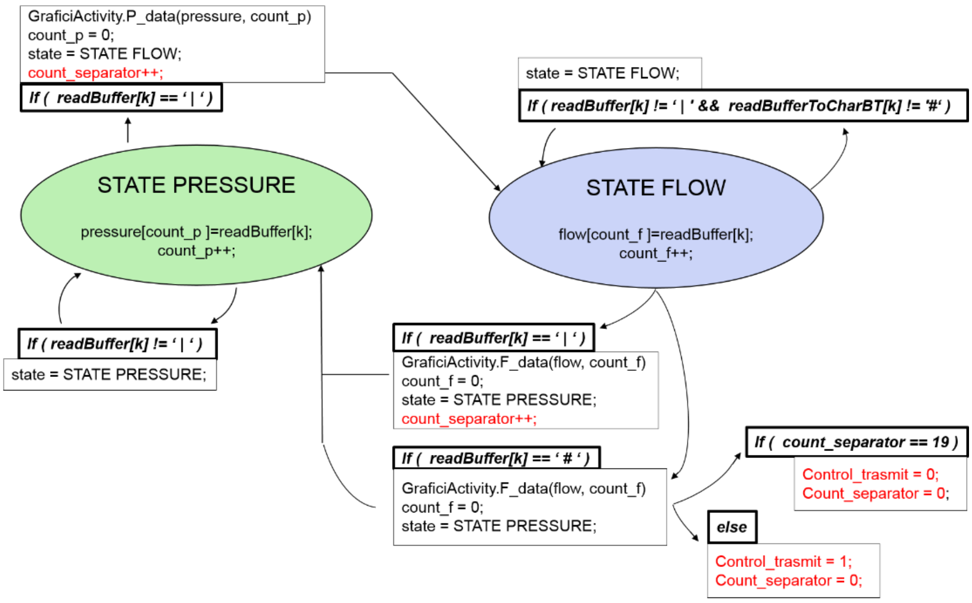


Fig. 35 Finite state machine for Bluetooth

The algorithm work as follow:

- At the beginning of the transmission of the data the state is PRESSURE. If the character read from the buffer is different from the separator character "|", this character is stored in an array of char. New characters are happened to the string until the separator "|" is received.

- At this point, the array pressure, with inside the characters representative of the pressure value, is sent to the GraficiActivity (paragraph **Errore. L'origine riferimento non è stata trovata.**). The counter used to increase the position within the array is set to zero and another counter is incremented to keep in memory the successful reading of a separator "|". The state switches to FLOW.
- In this state, if the character read is different from the characters "|" and "#", it is stored in an array similar to pressure, named flow.
- When the character "|" is received, the array flow is sent to the GraficiActivity (paragraph**Errore. L'origine riferimento non è stata trovata.**). The flow counter is reset. The separator charactercounter is incremented and the state returns to PRESSURE.
- This procedure is repeated until the last flow value before the character "#"
- Upon arrival at the "#" character it will again be sent the string flow data in the usual way to the GraficiActivity. Moreover, in case of data loss, the communication was realigned for the next samples. This character is sent by the Fabian at the beginning of each communication, therefore it is import because it allow to correctly initialize the communication.

In order to find some data loss, every time a "|" in received a counter is incremented. When a data arrive, it is putted back to zero. Therefore, it is possible to check whether data were received between the two "|" and sees if some data were lost. However, this is not enough, as a value of pressure or flow is made of more that only one char. Indeed, it might be chosen a standard length of the string to send, possibly different for pressure and flow, and by easily counting the char received for each value, it would be possible to find any data loss. Thus, if the number of char received is low or higher than the standard length, there is a loss of data to be managed. Once the data loss is identified, this sample can be estimated by using a simply predictor which consist in the discretization of the Taylor-McLaurin series of pressure or flow at the second order:

$$\boldsymbol{\hat{y}(t) = 2.5y(t-1) - 2y(t-2) + 0.5y(t-3)} \qquad \textbf{Equation 20}$$

The predictor in **Errore. L'origine riferimento non è stata trovata.** work well if there are not a lot samples lost.

The problem is that in the Fabian communication protocol there is not standard length of the string to send. If the number to send is 0, the Fabian will send only 1 char. Finally, at the moment, it is possible to see if there were data loss by using the "#" character, but it is not possible to repair the loss of data. This is an issue to take into consideration as, one value either of pressure or flow lost, bring at least 2 windows of data which can be all wrong. However, it is true aswell that the data loss was negligible during this work, especially when the Android device and the Fabian are at least in the same room and the RF signal is good.

2.5.2 Android application description – User Interface

When the application is started, the MainActivity is the one that start and the application will appear as in **Errore. L'origine riferimento non è stata trovata.**.

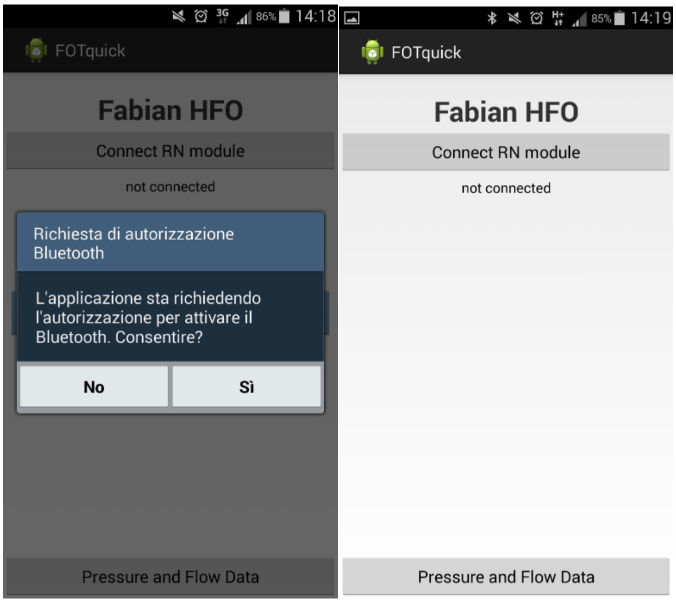


Fig. 36 Main Activity UI

Before allowing the user to do anything, the application will ask to the user to turn the Bluetooth on. Once the Bluetooth is on, it is needed to start a connection with another Bluetooth device. In this case, the RN42 module. Therefore, the button “Connect RN module” is to be pressed. At the first start, the DeviceListActivity will be launched. Here, the user has to choose the device which one is the device to be connected and eventually it is possible to scan new devices. The MAC address of the device will be saved once it is chosen, therefore in future there will be no need to go through the installation procedure (**Errore. L'origine riferimento non è stata trovata.**). Indeed, by pressing the button, the device will connect to the RN module if it is available.

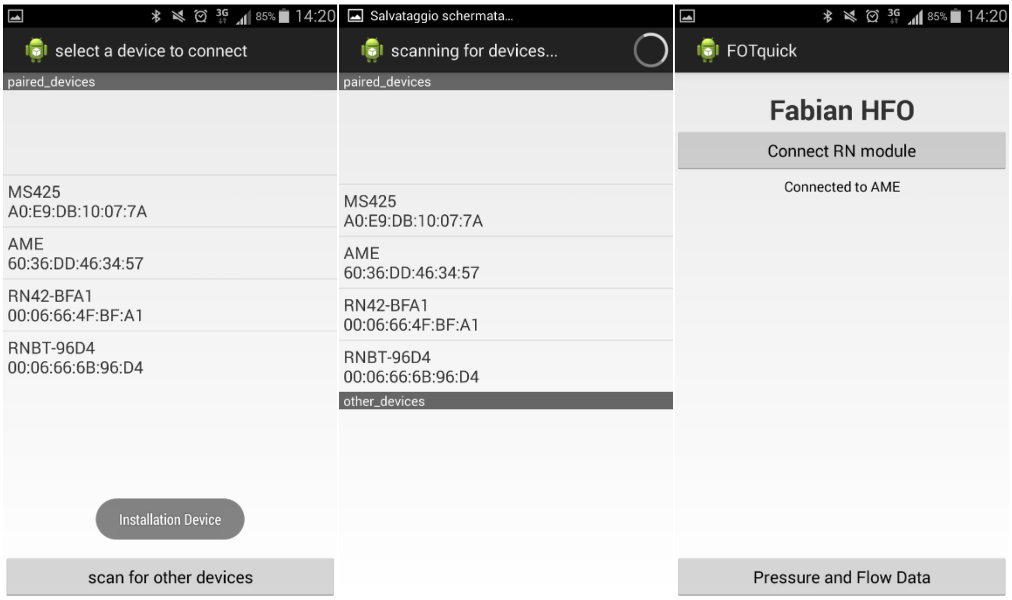


Fig. 37 Installation procedure

If in future the user want to change the device, this is possible by pressing the menu button (which is a standard button in Android and it usually stay at the left of the home button or on top at the right) where the option "delete device" can be pressed (**Errore. L'origine riferimento non è stata trovata.**). If the user presses again Connect RN module, the installation procedure will start again.

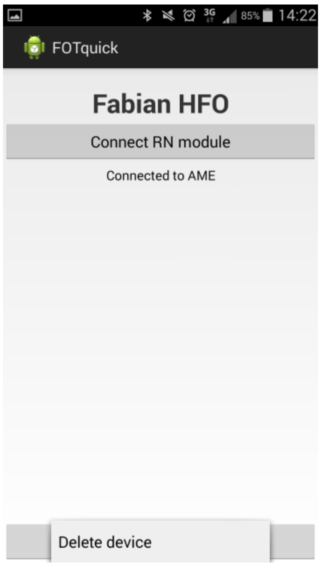


Fig. 38 Delete Device

Now it is possible to go in the Grafici_Activity, which is the actual core of the application, by pressing the bottom "Pressure and Flow Data".

In **Errore. L'origine riferimento non è stata trovata.**, there is the UI of the activity. The button will be explain and, eventually, part of the algorithm not discussed so far will be presented.

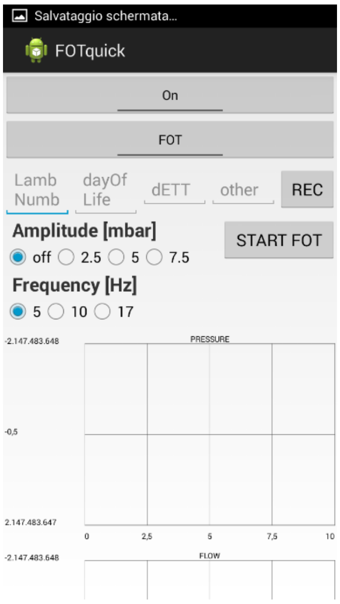


Fig. 39 Grafici Activity

The first button that can be pressed it the "On" button. This one permit to the user to start the communication with the Fabian. One pressed, the application will send the character 'M' and the data will start to flow. The button will have write "Off" as show in **Errore. L'origine riferimento non è stata trovata.** and by pressing on it now the communication will be stopped.

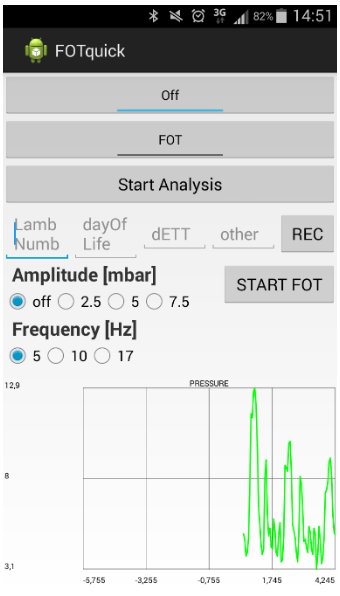


Fig. 40 Acquisition start

There is another button which is very important for this application: "START FOT". This button will take the value selected of amplitude and frequency from the menu on the left. Once pressed, communication will be stopped in order to allow the application to upload the matrix needed for the impedance evaluation. Then the communication will be started again and the command characters are sent. Therefore, to enable FOT the right parameters has to be set and then the button "START FOT" has to be pressed.

The bottom immediately below permit to the user to choose between modalities. Indeed, it is possible to have the evaluation of the PEEP in conventional FOT (therefore, CPAP or IPPV) or the mean Pressure using the HFOV as a strategy of ventilation. By default, the application start ready to deal with conventional FOT. By pressing the button FOT, the activity will change as shown in **Errore. L'origine riferimento non è stata trovata.**.

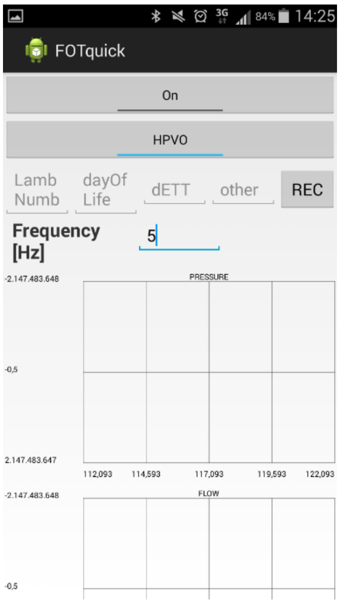


Fig. 41 HFOV

At the moment, there is a space where the frequency of the ventilation has to be inserted. This is because the ventilator does not send the respiratory frequency in HFOV, but it will be able to do it soon. Indeed, if the application send the ventilation frequency in HFOV, the application would not need the user to insert it manually increasing the usability of the device. Given the frequency, when the button “On” is pressed, the character of starting communication will be sent and the matrix A and B introduced in paragraph 3.1.1.1 are evaluated. Therefore, each time the communication is started the matrix are uploaded. The need to implement a specific UI and behaviour of the app in the HFOV modality is due to the need to manage the selection of data which is completely different (as describe in paragraph 3.1.2.6).

In both modalities it is present the button REC. When pressed, a file with the data will be created. This file will be written during the execution of the calculation.

This file is formatting as follow:

Time;Pressure;Flow;Resistance;Reactance;FSI;PSI;DSI;meanF; dmeanF;dmeanP;Result_selection

The last element, result_selection, will be 1 it the sample is good, 0 otherwise. Importantly, this variable takes into account only the output of the selection algorithm without the outlier’s elimination.

The recording will start anyway even if the file has no name or a similar file was already saved. However, the application will not overwrite any file and, when the recording will be stopped, a dialog will open when a name for the file will be asked. The name has to be unique, no overwrite are permitted. The application is doing the saving procedure in a temporary file as usually and, at the end, it simply copies the temp file in the new one. Finally, the temp file will be deleted. This was done in order to increase the usability of the device in a neonatal intensive care unit. Indeed, the environment can be very eventful and it might happen that there is not time to care about the name of the file at the beginning of the acquisition.

In both modalities, when the communication is started, a button appears: “Start Analysis”. When it is pressed, the application will initialize a handler to execute a runnable after 46 seconds and will start to evaluate the impedance and the parameters. Indeed, as the normalisation is need, 10 seconds are used in order to find the normalisation coefficients (see the Algorithm section for more details). Afterwards the resistance and reactance data selected are putted in two ArrayList<double>. Once the 46 seconds are passed, the runnable will do the outliers identification and it will evaluate the mean value of resistance and reactance. When those values are evaluated, a first point into a graph, which will be discussed below, is putted. Those are the graph that will be uploaded during the PEEP trial.

The Grafici_Activity manage several graphs. In order to do graphs in Android, the library *Android GraphView 3.1* was used. This library offer easy and fast method to develop high quality graphs.

The graphs built are:

1. Pressure
2. Flow
3. Volume
4. Impedance (Resistance and Reactance on the same graph)
5. Selected Resistance
6. Selected Reactance
7. Resistance vs PEEP
8. Reactance vs PEEP

Following, some picture of the application.

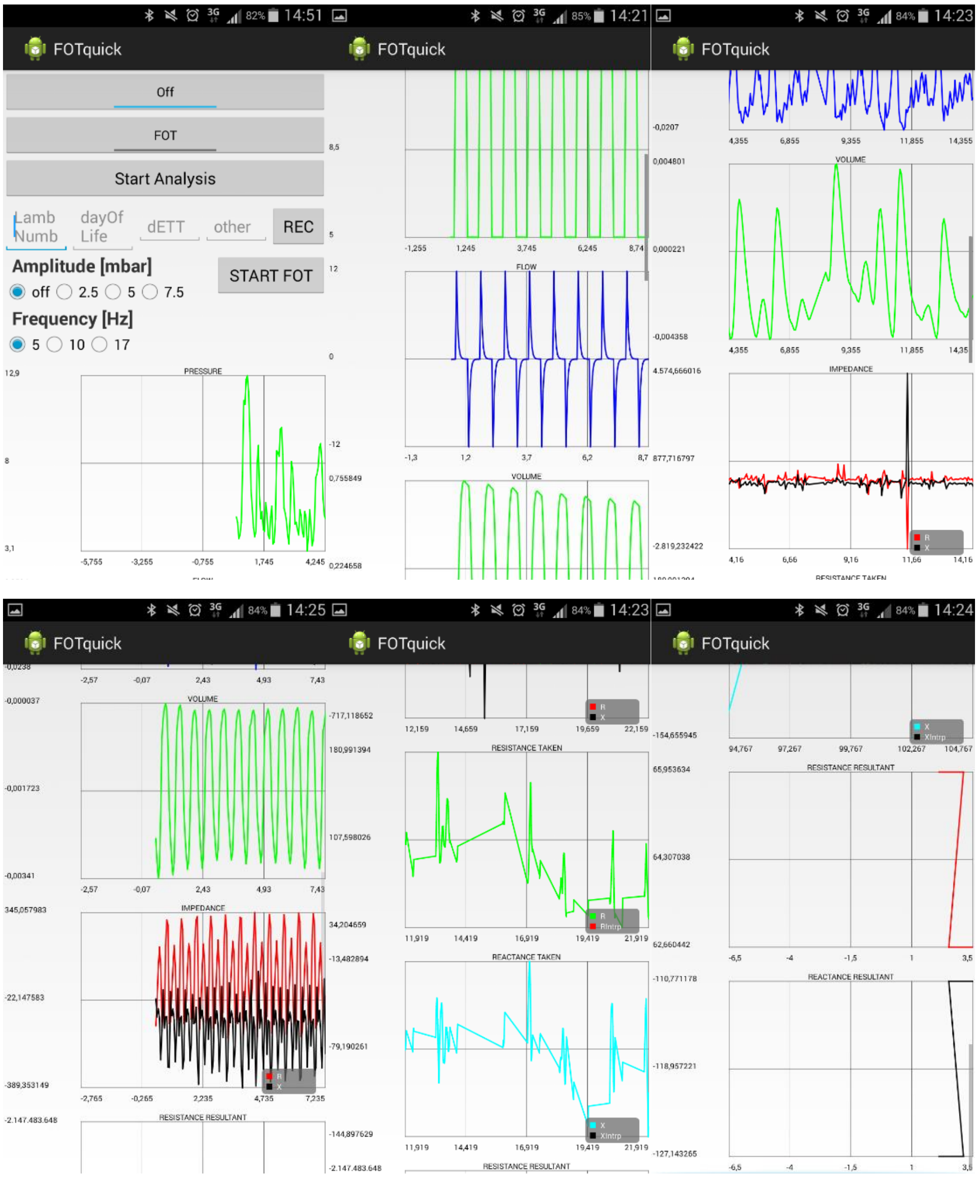


Fig. 42 Graphs

As said in paragraph **Errore. L'origine riferimento non è stata trovata.**, the *ConnectedThread* sent the data to an activity where there is a handler that manages extraction of Pressure and Flow. This activity is the MainActivity.

By using the following method

```
mGrafici_Activity.Pressure_data_analizer(pressure, char_countBT_p);
```

the data are sent to the Grafici_Activitiy where the function "Pressure_data_analizer" will proceed the data. This is for the Pressure: exactly the same thing is doing for the flow.

In this function, the data are converted into float from the string and are saved in an arraylist as follow:

```
flow_sample = Float.valueOf(codeBT_flow);
flow_sample /= 1000 * 30;
buffer_f.add( flow_sample );
```

```
pressure_sample = Float.valueOf(codeBT_pressure);
pressure_sample /= 10;
buffer_p.add( pressure_sample );
```

As it can be seen from the code, a scaling factor is applied to both pressure and flow in order to maximise the information sent in the few bytes available. In the Flow_data_analizer, the integration and filtering of volume is done. Therefore, exactly as seen for the pressure and flow, the value is added to its arraylist. In those function, the graphs of pressure, flow and volume are upload, but those graph are under sampled in order to have four samples for the stimulus frequency. If no frequency are present, the app is set by default at 5 Hz.

When the acquisition start, the application will fill the arraylist up to two windows for the impedance evaluation. Pressure, flow and volume are copied in other three arraylists which are used to send the data to a background thread which evaluate the impedance and select the good value. Doing an example at 5 Hz 106 samples are sent. The first thing to do is aligned flow, pressure and volume considering a delay of 26 samples for the volume. Therefore, it is possible to evaluate 40 impedance and selecting any of them which are good. Here, the file with the data is written if the rec button was pressed. All the data are aligned with the time at half window.

The thread is managed with the class AsyncTask described in paragraph 0. In the method onPostexecute proved by the class, the graphs of 4, 5, 6 are uploaded.

Once the buffer for volume, pressure and flow are fill with all the data for the background thread, any new data added will cause the elimination of the oldest one.

When On is pressed, a new button appears: Start Analysis. This button permits to enable the evaluation of mean Resistance and Reactance for 30 seconds in the signals. Therefore, once the data are acquired and the mean values add, it will add the new data elaborated in graph 7 and 8.

In order to satisfy the need of a user friendly interface, it was chosen to develop a “simplified” version to do the study. This UI does not ask to the user how to generate the FOT, but only a button “Start FOT”. When it is pressed, the FOT are enable with a peak-to-peak of 5 mbar at 5 Hz. The button changes text and it becames the “Stop FOT”. This UI was putted as default and it is possible to switch between the simplified and the complete version on the Android menu. This way allow the general user to perform and measure and the expert user to use different setting of the FOT. Therefore, when the user trys to change sometimes in the Android menu, an alert dialog appears in order to tell the user that he is doing important changes on the UI or the algorithm. Following in Fig. 43 the simplified UI and the procedure to change it are rappresented. It can be seen that it is possible to change a filter: the reason for that choice is explained on paragraph 3.1.2.5.

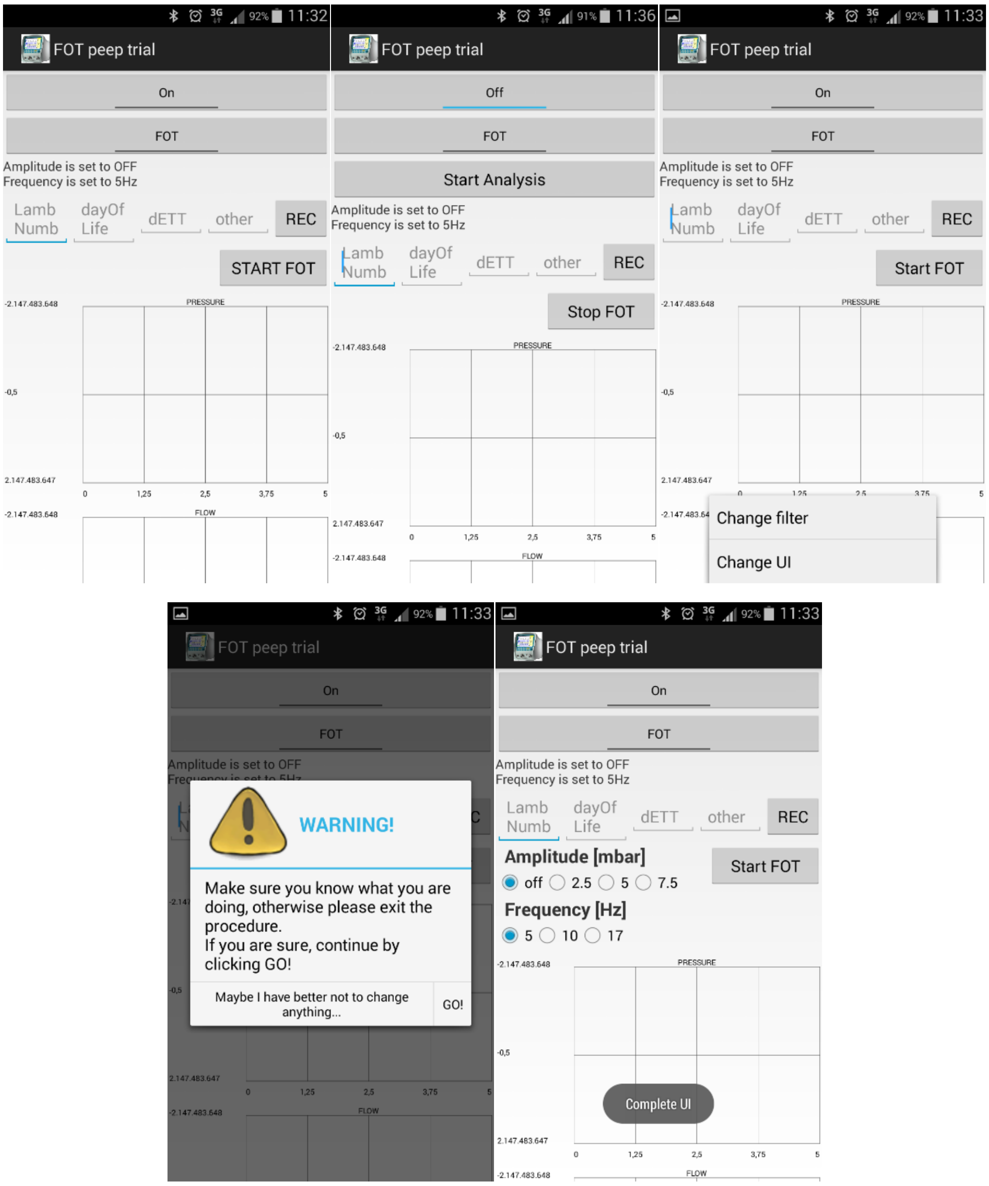


Fig. 43 Simplified UI and changing procedures

3 Data processing

The objective of the work is to develop a device which can be used to generate automatically the PEEP Reactance curve in order to see its effectiveness in asserting the optimal PEEP.
Therefore, this device has to perform an automatic selection of impedance data, evaluated with the FOT both during HFOV and conventional ventilation. While during HFOV is easier to find the mean value of impedance at end expiration, during conventional ventilation it become more difficult. Therefore, the aim of the work was to design and optimise an algorithm to select the end of expiration impedance automatically. The selection algorithm described is realised for conventional respiration modalities, while HFOV is quickly discussed in paragraph 3.1.2.6.

3.1 Algorithms

As mention above the algorithm has to evaluate the mean impedance for each step of a PEEP trial and provide an accurate PEEP-reactance curve in order to help the clinician in setting PEEP.

3.1.1 Impedance computation

The estimation of respiratory impedance can be done using both a Least Mean Square Method (LMSM) to estimate sinusoidal coefficients and the Fast Fourier Transform (FFT) method.
In this application only the LMSM is implemented. However, following both methods will be presented in order to justify this choice.

3.1.1.1 Least Mean Square Method (LMSM)

The algorithm uses a window containing a whole stimulus period and compares it with an ideal sine that is expressed as reported in the following equation:

$$S(t) = r(t) + a_0 + a_1 \cos(2\pi f t) + b_1 \sin(2\pi f t) \qquad \textbf{Equation 21}$$

$=rt+a0+a1\cos(2\pi ft)+b1\sin(2\pi ft)$ Equation 21 considers a sinusoidal function at a known frequency as the result of a weighted sum of the orthogonal bases that are sine and cosine at the same frequency. The weights are the coefficients a_1 and b_1 which represent how much the recorder stimulus is coherent with each of the two bases. The choice of this expression instead of a sinus characterized by its amplitude and phase leads to easier parameter estimation. r(t) is the superimposed noise while a_0 is the offset.
This equation can also be written for discrete signals, in this case the signal is evaluated for each sample that belongs to the selected window obtaining the following matrix form:

$$S = AX + R \qquad \textbf{Equation 22}$$

Where:

$$A = \begin{matrix} 1 & \cos(2\pi f t_1) & -\sin(2\pi f t_1) \\ \vdots & \vdots & \vdots \\ 1 & \cos(2\pi f t_n) & -\sin(2\pi f t_n) \end{matrix} \qquad X = \begin{matrix} a_0 \\ a_1 \\ b_1 \end{matrix} \qquad S = \begin{matrix} P(k) \\ \vdots \\ P(k + window - 1) \end{matrix} \qquad \textbf{Equation 23}$$

Where the X matrix contains the coefficients that have to be estimated for each sliding window. The solution of the fitting problem is given by the $\boldsymbol{X}$=$\boldsymbol{BS\ where\ B} = (\boldsymbol{A}^{\boldsymbol{T}}\boldsymbol{A})^{-\mathbf{1}}\boldsymbol{A}^{-\mathbf{1}}$

Equation 24.

$$\boldsymbol{X} = \boldsymbol{BS\ where\ B} = (\boldsymbol{A}^{\boldsymbol{T}}\boldsymbol{A})^{-\mathbf{1}}\boldsymbol{A}^{-\mathbf{1}}$$ **Equation 24**

B matrix is the pseudo-inverse of A and it is always the same for each window, thus there is no need to compute it at each iteration but it can be done just the first time. The evaluation of the pseudo-inverse is done in analytical form using the cofactor matrix as matrix AA^T is a 3x3 diagonal matrix when the FOT stimulus is enable. In HFOV modality, it will happen when the communication start. This is because the frequency is known by the ventilator. Moreover, as all the frequency between 5 and 20 Hz might be used, the device will evaluate the matrix whenever the ventilation frequency changes.

The computation of X vector is performed for the pressure (X_P) and flow (X_F) in each window. A window have a length of fc/fs, where fc is the sample frequency and fs is the stimulus frequency. Following, there is a table of the length of the window for 5, 10 and 17 Hz and for the frequency of 200 Hz and 600 Hz.

Table 4 Number of samples

	5 Hz	10 Hz	17 Hz
200 Hz	40	20	12
600 Hz	120	60	36

Known vectors XP and XF the impedance computation becomes:

$$\boldsymbol{Z_{Rs}} = \frac{\boldsymbol{P}}{\dot{\boldsymbol{V}}} = \frac{\boldsymbol{a_{p1}} + \boldsymbol{jb_{p1}}}{\boldsymbol{a_{\dot{V}1}} + \boldsymbol{jb_{\dot{V}1}}}$$ **Equation 25**

The window is shifted of one sample and the calculus is repeated. Therefore, for each time a sample of impedance is evaluated. However, the calculation is possible only when a window is acquired, therefore there is a delay of half window to have the data for the computation.

The advantage of computing the transfer function or impedance in this way is the high temporal resolution. However, the assumption that the system under analysis has to achieve a dynamic oscillatory steady state.

3.1.1.2 Fast Fourier Transform (FFT) method

For a simple system with one input x(t) and one output y(t), the transfer function (H) can be obtained as follows:

$$\boldsymbol{H} = \frac{\boldsymbol{S_Y}}{\boldsymbol{S_X}}$$ **Equation 26**

where SY is the FFT of the output while SX is the FFT of the input of the system.
If the input is a flow signal and the output a pressure one, the impedance (Z) of the system is simply the reciprocal of transfer function. Because of synchronization problems the computation of H and Z by this method is not practical. Therefore, the concept of power spectra is needed. SX and SY can be used for computing three power spectra: the input auto-spectrum, the output auto-spectrum and the cross-power spectrum respectively defined as

$$G_{XX} = \frac{S_X S_X^*}{N} \quad \text{Equation 27}$$

$$G_{YY} = \frac{S_Y S_Y^*}{N} \quad \text{Equation 28}$$

$$G_{XY} = \frac{S_Y S_X^*}{N} \quad \text{Equation 29}$$

Since the auto-spectra are obtained by squaring the magnitude of the Fourier transforms, they are always real and the phase information is lost. Contrarily, the cross-spectrum preserves the phase relationship between input and output signals. The impedance is computed as follow:

$$Z = \frac{G_{XX}}{G_{XY}} \quad \text{Equation 30}$$

The impedance is a complex term and can be expressed as magnitude and phase or as real and imaginary part. The advantage of computing the transfer function or impedance in this way is the rapidity with which both real and imaginary part can be obtained over a wide range of frequencies. Furthermore, the computation of Z does not depend on the character of x(t) since Z is obtained as a ratio of the input and cross-power spectra.
The estimators of a parameter has to satisfy two properties:

- Correctness: the mean of the estimator converges to the real parameter by increasing the number of samples (N);
- Consistency: the variance of the error of the estimator converges to zero by increasing the number of samples.

The estimation of the auto-spectra is done though the periodogram. The periodogram satisfies the first condition but not the second one. In order to respect also the second condition the Bartlett method should be used. This method consists in windowing the signal, calculating the periodogram for each window and computing the mean of all the periodograms. Bartlett method allows to reduce the variance and decreases bias error. The same approach is used for the estimation of the cross-spectrum when none of the previous properties is completely satisfies.
Even though in this way is possible to do the estimation of the spectrum, it causes a reduction of resolution from 1/N to 1/M, where M is the number of windows. The windows can be overlapped in

order to avoid that the samples at the borders of the single window are attenuated; in this case the Bartlett's method is called Welch's method.

When a random pressure wave is imposed on the respiratory system, it can be resolved into a series of terms which can be correlated with the resulting flow to obtain the impedance of the respiratory system at each frequency present in the input waveform. Thus, the impedance of respiratory system is defined as the complex ratio between pressure and flow signals and can be expressed as magnitude and phase or real and imaginary part:

$$\boldsymbol{Z} = \frac{\boldsymbol{G_{FF}}}{\boldsymbol{G_{PF}}} \qquad \textbf{Equation 31}$$

This method has the advantages to find the value of Z for all the frequency, and therefore it is very useful when a multiple frequencies are applied to the system. Moreover, it possible to analyse even periodic signals which are not completely sinusoidal.

However, in the current application only one stimulus is applied at a specific frequency. Therefore, it is convenient to use the LMSM as the time resolution is higher and gives the possibilities to have a higher number of data for the following algorithm.

3.1.2 Impedance selection : quality control and end expiration determination

After impedance computation with LMS method, a selection of the impedance is need. Therefore, an algorithm to select reactance at end expiration is required. This is because there is the need to evaluate the amount of alveoli that remains open through all the respiratory cycle and the end of expiration is the worst case. Therefore, in order to include only the worst case, some qualities controls are considered. This is done by using several parameters that will be discuss below which allows to avoid the inclusion of impedance values which may lead to errors, such as breathes with artefacts.

3.1.2.1 End of expiration

In order to recognise when the infant finishes a breath, three signals are taken into account: mean flow, mean pressure and volume.

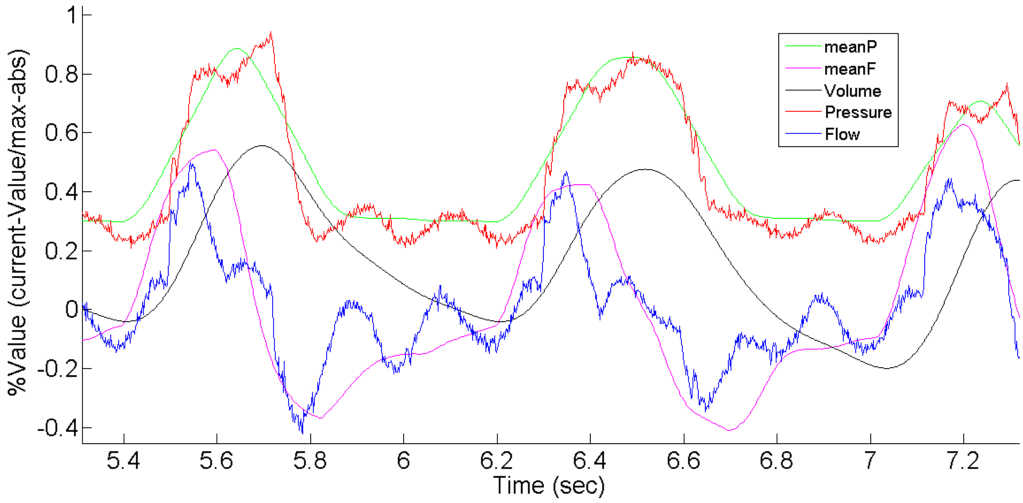


Fig. 44 Normalised Flow, Pressure, Volume and mean value of Flow and Pressure: the evaluation on the mean value of P and F was done with a mobile average that remove completely the stimulus frequency

In Fig. 44 mean flow and mean pressure are showed. The end of expiration part will take place when mean flow is 0 and mean pressure is at PEEP level. It is convenient to compute mean P and mean F before the impedance evaluation in order to solve the phase delay issue. In the paragraph 3.1.2.5 several different strategies in order to compute those signals are presented and discussed.

As the mean flow and pressure are evaluated before, for each window a number of samples equals to the number of data needed for the impedance evaluation are available. Indeed, for each window of mean pressure and mean flow, it is possible to take only the maximum values as they represents the worst case. This is checking that all the value used to compute the impedance are actually part of the end of expiration part of the breathing cycle. Those maximum values are used to create the signal of maximum mean Flow and Pressure which are showed in Fig. 45.

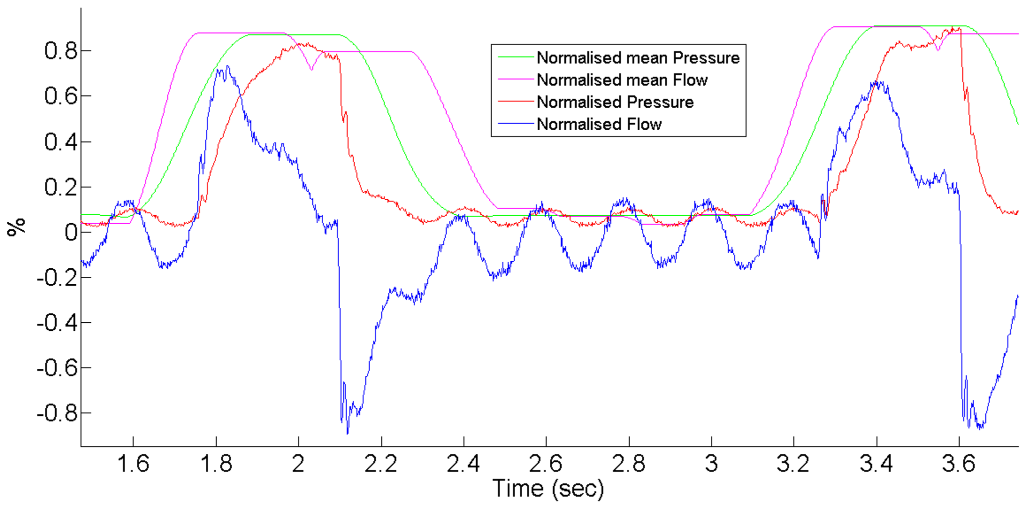


Fig. 45 Max mean Value in a window

Form those latter signals two more parameter might be obtained which are the derivative of the maximum value of mean pressure and flow (Fig. 46). Those signals have to be close to 0 or peep value for flow and pressure respectively.

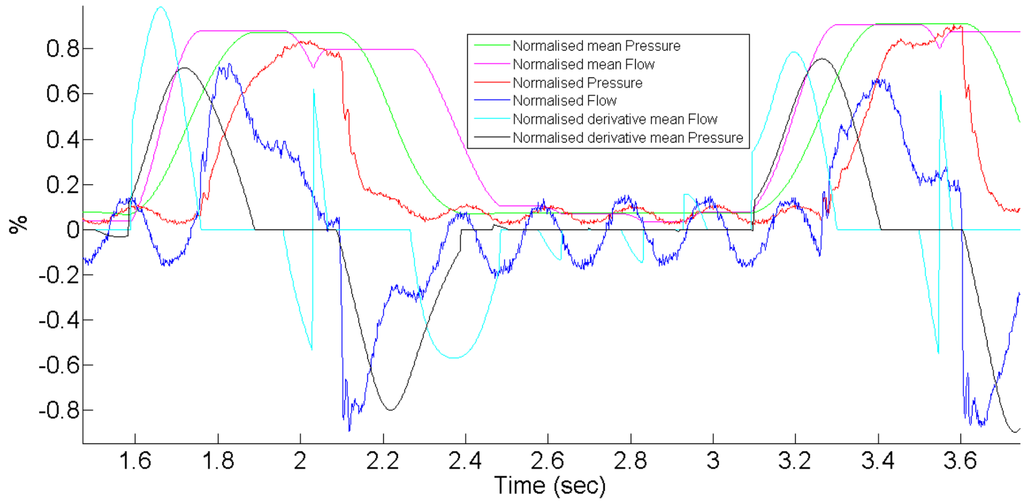


Fig. 46 Derivative of mean Flow and Pressure

As the PEEP may change, instead of mean pressure, the derivative of the mean pressure was considered. For this signal, the end expiratory value is when the signal is close to 0.

The derivative mean flow is used aswell in order to see how the maximum mean value of flow change and, in other word, to predict if the flow is going to stay still or it is starting to change.

NB Mean values and their derivative are aligned with flow and pressure.

The volume showed in Fig. 44 is evaluated through the integration of the mean flow and, afterward, it passes a high band filter with cut frequency at 0.01 Hz. This is because it is possible to remove the typical drift caused by integration. Therefore, a 2° order high pass Butterworth filter was used. Below the Bode diagrams are represented (Fig. 47).

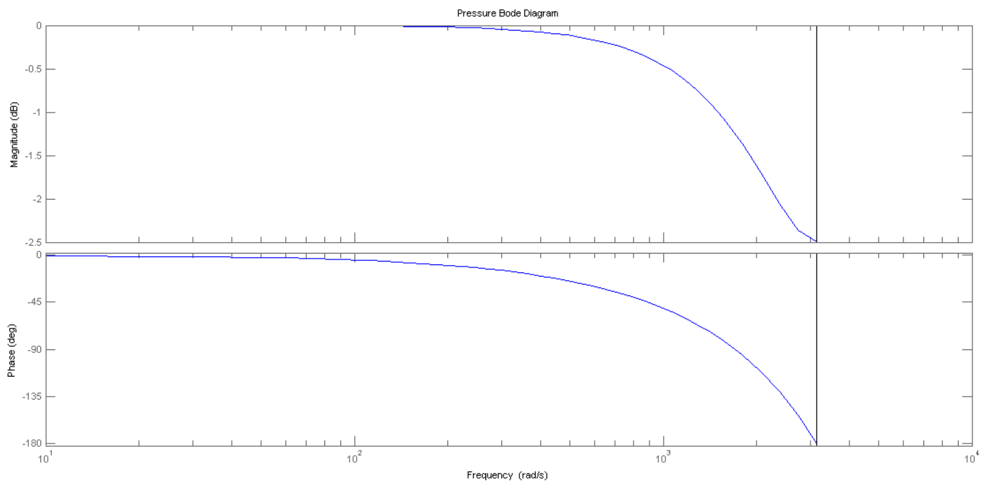


Fig. 47 Frequency response

As the filter used is one with infinite impulse response, distortion may arise.

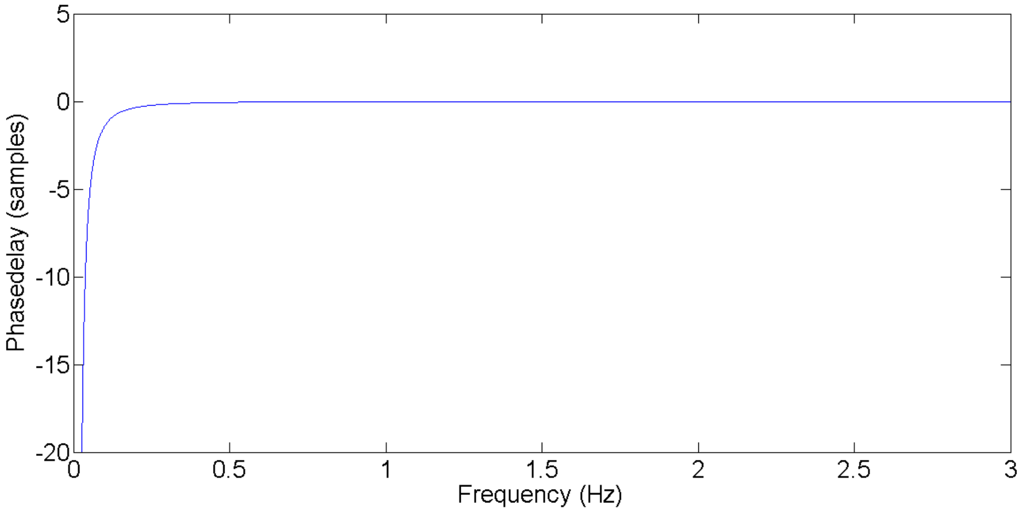


Fig. 48 Phase delay low pass filter

In Fig. 48 the phasedelay is represented. The median of samples delay is -0.0062. Therefore, its contribution to the phasedelay might be considered negligible in pass band.

However, the standard deviation is about 5.2349 samples. Therefore the error in the evaluation of the minimum value of volume might be high if frequencies below 0.1 Hz are present. Indeed, at that frequency the phasedelay is of 1 sample. Despite that, it has to be considered that the breathing pattern of infants is usually around 1 Hz and, thus, it is not affected by this filter.

In order to find the end of expiration, the minimum of data is taken into account. Indeed, with the data of Fig. 44, the position of the minimum value of volume was evaluated and kept in a vector (blue signal in Fig. 49). From that vector a binary signal was computed (red signal in Fig. 49).

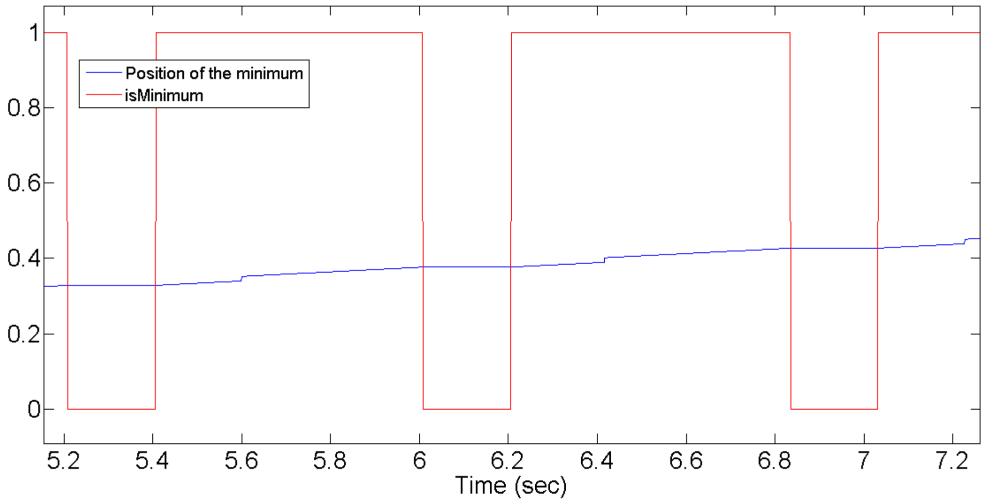


Fig. 49 Position of minimum

From that Fig. 49 appear clearly that the position of the minimum increase and stay still for a while. Indeed, taken a periodic signal the position of the local minimum stay still when the window contain the minimum. On the contrary, it keeps moving if the window does not contain it.

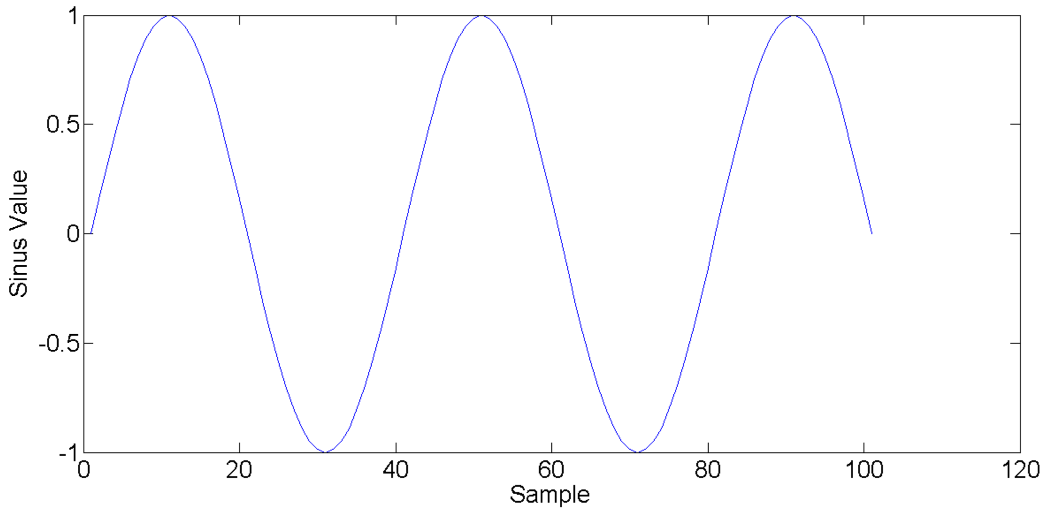


Fig. 50 Minimum explanation

Looking on Fig. 50, if a window goes from sample 20 to 40, the position of the minimum is 30. If I took a new window that goes from 25 to 45, the position of the minimum is still 30. I can argue the same thing until I get to the window that goes from 31 to 51. This time the position in starting to change and it became 31, then 32, then 33 and so on until I get to the window that goes from 41 to 61. From this window on, the position of the minimum is in 61. After that it will keep start to increase of one value again until I don't get to the window that goes from 50 to 70, where the minimum is going to be in 70 and it will stay still for a while as seen before. Finally, it is possible to argue that a window contain the minimum of volume if its position in the window is not the first or the last element of the window.

For what concern the convention FOT, however, it may happen that the minimum value of volume stay at the beginning of inspiration and it will bring error to the measurement. In order to avoid that, instead of any window that contain the minimum of volume, all the windows that don't have the minimum in the first position are taken into account. Those windows are located after the maximum of volume, therefore all the window that stay after a maximum of volume are considered.

Finally, the impedance at end of expiration may be selected by taking into consideration only the window that lay after the maximum of volume that has a mean flow, derivative of mean flow and derivative of pressure close to 0.

3.1.2.2 *Quality selection*

The LSLM method is valid if the stimulus and the output are mainly sinusoidal signal at the stimulus frequency. A way to check the quality of the selection is by checking the Flow Shape Index (FSI) and the Pressure Shape Index (PSI).

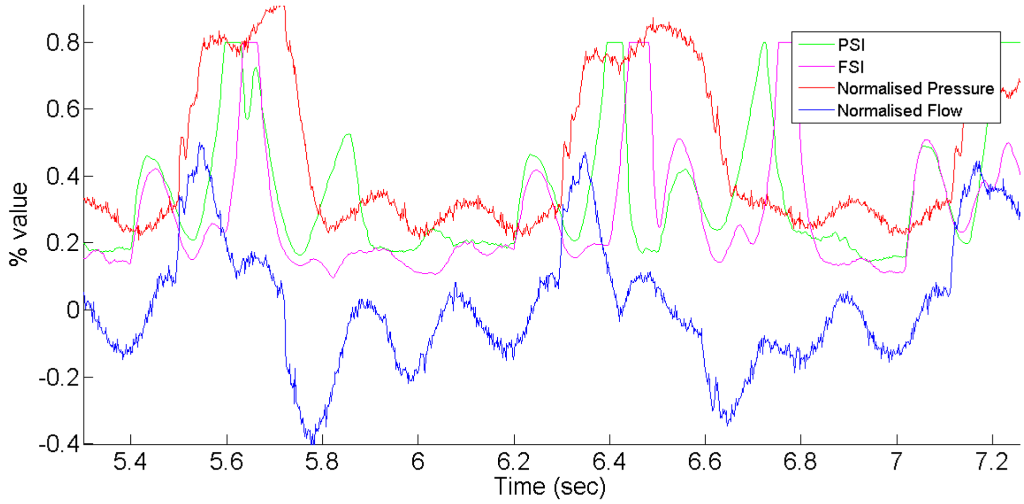


Fig. 51 Shape Indexes

Those Shape Index (SI) are computed for each window and they are defined as the mean sign-less difference between the observed oscillation and the ideal sine wave having the same Fourier coefficients. For normalization the difference is expressed as a percentage of the amplitude of the oscillation.

$$\boldsymbol{SI = \frac{mean(AX_S - S)}{\sqrt[2]{X_{S_1}^2 + X_{S_2}^2}}} \qquad \textbf{Equation 32}$$

Therefore, the algorithm returns a value that expresses how much the real signal is similar to a sinus: a SI of 0% means that the signal is a perfect sinus. Sinusoidal fitting can be consider accurate only if the SI is below the threshold of 20%. As it can be seen in Fig. 51 those signals show a good fitting when only the oscillation is present. [59]

If there are not disturbance, the PSI and FSI should be similar. Therefore, we implement a new parameter to check if the two fitting are close. This parameter is the Difference Shape Index (DSI) and it represents what is the difference in the fitting of sinus between flow and pressure.

$$\boldsymbol{DSI = \frac{FSI}{PSI} - 1} \qquad \textbf{Equation 33}$$

The DSI is equals to zero if the pressure and the flow signals are similar to a sinus in the same way. It is useful when there are, for example, leaks in the hydraulic circuit.

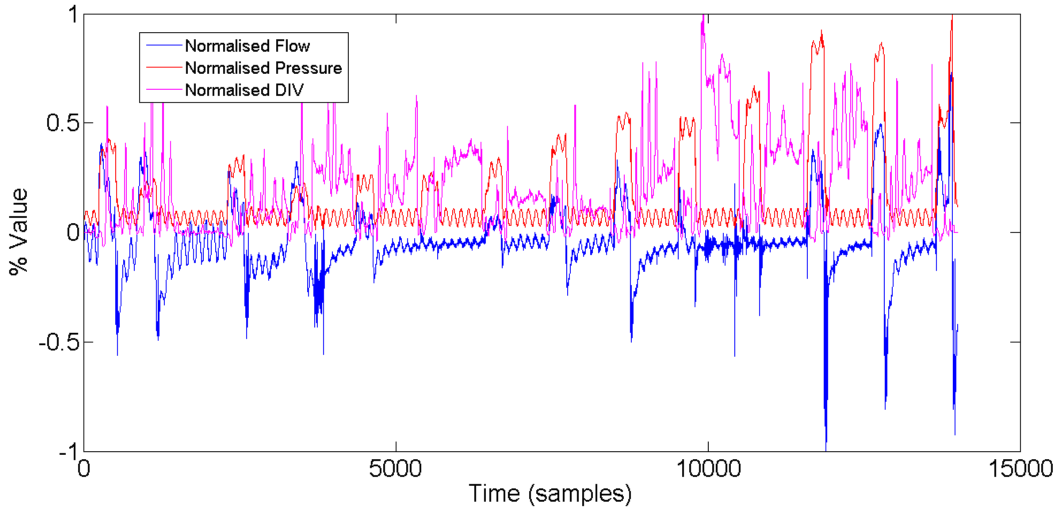


Fig. 52 DSI in presence of leaks

Up to now, there are two qualities indexes (PSI and FSI) useful to get the impedance data that satisfy the hypothesis of sinusoidal signals and there is one (DSI) that is useful to get the data where flow and pressure are similar in the way to a sinus.

However, an index that says something on the linear relationship between the two signals is still to be find.

Under the hypothesis of linear time invariant system it is true that:

$$f(t) = m_f + F\cos(2\pi f t + \alpha_{Flow} + \alpha_{Pressure})$$

and **Equation 34**

$$p(t) = m_p + P\cos(2\pi f t + \alpha_{Pressure})$$

Where f(t) and p(t) are respectfully the flow and the pressure. A possible solution might be the evaluation of the following signals:

$$s(t) = \frac{f(t)-m_f}{p(t)-m_p}\cos(2\pi f t + \alpha_{Pressure}) \qquad \textbf{Equation 35}$$

Therefore, by putting $\alpha_{pressure} = 0$ in order to simply the notation, and considering the signals with null mean, we come up with the following expression:

$$s(t) = \frac{F\cos(2\pi f t+\alpha_{Flow})}{P\cos(2\pi f t)}\cos(2\pi f t) = \frac{F}{P}\cos(2\pi f t + \alpha_{Flow}) \qquad \textbf{Equation 36}$$

Therefore, by proceeding to the estimation of the Fourier coefficient, as seen in paragraph 3.1.1.1, from the signal s(t) the gain and the phase displacement can be found. The parameter, which says how linear the relationship is, will be the mean squared error given by the following equation:

$$E = \sqrt[2]{\sum(f(t)\cos(2\pi f t + \alpha_{Pressure}) - p(t)s(t))^2} \qquad \textbf{Equation 37}$$

Although interesting, even to evaluate the impedance, this approach suffer of numerical instability. But, the hypothesis said above are still valid and the signal s(t) can be estimate as follow:

$$s(t) = |Z\_calc(j2\pi f)| \cos(2\pi ft + phase(Z\_calc(j2\pi f)))$$ **Equation 38**

Where Z_calc = Z_{rs}^(-1).

Finally, once estimated the impedance, E can be compute and used for a quality control.

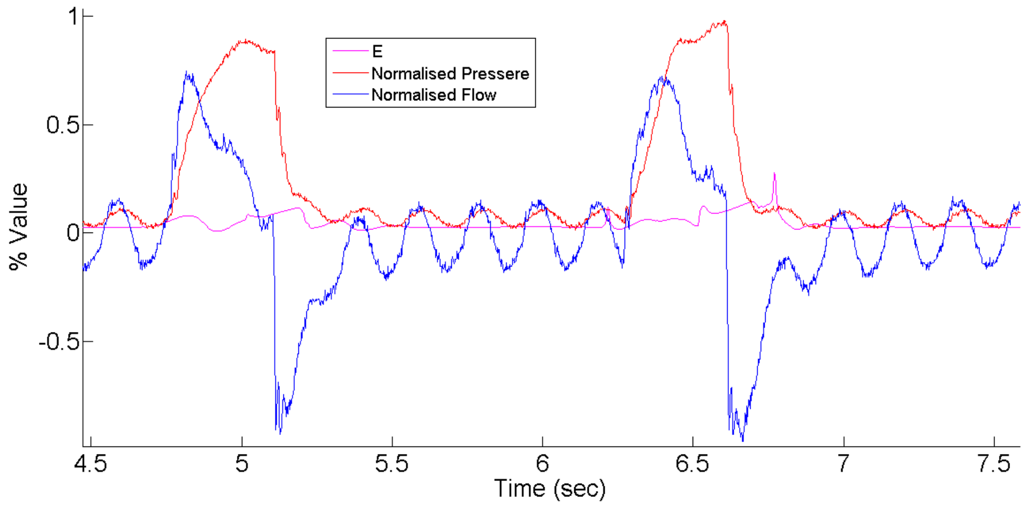


Fig. 53 Linearity

In the Fig. 53 the amplitude of E are quite low. However, it may be increased by multiplying s(t) and $\cos(2\pi ft + \alpha_{Pressure})$ by a number G (Fig. 54).

Indeed, the error becomes:

$$E_{amplified} = \sqrt[2]{\sum(Gf(t)\cos(2\pi ft + \alpha_{Pressure}) - Gp(t)s(t))^2} = GE$$ **Equation 39**

The amplification parameter chosen was 50 in Fig. 54.

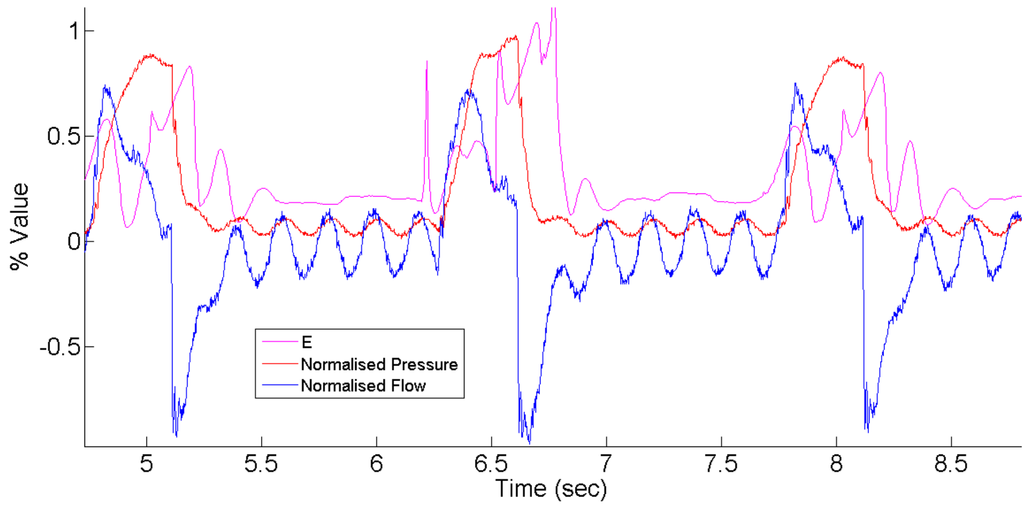


Fig. 54 Linearity amplified

$\alpha_{Pressure}$ is estimated from the Fourier coefficient calculated in the impedance calculation (paragraph 3.1.1.1) as follow:

$$p(t) = m_p + P\cos(2\pi ft + \alpha_{Pressure})$$

$$= m_p + P[\sin(\alpha_{Pressure})\cos(2\pi ft) + \cos(\alpha_{Pressure})\sin(2\pi ft)]$$

$$= \boldsymbol{m_p} + \left[\boldsymbol{a_p}\cos(2\boldsymbol{\pi f t}) + \boldsymbol{b_p}\sin(2\boldsymbol{\pi f t})\right]$$ **Equation 40**

$$\alpha_{\boldsymbol{Pressure}} = \tan^{-1}\left(\frac{\boldsymbol{a_P}}{\boldsymbol{b_p}}\right)$$

Finally, there are four parameters for the qualities control: FSI and PSI that check if the signals respect the hypothesis of sinus; DSI that check how close those signals are and E that check if the linearity hypothesis are respected.

3.1.2.3 Parameters usage

The algorithm will proceed as showed with a flow chart in Fig. 55 Algorithm flowchartFig. 55. Basically, when new data arrive, the impedance with FSI, PSI, DSI, meanF and meanP are estimated. Then dmeanP and dmeanF are estimated through numerical differentiation. MeanF, dmeanF and dmeanP are normalized with its maximum value in the step. For more accuracy of the normalisation, their maximum are evaluated at the beginning of each step of PEEP. The position of the minimum value of volume is searched. If the minimum is not in the first position, the first step of the algorithm is passed. Therefore, it is checked if FSI, PSI, DSI, meanF_normalised, dmeanF_normalised and dmeanP_normalised are below a threshold. Once this control have been passed, the control of linearity relationship between F and P is done by taking all the data in which E_normalised is below a threshold. E_normalised is evaluated through normalisation of E with the highest value of E of the data selected up to now. This means that all the data where the minimum of volume does not stay in the first position and with FSI, PSI, DSI, meanF_normalised, dmeanF_normalised and dmeanP_normalised below their threshold, E is computed and the maximum is searched between them. This will help to reduce the computation effort and will let pass only the data where the linear relation is strong.

Finally, the section algorithm is done and an outliers identification and elimination is to be done as describe in paragraph 3.1.2.4. While the selection part of the selection algorithm is run breath by breath, the outliers elimination is execute only at the end of a step of the PEEP trial.

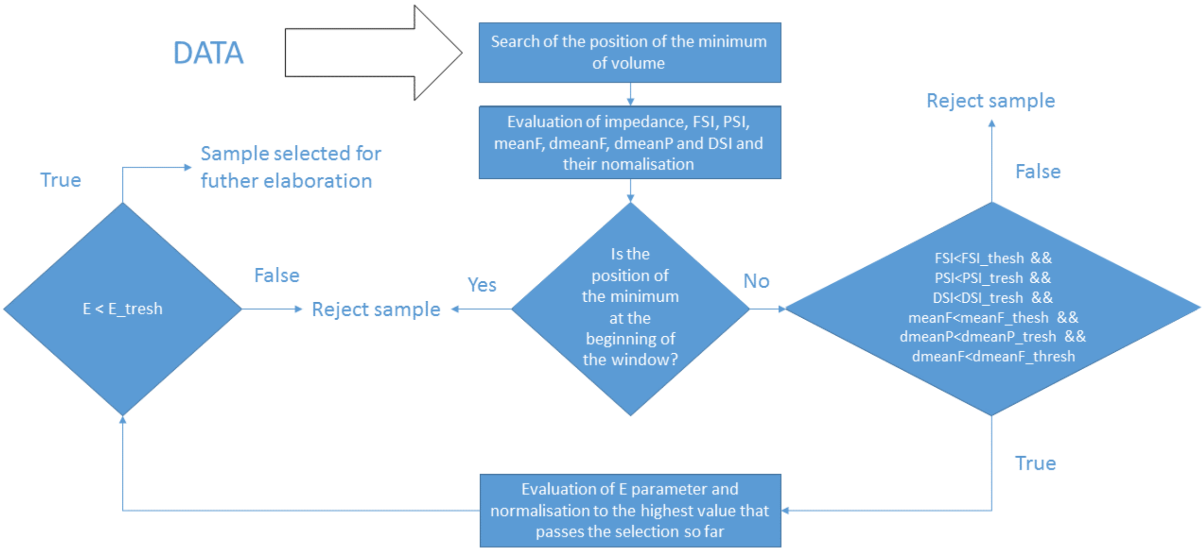


Fig. 55 Algorithm flowchart

Once the algorithm is written, the thresholds are to be determined as described in paragraph 3.2.2.

3.1.2.4 Outliers Identification

This part of the selection can be run only once the selection on one step of the PEEP trial is done. Firstly, in the unlucky condition that there are impedance where the resistance value is negative even after the selection, something as to be done. Indeed, this is physically speaking impossible as it would mean that air passing through a pipe can create energy. Therefore, all the impedance with negative resistance are rejected.

Secondly, as the number of data selected is usually high, an outlier's selection is done by using the z-index:

$$z_{index} = \frac{|MEAN - x|}{STANDARD\ DEVIATION} \qquad \textbf{Equation 41}$$

This parameter represent the number of standard deviation the data x is far from the mean value. Usually, under the hypothesis of not known distribution of data, if $z_{index} > 3$, the sample x is usually considered as an outliers. However, as the number of data is high, a normal distribution of the data can be assumed and, therefore, a threshold of two standard deviation can be taken into account (which means 95% of the data). Moreover, to improve the elimination of the outliers, it was taken the decision to doing the control until there are no more data eliminated (Fig. 56).

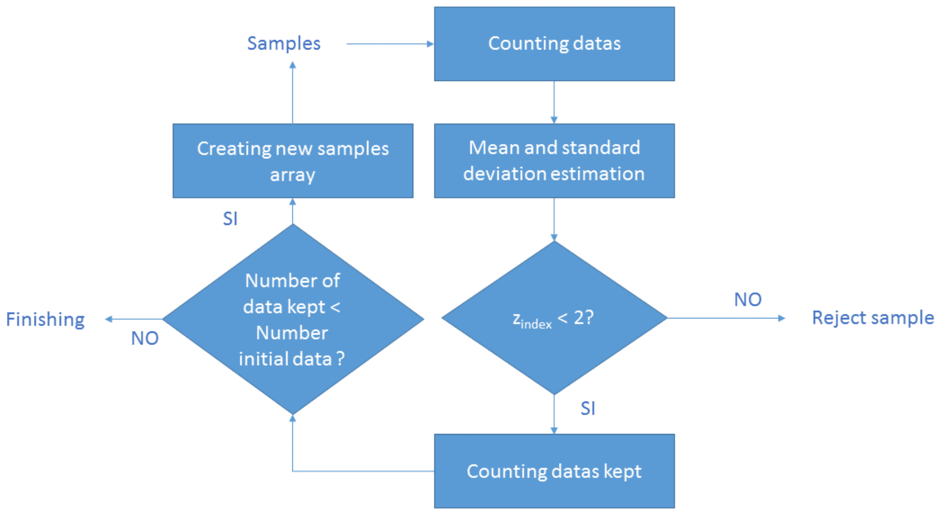


Fig. 56 Outliers removal

In the outliers elimination algorithm described above, resistance and reactance are processed as they are independent, but this is not true. Therefore, all the data were reactance or resistance are outliers in their distribution are eliminated.

The output of the section process should be something like in Fig. 57 Output SelectionFig. 57.

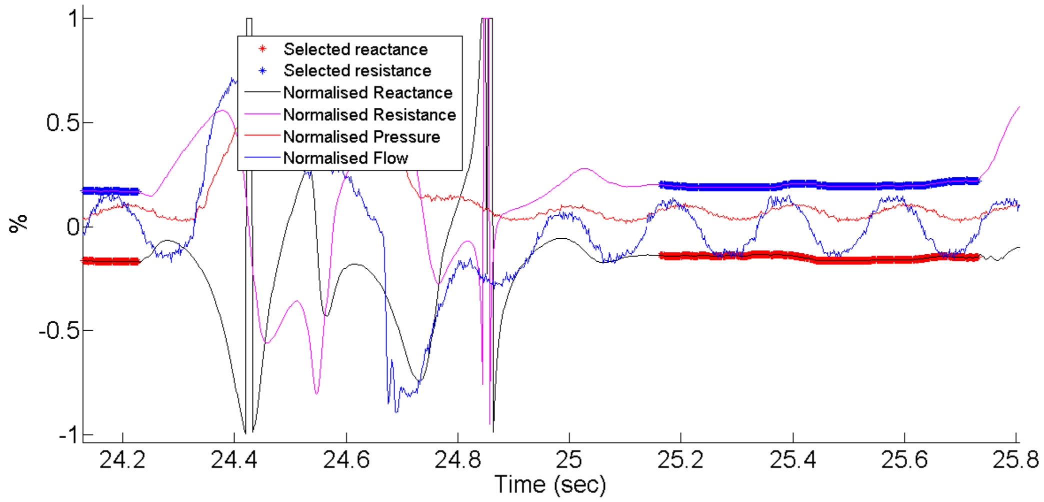


Fig. 57 Output Selection

However, this is a lucky situation where there are some sinusoidal periods of pressure and flow at end expiration. Often, it may happen that there are only one or two sinusoidal periods as the infant breath fast. In this situation is convenient to analyse reactance and resistance together as explained below.

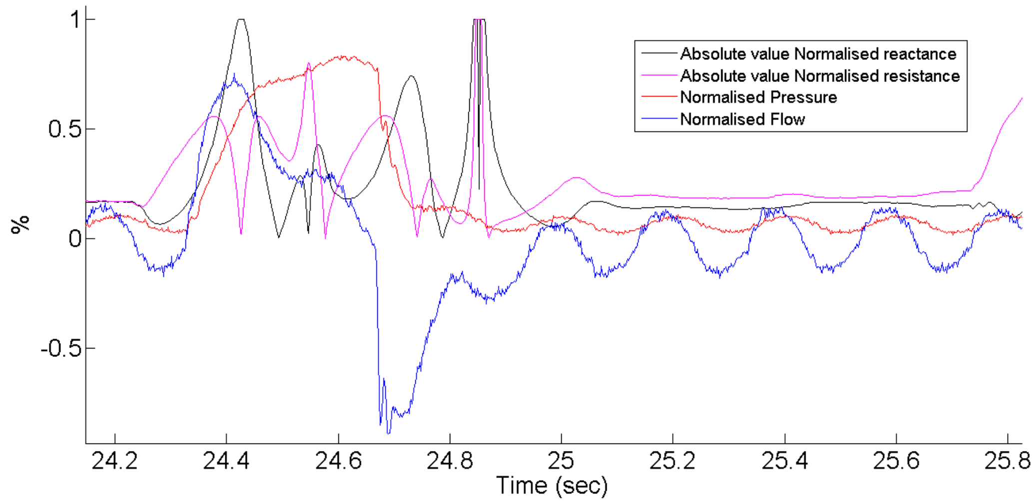


Fig. 58 Pressure, Flow, Reactance and Resistance

As it is shown in Fig. 58, resistance and reactance tend to a constant value when the end expiration start. Therefore, the output of the algorithms should create a dense cluster around the mean value of resistance and reactance in the complex plane (Fig. 61). Therefore, it might be interesting to perform the outliers elimination described in Fig. 56 using as input:

$$\boldsymbol{Sample} = \sqrt[2]{(\boldsymbol{Resistance} - \boldsymbol{mean\ Resistance})^2 + (\boldsymbol{Reactance} - \boldsymbol{mean\ Reactance})^2} \quad \textbf{Equation 42}$$

As standard deviation

$$\boldsymbol{SDT} = \sqrt[2]{\boldsymbol{SDT\ Resistance}^2 + \boldsymbol{SDT\ Reactance})^2} \quad \textbf{Equation 43}$$

and considering null mean. In this way, only the value closer that two standard deviation from the point (mean Resistance; mean Reactance) will passed the elimination process and will be used to estimate the mechanical property of the infant at the selected PEEP value.

Following, it is showed the effect of this second step of outlier's elimination and as some time the first step is simply not enough.

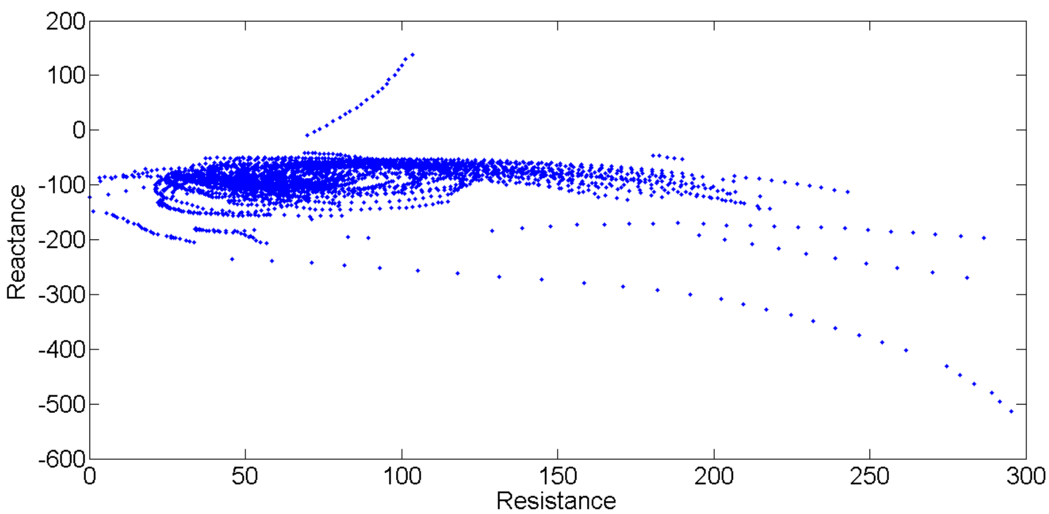


Fig. 59 With no outlier's elimination

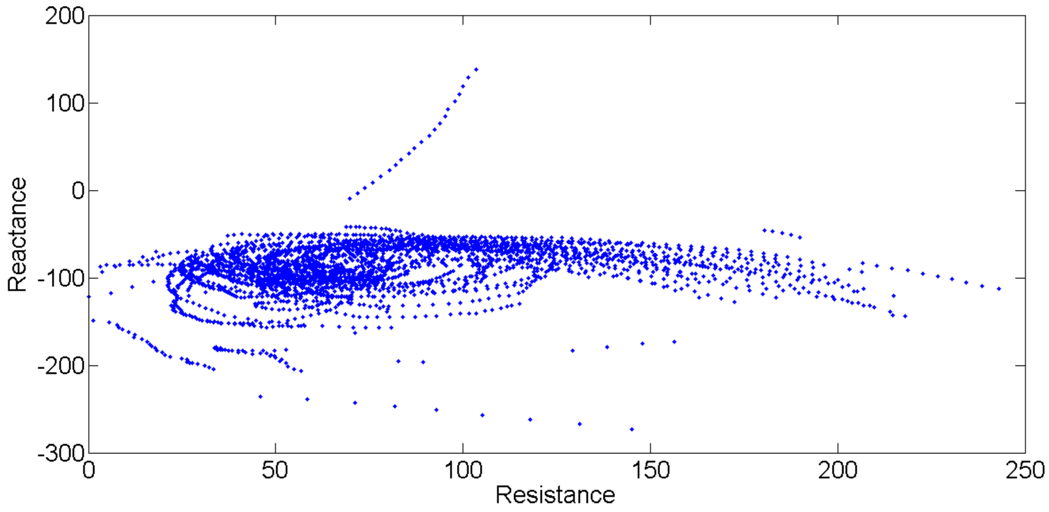


Fig. 60 First step elimination

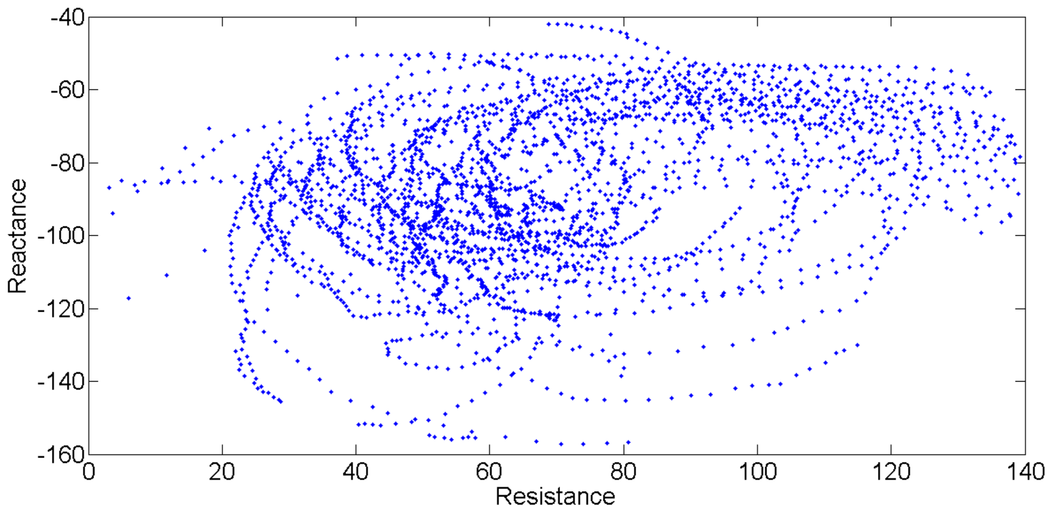
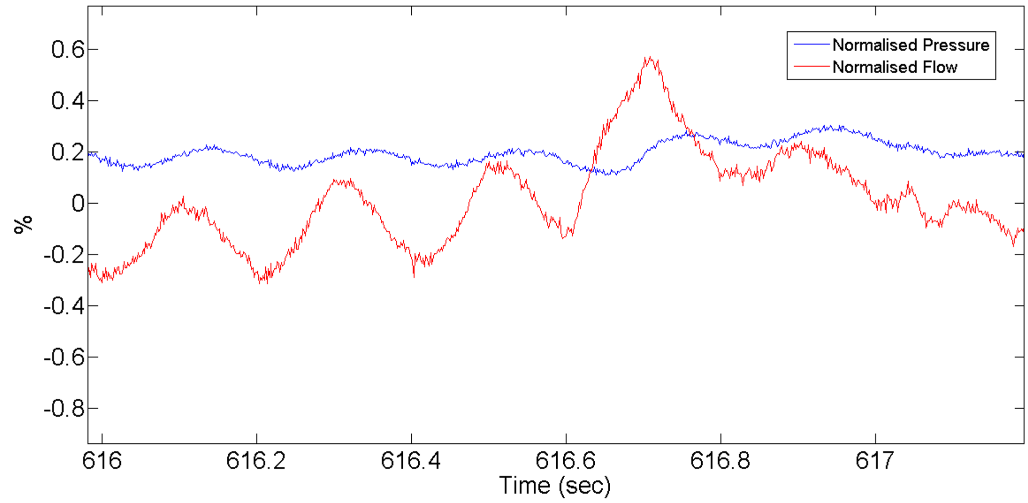


Fig. 61 Second step elimination

Following, an example of corrected selection.



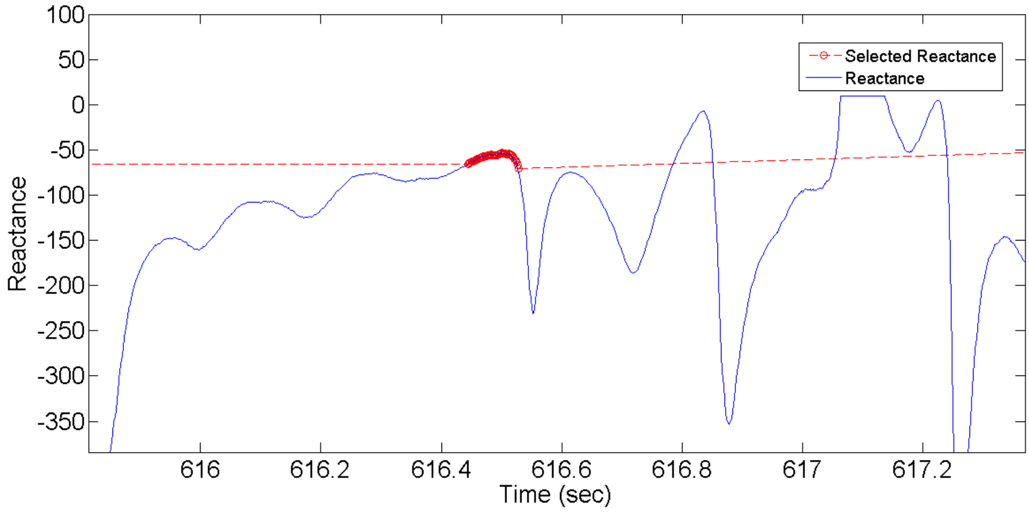


Fig. 62 Above: Pressure and Flow; Below: Reactance with its selection. It might be seen that the value taken are only those where the sinus are clear

Even though situation as in Fig. 62 are common, it is necessary to find an optimal value (paragraph 3.2.2) of the parameters in order to have better performances. Indeed, the outliers elimination works well only if the selection algorithm was accurate.

Once this elimination of outliers is done, those data are used to compute the mean resistance and mean reactance in the step.

The last step was to find the optimal values for the parameters as described in the paragraph 3.2.2.

3.1.2.5 Filtering strategies

In order to compute the mean value of pressure or flow some kind of filtering technique was considered: a low pass filter was considered with cut frequency at 3 Hz and with the need to have a modulus of -40dB at 5 Hz in order to completely remove the FOT stimulus.

The only way to achieve such specification a low order is by using an IIR filter.

On the contrary, as the only frequency out of the band of the breath is the stimulation signal, a filter which eliminate only the stimulus frequency might be another solution.

Butterworth Filter

The first filter to be analysed was a Butterworth filter of the second order (Fig. 63 Second order Butterworth filterFig. 63). This choice because if a higher order filter is need, it would be enough to use the same filter several times.

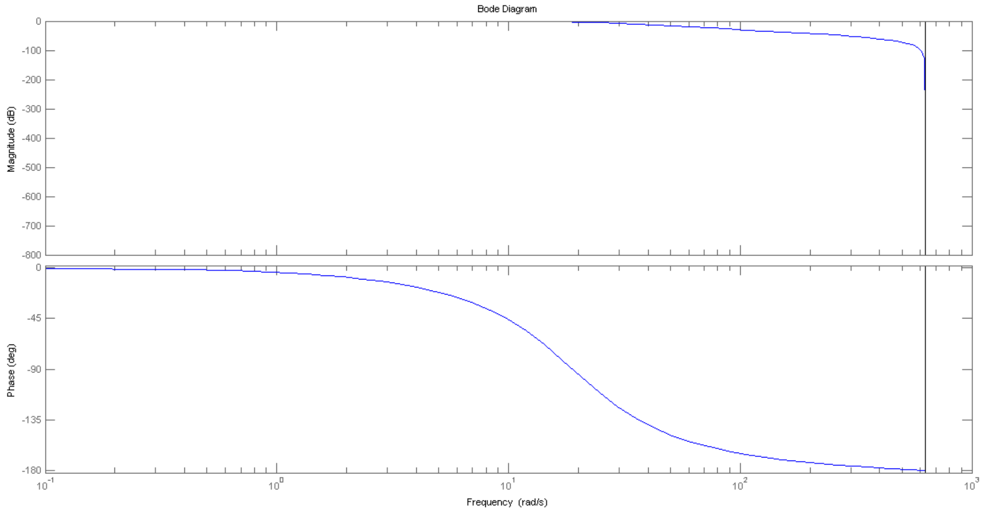


Fig. 63 Second order Butterworth filter

In order to achieve the requirement of -40dB at 5 Hz, a 12th order Butterworth filter was need, which means to use 6 times the filter shown above.

A second order Butterworth filter with cut-frequency at 3 Hz would have the phasedelay in Fig. 64.

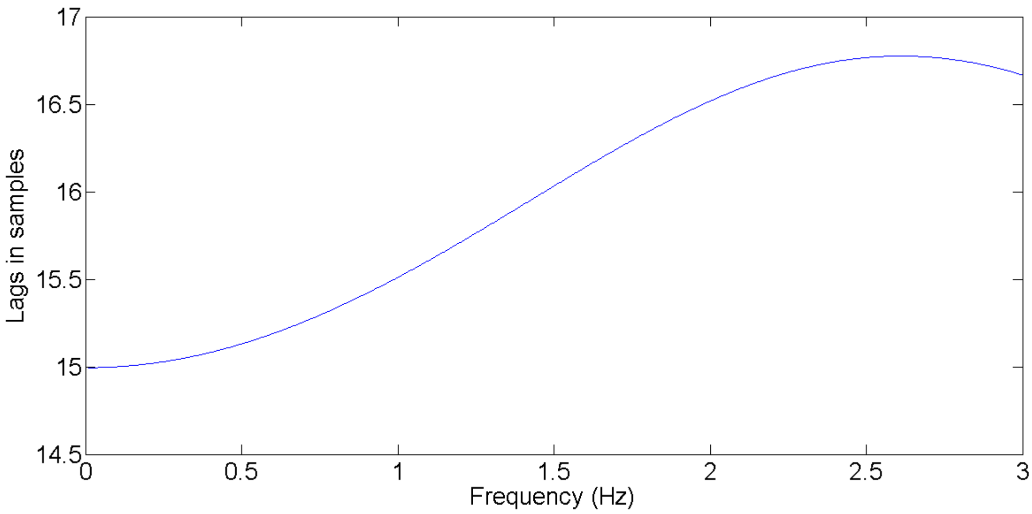


Fig. 64 Phasedelay Butterworth filter

The median value is 16 samples and, by correcting of this amount, an error of 1 sample is the worst case. However, if a 12 order has to be implemented, the filtering though this filter has to be done 6 time bringing the error up to 6 samples and a median shift of 96 samples. Therefore, the phase delay and the distortion is not suitable for the application, therefore it was discarded. [60]

Elliptic Filter

As a very selective filter is need, a possibility is to use an elliptic filter, which are the most selective digital filter. In order to satisfy the requirements, a 4th order filter is need (Fig. 65).

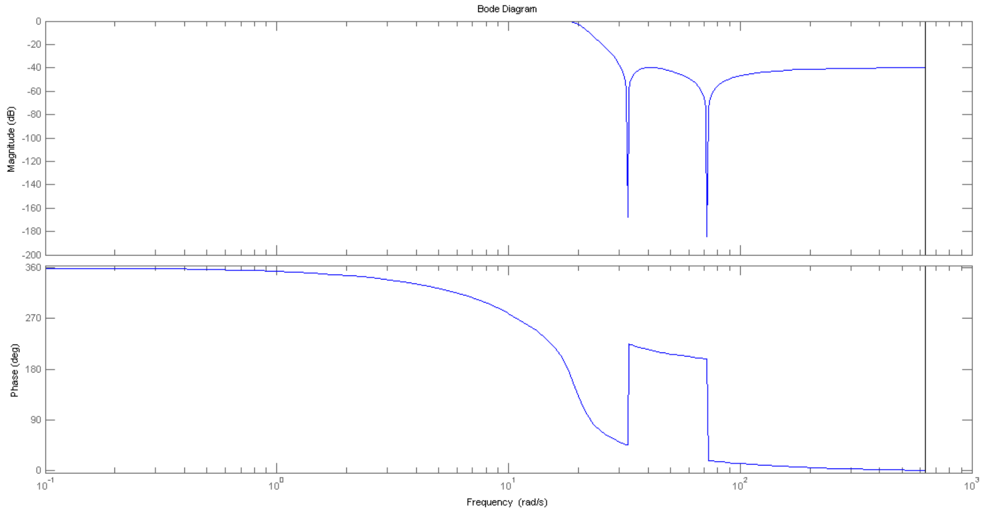


Fig. 65 Fourth order Elliptic filter

As the application has to run in real time, an IRR filter may lead to a distortion of the signal as the phase delay is not constant (Fig. 66).

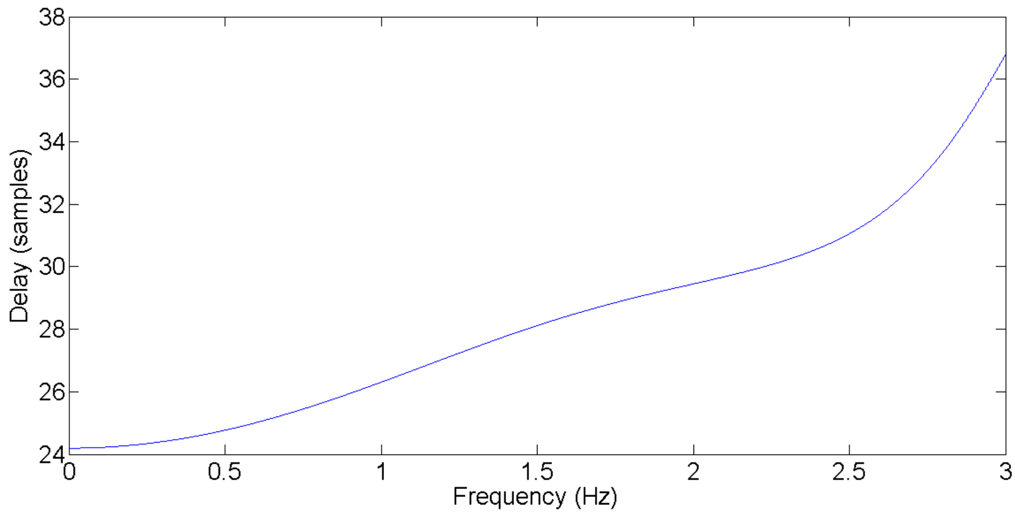


Fig. 66 Phase-delay high pass

As showed in the picture above, the delay for the high pass was evaluated in the passband and the median value was 26 samples. Therefore, there will be a lag of 26 samples in the evaluation of the impedance which correspond to 0.08 sec when the sample frequency is 200 Hz as the volume signal will be shifted by 26 samples. This delay is not constant for all the frequencies, and may lead to a realignment error of 10 samples. However, because the breath signal has a spectrum up to 1-1.5 Hz, correcting of 26 samples will lead to a realignment error of 2 samples, which is negligible for the current application. [60]

Mobile Average Filter

If this filter is used, for each frequency a different filter is used. Indeed, a mobile average on 40, 20, 12 samples will be required for respectively 5, 10, 17 Hz. The real advantage of this filter is its linearity in phase, bringing to a content phasedaley which is equals to half of the samples used to compute the output. Indeed, using a mobile average permits to completely eliminate only the stimulus frequency and leaving all the others, but employing a very high order. See table for the orders.

Table 5 Mobile Average order

Frequency	Filter order
5 Hz	40
10 Hz	20
17 Hz	12

In Fig. 67 the Bode diagrams for the mobile average at 5 Hz (therefore, on 40 samples) it is shown. However good it is, it is a very high order filter, not easy to implements real time, but with a constant phase delay of 20 samples (this is because it is a FIR filter with symmetric impulse response).

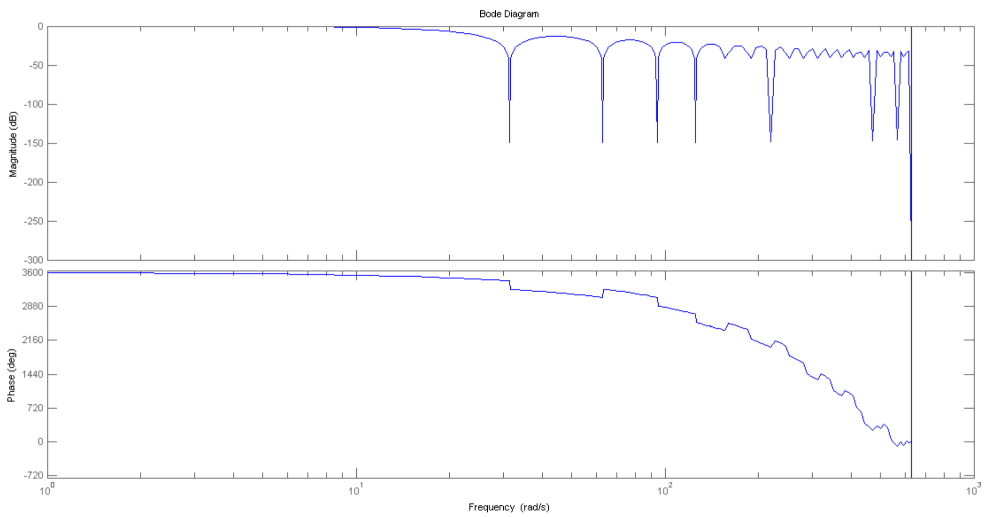


Fig. 67 Mobile Average for 5 Hz

The output of the mobile average filter is given by the $y(t) = \sum_{i=0}^{n-1} \frac{x(t-i)}{n}$

Equation 44.

$$y(t) = \sum_{i=0}^{n-1} \frac{x(t-i)}{n}$$ **Equation 44**

However this formulation is not computational efficient. Another solution is to uses the recursive

$= yt-1+x(t)n-x(t-n-1)n$ Equation 45.

$$\boldsymbol{y(t) = y(t-1) + \frac{x(t)}{n} - \frac{x(t-n-1)}{n}}$$ **Equation 45**

Following, the recursive formulation will be justified.

$$y(t) = \sum_{i=0}^{n-1} \frac{x(t-i)}{n} = \sum_{i=0}^{n-2} \frac{x(t-i)}{n} + \frac{x(t)}{n} =$$

Equation 46

$$= \sum_{i=0}^{n-1} \frac{x(t-i-1)}{n} + \frac{x(t)}{n} - \frac{x(t-n-1)}{n} = y(t-1) + \frac{x(t)}{n} - \frac{x(t-n-1)}{n}$$

[60]

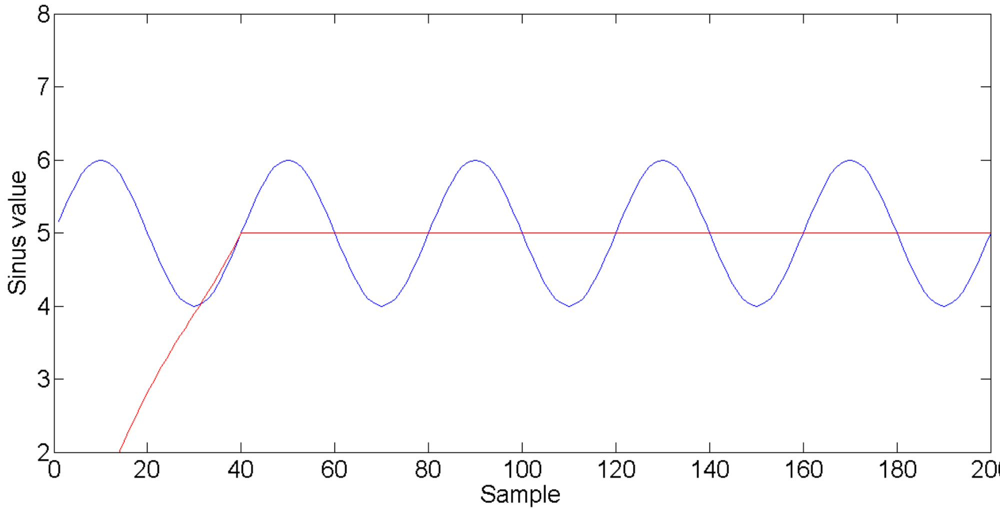


Fig. 68 Blue: sinus at 5 Hz with mean value equals 5; Red: blue signals passed through the recursive mobile average to remove 5 Hz

Filter Chosen

The two filters which guarantee the best behaviour are the mobile average filter and the elliptic filter. However, there is not a way to prefer one over another: the filtering technique will be both implemented in Android, but the median average filter will be set as default.

3.1.2.6 HFOV modalities

In this modalities, the recognition of end expiration is easier to realise. Indeed, the stimulus frequency is usually very sinusoidal and there is no need of a qualities control. Usually, despite ventilation is realised at high frequency, the infant tends to breath. The breathing pattern of the infant is usually at low frequency with low amplitude, while the stimulus is at high frequency and with high amplitude. This situation is exactly the opposite that happen in conventional modalities of ventilation. Therefore, it is enough to control the position of minimum of volume at frequency below 3 Hz and doing the outlier's elimination algorithm afterwards. Therefore, only the value of volume at low frequency has to be taken into account if the infant actually breathe. However, on this modalities no measurements were done, therefore it has to be validated.

3.1.2.7 Consideration on the Least Mean Square Method (LMSM)

Usually the Impedance evaluation is performed on the track of flow and pressure after that a pass band filter around the stimulus frequency is done.

This way allows removing all the possible sources of noise and error on the impedance evaluation. However, it is important to note that the IPPV waveform will always have some frequency in all the spectrum in order to create the square wave. Therefore the filtering strategy is not reliable in removing the ventilation support. .

Finally, a preliminary analysis has shown that the difference of impedance selected filtering or not filtering the signals is negligible (Fig. 69). This was confirmed by comparing the value of impedance in CPAP to the value selected during IPPV. Therefore, as filtering would add a computational effort not required, it was chosen not to filter at all the signals for the impedance evaluation.

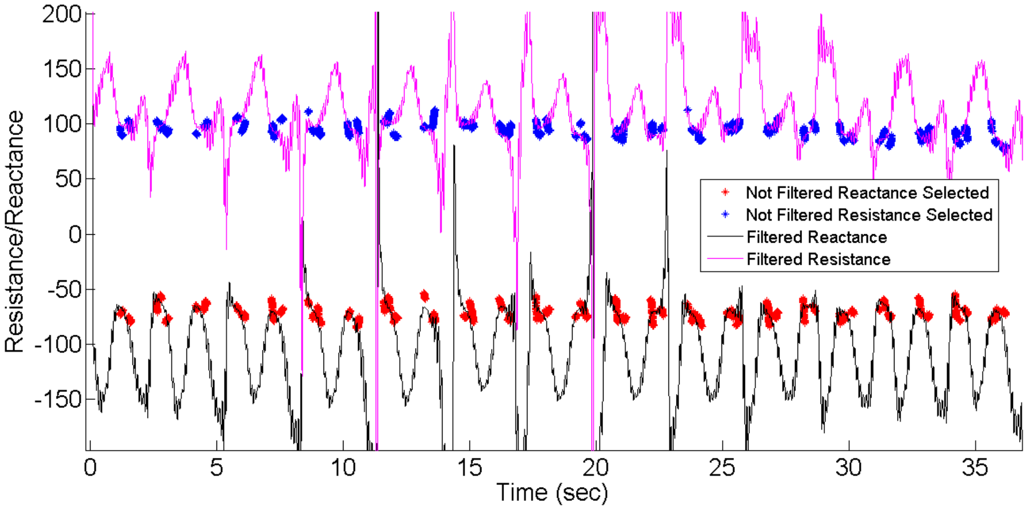


Fig. 69 Filtered impedance Vs Unfiltered impedance: it is plotted the impedance evaluated on filtered signals and the selected Unfiltered impedance is over plotted

3.2 Algorithm optimisation and sensor correction

Two steps are needed in order to have the device completely and nicely working:

1. there is the need to optimize the algorithm parameters,
2. there is the need to find the possible shift between pressure and flow signals.

While the former is due to the need of having a functioning algorithm, the latter is due to unsynchronized sampling of the pressure and flow signals.

Therefore in vitro tests were performed to find the sensor correction and data from a previous study were used to optimise the algorithm. [10] [61]

3.2.1 In vitro test for sensors correction

The in vitro tests were performed evaluating the impedance of a test object with fixed mechanical property. Indeed, a bottle with some capillaries was taken into consideration (Fig. 70). Indeed, any test lung needs to have a resistance part done by the capillary and a reactance on done by the volume of the bottle.

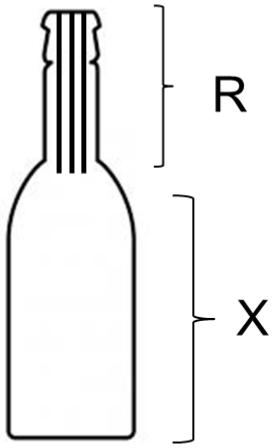


Fig. 70 Test object

In order to evaluate the frequency response of the FabianHFO sensors several measurements were performed on different test lungs by connecting the vent to the flow and pressure sensors used for reference described below.

A standard ventilator circuits was connected to a test object. Pressure and flow were acquired simultaneously with FabianHFO and sensors provided by the Politecnico di Milano. The pressure sensors were connected in the same point to the circuits. Flow sensors were placed in series.

The used set up is shown in Fig. 71.

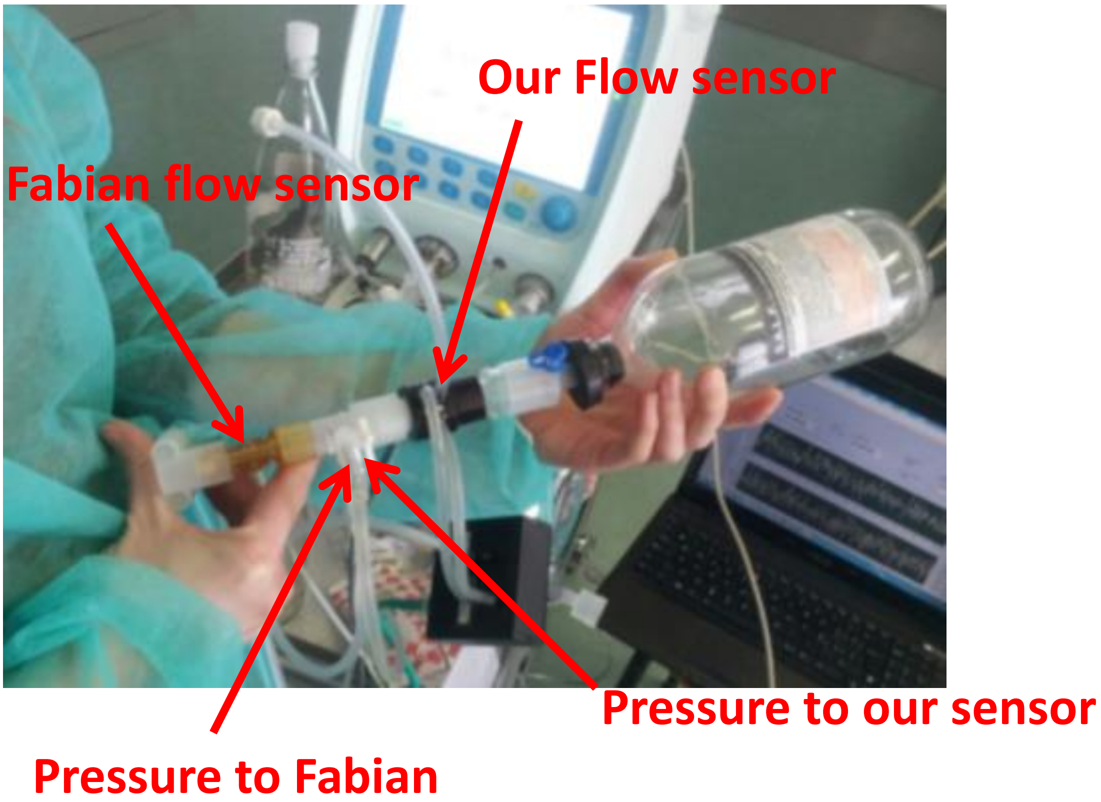


Fig. 71 Measurement set up

The Politecnico di Milano sensors used were considered to provide the correct data. Following there are some specification.

The pressure signal is measured by a differential pressure transducer (PXLA0075DN, Sensym, Milpitas, CA). The flow signal is measured by a mesh-type heated pneumotachograph (Hans Rudolph 8410A, resistance = 0.6 cmH2O·s/l at 0.27 l/s, dead space volume = 1.3 ml) coupled with a differential pressure transducer (PXLA02X5DN, Sensym, Milpitas, CA). The common mode rejection ratio of the flow channel, which may be critical with high impedances loads, like those of the preterm infants, is ≥ 50 dB up to 20 Hz. All the signals are sampled synchronously at 200 Hz by the same acquisition board and recorded on a personal computer.

As the pressure transducers used for pressure and flow measurements belong to the same products family (same mechanical frames and enclosures and same pneumatic connections) and the signal conditioning and digitalization is performed by identical circuits, pressure and flow signals measured by our sensors are considered synchronous.

3.2.1.1 Results

3.2.1.1.1 Pressure signal

It was needed to realign the two signals in order to compare them. In order to do that, the cross-correlation was employed. As the sampling frequency for the Fabian and the acquisition board is slightly different, only up to 1000 samples were used to realign the two signals. Indeed, this way allow to minimize the effect of delay brought by the difference between the two sampling frequency. Then, with the interp method provided by Matlab, the sample frequency was increased to have a better time resolution.

The pressure acquired by the two systems was realigned and compared (Fig. 72). There is a good linear relationship with a slope close to 1 at all the frequencies between 0.97 and 1.1 when the peak to peak amplitude is low (<4cmH2O).

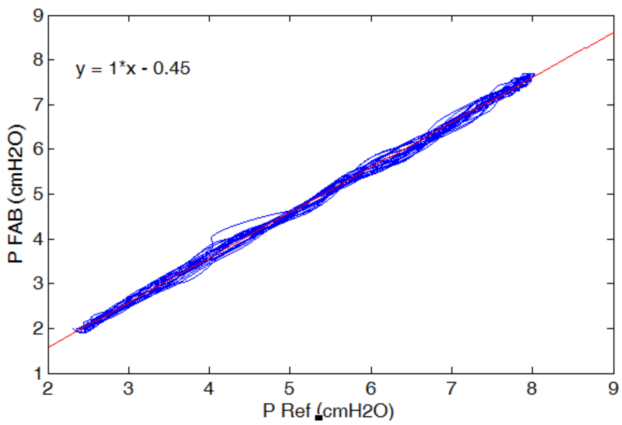


Fig. 72 Linear regression between airway opening pressure measured by FabianHFO and by Politecnico pressure sensor at 5Hz

Therefore the conclusion was that the pressure sensor is suitable in order to perform the pressure measurement for FOT with the standard low peak to peak.

3.2.1.1.2 Flow signal

For accurate FOT measurements, it is important to obtain accurate measurement in dynamic conditions, also around zero flow. Indeed, the anemometer is able to find the speed of the air that passes a rigid pipe and, by multiplying the velocity with the surface area of the pipe, the flow is available. However, the direction of the air has to be elaborated. This can be done by using particular geometry with more than one anemometer, but a death zone will arise. The death zone is due to the inability of the geometry chosen to provide good information of the direction of air when the speed is low. Therefore, because measures of flow around 0 is needed, a modified version of the software with the dead zone reduced to 19 ml/min, provided by Acutronics, was used and the measurements obtained by Politecnico sensors were compared to the one acquired by FabianHFO when different test lungs were connected to the ventilator.

After realigning the flow signals, a linear relationship between Politecnico measurements and FabianHFO was found as showed in Fig. 73.

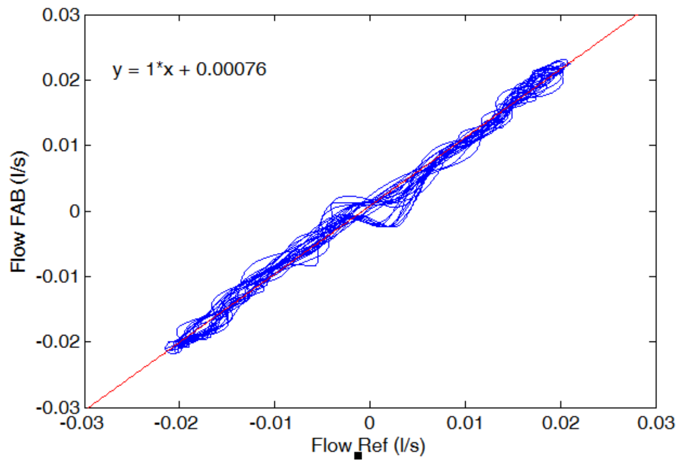


Fig. 73 Linear regression between flow measured by FabianHFO and our sensor at 5Hz

Therefore the conclusion was that the flow sensor is suitable in order to perform the flow measurement for FOT.

3.2.1.1.3 Delay between Pressure and Flow signals

Impedance computation requires that the pressure and flow signals are sampled synchronously. However, because of the differences in the mechanism of functioning of the flow and pressure sensors and in the analogical filtering procedure applied to pressure and flow signals, phase delays may arise between the two signals.

After realigning the pressure signal acquired by FabianHFO to the one provided by Politecnico sensor, we shifted the flow signals to the same extent used to realign the pressure signal. The residual delay between the two flow signals was used to estimate the delay between pressure and flow measurements in FabianHFO. Politecnico's flow and pressure measurements were considered perfectly synchronous and were used as reference.

3.2.1.1.3.1 Corrections estimation

A time delay between pressure and flow data was found in the FabianHFO. Measurements were repeated at all the available frequencies during CMV and from 5 to 11 Hz in HFOV. Moreover, it were used test lungs with different mechanical properties in order to test for possible load dependencies. The test lungs were realised using a bottle with capillary and adding water to change the compliance of the bottle. Three test lungs were measured: while test lung number one was used to find the correction, the others two were used to perform the validation test. The phase shift versus forcing frequency for each test lung is shown in Fig. 39 and Fig. 40 for CMV and HFOV modes, respectively.

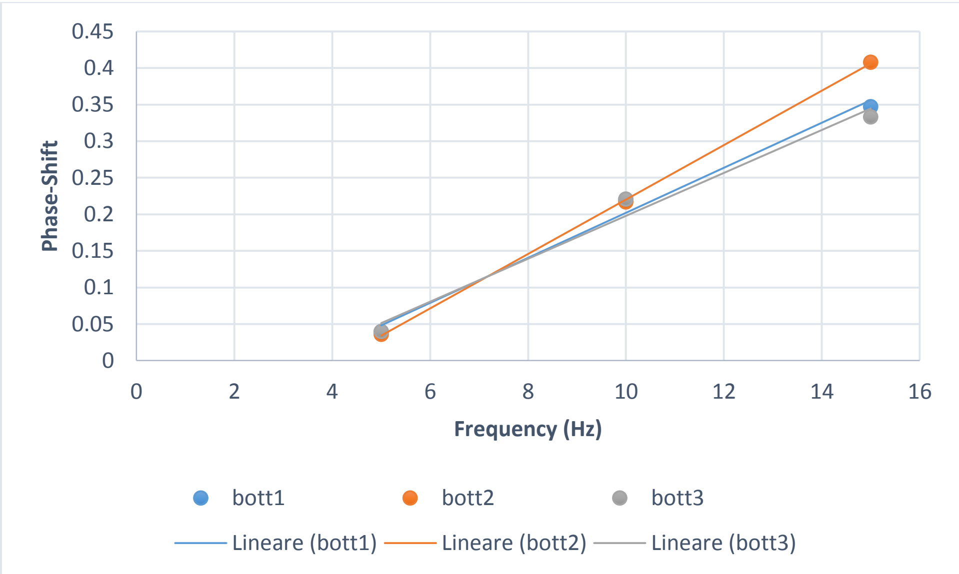


Fig. 74 Phase shift between flow and pressure measured by FabianHFO at different frequency during CMV

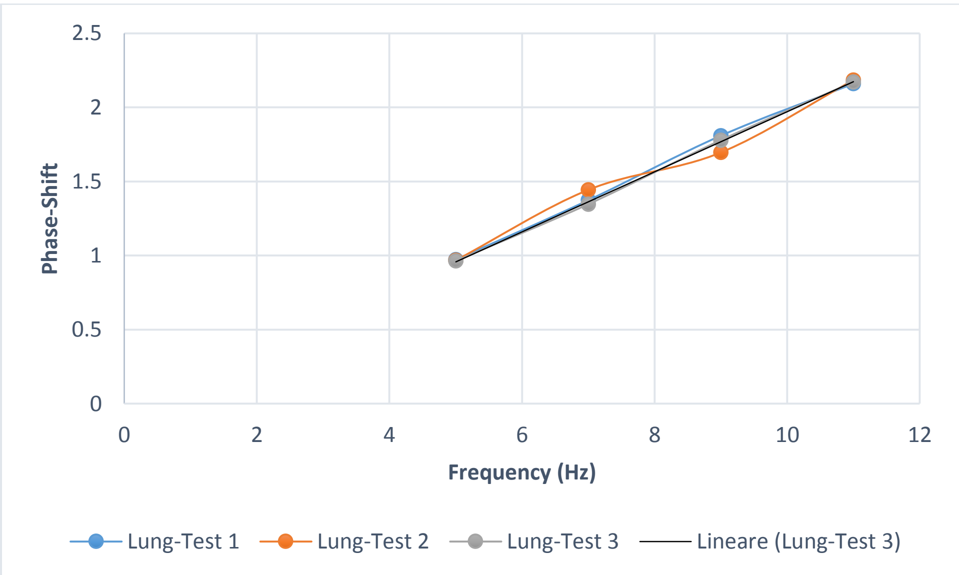


Fig. 75 : Phase shift between flow and pressure measured by FabianHFO at different frequency during HFOV

Those graphs show a linear behaviour of the phase shift. Therefore, we decide to use one of the test lung in order to find the shift in radians.

The evaluation of this delay was done by realigning flow from the Fabian and the pnt after realigning the pressure after resampling at 200 kHz. In the following table those data are showed for HFOV.

Table 6 Shift up to 11 Hz in HFOV

Test lung 1 HFOV	Shift sample	phase displacement (rad)
5 Hz	6187	0.97
7 Hz	6244	1.37
9 Hz	6397	1.81
11 Hz	6248	2.16
Test lung 2 HFOV	Shift sample	phase displacement (rad)
5 Hz	6158	0.97
7 Hz	6562	1.44
9 Hz	5996	1.69
11 Hz	6319	2.18
Test lung 3 HFOV	Shift sample	phase displacement (rad)
5 Hz	6135	0.96
7 Hz	6123	1.35
9 Hz	6290	1.78
11 Hz	6283	2.17

The mean shift sample of the first test lung was computed and used for the correction: it is 6256 (or 6.256 at 200 Hz). The phase correction to apply was obtained with the following equation:

$$\boldsymbol{\varphi = \frac{mean\ shift\ sample}{200} 2\pi * frequency}$$ **Equation 47**

The same elaborations were done in CMV and are showed in the following table.

Table

Test lung 1	Shift sample	phase displacement (rad)
5 Hz	244	0.038
10 Hz	822	0.26
17 Hz	681	0.36
Test lung 2	Shift sample	phase displacement (rad)
5 Hz	98	0.015
10 Hz	908	0.29
17 Hz	555	0.29
Test lung 3	Shift sample	phase displacement (rad)
5 Hz	85	0.013
10 Hz	847	0.27
17 Hz	635	0.34

$\boldsymbol{mean\ shift\ sample2002\pi{*}frequency}$ Equation 47 in order to evaluate the phase-shift.

3.2.1.1.3.2 Validation

Once, the corrections were found, the impedance was computed and the residual error both in HFOV modality and in CMV was obtained.

In order to obtain those data, the stimulus pressure was chosen with a peak to peak of 5 mbar as those was the peak to peak required for the current application and the only one analysed in order to see the goodness of the sensors.

The analysis done during CMV modality brought the results of the following table.

Table 8 Error applying correction in CMV

Lung Test 1	M_{RIF}/M_{FAB}	$Phase_{RIF}$ - $Phase_{FAB}$	Error Resistance	Error Reactance
Frequency		rad	cmH_2O*s/l	cmH_2O*s/l
5 Hz	0.99	0.31	30.75	17.17
10 Hz	1.09	0.05	7.05	2.23
17 Hz	1.26	-0.15	7.52	6.86
Lung Test 2	M_{RIF}/M_{FAB}	$Phase_{RIF}$ - $Phase_{FAB}$	Error Resistance	Error Reactance
Frequency		rad	cmH_2O*s/l	cmH_2O*s/l
5 Hz	0.93	0.15	19.94	29.26
10 Hz	1.09	0.17	20.44	2.04
17 Hz	0.95	0.23	8.06	16.80
Lung Test 3	M_{RIF}/M_{FAB}	$Phase_{RIF}$ - $Phase_{FAB}$	Error Resistance	Error Reactance
Frequency		rad	cmH_2O*s/l	cmH_2O*s/l
5 Hz	0.98	0.11	15.58	25.36
10 Hz	1.24	0.31	40.70	5.34
17 Hz	1.19	-0.01	10.19	4.99

Legend:

- M_{RIF}/M_{FAB} = Modulus ratio
- $Phase_{RIF}$ - $Phase_{FAB}$ = phase difference
- (Resistance) Reactance Relative error = Absolute error/ Reference (Resistance) Reactance

In CMV the errors are significant and not negligible at all. This is because only 3 frequencies are available and, therefore, it is more difficult to find the actual correction to apply.

Moreover, there are problem in the stimulus generation as described below. As showed in **Errore. L'origine riferimento non è stata trovata.**, the sinus fitting showed that the stimulus generation is not completely symmetric because of the lack of a close loop control on the pressure. This can impact on the sinusoidal fitting, and consequently the impedance, with a greater error as the flow get smaller.

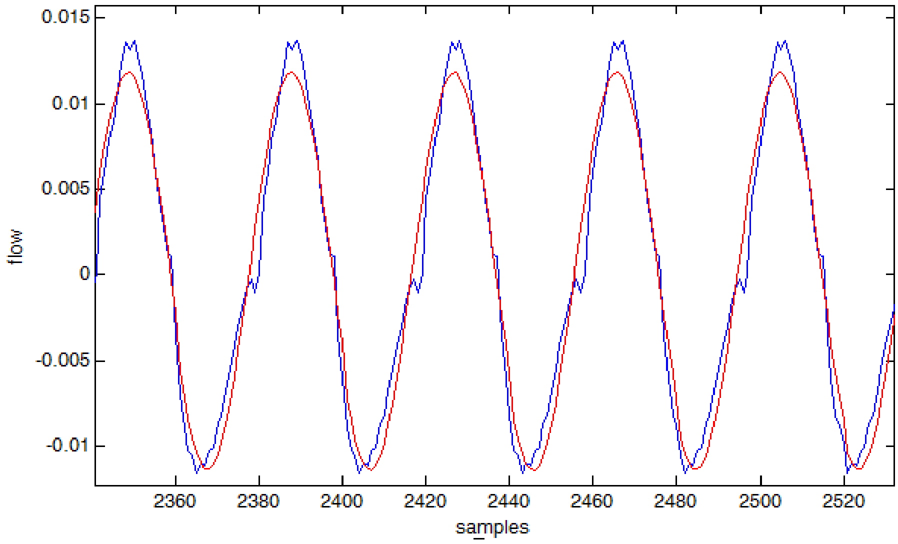


Fig. 76 Flow trace by FabianHFO (blue line) with sinusoidal fitting (red line).

Moreover, the fact that the generation of the stimulus pressure signals is currently done in open-loop impacts also on the amplitude of the stimulus.

Table 9 Mechanical property changes with peak to peak stimulus

	ΔP (cmH_2O)	Rrs (cmH_2O*s/l)	Xrs (cmH_2O*s/l)
CPAP=3 cmH2O	1.42	13.05	-44.75
CPAP=5 cmH2O	2.80	15.11	-46.08
CPAP=8 cmH2O	4.96	17.69	-46.89
CPAP=12 cmH2O	6.57	18.17	-47.59
CPAP=16 cmH2O	6.20	19.50	-48.01
CPAP=20 cmH2O	6.20	20.24	-48.58
IPPV; PEEP= 5 cmH2O	1.70	13.31	-44.45

The pressure peak to peak tends to change with CPAP impacting also on impedance values as shown in Table 9. Moreover, as the peak to peak is controlled only in open loop, it may happen that, even using the same CPAP, two analysis on the same object at the same CPAP will lead to different results. Least but not last the digital filtering was not linear in phase: this situation might bring a non-linear shift between pressure and flow in phase. Therefore, comparing two measures in CMV cannot be used to claim how good the correction is. A possible solution might be to have the data before any digital filtering (so that the correction in HFOV can be used) and to correct the problem in the stimulus generation described above.

Therefore, in order to analyse the correct behaviour of the sensors, some measure in HFOV were performed up to 11 Hz in order to see if it was possible to find some correction. HFOV allow us to have a perfect pressure sinusoidal wave with a controlled peak to peak. Moreover, the data in HFOV are sent before any kind of digital elaboration.

The following table show the results obtained.

Table 10 Error applying correction in HFOV

Lung Test 1	M_{RIF}/M_{FAB}	$Phase_{RIF}$ - $Phase_{FAB}$	Error Resistance	Error Reactance
Frequency		rad	cmH_2O*s/l	cmH_2O*s/l
5 Hz	1.040	-0.030	0.908	2.709
7 Hz	1.030	-0.028	0.308	1.627
9 Hz	1.018	0.000	0.443	0.421
11 Hz	1.117	-0.046	3.515	4.244
Lung Test 2	M_{RIF}/M_{FAB}	$Phase_{RIF}$ - $Phase_{FAB}$	Error Resistance	Error Reactance
Frequency		rad	cmH_2O*s/l	cmH_2O*s/l
5 Hz	1.010	-0.042	4.151	2.124
7 Hz	1.019	-0.437	4.478	1.679
9 Hz	1.046	-0.410	4.108	5.260
11 Hz	1.076	-0.418	4.749	5.166
Lung Test 3	M_{RIF}/M_{FAB}	$Phase_{RIF}$ - $Phase_{FAB}$	Error Resistance	Error Reactance
Frequency		rad	cmH_2O*s/l	cmH_2O*s/l
5 Hz	1.079	-0.054	2.681	4.179
7 Hz	0.952	-0.023	2.546	2.240
9 Hz	1.003	-0.021	0.748	0.605
11 Hz	1.194	0.154	1.412	1.670

Legend:

- M_{RIF}/M_{FAB} = Modulus ratio
- $Phase_{RIF}$ - $Phase_{FAB}$ = phase difference
- (Resistance) Reactance Relative error = Absolute error/ Reference (Resistance) Reactance

The error on resistance and reactance is computed as the absolute difference between the values evaluated with the Politecnico sensors and with the Fabian. It is considered negligible if the absolute error is less than 5 (cmH_2O*s/l). Therefore, the error seemed to be small in all those data with the correction applied. Those are good results as it might be asked to Acutronics to send the data before they perform any kind of digital elaboration. This way would allow us to use those corrections in order to obtain good impedance evaluation both in CMV and HFOV.

Finally, due to the problem of generation of the stimulus, those corrections seem to work well only up to 11 Hz in HFOV modality while it was not possible to find a proper correction in CMV because of several problems found. However, for the needs the device has to encounter now, it is enough (indeed, both in HFOV and in CMV is possible to have measure which can be used to build the PEEP-Reactance curve). Indeed, the error brought in CMV is a polarization error which does not affect the results of the automatic selection algorithm.

3.2.2 Parameters Optimisation

Once the algorithm was written, the need to optimise its parameters arises. As there are not analytic methods, it was chosen to identify a range of possible good values. Then, the algorithm was tried on all these values and the parameters that minimise a cost function were chosen.

In particular, the range of possible values are listed below.

Table 11 Parameters range

Parameter	Minimum value	Maximum value
FSI	0.1	0.6
PSI	0.1	0.6
DSI	0.1	0.6
Derivative Mean Flow	0.1	0.6
Mean Flow	0.1	0.6
Derivative Mean Pressure	0.1	0.6
E	0.4	0.9

For each parameter, 25 values equispaced between the maximum and the minimum were tried.

In order to do that, the algorithm was implemented in Matlab and data from a previous study were used. From this study, done by Raffaele Dellacà et al. in 2013, 13 traces of pressure and flow from infants, where a reliable semi-automatic selection, were available. Therefore, the aim of the optimisation was to perform a parameters tuning which permits to obtain the most similar results. Consequently, it was chosen the cost function in $\boldsymbol{F}$=$(\mathbf{1}-\boldsymbol{xcor})+\boldsymbol{normalised\_squared\_error}$

Equation 48.

$$\boldsymbol{F}=(\mathbf{1}-\boldsymbol{xcor})+\boldsymbol{normalised\_squared\_error} \qquad \textbf{Equation 48}$$

Where xcor is the normalised cross-correlation between the reactance vs PEEP curve taken with the new algorithms and with the semi-automatic selection and normalised_squared_error is the squared error of the curve normalised to the highest value for each track. The optimal value of the parameter is those that minimize the cost-function.

If for any reason the algorithm did not provide any value, xcor and squared_error were assigned equal to 100.

In order to find each parameter, the algorithm tries all the 25 values for each parameters at the time. Therefore, the algorithm was execute 17*25*7 = 2975 times. The Following table contain the best value for each infant and mean, median, maximum and mode value.

Table 12 Optimal value found

	dP_Mean	F_mean	FSI	PSI	DIV	E	dF_Mean
1	0.58	0.10	0.41	0.48	0.37	0.40	0.60
2	0.60	0.39	0.10	0.10	0.35	0.82	0.60
3	0.58	0.37	0.18	0.10	0.48	0.44	0.50
4	0.16	0.41	0.25	0.25	0.20	0.90	0.60
5	0.10	0.23	0.10	0.20	0.60	0.40	0.10
6	0.56	0.37	0.16	0.10	0.16	0.90	0.54
7	0.60	0.52	0.12	0.10	0.60	0.40	0.60
8	0.10	0.60	0.20	0.10	0.16	0.42	0.60
9	0.48	0.12	0.18	0.18	0.41	0.50	0.33
10	0.49	0.60	0.14	0.14	0.41	0.40	0.58
11	0.52	0.16	0.10	0.10	0.29	0.71	0.35
12	0.39	0.48	0.16	0.16	0.54	0.90	0.60
13	0.10	0.31	0.18	0.31	0.60	0.44	0.10
Mean	0.34	0.37	0.20	0.21	0.44	0.63	0.50
Median	0.32	0.38	0.18	0.16	0.48	0.57	0.60
Mode	0.10	0.60	0.18	0.10	0.60	0.90	0.60
Max	0.58	0.56	0.41	0.48	0.58	0.86	0.58
Results	**0.58**	**0.56**	**0.41**	**0.48**	**0.58**	**0.86**	**0.58**

The table above showed a high variability of the best value for each infant. However, the parameters have to be the most generic possible in order to accept a certain number of breathes for each infant. Therefore, the maximum values for each parameters were taken.

Finally, the algorithm was run again on the 13 tracks using the above parameter. As the interest output is the maximum in the decreasing part of PEEP, the results from the semi-automatic selection and the algorithm were compared both in statistical term and mean error. Moreover, the similarity of the two selections was evaluated using the cross-correlation, a t-test and a var-test.

In the following table, the results are reported.

Table 13 Results obtained

Traks	x_cor	New_maximum	Old_maximum	Absolute error	t-test	var-test
1	0.85	3	4	1	0	0
2	0.87	6	6	0	0	0
3	0.90	3	3	0	0	0
4	0.64	8	8	0	0	1
5	0.97	2	3	1	0	0
6	0.80	2	3	1	0	0
7	0.76	3	3	0	1	0
8	0.62	4	2	2	1	0
9	0.99	3	2	1	0	0
10	0.87	2	2	0	0	0
11	0.96	7	6	1	0	0

12	0.89	2	2	0	0	0
13	0.68	5	8	3	0	0

As it can be seen, in all the tracks the cross-correlation was higher than 60% and the var-test cannot reject the null hypothesis in 12 cases. This means that in those 12 tracks the PEEP vs Reactance curve has a similar shape and that it opens in the same way.

The mean absolute error of the maximum selected is equals to 0.98 mbar and the t-test and var-test cannot reject the null hypothesis. Therefore, it means that the distribution of PEEP selected has the same mean and variance. Therefore, the two different approach does not show any significance difference. However, it has to be underlined that the semi-automatic selection is different from the automatic selection. This is because, while the automatic selection uses all the data "good enough" to compute the mean mechanical property in the PEEP step, the semi-automatic selection took only the five best breaths at the end of each step.

Table 14 Statistical results

F-test

	Variable 1	*Variable 2*
Mean	4	4.04
Variance	4.52	3.43
Samples	13	13
gdl	12	12
F	1.32	
P(F<=f) one tail	0.26	
F one tail critic	2.01	F_crt > F

T-test assuming same variance

	Variable 1	*Variable 2*
Mean	4.04	4
Variance	3.43	4.52
Samples	13	13
Total variance	3.98	
Null hypothesis	Same mean	
gdl	46	
Stat t	0.07	
P(T<=t) one tail	0.47	
t one tail critic	1.68	
P(T<=t) two tails	0.94	
t two tails critic	2.01	abs(Star t) < t_crt

Finally, it might be possible to conclude that there are not any significance difference between the new approach and the semi-automatic selection. However, deeper analysis should be done in order to confirm those results.

4 Validation

Finally, it is need to evaluate the performance of the algorithm by doing in vitro and in vivo tests. By doing this test was it possible to find out weakness and goodness of the algorithm and the set up.

4.1 In vitro Test

Firstly, it was need to check how good the selection of end expiration impedance and outlier's elimination algorithms are in measuring an object with fixed mechanical properties. Therefore, one measure were realised on the same object. The object is the bottle shown it **Errore. L'origine riferimento non è stata trovata.**.

Fig. 77 Sample object number one

Firstly, it was conduced a CPAP (which mean with only the stimulus frequency applied) analysis where only the pressure stimulus was applied, afterwards the bottle was measured during IPPV. The impedance evaluated in CPAP was taken as corrected one, therefore the data selected in IPPV were compared to it.

In the following table are reported the results of the first and the second measure.

Table 15 Bottle measure results

Measure	Re cmH_2O*s/l	Std Re	Reat cmH_2O*s/l	Std Reat	Err Re cmH_2O*s/l	Err Reat cmH_2O*s/l
CPAP	8.96	1.12	-56.02	0.75	1.02	3.22
SELECTION	7.94	0.18	-52.80	0.30		

The error are considered negligible if it is less than 3 cmH_2O*s/l and only in the measure realises this requirement was satisfied. The standard deviation of the selected data is standard deviation of the mean value, therefore the one in **Errore. L'origine riferimento non è stata trovata.**.

$$\boldsymbol{meanSTD(x) = \frac{STD(x)}{\sqrt{N}}\ where\ N\ is\ the\ numeber\ of\ X\ datas} \qquad \textbf{Equation 49}$$

The measurement of rigid object, like a bottle, brings other issues: the signals of flow and pressure have important harmonics higher that 1.5 Hz (**Errore. L'origine riferimento non è stata trovata.**) which are probably due to the IPPV generation. Indeed, it behaves like a square wave taking within all the frequencies. Thus, using the elliptic filter undesirable oscillation arise.

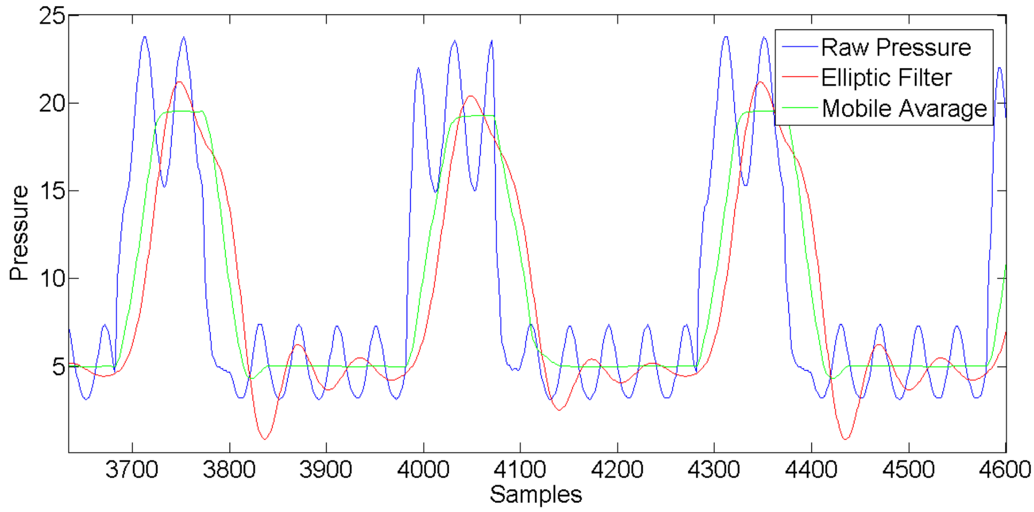


Fig. 78 Elliptic Filter vs Mobile average

However, this problem does not affect the current measure and it arises only on test object. Indeed, as this behaviour might be due to the frequency needed to generate the IPPV ventilation modalities, it was chosen to perform the same measures using the mobile average.

As claim in the paragraph 3.1.2.5, it was not clear before doing any measurement which filtering strategies to use. Therefore, a measurement of a test lung with different mechanical properties was done in order to compare the behaviour of the two different filtering strategies implemented.

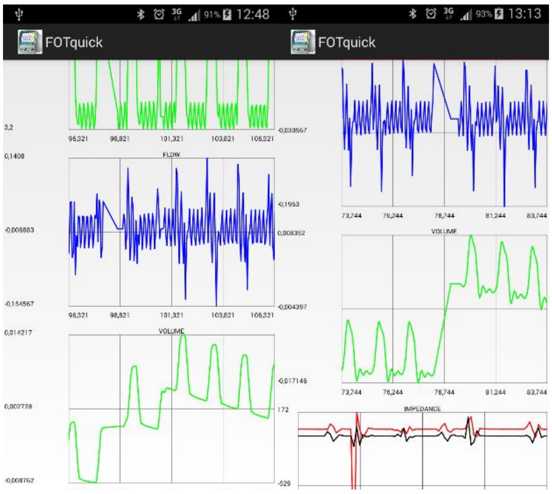


Fig. 79 On the left volume signal using Mobile Average, on the right volume signal using a elliptic filter

It is clear, by looking the signals in **Errore. L'origine riferimento non è stata trovata.**, that the elliptic filter removes all the frequency above 3 Hz, but unwanted oscillation at 2.5 Hz in the signal arises. Those oscillations appear like as a transient behaviour of the signals which may mislead in the selection. This means that it is appropriate to use the elliptic filter only if there is enough time for the filter to arrive at the equilibrium point or, in other word, signals that change with frequency below 1.5 Hz.

Finally, the impedance computed in CPAP and computed using the selection with the two different filters were compared.

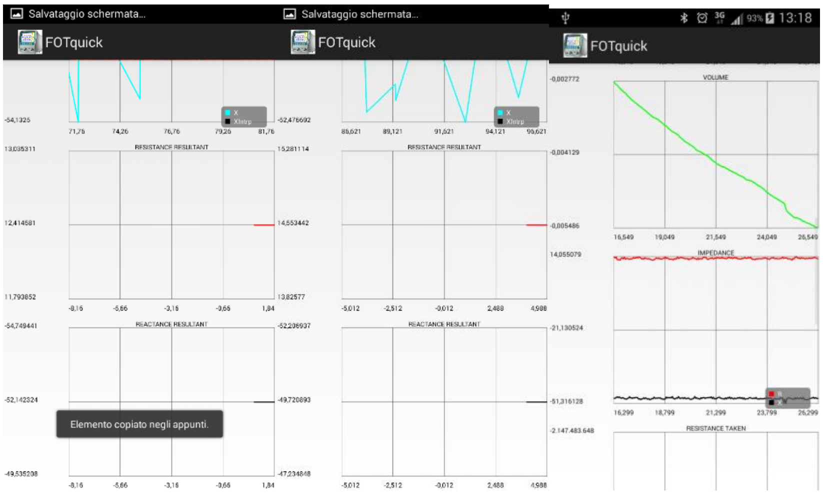


Fig. 80 On the left: result of the selection using the Mobile Average; In the centre: result of the selection using the Elliptic filter; On the left: impedance in CPAP

In **Errore. L'origine riferimento non è stata trovata.** are showed the results of the two different strategies of filtering. Even though numerical calculations were not performed, it can be seen that both selections have an error which is acceptable and there is not a big difference between them. Therefore, a choice between the elliptic filter and the mobile average cannot be done looking only on this data. Anyways, the mobile average filter seems to be more robust and it is perhaps preferable because it only removes the stimulus frequency and no oscillation arises. Therefore, from those results it was chosen as default filtering strategies.

In **Errore. L'origine riferimento non è stata trovata.** there is the reactance, resistance plane of measure 1. It can be seen that the algorithm tend to get data in the same area touched by the CPAP, but another cluster appear. This can be due to parameters which are not optimised for the bottle measurement. Moreover, for the outliers' elimination to work well, a high number of data is required.

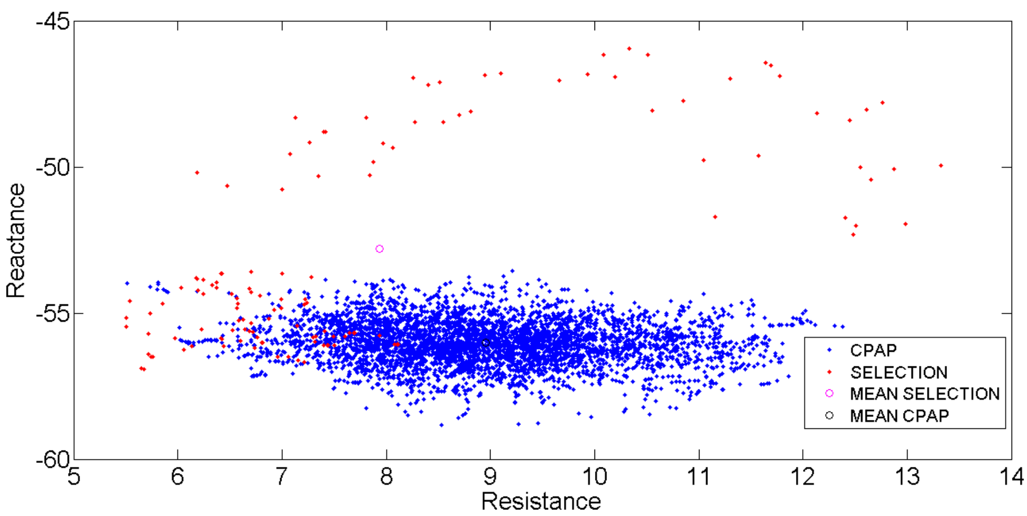


Fig. 81 Resistance-Reactance for bottle 1

Finally, a long acquisition and customized parameters are needed in order to have a better selection. While the former can be achieved for some extends, the latter is not easy to achieve. Therefore, some other clustering [62] technique based of the density might be employed in order to have a better performance. However, the results so far are good enough and there is no need to implement any clustering technique. Indeed, it can be possible to achieve good results using a mobile average filter with an acquisition which last for about 20-30 sec. This is because there is the need to find the normalisation coefficient for the parameters of the algorithm for each selection.

The purpose of the device is to build the PEEP vs Reactance, there for a flexible lung test as the one in **Errore. L'origine riferimento non è stata trovata.**.

Fig. 82 Flexible test lung

For this trial, the PEEP was putted at 5 mbar, it was increased of 1 mbar until 10 mbar were reached and afterwards it was decreased back to 5 mbar always with step of 1 mbar. The curve in **Errore. L'origine riferimento non è stata trovata.** for Reactance and Resistance were obtained.

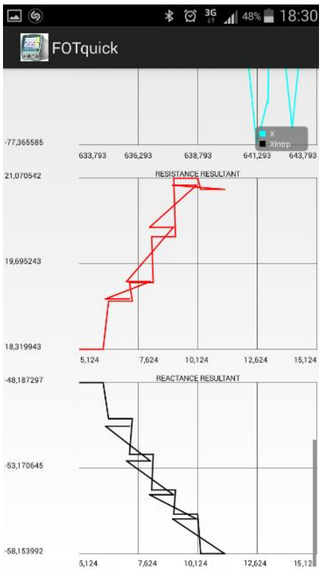


Fig. 83 PEEP vs Impedance

As expected, the value in the rising and the descent of PEEP are exactly the same. As it can be seen, it is possible to distinguish the rising and the descent limb of the curve because the shape of the step is reversed.

In order to see the correctness of the automatic selection, a manual one was performed. The manual selection consists in selecting one value of impedance for each step of pressure and comparing to the automatic selection. The curves in **Errore. L'origine riferimento non è stata trovata.** are obtained.

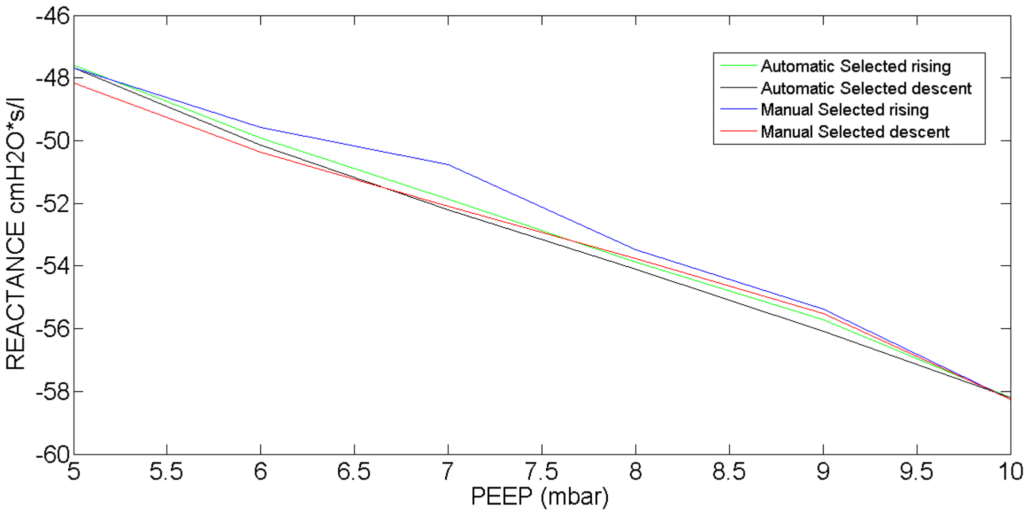


Fig. 84 Manual Selection vs Automatic Selection

Those curve are similar, with a mean squared error of 0.4625 cmH_2O*s/l, which, being below 3 cmH_2O*s/l, is acceptable.

A rising of PEEP vs Reactance trial was realised on the balloon in **Errore. L'origine riferimento non è stata trovata.**.

Fig. 85 Balloon

The curves in **Errore. L'origine riferimento non è stata trovata.** were obtained on the app.

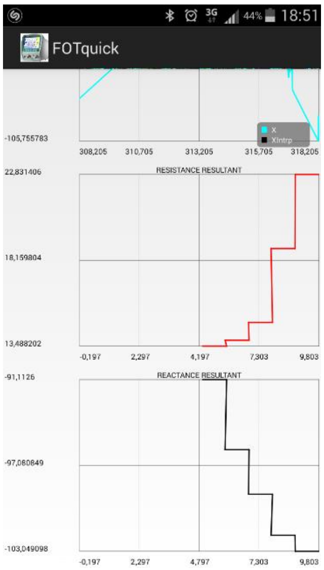


Fig. 86 PEEP vs Reactance rising Balloon

The same comparison between a manual selection and the automatic one were performed obtaining the curves in **Errore. L'origine riferimento non è stata trovata.**.

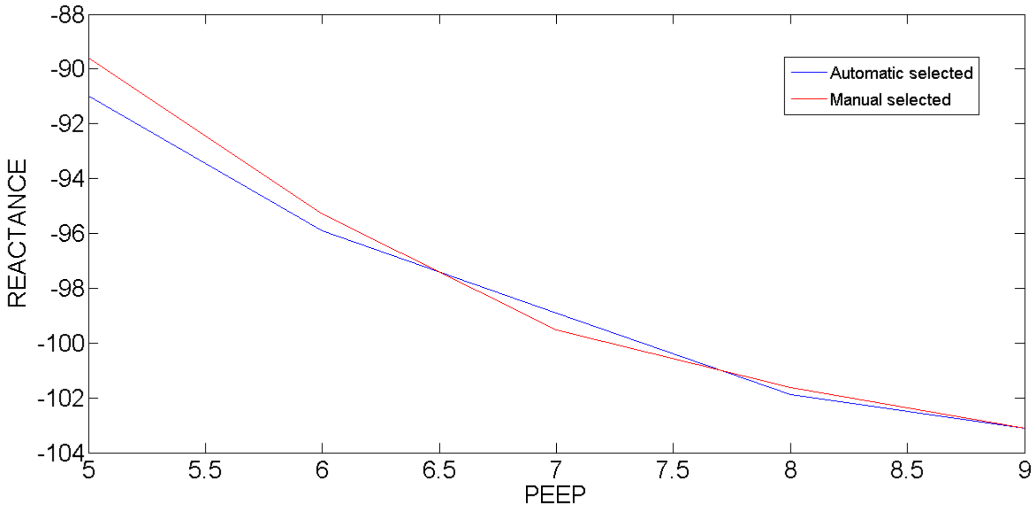


Fig. 87 Manual Selection vs Automatic Selection on the balloon

As before, those curves are similar, with a mean squared error of 0.73 cmH_2O*s/l which, being below 3 cmH_2O*s/l, is acceptable.

Finally, in case of long acquisition (more than 30 sec) using the mobile average filtering strategy, the algorithm is suitable to select the correct data. Moreover, the PEEP vs Reactance curve were correctly done by the Android application as it is showed above. Therefore, some in vivo test are necessary in order to evaluate the performance of the algorithm in presence of spontaneous breathing and breathing pattern variability.

4.2 In vivo Test

As measurements on infants are not possible for safety reasons, data from lambs were used. Indeed, preterm lambs are the most similar to pre-term infants.

Firstly, in order to analyse the capability of the algorithm identifying the end expiration and to exclude breathes with artefacts, it was chosen to compare the manual selection done by a trained operator with the automatic selection.

We measured the impedance of the respiratory system in 10 lambs. Measurements were conducted in collaboration with University of Western Australia (Perth, Australia) and with University of Utah (Salt lake City, Utah).

Those measures are all performed with a stimulus frequency of 5 Hz and with the lamb in IPPV or spontaneous breathing. In total, we obtained 35 data of resistance and reactance for both selections. On those data the linear regression both for resistance and reactance were computed. Indeed, the data should stay on the bisector of first and third quadrants if the automatic selection performs as the manual one which is the gold standard. The linear regression provides the results in Table 16.

Table 16 Linear regression

	Angular coefficient	R^2
Resistance	1.0371	0.9978
Reactance	0.9547	0.9478

The results show that data tends to lay close to bisector with a strong linear relationship. Indeed, the mean squared errors are evaluated and they are 1.0740 cmH_2O*s/l for resistance and 0.6718 cmH_2O*s/l for reactance. In order to see if the error is negligible, in the following graphs (Fig. 91Fig. 88 and Fig. 89) the data were plotted with the bisector and a tolerance zone. The tolerance zone, in which the data can lay in order to be considered equivalent in both selection, is reported in black. In this area the error is below the maximum permitted, which is of 3 cmH_2O*s/l. Therefore, the black lines are the bisector plus (minus) 3 cmH_2O*s/l.

The green lines represent the area which stays below 3 standard deviation of the error. Indeed, it was compute the standard deviation of the absolute error, which is 0.6328 cmH_2O*s/l for the reactance and 1.0519 cmH_2O*s/l for the resistance.

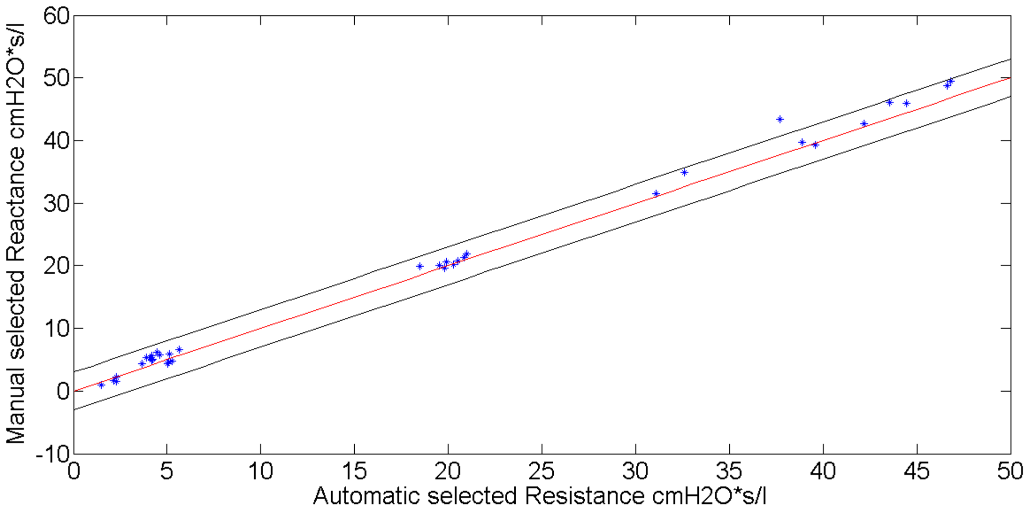


Fig. 88 Limits Automatic vs Manual Resistance

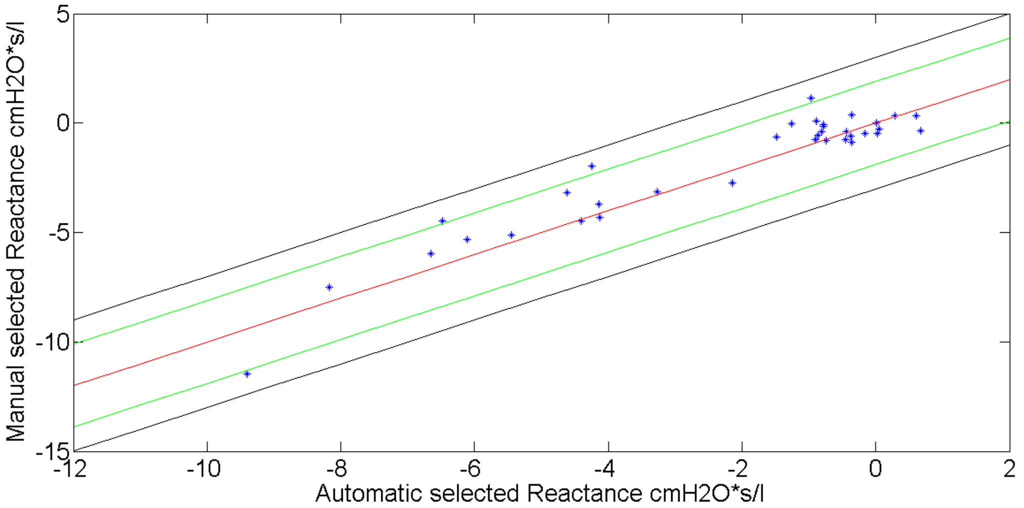


Fig. 89 Limits Automatic vs Manual Reactance

Those graphs show that the error is negligible for all the data, proving again the similarity of the two techniques. Moreover, it is shown that the error of the algorithm is usually below 3 cmH_2O*s/l. This is because the green lines, which represent the area within three standard deviations, are inside the tolerance zone. Indeed, for any statistical distribution (normal distribution), its values will fall, in almost the 90% (100%) of the case, into 3 standard deviations from the mean value. (Tchebysheff theorem) (Central limit theorem)

In the data analysed, two PEEP trials were available. Therefore, the PEEP Reactance curve was built for both trials. The PEEP trial was performed by increasing the PEEP up to 10 cmH_2O and, afterward, decreasing it by 2 cmH_2O for each step of the test as showed in Fig. 90.

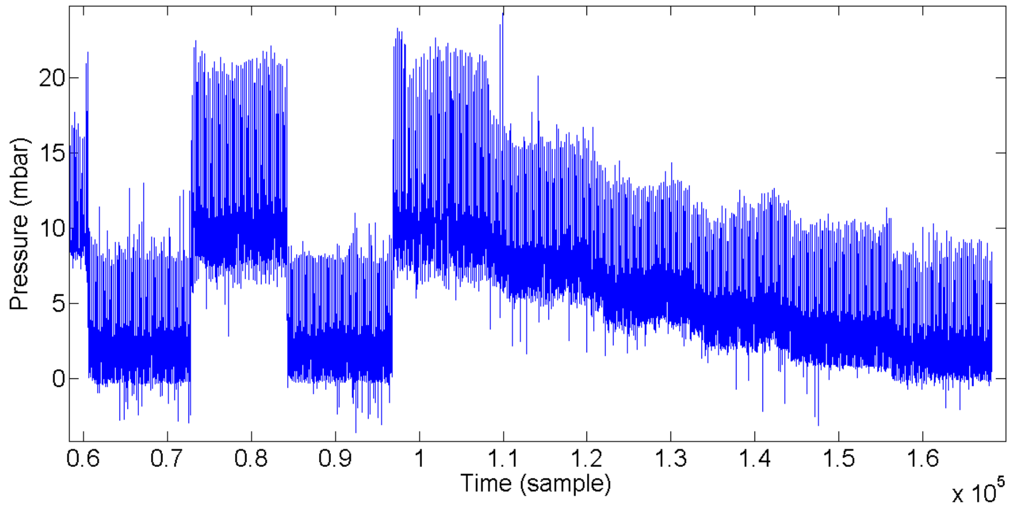


Fig. 90 PEEP trial

On those data, a manual selection of end expiration impedance was performed and it was compared to the automatic one.

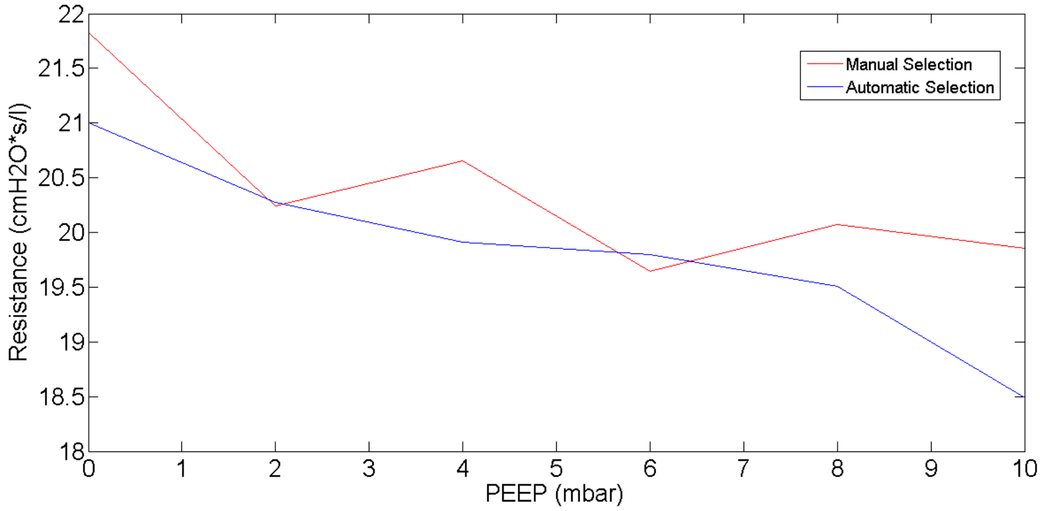


Fig. 91 Resistance Automatic vs Manual Selection

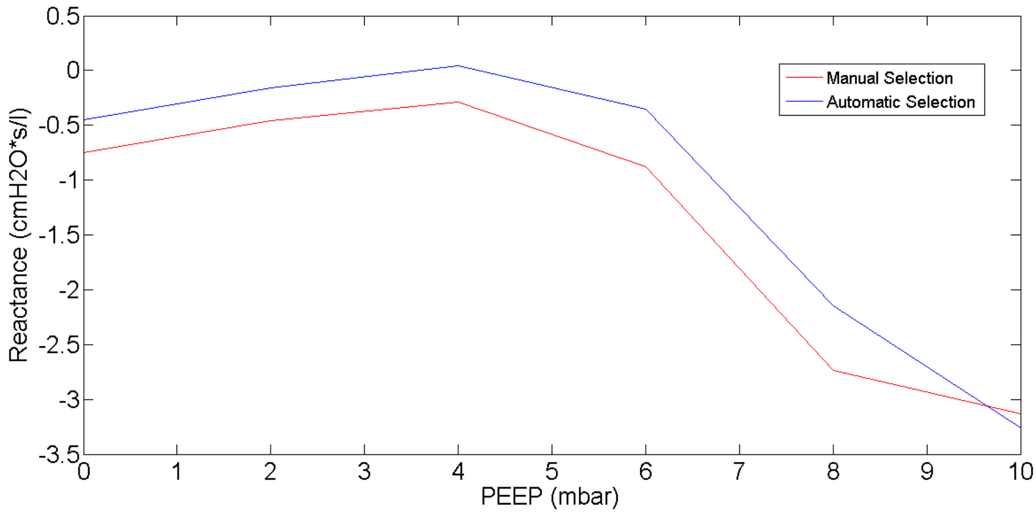


Fig. 92 Reactance Automatic vs Manual Selection

In Fig. 91 and in Fig. 92 the results from the first trial are shown. It is easy to see that the two curves, especially the reactance curve, have a very similar shape. Moreover, the optimal value of PEEP suggested by both selections is the same: 4 cmH_2O. The squared mean error of the selection is 0.6143 cmH_2O*s/l for the resistance and 0.3626 cmH_2O*s/l for the reactance.

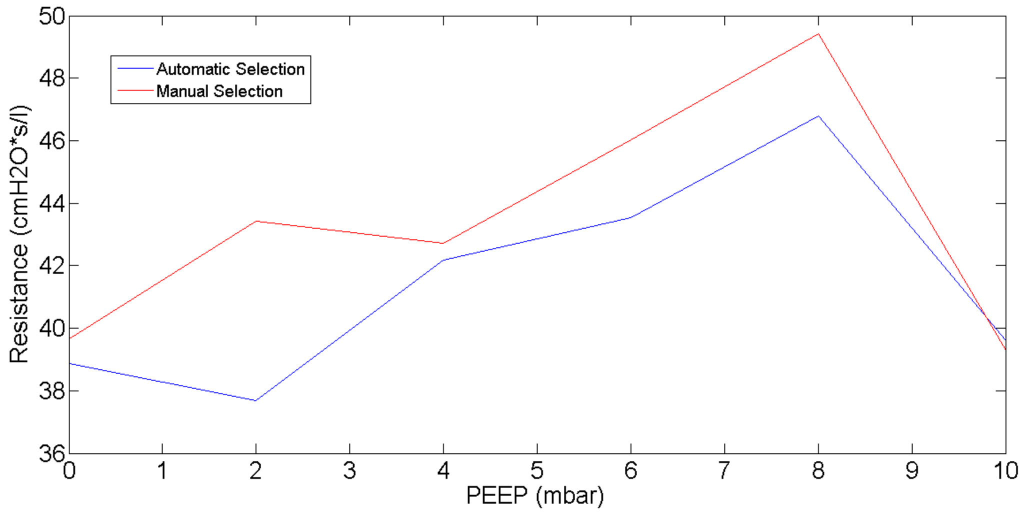


Fig. 93 Resistance Automatic vs Manual Selection

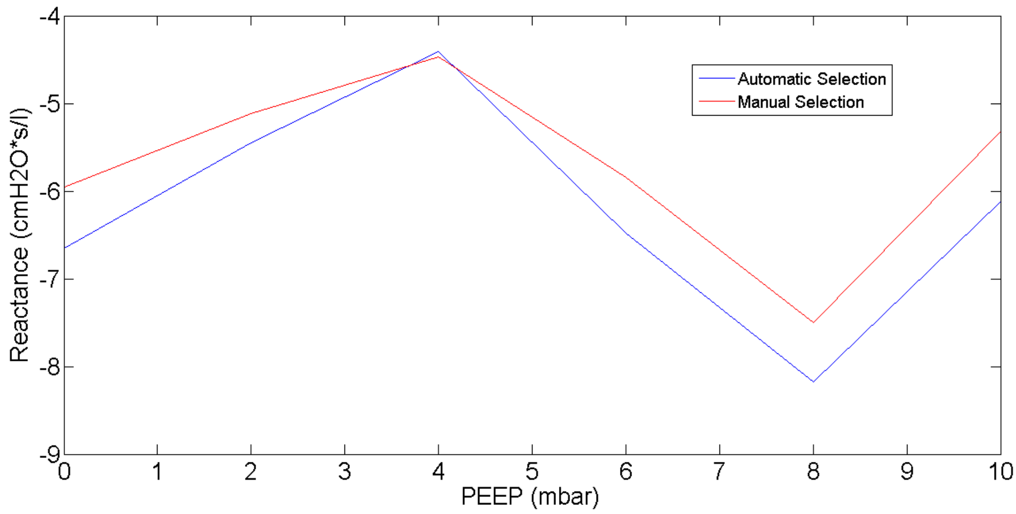


Fig. 94 Reactance Automatic vs Manual Selection

In Fig. 93 and Fig. 94 the results from the second trial are shown. Once again the shape of the curve is the same and the PEEP suggested is 4 cmH_2O for both techniques. The squared mean error of the selection is 2.0766 cmH_2O*s/l for the resistance and 0.5351 cmH_2O*s/l for the reactance.

The error is below 3 cmH_2O*s/l for both trials, therefore it is negligible.

In conclusion, as the error between the manual and automatic selection is always negligible, we are allowed to claim that the automatic selection algorithm is reliable and effective. Therefore, it can be successfully used in building the PEEP vs Reactance curve. Moreover, the measure done on lambs by clinician proved the capability of the methodology to provide the optimal PEEP and its usage in a clinical environment. Indeed, the Android application was easily understood and used by them to perform those measures.

5 Conclusions

To begin with, it was developed a system able to build Pressure at the End of Expiration-reactance curve during PEEP trial which might be used to optimise PEEP level. This is a hybrid system which integrate the functionality of a mechanical ventilator (the Fabian HFO) with a user friendly Android application specially designed and developed. The system has to monitor the mechanical status of the infant in real time, therefore, it was realized an automatic selection algorithm which can select the data at the end of expiration and which is able to reject artefact.

Secondly, the system was validated with measures on an animal model which proved its capabilities in selecting good data at the end of expiration and in building the PEEP-Reactance curve.

In conclusion, the developed application is ready to be used in clinical studies in order to find out how effective the usage of PEEP trial with FOT is in order to optimise the end of expiratory pressure on infants.

5.1 Future development

1) Developement of preclinical and clinical trials;
2) Refinement of quality control algorithms;
3) Finally, once the method has been proved, it should be implemented in a mechanical ventilator in order to have a compact and easy to use device which provides ventilation support without causing damages.

APPENDIX A: Android Apps Development

Because of the intuitive user interface and the ease to cleanability, an Android device such as a Tablet or a Smartphone seemed to be a good choice for the clinical practice. Indeed, it permits to give to the clinician a device easy to use and with which they are familiar because of the diffusion of such technology.

Following the basis of Android will be presented with some example code. Only the method uses in the development of the device will be discussed.

Android Application

The development of a mobile-based application stems from the growing need to keep always their data along through a portable device that is available to anyone. The state of the art of these devices, now arrived at the concept of the tablet, provides this possibility of use in conjunction with the user-friendly display of these data.

The first goal is the transformation of this information into knowledge through an analytical process as much as possible linked to the surrounding reality, so that a real-time approach is used to present the data.

For the development of the App, it is common to use the Object Oriented language "Java for Android" because it is the most used with the largest number of open source modules and implementable freeware libraries. The development environment is usually do with the IDE Eclipse and its SDK tools. Recently, the official development IDE provided by Google, Android Studio, was realised as an extension of the Eclipse which allows a more intuitive and graphical approach to the MVC (Model View Controller).

Very important in the development of an Android App is the GUI (Graphical User Interface). Usually the GUI of an application is created through a wrapper native development environment that exploits the Mark-up Language (XML).

Unlike other programming paradigms in which apps are launched with a main() method, the Android system initiates code in an Activity instance by invoking specific callback methods that correspond to specific stages of its lifecycle. There is a sequence of callback methods that start up an activity and a sequence of callback methods that tear down an activity. Other type of app components exists: service and broadcast communication. Those two can be used to do action in background. Usually, they are called by intents. Even activities may be called with intent.

[63]

OS Android

Android is an open source platform for mobile devices developed by Google Inc. since 2007 and it is the most popular OS in the mobile arena. Usually, Android ensure high-quality graphics and easy and

intuitive user interface. Moreover, it is not expensive either to buy it or as a developer (which near zero if the cost of the device is not considered). Thanks to these characteristics, Android is a flexible platform for the development of software. In particular, it is very feasible in a clinic environment due to the user-friendly interface and, its compact size, simplify the sterilization process.
The software architecture based on which Android is constituted by an operating system, a layer of middleware that supports and services provides to the application layer overlying. Finally, there is the application layer which proved some basic functionality of the devices (Fig. 95).

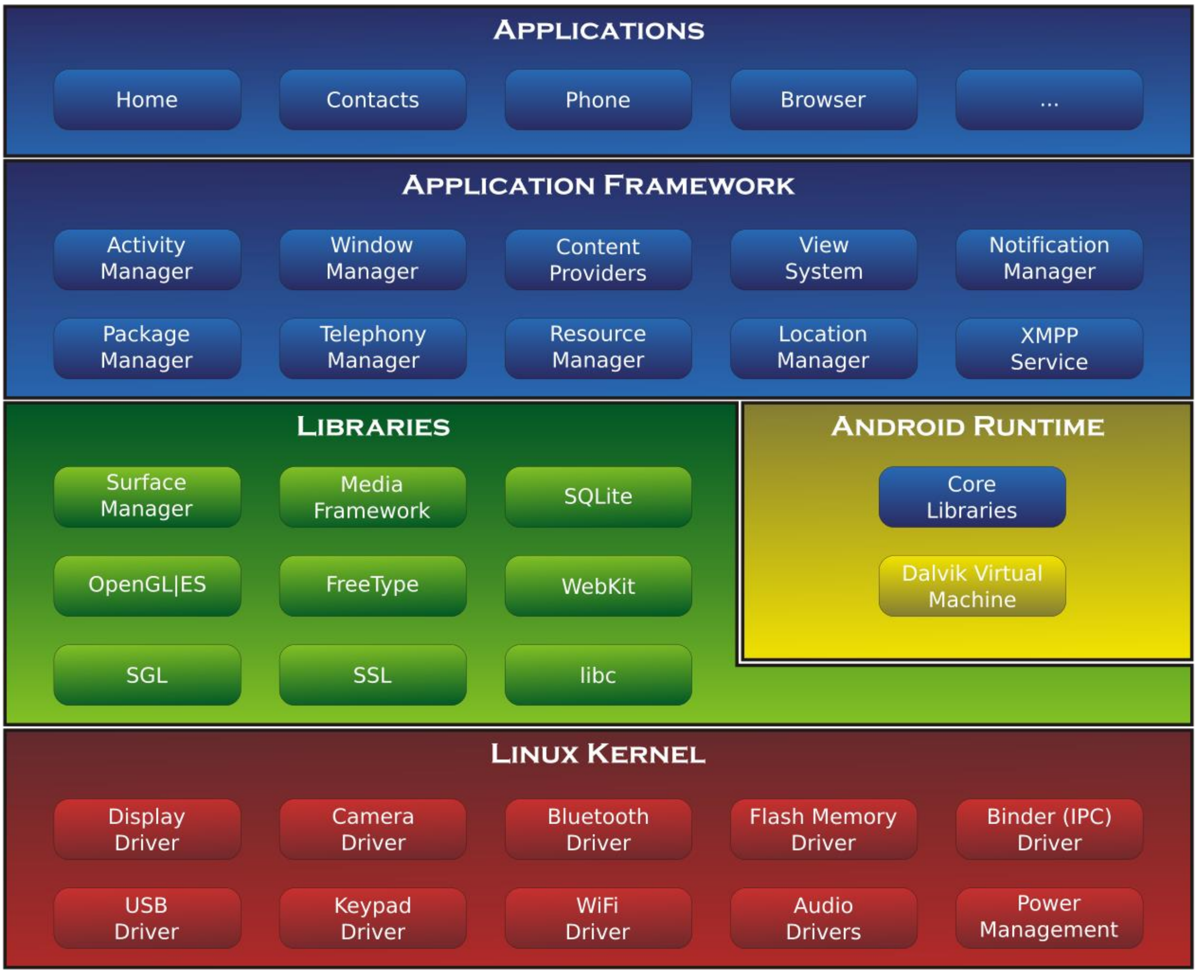


Fig. 95 Android structure

Android consists primarily of a kernel based on Linux 2.6 kernel (3.x from Android 4.0 onwards) which deals with service management system also working from abstraction layer between the hardware and the software architecture.
Android also uses the Dalvik virtual machine, a virtual machine optimized to deal with a limited memory in mobile devices, allowing to run multiple instances simultaneously keeping its activities hidden from the operating system. Each application runs in its own Linux process. For each process, it is instantiated a virtual machine, so that the application code runs in isolation from all the others. This increases the robustness of the first platform, an error in a process does not go to impact on other executions in progress and provides greater security for the entire system. Indeed, in this way

each application has an address space and a memory independent and inaccessible from the other, avoiding interference at this level.
The Android Core Libraries, however, provide the capabilities for developers to create new applications, in addition to the base provided by the system, through services made available at the Application Framework.
These applications are for high-level services for the management of the graphical interface, for use of data from hardware to communicate with other applications, to have access to media assets.
In addition, the application architecture facilitates reuse, with the publication of the functions performed by each component. This same mechanism allows the extension of the components and customization.
The applications included in the base system (e-mail client, browser, managing contacts, send and receive SMS), which offer the core functionality to use mobile devices, they are also developed through the API Application Framework.
Applications for Android, based on the components provided by the Application Framework, are written in the Java programming language. The compiled Java code, along with any and all data files and resources necessary for the application, is placed in an archive with extension apk.
The APK file (Android Package) is the means to distribute and install applications on devices. An application is considered to be composed of all of the code contained in a file APK. The compiled Java classes in files with the extension class are converted to a format optimized and executable by the Dalvik Virtual Machine, creating a single file with the extension dex (Dalvik Executable).
[63]

Intents

More in general, an Intent is a messaging object that can be used to request an action from another app component. Although intents facilitate communication between components in several ways, there are three fundamental use-cases:

- To start an activity: an Activity represents a single screen in an app. it can start a new instance of an Activity by passing an Intent to startActivity(). The Intent describes the activity to start and carries any necessary data. If a result from the activity when it finishes need to be received, it is enough to call startActivityForResult(). In this way the activity receives the result as a separate Intent object in your activity's onActivityResult() callback.
- To start a service: a Service is a component that performs operations in the background without a user interface. It can be started a service to perform a one-time operation (such as download a file) by passing an Intent to startService(). The Intent describes the service to start and carries any necessary data. If the service is designed with a client-server interface, it can be binded to the service from another component by passing an Intent to bindService().

- To deliver a broadcast: a broadcast is a message that any app can receive. The system delivers various broadcasts for system events, such as when the system boots up or the device starts charging. It can deliver a broadcast to other apps by passing an Intent to sendBroadcast(), sendOrderedBroadcast(), or sendStickyBroadcast().

The intents can be explicit or implicit:

- Explicit intents specify the component to start by name (the fully-qualified class name). Typically they will be used when it i.e. necessary to start a component in the same app, because the class name of the activity or service is known.
- Implicit intents do not name a specific component, but instead declare a general action to perform, which allows a component from another app to handle it (Fig. 96).

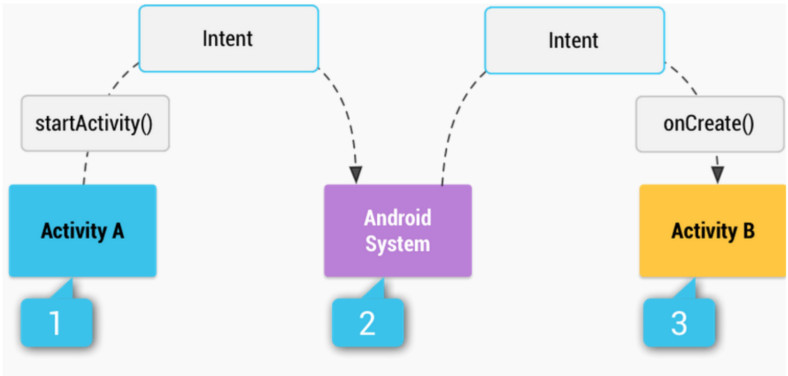


Fig. 96 Illustration of how an implicit intent is delivered through the system to start another activity: [1] Activity A creates an Intent with an action description and passes it to startActivity(). [2] The Android System searches all apps for an intent filter

[63]

Android Activity

An Activity is an application component that provides a screen with which users can interact in order to do something, such as dial the phone, take a photo, send an email, or view a map. Each activity is given a window in which to draw its user interface. The window typically fills the screen, but may be smaller than the screen and float on top of other windows.

An application usually consists of multiple activities that are loosely bound to each other. Typically, one activity in an application is specified as the "main" activity, which is presented to the user when launching the application for the first time. Each activity can then start another activity in order to perform different actions. Each time a new activity starts, the previous activity is stopped, but the system preserves the activity in a stack (the "back stack"). When a new activity starts, it is pushed onto the back stack and takes user focus. The back stack abides to the basic "last in, first out" stack mechanism, so, when the user is done with the current activity and presses the Back button, it is popped from the stack (and destroyed) and the previous activity resumes.

When an activity is stopped because a new activity starts, it is notified of this change in state through the activity's lifecycle callback methods. There are several callback methods that an activity might receive, due to a change in its state—whether the system is creating it, stopping it, resuming it, or destroying it—and each callback provides you the opportunity to perform specific work that's appropriate to that state change. For instance, when stopped, your activity should release any large objects, such as network or database connections. When the activity resumes, you can reacquire the necessary resources and resume actions that were interrupted. These state transitions are all part of the activity lifecycle. Usually, each activity brings along an xml layout which is the GUI of the activity. It is possible to start on activity from a different activity, eventually returning some information between the two activities. All this is possible by defining intents.

Activity lifecycle

When an activity is launched, a series of function that creates it are execute (Fig. 97).

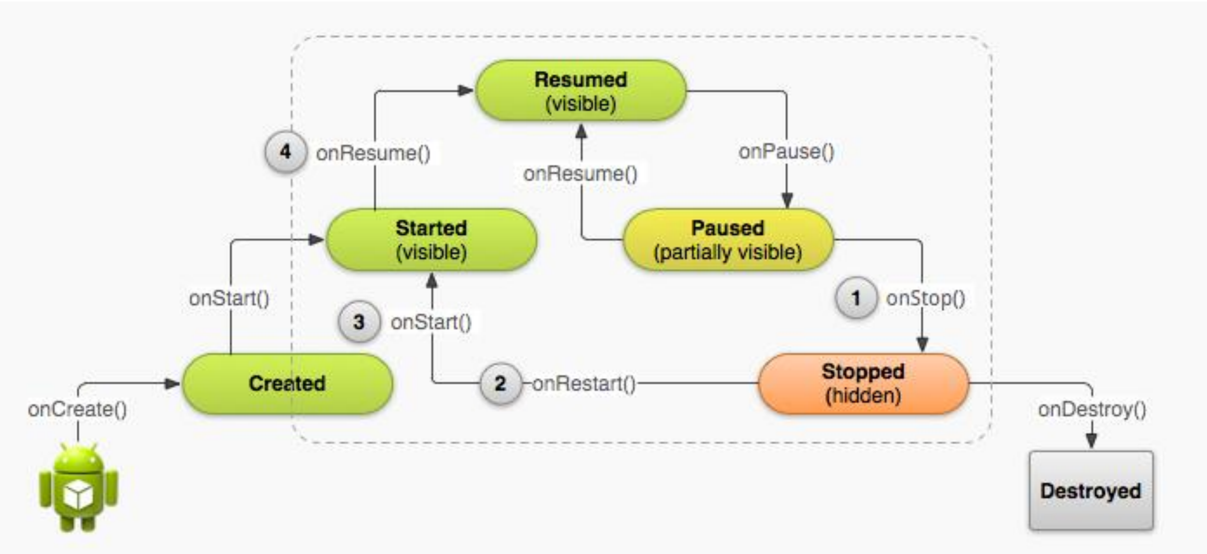


Fig. 97 Activity lifecycle: when the user leaves the activity, the system calls onStop() to stop the activity (1). If the user returns while the activity is stopped, the system calls onRestart() (2), quickly followed by onStart() (3) and onResume() (4). Notice that no matter what scenario causes the activity to stop, the system always calls onPause() before calling onStop().

To create an activity, a subclass of Activity (or an existing subclass of it) must be created. In this subclass, it is needed to implement callback methods that the system calls when the activity transitions between various states of its lifecycle, such as when the activity is being created, stopped, resumed, or destroyed. Following all the callback methods ():

- onCreate(): this method must be implement. The system calls this when creating the new activity. The essential components of activity should be initialized within this implementation. Most importantly, this is where the link with the layout .xml is done by the mandatory calling of setContentView(). It is followed always by onStart().
- onStart(): called just before the activity becomes visible to the user. Followed by onResume() if the activity comes to the foreground, or onStop() if it becomes hidden.

- onRestart(): called after the activity has been stopped, just prior to it being started again. Always followed by onStart().
- onResume(): called just before the activity starts interacting with the user. At this point the activity is at the top of the activity stack, with user input going to it. Always followed by onPause().
- onPause(): called when the system is about to start resuming another activity. This method is typically used to commit unsaved changes to persistent data, stop animations and other things that may be consuming CPU, and so on. It should do whatever it does very quickly, because the next activity will not be resumed until it returns. Followed either by onResume() if the activity returns back to the front, or by onStop() if it becomes invisible to the user.
- onStop(): called when the activity is no longer visible to the user. This may happen because it is being destroyed, or because another activity (either an existing one or a new one) has been resumed and is covering it. Followed either by onRestart() if the activity is coming back to interact with the user, or by onDestroy() if this activity is going away.
- onDestroy(): called before the activity is destroyed. This is the final call that the activity will receive. It could be called either because the activity is finishing (someone called finish() on it), or because the system is temporarily destroying this instance of the activity to save space

[63]

Android Service

A Service is an application component that can perform long-running operations in the background and does not provide a user interface. Another application component can start a service and it will continue to run in the background even if the user switches to another application. Additionally, a component can bind to a service to interact with it and even perform interprocess communication (IPC). For example, a service might handle network transactions, play music, perform file I/O, or interact with a content provider, all from the background.

A service can essentially take two forms (Fig. 98):

- Started: a service is "started" when an application component (such as an activity) starts it by calling startService(). Once started, a service can run in the background indefinitely, even if the component that started it is destroyed. Usually, a started service performs a single operation and does not return a result to the caller. For example, it might download or upload a file over the network. When the operation is done, the service should stop itself.
- Bound: a service is "bound" when an application component binds to it by calling bindService(). A bound service offers a client-server interface that allows components to interact with the service, send requests, get results, and even do so across processes with interprocess communication (IPC). A bound service runs only as long as another application component is

bound to it. Multiple components can bind to the service at once, but when all of them unbind, the service is destroyed.

Like the activity lifecycle, the services uses the same callback used for the activity. The other callback methods you are:

- onStartCommand(): the system calls this method when another component, such as an activity, requests that the service be started, by calling startService(). Once this method executes, the service is started and can run in the background indefinitely. If this is implemented, the service has to be stopped when its work is done, by calling stopSelf() or stopService().
- onBind(): the system calls this method when another component wants to bind with the service (such as to perform RPC), by calling bindService(). In implementation of this method, it must be provided by an interface that clients use to communicate with the service, by returning an IBinder.

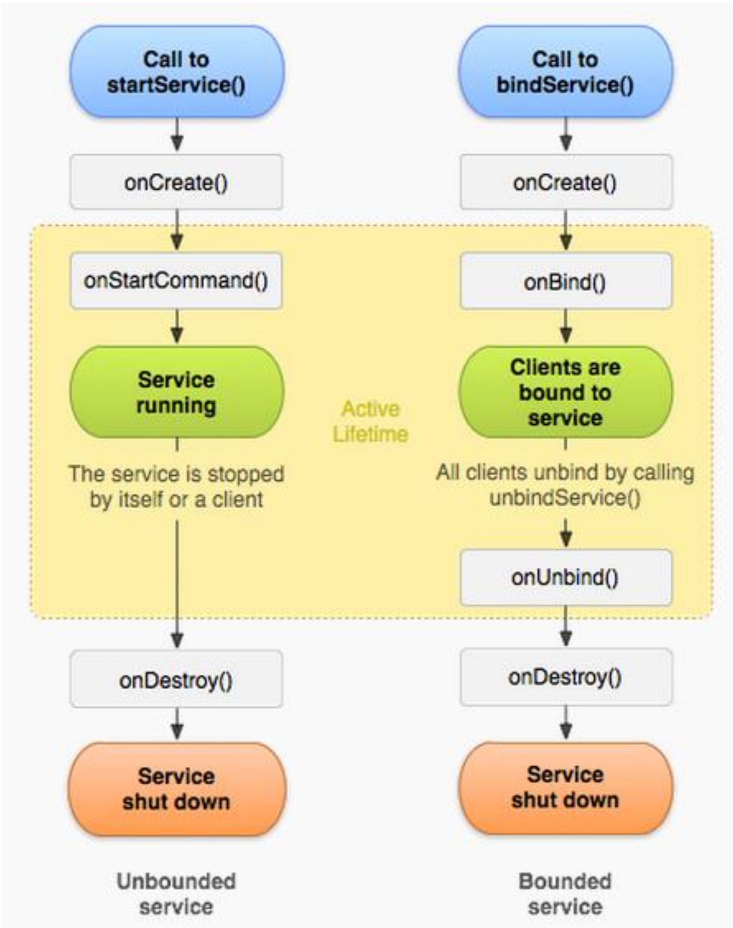


Fig. 98 The service lifecycle. The diagram on the left shows the lifecycle when the service is created with startService() and the diagram on the right shows the lifecycle when the service is created with bindService()

[63]

Handler

A Handler allows to send and process Message and Runnable objects associated with a thread's MessageQueue. Each Handler instance is associated with a single thread and that thread's message queue. When you create a new Handler, it is bound to the thread / message queue of the thread that is creating it: from that point on, it will deliver messages and runnable to that message queue and execute them as they come out of the message queue.

There are two main uses for a Handler: (1) to schedule messages and runnable to be executed as some point in the future and (2) to enqueue an action to be performed on a different thread than your own.

Scheduling messages is accomplished with the post(Runnable), postAtTime(Runnable, long), postDelayed(Runnable, long), sendEmptyMessage(int), sendMessage(Message), sendMessageAtTime(Message, long), and sendMessageDelayed(Message, long) methods. The post versions allow to enqueue Runnable objects to be called by the message queue when they are received; the sendMessage versions allow to enqueue a Message object containing a bundle of data that will be processed by the Handler's handleMessage(Message) method (requiring that you implement a subclass of Handler).

When posting or sending to a Handler, the item might be processed as soon as the message queue is ready to do so, or a delay can be specify before it gets processed or absolute time for it to be processed. The latter two allow you to implement timeouts, ticks, and other timing-based behaviour.

When a process is created for your application, its main thread is dedicated to running a message queue that takes care of managing the top-level application objects (activities, broadcast receivers, etc.) and any windows they create. News threads can be created, and communicate back with the main application thread through a Handler. This is done by calling the same post or sendMessage methods as before, but from new thread. The given Runnable or Message will then be scheduled in the Handler's message queue and processed when appropriate.

Handler are very useful, especially when some action has to be delated by certain time after some events. It is important to underline that handler are run in the thread when they are launched. Therefore, if the handler call a runnable, it will be execute in the handler thread. This is to say that if the thread has to follow any timing, they might be lost due to the runnable execution. Apart for the Android Service already seen (paragraph 0), following other techniques to do quick action in background will be presented.

[64]

Thread

Other ways to do actions in background is to call thread. There are several way to build a thread in Android: thread as in Java and AsyncTask. When starting a new thread, the problem that arises is to share variables between threads and it is difficult to upload the GUI. Indeed, an android application usually has at least the main thread which is the User Interface (UI) thread. The peculiarity of this thread is that it has to stay always ready to interact which the user. Therefore, if it start doing operation longer than 5 seconds, Android simply ask the user to close the application as it is not responding. Finally, there is necessity to have several background threads that run time consuming operation.

Thread as in Java can called as followed:

```
new Thread()
  {
    @Override
    public void run()
    {
      /*
       * Insert HERE the code
       * to execute in the secondary thread
       */
    }
  }.start();
```

However, in this way the communication and synchronization of variable access has to be set properly.

Indeed, usually a thread is composed of coupled components: Handler, Runnable, and Thread. The code showed above is how to handle with threads in Java. However, in Android it is possible to find the HandlerThread class which allow us to work with Thread. The only significant difference between HandlerThread and Thread is that the first one incorporates Looper, Thread and MessageQueue (Fig. 99).

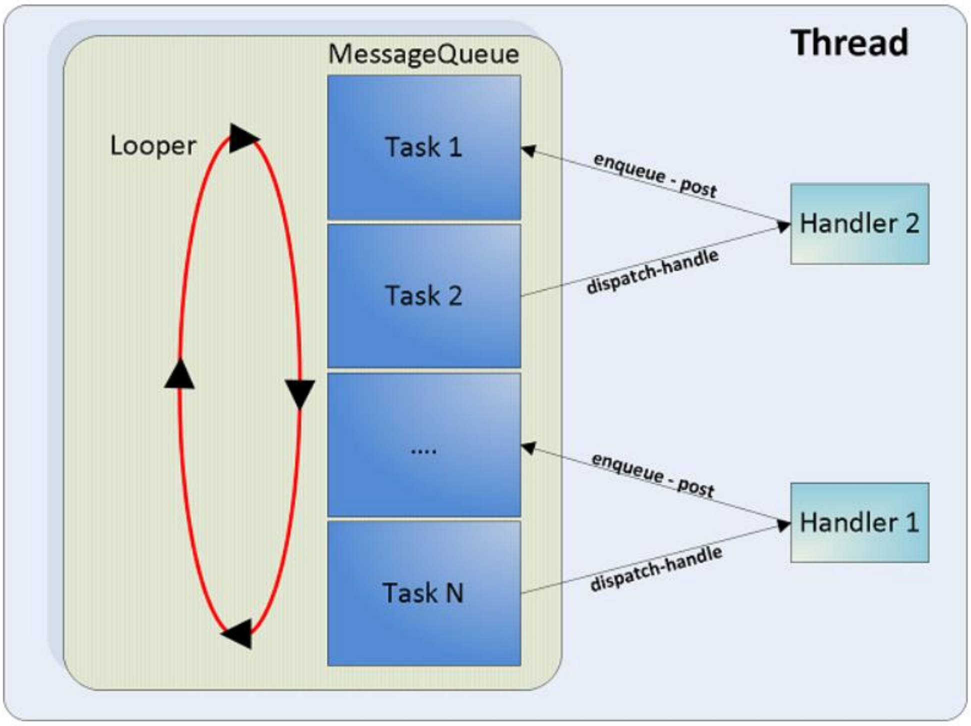


Fig. 99 HandlerThread

Looper is a worker that serves a MessageQueue for a current thread. MessageQueue is a queue that has tasks called messages which should be processed. Looper loops through this queue and sends messages to corresponding handlers to process. Any thread can have only one unique Looper, this constraint is achieved by using a concept of ThreadLocal storage.

The complexity of this implementation in Android gives at least 2 advantages:

- It helps you to avoid race conditions, when concurrent threads can make changes and when sequential execution is desired.
- Thread cannot be reused after the job is completed while thread with Looper is kept alive by Looper until you call quit method, so you don't need to create a new instance each time you want to run a job in background.

Basically, once the looper is created it has to be connected with through handlers to the runnable objects. It may be tricky to implement, but Android offers the AsynTask class that already have all implemented.

[65]

AsyncTask

AsyncTask enables proper and easy use of the UI thread. This class allows to perform background operations and publish results on the UI thread without having to manipulate threads and/or handlers.

AsyncTask is designed to be a helper class around Thread and Handler and does not constitute a generic threading framework. AsyncTasks should ideally be used for short operations (a few seconds at the most).

An asynchronous task is defined by a computation that runs on a background thread and whose result is published on the UI thread. An asynchronous task is defined by 3 generic types, called Params, Progress and Result, and 4 steps, called onPreExecute, doInBackground, onProgressUpdate and onPostExecute. The only method which is actually execute in the background thread is doInBackground.

onPreExecute

It invoked on the UI thread before the task is executed. This step is normally used to setup the task, for instance by showing a progress bar in the user interface.

doInBackground

It invoked on the background thread immediately after onPreExecute() finishes executing. This step is used to perform background computation that can take a long time. The parameters of the asynchronous task are passed to this step. The result of the computation must be returned by this step and will be passed back to the last step. This step can also use publishProgress(Progress...) to publish one or more units of progress. These values are published on the UI thread, in the onProgressUpdate(Progress...) step.

onProgressUpdate

It invoked on the UI thread after a call to publishProgress(Progress...). The timing of the execution is undefined. This method is used to display any form of progress in the user interface while the background computation is still executing. For instance, it can be used to animate a progress bar or show logs in a text field.

onPostExecute

It invoked on the UI thread after the background computation finishes. The result of the background computation is passed to this step as a parameter.

[64]

Dialog and Toast

One of the most common interaction app-user is notified of messages through the so-called dialogs. Among other things, the constant presence of Alertbox, MessageBox and dialogs in different web technologies, and desktop of every age has made this form of communication is particularly familiar to the user.

Toast

Using an Android device, a type of notification that you meet soon is called Toast. It is a small rectangular black box that appears in the lower part of the display containing a message written in the white. Its visibility is short, a few seconds, and his sudden appearances on the bottom has given him this name because it remind the way the bread popping out of the toaster. The Toast is the most immediate form of notification that exists and make it happen is very simple:

```
Toast.makeText(this, "Ciao a tutti!", Toast.LENGTH_SHORT).show();
```

Fig. 100 Toast example

Dialog

A fast communication and ease of implementation are the main advantages of Toast but what it offers is often not enough. Soon comes time to use real dialogs.

Android offers the ability to have raw Dialog to configure or alternatively certain types ready to reflect the most common uses: AlertDialog for alerts, ProgressDialog to show progress bars and more. Dialog is the superclass of all dialog boxes, and it is the most versatile type but that leaves more work to the programmer.

The following example shows code that can be executed within a method of the Activity:

```
Dialog d=new Dialog(this);
d.setTitle("Login");
d.setCancelable(false);
d.setContentView(R.layout.dialog);
d.show();
```

What happens with the code above is described below:

- instantiate an object of class Dialog passing a reference to Context;
- a title, which is already a property of the same window, is set;
- the window is defined as modal calling for his non-erasability by setCancelable. This will prevent that touching the display outside of the dialog box will be closed;
- assign a layout of the dialog box as we would for an Activity;
- Last but not least, the show() method has to be invoked the show() method without.

The dialog d in the example has to be defined as follow:

```
final Dialog d=new Dialog(this);
/*
 * OMISSIS: varius configuration of the dialog window
 * */
Button b=(Button) d.findViewById(R.id.login);
b.setOnClickListener(new OnClickListener()
{
  @Override
```

```
  public void onClick(View arg0)
  {
   Toast.makeText(d.getContext(), "cliccato", Toast.LENGTH_LONG).show();
  }
});
d.show();
```

This is the result:

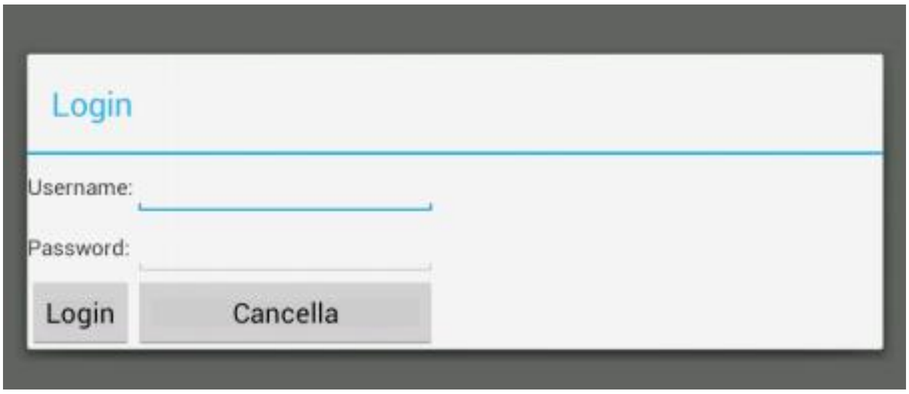


Fig. 101 Example dialog

More in general, in a dialog complex quick interation with the user are performed. Apart for this dialog, there are some dialog already implemented as classes for the more common interaction. However, those dialogs will not be discussed.

[66]

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