PhD Research Proposal

A low-cost, portable or non-invasive approach to delivering crucial lung function tests through directly measuring underlying pulmonary mechanics for the improvement of guiding respiratory care

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1 Research Motivation

Respiratory disease is one of four non-communicable diseases [1–5] that kills 41 million people each year, equivalent to 71% of all deaths globally. According to the American Lung Association, 12.7 million U.S. adults were reported to have Chronic Obstructive pulmonary disease (COPD) [6]. Respiratory disease affects 1 in 6 people in New Zealand and costs the economy 7 billion NZD per annum [7–9]. Respiratory disease is thus a global problem that effects quality of life, mortality rates and also has a financial impact on economies.

While respiratory disease is a known major health problem in society, diagnosing the type and severity of the disease requires costly and time consuming individual testing. COPD diagnosis is made possible with a spirometry test. The nature of this testing and the equipment required decreases accessibility to those most vulnerable. The most common pulmonary function test is spirometry, applied by clinicians as a gold standard method in outpatient care [10–13]. Clinicians have various tools with which to make diagnoses and treat patients who have some form of respiratory illness. While spirometry confirms obstruction, a narrowing of the airway or restriction as a stiffening of the lung, plethysmography looks at the predicted value of the flow volume loop [14].

Data captured from spirometry provides health professionals results in the form of flow and volume information. Running this information through some computation nets the result of being able to discern the mechanical properties of a lung. This information provides a clearer picture of a patients specific breathing manoeuvres and enables informed diagnosis [15]. Understanding the underlying mechanics of each individual lung is not possible without further testing [16–18]. This is due to the dynamic nature of the material properties of the lung changing with changes in pressure and time [19–22].

For more serious patients, as we have witnessed with COVID-19 patients, mechanical ventilation (MV) may be required as a form of treatment. MV is used specifically for patients with acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) to fully control breathing as treatment of respiratory failure. Providing positive end expiratory pressure (PEEP), using MV also prevents alveolar lung collapse. ARDS patients have high mortality rates of up to 60% and a high financial daily cost of medical care. Current care regimes include clinical intuition and a generalised "one size fits all" approach, often leading to poor outcomes such as ventilator induced lung injury (VILI), where the alveoli are over-distended and damaged during recruitment manoeuvres.

Mechanical Ventilation (MV) is an essential tool used by clinicians to assist patients to recover from respiratory illness. Some patients require the full control that MV offers for breathing in the intensive care unit (ICU) setting. This type of therapy is applied across all age groups and is found in the paediatric ICU (PICU) and the neonatal ICU (NICU) for children and infants suffering from respiratory distress syndrome (RDS). RDS is common in premature infants due to a lack of surfactant [23–29].

A "one size fits all" approach or "clinical intuition" is commonly found in current clinical practice to treat respiratory failure [30–32]. This approach carries a higher level of risk as the inter-patient variability and lung heterogeneity requires a finer or more bespoke approach in terms of ventilator settings. Over distending alveoli by applying the incorrect MV settings leads to ventilator induced lung injury (VILI), decreasing the well-being of the patient and the effectiveness of MV treatment.

Model-based methods use the modern-age computational advantage to create smart algorithms for ventilator settings that can adjust responses to the resistance and elastance of each individual lung in real-time. This patient specific approach, without increasing the clinical workload leads to personalised care, optimising a patients recovery. While this method has been applied in the adult ICU[REFS - KT], there is a clear lack of study for these methods in the PICU and NICU.

2 Background

Respiratory diseases are separated into two classes, obstructive or restrictive. Obstructive lung disease is classified by an airway obstruction. The most common causes of obstructive lung disease are COPD which includes emphysema and chronic bronchitis, asthma, bronchiectasis and cystic fibrosis. Obstructive diseases are commonly treated with inhalers and steroids to relax smooth muscles. This results in a reduction of

available air and gas exchange due to air being trapped in the lungs. An obstructive lung disease patient typically has difficulty in emptying the air from the lung and therefore has too much CO_2.

Restrictive lung disease is a reduction of the ability to inhale air into the lungs, and thus a reduction in oxygen into the lung for gas exchange to take place. This occurs due to a stiffening of the lung otherwise known as an increase in elastance. Examples of this include fibrotic diseases of the lung, neuromuscular disorders and obesity. Examples of treatments include antibiotics, immunosuppresants, oxygen therapy or non-invasive MV to assist breathing. These therapies are often unable to reverse the effects of the disease but rather aim to improve the quality of life for the patient.

These two classifications of diseases can be summarised as a problem with inspiration (restrictive diseases) and expiration (obstructive diseases). A reduction in inspiration affects the lungs ability to take in enough oxygen. Obstructing expiration reduces the ability to exhale CO_2. For both of these cases, the blood oxygen level in the body decreases and the body suffers the effects of low oxygen.

Spirometry is a lung function test used by clinicians to asses how well the lung is working. It includes a series of breathing manoeuvres and provides information critical to understanding reduced airflow or lung capacity, a crucial tool in diagnosis of lung disease. The accuracy of the information provided by the test is highly dependent on the patient performing the breathing manoeuvres correctly. This increases the risk of misdiagnosis and has an increased effect when attempting to perform spirometry on the elderly or children.

The results of the spirometry test are compared against reference values to diagnose respiratory disease. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification is used widely as a standard for diagnosis [33]. GOLD uses cut-off values for FEV1/FEC to rank the severity of COPD by placing patients into one of four categories ranging from mild to very severe COPD. GOLD also specifies a recommended treatment plan based on the level of COPD diagnosed. The parameters used in spirometry are shown in Table 1.

Table 1: Spirometry parameters

Abbreviation	**Parameter**	**Detail**
VC	Vital Capacity	Volume exhaled after full inspiration
FVC	Forced Vital Capacity	Volume forcibly exhaled after full inspiration
FEV1	Forced Expiratory Volume in 1 second	Volume forcibly exhaled the first second after full inspiration
FRC	Functional Residual Capacity	Volume of air remaining in the lungs after forced expiration
RV	Residual Volume	Volume of air remaining in the lungs after normal expiration
PEF	Peak Expiratory Flow	Maximum flow rate in a forced expiration measured with a peak flow meter
TLC	Total Lung Capacity	Total volume of the lungs after full inhalation. The sum of RV and VC

GOLD defines a diagnosis ratio of FEV1/FVC below 0.7 as indicative of obstructive disease which as a fixed value sometimes causes misclassification [34–36]. This seems to lead to an over diagnosis of the elderly and an under diagnosis of children. The current standards to predict asthma, COPD and other obstructive conditions are under ongoing debate [37, 38].

To assist with a greater understanding of the various subdivisions of lung volumes, a graph showing lung volume over time is shown in Figure 1. The volume of air taken into the lungs with each breath, termed the *tidal volume*, is substantially less than the total volume that can be forcibly expired from a maximal inspiration. This total volume, called *vital capacity*, is equal to the difference between *total lung capacity* and *residual volume*, the latter defined as the volume of air left in the lungs after maximum expiratory effort. Residual volume is substantially less than the the volume of air in the lungs at the end of normal passive expiration, termed *functional residual capacity*.

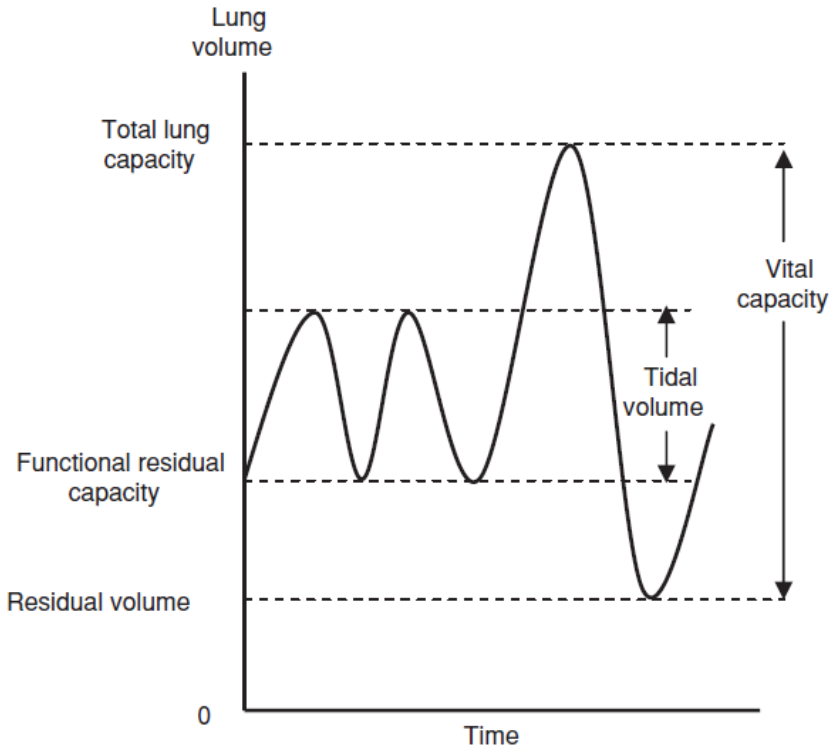

Figure 1: Standard subdivisions of lung volume [20].

2.1 Lung Mechanics

"Being able to breathe without any apparent difficulty is something that healthy people take for granted, and most of us generally go about our daily lives without giving it a second thought" [20]. Breathing is essentially a mechanical process in which the muscles of the thorax and abdomen, working together under the control of the brain, produce the pressures required to expand the lung so that air is sucked into it from the environment. This difference in pressure must be sufficient to overcome the tendencies of the lung and chest wall tissues to recoil, much like blowing up a balloon. The mechanical properties of the lungs therefore determine how muscular pressures, airway flows and lung volumes are related to one another as shown in Figure 2. The field of lung mechanics is concerned with the study of these properties.

A healthy blood-gas barrier and functioning respiratory control system are not enough to guarantee effective gas exchange, unless the mechanical properties of the lung are also up to the task. The mechanical properties are the flow resistance and the elastic recoil of forces. These properties must be overcome by the respiratory muscles with each breath, if fresh air is to be supplied to the blood-gas barrier.

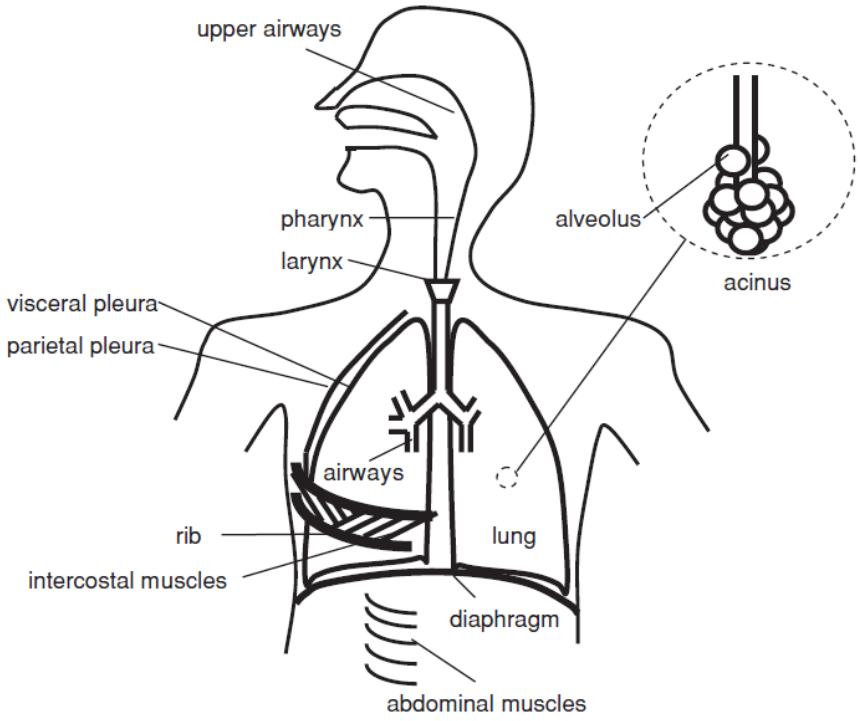

Figure 2: Principal mechanical components of the respiratory system [20]

2.2 Gas Exchange

The primary function of the respiratory system is to take in oxygen and eliminate carbon dioxide. Inhaled oxygen enters the lungs and reaches the alveoli [39]. The layers of cells lining the alveoli and the surrounding capillaries are each only one cell thick and are in very close contact with each other. The barrier between air and blood averages about 1 micron in thickness. O_2 passes quickly through this air-blood barrier into the blood in the capillaries. Similarly, CO_2 passes from the blood into the alveoli and is then exhaled. To support the absorption of oxygen and release of carbon dioxide, about 5 to 8 litres of air per minute are brought in and out of the lungs and about 300mL of O_2 is transferred from the alveoli to the blood each minute. At the same time, a similar volume of CO_2 moves from the blood of the alveoli and is exhaled. During exercise, it is possible to breathe in and out more than 100L of air per minute and extract approximately 3L of O_2 from this air per minute. Graphic illustration of this process is found in Figure 3.

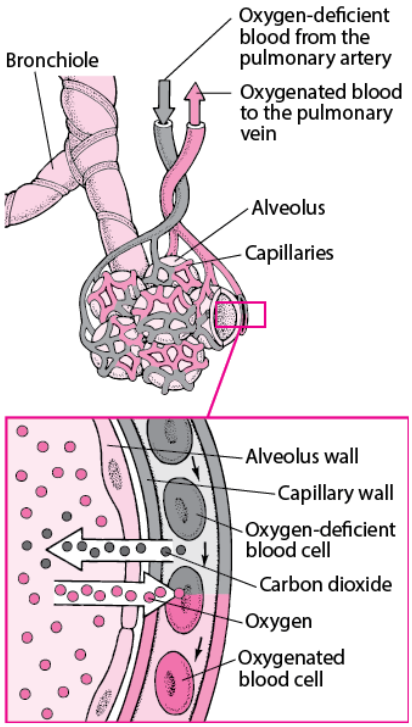

Figure 3: Gas Exchange

3 Thesis Statement

A low-cost, portable or non-invasive approach to delivering crucial lung function tests through directly measuring underlying pulmonary mechanics for the improvement of guiding respiratory care.

4 Research Plan

Phase 1: 0-12 months

1. Familiarisation with project
2. Model development
   (a) First analysis of data.
   (b) Develop a lung model for lung mechanics using spirometry data
   (c) Validation of model
3. Publication of results

Phase 2: 6-12 months

1. Develop a prototype for a custom, portable spirometer
    (a) Validation of model
    (b) Assess alternative methods for collecting data
2. Publication of design (Open source)

Phase 3: 12-24 months

1. Test methods for data collection (N=5 to 10 healthy subjects)
    (a) Reassess concepts
2. Publication of results

Phase 4: 18-36 months

1. Clinical verification
    (a) N = 10+ in respiratory care clinic
    (b) Final clinical validation
2. Publication of results

Phase 5: 9-30 months

1. Create modelling to optimise data and model-based metric identifying dynamics
2. Iterative process of using clinic, gathering data and optimising models and methods

Phase 6: 30-36 months

1. Write thesis

5 Publication Plan

· Application of lung mechanics modelling to clinical spirometric data (Phase 1)

· Development of prototype for custom spirometer (Phase 2)

· Early results of modelling on healthy subjects (Phase 3)

· Clinical verification of models in Belgium Respiratory Care Clinic (Phase 4)

· Modelling to optimise data and model-based metric identifying dynamics (All phases)

· Final clinical validation of models (Phase 4)

6 Project Risks

The risks to this project include not being able to run clinical trials and a lack of success with the development of a prototype. Trials take the most amount of collaboration between engineers and clinicians and have a high risk of taking longer to initiate than other parts of the project. Risks associated with this project are:

- Ethics approval
    - The team lead by Prof Chase and partners have extensive experience in gaining ethics approvals
- Funding for the project
    - Prof Chase has MedTech CoRE funding for this project
- Interference to access of clinical trials and analysis of data caused by the global pandemic
    - Analysis can be done off site and access to data already in the possession of the department could be made available for the purposes of this study
- Collaboration of parties with clinical access and recruitment of subjects to participate in a trial
    - There is significant prior experience with the CDHB and partners at The University of Liege (ULG) in Belgium and the Institute of Technical Medicine (ITeM) in Germany

7 Costs and Resources

The majority of the resources required are access to my department computer with appropriate software licensing, access to data from our partners in Germany and Belgium and support from my Supervisor, Prof Chase. Most resources will be covered by E6391, a grant by the MedTech CoRE and Prof Chases other grants.

Item		Cost (NZD)
Equipment		
	Custom Spirometer	$600
Other		
	Printing Costs	$300
Total		$700

8 Collaborations

- Dist Prof J. Geoffrey Chase, senior supervisor. Prof. Chase will manage the administrative and funding aspects.
- Dr Jennifer L. Knopp (nee Dickson), co-supervisor. Dr Knopp has experience in the computation and mathematical modelling as well as the clinical trial aspects of the project.
- Dr Thomas Desaive at the University of Liege, Belgium. Dr Desaive has experience in the clinical analysis of respiratory data.
- Dr Knut Möller at the Institute of Technical Medicine at Furtwangen University, Villingen-Schwenningen, Germany. Dr Möller has extensive experience in the analysis and modelling of pulmonary mechanics.

9 Ethics

To be applied as required at ULG and the CDHB and/or UC between 6-12 months.

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