CRANFIELD UNIVERSITY

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OPTIMISING OSCILLATORY POSITIVE EXPIRATORY PRESSURE DEVICES FOR EFFECTIVE AIRWAY CLEARANCE

SCHOOL OF AEROSPACE, TRANSPORT AND MANUFACTURING (SATM)

DOCTOR OF PHILOSOPHY
Academic Year: 2013 - 2016

Supervisors: Dr. Jeffrey Alcock and Prof. Ashutosh Tiwari

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This thesis is submitted in partial fulfilment of the requirements for the degree of doctor of philosophy

“We all die. The goal isn't to live forever*, the goal is to create something that will”*

Chuck Palahniuk

ABSTRACT

Oscillatory positive expiratory pressure (OPEP) devices are a form of airway clearance techniques that are wildly used in the clinical practice and well accepted by patients. Clinicians and respiratory therapists are responsible for choosing the appropriate OPEP device for their patients. In addition, they are responsible for optimising the mechanical behaviour of the device to achieve effective airway clearance results. The effectiveness of OPEP devices is critically dependent on the properties of the oscillatory pressure wave generated by these devices. However, the pressure wave parameters vary at different settings (flow rates and resistance levels combinations). Despite OPEP devices been around for several years and routinely used in clinical practice, the question remains as to "which settings are appropriate for optimum airway clearance results".

The mechanical behaviour of several OPEP devices has been investigated in previous studies. However, experimental set up variations makes a direct comparison between the results very difficult, especially for devices from different manufacturers. Also, previous attempts to inform the clinical practice on how to use OPEP devices were limited by the lack of technical performance criteria to guide optimising these devices according to patients underlying physiological dysfunction and airway clearance aims.

The aim of this research is to characterise the optimum mechanical behaviour of OPEP devices for effective airway clearance. In this research, the mechanical behaviour of OPEP devices was characterised using a validated measurement system and a systematic experiment design that takes into account the findings and limitations of previous studies. The mechanical behaviour was mathematically modelled and validated using regression analysis techniques. Desirability optimisation function was used to characterise OPEP device settings that satisfy optimum technical performance criteria. Based on these findings, the research discussed how OPEP devices could be optimised in clinical practice for different disease groups and airway clearance therapy aims.

In the field of airway clearance research, devices evaluation lies at the base of the evidence appraisal hierarchy. In this research, optimum technical performance criteria for effective airway clearance are proposed. This research offers a comprehensive characterisation of the mechanical behaviour of OPEP devices under a unified experimental setup and flow ranges commonly found in clinical practice. Also, this research provided a comprehensive characterisation of the optimum mechanical behaviour of OPEP devices for different disease groups and airway clearance therapy aims.

A possible area for future work would be to investigate the pressure wave parameters effect on airway clearance from a fluid dynamic perspective.

Keywords:

Airway clearance therapy, airway clearance by oscillation, Acapella, Aerobika, chest physiotherapy, mucus, modelling and optimisation of medical devices.

DEDICATION

To the stars that shine in my life;

***To my sisters**; "Hadeel, Areej, Lubna, Eman and Malak"*

To the best friends I have in life;

***To my brothers** "Tareq and Mostafa"*

To the man who made me believe that I can;

***To my father**; "Qassim"*

To the woman who gave me her unconditional love, prayer and support throughout my life.

***To my mother**; "Basma"*

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LIST OF ABBREVIATIONS

ACT	Airway Clearance Techniques
ANOVA	Analysis of Variance
EPP	Equal Pressure Point
FFT	Fast Fourier Transformer
FOT	Forced Oscillation Technique
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HFCC	High-Frequency Chest Compression
IOS	Impulse Oscillation System
MCC	Mucociliary Clearance
OPEP	Oscillatory Positive Expiratory Pressure
PEP	Positive Expiratory Pressure
RCBD	Randomised Complete Block Design
RSM	Response Surface Model
SD	Standard Deviation
TPGLI	Two Phase Gas Liquid Interaction
TV	Tidal Volume

1 INTRODUCTION

This chapter gives a brief background to the airway clearance techniques and the historical development in this area. It also introduces the need to optimise oscillatory airway clearance techniques generally and oscillatory positive expiratory pressure specifically. A formulation of the research problem from a systems perspective is presented. The chapter also describes the motivation for this research, as well as the aims and objectives. The research contributions to knowledge are presented. The chapter finishes with an overall view of the thesis structure.

1.1 Background

The process of respiration exposes the lungs to a variety of particulate matter, bacteria and viruses [1,2]. In healthy individuals, the respiratory system is protected against these by the continuous production of mucus that is being continuously moved up to the mouth where it can be expectorated or swallowed [3]. However, patients with respiratory system diseases (i.e. Asthma, COPD, Cystic Fibrosis) suffer from a prominent pathophysiological feature manifested by an imbalance between mucus transport, secretion or both. Such pathophysiologic problem results in mucus retention in the respiratory system, expectoration of mucus, or both [3,4]. The functional consequence of this problem on the respiratory system includes but is not limited to; an increase in the resistance of the airways, increased the risk of infection, hypoventilation of the alveoli or even a failure in the overall ventilation process. Consequently, an intervention that works effectively towards clearing the mucus from the respiratory system and compensates for the existing malfunction in the natural mucus clearance system becomes crucial and lifesaving [5].

1.2 History of Airway Clearance Techniques

Airway Clearance Techniques (ACT) are various techniques used to help clear mucus from the lungs [6]. The history of ACT goes back to 1000BC. One of the oldest documented ACT was found carved on an Assyrian clay tablet that stated:

"If the patient suffers from hissing cough, if his windpipe is full of murmurs, if he coughs, if he has coughing fits, if he has phlegm: bray together roses and mustard in purified oil,

drop it on his tongue, fill, moreover, a tube with it and blow it into his nostrils. Thereafter, he shall drink several times beer of the finest quality. Thus he will recover" [7,8].

Over the years, ACT has developed into different shapes and forms [8]. Some of these techniques are pharmacological (i.e. medications), while others are physical (i.e. chest physiotherapy). The physical airway clearance techniques can be classified further into manual and instrumental techniques [9]. Figure 1-1 gives a brief overview of the breakdown of ACT.

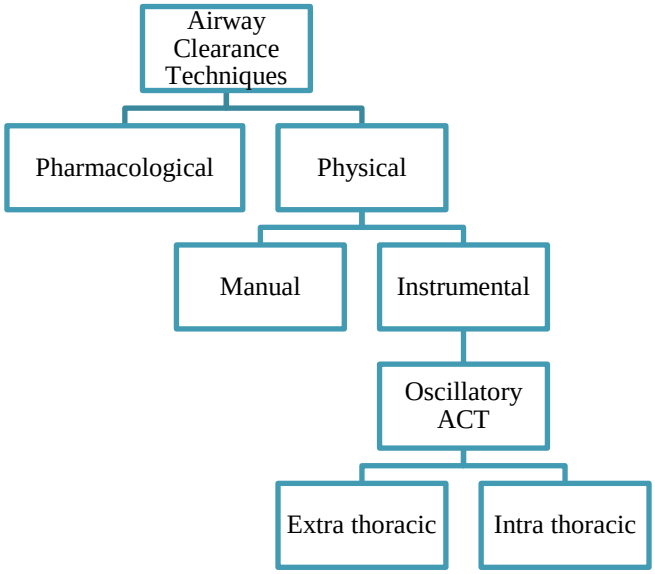


Figure 1-1 Airway clearance techniques classification

1.2.1 Brief History of Manual ACT

The history of manual ACT goes back to the 1900s when Cortlandt MacMahon started in 1915 prescribing a simple form of ACT for his soldier patients who suffered from lung injuries. He prescribed ACT included simple breathing and physical exercise. He described the improvement in patient condition after one week of starting the treatment as "remarkable" [10]. By 1919, the importance of ACT in the form of breathing and physical exercise was well recognised for patients with serious lung problems [11]. Ewart described another form of ACT in 1901. The technique was prescribed for patients with bronchiectasis and chronic bronchial infection. It involved clearing secretions by making the patients assume a certain posture for given time period and number of times per day. The technique was named as "The continues postural method" [12]. By 1953 the "the continuous postural method" technique had been developed further to be used in

combination with clapping percussion and bronchodilators as it was documented to be more effective [13]. Such combinations became the "gold ACT standard" years until newer ACT`s apeared in the 1960s [14,15].

1.2.2 Brief History of Instrumental ACT

In the 1950s and 1960s, the problem of secretion retention particularly after surgery and its impact on the success rate and survival from post operation complications were well recognised [16]. The need for a solution that improved survival rates and reduced complication after surgery was one of the major drivers behind the move towards instrumental ACT. The “formal” beginning of instrumental ACT started in the 1970s with the invention of the incentive spirometer (IS) [16]. It was thought that the IS is an effective ACT as it can be performed by the patient [17], it is reproducible, provides feedback because the patient could see actual results, and therefore goals could be set [16].

The concept of positive expiratory pressure (PEP) was first introduced in Denmark in the 1970s [18]. PEP is the pressure in the lungs above atmospheric pressure that exists during expiration [4]. The generation of the PEP encompasses having resistance to the exhalation flow [19].

1.2.3 Oscillatory ACT

The use of oscillations for airway clearance was an anecdotal discovery during a research which observed that applying pulsatile gas flow to the chest or airway increases the volume of secretion in the upper airway [21]. Recently, instrumental ACT that relies on oscillation were classified into; intrathoracic (i.e. oscillatory positive expiratory pressure) and extrathoracic (i.e. high-frequency chest compression) Figure 1-2 [22].

Figure 1-2 Expamle of high-frequency chest compression (Left) [26] and oscillatory positive expiratory pressure (Right) [80]

1.2.3.1 High-Frequency Chest Compression (HFCC)

The use of chest oscillation for airway clearance was reported in 1966 to effectively relieve respiratory airway obstruction due to retained secretions, thereby increasing vital capacity [23]. The term high-frequency chest compression (HFCC) is often used to describe an extra-thoracic, mechanical, self-administered and portable ACT instrument [24]. This instrument works by pneumatically applying air pressure oscillations to the chest [25] via a vest that surrounds the thorax [26]. A commercial HFCC system was developed in the 1980s by Hansen and Warwick in Minnesota [27]. HFCC systems can be "tuned" to pulsate at different frequencies and pressure levels [28].

1.2.3.2 Oscillatory Positive Expiratory Pressure (OPEP)

Oscillatory PEP (OPEP) is a term used to describe the application of PEP combined with airway vibrations or oscillations through the mouth [29]. The "therapy" part of OPEP is composed of two main components; the positive expiratory pressure, and the oscillations Figure 1-3 (84). The PEP element was thought to prevent the airway and alveolar from collapsing keeping them open [30]. Also, it is though that PEP would promote collateral ventilation in the peripheral airways, which in turn would allow the pressure of air to enter behind the secretions, pushing it towards the larger airways where it can be easily expelled [31]. On the other hand, it is thought that the addition of oscillation to the PEP will result in series of effects that complement the previously described PEP benefit of airway clearance. These effects include; changes in the secretions properties, airflow, shear forces, and enhanced cilia function [21].

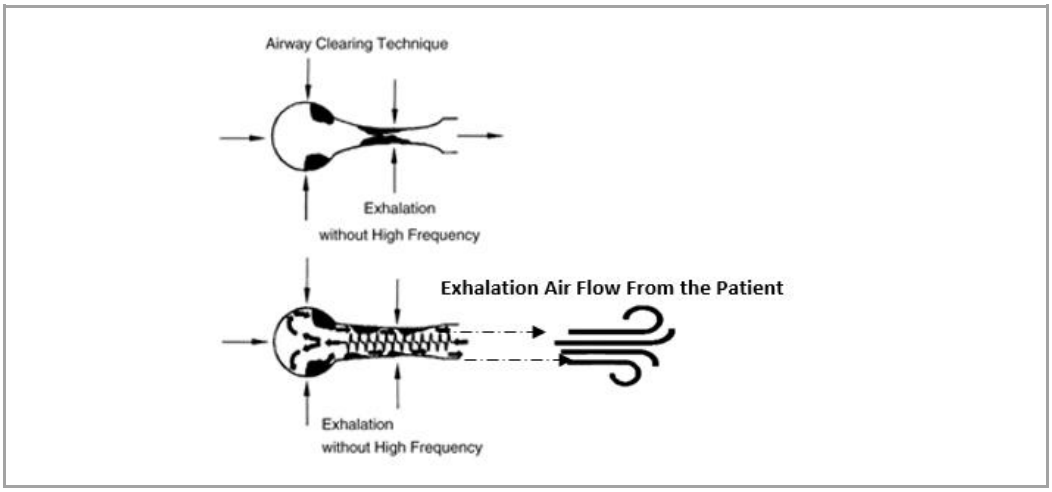


Figure 1-3 Oscillatory positive expiratory pressure therapy [30,32]

The first commercial OPEP device called “Flutter” (Figure appeared in Switzerland in the 1980s and later in the US in the 1990s [33]. Being a self-administered, easy to use form of ACT, these devices are well accepted by patients [24,34–36] and are increasingly used as an alternative to conventional chest physiotherapy [37].

Figure 1-4 Flutter device (Picture obtained from http://med.stanford.edu/cfcenter)

1.3 The Need to Optimise Oscillatory ACT

Historically, the use of ACT has often been based on “anecdotal evidence or historical practice rather than empirical evidence” [38]. Also, it is acknowledged that “there is a significant lack of high-level evidence for airway clearance techniques” [39,40]. It is also stated that “although lack of evidence does not mean lack of benefit, it is desirable to have better evidence to support this practice. Therefore, appropriately powered and methodologically sound research is desperately needed in this area” [40,41].

1.3.1 Optimising HFCC

The need to optimise HFCC systems has emerged from a mix of the experience of the HFCC inventors (Hansen and Warwick), clinician`s and patient’s feedback. There was an indication that some HFCC system settings (i.e. oscillation frequency and pressure) achieve better results than others [42].

In an attempt to find the best pulsation frequency, Hansen and Warwick devised a method for measuring, at the mouth, the induced airflow and the integrated volume displacement. This method was tested in a pilot study with HFCC compression frequencies from 5 to 25 Hz [43,44]. However, it was found that no single frequency was the best, and each frequency was sometimes the best. This study also found that best frequencies based on induced airflow were different from the frequencies based on best volume displacement [44].Nevertheless, Hansen and Warwick selected the best three frequencies for volume displacement and flow inducement and decided to test the effectiveness of these frequencies in a clinical trial on 16 cystic fibrosis patients. The trial results reported an improvement in forced vital capacity using these frequencies [45].

However, the best frequencies found in Hansen and Warwick`s results were only applicable to one HFCC system, and one form of pressure wave (square wave). Therefore, later when a new HFCC system model was introduced with more than one pressure waveform, tuning the new system became problematic [42]. As they not only found a difference in the best oscillation frequency, but they also found the best frequency to be dependent on the HFCC system model used and the form of the pressure wave [42,44].

In 2009, Yong Won Lee, conducted a PhD research, in which he analysed six HFCC systems and built a mathematical model for the respiration system with HFCC. Lee

identified the variables relevant to the HFCC systems function and mathematically modelled the HFCC machines components and the lung as one system. Then he used the mathematical model he built to predict the optimum pressure and frequency combinations that will result in the maximum flow and volume change [42].

In his research, Lee found that each HFCC system has a unique transfer of energy from the machine to the vest to the chest. Based on the results of his research, he also proposed prescribed frequencies and pressures settings in the form of a table to provide guidance on how the frequency and pressure generated by different HFCC systems could be adjusted to maximise the benefits [42]. This table is known as the Minnesota table, and it is now sporadically used around the United States [46,47] and recommended by the manufacturers of HFCC systems [46].

Nevertheless, these are not the only efforts to optimise airway clearance using HFCC systems [44,46,48,49].

1.3.2 The need for OPEP Device Optimisation

When it comes to OPEP devices, currently there is a range of commercial OPEP devices in the market. During exhalation, these devices utilise the patient exhalation flow to produce an oscillatory disruptive pressure wave [50], that works on aiding airway clearance [21]. Therefore, it is recognised that the clinical effectiveness of OPEP devices is critically dependent on the properties of the oscillatory pressure wave generated by these devices [50–56]. However, different OPEP devices utilise different mechanical apparatus to generate [30] and adjust the pressure wave [20,57]. Therefore, the generated pressure wave not only differs from one OPEP device to another but also differs across the spectrum of flow rate ranges. In addition, patients with respiratory system diseases have various degrees of flow limitation, lung volumes and lung mechanics [57].

Typically, clinicians or respiratory therapists are responsible for selecting the appropriate OPEP device for their patients [57–59]. In addition, they are also responsible for optimising the operation of the device to achieve the therapy goals [20,29,59]. As such, clinicians and respiratory therapists need to understand how certain OPEP devices will perform across the spectrum of flow ranges when prescribing the therapy [20,57]. Such knowledge will not only contribute to the ability to make an informed decision when

selecting the appropriate OPEP device but also gives the ability to optimise the use of the device to suit patient needs [57].

Nevertheless, despite that OPEP devices performance information is recognised as one of the most valuable information clinicians could rely on when choosing, prescribing and optimising OPEP devices for their patients. It is uncommon to find a detailed summary of this information in the literature [55,60]. Also, no guidelines exist to aid clinicians and respiratory therapists in choosing exhalation flow rate and resistance levels to optimise the device's operation according to the disease features of each patient and the technical capabilities of each device [57]. On top of this, manufacturers' instructions for use are vague and often lack the required specifications [54,55,61]. In a recent review, it was emphasised that despite the fact OPEP devices have been around for several years and are routinely used in clinical practice, the question remains as to "which settings is appropriate for optimum airway clearance results" [38].

1.4 Research Motivation

The research conducted by Yong Won Lee [42] to optimise HFCC systems has inspired this research. An initial review of the literature uncovered the previously described problems in optimising OPEP device use in practice. In addition, the experience of the researcher and various discussions with relevant experts have indicated that airway clearance using OPEP devices can be optimised in a similar way to the parallel area of HFCC. Smiths Medical is a company that manufactures one of the widely used OPEP devices (Acapella). The researcher has received a financial aid (tuition fees) from this company to investigate this particular problem.

The findings of this research will have the two main potential implications. Firstly, by guiding the clinical practice and allowing an informed decision to be made when prescribing and optimising OPEP devices for patients.

Secondly, effective use of OPEP devices has been linked to a reduction in re-hospitalisation incidence caused by exacerbation [62]. In addition to a reduction in the overall length of hospital stay for patients with respiratory system diseases (i.e. COPD) [63]. Hence, the findings of this research have the potential to improve the overall clinical

outcome for patients with airway clearance problems, which have many implications for health care system (i.e. cost reductions).

1.5 Problem Formulation

1.5.1 OPEP Devices as a System

A system can be defined as a set of elements interconnected by structure and function. Inputs and outputs are two concepts related to the system structure [64]. System inputs are the elements that enter the system for processing, while outputs are the outcome of procession [65]. The goal of a system is to transform inputs into outputs that correspond to a pre-set goal(s). The function of a system refers to the transfer or transformation of operating inputs into functional outputs. The system function is borne by the system structure. [66]. The behaviour of a system is the manner in which the whole or part of a system acts and reacts to perform its function [66]. Systems can be classified based on their functional behaviour into; steady and dynamic. A steady system is a system with stationery inputs and outputs. A dynamic system is a system with inputs and outputs varying over time. The relation between inputs and outputs of a dynamic system can often be expressed mathematically [66].

OPEP devices are a form of a mechanical system that works by taking exhalation flow and a pre-set resistance to the flow as input and produce a disruptive pressure wave to that flow as an output [50]. Both the inputs and outputs to such a system vary over time. Therefore OPEP devices can be thought of as a dynamic mechanical system with a pre-set overall goal of aiding airway clearance [61,67–69].

1.5.2 Performance

The degree of correspondence between a system outputs to pre-set goals represents the performance of that system [64]. However, since performance can have different meanings in different contexts, it is important to define what it means in the context of a medical device.

In a document titled “medical device regulations; global overview and guiding principles”, the World Health Organisation (WHO) gave a harmonised definition for different concepts and what they mean in the context of medical devices. According to

the WHO, when talking about medical devices, the word performance refers to two things; 1) technical performance and 2) effectiveness. Any medical device has been designed to serve a purpose. A medical device is "clinically effective when it produces the effect intended by the manufacturer relative to the medical condition". Therefore, "Clinical effectiveness is a good indicator of device performance". However, "performance may include technical functions in addition to clinical effectiveness" [70].

One of the main knowledge shortages surrounding OPEP devices is the lack of understanding of the technical capabilities of these devices and how to adjust these according to the disease features of each patient [54,55,61]. In the systems contexts, technical performance of a system is defined as a measured quantity that can be compared to the requirement [71]. Therefore, technical performance measure can be defined as; a measure of system output attributes to determine how well the system or system element is satisfying specified requirements [72].

1.5.3 Optimality

Optimality is the study of superlatives. In applied sciences, optimality is used to decide "how we should do something out of all the possible ways in which we could do it". In this context, the emphasis is on design or analysis. Optimality problems are approached in applied sciences by expressing a system behaviour as a function of the system elements [73].

The optimality problem that this research is attempting to solve is to "characterising the appropriate settings for producing pressure wave parameters that satisfy optimum technical performance requirements."

1.5.4 Problem Formulation Summary

OPEP devices are a mechanical system designed for the purpose of aiding airway clearance. This system has a set of inputs that get transformed into outputs. In this research, the set of inputs to OPEP devices will be referred to as settings. The set of outputs from these devices will be referred to as pressure wave parameters. The measured output from OPEP devices will be referred to as technical performance. The manner in which OPEP devices as a whole system reacts to perform its function will be referred to as mechanical behaviour.

The problem that this research is trying to address is; characterising the appropriate settings for producing pressure wave parameters that will satisfy optimum technical performance requirements. Figure 1-5 shows a summary of the research problem from a system levels perspective.

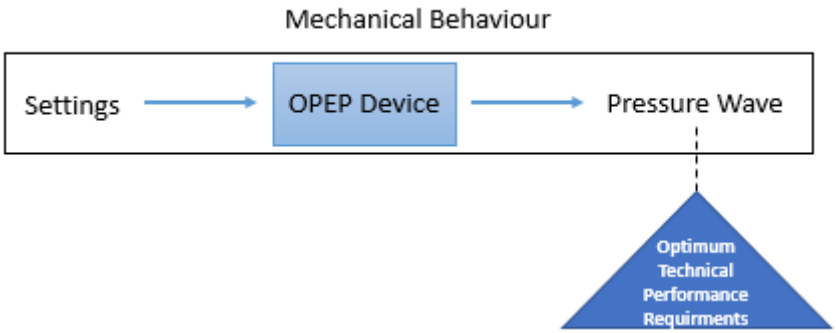


Figure 1-5 Problem formulation summary

1.5.5 Overall Approach to the Research

The optimisation attempt of HFCC systems by Yong Lee [42] started by identifying and understanding the components of the system he was studying. He then modelled these components mathematically and used this model to address his research aim.

This research will follow a similar approach to address the research problem. This research will start by identifying the settings and the pressure wave parameters that governs the mechanical behaviour of OPEP devices. In addition, optimal technical performance requirements criteria for effective airway clearance will be established from the literature. The mechanical behaviour of OPEP devices will be mathematically expressed, using data collected through a valid measurement system. An Optimisation technique will be applied to characterise the OPEP devices setting that satisfies the optimal technical performance criteria. The optimisation results will be validated with clinicians and respiratory therapist. The methodology chapter will expand on the rationale behind the choice of this approach.

1.6 Research Question and Aim

The starting point for this research was the gap question asked in [38] review "Although PEP (with and without oscillation) oscillation has been used for several years, question remains; which settings are appropriate for optimum results?" [38].

Based on this question, the aim of this research is "to characterise the optimum mechanical behaviour of OPEP devices for effective airway clearance".

1.7 Research Objectives

Based on the previously described overall approach in section 1.5.5, the following objectives have been derived to address the aim:

1- To review the current "state of the art" in the mechanical behaviour of OPEP devices

2- To identify the optimum technical performance requirements for effective airway clearance by oscillation

3- To develop and validate a system for measuring the mechanical behaviour of OPEP devices.

4- To model the mechanical behaviour of OPEP devices

5- To characterise and validate the optimum mechanical behaviour of OPEP devices for effective airway clearance

1.8 Research Contributions

This section identifies the main research contributions of this thesis based on the research gaps that have been identified in the next literature review chapter (Section 2.5).

There are several novel aspects of this research through which contributions to knowledge is demonstrated. These aspects are as following:

1- Lack of optimum technical performance criteria has been identified as a gap and a limitation to optimising OPEP devices mechanical behaviour. Therefore, the first contribution to knowledge made by this research is the proposal of technical

performance criteria to guide the optimisation of OPEP devices, according to different diseases and airway clearance therapy aims.

2- Information describing and characterising the mechanical behaviour of OPEP devices is one of the most valuable information for clinicians and respiratory therapist. The second contribution to knowledge of this research is the comprehensive characterisation of the mechanical behaviour of five OPEP devices under a unified experimental setup and flow ranges commonly found in clinical practice.

3- Optimum OPEP devices settings for effective airway clearance has been identified as a knowledge gap. Therefore, the third contribution to knowledge of this research is filling this knowledge gap by characterising the optimum mechanical behaviour of OPEP devices for effective airway clearance.

1.9 Thesis Structure

The structure of this thesis has seven major building blocks. These are; introduction, literature review, research design, measurement system validation, model building, optimisation, discussion and conclusion. Figure 1-6 below show the structure of this thesis

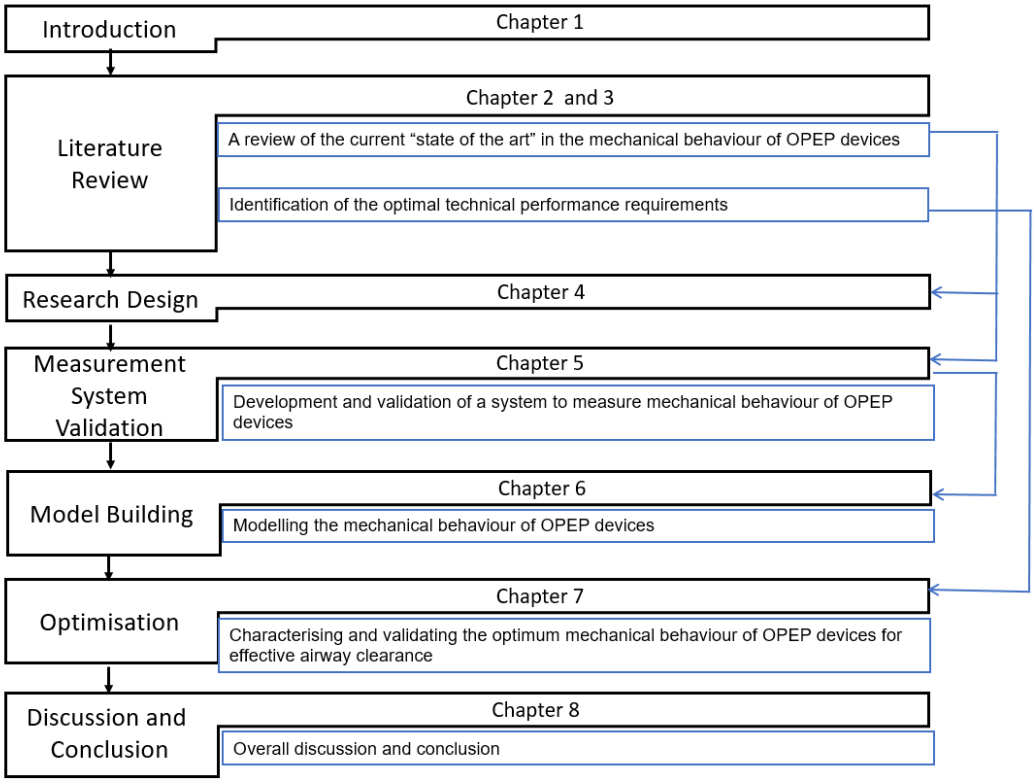


Figure 1-6 Thesis structure

Chapter 2: A review of the current "state of the art" in the mechanical behaviour of OPEP devices. This chapter addresses the first objective of this research. The chapter will give a summary and a discussion of previous studies that investigated the mechanical behaviour of OPEP devices. The chapter will identify the variables relevant to the mechanical behaviours of these devices and the considerations for designing an experiment to investigate the mechanical behaviour of OPEP devices. The chapter will also discuss previous attempts to optimise the mechanical behaviour of OPEP devices mechanical behaviour.

Chapter 3: Identification of the optimal technical performance requirements. This chapter addresses the second objective of this research. This chapter will review previous studies to identify and describe the role of each of the pressure wave parameters in airway clearance from a physiological perspective. In addition, the chapter will identify each of the pressure wave parameters optimum values for effective airway clearance.

Chapter 4: Research design. This chapter will describe the overall methodology and methods used to address the aim of this research. The chapter will also describe the

philosophical and theoretical perspective adopted in this research, in addition to the research approach strategy and choice. The chapter will also define the methods followed to collect, process and analyse the data used to address the aim of this research.

Chapter 5: Development and validation of a system to measure mechanical behaviour of OPEP devices. This chapter addresses the third aim of this research. This chapter will present the validation results of the measurement system developed to measure OPEP devices mechanical behaviour. In addition, the pressure wave parameters variability in a repeated experiment will be presented in this chapter.

Chapter 6: Modelling the mechanical behaviour of OPEP devices. This chapter addresses the fourth aim of this research. This chapter presents the mechanical behaviour results for the OPEP devices investigated in this research. In addition, regression models built for each of the pressure wave parameters for OPEP devices will be described in this chapter. Also, the validation results for the built models will be presented.

Chapter 7: Characterising and validating the optimum mechanical behaviour of OPEP devices for effective airway clearance. This chapter addresses the fifth objective of this research. The optimum mechanical behaviour results will be presented in this chapter. The chapter will also discuss the implication of the results for clinical practice. Validation of the findings with clinician and respiratory therapist will also be presented and discussed in this chapter.

Chapter 8: Overall discussion and conclusion

This chapter will present an overall discussion of how the research aim and objectives were met and the contributions to knowledge. It will also present the limitations encountered and suggestion for future work. The chapter will conclude with the overall research conclusions.

1.10 Chapter Summary

For patients with respiratory system diseases, mucus retention has serious pathophysiological consequences that can be life-threating. Airway clearance techniques are various methods used to aid mucus clearance from the lungs. These methods have been developed over the years through observations and trial and error in practice.

Oscillatory positive expiratory pressure devices are an instrumental airway clearance technique that combines the application of positive expiratory pressure with airway oscillations through the mouth. The oscillatory pressure wave is thought to prevent the airway and alveoli from collapsing and promote collateral ventilation, allowing the pressure of air to enter behind the secretions, pushing them towards the larger airways. In addition, the oscillations are thought to change the mucus rheological properties, providing the shear forces required to expel the mucus as well as enhance the respiratory system cilia function. The effectiveness of OPEP devices is dependent on the characteristics of the oscillatory pressure wave generated by these devices.

Today, a range of commercial OPEP devices are available. The pressure wave generated varies from one device to another. Clinicians or respiratory therapists are responsible for prescribing and optimism the operation of the device for effective airway clearance. However, despite the fact that information describing the mechanical behaviour of OPEP devices is valuable for such tasks, guidelines exist to aid clinicians and respiratory therapists in choosing exhalation flow rate and resistance level to optimise the device's operation according to the features of each patient and the technical capabilities of each device. Despite OPEP devices have been around for several years and have been routinely used in clinical practice, the question remains as to "which settings are appropriate for optimum airway clearance.

From a systems perspective, OPEP devices transform an input into an output. In this research, the input in OPEP devices will be referred to as settings. The set of outputs from these devices will be referred to as pressure wave parameters. The measured output from OPEP devices will be referred to as technical performance. The manner in which OPEP devices react as a system will be referred to as mechanical behaviour.

The aim of this research is to characterise the optimum mechanical behaviour of OPEP devices for effective airway clearance. The research objectives to address this aim have been described in this chapter. The novelty and contribution of this research are also described here. Lastly, an overall thesis structure is provided.

2 A REVIEW OF THE CURRENT "STATE OF THE ART" IN THE MECHANICAL BEHAVIOUR OF OPEP DEVICES

This chapter addresses the first objective of this research (to review the current "state of the art" in the mechanical behaviour of OPEP devices). This chapter will review previous studies that have investigated the mechanical behaviour of OPEP devices. It will describe the experimental methods used by previous studies and identify the variables that influence the mechanical behaviour of OPEP devices. It will also summarise and discuss the main findings from previous studies. In addition, previous attempts to optimise the mechanical behaviour of OPEP devices will be discussed. Identified knowledge gaps will be highlighted at the end of this chapter.

2.1 Introduction

OPEP devices are well accepted by patients as they allow independent, simple and unsupervised airway clearance therapy [24,34–36]. Therefore, such devices are increasingly used as an alternative to manual physiotherapy [37], and a variety of these devices are now commercially available to choose from (i.e. Flutter, Acapella, Aerobika, RC-Cornet,Shaker) [61,74].

To use an OPEP device, a patient needs to exhale into the device after taking a deep breath. The exhalation needs to be steady and to last approximately 4 seconds. Typically, this process is repeated for around 30 breaths [57,75]. As the patient is exhaling, OPEP devices produce a disruptive pressure wave to the exhalation flow (Figure 2-1) [50]. This short and successive disruption to the air flow is produced by an apparatus of a resistance element embedded in the devices [60] and a valve that alternates between the open and closed positions [55]. The alternating valve arrangement employed varies from one commercial OPEP device to another [30]. The level of resistance to the exhalation flow can be adjusted using a resistance level dial or by changing the device position [34,61]. The flow and pressure level can be monitored by an attachment added to these devices [29]

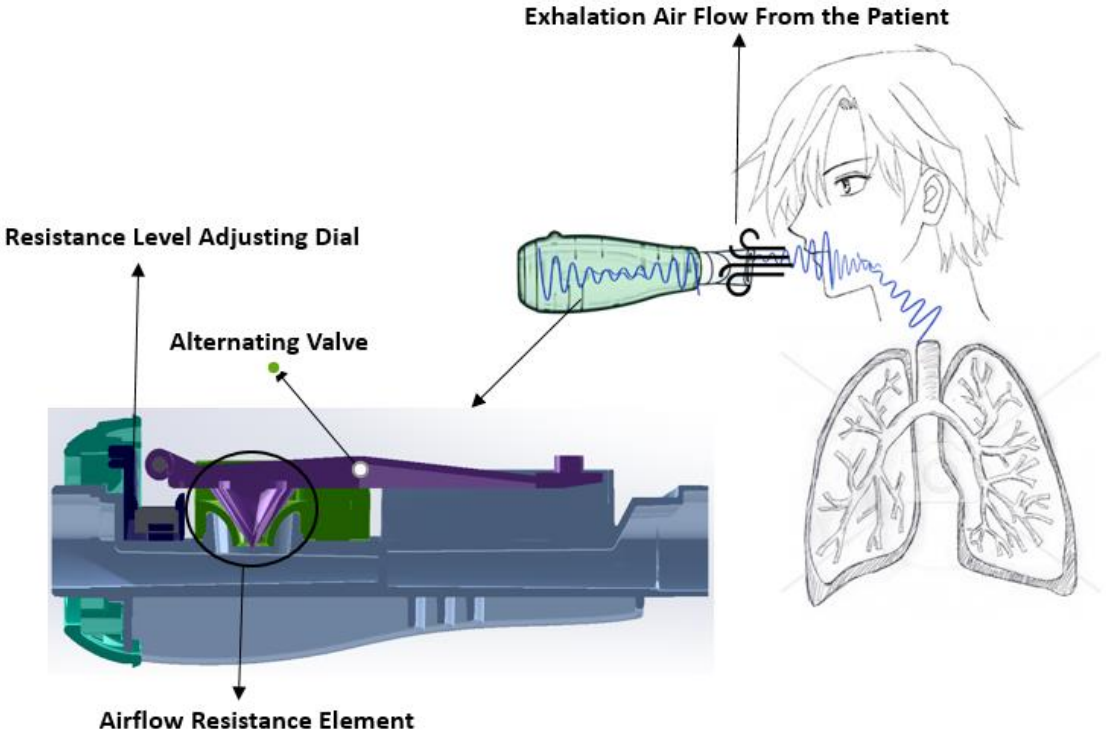


Figure 2-1 Oscillatory pressure wave produced by OPEP devices and the internal components of OPEP device

The pressure wave generated by OPEP devices is crucial for achieving the desired airway clearance effect [50–56]. It is noted that the disruptive pressure wave generated by different OPEP devices varies across the spectrum of flow rates [20,57]. In addition, different OPEP devices employ different apparatuses for adjusting the resistance level to the exhalation flow and consequently changing the characteristics of the disruptive pressure wave produced [34,61]. On top of that, patients with respiratory system diseases have varying degrees of flow limitation [57].

In the field of airway clearance research, studies evaluating mechanical devices behaviour of devices is a form of original research. Along with clinical trials, devices evaluations, lays at the base of evidence appraisal hierarchy in this field (Figure 2-2) [76]. Information that describes the mechanical behaviour of OPEP devices is valuable information for clinicians and respiratory therapist when choosing, prescribing and optimising OPEP devices for their patients [57]. Several studies have described the mechanical behaviour

of different OPEP devices [34,50,55,60]. However, to our knowledge, there is no paper that has reviewed, summarised and compared the evidence from these studies.

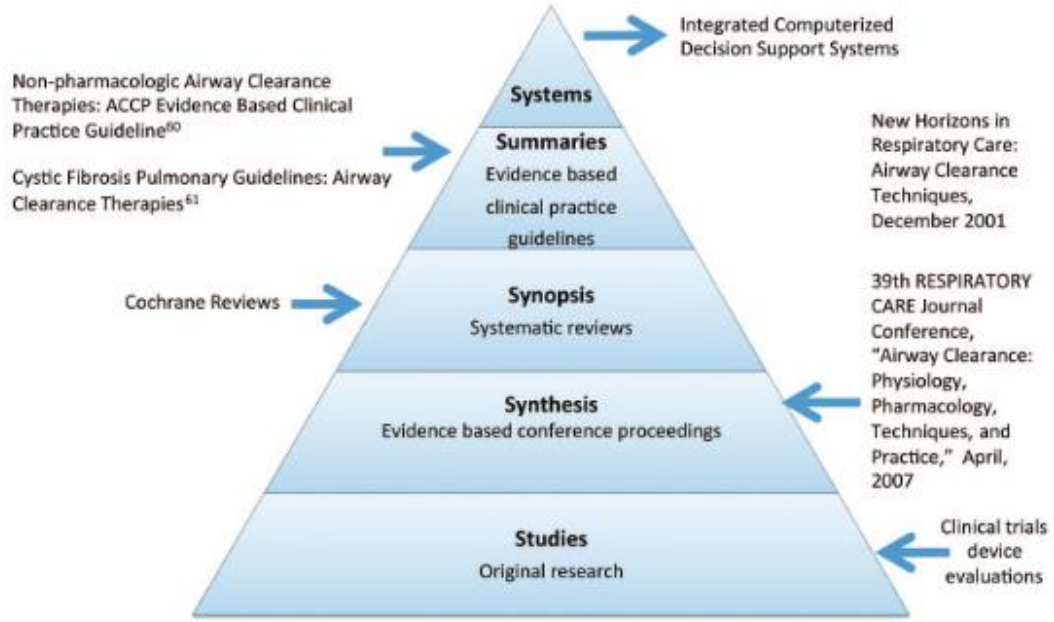


Figure 2-2 Evidence appraisal hierarchy in the field of airway clearance [76]

This review has a twofold aim; first is to review the results from studies that evaluated mechanical behaviour of commercial OPEP devices; second is to identify the settings and pressure wave parameters that govern OPEP device mechanical behaviour.

2.2 Method in this chapter

2.2.1 Search Strategy

The databases PubMed and Scopus were used as part of the search strategy to identify relevant publications within the topic of interest. The keywords used were associated with the topic of this review. During the search for appropriate articles, these keywords were refined. The following is the final list of keywords used in the search process: ‘mucus vibration’, ‘mucus oscillation’, ‘airway oscillation’, ‘oscillation positive expiratory pressure’, ‘OPEP’, ‘high frequency vibration’, ‘mucus clearance by oscillation’, ‘airway clearance techniques’, ‘airway clearance by oscillation’, ‘OPEP mechanical performance’

‘Acapella’, ‘flutter’, ‘shaker’, ‘Aerobika’, ‘RC cornet’, ‘vibration positive expiratory pressure devices’ and ‘VPEP’.

The search time was set to be between “1965 to 2016”. Although the search was limited to articles in English, articles in other languages that were frequently cited in the literature were also included if they were found to be relevant to the topic of the study and pass the selection criteria.

The selection and refining process of the results was done in two stages. In the first stage, articles were screened by title for their relevance so that an initial list of possible relevant articles was compiled. In the second stage, the initial list was screened by abstract. Selection criteria were applied during the screening process. Also, articles in the reference list of the selected articles were retrieved if they were found to be relevant to the topic of the study and passed the selection criteria.

Data from each article was populated into a table for further analysis. This data included: year of the study, method, experimental setup, experiment variables, main findings, observations and conclusion.

2.2.2 Selection Criteria

The selection criteria that were devised based on the aim of this review is shown below:

1-Only articles published between 1965 and 2016 were included in the review.

2- Only articles that studied the mechanical behaviour of any of OPEP devices were included.

3-Articles that investigated the clinical treatment outcome of using OPEP devices were excluded.

4- Articles with only abstract available were not included

5-Studies that investigated non-commercial OPEP devices were not included in this review.

2.2.3 Results Presentation

The results section will be split into three main sections; results overview, experimental setup and OPEP devices mechanical behaviour. The results overview section gives a brief summary of the mechanical behaviour reported in different studies. The experimental set-up section will give an overview of the experimental setup employed in previous studies to investigate the mechanical behaviour of OPEP devices. The OPEP devices mechanical behaviour section will present the mechanical behaviour for different commercial OPEP devices reported by previous studies.

The results of this review will be discussed in two main sections; experimental setup, and the pressure wave parameters. A final section will shed light on the previous attempt to optimise mechanical behaviour of OPEP devices.

2.3 Results

2.3.1 Results overview

The literature search has identified nine studies that investigated the mechanical behaviour of different commercial OPEP devices. In all nine studies, the mechanical behaviour was investigated under simulated laboratory conditions. The mechanical behaviour was investigated by manipulating two setting variables; exhalation flow and resistance level. These variables were thought to be responsible for the change in pressure wave parameters generated by OPEP devices. In addition, three pressure wave parameters were observed in the majority of the nine studies. These are; oscillation frequency, the value of the PEP and oscillation amplitude. In total three commercial OPEP devices were evaluated in previous studies; Flutter, Acapella Green, Acapella Blue, Acapella Choice and Shaker. Table 2-1 summarises the results from the nine studies.

It is worth noting that , in one study, [55] posted mechanical behaviour results for Acapella Green. However, the OPEP device picture posted in the article and the published data suggest that the results are for Acapella Choice. Hence, it is going to be assumed in this research that data posted in [55] paper is for Acapella Choice.

Table 2-1 Summary of previous studies results

		Settings		Pressure Wave Parameters		
Reference	**Device**	**Flow (L/min)**	**Resistance Levels**	**Frequency (Hz)**	**PEP (cmH2O)**	**Amplitude (cmH2O)**
[34]	Flutter	5,10,15,20,26,32	Low (-30^o) Intermediate (0^o) High ($+30^o$)	Overall Range 6.38-23 Low 6.38 (8.3–6) Intermediate 18.11 (15–23) High 18.45 (16–19)	Overall Range 5-19 Low 11.18 (5–17.7) Intermediate 14.53 (11.3–18.2) High 16.86 (14.3–19)	Overall Range 5.2-16.5 Low 10.48 (5.2–16.5) Intermediate 7.26 (2.7–10.6) High 7.25 (3.3–12)
[50]	Flutter	5,10,15,20,25,30	Low (0^o) Intermediate ($+20^o$) High ($+40^o$)	Overall Range 15-29	Overall Range 5-19	Overall Range 2-10
[69]	Flutter	30-350	Low (-30^o) Intermediate (0^o) High ($+30^o$)	Overall Range 22.8-27.25	Overall Range 5-150	Not reported
[54]	Flutter	12,24,36,48,60,72,84,96,108,120	+30°,+15°,0°,-15°,–30°	Overall Range 6-31	Overall Range ~3-53	Not reported
[77]	Flutter	12, 15,18,20,24, 27,30, 33,36, 39, 42,45,48	+30°,+20°,+10°,0°, -10°,-20°, –30°	Overall Range 2-22	Overall Range 4-20	Overall Range 1-8
[78]	Flutter	48,60,72,84,96,108	+40°,+30°,+20°,°,+10°,0°,-10°,–20°,–30°, –40°	Overall Range 0-30.9	Overall Range 3-32.9	Not Reported

		Settings		Pressure Wave Parameters		
Reference	**Device**	**Flow (L/min)**	**Resistance Levels**	**Frequency (Hz)**	**PEP (cmH2O)**	**Amplitude (cmH2O)**
[50]	Acapella Blue	5,10,15	Low (1) Intermediate (3) High (5)	Overall Range 8-25	Overall Range 3-24	Overall Range 3-11
[60]	Acapella Blue	3,6,9,12,15	1,2,3,4,5	Overall Range 0-23	Overall Range 1.2-13.5	Overall Range 0.2-2.8
[61]	Acapella Blue	6, 12, 20, 30, 40, and 50	1,2,3,4,5	Overall Range ~0-23	Overall Range 1-120	Overall Range ~0-5.2
[50]	Acapella Green	20,25,30	1, 3, 5	Overall Range 13-30	Overall Range 6-21	Overall Range 1-12
[61]	Acapella Green	12,15,18,21,24,27,30,33,36,39,42,45,48	1,2,3,4,5	Overall Range ~6-24	Overall Range 2-27	Overall Range ~0-8
[34]	Acapella Blue	5,10,15	Low(1), Intermediate (3), High (5)	Overall Range 8-26 Low 11.33 (8–17) Intermediate 11.4 (14.7–11) High 20.15 (19.3–26)	Overall Range 4.8-26.6 Low 10.31 (4.8–15.6) Intermediate 13.48 (6.5–20.6) High 19.41 (14.9–26.6)	Overall Range 3.9-12.6 Low 6.48 (3.9–6.1) Intermediate 9.48 (6.7–12.6) High 5.15 (0.2–0.17)
	Acapella Green	20,26,32	Low(1), Intermediate (3), High (5)			
[61]	Acapella Choice	6, 12, 20, 30, 40, and 50	1,2,3,4,5	Overall Range ~9-25	Overall Range 2-30	Overall Range ~0-6
[55]	Acapella Choice	12,15,18,21,24,27,30,33,36,39,42,45,48	1,2,3,4,5	Overall Range 8-21	Overall Range 3-23	Overall Range 4-9
[34]	Shaker	5,10,15,20,26,32	Low (-30^o)	Overall Range	Overall Range	Overall Range

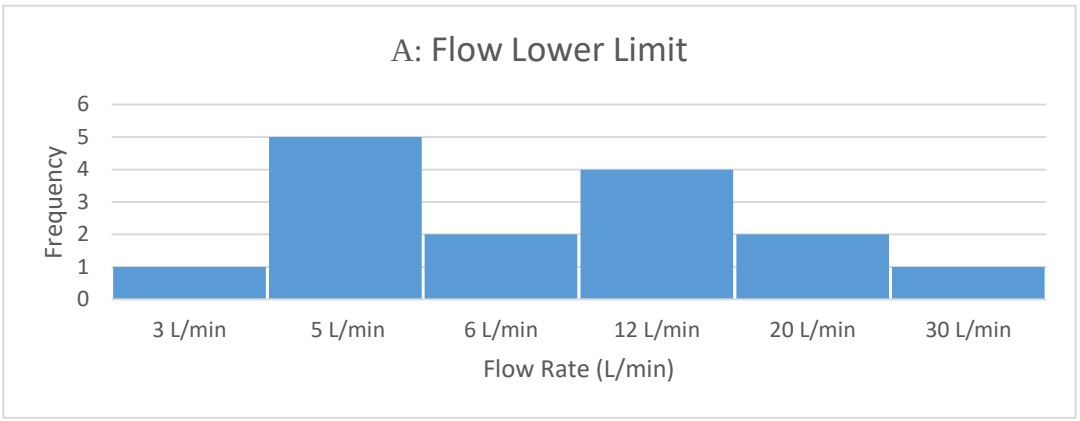
		Settings		Pressure Wave Parameters		
Reference	**Device**	**Flow (L/min)**	**Resistance Levels**	**Frequency (Hz)**	**PEP (cmH2O)**	**Amplitude (cmH2O)**
			Intermediate (0^o) High ($+30^o$)	7.7-20 Low 6.85 (7.7–9.7) Intermediate 17.73 (17.3–20) High 18.26 (16.3–19.3)	5-19.7 Low 11.48 (5–16.4) Intermediate 14.9 (11.2–16.9) High 16.88 (13.7–19.7)	4.2-14.5 Low 10.36 (4.2–14.5) Intermediate 7.4 (2.4–10.5) High 6.41 (2.7–9.6)

2.3.2 Experimental Setup

2.3.2.1 Exhalation Flow Levels

In all nine studies, the exhalation flow was simulated in experimental laboratory conditions as a constant flow mode.

In terms of the exhalation flow range, Figure 2-3 shows the distribution of the exhalation flow range (lower limit and upper limit) under which different OPEP devices were investigated in previous studies. The majority of previous studies (53%) selected a lower flow limit of 6 L/min or less. The majority (50%) of previous studies also selected an upper flow limit 32 L/min flow or less.



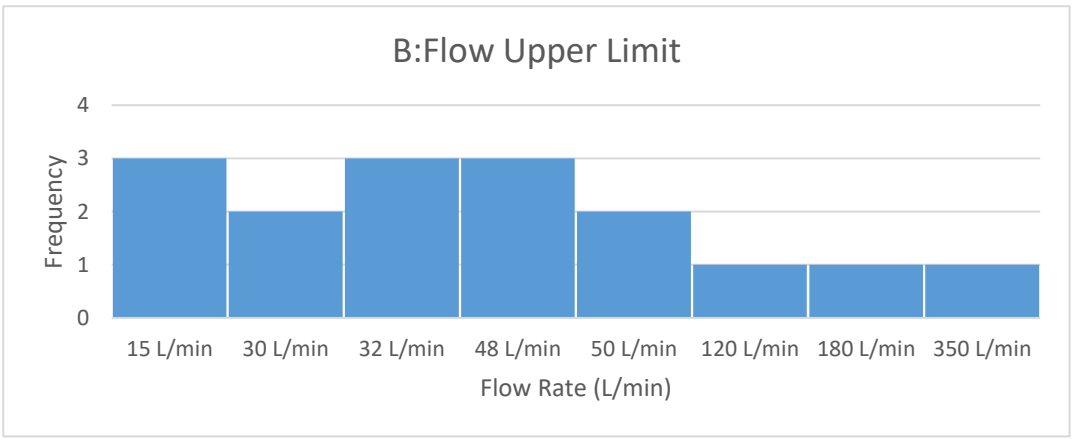


Figure 2-3 Experimental setup: Exhalation flow range used in previous studies. A: Flow lower limit. B Flow upper limit

2.3.2.2 Resistance Levels

In terms of resistance levels, Figure 2-4 shows the number of resistance levels under which the mechanical behaviour of different OPEP devices was investigated. As can be seen from the figure, 50% of previous studies have only covered three resistance levels when investigating mechanical behaviour of OPEP devices. It is worth mentioning that some OPEP devices have a defined number of resistance level (i.e. Acapella resistance dial has five levels), while others do not (i.e. flutter resistance level is adjustable by adjusting the angle of the device.).

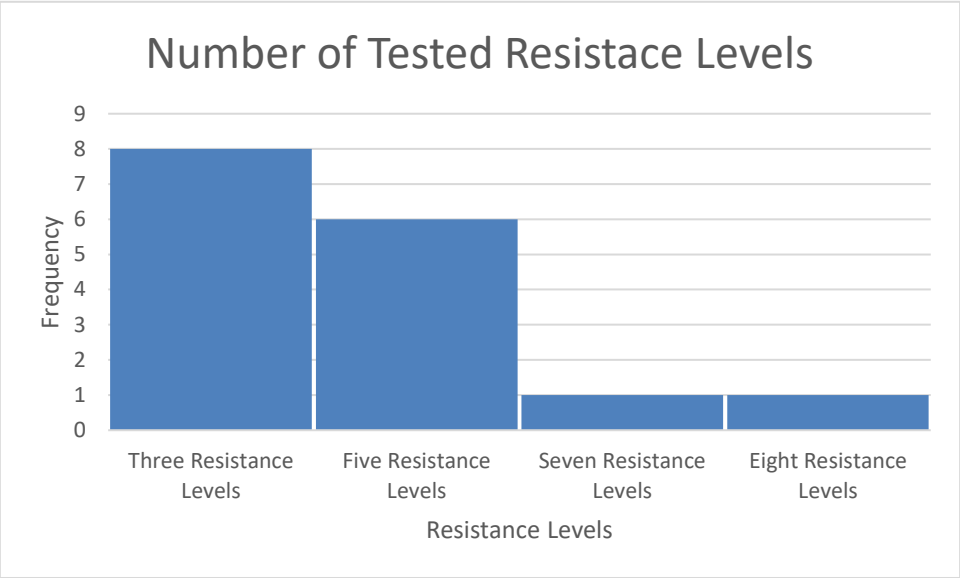


Figure 2-4 Experimental setup: Resistance levels tested in previous studies

2.3.2.3 Equipment

In terms of the equipment used to investigate mechanical behaviour OPEP devices, previous studies have used different equipment for this purpose. These can be split into two groups, specialised and non-specialised equipment (Figure 2-5). Specialised equipment includes tool that are either commercially available or designed by the researcher to collect data about the variables of interest. On the other hand, the none-specialised equipment are tools that is indented for a purpose other than data collection but was adapted and used for data collation by the researcher.

In terms of the specialised equipment, seven of the previous studies, (78%) have used a specialised system to investigate the mechanical performance of various OPEP devices.

Such systems include a method for sensing pressure, software to capture the data recorded by the sensor and a computer to analyse the data.

On the other hand, two of the previous studies (22%) have used non-specialised tools. In one of these studies, data was collected using an intensive care unit ventilator. The graph function on the ventilator was used to record the data. In the other study, data was collected using a system designed for blood pressure measurement.

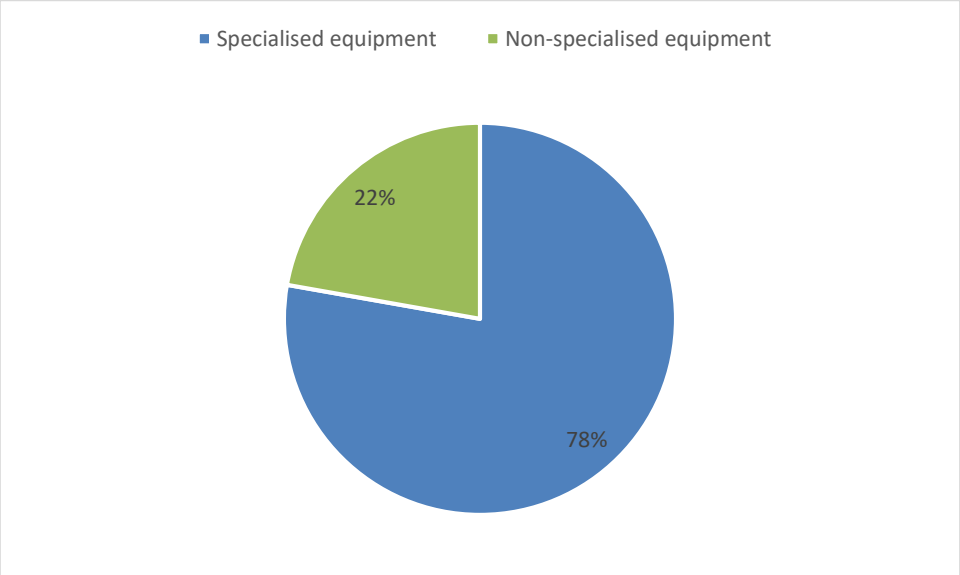


Figure 2-5 Experimental setup: Pressure measuring equipment used in previous studies

2.3.3 OPEP Device Mechanical Behaviour

In total three commercial OPEP devices were evaluated in previous studies; Flutter, Acapella and Shaker. The following sections will summarise the results from previous studies that evaluated the mechanical behaviour of these device.

2.3.3.1 Flutter

Flutter is a small pipe-like OPEP device that is made by Axcan Scandipharm, Inc. Flutter is composed of "a mouthpiece, a cone, a stainless steel ball and a removable lid. During exhalation, the airflow causes the steel ball inside the device to vibrate inside the cone generating the OPEP therapy [69]. The mechanical behaviour of this device was evaluated by six studies in the literature between the years of 2002 and 2008.

Brooks et al. (2002) [79]

In 2002, Brooks and her colleagues evaluated the mechanical behaviour of Flutter under a flow range (48 to 108 L/min) and nine resistance levels (+40°,+30°,+20°,°,+10°,0°,-10°,–20°,–30°, –40°). The results of this study reported that Flutter is capable of generating an overall oscillation frequency range between 0 to 31 Hz and PEP range between 3 and 33 cmH2O. The oscillation amplitude value was not observed in this study.

In terms of the statistical significance of the settings effect on the pressure wave parameter, the authors found a significant correlation between flow and both the PEP and frequency at all resistance levels. The author noted that at positive resistance levels the oscillation frequency was significantly different from those at negative resistance levels. In addition, it was reported that a significant reduction in the PEP occurs at negative resistance levels in comparison to an increase in the PEP value which occurs at large airflow and positive resistant levels [79].

In terms of recommendation to the clinical practice, the study noted that the Flutter device is capable of generating oscillation frequencies within the natural resonance frequency of the chest (12 to 15 Hz). In addition, the author has emphasised that when using Flutter devices, clinicians and respiratory therapist need to be aware that this device is capable of generating pressure levels exceeding 20 cmH2O at relatively low flow rates. Thus, it is important to give clear instructions to the patient regarding the correct exhalation maneuvere to ensure that excessive and potentially harmful expiratory pressures levels are not generated. In addition, clinicians need to understand that positive resistance levels results in higher PEP values. Therefore, for patients with susceptible airways where concern about the potentially harmful effects of a large positive pressure is present. The author suggested that clinicians should caution those patients from using positive resistance levels or high flows as these may result in pressure values greater than 20 cm of H2O.

Volsko et al. 2003 [50]

In 2003, Volsko and her colleagues investigated and compared the mechanical behaviour of three OPEP devices (Flutter, Acapella Green and Acapella Blue). In this study, flutter was investigated under the flow range of 5-30 L/min and three resistance levels of (0°, + 20°, +40°). The authors reported that under these conditions, Flutter was found to be capable of generating an oscillation frequency range between 15 Hz and 29 Hz, a PEP range of 5 to 19cmH2O and an oscillation amplitude of 2-10cmH2O.

In terms of the settings effect on the pressure wave parameters, this study reported that for all tested devices, the effect of flow on the frequency was only significant at certain resistance levels. [50]. In term of settings effect on the PEP value, flow was found to have a significantly statistical effect on the PEP value. The author also reported a proportional relation between the flow and PEP values, however the increase in the PEP value as flow increases was described to be small.

In terms of recommendations for clinical practice, the author reported that although both the Flutter and Acapella devices produced a similar pressure wave under flow range of 10-25 L/min, at flow rate of 5-30 L/min the Flutter device was found to generate a less stable pressure wave with more variation in the amplitude and the frequency than the Acapella device.

Lima et al. (2005) [69]

In 2005, Lima and his colleagues conducted another study to evaluate the mechanical behaviour of the Flutter device. The authors started their investigation by formulating a mathematical model that describes the oscillatory motion of the sphere in the device. In addition, the authors devised an experimental setup to study the mechanical behaviour of the device under flow ranges of 30-350 L/min and three resistance levels (+30°, 0°,–30°). Under these conditions, the authors reported that Flutter is capable of producing oscillation frequency range of 22.8-27.25 Hz and PEP ranging between 5 and 150cmH2O. The amplitude data was not reported in this study.

In terms of the settings effect on the pressure wave parameters, the author reported that oscillation frequency was found to be dependent on the air flow rate. In addition, the oscillation frequency was found to increase with the resistance levels increase. However, the author reported that oscillation frequency has an inverse relationship with flow rate.

In terms of recommendations for clinical practice, the author reported that in order to generate oscillation frequencies that match the natural respiratory system resonance frequency (5-11 Hz), exhalation to this device should be limited to 100 L/min as exceeding this flow rate would result in oscillation frequencies outside the required range. In addition, exhalation into this device in its horizontal orientation could result in PEP as high as 75cmH2O which could be harmful to the patient. In order to avoid these harmful PEP levels, the author recommended that exhalation to the device should be limited to 120 L/min.

Alves CE et al. (2008) [60]

In 2008, [60] evaluated the mechanical behaviour of Flutter under flow ranges of 12-48 L/min and seven resistance levels (+30°,+20°,+10°,0°,-10°,-20°, –30°). The mechanical behaviour of Flutter was modelled using regression analysis. The author posted a plot of the response surface for each of the three pressure wave parameters. The pressure wave parameters values reported in this study for Flutter were: 2-22 Hz for the frequency, 4-20 cmH2O for the PEP and 1-8 cmH2O for the amplitude.

In terms of the settings effect on the pressure wave parameters, the author reported that the oscillation frequency value generated by Flutter is influenced by both resistance level and the exhalation flow. However, exhalation flow had a greater influence on the oscillation frequency value than flow. The author also reported that higher oscillation frequencies are found to be generated at positive resistance levels. In terms of settings effect on the PEP value, it was reported that PEP was found to be more sensitive to change in resistance level than the flow change. Similarly, the change in resistance level was found to have a higher influence on the oscillation amplitude than the change in flow. In addition, the oscillation amplitudes were found to be different at positive resistance level than the values obtained at negative resistance levels.

In terms of recommendations for clinical practice, the author devised a piece of computer software based on the developed regression mechanical behaviour equations. The author stated that this programme has a high potential for clinical use, as it can provide respiratory therapist and clinicians with the oscillation frequency, mean pressure and amplitude values generated by the Flutter device at different resistance levels and exhalation flow combinations. In addition, the program would alert the user of exhalation

flow and resistant levels that result in potentially dangerous PEP to the patient (> 20 cmH2O).

Alves PT et al. (2008) [54]

Another study in 2008 investigated Flutter mechanical behaviour under flow ranges of 12-120 L/min and setting levels of (+30°, +15°, 0°,-15°,–30°) [54]. In this study, the oscillation frequency produced by Flutter was found to range between 6-31 Hz. The authors did not explicitly report the obtained range of PEP, however, a plot figure of the data was presented for each parameter. Based on the figure, the PEP was found to approximately ranges between 3-53 cmH2O. The authors did not report the amplitude of the pressure wave, but instead they reported the amplitude of the flow change, which ranged between approximately 1.8 to 10.92 L/min [54]. The pressure amplitude values were not reported in this study.

In terms of the settings effect on the pressure wave parameters, both the flow and resistance levels were found to have a significant effect on the oscillation frequency. On the other hand, the effect of the flow on the PEP was only significant on flow range of 24 to 120 L/min. In addition, a resistance level of +15° was found to produce higher PEP with the majority of flow rates.

Based on the mechanical behaviour characterisation results, the author provided recommendations to the clinical practice as a table (Figure 2-6) that lists the resistance levels and flow combinations that achieve theoretical best conditions for airway clearance.

Physical Variable	Airway Clearance Effect	Best Expiratory Flow	Best Inclination
Mean flow	Huff	Lower flows and lower lung volumes for secretions in distal airways Higher flows and higher lung volumes for secretions in proximal airways	–30° +30°
Mean pressure	Positive expiratory pressure (PEP)	0.2 L/s at PEP of 10 cm H_2O and above 1.0 L/s at PEP of 20 cm H_2O	+15°/+30°
Oscillation frequency	High-frequency airway oscillation	≥ 0.2 L/s	All except –30°
Flow amplitude	Flow amplitude	> 1.4 L/s	0°/+15°/+30°

Figure 2-6 Recommendation to the clinical practice posted by [54]

Santos et al. (2013) [34]

In 2013, [34] investigated and compared the mechanical behaviour of four OPEP devices (Flutter, Shaker, Acapella Green and Acapella Blue).

In this study, the mechanical behaviour of Flutter was evaluated under flow range of 5 to 32 L/min and resistance levels of +30°, 0° and –30°. Under these conditions, the authors reported that the oscillation frequency Flutter could generate ranges between 6 and 23 Hz, with an amplitude ranging between 5.2 to 19 cmH2O. The PEP that this device was able to produce was reported to range between 5 and 19 cmH2O. The effect of settings on the pressure wave parameters was not reported in this study.

The author concluded that; from the perspective that the optimum oscillation frequency is the one that matches the cilia frequency range (13 to 15 Hz). The author reported that exhalation flow rates of 20, 26 and 32 should be avoided when using the Flutter device as they were found to produce oscillation frequencies above the optimal range.

2.3.3.2 Acapella

Acapella is another hand-held OPEP device made by Smiths Medical. The Acapella product range (Figure 2-7) includes Acapella Choice, Acapella Green, Acapella Blue and Acapella Duet. To generate OPEP therapy, Acapella devices employ a counterweighted lever and magnet. When the patient exhales through the device, the air passes through a rocker valve which intermittently occlude the airflow generating the OPEP therapy. The rocker level of resistance to the airflow is determined by the proximity of the magnet and counterweighted plug on the rocker. Such proximity can be adjusted by a dial located at the distal end of the device [50,68]. The Acapella Devices are intended to be used by different patients depending on their exhalation flow capabilities. Acapella Green is intended for patients who can sustain at least 3 seconds of expiratory flow ≥ 15 L/min. On the other hand, Acapella Blue is designed for patients who can sustain a maximum expiratory flow ≤ 15 L/min. Acapella Duet and Choice are intended for patients who can sustain a minimum of 10 L/min [80] In total, five studies have evaluated the mechanical behaviour of one or more of the Acapella devices between 2003 and 2014.

Acapella Choice **Acapella Green** **Acapella Blue** **Acapella Duet**

Figure 2-7 Acapella product range [80]

Volsko et al. 2003 [50]

One of the first studies that evaluated the mechanical behaviour of Acapella devices was a study in 2003 by [50]. In this study, the mechanical behaviour of two Acapella devices was investigated (Acapella Green and Acapella Blue) and compared to the Flutter. Both Acapella devices were investigated under three resistance levels (Low (1), Intermediate (3) and High (5)). Acapella Blue was investigated under a flow range of 5-15 L/min, while Acapella Green was investigated under a flow range of 15-30 L/min. The reported pressure wave parameter ranges for Acapella Blue were 8-25 Hz for the frequency, 3-24 cmH2O for the PEP and 3-11 cmH2O for the amplitude. For Acapella Green, the reported frequency range was 13-30 Hz, the PEP range 6-21cmH2O and amplitude 1-12cmH2O. The authors noted that both Acapella devices produced a stable pressure wave in terms of frequency and amplitude, even at high flow. In addition, at high settings, the Acapella devices generated greater pressures than the Flutter.

In terms of the settings effect on the pressure wave parameters, the author reported that the effect of flow on the frequency was only significant at certain resistance levels. [50]. In terms of settings effect on the PEP value, flow was found to have a significant statistically effect on the PEP value. The author also reported a proportional relation between the flow and PEP values, however the increase in the PEP value as flow increases was described to be small. In terms of oscillation amplitude, the author reported that the amplitude generated by Acapella Green and Blue, was found to be higher at intermediate and high resistance levels but not at low resistance levels.

In terms of recommendations for clinical practice, the author argued that, at flow rate of 5-30 L/min, Acapella devices were found to generate a more stable pressure wave with less variation in the amplitude and the frequency than the Flutter device. The author stated

that the ability of Acapella devices to generate "effective" oscillation at lower flow rates allows the use of this device with a broader spectrum of patients. Especially for patients with low expiratory flow due to severe obstruction or age.

Alves SCE et al. (2009) [55]

In 2009, the mechanical behaviour of Acapella Choice was investigated under a flow range of 12-48L/min and 5 resistance levels (1-5). The authors reported that the overall range of frequency for this device under these test conditions was 8 to 21 Hz. In addition, the PEP was 3-23 cmH2O and amplitude was 4-9 cmH2O [55].

In terms of the settings effect on the pressure wave parameters, the author noted that the oscillation frequency value was found to be significantly affected by the change in flow level. However, the resistance levels adjustment had a significant effect on the frequency value only at certain flow levels (12-30 L/min). In terms of settings effect on the PEP value, the study found that the PEP value was significantly influenced by the flow level, however, resistance levels adjustment did not significantly influence this parameter. Similarly, the oscillation amplitude was found to be significantly influenced by the flow level and unaffected by resistance levels adjustment [55].

In order to guide clinical practice when using Acapella Choice, the author devised a computer software based on the mechanism behaviour data collected in the study. The author noted that; from the perspective that the best oscillation frequency for effective mucus clearance is the one that matches the respiratory system resonance (8-30Hz). Acapella Choice might not be beneficial for patients with progressive respiratory diseases as the resonance frequencies for their lungs might be higher than what this device capable of producing. However, the author proposed exhalation flow of 12 L/min and resistance level 5, as the optimum mechanical behaviour for Acapella Choice as these settings combinations would result in an oscillation frequency value of 12 Hz (a value that matches the cilia beat frequency) and require at a low flow rate, which is thought to favour patients with airflow limitation. The author also noted that, in order to achieve a minimum PEP value of 10 cmH2O, the exhalation flow rate need to be at least 24 L/min. In addition, the author pointed that exhalation flow exceeding 45 L/min would result in PEP above 20 cmH2O which might represent a risk to the patient.

Alves CE et al. 2010 [60]

In 2010, the mechanical behaviour of Acapella Blue was evaluated under a flow range of 3-15 L/min and 5 resistance levels (1-5). Under these experimental conditions, the frequency range was reported to be between 0-23 Hz, PEP 1.2-13.5 cmH2O and amplitude 0.2-2.8 cmH2O. In this study, the author reported that the device did not oscillate at 3 L/min. In addition, at a flow level of 6 L/min, the device only oscillated in the resistance levels 1, 2 and 3.

In terms of the settings effect on the pressure wave parameters, in this study, it was found that oscillation frequency increased significantly with resistance level changes at flow levels between 9-15 L/min. In terms of PEP, the study found that flow has a significant effect on the PEP value, however, changes in the resistance levels did not have a significant effect on this parameter [60]. In addition, oscillation amplitudes were reported to increase significantly with airflow.

In terms of recommendations for clinical practice, the author noted that in order to achieve effective airway clearance results, the pressure wave parameters produced by the devices must be precisely controlled. Therefore, the author proposed the settings combinations for achieving the optimal theoretical range for each pressure wave parameter. For instance, the author suggested that resistance levels 3, 4 and 5 may achieve a frequency that matches the cilia beating frequency (12 Hz). The “ideal” settings combination proposed is; resistance level 3 and exhalation flow of 6 L/min since it would favour patients with severe flow limitations. In terms of PEP, from the perspective that the optimum PEP value for effective airway clearance ranges between 10 to 20 cmH2O, the author recommended a minimum of 9 L/min to produce a PEP value within the perceived optimum range. In terms of the amplitude, from the perspective that the higher the oscillation amplitude, the more effective the airway clearance, the author suggested that resistance levels 1, 2 and 3 were found to produce the highest amplitude under airflow rates of 6 to 15 L/min.

However, the author noted that; from the perspective that mucus clearance is optimum when oscillation frequency matches the resonance frequency of the respiratory system, patients with a high level of obstruction in the airway might have resonance frequencies higher than those produced by Acapella Blue.

Santos et al. (2013) [34]

In 2013, the mechanical behaviour of four OPEP devices (Flutter, Shaker, Acapella Green and Acapella Blue) was evaluated in one study. The mechanical behaviour of Acapella Green and Blue was evaluated under three resistance levels (Low (1), Intermediate (3) and High (5)). The devices were tested under a flow range of 5-15 L/min for Acapella Blue and 15-30 L/min for Acapella Green. However, in this study, the results for the two Acapella device types were combined and presented as one device. The reported pressure wave parameters in this study were; frequency range between 8-26 Hz, PEP 4.8-26.6 cmH2O and amplitude 3.9-12.6 cmH2O [34]. The effect of settings on the pressure wave parameters was not reported in this study.

In terms of recommendations for clinical practice, the author concluded that; from the perspective that airway clearance is optimum at the cilia frequency range (13 to 15 Hz), both Acapella devices produced oscillation frequency values within the optimum frequency range. Also air flow up to 15 L/min has been proposed by the author as appropriate for clinical use with respect to the oscillation frequency.

Mueller et al. (2014) [61]

In a recent study in 2014, [61] evaluated the mechanical performance of three Acapella devices: Acapella Choice, Acapella Green and Acapella Blue. Unlike previous studies, the authors decided to evaluate all three devices under the same flow range (6-50 L/min) in order to provide a direct comparison between the devices. All three devices were evaluated under five setting levels (1-5). The frequency range exhibited by each of the three devices was: 9-25 Hz for Acapella Choice, Acapella Green 6-24 Hz and for Acapella Blue 0-23 Hz. The PEP ranges reported in this study were: 2-30cmH2O for Acapella Choice, 2-27cmH2O for Acapella Green and 1-120cmH2O for Acapella Blue. The amplitude ranges reported in this study were as follow; Acapella Blue 0-5 cmH2O, Acapella Choice 0-6 cmH2O, Acapella Green 0-8 cmH2O

In terms of the settings effect on the pressure wave parameters and the oscillation frequency, Acapella Green and Choice were found to have a proportional relationship with flow. However, the authors also reported that the frequency-flow relationship of the Acapella Blue device showed an inverse pattern. On the other hand, the authors noted that for all three devices, the PEP value increased with the flow than with the increase in

resistance levels. In terms of. oscillation amplitude, it was noted that despite that there was no clear pattern to the amplitude, Acapella Blue produced lower amplitudes at different flow rates compared to the other two devices

In terms of recommendations for clinical practice, the author produced a table of the optimal settings combinations and the resultant pressure wave parameters for each one of the investigated devices (Figure 2-8). The construction of the table was based on the perspective that the optimal airway clearance occurs with oscillation frequency that coincides with the cilia beating frequency (11 to 15 Hz) and the greatest amplitude. Therefore, the table was populated with the settings combinations that achieve these criteria. The author noted that Acapella Green was found to generate the greatest amplitude in the optimal frequency range. On the other hand, the author stated that the benefit of Acapella Choice is questionable as it was found to produce the lowest amplitude at the optimal frequency range.

Device	Setting/Filling Height, cm	Flow, L/min	Pressure, cm H_2O	Frequency, Hz	Amplitude, cm H_2O
Acapella Choice	4	30	11	15	8
Acapella blue	4	12	8	13	5
Acapella green	4	30	11	13	6

Figure 2-8 Optimal OPEP device settings posted by [61]

The author proposed the following approach to clinical practice when using Acapella devices; Acapella Green is best used when patients are able to sustain a minimal flow of 30 L/min. Acapella Blue is best used by weaker patients who are able to generate flows of only 12 L/min.

2.3.3.3 Shaker

The Shaker (Figure 2-9) is an OPEP device that was developed based on the therapeutic response obtained with the Flutter. The device is also pipe-shaped and contains a circular cone and a stainless steel ball with a protective cap.

Figure 2-9 Shaker device (picture obtained from http://www.habdirect.co.uk)

Santos et al. 2013 [34]

The mechanical behaviour of the Shaker was evaluated only in one study in the literature. [34] evaluated the Shaker device under a flow level of 5-32 L/min and under three setting levels (+30°, 0°,–30°). The authors reported a frequency range for this device of between 6-23 Hz, PEP range between 5-18.5 cmH2O and amplitude values between 5.2 to 16.5 cmH2O. The effect of settings on the pressure wave parameters was not reported in this study. [34].

In terms of recommendations for clinical practice, the author concluded that; from the perspective that airway clearance is optimum at the cilia frequency range (13 to 15 Hz), the Shaker devices produced oscillation frequency values within the optimum frequency range. Also, air flow up to 15 L/min has been proposed by the author as appropriate for clinical use with respect to the oscillation frequency.

2.4 Discussion

2.4.1 Experimental Set-up

One of the main observations to be noted about the reviewed studies is the experimental setup variation employed in each study. Especially in terms of the exhalation flow range, the resistance levels and the measurement equipment used to investigate the mechanical behaviour of OPEP devices.

In terms of exhalation flow range, some studies did not specify the rationale behind the choice of airflow range [69,79]. However, other chose flow ranges that fit with the

specification of the device under investigation and the flow cabalities of the patients who used the device [34,50]. Other studies chose flow ranges that purely mimicked the flow range exhibited by patients clinically, regardless of the device specification [54,55,60,61,77]. The given rationale for this last approach was that it would allow a direct comparison of the devices and hence a better insight of how to choose and use these devices [61]. Lastly it has been stated that in many of the of the previous studies the airflow used to investigate the mechanical behaviour of OPEP devices was "significantly higher than those normally used in clinical practice, which justifies the need for a more detailed study of the mechanical behaviour of OPEP devices" under flow rates that are closer to those found in clinical practice [34].

In terms of the exhalation flow mode, it has been expressed that investigating the mechanical behaviour of OPEP devices, under constant flow will allow for precise control of the experiment and will lead to a better characterisation and understanding of the mechanical behaviour of these devices [50,78]

In terms of the resistance levels under which OPEP devices mechanical behaviour was investigated, the authors had two approaches; the first was to investigate the mechanical behaviour under three levels which was thought to be representative of the device's mechanical performance, while the other approach was to cover a wider range of device resistance levels. It is worth noting that the mechanical behaviour graphs presented in the different studies suggest that the influence of resistance levels on some pressure wave parameters is not always incremental [54,60,61]. As such, testing a wider range of resistance levels might lead to a better characterisation of the mechanical behaviour of OPEP devices.

In terms of the equipment, when evaluating the mechanical behaviour of OPEP devices, it is important to have a measurement system that is capable of measuring the mechanical behaviour. It has also been suggested that a specialised measurement system is required for such a task. [57]. In addition, investigating OPEP device requires software that is sensitive enough to detect pressure and airflow oscillation changes. Nevertheless, despite the importance of the measurement system, the capability of the measurement system used in previous studies and its effect on the disparity of the results in different studies

has been raised by one author [77]. In future studies, it is recommended that the system being used to measure the performance of OPEP device is evaluated.

2.4.2 Pressure Wave Parameters

There is an agreement between authors that certain pressure wave parameters values are optimum for effective airway clearance [55,60,61,69,77]. When providing a recommendation for the clinical practice regarding the OPEP device mechanical behaviour that generates the optimum frequency value. Previous studies based their recommendations on the theoretical mechanism of actions. These mechanism of actions include; matching cilia frequency [55,60,61], matching respiratory resonance frequency [55,61] and chest natural frequency [78]. In addition, frequencies known to increase mucus transport and altering mucus rheology have also been suggested [34]. Nevertheless, recently it has been stated that the literature is very sparse regarding optimum frequency range [61]. Similarly, the literature is very sparse regarding the effect of flow and resistance levels on the oscillation frequency. Such difference has been referred back to the difference in the overall experimental setup used in each study [34,54,55,61].

When providing a recommendations for clinical practice regarding the mechanical behaviour that generates the optimum PEP value, previous studies have based their recommendation on the following PEP values ; a PEP between 10-20 cmh2O [54,55,60,69] as the optimum PEP values for effective airway clearance. However, Oberwaldner et al. (1986) have reported that the optimum PEP value to promote mucus clearance varies between patients, hence this value should be individualised. [81].

When providing recommendations for clinical practice regarding the mechanical behaviour that generates the optimum amplitude value, previous studies based their recommendation on the theoretical perspective that higher amplitude values are optimum for effective airway clearance [61,69].

Despite that previous studies have consistently observed and reported the same pressure wave parameters, the experimental set up (flow range and resistance levels) variations used in these studies makes a direct comparison between the results very difficult. This problem has been expressed by several authors [34,60,61,78]. In addition, in a recent

study it has been emphasised that there is a need for new studies evaluating the mechanical behaviour of OPEP devices under a unified test set up and flow range to allow for a direct comparison between devices from the same manufacturer and different manufacturers [61]. Furthermore, several authors emphasised that, despite the importance of a technical performance criteria to guide providing recommendations to clinical practice regarding OPEP devices mechanical behaviour, it is uncommon to find such criteria in the literature [55,60,77]. Therefore there is a need for technical performance criteria that take into account the underlying pathophysiological problem for patients with airway clearance problems as well as the principles of ACT techniques [50,54,57]. It has been stated that in the absence of such criteria, only speculation can be made when optimising mechanical behaviour of OPEP devices [50]. Furthermore, in a recent review, it was stated that despite previous efforts to investigate mechanical behaviour of OPEP devices and these devices being routinely used in clinical practice for several years, the question remains as to which settings are appropriate for effective airway clearance [38].

2.4.3 Previous Optimisation Attempts

In total, there was four attempts to inform clinical practice by optimising the use of OPEP devices based on mechanical behaviour data. In two of these attempts [55,77] computer software that incorporates the mechanical behaviour data was developed. The software allowed clinicians to enter the desired exhalation flow and the chosen resistance level on the device. The software feeds back the resultant mechanical behaviour based on these parameters. Two software were developed, one for flutter and one for Acapella Choice [55,77].

In the other two optimisation attempts, [54,61], the authors provided table that list the exhalation flow rate and resistance levels required to achieve the optimum mechanical behaviour. The construction process of these tables was based on the theoretical mechanism of action for airway clearance by oscillating.

However, these optimisation attempts were limited for several reasons; firstly, the technical performance data was the cornerstone in these attempts. However, based on the results of this review, both the methodological variation and difference in the results reported by the different authors leaves a question mark as to which one should be accredited as the correct one. Secondly, these attempts were primarily based on

recommending settings for achieving optimum mechanical behaviour for each pressure wave parameter individually, rather than all three pressure wave parameters simultaneously. Lastly and most importantly; none of these attempts considered the optimal use of these devices from the point of view of relating the mechanical behaviour to the physiological mechanism for airway clearance by oscillation. Hence, despite these efforts, the question of which settings are appropriate for optimum airway clearance remains [38].

2.5 Research Gaps

Studies evaluating the mechanical behaviour of OPEP devices, lie (along with clinical trials) at the base of the evidence appraisal hierarchy in the airway clearance field [76]. In this literature review, the methodological variation has been identified as a major limitation of previous studies that evaluated OPEP device mechanical behaviour. In particular, there is a lack of studies evaluating OPEP devices under a unified experimental setup and under flow ranges commonly found in clinical practice. Hence, new studies evaluating mechanical behaviour of OPEP devices has been encouraged [61].

The review has also identified that; one of the major challenges in providing recommendations to clinical practice regarding OPEP devices mechanical behaviour for effective airway clearance is the lack of documented optimum technical performance criteria.

Lastly, this review has identified that despite OPEP devices being around for several years and routinely used in the clinical practice, the optimum settings for effective airway clearance are still unknown.

In summary, the literature review has identified the following three knowledge gaps:

1- Lack of OPEP devices optimum technical performance criteria
2- Lack of studies evaluating OPEP devices under a unified experiment set and flow range commonly found in clinical practice
3- Lack of characterisation optimum mechanical behaviour of OPEP devices for effective airway clearance

2.6 Chapter Summary

In summary, in the field of airway clearance research, studies evaluating the mechanical behaviour of devices is a form of original research. Along with clinical trials, device evaluations lie at the base of the evidence appraisal hierarchy in this field.

In this chapter it was found that:

- The mechanical behaviour of OPEP devices is thought to be controlled by two setting variables: exhalation flow and resistance level.
- The pressure wave parameters of OPEP devices can be expressed in terms of three main variables: frequency of the oscillation, value of the PEP, and amplitude of the oscillation.
- When designing an experiment to investigate the mechanical behaviour of OPEP devices, it is important to choose an exhalation flow range that mimics those commonly found in clinical practice, in addition to verifying the capability of the measurement system for the task at hand.
- Also, investigating OPEP devices, under constant flow mode and all resistance levels, has been suggested to lead to a better characterisation and understanding of OPEP devices' mechanical behaviour.
- Different commercial OPEP devices have been investigated in previous studies. Experimental setup variation makes a direct comparison between results very difficult.
- New studies evaluating mechanical behaviour of OPEP devices under a unified test set up and flow range commonly found in clinical practice have been encouraged.
- A major limitation encountered by previous studies is the lack of technical performance criteria that take into account the underlying pathophysiological problems for patients with airway clearance problems, as well as the principles of ACT techniques.
- Despite previous efforts to investigate OPEP devices` mechanical behaviour and despite these devices being routinely used in clinical practice for several years, the question remains as to which settings are appropriate for effective airway clearance.

3 IDENTIFICATION OF THE OPTIMAL TECHNICAL PERFORMANCE REQUIREMENTS

In chapter 2, the literature was reviewed to identify the current "state of the art" in the mechanical behaviour of OPEP devices. Chpater 2 has identified that one of the major limitations in previous attempts to optimise the mechanical behaviour of OPEP devices is the lack of correlation between the mechanical behaviour data and established technical performance criteria.

This chapter addresses the second objective of this research. It will review previous studies to identify technical performance criteria for effective mucus clearance by airway oscillation. The chapter will describe the role of each of the pressure wave parameters in airway clearance from a physiological perspective. In addition, the chapter will identify the optimum values of each of the pressure wave parameters for effective airway clearance.

3.1 Introduction

One of the main principles of ACT is that; the application of the technique "must be based on the patient's respiratory dysfunction in order to result in the intended airway clearance effects" [9,82]. As a form of ACT, OPEP devices are no different [74]. In fact, it has been concluded that the effect of a device can be optimised in clinical practice by taking into account the patient`s lung condition and the technical performance of the device [54]. However, OPEP device technical performance criteria that takes into account the relative pathophysiological impact of the oscillatory pressure wave parameters has not been established in literature previously [166, 193].

In chapter 2, it was found that, previous studies have attempted to provide recommendations to clinical practice by correlating the technical performance of OPEP devices to the theoretical mechanism of action for each pressure wave parameter. However, it was also found that the literature is very sparse regarding the optimum values for each of the pressure wave parameters for effective airway clearance. Moreover, a major limitation encountered by previous studies is the lack of technical performance criteria that take into account the underlying pathophysiological problems for patients with airway clearance problems, as well as the principles of ACT techniques. Moreover,

it has been stated that, in the absence of such criteria, OPEP devices are considered "black boxes" and only speculation can be made about optimising their effect [50].

The aim of this review is twofold, firstly is to describe the physiological effect of OPEP devices pressure wave parameters on airway clearance. Secondly is to identify the optimum pressure wave parameters for effective airway clearance by airway oscillation.

3.1.1 Action Theories

Effectiveness of airway clearance by airway oscillation is thought to be critically dependent on three pressure wave parameters; oscillation frequency, PEP and oscillation amplitude [50–55]. In terms of the physiological effect of each of the pressure wave parameters, several "mechanism of action" theories have been proposed for each parameter. These theories will serve as the framework for this review and will be outlined in this section

In terms of oscillation frequency mechanisms of actions; an early work by King et al. (1983) proposed 1) enhancing the cilia beating, 2) changing the mucus rheology and 3) mucus mobilisation as three possible mechanisms of action for clearing mucus by oscillation [52]. These perspectives were later adopted by several authors [21,34,44,49,50,60,61,83]. In addition, 4) matching the resonance frequency of the respiratory system has also been proposed and adopted as a possible oscillation frequency mechanism of action [60,61,69]. In terms of PEP, it is thought that expiring against resistance promotes airway clearance through two possible mechanisms of action; 1) recruit clogged airways [30,31], and 2) move the equal pressure point peripherally [82]. In term of amplitude mechanism of action, the amplitude is thought to promote micro-movements of the mucus towards the mouth [77].

3.2 Method in this chapter

This review aims to describe the physiological effect of OPEP pressure wave parameters and identify the optimum values for these parameters. Therefore, the review will be split into three main topic areas; frequency, PEP and amplitude. The frequency parameter has been divided based on mechanisms of action into further four topic areas; enhance cilia beating, change mucus rheology, alter mucus movement and match the respiratory system resonance.

3.2.1 Search Strategy

The databases PubMed and Scopus were used to identify relevant publications for each topic of interest. The search was set to include articles between 1950 and 2016. Initially, keywords for each topic area were generated using the Medical Subject Heading (MeSH). Further keywords from the sourced articles were then used to refine the search.

Table 3-1 outlines the search strategy used in this review for each topic area. The table lists the keywords used for each one. After an initial screening for the returned search results, it was found that review articles already exist for some of the topic areas or a comprehensive review were not required to establish the optimum for values. Hence this review was not comprehensive for these areas. However, for other topic areas, it was found that no reviews exist, therefore a comprehensive review was conducted.

In terms of results presentation, for each of the topic areas reviewed, the results section will start by outlining the physiological effect for each of the pressure wave parameters, followed by an overview of the search results and a final section that presents the optimum value for each parameter.

Table 3-1 Method outline for optimum pressure waveform parameter identification – Review type, topic area and keywords used

Review Type	Topic Area	Keywords
Comprehensive Review	**Frequency**- Change mucus rheology	sputum viscoelasticity, sputum clearance, sputum clearance by oscillation, sputum oscillation, mucus oscillation, mucus clearance by oscillation, mucus rheology, mucus rheology oscillation
	Frequency- Alter mucus movement	"mucus clearance oscillation", "high frequency oscillation", "oscillating positive expiratory pressure", "mucus velocity, pulmonary secretion transport", "mucus transport oscillation", "mucus transport", "tracheal mucus clearance", "airway oscillation"
	Amplitude	"airway clearance amplitude" "mucus clearance oscillation", "pressure wave amplitude "oscillating positive expiratory pressure", "mucus transport oscillation", "airway oscillation"
Non-Comprehensive Review	**Frequency**- Enhance cilia beating	"cilia beating frequency", "respiratory cilia", "cilia frequency", "mucociliary clearance", respiratory cilia frequency"
	Frequency- Match the respiratory system resonance frequency	"resonance frequency lungs", "resonance frequency respiratory system", "resonance frequency cystic fibrosis", "resonance frequency COPD", "resonance frequency asthma", "chest natural frequency".
	PEP	"Positive airway pressure", "PEP airway clearance", "oscillatory positive expiratory pressure", "high positive expiratory pressure", "HiPEP"

3.3 Results

3.3.1 Oscillation Frequency

3.3.1.1 Matching Respiratory System Resonance Frequency

Physiological Effect

Resonance is “the condition in which an object or system is subjected to an oscillating force having a frequency close to its own natural frequency” [84]. Objects or systems tend to oscillate at greater amplitude at its own natural frequency [85].

The resonance frequency has been proposed to be effective for clearing mucus by oscillation [54,69,86–88]. It is thought airway oscillation at the lungs resonance frequency results in the highest flow amplitude [55]. Alves and his colleagues argued that as a physical object, the respiratory system have energy storage capacity properties. Such properties are determined by the elastic property of the lungs or what is known as “lungs compliance”. Energy storage is “dominant at low oscillation frequencies, in combination with the inertive properties, which become progressively more important with the increase in frequency. At the respiratory system resonance frequency, the elastic and inertial forces are equal in magnitude, resulting in the cancellation of the effect of these two properties and in the increase of the air flow” [55]. As a physiologic result, “this increase in air flow may, theoretically, improve mucus transport” [55,69]. Nevertheless, resonance frequency is not the same for everybody, it varies by diseases states [55], and it also increases with airway obstruction [89,90].

A search of the PubMed and Scopus databases was used to identify relevant publications that examined the resonance frequency of patients with various respiratory system diseases. COPD, Cystic fibrosis, and asthma disease were chosen because they are usually accompanied with excessive secretions [2]. In addition, these patients groups usually use OPEP devices for secretion clearance [29]. Because the resonance frequency varies depending on the level of defection in the airway [89,90]. Hence, for COPD and asthma, only studies that reported the resonance frequency according to the progression stage of each disease were selected.

Forced Oscillation Technique (FOT) and Impulse Oscillation Systems (IOS) are tools for measuring lung function using sound waves generated by a loudspeaker which is passed

into the lungs during tidal breathing [91]. The resonance frequency as measured by these systems is the frequency at which reactance becomes zero [92]. More can be found here about this technique [91,93]. Both systems are capable of determining the resonance frequency of the respiratory system with high accuracy [91,94]. Hence, only studies that have used FOT or IOS to determine the resonance of the respiratory system were included. In addition, because the FOT and IOS are considered to be able to measure the respiratory system resonance accurately, the review was not broadened to become comprehensive. However, the studies with the largest sample sizes were selected.

Optimum Values

In total three studies were included in this review to establish the resonance frequency for patients with selected respiratory system dieses. Table 3-2 shows a summary of the resonance frequency as found by these studies.

Table 3-2 Respiratory system resonance frequencies for patients with Cystic Fibrosis, COPD and Asthma

Reference	Sample Size	Disease	Stage	Frequency
[95] N=43	43	Cystic Fibrosis	N/A	10.8-23.4 Hz
[96] N=2054	915	COPD	GOLD 2	14-22.6 Hz
	861		GOLD 3	17.1-26.5 Hz
	278		GOLD 4	19.8-30.8 Hz
[92] N=216	111	Asthma	Mild	11.4-20.8 Hz
	78		Moderate	12.3-23.9 Hz
	27		Sever	17.1-30.9 Hz

In regards to cystic fibrosis,[95] measured the resonance frequency of 43 cystic fibrosis patients aged 6-21 years. The study reported that the renounce frequency for this sample had a mean value of 17.1 Hz and a range of 10.8 – 23.4 Hz. These values were in agreement with reference values published previously [97]. In terms of COPD, [96] attempted to establish the usefulness of impulse oscillatory system to measure pulmonary function in a large patient group. This study reported that as the resistance of the airway increases as COPD patients progress through different stages, the resonance frequency also increases. The study reported that COPD patients at stage GOLD 2 have a mean

resonance frequency of 18.3 Hz and a range of 14-22.6 Hz, while patients who are at stage GOLD 3 have a mean resonance frequency of 21.8 Hz and a range of 17.1-26.5 Hz and patients at GOLD stage 4 were found to have the highest mean resonance frequency of 25.3 Hz and range of 19.8-30.8 Hz. In regards to Asthma patients, a similar study was conducted to evaluate the usefulness of forced oscillatory system to measure the pulmonary function of a large group of patients suffering from asthma. This study found that the resonance frequency increases as the patient progress into more advanced stages of the diseases [92]. For patients with mild asthma, the study reported that those patients have a mean resonance frequency of 16.1 Hz and a range of 11.4-20.8 Hz. While patients with moderate asthma were found to have a meant frequency of 18.1 Hz and a range of 12.3-23.9 Hz. Lastly patients with severe asthma were found to have a mean resonance frequency of 24 Hz and a range of 17.1-30.9 Hz.

3.3.1.2 Mucus Mobilisation

Physiological Effect

The movement of mucus is governed by the frictional and inertial forces counteracted by the two natural clearance mechanisms; the cilia (what is known as the Mucociliary Clearance System MCC) and cough [3,53,98,99]. However, for patients with respiratory system diseases, the MCC function often becomes impaired and less functional. For those patients, mucus clearance by cough plays a more crucial and central role [100,101]. Coughing works on clearing mucus by achieving rapid acceleration of airflow and high flow rate. When these two (rapid acceleration and high flow rate) are coupled with the dynamic compression of the airway, it works on pushing the mucus up the airway towards the mouth. [102]. The Two- Phase Gas Liquid Interaction (TPGLI) has been recognised as the mechanism by which cough works on clearing mucus from the airways [101,103–105]. TPGLI refers to the interaction that occurs as a result of simultaneous flow of gas and liquid in a tube [106]. When airflow, induced by a cough, flows through airways that are lined with mucus the airflow interacts with the mucus developing a sheer force on the interfacial surface of the mucus (Figure 3-1) [105,107].

Figure 3-1 Mucus mobilisation via two- phase gas liquid interaction principle [108]

The TPGLI has been proposed as a mechanism of action for the effective clearing of mucus by oscillation. [50,53,109–112]. It is thought that the short and successive disruptions to the airflow, produced by airway oscillation have a fundamental resemblance to mucus clearance by cough in the human body (Figure 3-2) [32,113,114]. The source of the resemblance comes from the nature of the oscillatory positive pressure produced by OPEP devices which is described as "akin to a rapid series of short coughs" [32,50]. It is thought that this series of short coughs works on mobilising mucus by "increasing the absolute peak expiratory flow rates to move the secretion towards the mouth" [29,115,116] and/or "improve the expiratory bias of airflow to increase the annular flow of mucus towards the mouth" [117].

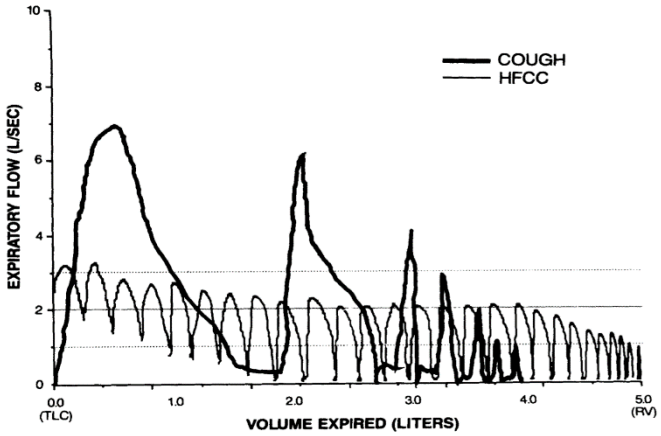


Figure 3-2 Resemblance between cough and airway oscillation [114]

A literature review of the best frequency value for effective mucus mobilisation has not been conducted before. Hence, a comprehensive search of the PubMed and Scopus databases was used to identify relevant publications on the topic of interest in this research.

It was found that several studies (n=18) have examined mucus clearance by oscillation. However, because the aim of this review is to identify the optimal parameters for mucus clearance by airway oscillation, only studies that have investigated mucus mobilisation using airway oscillation were included (i.e. studies that applied airway oscillation to the chest have been excluded). In addition, only studies that applied, compared and reported more than one frequency were included.

Optimum Values

A total 5 studies that have examined oscillation frequency that maximises mucus mobilisation matched the selection criteria [53,112,118–120]. Some of these studies have observed the mucus transport rate [53,118,119], while one study observed the weight of the expectorated mucus [120]. Table 3-3 shows the frequency value that was found to be the best by each one of these studies.

Table 3-3 Optimum frequencies to alter mucus movement

Reference	Optimum Frequency
[53]	8-13 Hz
[119]	8 Hz, 14 Hz and 20 Hz
[118]	14 Hz and 20 Hz
[120]	8 Hz and 14 Hz
[112]	13 Hz , 20 Hz

[53] conducted an experimental -theoretical study. In this study, the transport rate of a mucus layer lining the inside of rectangular trough was measured using two different methods while oscillatory air flow were applied. The results show that the transport rate increased between frequencies of 8-13 Hz, but not 1-7 Hz. In another study, [119] investigated the effect of sine wave oscillation on mucus transport. In this study oscillation of frequency 8, 14 and 20 Hz was applied using a loud speaker on 8 healthy subjects (5male, 3 females, with a mean age of 25.7). The authors reported that mucus transport increased at all frequencies applied. In another study on human subjects, [120] observed the effect of oscillation frequency (8 and14 Hz) on the weight of expectorated sputum from 14 cystic fibrosis patients. The study found an increase in the weight of the expectorated mucus at both frequencies. Mucus transport rate, was investigated by [118]

in an in vitro experiment using ovine tracheas. The authors applied oscillation frequencies at 14 and 20 Hz. The authors reported that mucus transport velocity increased at both frequencies [118]. Lastly in a study conducted on dogs, [112] applied airway oscillation at frequencies between 13-20 Hz. This study observed that mucus transport rate was highest at 13 and 20 Hz.

3.3.1.3 Change Mucus Rheology

Physiological Effect

Mucus lining the inside of the tracheobronchial tree has been identified as a non-Newtonian viscoelastic fluid [121,122] that has both viscosity (resistant to flow) and elasticity (a recoil energy in response to an applied stress) behaviours. The viscoelasticity property of this fluid comes from the building blocks that mucus is made of (Figure 3-3 Top); especially the type of glycoprotein (mucin), the water content of the mucus and the degree of entanglement and crosslinking bonds in the mucus (Figure 3-3 Bottom)[123,124]. When stress is applied to the mucus, it will respond initially as solid to the applied stress, followed by a viscoelastic deformation (occurring at the yield stress) and then a steady flow resulting in permanent deformation [122]. Mucus viscosity decreases as the shear rate increases (i.e. as the applied force increases). This is referred to as shear thinning [125].

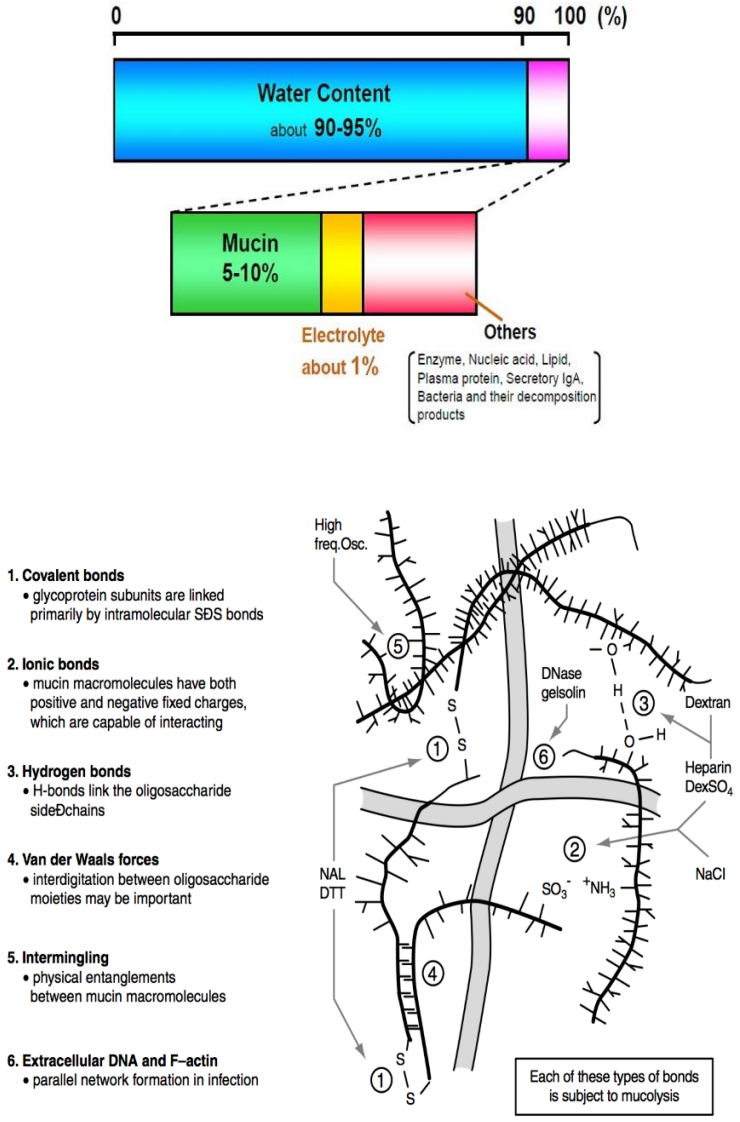


Figure 3-3 Respiratory system mucus contents and bonds structure. Contents of mucus, (top) Bonds between mucus molecues (buttom) [101]

Changes in the mucus rheology have been proposed as a possible mechanism for effective mucus clearance by oscillation [52,118,126–128]. The degree of crosslinking or the rheological properties of mucus play an important role in mucus clearance [52,126,129]. It is thought that clearance is likely to be enhanced by a reduction in the cross-link and viscosity [52,118,129]. Reduction in mucus cross-linking through airway oscillation has been demonstrated in both in-vivo and in-vitro studies [52,126,130]. Although "the mechanism or mechanisms for the reduction in viscoelasticity or degree of crosslinking of the mucous gel by oscillation are not known" [126]. One proposed

possibility “involves the cooperative unfolding of the physical entanglements between the primary network of mucous glycoproteins and other structural macromolecules, the rupture of crosslinking bonds such as disulfide bridges, or perhaps the fragmentation of larger molecules such as DNA or F-actin, which are present as a byproduct of infection and can increase mucus viscosity” [126,127]. Another proposed possibility suggests that vagal stimulation may be caused by oscillation, which in turn leads to an increase in the water content of the mucus [109,127].

A review of the best frequency value to change respiratory mucus rheology has not been conducted before. Hence, a comprehensive search of the PubMed and Scopus databases was used to identify relevant publications. It was found that several studies (n=23) have examined the change in mucus rheology when subjected to oscillatory pressure. However, because the aim of this review is to identify the optimal parameters for mucus clearance by airway oscillation, hence, only studies that have investigated the change in mucus rheology as a result of airway oscillation were selected. Also, only studies that applied more than one oscillation frequency and reported these frequencies were selected. In addition, because pressure waves propagate and travel differently in different mediums [85], hence studies that investigated the change in mucus rheology as a result of chest wall oscillation were excluded.

Optimum Values

In total 4 studies were found that matched the selection criteria [52,126,127,130]. Table 3-4 shows the frequency value that was found to change mucus rheology in each of these studies.

Table 3-4 Optimum frequencies to alter mucus rheology

Reference	Optimum Frequencies to Alter Mucus Rheology
[52]	8-16 Hz
[127]	12 Hz & 22 Hz
[130]	19 Hz
[126]	19 Hz

One of the first studies that observed the change in mucus rheology at different oscillation frequencies was a study by King et al (1983). In this study airway oscillation was applied

to in-vitro mucus samples obtained from patients with pneumonia. A decrease in the mucus viscosity was observed for frequencies between 4-16 Hz. In another in-vitro study, [127] observed the effect of different frequencies on the viscosity, elasticity and spinnablity of a mucus simulant. The authors reported that oscillating mucus at 12 & 22 Hz decreased the observed rheology properties, making it more favourable for mucociliary clearance. Flutter was used in one in-vitro [130] and another in-vivo study [126] to observe the change in mucus rheology caused by the oscillations produced by this device. Both studies reported a change in the mucus rheology. The oscillation frequency to cause such effect was reported in both studies to be 19 Hz.

3.3.1.4 Enhance Cilia Beating

Physiological Effect

Cilia are small hair-like organelles, generally 5-8 µm long lining the inside of the tracheobronchial tree (Figure 3-4A). Through regular beating, cilia work in concert to transport mucus up the pulmonary tree. Cilia impel mucus in one direction by a rapid two phase movement composed of an effective stroke (forward movement) followed by a recovery stroke (slower return movement) (Figure 3-4B) [105].

Figure 3-4 A: Mucus transport by cilia. B: Cilia movement stages; effective stroke and recovery stroke [131]

It is thought that secretion clearance is effective when the frequency of the applied oscillations coincides with the cilia beating frequency [2,52,60,115,132]. The theory is that stimulation of the ciliated epithelial cells through airway oscillation stimulates cilia beating [115,133,134]. Such stimulation may also involve an increase in "the amplitude of the cephalad-ciliary beat, which could in turn increase mucus transport" [135]. The

increase in the amplitude was explained by Hansen et al (1994) who stated that the interaction between the mucus and the airflow when oscillations are applied to resonate with the cilia beating frequency may increase the effective portion of the cilia stroke [114].

Since the aim is to establish the normal cilia beating frequency range and because this topic has been extensively investigated previously, hence, the review was not broadened to become comprehensive. Only 3 studies were selected; in these studies respiratory cilia beating frequency was measured using variety of methods (i.e. digital high speed video, photodiode and photomultiplier).

Optimum Values

The results from the three selected studies showed that the average beating frequency of cilia in the human respiratory system is between 11 Hz to 15 Hz [136–138]. Table 3-5 shows the cilia beating frequency range reported in each of the selected studies

Table 3-5 Cilia beating frequency

Reference	Cilia Beating Frequency
[136]	Digital High-Speed Video: 13.5 Hz±1.4 Photomultiplier: 12 Hz±1.2 Photodiode: 11.2 Hz ± 1.3
[137]	Paediatric 12.8 Hz ±0.5 Adult: 11.5 Hz ± 1.2:
[139]	11.72 Hz ±2.8

In a study by [136], the authors measured the cilia beating frequency using three methods; digital high-speed video, photomultiplier and photodiode. Ciliated epithelium samples were obtained from 20 healthy subjects aged 3-38 (13 males). The author reported that that there was a difference in the beating frequency as measured by digital high-speed video, photomultiplier and photodiode (13.2 Hz, 12 Hz, and 11.2 Hz respectively). The authors concluded that “digital high-speed video imaging allows both ciliary beat frequency and beat pattern to be evaluated”. In another study, [137] measured the cilia beating frequency using digital high-speed video. Ciliated epithelium samples were

obtained from 76 subjects (53 healthy children aged 6-17 years and 23 healthy adults, aged 18-43). The author reported that the mean cilia beating frequency for the paediatric population were 12.8 Hz which was higher than the mean value for the adult population, 11.5 Hz. In a third study [139], a 100 measurements were taken of the respiratory ciliary beat frequency using high-speed video analysis. In this study, it was reported that the respiratory cilia beat frequency is around 11.72 Hz.

3.3.2 Positive Expiratory Pressure (PEP)

Physiological Effect

Airway Recruitment

In terms of recruiting clogged airways, it is thought that breathing against a resistant, works by temporarily increasing the functional residual capacity (FRC) and tidal volume (TV) [19,87,140–144]. This increase helps "recruiting otherwise collapsed airways in order to get air behind secretions, thereby making it possible to mobilise and evacuate it" (Figure 3-5) [20,32,82,145,146].

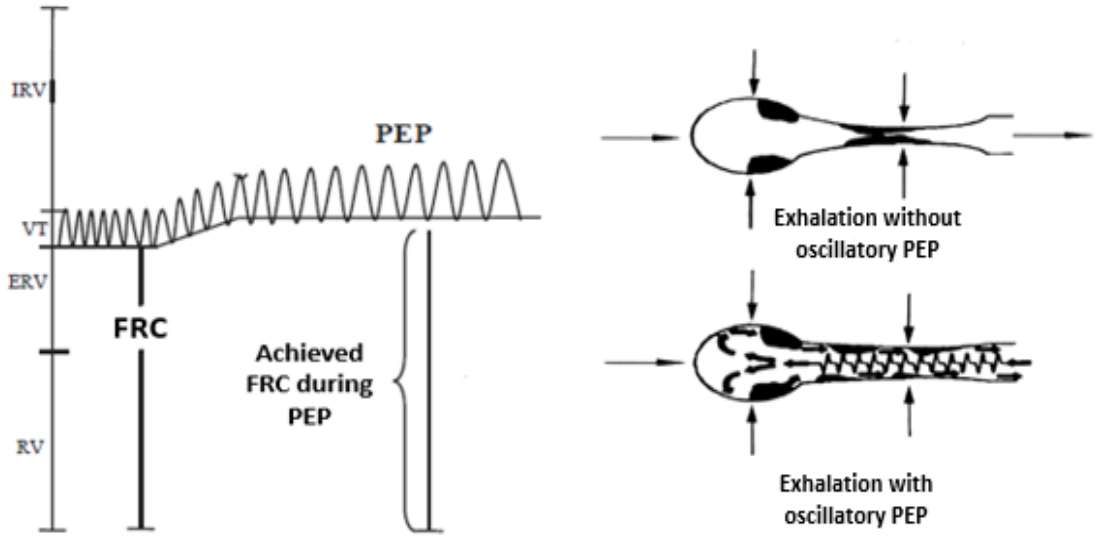


Figure 3-5 Airway recruitment- change in the lung volumes as a result of PEP [30,82]

Moving EPP

In terms of moving the equal pressure point, it is known patients with collapsed airway have air tapped behind the collapsed parts of the airways. For those patients, during

exhalation, only the non-collapsed parts of the airway are emptied [147]. All of which leads to heterogeneous emptying of the lungs especially during forced expirations [148].

It is thought that breathing against a resistant works on homogenizing lung emptying during exhalation if used on a regular basis [81,82,87].The improved emptying is due to "the homogenised expiratory flow behaviour and caused by facilitating the EPP to move more peripherally during the expiration which avoids airway collapse and trapped gas" [81,82]. This results in "reduced respiratory flow expressed as a flow plateau during a large part of the flow volume curve and increased end-expiratory flow in combination with an increased FRC" (Figure 3-6) [81,82,87]. Thereby, "the increased FVC and end expiratory flow makes it possible to mobilise secretion in otherwise closed or collapsed, and not reachable, parts of the lungs" [19,81,82,87,149].

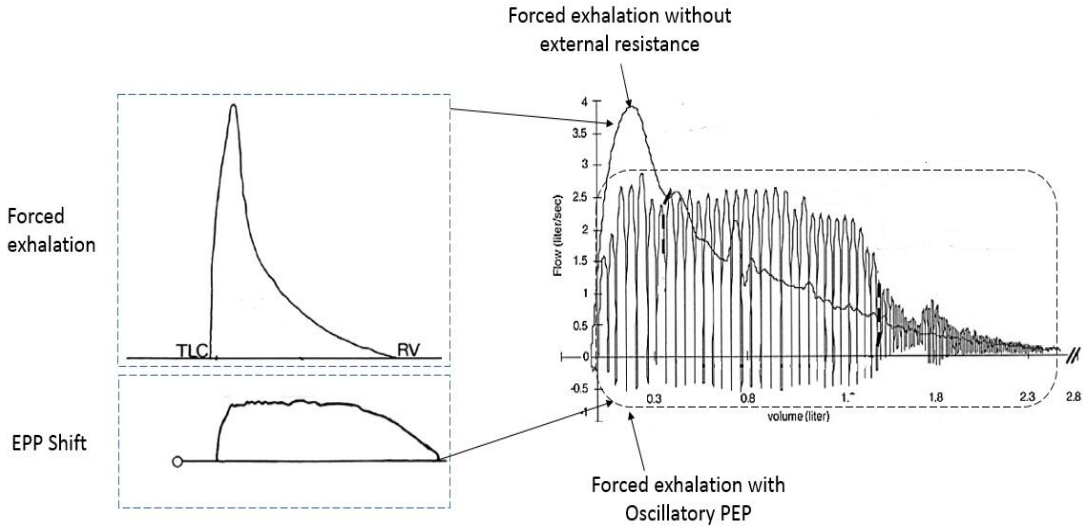


Figure 3-6 Moving the equal pressure point in the airways using PEP [82]

A comprehensive literature search was not conducted as guidelines for using PEP for airway clearance were published by several international originations [150–152]. In addition serval reviews on the topic have been identified [29,116,145,153–155].

Optimum Values

The results from both the best clinical practice guidelines and literature reviews recommend the use of PEP 10-20cmH2O to improve airway clearance without causing any barotrauma to the patients. Table 3-6 shows a list of these review and clinical guidelines.

Table 3-6 Optimum PEP value for effective airway clearance

Reference	Optimum PEP Value for Airway Clearance
[150]	10-20cmH2O
[145]	10-20cmH2O
[156]	10-20cmH2O
[29]	10-20cmH2O
[154]	10-20cmH2O
[153]	10-20cmH2O
[140]	10-20cmH2O

3.3.3 Amplitude

Physiological Effect

Amplitude of a wave can be defined as a measure of its change over a single period [157]. The role of the amplitude in airway clearance by oscillation is the least explored in the literature. In fact only one author proposed that based on the theory that oscillation in airflow promotes micro-movements of the mucus towards the mouth. It was rationalised that such micro-movements are governed by the amplitude of that oscillation wave [54]. It is thought that higher flow rates are generated at higher amplitudes. [55]. In an experiment that was conducted by Van vliet et al. (2005), oscillation amplitude was related to mucus elongation in a tube [128].

A review of the best oscillation amplitude for mucus clearance has not been conducted before. Hence, a comprehensive search of the PubMed and Scopus databases were used to identify relevant publications. Only studies that examined the role of different amplitudes on mucus clearance were included. Also, only studies that applied airway oscillation were included.

Optimum Values

In total 3 studies were found to match the selection criteria. Table 3-7 shows a summary of the optimal amplitude recommended in each one and the method followed in recommending the optimal amplitude.

Table 3-7 Optimum amplitude for effective airway clearance

Reference	Optimum Amplitude for Effective Airway Clearance	Method
[128]	Higher amplitude increases mucus elongation	Experimental
[54,158]	"The higher the flow amplitude the higher the effectiveness"	Theoretical
[159]	"Results suggest that oscillators which generate larger amplitude waves may significantly enhance secretion clearance"	Experimental

Van Vliet et al. (2005) have reported in their experimental study that applying oscillation with an amplitude of 1mm (peak to peak) at 25 Hz and 2 mm (peak to peak) for the 15 Hz frequency showed a consistent increase in mucus clearance [128]. Alves et al. (2008) on the other hand stated that based on the theory that oscillation in airflow promotes micro-movements of the mucus towards the mouth, the higher the flow amplitude, the higher the effectiveness [54]. This study was included because it was the only study that offered a theoretical explanation for the role of amplitude in mucus clearance. Ragavan et al. 2010 on the other hand superimposed oscillation with large amplitudes on cough using different OPEP devices and found that devices which generate larger amplitude waves may significantly enhance secretion clearance [159].

3.4 Discussion

One of the major limitations of previous attempts to optimise the mechanical behaviour of OPEP devices is the lack of correlation between the devices` mechanical behaviour and established technical performance criteria. In this review, the optimum pressure wave parameter values have been established by considering the airway clearance by oscillation mechanisms of action for each parameter and understanding the physiological effect for each one.

The oscillation frequency pressure wave parameter was found to have several proposed mechanisms of action. However, this review was unable to identify any clinical validation that shows the superiority of any one of the mechanisms over another. The Figure 3-7 shows a summary of the optimal frequency values for all different mechanisms of action

as derived from the literature. The figure shows the mean value for the oscillation frequency and the standard deviation.

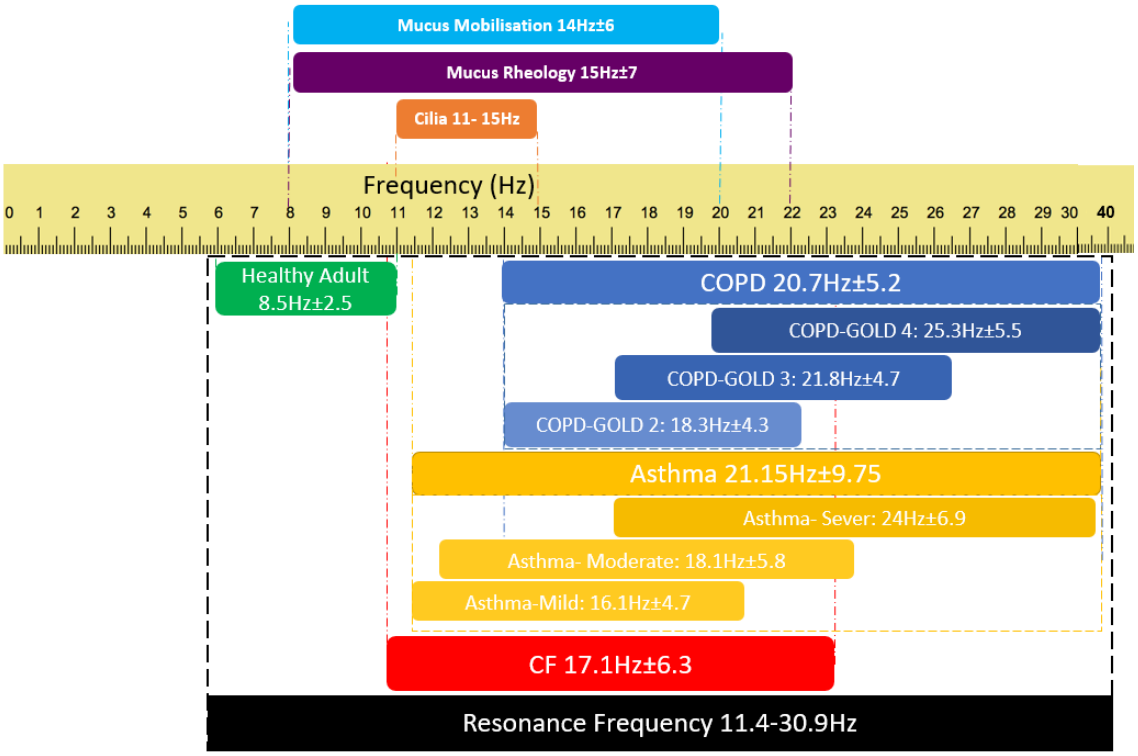


Figure 3-7 Optimum oscillation frequency range for effective mucus clearance by oscillation grouped according to different mechanisms of action

In terms of the PEP optimal value for airway clearance, there is a consensus in the literature that that the optimal PEP value required for effective airway clearance is between 10-20 cmH2O. In terms of the optimum amplitude value, despite the acknowledgement of the importance of this parameter in mucus clearance by oscillation in the literature, the effect of amplitude on mucus clearance by oscillation has been explored in only three studies in the literature. Although the optimum value for the amplitude parameters could not be established, there is an agreement in the literature that higher oscillation amplitude is more effective for airway clearance.

Based on the results of this review, the researcher proposes the following table (Table 3-8) to guide optimising the mechanical behaviour of OPEP devices. The table is a synthesis of the findings of this review. The table proposes the optimum technical performance required for different patient diseases and airway clearance goals. In this

criteria, both patient's diseases and airway clearance goals are grouped under the tiles therapy aims.

Table 3-8 Proposed optimum technical performance criteria for effective mucus clearance by oscillation

Therapy Aim	Disease	Stage	Frequency	PEP	Amplitude
Match Resonance Frequency	Cystic Fibrosis	N/A	17.1 ± 6.3 Hz	10 - 20 cmH2O	As high as can be possibly achieved
	COPD	GOLD 2	18.3 ± 4.3 Hz		
		GOLD 3	21.8 ± 4.7 Hz		
		GOLD 4	25.3 ± 5.5 Hz		
	Asthma	Mild	16.1 ±4.7 Hz		
		Moderate	18.1 ± 5.8 Hz		
		Sever	24 ± 6.9 Hz		
Match Cilia Frequency	Any	Any	14 ± 6 Hz		
Alter Mucus Rheology	Any	Any	15 ± 7 Hz		
Alter Mucus Movement	Any	Any	13 ± 2 Hz		

In terms of how this knowledge can be applied in clinical practice. In the absence of clinical validation of the superiority of different mechanisms of action. The therapy aims proposed above could be looked at in clinical practice from the two points of view; the first is "what works best for a particular patient" rather than "which one is the best". This point of view resembles one of the main principles of physiotherapy ("the application of the technique must be based on the patient's respiratory dysfunction in order to result in the intended airway clearance effects") [9,82]. For example, it is well known that cystic fibrosis patients suffer from large quantities of very viscous mucus [160]. Therefore, optimising OPEP devices mechanical behaviour to the values that are optimum for changing the rheology of the mucus might result in the most effective airway clearance effect. As these values best match the existing respiratory dysfunction for these patients.

Similarly, optimising OPEP devices mechanical behaviour according to the prognosis stage of COPD patients might allow for better airway clearance results [60].

The second point of view is; rather than thinking that "there is one mechanism of action that is responsible for the airway clearance effect", the different theoretical perspective can be thought of from the point of view that "a combination of these mechanisms work together to produce the airway clearance effect". Therefore, combining more than one therapy aim as part of an OPEP device treatment plan might be most beneficial to achieve better airway clearance results. This last point was proposed in one paper [161]. For example, for cystic fibrosis patients, in addition to adjusting OPEP device mechanical behaviour to the optimum values for altering mucus rheology, it might be more effective to also adjust the device to the optimum pressure wave parameters for cystic fibrosis, as part of a therapy program that alternates between these aims.

3.5 Chapter Summary

The effectiveness of mucus clearance by oscillation is thought to be dependent on the pressure wave parameters of the oscillatory pressure wave. Several mechanisms of action have been proposed to explain the role of each parameter.

In this chapter it was found that:

- For the frequency parameter, the mechanisms of action are still debatable, and there is a lack of clinical validation of the relative superiority of any of these mechanisms.
- The optimum oscillation frequency value varies widely from one mechanism of action to another. Furthermore, the optimum values for each mechanism are identified.
- In terms of PEP, there is consensus in the literature about the role of this parameter in airway clearance. In addition, a range of optimum PEP values is identified to be between 10 to 20 cmH2O in several studies and clinical guidelines.
- For the amplitude, in-vivo and in-vitro studies are needed to identify the optimum value for effective airway clearance. However, higher oscillation amplitude is thought to result in better airway clearance.

Finally, the findings of this review have been synthesised in the form of a table. In the absence of clinical validation of the superiority of different mechanisms of action. The proposed table could be looked at in clinical practice from two points of view; the first is "what works best for a particular patient" rather than "which one is the best". The second point of view is that, rather than thinking that "there is one mechanism of action that is responsible for the airway clearance effect", the different theoretical perspectives can be thought of from the point of view that "a combination of these mechanisms work together to produce the airway clearance effect".

4 RESEARCH DESIGN

This chapter describes the overall methodology and methods used to address the aim and objectives of this research. The chapter will also describe the philosophical and theoretical perspectives adopted in this research, in addition to the research approach, strategy, and choice, the chapter will also describe the methods followed to collect and analyse data to address the aim of this research.

4.1 Introduction

Research design refers to "the overall strategy that the researcher chooses to integrate the different components of the study in a coherent and logical way, thereby, ensuring he will effectively address the research problem" [162] as unambiguously as possible [163]. The methodological Choices when designing research have multiplied to a point where researchers have many Choices. Therefore, it is recommended to have a framework to guide the research design, from assessing the philosophical stance to the data collection and analysis procedures [164].

Nevertheless, one of the main challenges in framing the research design is the disagreement among scholars about the names, the order and the nature of research stages [165]. Such disagreement was very clear between Crotty's [166] and Sunders et al. [167] research frameworks. According to Saunders et al. (2007), research can be classified into several stages. These include; philosophies, approaches, strategies, Choices, time horizons; techniques and procedures. These "layers" of classification describe the general steps of a research process as seen by Saunders et al. On the other hand, [166] has narrowed the stages of classification to include; epistemology, theoretical perspective, methodology and method. In a similar way to Saunders`s layers' classifications, Crotty`s narrows the research process to stages that also serve as the general steps of research.

A main issue with the Saunders et al. model, is the mix between the epistemology and the theoretical perspective (i.e. according to this model, positivism and subjectivism are classified as philosophies). In comparison, Crotty`s model was not only clearer in distinguishing between the epistemology and theoretical perspective, but also more helpful in justifying the researcher decision at each layer or stage since they are related to each other. Nevertheless, the Saunders et al. framework gives a clearer breakdown of the

methodological process. Crotty`s model, on the other hand, did not give a clear breakdown of the various methodological choices and order of these.

This research adopts a framework constructed by the researcher but based on both Crotty`s and Saunders`s frameworks (Figure 4-1). According to this framework, the first stage of the research design starts with deciding on the philosophy of the research from both the epistemological and theoretical perspective. The second stage is defining the methodological approach to the research. This includes; approach, strategy and Choice. The last stage is describing the method (the exact steps and procedures according to which the research will be conducted).

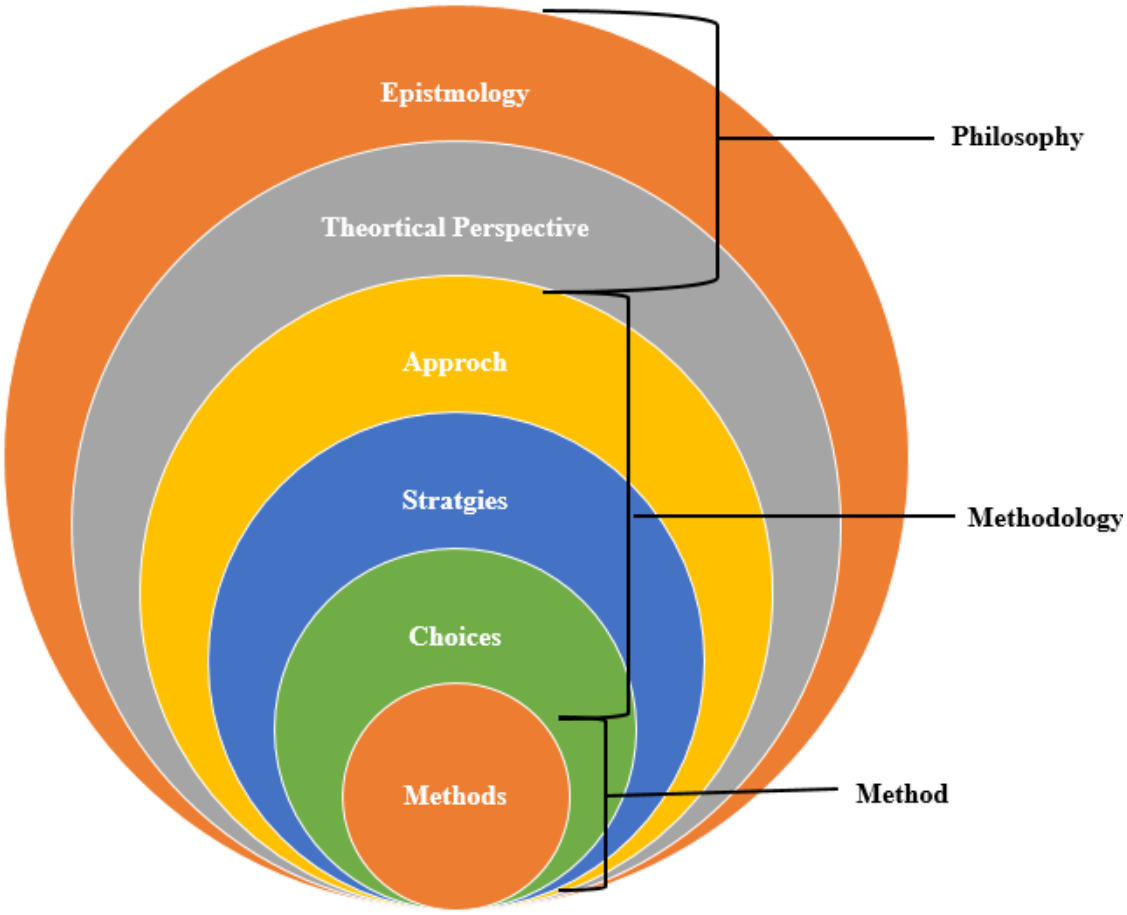


Figure 4-1 Research design framework [166,167]

4.2 Philosophy Used in this Research

4.2.1 Epistemology

Contributing to knowledge is the aim of all research studies. However, when it comes to understanding what constitutes knowledge and how it can be acquired from the world, there are different philosophical perspectives that exists in this regard. Epistemology, is a term that is used to describe the philosophy of knowledge. Therefore, it is sometimes referred to as the theory of knowledge [168].

According to Crotty, epistemology is about "how we know what we know" [166,169], or "the nature of the relation between the knower and what can be known" [170]. It is also related to ontology "the study of being" or "the nature of reality" [166]. Since both epistemology and ontology are related choosing one will have implication for the other and vice versa [166]. Epistemology can be thought of as the principles by which the researcher decides what does and does not constitute warranted, or scientific knowledge [171]. Adopting certain epistemological perspectives forms the base for the research approach[172]. In addition, an epistemological perspective upon which the research is based dictates how the researcher views the knowledge and how the contribution of the research should be perceived by others [173,174].

Crotty (2007) suggests that there are three main epistemological perspectives; objectivism; subjectivism and constructivism. Objectivism holds the ontological view that reality exists apart from the operation of any consciousness. It also holds the epistemological view that "things have truth and meaning residing in them as objects, and that such objective truth and meaning can be discovered through appropriate methods of inquiry" [166,169]. From this standpoint, the purpose of knowledge is often to explain, predict and control [175]. In addition, according to this perspective, the researcher tries to find causes, effects, and explanations. They try to "predict events and test theories and hypotheses". On the other hand, subjectivism holds the ontological view that reality is a constructed cognition and the epistemological view that "meanings are created out of whole cloth and simply imposed upon reality" [166,169]. In contrast to subjectivism and objectivism, constructivism holds the ontological view that reality and objects are inextricably intertwined with human consciousness and that "reality is socially constructed", therefore reality is different according to its context and the case under

investigation. Therefore, constructivism holds the epistemological view that "truth is not discovered but constructed" [166].

This research is not an individual reconstruction coalescing around consensus, as would be done in constructivism [170] and it did not create something out of nothing as would be done in subjectivism [166]. This research adopts an objectivist epistemology. This research believes that the optimum mechanical behaviour of OPEP device is something that exists regardless of the current state of consciousness of such knowledge or truth. The researcher also believes that such truth can be discovered using appropriate methods of inquiry. The existence of this truth will be investigated through cause and effect observation of the object (OPEP device) while maintaining the independence between the observed (i.e. variables of interest) and the observer (researcher).

4.2.2 Theoretical Perspective

Crotty (2007) defines theoretical perspectives as "the philosophical stance informing the methodology and thus providing a context for the process and grounding its logic and criteria". According to Crotty (2007), there are several theoretical positions; positivism, post-positivism, pragmatism, interpretivism, participatory and postmodern (Figure 4-2). These theoretical perspectives are a continuum of epistemological positions [166].

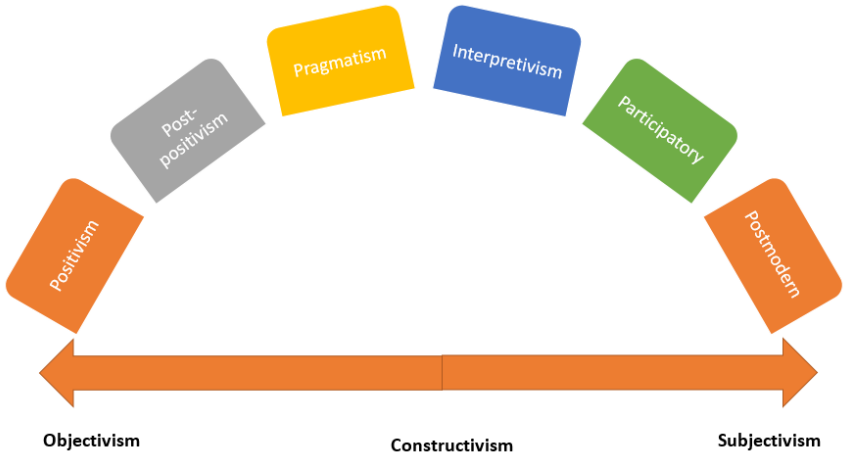


Figure 4-2 Research theoretical perspectives and their relation to epistemology [166]

Post-positivism is a theoretical perspective that amend positivism and build on its shortages. Post-positivism holds a deterministic perspective in which "causes (probably) determine effects or outcomes". In this sense, while post-positivism hold into the

objective reality, unlike positivism, it believes that such reality "can be known only within a certain level of probability" [166,176]. Therefore post- positivists are "aware that the inquiry is value-laden (the inquiry is influenced by the researcher's theories and values), that facts are theory-laden (research is influenced by the theories investigators use), and that the same facts can be explained by several theories" (also called under-determination of theory by fact) [176]. Yet, post-positivists "reflect the need to identify and assess the causes that influence outcomes, such as found in experiments". Post-positivism is also "reductionistic in that the intent is to reduce the ideas into a small, discrete set to test, such as the variables that comprise hypotheses and research questions". Also, the knowledge that develops through a post-positivist lens "is based on careful observation and measurement of the objective reality that exists "out there" in the world" [164]. Thus, developing numeric measures of observations becomes paramount for a post-positivist [164].

This research adopts the post-positivist perspective. This research tries to uncover the optimum OPEP device mechanical behaviour as best as possible using appropriate methods of inquiry. The process of uncovering such truth was both "based on and influenced by" the previous research and existing theories, which influenced the methodological design of this research as well as the explanation of the results.

4.3 Methodology Used in this Research

Research methodology can be defined as "The strategy, plan of action, process or design lying behind the Choice and use of particular methods and linking the Choice and use of methods to the desired outcomes" [166]

4.3.1 Research Approach

Research can be classified based on approach into, deductive and inductive. In general terms, "deductive research works from the more general to the more specific, while inductive research works the other way around, moving from specific observations to broader generalisations". In the deductive approach, "research begins with forming hypotheses and theories, which are later, tested by the research strategy developed specifically for that matter. Deductive types of research are mostly applied to research areas in which there are pre-defined theories are available. The inductive research follows

the reverse logic of the deductive approach. This means that inductive research it aims to develop theories based on data analysis results. This type of research is carried out in disciplines where there are no or little theories available and the body of science needs theories and structures defined" [167,177].

In terms of the relationship between the research approach and the philosophy of both the epistemology and the theoretical perspective, according to [178] "…which come first: the theory or the data?...represents the split between the positivist and constructionist paradigms in relation to how researcher should go about his or her work" [178]. However, different authors have argued that "the deductive approach to research has become synonymous with positivism and post-positivism, whilst inductive approach with social constructionism" [167,179–181]. In the case of post positivism, it can be argued that logic governing and influencing both the design of the research and the results explanation is primarily deductive [164,176].

In this research, the literature review has identified a set of variables that influence the mechanical behaviour of OPEP devices, in addition to optimum technical performance requirements based on several existing theories. This research will utilise these findings as the basis to address the research aim. In that sense, the process to uncover the truth is proposed and deduced in a logical manner from the literature.

4.3.2 Research Strategy

Research strategy is a key part of the research methodology because "it defines the method of data collection based on the research objectives, the existing knowledge in the field of research, the available time as well as other resources and the underpinning research philosophy" [167]. According to [167] there are seven research strategies (experiment, survey, case study, action research, grounded theory, ethnography and archival studies). It is important to stress out that none of these strategies is considered superior to another [182].

As described in the previous sections, objectivity and post-positivism have been adopted as the epistemological stance and theoretical perspective respectively. Objectivists believe in causality, that is, "there are independent causes that lead to the observed effects", and hypotheses are either verified or refuted by the observed effects [183]. When

it comes to research strategy, objectivism is predominantly characterised by the feature of experimental research strategies [164,167,183]. In the same vein, post-positivism implies that "the researcher is working with an observable ... reality and that the end product of such research can be the derivation of laws or law-like generalisations similar to those produced by the physical and natural scientists" [183]. Post-positivism also holds a deterministic view of the world and knowledge according to which the world is governed by cause and effect. Such cause and effect are understood through a methodology of careful observation and experiments that are repeatable [164].

Experimentation can be defined as; the process of examining the truth relating to some research problem [184]. Experimental research aims to "investigate the possible cause and effect relationship by manipulating one independent variable to influence the other variable(s) in the experimental group, and by controlling the other relevant variables, and measuring the effects of the manipulation by some statistical means" [185].

The current research aims to identify OPEP devices optimum mechanical behaviour for effective airway clearance. This research holds both; a deterministic and a reductionistic view, both of which have unfolded from the epistemological and theoretical perspective adopted in this research. The pursuit of "scientific truth" in this research (optimum mechanical behaviour for effective airway clearance) held a deterministic view that events have causes which are distinct and analytically separate from them (OPEP device settings that will achieve pressure wave parameters satisfying optimum technical performance requirement). It also holds the reductionistic view that in the form of the scientific attempt to provide explanation in terms of ever smaller entities (i.e. variables that influence the mechanical behaviour of OPEP devices). Therefore, the research began with a literature review to identify and define OPEP device mechanical behaviour variables and the optimum technical performance requirements for effective airway clearance by oscillation. The relationship between the mechanical behaviour variables will then be tested in an objective repeatable experiment, and such relationships will be mathematically modelled. Finally, the research aim will be achieved by optimisation methods to the mathematical models to characterise the optimum mechanical behaviour of OPEP devices.

4.3.3 Research Choice

There are two main methods for research; qualitative and quantitative. In broad terms, quantitative research involves numeric data. In this type of research, the collected data is numerical and it is analysed in numerical and statistical fashion. In contrast to quantitative research, qualitative research "utilises data collection and analysis methods that are specifically designed for non-numeric data" [164]. Fundamentally, quantitative research is concerned with data that can be quantified numerically, whereas qualitative research adds a contextual dimension providing rich descriptions that are not easily measured using quantitative methods alone [186,187].

From a research philosophy point of view, qualitative research assumes that "reality is subjective and multiple as seen by participants in a study" and "the researcher interacts with that being researched". On the other hand, quantitative assumes that "reality is objective and singular apart from the researcher" and "the researcher is independent from that being researched". Hence, conventionally, quantitative research is based on and related to an objective philosophy [164]. From a research strategy perspective , it can be argued that quantitative methods are not only inherently linked to experimental design, but also that experiential research is a classification of quantitative research [188]. Quantitative research by definition is "a systematic, empirical investigation of observable phenomena via statistical, mathematical or computational techniques" [189]. Therefore, experimental research has emphasis on the generation and use of quantitative data [190].

This research tries to objectively uncover the scientific truth stated in the aim of the research. As explained previously, quantitative method is inherently linked to the objective research philosophy. Therefore, a quantitative Choice corresponds with the philosophical perspective of this research. In addition, quantitative research has been the method of Choice primarily because the current research is based on an experimental strategy that investigates a causal relationship between sets of variables. This relationship is central for the truth being pursued in this research. The set of variables under investigation in this research were found to be primarily numeric. Also the relationship between these variables will be expressed, represented and optimised utilising a mathematical model.

4.4 Methods Used in this Research

Research methods can be defined as “the techniques or procedures used to gather and analyse data related to a research question. Therefore it is important to find a method which is compatible with the kind of thing one is trying to investigate” [166].

4.4.1 Method Overview

This research will first start by developing and validating an experimental set up capable of measuring OPEP device mechanical behaviour. This experimental set up will be used to collect mechanical behaviour data from several OPEP devices. The data will be used to build a mathematical model of such behaviour. Then optimisation techniques will be applied to the model to identify and characterise optimum mechanical behaviour of OPEP devices for effective airway clearance. The optimum mechanical behaviour characterisation will be validated for feasibility and usefulness with clinicians and respiratory therapist.

The research method falls in two main sections; experiment method and optimisation method. Figure 4-3 shows an over view of the research method.

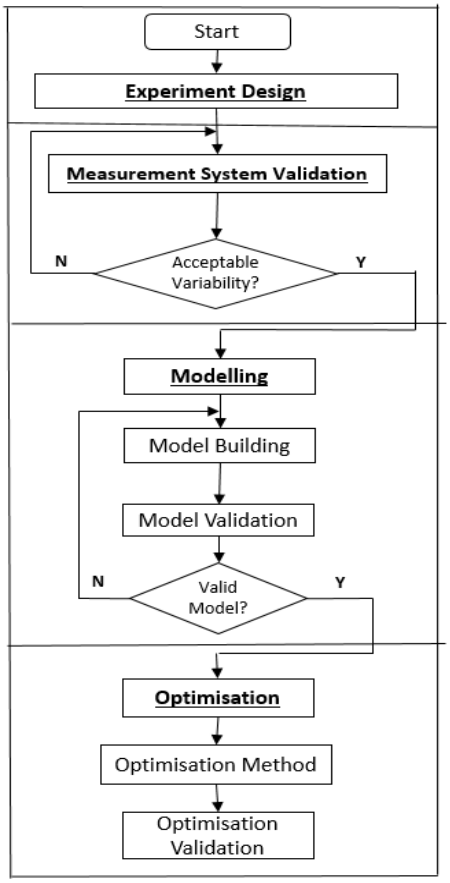


Figure 4-3 Research Method Overview

4.4.2 Experimental Method

4.4.2.1 Experiment Design

A well-designed experiment is crucial in experimental research [191]. Experimental research methodology is based on three principles of experiment design; replication; randomization and local control. According to the principle of replication, repeating the experiment more than once will increase the statistical accuracy of the experiment [184]. It is important here to clarify that replication and repetition are two terms used in experiment design, but they have different meanings. Replication means that the repetition will be carried out in a specific manner [192]. So replication occurs when the entire experiment is performed more than once for a given set of independent variables. Therefore, each set of the experiment is called a replicate. On the other hand, repetition is the measurement of a dependent variable more than once under the same conditions. So repeating occurs when each run is conducted N numbers in a row. While the

replication occurs whereby the entire experiment is repeated N numbers in a row [193] While repetition allows one to determine the inherent variability in the measurement process [193], replication increases the precision of the estimate of the effects in an experiment and allows the researcher to obtain an estimate of the experimental error [191].

In terms of the randomization principle, the experiment is designed "in such a way that the variations caused by extraneous factors can all be combined under the general heading of chance." In this sense, the extraneous factor is the undesirable variables or experiment error that influence the relationship between the variables that an experimenter is examining [184]. Randomization ensures that the measured effect is protected from any extraneous factors effect.

According to the principle of local control on the other hand, when conducting an experiment, "the extraneous factors and the known source of variability are made to vary deliberately over as wide a range as necessary and this needs to be done in such a way that the variability it causes can be measured and hence eliminated from the experimental error" [184].

Experimental design refers to "the framework or structure of an experiment" [184]. Experiment designs can be classified into formal and informal design. Informal experimental designs normally uses a "less sophisticated form of analysis based on differences in magnitudes", whereas formal experimental designs "offer relatively more control and use precise statistical procedures for analysis" [184]. As this research seeks to systemically investigate a problem and collect data in order for valid conclusions to be drawn, a formal experimental design was followed.

Formal experiment designs can be split into; complete randomised design, complete randomised block design, latin square design and factorial designs. Randomised complete block design (RCBD) is an experiment design in which all three of the previously described principles of experiment can be applied [184]. The word block refers to the relatively homogenous experimental unit, and it represents a restriction on complete randomization because the treatment combinations are are randomised in blocks. Blocking can be used to systematically eliminate the effect of a known and controllable

source of variability on the statistical comparisons among treatments. The word complete means that each block contains all the treatments [191].

This research adopted a randomised complete block design. The experiment design incorporated all three previously described experiment principles.

4.4.2.2 OPEP Device Selection

Because of the time constraints for this research, the optimising effort in this research was limited to five commercial OPEP devices. For confidentiality reasons device names will be anonymised. The selected OPEP device will be classified based on their mechanical components arrangements to generate the OPEP therapy into type A and B. Table 4-1 shows a summary of the selected OPEP devices.

Table 4-1 Investigated OPEP devices (Devices types and anonymised names)

Device Type	Device Anonymised Name
Type A	Device A
	Device B
	Device C
	Device D
Type B	Device E

Type A devices range has been selected because they are commonly used in clinical practice [20,194] and a lack of evidence to support clinical practice has been reported for these devices [22]. Type B is a new OPEP device that was included because it`s technical performance has not been evaluated before and increasing being used in the clinical practice.

4.4.2.3 Experiment Variables and Their Levels

The literature review has identified two sets of variables relevant to OPEP device mechanical behaviour. Exhalation flow and resistance level are independent variables. In addition to the oscillation frequency, PEP and oscillation amplitude are dependent variables to be observed in the experiment.

When using OPEP devices in real life scenarios, the expiratory manoeuvre results in an exponential decay of the exhalation flow. However, investigating OPEP device mechanical behaviour at constant flow would describe the performance envelope for exponential flow [50]. In addition, using constant flow will allow for precise control of the experiment and will lead to a better characterisation and understanding of the mechanical behaviour of these devices [50,78].

In order to allow for a direct comparison between the devices, all devices were tested under the same exhalation flow range. In addition, this research investigated OPEP devices under all resistance levels as it allows for better characterisation of their mechanical behaviour.

In terms of the exhalation flow range under which OPEP devices were investigated, this research used the reasoning proposed by [50] to decide on the upper and the lower exhalation flow limits. The exhalation flow range was reasoned as following; when using OPEP devices, clinical procedure instructs the patient to take a deep breath but not to completely fill their lungs (around 80% of their lung capacity), then to exhale steadily for at least 4 seconds, but not to exhale completely to functional residual capacity [57,75]. Therefore the exhaled volume would be somewhere between a large tidal volume and a forced vital capacity (Figure 4-4) [50].

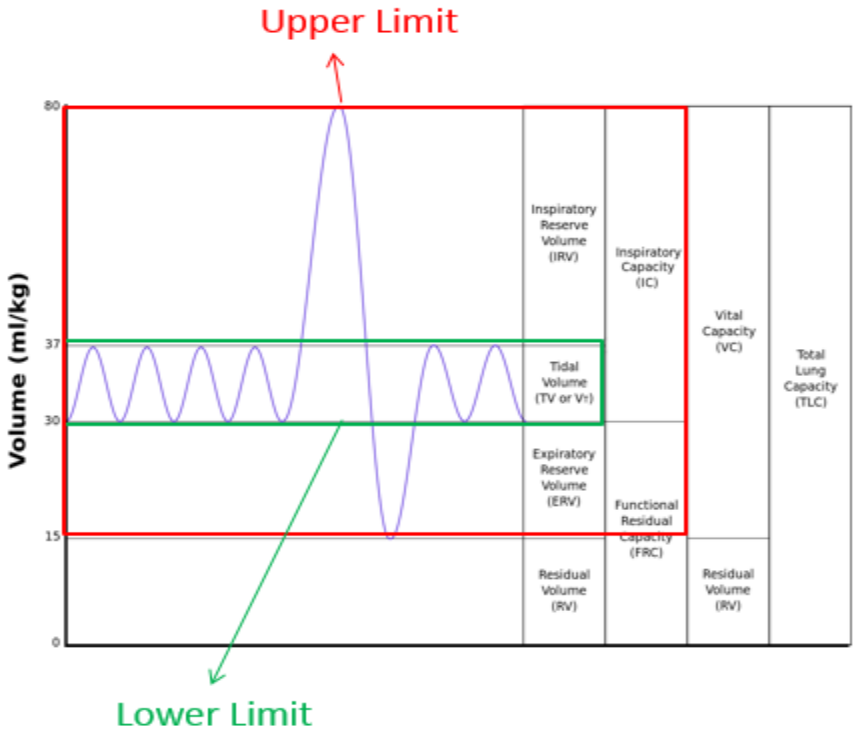


Figure 4-4 Exhalation flow range rationale based on lung volumes [4]

A general rule of thumb used in clinical practice to calculate the tidal volume of the patient is 10ml/Kg [195]. Therefore, the lower value for expiratory flow would be the multiplication of body weight with 10mL. Then, dividing the obtained value by 4 (the length of time it takes to exhale this volume of the OPEP exhalation procedure was followed correctly). Hence, the lower exhalation flow value would be as following (10 mL/kg × 40 kg = 400 mL divided by 4 section = about 6 L/min). For the upper flow limit, forced vital capacity for patients has been observed in clinical practice to be 2 L which is a high value. The 2L exhaled in 4 seconds will result in 30 L/min exhalation flow.

Table 4-2 shows a list of the experiment independent variables and the levels that used in this research experiment.

Table 4-2 Levels of the experiment variables

Variables	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6
Flow (L/min)	5	10	15	20	25	30
Resistance Levels	1	2	3	4	5	-

4.4.2.4 Experiment Table Design

The routine or the process used in collecting experiment data represent the corner stone for the results and conclusions that can be drawn from this data. Therefore, a well-designed experiment is crucial [191]. Nevertheless, variability is a natural part of any experimentally collected data [196,197]. As such, understanding the amount and the source of experiment variability is crucial to collect valid data from which a valid conclusion can be drawn [197]. The variability in experimentally collated data can be systematic, which is variability attributed to changes in the independent variables (i.e. exhalation flow, resistance levels). Unsystematic variability which the variability attributed to extraneous factors (i.e. measurement system error, human error, inherit variability in the object being measured) [196,197].

When conducting an experiment, each experimental run is a test [191]. In the case of this research, every combination of the independent variables is a run. Hence a full experiment is composed of 30 experimental runs.

In this research, an experiment table (Table 4-3) was constructed using Commercial Software (JMP 12.0) (SAS Inc., USA). The standard order in the experiment table specifies the order in which the experiment should be conducted and the combination of flow and resistance levels to be set in each run. The standard order was randomised to satisfy the randomization principle of experiment design.

Table 4-3 Experiment table

St Order	**23**	**24**	**16**	**22**	**14**	**30**	**20**	**6**	**2**	**1**	**27**	**25**	**17**	**3**	**19**
Flow	25	25	20	25	15	30	20	10	5	5	30	25	20	5	20
Resistance	3	4	1	2	4	5	5	1	2	1	2	5	2	3	4
St Order	**11**	**4**	**5**	**10**	**12**	**7**	**29**	**18**	**26**	**13**	**15**	**9**	**28**	**8**	**21**
Flow	15	5	5	10	15	10	30	20	30	15	15	10	30	10	25
Resistance	1	4	5	5	2	2	4	3	1	3	5	4	3	3	1

4.4.2.5 Data Acquisition System

According to [57], in order to properly evaluate the mechanical behaviour OPEP devices, a specialised measurement system is required. As such a sensitive flow and pressure transducer is central for the measurement system [57]. According to a rule of thumb

suggested by Nyquist theorem; “the sampling rate of the pressure transducer should be at least 2 times the highest frequency of the measured signal from the device being tested” [198].

TSI Certifier Plus (4080, TSI Inc., Minnesota) is a data acquisition system mainly used for testing and validating ventilators and different respiratory care medical equipment (Figure 4-5). This system was used in this study for collecting pressure data and monitoring flow. It is equipped with high resolution flow (accuracy: ±0.075 L/min, range: -200 to +300 L/min) and differential pressure (accuracy: ±0.15 cm H_2O, range: -25 to +150 cm H_2O) sensors. The system is capable of collecting flow and pressure data at a 1000 Hz sampling rate. The system is also capable of exporting the data to an external SD card for further analysis [199]. The system was calibrated prior to use, by the manufacturer.

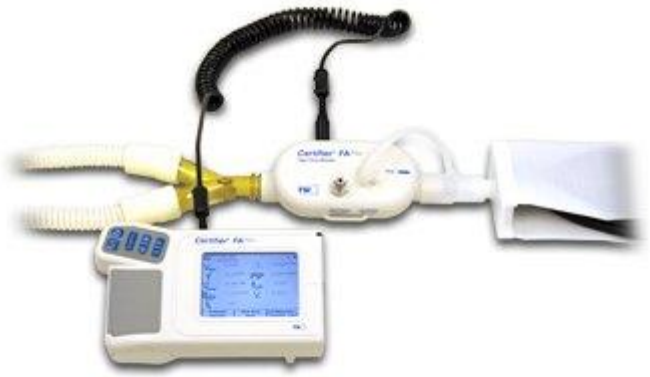


Figure 4-5 TSI certifier plus data acquisition system (picture obtained from http://www.tsi.com/certifierfaplus)

4.4.2.6 Experimental Setup

The experiment setup is shown in Figure 4-6. All devices were studied with the long axis parallel to the counter, which simulates the patient use position when holding the device. Each OPEP device was evaluated at constant adjustable air flows from a manually operated compressed wall air gas source. The pressure of the compressed air was regulated to 60psi throughout the test using a calibrated pressure gauge. Regulating the

pressure of the gas source reduces any unwanted fluctuations in the gas flow. The wall air gas source was connected to the proximal end of a flow controller valve. The distal flow controller valve was connected to the calibrated TSI flow measurement module. The flow was measured and monitored throughout the test on the TSI interface module. In order to capture the oscillatory pressure wave produced by the OPEP devices, the calibrated TSI pressure measurement module was positioned in series with the wall air gas source and the OPEP device. The OPEP devices were connected at the distal end of the TSI pressure measurement module. Each OPEP device was placed in normal 0-degree orientation. Both the pressure and flow measurement module were connected to the TSI interface module.

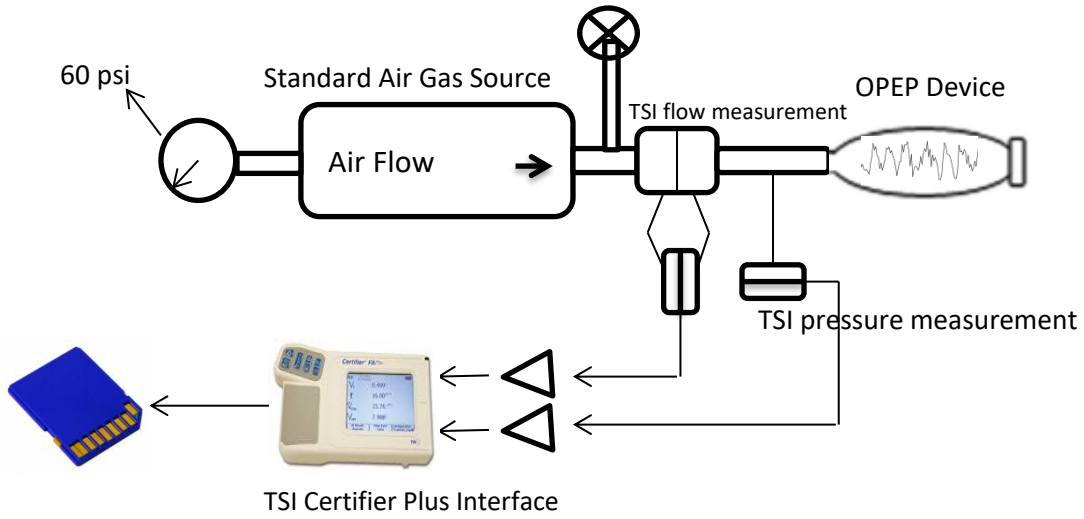


Figure 4-6 Experimental setup diagram

4.4.2.7 Experimental Procedure

The OPEP devices were connected one at a time and an experimental run was made on each device as per Table 2 in one session (including any repeats of replicates). The experiment began with adjusting the flow and resistance levels as per experiment Table 2. Once the desired flow was reached, the system was allowed to stabilise for 5 seconds. The stabilisation time ensures that the system had reached stability before samples were collected. Following the stabilisation wait time, the pressure data was recorded at a sampling rate of 1000 Hz continuously for 15 seconds and then exported onto an SD card. The pressure data was stored on the SD card in the form of a CSV file. The CSV file

contained 150,000 pressure and flow readings, each stamped with time. A full reset was performed between each experimental run.

4.4.2.8 Data Processing

Data processing was conducted on a platform constituting Intel i5-3360M microcomputer, 2.8 GHz, 16GB of RAM, 1TB HD and Windows 7 64-bit operating system (Microsoft Inc.). For the purpose of calculating the values for each of the three responses from the collected raw pressure data, a specialised software module was built (8.5Appendix A1 and A2). A LabVIEW 2014 32-bit version (National Instruments, Austin, TX) was used to build the module. The built LabVIEW module was validated by collecting representative data and calculating the value for each of the three pressure wave parameters manually, then comparing results to the values obtained by the module.

The pressure wave parameters were calculated using the whole 15 second acquired row pressure data. The value of the PEP was calculated by averaging the collected pressure values. Both the frequency and amplitude were calculated using a Fast Fourier Transformer (FFT) power spectrum algorithm. Such algorithms have been used before by [55] to calculate the frequency and amplitudes of the Flutter OPEP device from pressure data.

In order to calculate the amplitude value from the pressure row data, in addition to the FFT algorithm, a LABVIEW algorithm, "multi-scale peak detection" was used to detect the values of peaks and valleys of the oscillation, then the values of peaks and valleys were subtracted to calculate the amplitude. Furthermore, the amplitude value was calculated manually by taking three peak and valley readings from beginning, middle and end of the wave. The two results were compared as a sanity check.

4.4.2.9 Measurement System Validation

Experiment Repetition

The purpose of measurement system validation in an experiment is to establish if the experiment as a whole is valid to be used for the purpose of measuring OPEP device mechanical behaviour. Data was collected from all five OPEP devices using the data acquisition system described in 4.4.2.5 and using the experiment set up described in 4.4.2.6. The experiment procedure described in 4.4.2.7 was followed when collecting the

data. In order to evaluate the inherent variability in the measurement system, the whole experiment was repeated three times on the same OPEP device sample under the same conditions for all five OPEP devices.

Data Analysis

Standard deviation, is a mathematical formula that is used to describe a variation or dispersion of a set of data values [184]. Analysis of variance (ANOVA) is a collection of statistical methods used to breakdown the "total amount of variation in a set of data into two types; the amount which can be attributed to chance and the amount which can be attributed to specified causes" [184]. The equations for ANOVA can be found in [200].

The analysis of the data collected for measurement system validation was done in two ways; firstly, the variability in each of the pressure wave parameters was analysed by calculating the arithmetic mean of the experiment repeats at every standard order point. The standard deviation of the three repeats at each standard order point was calculated. In addition, the average standard deviation (arithmetic mean of all standard deviations) was calculated.

Secondly, the contribution percentage of the systematic variability source and unsystematic variability was calculated using ANOVA. According to [200] a general rule of thumb for measurement system acceptability is; an unsystematic variability percentage under 10% indicates an acceptable measurement system. While a value between 10% and 30% the measurement device may be acceptable depending on the importance of the application and the initial and operational costs of the device [200].

4.4.2.10 Model Building Method

Experiment Replication

In order to build the model, data was collected from all five OPEP devices using the data acquisition system described in section 4.4.2.5 and using the experiment set up described in 4.4.2.6. The experiment procedure described in section 4.4.2.7 was followed when collecting the data. However, for the purpose of model building, the experiment was replicated on three different samples for each of the five OPEP devices instead of repeating the experiment three times on the same sample. Data was also processed as described in section 4.4.2.8.

In terms of data analysis, the ANOVA method was used first to establish the level of unsystematic variability in the collected data. Once the unsystematic variability was confirmed to be acceptable, data collected from the three samples for each device was averaged and used for model building.

Model Specification

When a certain phenomenon and it`s characteristics are so well understood, models can be developed to describe this phenomenon. Models can be of two types, mechanistic and empirical. A model that directly represent the physical components or mechanism of a system is called mechanistic. While experimentally determined models are referred to as empirical models [191]. Mechanistic models take account how the system works in the real world and how the components interact with each other. While an empirical model the model tries to account quantitatively for changes in the system associated with different conditions. [201]. Empirical models offers the advantage of being able to describe the infinite complexity underlying a system or a phenomena [202].

An empirical model is a quantitative equation that describes the relationship between the independent and dependent variables of a system [191]. Response surface methodology (RSM) is "a collection of mathematical and statistical techniques useful for the modelling and analysis of problems in which a response of interest is influenced by several variables, and the objective is to optimise this response" [191]. RSM has been used in a previous OPEP device optimisation attempt [77]. Therefore, RSM has been adopted in this research to address the research aim.

Regression analysis is a statistical tool that is wildly used for building empirical models (including RSM) by estimating the relationship between variables [191,203]. The relationship between factors and responses being explained by the model, and number of these factors and responses determines the type of regression to be used for model building. Regression analysis can be split based on the number of factors into simple and multiple, based on the number of responses into univariate or multivariate and based on the relationship between the factors and responses into linear and non-linear [204]. Table 4-4 shows these different types of regressions and the conditions for each. The modelling of the mechanical behaviour of OPEP devices in this research is a multivariate multiple linear regression.

Table 4-4 Regression analysis types [204]

Type of Regression	**Conditions**
Univariate	Only one quantitative response variable
Multivariate	Two or more quantitative response variables
Simple	Only one predictor variable
Multiple	Two or more predictor variables
Linear	All parameters enter the equation linearly, possibly after transformation of the data
Nonlinear	The relationship between the response and some of the predictors is nonlinear or some of the parameters appear nonlinearly, but no transformation is possible to make the parameters appear linearly

Model Fitting

The process of estimating the model parameters based on collected data is referred to as model fitting [204]. The method of least squares is often using when building regression models to estimate the models parameters [191,204]. The least square method is a "mathematical procedure for finding the best-fitting curve to a given set of points by minimising the sum of the squares of the offsets ("the residuals") of the points from the curve". The least square method has been described in detail in [191]. In general, "goodness of model fit" is assessed based how close are the predicted values to the observed data values. R-square (R^2 or Coefficient of determination) is a number that the "goodness of the fitting". The R square value is the number that describes how well the observed outcomes are predicted by the model, as the proportion of total variation of outcomes explained by the model [197]. It is worth pointing out that curve fitting using least square method is an iterative process, therefore, the process has to be repeated until a satisfactory output has been obtained [204].

Least square and the best-fitting curve were used to model the relationship between the OPEP device settings and pressure wave parameters. The model order was decided based on the value of R square (R^2) in an iterative approach until the best fit was achieved.

Evaluating model coefficients

In order to fit the simplest model that described the system under investigation, the significance of the model terms should be evaluated. AVOA method is usually used for this purpose. Backwards elimination is a strategy that can be used to evaluate the significance of the model terms. Using this strategy, the model is first built; then each term is evaluated by the ANOVA method. The least significant term is removed from the model. This iterative evaluation strategy stops when all the model terms satisfy the specified alpha value [205].

In this research, the backward elimination strategy was used to evaluate model terms. Alpha was set to be 0.05.

Model Adequacy Checking

Regression analysis has the following assumptions [206]:

“

1- The relationship between the response y and the repressors is linear, at least approximately.
2- The error term has constant variance.
3- The errors are uncorrelated.
4- The errors are normally distributed.

”

Violation of any of the regression assumptions will result in an unstable model. Violation of regression assumptions can be detected by the examination of the standard summary statistics, (i.e. the t or F statistics, or R^2) [206]. A model is considered satisfactory when the regressing is significant and has a high R square (R^2) value [205]

Nevertheless, a model that is significant and has a high R-square (R^2) value does not always mean that the model is correctly explaining the variation in the data. Therefore it is necessary to evaluate the residuals plot [205]. Studying residuals (the difference

between predicted and residual values) is the primary method widely used for model adequacy checking [206]. Plotting residuals and studying the plot is a very effective way to investigate how well the regression model fits the data and to check for any violations of the regression assumptions [191]. In this research standardized residual plot was used for model adequacy check.

Model Validation

Regression models can be validated in several ways. According to [206], a collection of new data with which to investigate the model`s predictive performance is one of the most effective methods to validate regression models. If the model gives accurate predictions of new data, this will give greater confidence in both the model and the model building process.

R square prediction ($R^2\ prediction$) is a statistical method used to show how well the regression model predicts responses of new data. If the ($R^2\ prediction$) drops significantly lower than the original (R^2), this will indicate a problem with the model (i.e., too many terms in the model) [206]

In order to validate the built model, a new set of data was collected from all five OPEP devices. Data was collected from three new samples, different to those used for model building. Data was collected using the same procedure for modelling data collection described in section 0. Finally $R^2\ prediction$ was calculated for each model. The equations can be found here [206].

4.4.3 Optimisation Method

4.4.3.1 Defining the Optimisation Problem

The word optimisation refers to the procedure of finding and comparing feasible solutions until no better solution can be found [207]. Optimisation holds an important place in both the practical and scientific worlds. Optimisation methods are utilised to solve numerous problems in several fields of science (i.e. engineering, economics, finance, medicine) [208,209]. An optimisation problem refers to a problem with the aim of finding the best solution among all possible ones [205].

The optimisation problem in this research is to characterise the appropriate settings for producing pressure wave parameters that satisfy optimum technical performance requirements for different therapy aims

4.4.3.2 Design Variables

A design variable is "any quantity that is allowed to vary during the search for the optimum objective" [210]. These variables, are a set of unknowns that control the value of the objective function and are manipulated to drive the objective function to achieve the optimisation aim [211]. The OPEP device settings (flow range and resistance level) have been identified in this research as the design variables for the optimisation problem at hand.

4.4.3.3 Objective Function

In optimisation, the objective function is a function that describes one or more quantities which are to be minimised or maximised.[210]. An optimisation problem might have one or more objective functions [211]. This research has identified three measurable quantities (oscillation frequency, PEP and oscillation amplitude) that represent the technical performance of OPEP devices. The relationship between each one of these quantities and the OPEP device settings was modelled using mathematical equations. These equations represent the objective function to be used for solving the optimisation problem of this research.

4.4.3.4 Optimisation Goals and Constraints

In chapter 3, the optimum values for OPEP devices pressure parameters have been established. In addition, a set of therapy aims and the corresponding optimum pressure wave parameters for each aim has been proposed in Table 4-5. This table was utilised to define the optimisation problem goals and constraints.

In terms of the goals for each of the three objective functions. Since airway clearance by oscillation is optimum at certain frequencies [2,32,44,52,60,61,82,115,212], therefore, the goal for the frequency objective function is to achieve a certain target. In chapter 3 the optimum mean frequency and range for different therapy aims have been established. The mean frequency value was used as the target to be achieved for every therapy aim. While the frequency range was used to define the upper and lower limit of the boundaries

for solution space. The decision to target the mean frequency has been rationalised by the fact that when using OPEP devices in real life scenarios, the expiratory manoeuvre would result in an exponential decay in flow (54), therefore choosing a target in the middle of the range will increase the likelihood of achieving an oscillation frequency within the optimum range for the longest possible period.

In terms of the PEP, there is a consensus in the literature that airway clearance is optimum between 10 and 20 cmH2O. These values were used to define the upper and lower boundaries for solution space. However, the goal for the PEP function is to achieve a target of 15cmH2O. The decision to match this target has been rationalised by the fact that when using OPEP devices in real life scenarios, the expiratory manoeuvre would result in an exponential decay in flow (54), therefore choosing a target in the middle of the range will increase the likelihood of achieving the optimum value within the range for the longest possible period.

In terms of the oscillation amplitude, from the perspective that the higher the flow amplitude the higher the effectiveness [54], therefore the goal is to maximise the amplitude objective functions. No constraints will applied to this objective function.

Table 4-5 shows the goals and constraints for each of the objective functions.

Table 4-5 Optimisation goals and constraints for each objective function

<table>
<tr><th></th><th></th><th></th><th colspan="3">Objective Function Goals and Constraints</th></tr>
<tr><th>Therapy Aim</th><th>Disease</th><th>Stage</th><th>Frequency Goal: Achieve Target</th><th>PEP Goal: Achieve Target</th><th>Amplitude Goal: Maximise</th></tr>
<tr><td rowspan="8">Match Resonance Frequency</td><td>Cystic Fibrosis</td><td>N/A</td><td>17.1 ± 6.3 Hz</td><td rowspan="9">10 ± 5 cmH2O</td><td rowspan="9">No constraint</td></tr>
<tr><td rowspan="3">COPD</td><td>GOLD 2</td><td>18.3 ± 4.3 Hz</td></tr>
<tr><td>GOLD 3</td><td>21.8 ± 4.7 Hz</td></tr>
<tr><td>GOLD 4</td><td>25.3 ± 5.5 Hz</td></tr>
<tr><td rowspan="3">Asthma</td><td>Mild</td><td>16.1 ±4.7 Hz</td></tr>
<tr><td>Moderate</td><td>18.1 ± 5.8 Hz</td></tr>
<tr><td>Sever</td><td>24 ± 6.9 Hz</td></tr>
<tr><td>Alter Mucus Movement</td><td>Any</td><td>Any</td><td>14 ± 6 Hz</td></tr>
</table>

Alter Mucus Rheology	Any	Any	15 ± 7 Hz		
Match Cilia Frequency	Any	Any	13 ± 2 Hz		

Solving the optimisation problem

The desirability function is a solution to solve optimisation problems with more than one objective function at the same time. The function is based on the idea that "the quality of a product or process that has many features is completely unacceptable if one of them is outside of a desirable limit". The function aims to find operating conditions that ensure compliance of all solutions with the criteria of all the involved objective functions [205,213]. This is achieved by converting the multiple responses into a single one, combining the individual responses into a composite function followed by its optimisation [205]. The function always returns a value between 0 and 1, where 0 represents an undesirable response and 1 represents a completely desirable value (i.e. ideal response). Desirability function is widely used in the response surface models optimisation [191].

In this research, the desirability function was used to solve the optimisation problem in this research. The desirability function equations structure used in this research can be found here [205]. The desirability function is a built-in feature in commercial software (JMP 12.0) (SAS Inc., USA). This software was used to solve the optimisation problem in this research. The optimisation problem was solved in two stages; first, the JMP perdition profiler feature was used to find the exhalation flow rate and resistance level out of all possible combinations that satisfy the optimum technical performance criteria for different therapy aims. This will be referred to as global optimum. At the second stage, the JMP perdition profiler feature was also used find the best flow rate of all possibilities that satisfies optimum the technical performance criteria at every resistance level. This will be referred to as the local optimum.

Optimisation validation

Currently, no guidelines exist to aid clinicians and respiratory therapists in choosing exhalation flow rate and resistance levels to optimise the device's operation according to the disease features of each patient and the technical capabilities of each device [58]. The results of solving the optimisation problem will help address this issue in the clinical

practice. Therefore, these results will be validated with clinicians and respiratory therapists. This validation will ensure obtaining the opinions and feedback of the target audience of these findings.

Questionnaire design

In order to capture the opinions and feedback of clinicians and respiratory therapists about the characterisation of the optimum mechanical of OPEP devices, it is necessary to design a tool to capture these opinions. Questionnaires are a "'tool' for collecting and recording information about a particular issue of interest" [214]. They are regularly used to capture views, comments and feedbacks of a target audience in relation to a particular issue or a topic of interest. Questionnaires have been chosen in this research because they are a practical tool that generates data which can be analysed and interpreted in a scientific objective manner than other forms of research [215].

A questionnaire has been designed to capture feasibility and usefulness of the optimisation results. The questionnaire has been developed based on previous work from [216]. The questions have been developed to capture the opinions and feedback of clinicians and respiratory therapists at a high level of abstraction. The feasibility questions are intended to gather feedback regarding the practicality of the findings, while the usefulness questions are intended to gather feedback about how useful the findings are in aiding the choice of exhalation flow rate and resistance levels to optimise the device's operation according to the disease features of each patient and the technical capabilities of OPEP devices. In addition, each question concludes with an open-ended question to provide an opportunity to make any additional comments. The open-ended question was intended to capture feedback in an unstructured way. Table 4-6 gives an overview of the questionnaire

Table 4-6 OPEP devices optimum mechanical behaviour validations questions

Type	Questions
Feasibility	1- The research investigated a problem commonly encountered in the clinical practice?
	2- The findings of this research contains the relevant information needed to optimise mechanical behaviour of OPEP devices in the clinical practice?
	3- The findings of this research could be successfully adopted in the clinical practice to optimise OPEP devices mechanical behaviour?
Usefulness	4- The findings of this research are beneficial to the clinical practice when prescribing and optimising OPEP devices?
	5- The findings of this research aid the selection of the right OPEP devices for patients?
	6- The findings of this research aid the selection of the appropriate exhalation flow and resistance level for patients?
	7- The findings of this research provide a good understanding of the advantages and disadvantages of different OPEP devices?

Likert scale is commonly used to capture answers in questionnaires as a reliable scale that is easy to understand and easily quantifiable [215]. Hence, a standardised Likert scale was used to answer each of the questions (Figure 4-7). A full version of the validation questionnaire can be found in Appendix B.

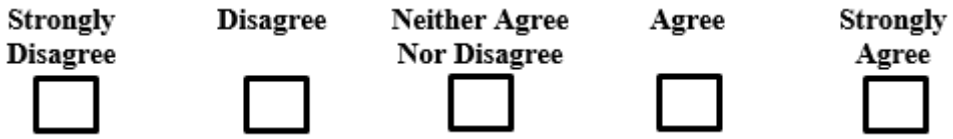


Figure 4-7 Standardised Likert scale

Participant selection and questionnaire delivery

The validation will be conducted with only two target groups (clinicians and respiratory therapists). An invitation will be sent by email to the potential participants to take part in this validation. Only participants who currently or previously prescribed OPEP devices will be included. An individual one-hour web conference will be scheduled with each participant who agrees to take part in this validation. During the web conference, a presentation of the research purpose and main findings will be given (Appendix C), followed by asking the participants to fill out the questionnaire.

4.5 Chapter Summary

In order to guide the overall process of this research design, a research design framework was constructed based on previous work by Crotty's [166] and Sunders et al. [167]. The overall research design steps were split into philosophy, methodology, and method.

- In term of the philosophical design, this research adopted an objective epistemology and a post-positivist theoretical perceptive.
- In term of the overall methodology design, this research adopted a deductive approach. In addition, this research adopted an experimental strategy and a quantitative choice to address the research problem..
- In terms of method design, the method has been described in this chapter in two main sections about the experiment method and optimisation method. This research will:
  - a- First start by validating the experimental set up through experiment repetition.
  - b- The experimental setup will be used to collect mechanical behaviour data from several OPEP devices.
  - c- The data will be used to build a mathematical model of OPEP devices' mechanical behaviour. A regression analysis will be used for the modelling process.

d- The built models will be validated by collecting new data sets to evaluate the models' abilities to predict the new data.

e- In terms of the optimisation method, the optimisation problem, design variables, and the optimisation goals and constraints have been justifiably discussed in this chapter. The method to solve the optimisation problem using the desirability function has also been described and justifiably discussed in this chapter. Also, the method for validating the findings that emerge from solving the optimisation problem has been justifiably described.

5 DEVELOPMENT AND VALIDATION OF A SYSTEM TO MEASURE MECHANICAL BEHAVIOUR OF OPEP DEVICES

This chapter addresses the third objective of this research (to develop and validate a system for measuring the mechanical behaviour of OPEP devices). In Chapter 2, verifying the capability of the measurement system when investigating mechanical behaviour was recognised to be important. In Chapter 4, a measurement system was developed to investigate the mechanical behaviour of OPEP devices. This chapter will present the measurement system's validation results and establish the acceptability of the measurement system to be used for investigating the mechanical behaviour of OPEP devices. In addition, the results of pressure wave parameter variability will be presented.

5.1 Introduction

The measurement system validation experiment was conducted as described in section 4.4.2.9. Each experiment was composed of 30 runs. The experiment was repeated three times. A total of 90 experiment runs were conducted for each of the five OPEP devices. Pressure data was collected, and the three pressure wave parameters of interest (frequency, PEP and amplitude) were calculated from the data as per the data processing section 4.4.2.8. The purpose of repeating the experiment was to quantify the variability in the collected data and to decide if the experiment as a whole is valid to be used for the purpose of measuring OPEP device mechanical behaviour.

The measurement system validation results will be presented in two main sections; acceptability of the measurement system and pressure wave parameter variability. The measurement system acceptability section will present the contribution percentage of the systematic and unsystematic variability in the collected data as derived by the ANOVA method.

On the other hand, the pressure wave parameter variability section will present the unsystematic variability for each of the pressure wave parameters at every exhalation flow and resistance level combination. Such variability will be expressed in terms of the standard deviation of the three repeated measurements.

5.2 Results

5.2.1 Measurement System Acceptability

Figure 5-1 shows the percentage of the systematic and unsystematic variability in the collected data. The percentage of the unsystematic variability is of special interest in this research, as it reflects the error in the experiment.

The average unsystematic variability for the frequency parameter for all five OPEP device was 5.96% ± 2.3. In addition, the average unsystematic variability for the PEP parameter was 3.8% ± 2.6. On the other hand, the average unsystematic variability in the amplitude parameter was 4.6% ± 2.97. The highest unsystematic variability was observed to be in the frequency parameter for device D (9.7%). The lowest unsystematic variability was observed for the amplitude for device E (0.9%).

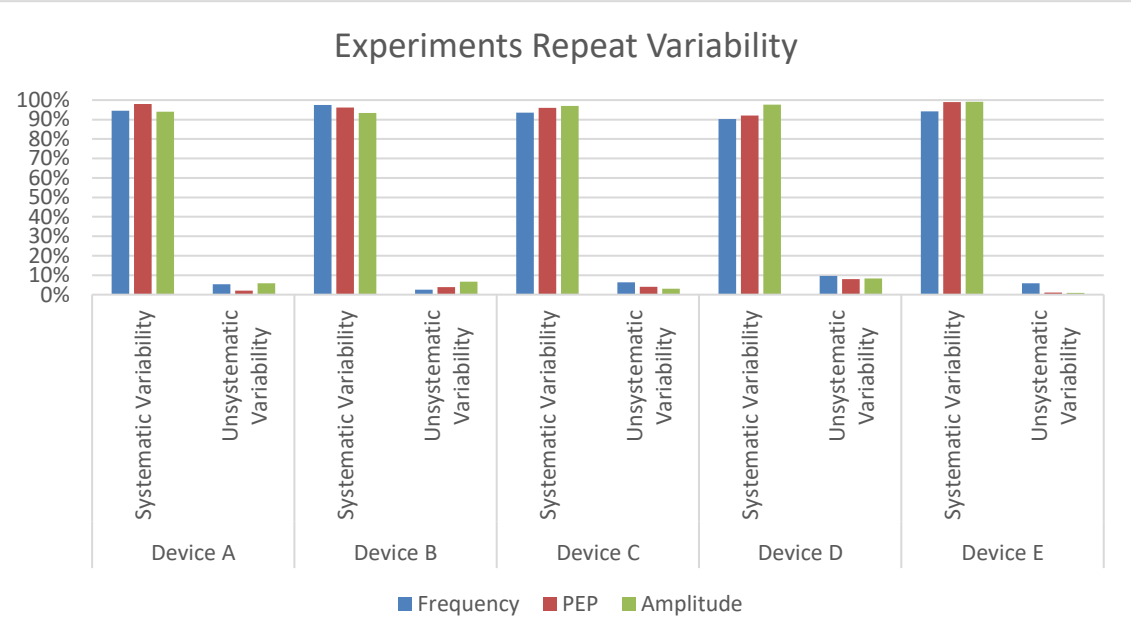


Figure 5-1 Experiment repeat variability –systematic and unsystematic variability

5.2.2 Pressure Wave Parameter Variability

Figure 5-2 shows the standard deviation (SD) of the measurement repeats for the frequency pressure wave parameter. Device B pressure wave values were found to have the highest average SD between repeats (1.3 ± 1.36) while device E was found to have the lowest average standard deviation between repeats (0.57±0.86). The measurement

repeats average SD for devices D, A and C were 1.02 ± 0.71, 0.70 ± 0.49 and 0.69 ± 0.54 respectively.

It can be noted from Figure 5-2 that the measurements of SD appear to increase at certain standard order points. For instance, it can be observed that the frequency SD value for device D, seems to increase at standard order points 24 and 12. For device C at standard order points 24, 19 and 12. For device A, the highest measurement SD values seem to be at standard order points 26 and 21. For device E, the SD values seem to increase at standard order points 1, 2 and 7. However, for device B, the measurement repeat SD values seem to increase at standard order points 12, 23 to 27 and 29.

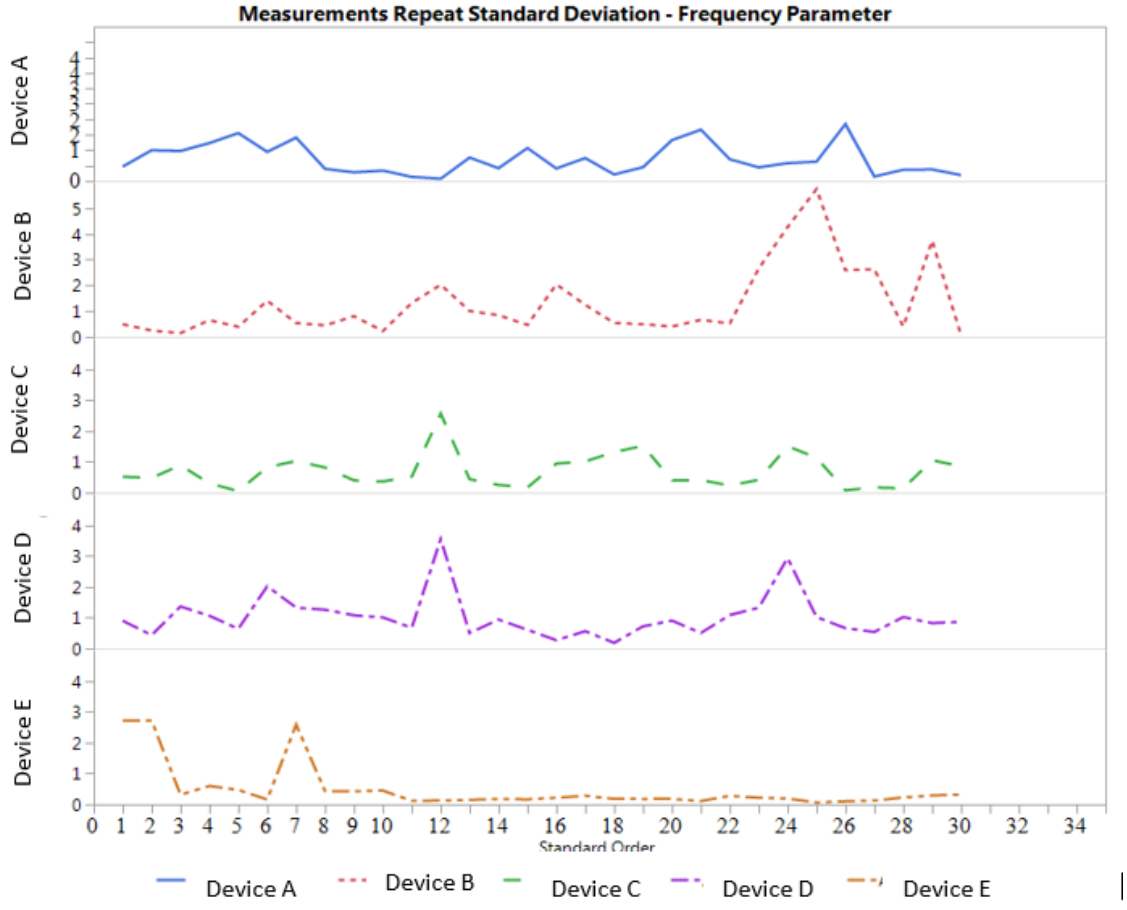


Figure 5-2 Measurements repeat standard deviation - frequency parameter

Figure 5-3 shows the SD of the measurement repeats for the PEP parameter. The highest average of the SD was found to be for device B (2.8 ± 3.4). On the other hand, the lowest average SD was found to be for device E (0.54 ± 0.45). The average of the measurement

repeats SD for devices D, A and C were 0.83 ± 0.79, 0.60 ± 0.35 and 0.55 ± 0.45 respectively.

The pattern of increasing measurements SD at certain standard order points more than others can also be observed for the PEP parameter. For instance, the measurements repeat SD for device D seem to increase at standard order points 12 and 24. For device C, at standard order points 12 and 24. For device B, in overall, the measurement repeated SD seem to increase from standard order point 12 and 20 to 30. However, the measurement repeats SD for both devices A and E seem to stay relatively constant, with no obvious patterns.

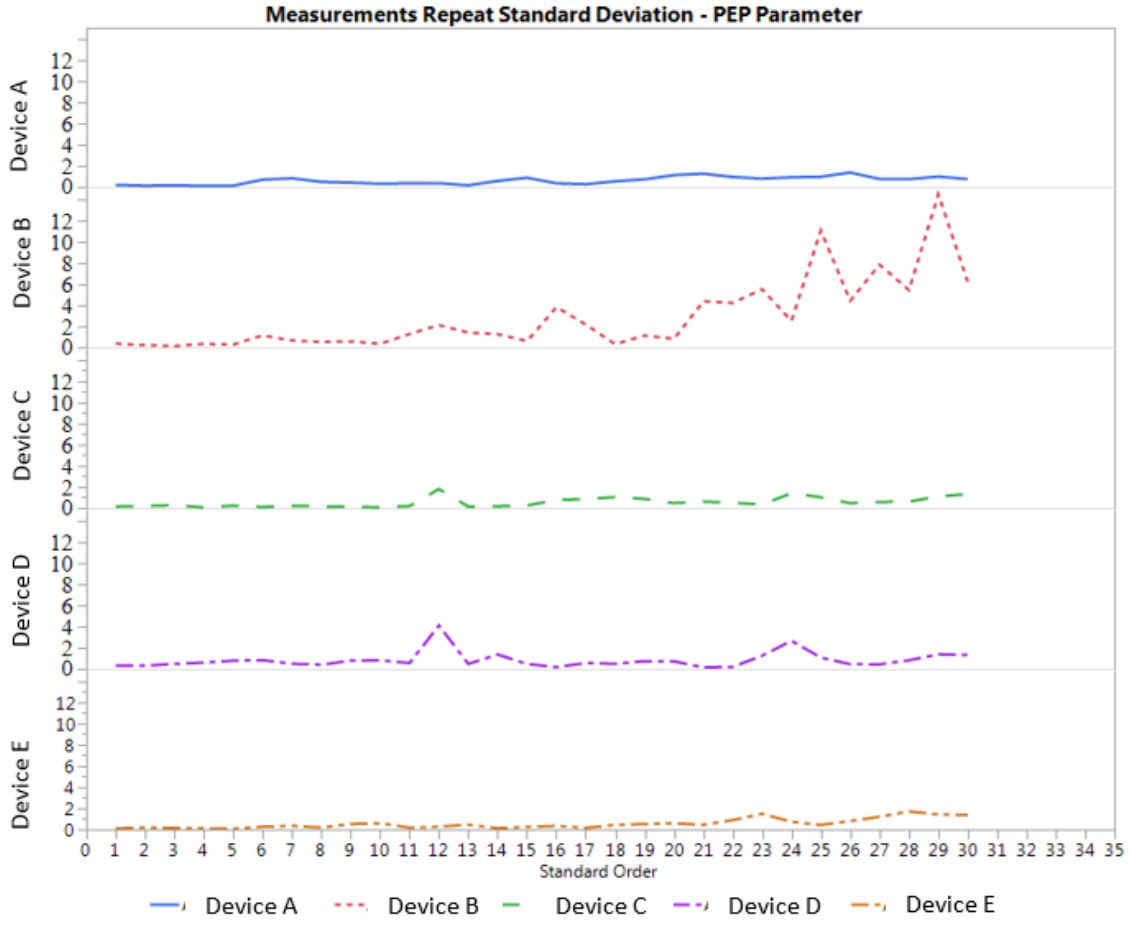


Figure 5-3 Measurements repeat standard deviation - PEP parameter

Figure 5-4shows the SD of the measurement repeats for the amplitude pressure wave parameter for all five OPEP devices. The highest average of the SD in measurement repeats was found to be for device B (1.31±0.8). On the other hand, the lowest average

SD was for device C (1.02±1.004). The measurement repeats SD averages for devices E, D and A were 1.07±0.93, 1.19±1.12 and 0.88±0.67 respectively.

The pattern of increasing measurement repeats SD at certain standard order points more than others can also be observed for the amplitude parameter. For device D, the three biggest increases in measurement repeats SD seem to be at standard order points 16 and 23 and 28. For device C, the two biggest increases seem to be at standard order points 24 and 29. For device A, the biggest increase in measurement repeats SD seems to be at standard order point 21. For device E, the two biggest increases seem to be at standard order points 23 and 28. Still, device B showed no clear pattern as measurement repeats SD were found to vary across several standard order points.

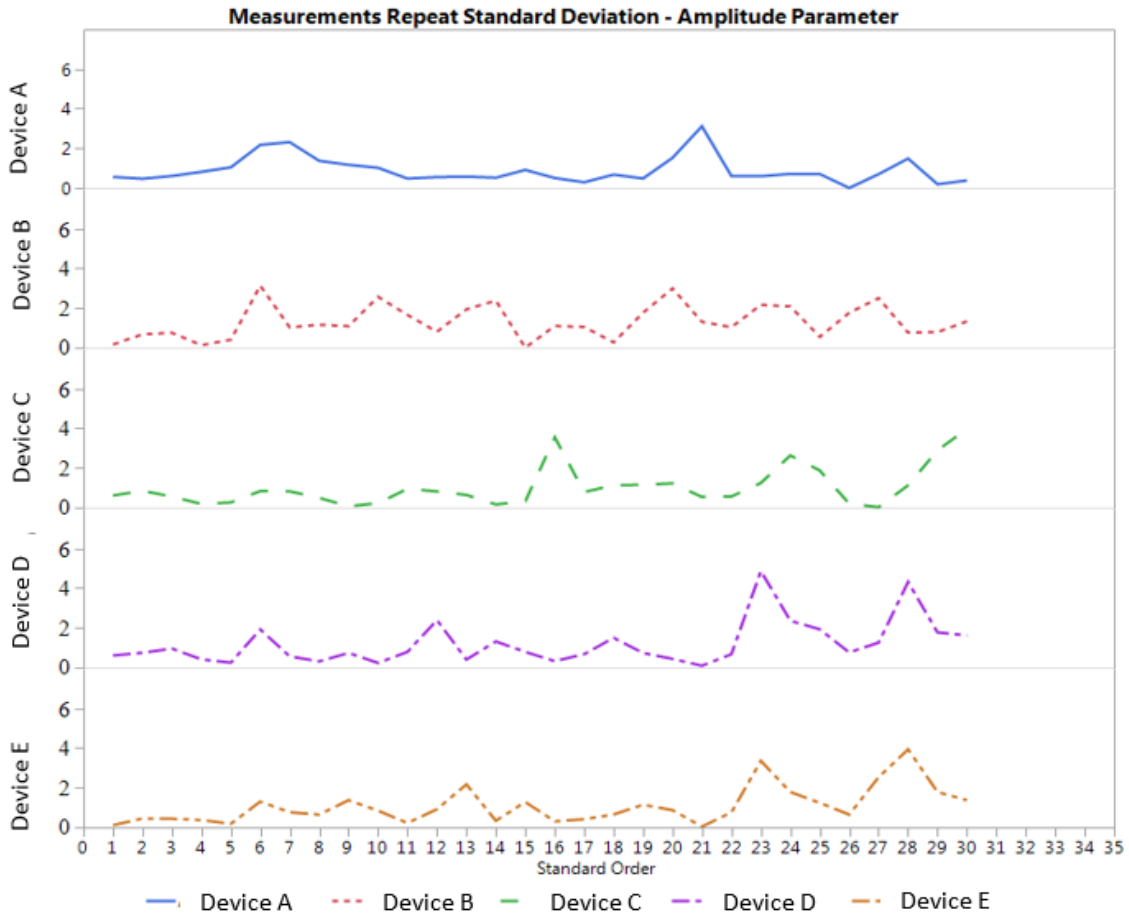


Figure 5-4 Measurements repeat standard deviation - amplitude parameter

5.3 Discussion

5.3.1 Measurement System Acceptability

According to [200]; an unsystematic variability percentage under 10% indicates an acceptable measurement system. The contribution percentage of the unsystematic viability to the overall variability was found to be below 10% for all three pressure wave parameters for all five devices. Hence the measurement system and experimental setup is adequate for benchmarking the mechanical behaviour of OPEP devices.

The variability in an experiment that measures the mechanical behaviour of OPEP devices has been reported in only one study in the literature. [55]. In this study, the experiment was repeated on device D at an exhalation flow of 18 L/min and a resistance level 3 [55]. However, the experiment variability at various exhalation flow and resistance level combinations (i.e. more than one combination) has not been investigated previously. In the referenced study, [55] found that the oscillation frequency parameter for device D had the lowest unsystematic variability (0.4%) followed by PEP (1.5%). Oscillation amplitude were found to have the highest unsystematic variability (4.6%). However, the results found in this research for device D differ from those found by [55]. In this study, it was found that frequency had the highest unsystematic variability for device D (6.3%). In addition, it was found that the PEP and amplitude had a similar unsystematic variability percentage (8% and 8.3% respectively). The contradiction in the results could be explained by the wider range of flows and resistant level combinations that were investigated in this study in comparison to [55].

5.3.2 Pressure Wave Stability

“Stability” of the pressure wave parameters produced by an OPEP device has been described by [50] as the variation in these parameters over time. [50] examined the stability of pressure wave parameters by plotting the pressure wave for three OPEP devices at different flow and resistance level combinations. Then visually observing the “consistency of that wave”. [50] concluded that for type A device (devices D and B) generated more “stable” oscillatory pressure waves in comparison to the Flutter device.

In this research, the SD of the measurement repeats includes the variability caused by several factors (i.e. measurement system and the experiment error). It also represents the inherent variability of the pressure wave parameters caused by the OPEP devices themselves. Since the increase in the measurement repeats SD was only observed at certain standard order points but not others and was only observed for some of the investigated OPEP devices but not others. It has been concluded that such variability is caused by the OPEP devices themselves, rather than the measurement system used.

Considering the average SD of measurement repeats average SD, device E was found to produce the most stable frequency and PEP parameters, while device C was found to produce the most stable amplitude parameter. Nevertheless, all five investigated OPEP devices were found to have a relatively low overall SD between measurement repeats, (the highest average SD was 2.8) for all pressure wave parameters. Hence, all five devices were thought to produce stable pressure wave parameters.

Nonetheless, while the results of the average SD suggest that all five tested OPEP devices are capable of producing a stable pressure wave. Looking at the measurement repeats SD plot of pressure wave parameters at every standard order point, it can be observed that variability of some pressure wave parameters seems to increase at certain flow and resistance level combinations more than others. At these particular flow and resistance level combinations the pressure wave seems to be less stable.

Since understanding OPEP device mechanical behaviour and how these devices will perform at different flow ranges is important when prescribing and using these devices [20,57], Table 5-1 shows a list of these instability points and the corresponding flow and resistance levels. The instability points are certain exhalation flow and resistant level combinations at which one or more of the pressure wave parameter become inconsistent

Table 5-1 Exhalation flow and resistance levels that produce pressure wave parameter instability

	Frequency		PEP		Amplitude	
	Flow L/Min	**Resistance Level**	**Flow L/Min**	**Resistance Level**	**Flow L/Min**	**Resistance Level**
Device A	30	1	No Instability Points		25	1
	25	1				
Device B	15	2	15	2	No Instability Points	
	25	2, 3, 4, 5	20	5		
	30	1 ,2	25	1 ,2 3, 4 , 5		
	30	4	30	1 ,2 3, 4 , 5		
Device C	15	2	15	2	25	4
	25	4	25	4	30	43
	20	4				
Device D	15	2	15	2	20	1
	25	4	25	4	25	3
					30	3
Device E	5	1	No Instability Points		25	3
	5	2			30	3
	10	2				

5.3.2.1 Potential Causes of Pressure Wave Instability

The observed variability between measurement repeats can be related to two potential causes. Firstly; OPEP devices are mechanical systems that generate the oscillatory pressure wave by utilising an arrangement of physical components that work together – mechanically - to produce this oscillatory pressure wave. Therefore, the observed variability between measurement repeats might be related to the arrangement of the physical components in the OPEP devices. For instance, an increase in the variability of frequency and PEP pressure wave has been observed for three out of the type A devices

at certain flow and resistance level combinations. However, this increase was not observed for type B device at the same settings combination. All type A devices employ the same mechanical apparatus for generating OPEP therapy, while type B device employs a different apparatus [68]. Hence, the observed variability between measurement repeats might be related to the mechanical apparatus employed in each device.

The second possible explanation for observed variability between measurement repeats is an exhalation flow that exceeds the specification of OPEP devices. For instance, device B is intended for patients who can sustain a maximum expiratory flow ≤ 15 L/min [80,217]. The variability data for device B suggest that exhaling to this device at a flow that exceeds its specification will result in an unstable pressure wave.

5.4 Chapter Summary

In Chapter 4, a developed system to measure the mechanical behaviour of OPEP devices was described. In this chapter:

- The validity of using this system for such a purpose was established. The level of unsystematic variability in the collected data was found to be acceptable, and it was concluded that the measurement system is valid to be used for measuring the mechanical behaviour of OEPP devices.
- Overall, all five OPEP devices were found to produce a stable pressure wave.
- However, the stability of the pressure wave parameters was found to change at certain combinations of exhalation flow rate and resistance levels.
- As part understanding OPEP devices' mechanical behaviours and how these devices will perform at different flow ranges is important when prescribing and using these devices, a list of these instability points is provided in Table 5-1.
- The points of instability were observed to occur at different settings for devices from different types and the same settings for devices of the same type. Hence, the causes of the observed instability can be related to the mechanical apparatus employed in each to generate the oscillatory pressure wave.
- In addition, it was observed that the pressure wave stability tended to decrease when devices were used outside their exhalation flow rate specification.

6 MODELLING THE MECHANICAL BEHAVIOUR OF OPEP DEVICES

This chapter addresses the fourth objective of this research (to model the mechanical behaviour of OPEP devices). In chapter 5, the developed measurement system was found to be valid for measuring the mechanical behaviours of OPEP devices. The measurement system was used to collect mechanical behaviour data from the five OPEP devices under investigation in this research. Data was collected under a unified experiment setup and exhalation flow rates commonly found in the clinical practice. This chapter presents the mechanical behaviour results for those five devices. In addition, the regression models built for each of the pressure wave parameters of all five OPEP devices will be described in this chapter. Also, this chapter will present the validation results for the built models.

6.1 Introduction

It is thought that the effectiveness of OPEP devices is critically dependent on the mechanical parameters of the pressure waveform produced by these devices [50–55]. Such parameters include; frequency, amplitude and mean value for the positive expiratory pressure (PEP) [50,55,60,132]. However, it was noted that the pressure waveform parameters of different OPEP devices vary across the spectrum of flow ranges [20,57]. In addition, successful use of these devices is dependent on the correct adjustment of the device resistance levels to produce the desired therapeutic parameters [61].

Evaluating the mechanical behaviour of OPEP devices represents an original research that lies at the base of the evidence appraisal hierarchy in airway clearance field [76]. In chapter 2, experimental variations have been identified as a major limitation of previous studies that evaluated OPEP device mechanical behaviour. In particular, there is a lack of studies evaluating OPEP devices under a unified experimental set up and under flow ranges commonly found in clinical practice. All of which make a direct comparison between devices very difficult, especially for devices from different manufacturers. Hence, new studies evaluating the mechanical behaviour of OPEP devices have been encouraged.

The mechanical behaviour of both devices C and E has never been characterised previously in the literature. In addition, only one study has characterised and compared

the performance of more than one OPEP device type (3 type A devices) under similar flow ranges and across all resistance levels [61]. Furthermore, no previous study has characterised the mechanical performance of different OPEP device types from different manufacturers across all resistance levels under similar flow range. Aslo, the experiment set up (flow range and resistance levels) variations used in previous studies makes a direct comparison between the results very difficult [34,60,61,78]. In addition, in previous studies, authors used flow range values significantly higher than those normally found in clinical practice [34]. New studies evaluating the mechanical behaviour of OPEP devices has been encouraged [61]. Such studies lie at the base of the evidence appraisal hierarchy in the field of airway clearance along with clinical trials [76].

This chapter has a twofold aim; first is to characterise the mechanical behaviour of five OPEP devices under flow ranges commonly found in clinical practice and across all resistance levels. Second is to model the mechanical behaviour for all five devices.

According to the principle of experiment replication, repeating the experiment more than once, will increase the statistical accuracy of the experiment and allow for better estimation for the effect the research trying to measure [184]. For the purpose of characterising and modelling the mechanical behaviour of the OPEP devices under investigation, data was collected from three samples of each of the five OPEP devices. The unsystematic variability was quantified using ANOVA and evaluated for acceptability.

The results of this chapter will be presented in three main sections; unsystematic variability, OPEP device mechanical behaviour, and model building results.

6.2 Results

6.2.1 Unsystematic Variability

Figure 6-1 shows the contribution percentage of the unsystematic variability (sample to sample variability and experiment error) to the overall variability in the data collected for model building from three different samples. The average unsystematic variability of the frequency parameter for all five devices was 5.3% ± 3.5. In addition, the average unsystematic variability in the PEP parameter data for all five devices was 3.0% ± 2.8. On the other hand, the average unsystematic variability in the amplitude parameter was

6.25% ± 2.8. The highest unsystematic variability was observed in the frequency parameter for the device D (8.70%). The lowest unsystematic variability was observed in the PEP parameter for the device C (0.95%). These values are in agreement with the measurement system validation results found in chapter 5.

Since the unsystematic variability of the pressure wave parameters for all five devices was below 10%, it was considered to be acceptable. Hence, the three samples of data were averaged and used for model building.

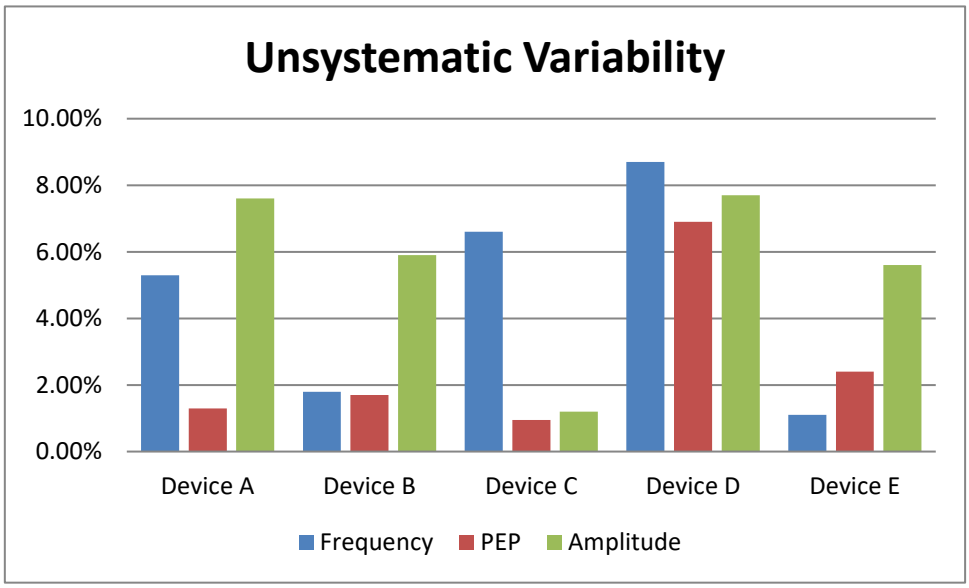


Figure 6-1 Unsystematic variability – replicated experiment with three samples of each OPEP device

6.2.2 Characterisation of the Mechanical Behaviour OPEP Devices

6.2.2.1 Frequency

Table 6-1 shows the mean, minimum and maximum values of the frequency parameter produced by all five tested OPEP devices at different flow rates. Device E was found to have the lowest overall mean frequency (9.7 Hz). On the other hand, device B was found to have the highest overall mean oscillation frequency value (23.1 Hz). The overall mean frequency values for devices A, D and C were very similar (15.4 Hz, 14.4 Hz and 16.4 Hz respectively). In terms of the frequency range produced by each device, device B produced the widest overall range of frequencies (12.4-47.1 Hz). On the other hand, device D produced the narrowest overall range of frequencies (10.18-22.5 Hz). The

overall oscillation frequency range for device A was 9.4-26.5 Hz, for device C 8.8-30.1 Hz and for device E 0-20.9 Hz.

Table 6-1 Oscillation frequency value for all five devices at different flow rates. Mean (Minimum – Maximum)

	Exhalation Flow (L/min)					
	5	**10**	**15**	**20**	**25**	**30**
Device A	19.53 (15.4-26.56)	12.06 (9.4-15.73)	10.72 (9.5-12.76)	12.90 (11.93-14.73)	16.47 (15.37-18.4)	21.17 (20.6-22.4)
Device B	13.19 (12.46-13.68)	14.62 (14.31-15.06)	15.73 (13.32-17.84)	21.79 (19.6-24.84)	30.89 (28.31-36.25)	42.74 (38.85-47.12)
Device C	22.59 (18.46-30.13)	11.80 (10.06-15.16)	10.93 (8.86-14.13)	13.65 (12.47-16.03)	17.614 (16.8-19.23)	22.11 (21.5-23.1)
Device D	13.21 (12.98-21.35)	11.87 (10.18-15.49)	11.46 (10.54-12.61)	11.79 (10.43-13.89)	16.05 (14.56-17.05)	22.14 (21.72-22.54)
Device E	3.55 (0-4.863)	6.62 (5.063-7.58)	8.93 (7.5-10.49)	10.98 (9.47-13.68)	13.22 (11.35-17.85)	15.20 (12.63-20.99)

Figure 6-2 shows the flow-frequency relationship for the five OPEP devices at all resistance levels. In terms of general trends for the frequency, devices A and C exhibited a similar trend. Oscillation flow-frequency relationship for these two devices showed an inverse relation between flow levels of 5-10 L/min, but this relation was shown to be proportional between flow levels of 10 -30 L/min. In contrast, devices B and E exhibited an overall proportional frequency-flow relationship. It is worth noting that device E did not oscillate at 5 L/min and resistance level 1. On the other hand, device D exhibited an overall proportional flow-frequency relationship between flow rates of 20-30 L/min. However, the relationship was shown to be of an inverse type at flow range 5 to 20 L/min at resistance levels 5 and 4.

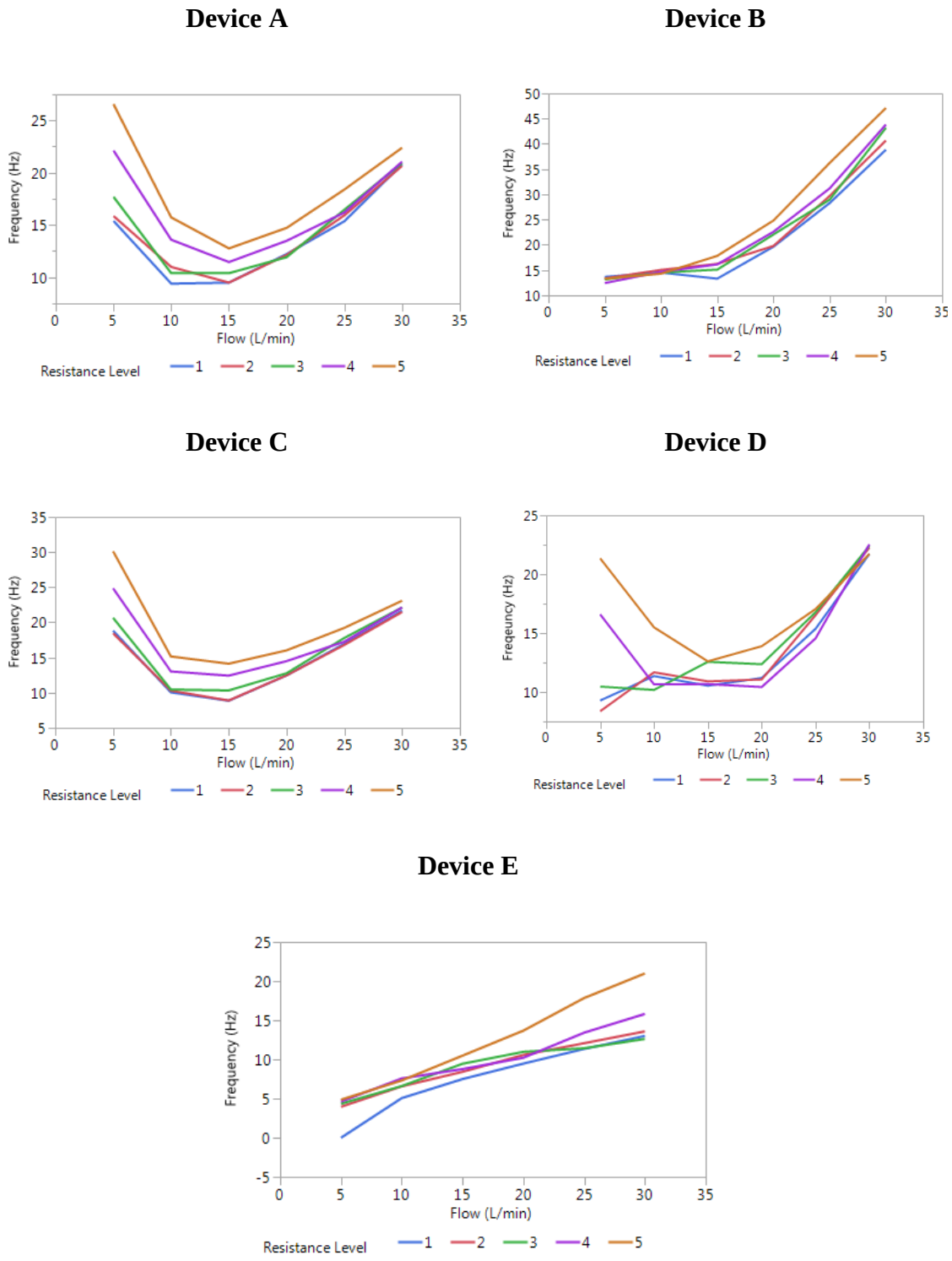
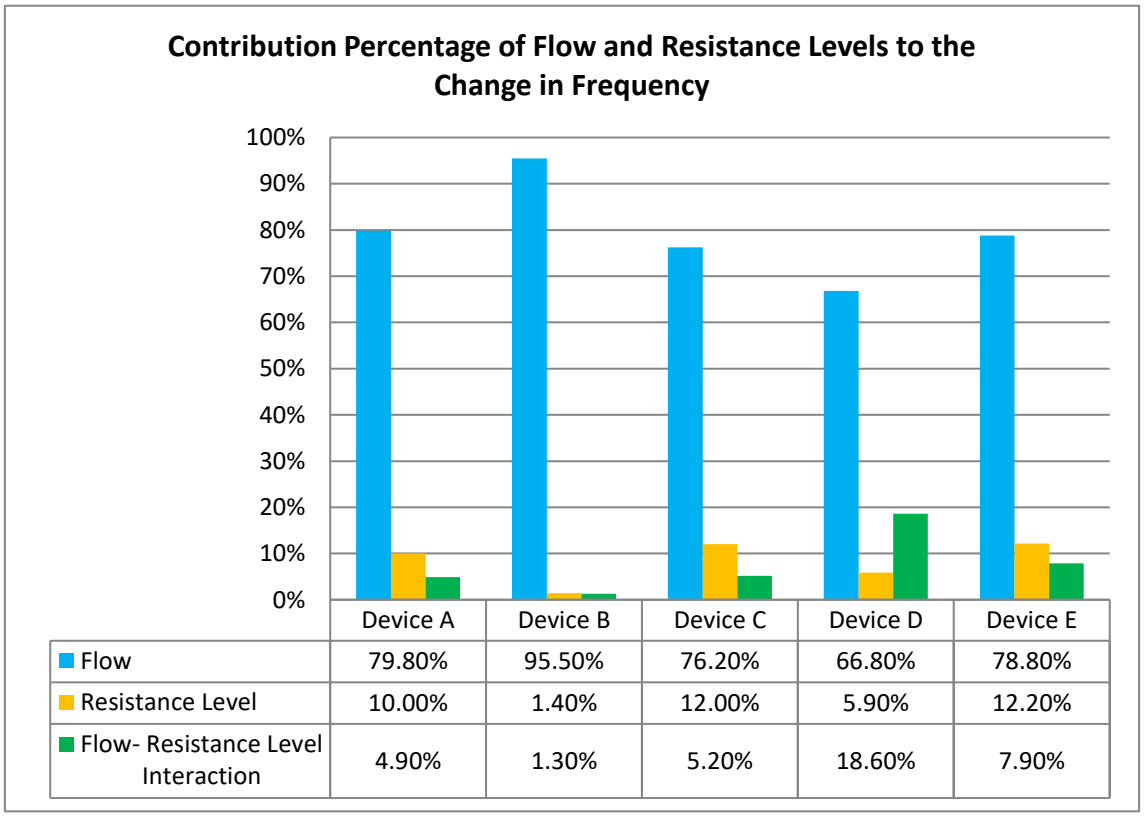


Figure 6-2 Frequency-flow relationship at five different resistance levels for all five devices.

Figure 6-3 shows the contribution percentage of flow, resistance level and the interaction between the two to the change in the oscillation frequency for each of the five OPEP device. The interaction between the flow and the resistance level refers to a change in the

oscillation frequency that is dependent on both the flow rate and resistance level. As can be seen from the figure, the oscillation frequency value produced by all five devices was predominantly influenced by the change in flow rate alone. Such influence was found to be statistically significant (p<0.0001 for all five devices). The change in the resistance level alone had less influence on the oscillation frequency value. In addition, the magnitude of such influence found to vary from one device to the other. In the case of device D, changing the resistance level alone was found to have no statistically significant (p=0.0636) influence on the oscillation frequency value. For the other four devices the resistance level influence was found to be statistically significant (devices A and E p=0.0001, device B p=0.0035, device C p<0.0001). The interaction of flow rate and resistance level was found to have a statistically significant influence on the oscillation frequency value for all five OPEP devices (devices A, D and E p<0.001, device C p=0.0001, device B p=0.0005).



	Device A	Device B	Device C	Device D	Device E
Flow	79.80%	95.50%	76.20%	66.80%	78.80%
Resistance Level	10.00%	1.40%	12.00%	5.90%	12.20%
Flow- Resistance Level Interaction	4.90%	1.30%	5.20%	18.60%	7.90%

Figure 6-3 Contribution percentage of flow and resistance levels to the change in frequency

6.2.2.2 PEP

Table 6-2 shows the mean, minimum and maximum values of the PEP parameter produced by all five tested OPEP devices at different flow rates. Device D was found to have the lowest overall mean PEP value at 9.02 cmH2O. On the other hand, device B was found to have the highest overall mean PEP value (23.6 cmH2O). The overall mean PEP for device A, C and E were very similar at 9.4 cmH2O, 10.3 cmH2O and 10.3 cmH2O respectively. In terms of the overall PEP range produced by each device, device B produced the highest range of PEP (4.5-63.8 cmH2O). On the other hand, device A produced the lowest overall range of PEP (3.2-23.7 cmH2O). The overall PEP range for device D was (1.9-20.9 cmH2O), device C (3.6-22.7 cmH2O) and for device E (0.5-30.7 cmH2O).

Table 6-2 PEP Value for all five devices at different flow rates. Mean (Minimum – Maximum).

	Exhalation Flow (L/min)					
	5	**10**	**15**	**20**	**25**	**30**
Device A	4.44 (3.2-6.16)	4.48 (3.5-12.55)	6.07 (5.2-17.30)	9.14(8.16-21.60)	13.52 (12.16-22.63)	19.14 (17.76-23.76)
Device B	5.17 (4.51-6.4)	9.17 (7.29-11.02)	12.98 (8.96-17.47)	21.83 (16.56-29.24)	36.89 (29.49-48.98)	55.79 (51.29-63.86)
Device C	5.32 (3.93-7.4)	4.79 (3.6-6.76)	6.47 (5.2-8.3)	10.08 (8.9-12.33)	14.80 (13.61-16.83)	20.48 (19-22.76)
Device D	4.27 (1.92-7.75)	4.5 (3.72-6.75)	6.59 (4.80-8.726)	7.93 (6.34-10.07)	12.63 (10.30-15.38)	18.18 (15.53-20.93)
Device E	1.78 (0.50-2.93)	4.79 (2.43-2.93)	7.92 (4.47-9.757)	11.60 (7.093-14.65)	15.43 (9.597-20.97)	20.50 (12.41-30.77)

Figure 6-4 shows the flow-PEP relationship for the five OPEP device at different resistance levels. In terms of general trends for the PEP, all five devices exhibited an overall increase in the mean PEP value as flow increases (proportional relationship).

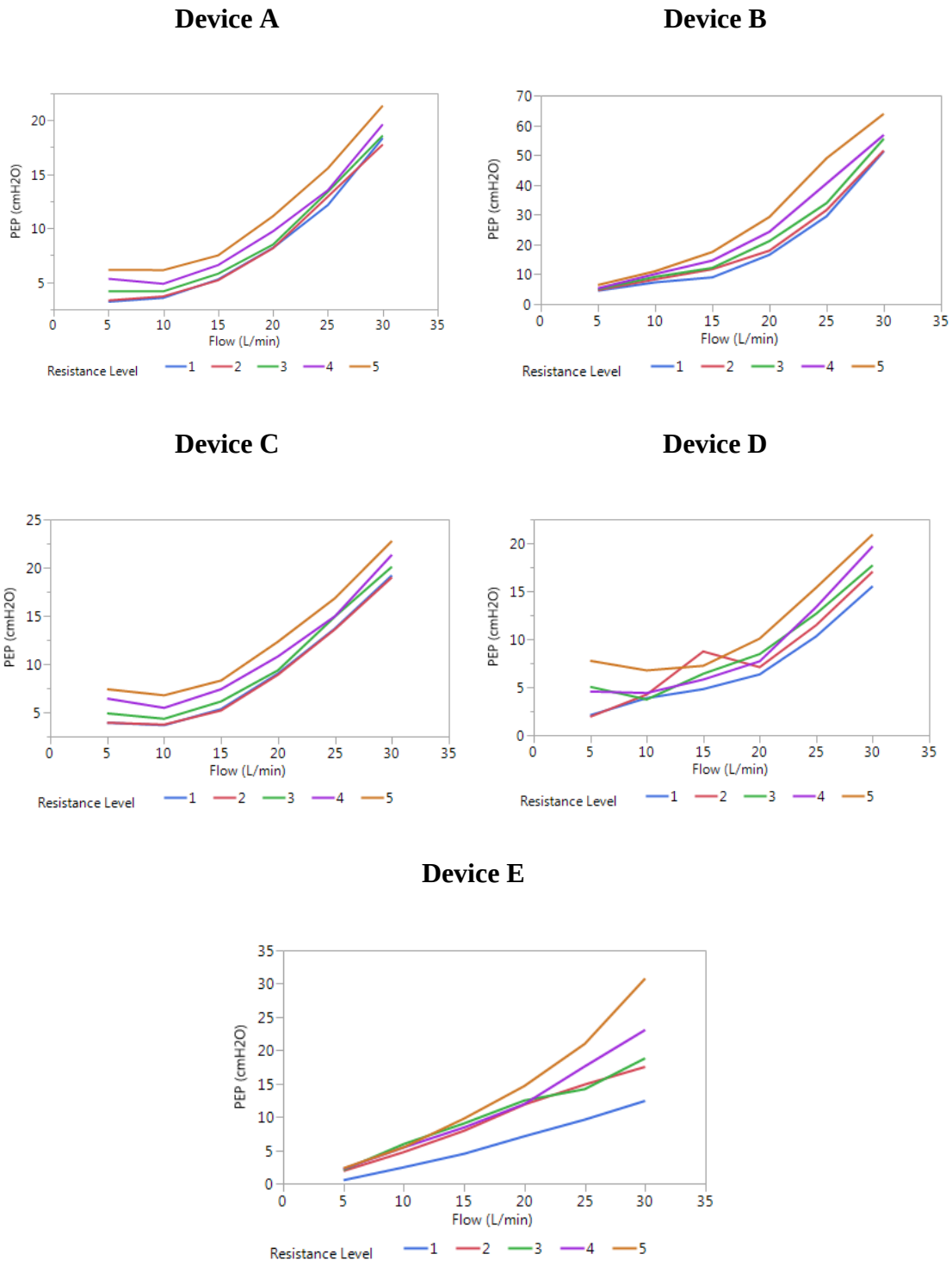
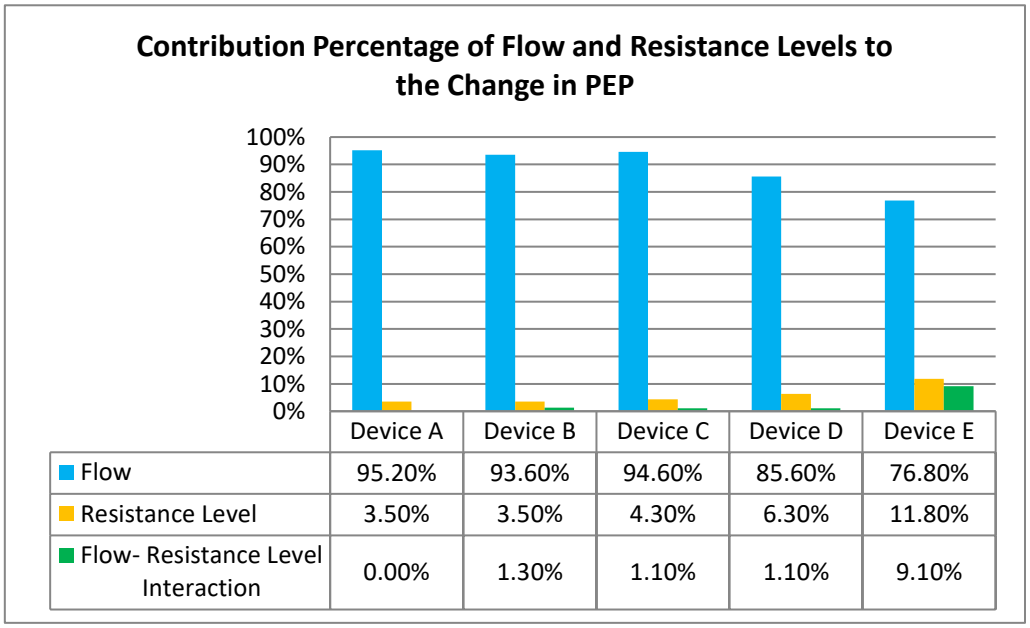


Figure 6-4 Flow-PEP relationship at five different resistance levels for all five devices. A:

Figure 6-5 shows the contribution percentage of flow and resistance level on the change in the PEP value for each of the five OPEP devices. The interaction between the flow and the resistance level refers to a change in the PEP value that is dependent on s change in

both the flow rate and resistance levels. As can be seen from the figure, the PEP produced by all five devices was predominantly influenced by a change in flow level. Such influence was found to be statistically significant (p<0.0001 for all five devices). The resistance level had a relatively small (less than 12%) influence on the change in the PEP value. However, the magnitude of such influence varies from one device to another. Nevertheless, the resistance level effect was found to be statistically significant for all five devices (Device A, B, C and D p<0.0001, device E p=0.0004). The flow and resistance level interaction influence on the PEP value was found to be insignificant for devices A, C and D (p=0.4733, 0.4691 and 0.1182 respectively). However, such interaction was found to be statistically significant for devices B (p=0.0001) and E (p<0.0001).



	Device A	Device B	Device C	Device D	Device E
Flow	95.20%	93.60%	94.60%	85.60%	76.80%
Resistance Level	3.50%	3.50%	4.30%	6.30%	11.80%
Flow- Resistance Level Interaction	0.00%	1.30%	1.10%	1.10%	9.10%

Figure 6-5 Contribution percentage of flow and resistance levels to the change in PEP

6.2.2.3 Amplitude

Table 6-3 shows the mean, minimum and maximum values of the amplitude produced by all five tested OPEP devices at different flow rates. Device E was found to have the highest overall mean amplitude value (25.9 cmH2O). The overall mean amplitude for devices A, C, B and D was very similar at 15.4 cmH2O, 15.9 cmH2O, 15.7 cmH2O and 17.7 cmH2O respectively. In terms of the overall amplitude range produced by each device, device E produced the highest overall amplitude range (0-48.9 cmH2O). On the

other hand device A produced the lowest overall range (2.8-23.7cmH2O). The overall amplitude range for device D was (3.1-35.2 cmH2O), device C (0.3-27.4 cmH2O) and for device B (5.1-26.6 cmH2O).

Table 6-3 Oscillating amplitude value for all five devices at different flow rates. Mean (Minimum – Maximum)

	Exhalation Flow (L/min)					
	5	**10**	**15**	**20**	**25**	**30**
Device A	3.80 (2.84-4.56)	12.11 (11.66-12.55)	16.83 (16.13-17.30)	20.08 (19.22-21.60)	20.8 (19.22-22.63)	19.02 (14.96-23.766)
Device B	13.30 (11.74-15.05)	18.36 (14.72-20.85)	19.52 (5.14-26.23)	19.36 (13.76-23.99)	15.44 (13.23-19.07)	8.33 (5.32-14.72)
Device C	2.04 (0.3-3.35)	11.758 (11.55-11.91)	16.73 (16.42-17.2)	20.37 (19.67-21.55)	22.01 (20.32-24.39)	22.64 (20.20-27.46)
Device D	10.00 (9.6-10.71)	15.47 (13.93-16.16)	20.53 (14.775-22.1)	22.292 (7.2-28.46)	20.29 (3.13-34.79)	17.78 (5.2-35.2)
Device E	8.52 (0-11.14)	16.86 (7.92-19.97)	23.89 (12.35-28.56)	30.23 (17.97-35.70)	34.89 (22.33-42.04)	41.43 (27-48.93)

Figure 6-6 shows the flow - amplitude relationship for the five OPEP devices at different resistance levels. In term of general trends, devices A, C and E exhibited a similar overall trend, where the amplitude value increased as the flow increased. However, device B showed an overall increase in the amplitude value as flow increases from 5 to 15 L/min. However this trend was found to be decreasing for flow levels between 15-30 L/min. The trend for device D was different for each resistance level.

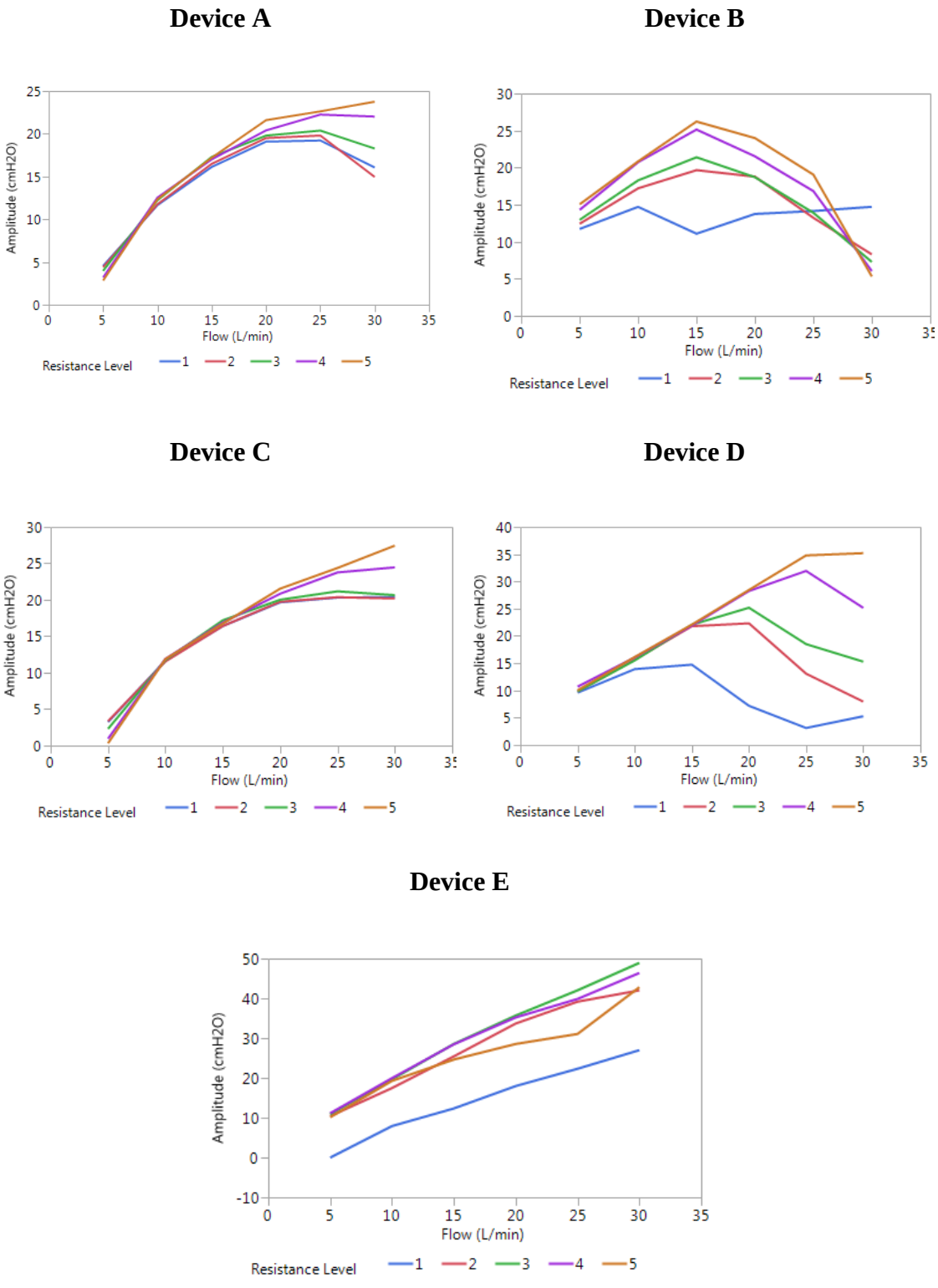
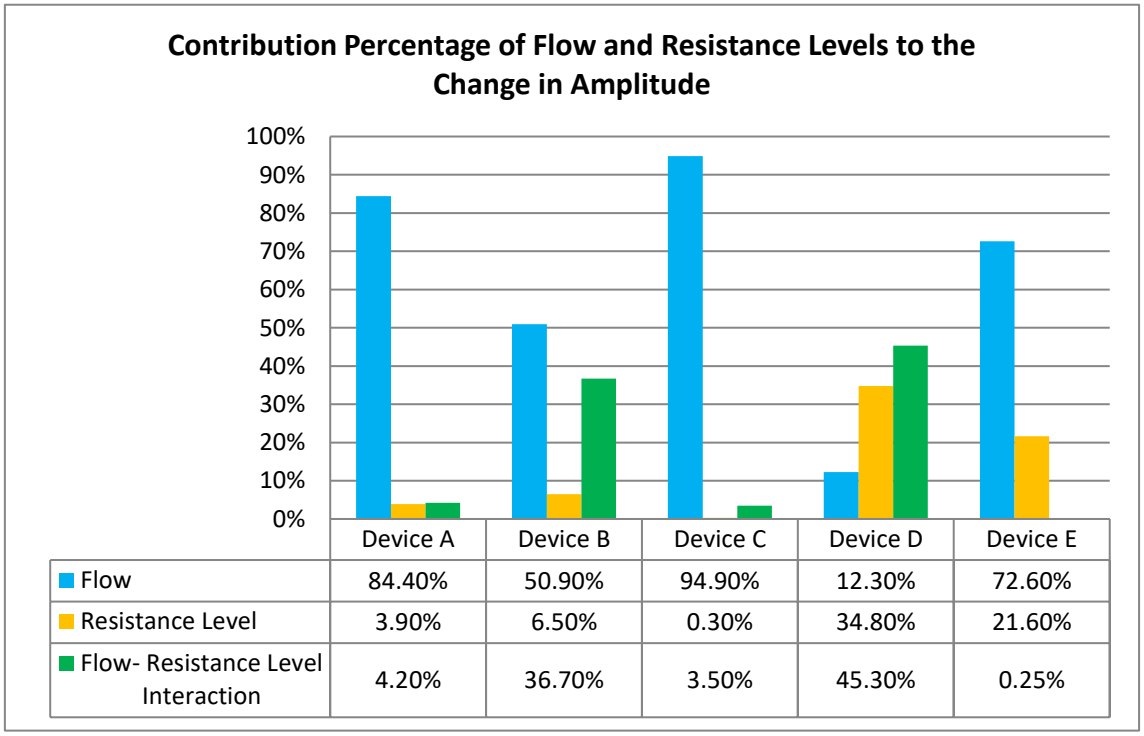


Figure 6-6 Flow- amplitude relationship at five different resistance levels for all five devices.

Figure 6-7 shows the contribution percentage of the flow and resistance level on the change in the amplitude value for each of the five OPEP device. The interaction between

the flow and the resistance level refers to a change in the amplitude that is dependent on the level of both flow and resistance. As can be seen from the figure, apart from device D, the amplitude value produced by the other four OPEP devices was predominantly influenced by a change in flow level. Such influence was statistically significant for devices A, C, E (p<0.0001) and device B (0.0004) but not for device D (p=0.0855). The resistance level adjustment was found to have no statistical significance in the case of devices B and C (p=0.132 and 0.2383 respectively). However, resistance adjustment influence on the amplitude values was found to have a statistical significance in the case of devices A, D and E (p=0.01, p=0.0042, p<0.0001 respectively).

For all type A devices, flow-resistance level interaction was found to not have a statistically significant influence on the amplitude value (device A p=0.0019, devices B, D and C p<0.0001). In case of device E, the flow- resistance level interaction was found to have no statistical influence on the amplitude value (p=0.3421).



	Device A	Device B	Device C	Device D	Device E
Flow	84.40%	50.90%	94.90%	12.30%	72.60%
Resistance Level	3.90%	6.50%	0.30%	34.80%	21.60%
Flow- Resistance Level Interaction	4.20%	36.70%	3.50%	45.30%	0.25%

Figure 6-7 Contribution percentage of flow and resistance levels to the change in oscillation amplitude parameter

6.2.3 Model Building Results

Regression models were built initially in an iterative manner until the highest the R^2 value was achieved. Then each of the model terms was evaluated for its statistical significance using the ANOVA technique. All non-significant terms were removed from the model. Also, the residuals of each model were evaluated for any patterns. Finally, the performance of the built models was validated based on their ability to predict the points in a new data set collected for this purpose.

Table 6-4 shows a summary of the best fit models for the frequency parameter for all five investigated devices. The root mean square error (RMSE) represents the average model prediction error (the difference between the values predicted by the model and the experimental values). The R^2column represents how well the data points fit the model (goodness of fit). The columns labelled as; model *p*-value, flow, resistance level, $\text{Flow}^2$and Flow^3, represent the significance of the model terms (alpha = 0.05) obtained by ANOVA analysis. The equations of the regression, a plot of the regression and a plot of the model prediction against the experimentally collected data can be found in Appendix D.1, D.2 and D3 respectively.

In total, 15 models were built (one model for each pressure wave parameter, three models per device). All models were found to be statistically significant ($p < 0.0001$). The lowest R^2 value was for the device B amplitude model ($R^2 = 0.87$). However, according to Man, Behera and Park (2010) and Chauhan and Gupta (2004), an $R^2 > 75$ is sufficient to accept a model [218,219]. For 12 out of the 15 models, the best fit was achieved using a second order polynomial. For devices A and C frequency models, the best fit was achieved using a third order polynomial. For device E, the best model fit to the frequency parameter was achieved using a linear regression model. It is worth noting that the interaction had no statistically significant effect in the PEP parameter models for devices A, D and C, and the amplitude parameter model for device B.

The residual plot for all 15 models was evaluated for any patterns (a plot of residuals can be found in Appendix D.4). The residuals were homoscedastic and randomly dispersed around the horizontal axis with no observable pattern. Hence the models were considered to be appropriate for the data with no violation of any of the regression analysis assumptions.

Table 6-4 Summary of the best fit models for all pressure wave parameters for all the five OPEP devices

Frequency								
	RMSE	R^2	**Model *p*-value**	**Flow**	**Resistance Level**	**Interaction (Flow*Resistance Level)**	**Flow^2**	**Flow^3**
Device A	0.8646	0.98	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Device B	1.0613	0.99	<0.0001	<0.0001	<0.0001	0.0003	<0.0001	N/A
Device C	0.9348	0.98	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Device D	1.5917	0.92	<0.0001	<0.0001	0.0002	0.0037	<0.0001	N/A
Device E	0.7263	0.98	<0.0001	<0.0001	0.0033	<0.0001	N/A	N/A
PEP								
	RMSE	R^2	**Model *p*-value**	**Flow**	**Resistance Level**	**Interaction (Flow*Resistance Level)**	**Flow^2**	**Flow^3**
Device A	0.2806	0.99	<0.0001	<0.0001	<0.0001	N/A	<0.0001	N/A
Device B	1.9035	0.99	<0.0001	<0.0001	<0.0001	0.0009	<0.0001	N/A
Device C	0.4098	0.99	<0.0001	<0.0001	<0.0001	N/A	<0.0001	N/A
Device D	1.1768	0.97	<0.0001	<0.0001	<0.0001	N/A	<0.0001	N/A
Device E	1.0351	0.99	<0.0001	<0.0001	<0.0001	<0.0001	0.0059	N/A
Amplitude								
	RMSE	R^2	**Model *p*-value**	**Flow**	**Resistance Level**	**Interaction (Flow*Resistance Level)**	**Flow^2**	**Flow^3**

Device A	0.7167	0.99	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	N/A
Device B	2.1326	0.87	<0.0001	<0.0001	0.0043	N/A	<0.0001	N/A
Device C	0.8529	0.99	<0.0001	<0.0001	0.0048	<0.0001	<0.0001	N/A
Device D	3.0704	0.92	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
Device E	1.4933	0.99	<0.0001	<0.0001	<0.0001	0.0017	0.0071	N/A

6.2.3.1 Model Validation

Table 6-5 shows the R^2 value of the built models and the prediction R^2 value. The prediction R^2 value represents the amount of the new data that was predicted by the model. Since the prediction R square value did not drop significantly from the model R^2 value the model was considered to be capable of describing the mechanical behaviour of all five devices under investigation and valid to be used for the purpose of solving the optimisation problem in this research.

Table 6-5 Model validation results for all pressure wave parameters for the five OPEP devices

	Model R^2	**Prediction R^2**	**Model R^2**	**Prediction R^2**	**Model R^2**	**Prediction R^2**
	Frequency		**PEP**		**Amplitude**	
Device A	0.98	0.94	0.99	0.96	0.99	0.93
Device B	0.99	0.95	0.99	0.97	0.87	0.82
Device C	0.98	0.96	0.99	0.99	0.99	0.98
Device D	0.92	0.81	0.97	0.94	0.92	0.83
Device E	0.98	0.96	0.99	0.95	0.99	0.96

6.2.3.2 Response Surfaces

Table 6-6, Table 6-7 and Table 6-8 shows the surface plot for each of the pressure wave parameters for all five OPEP devices. These surfaces were generated based on the model equations described in the previous section.

Table 6-6 Oscillation frequency response surface plot for all five OPEP devices

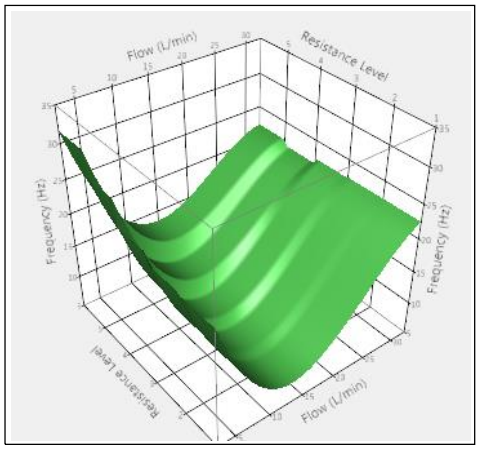
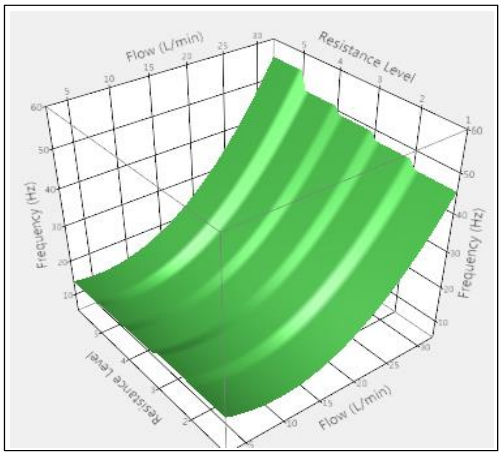
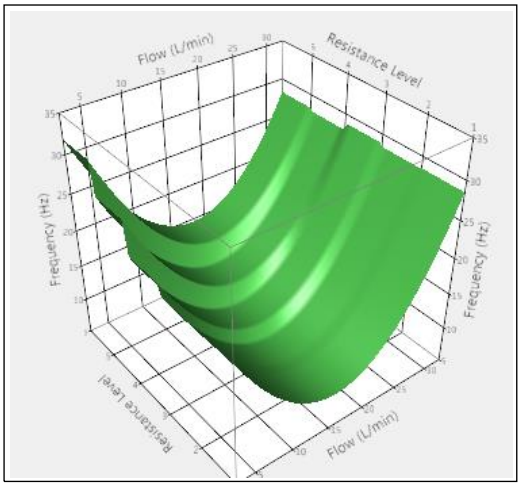
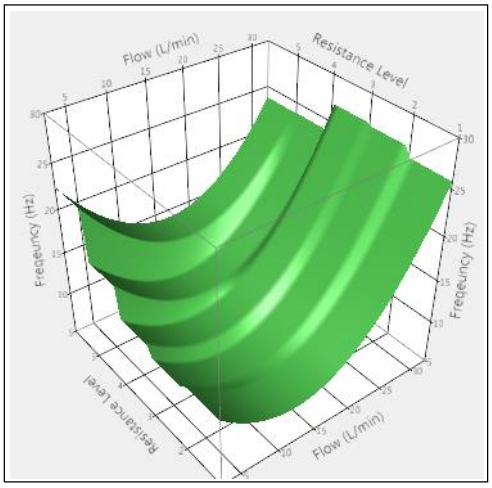
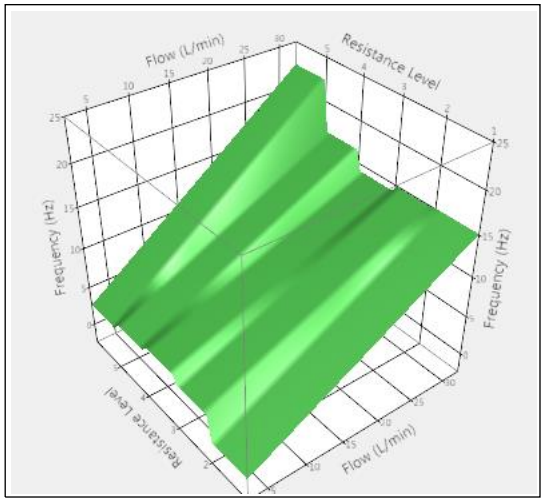
Frequency	
Device A	**Device B**
	
Device C	**Device D**
	
Device E	
	

Table 6-7 PEP response surface plot for all five OPEP devices

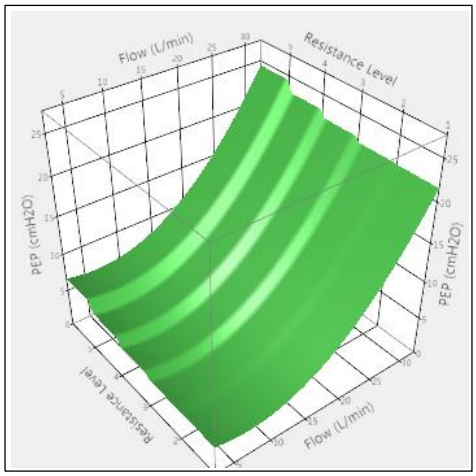
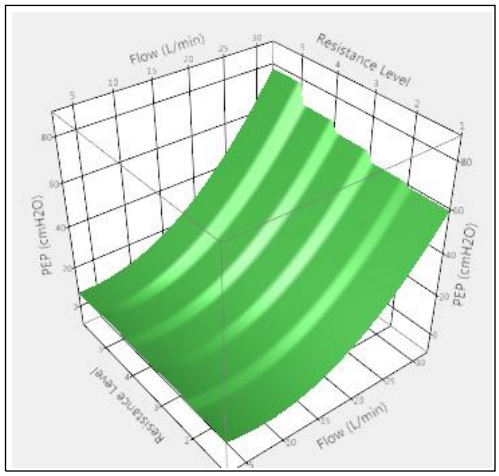
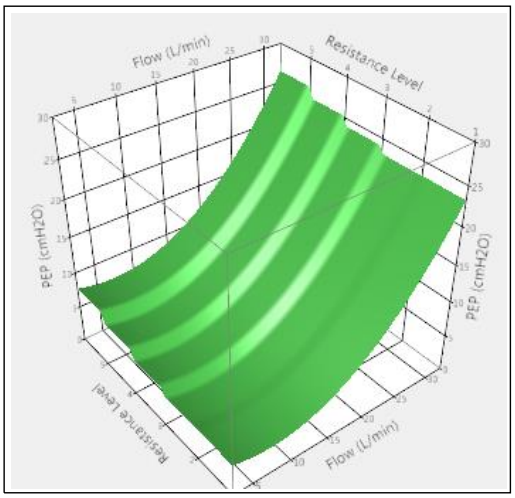
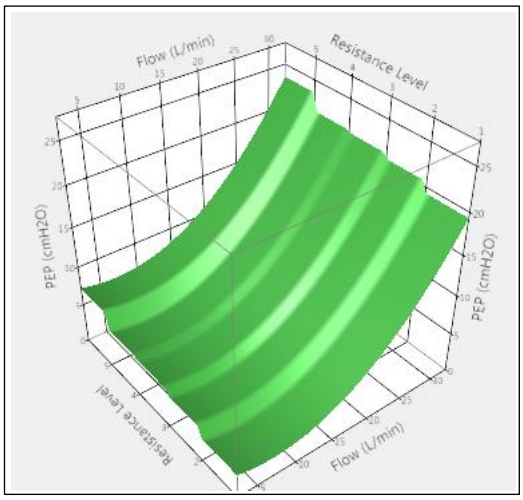
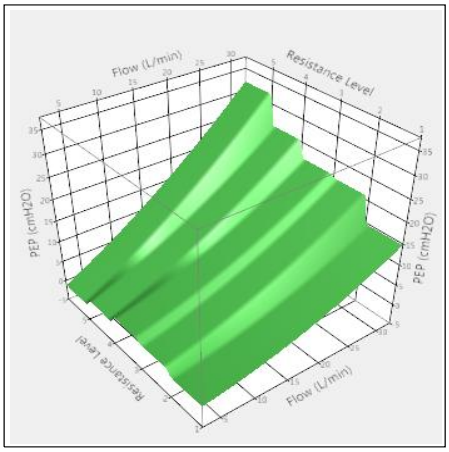
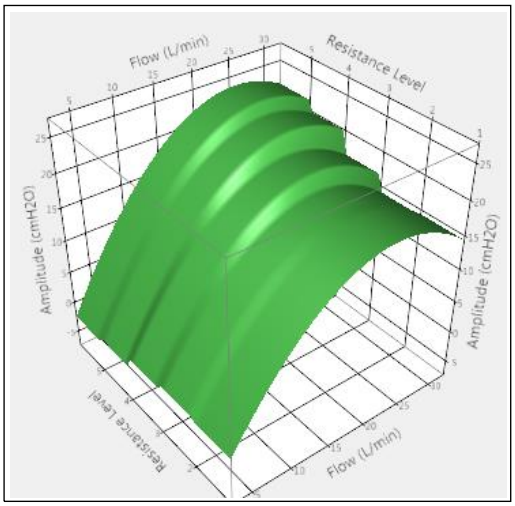
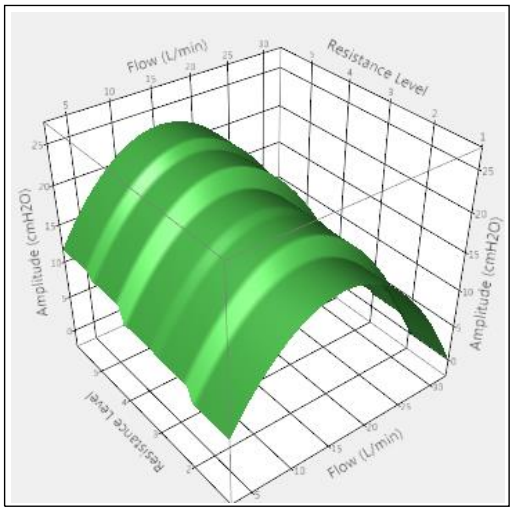
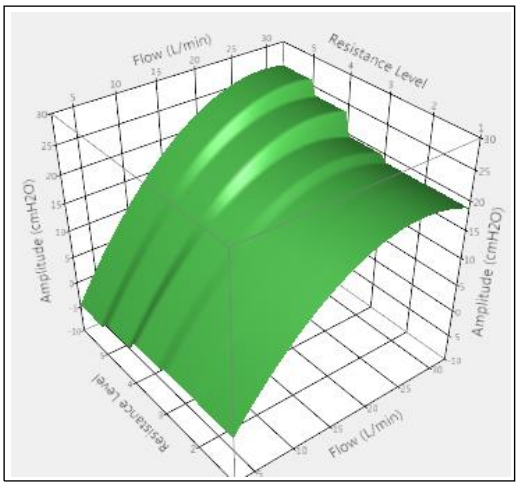
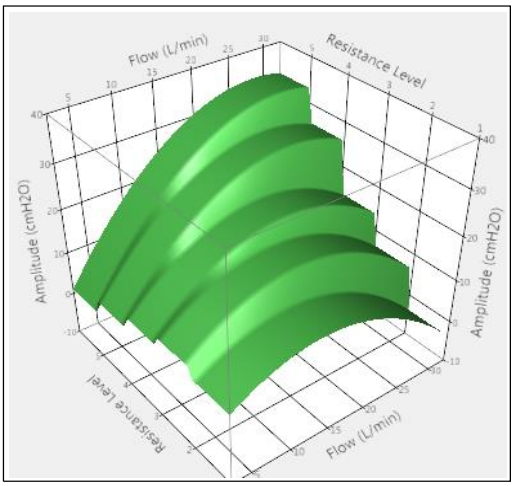
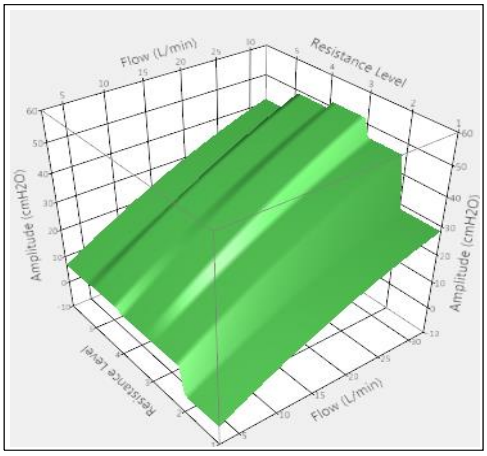
PEP	
Device A	**Device B**
	
Device C	**Device D**
	
Device E	
	

Table 6-8 Oscillation amplitude response surface for all five OPEP devices

Amplitude	
Device A	**Device B**
	
Device C	**Device D**
	
Device E	
	

6.3 Discussion

6.3.1 OPEP Device Pressure Wave Parameters

6.3.1.1 Frequency

There is a consensus in the literature that airway clearance by oscillation is optimum at certain frequencies [2,32,44,52,60,61,82,115,212]. Several, theoretical perspectives have been proposed regarding oscillation frequency mechanism of action. Chapter 2, has captured the optimum frequency values for these different perspectives.

Table 6-9 shows the flow ranges required for achieving oscillation frequency within the optimum range for each of the five investigated OPEP devices. As can be seen from the table, all five devices are capable of achieving the oscillation frequency within the optimum range. However, the range of exhalation flow required to achieve the oscillation frequency value within the optimum range varies from one device to another and depends on the optimum frequency aim sought to be achieved. Previous studies posted the exhalation flow required to achieve an oscillation frequency that matches the cilia beating frequency for device A (12-30 L/min) [55], device B (9-15 L/min) [60] and device C (30 L/min) [61]. These results are in agreement with the findings of this research.

Previous studies have pointed out that patients with severe disease conditions will have high resonance frequency, therefore type A devices might not be able to generate oscillation that matches the resonance for those patients [55,60]. However, the results of this research show that all devices are able to generate an oscillation frequency within the optimum range for patients with severe disease conditions (i.e. COPD GOLD stage 4 and severe asthma). However, for those patients, it was noticed that the exhalation flow required to achieve an oscillation frequency within the optimum range is higher.

Table 6-9 Exhalation flow rate (L/min) ranges required to achieve the optimum oscillation frequency for different therapy aims for each of the five investigated OPEP devices.

		Exhalation Flow Rate (L/min) to Achieve Optimum Frequency Range				
	Optimum Frequency Range (Hz)	**Device A**	**Device B**	**Device C**	**Device D**	**Device E**
Match Resonance Frequency for Cystic Fibrosis	10.7-23.3	5-30	5-20	5-30	5-30	15-30
Match Resonance Frequency COPD GOLD2	18.3±4.3	20-30	5-20	15-30	25-30	25-30
Match Resonance Frequency COPD GOLD 3	21.8±4.7	25-30	15-20	25-30	25-30	25-30
Match Resonance Frequency COPD GOLD 4	25.3±5.5	30	20-25	30	30	30
Match Resonance Frequency for Mild Asthma	16.1±4.7	5-25	5-15	5-25	5-25	20-30
Match Resonance Frequency for Moderate Asthma	18.1±5.8	5-30	5-20	5-30	5-30	25-30
Match Resonance Frequency for Severe Asthma	24±6.9	5 , 25-30	15-20	5, 25-30	5 , 25-30	25-30
Match Cilia Oscillation Frequency	13±2	10-25	5-15	10-20	10-20	20-25
Alter Mucus Rheology	15±7	5-30	5-20	5-30	5-30	15-30
Alter Mucus Movement	14±6	5-25	5-20	5-25	5-25	15-30

6.3.1.2 PEP

There is a consensus that for effective airway clearance the optimum PEP value needs to be between 10 and 20cmH2O. Table 6-10 shows the flow ranges required for achieving a PEP value within the optimum range for each of the five investigated devices. Device B was found to require the lowest exhalation flow (10-15 L/min) to achieve PEP within the optimum range, while device D was found to require the highest flow (20 to 30 L/min). On the other hand, devices E, A and C were found to require 20-30 L/min, 15-25 L/min and 20-25 L/min respectively to achieve a PEP value within the optimum range. These results are in agreement with results posted by prior studies for device A, D and B [34,55,60,61]. It is worth noting that device B was found to be able to achieve PEP values above 20cmH2O at relatively low flow rates, which might pose a risk to the patient. Therefore, the mechanical behaviour of device B must be precisely controlled. Similar results are reported in previous work [60].

However, in clinical practice, it should be noted that the exhalation flow required to achieve the optimum PEP value is also dependent on the resistance level. In Table 6-10, for the lower end of the flow range, it is best to set the device to resistance level 5 to ensure that the optimum PEP value is achieved.

Table 6-10 Exhalation flow rate (L/min) ranges required to achieve the optimum PEP value for each of all five investigated OPEP devices.

	Optimum PEP Range (cmH2O)	**Device A**	**Device B**	**Device C**	**Device D**	**Device E**
Exhalation Flow Rate (L/min) Ranges	10- 20	15-25	10-15	20-25	20-30	20-30

6.3.1.3 Amplitude

Higher oscillation amplitude is thought to produce better airway clearance results [54,158]. However, the optimum oscillation value is a knowledge gap yet to be filled. Therefore, the exhalation flow rate for achieving the optimum oscillation amplitude cannot be recommended. However, it can be concluded that device E might be the best choice in clinical practice as it was found to produce the highest amplitude value at all

flow rates. On the other hand, in clinical practice should be noted that the oscillation amplitude values produced by device A were found to be the smallest in comparison to the other OPEP devices investigated. In previous work the usefulness of this device has also been questioned due to of the small oscillation amplitude it produces [61].

6.3.2 Flow - Pressure Wave Parameter Relationship

6.3.2.1 Flow-Frequency Relationship

One of the main observations noted about the frequency-flow relationship, is that the pattern of this relationship seems to be of a proportional type under flow ranges that match the device specification and of an inverse type under flow ranges outside of the device specification. For instance, device D is designed to work with expiratory flow of ≥ 15 L/min (Smiths Medical 2013), hence the observed proportional pattern for this device under a flow range of 15 to 30 L/min. On the other hand, devices A and C are designed to work for expiratory flow ≤ 10 L/min (Smiths Medical 2013), hence the proportional relationship between 10 to 30 L/min flow range. Device E, on the other hand, which is designed to work with a flow range of ≥ 10 L/min up to 30 L/min showed a proportional flow-frequency relationship under a flow range of 5-to 30 L/min.

Such a pattern can also be noted in previous studies. For instance, the flow-frequency plot posted by [61] for devices D and A shows an overall proportional trend under a flow range of 6 to 50L/min. However, the trend is of an inverse type under a flow range between 6 to 20 L/min, and of a proportional type under a flow range of 20 to 50 L/min. Similarly, the frequency plot posted by (Alves Silva et al 2009) shows an overall proportional flow-frequency relationship for device A under a flow range of 12 to 48 L/min. For device B, although in our results an inverse pattern of the flow-frequency relationship was not observed under flow range of 15-to 30 L/min, in prior work, [61] reported an inverse flow-frequency relationship for device B under flow range of 30-50 L/min, in comparison to a proportional flow-frequency relation at a flow range of 5-30 L/min. In another study [60] reported that frequency – flow has a proportional relationship under flow range of 3-15 L/min .

The observed flow – frequency relation, can be explained by the fact that OPEP devices are pressure regulated devices that work as pressure threshold resistors [82]. Reaching

the threshold required to fully open the valve will increase the airflow that passes throw the valve, hence increasing the speed of the oscillatory vane that alternates between opened and closed position, which explains the observed proportional relationship (Figure 6-8 and Figure 6-9). However, exceeding the device specification or not reaching the valve pressure threshold will prevent the alternating vane from returning to its starting position, hence causing the produced oscillation frequency to show the exhibited inverse relation.

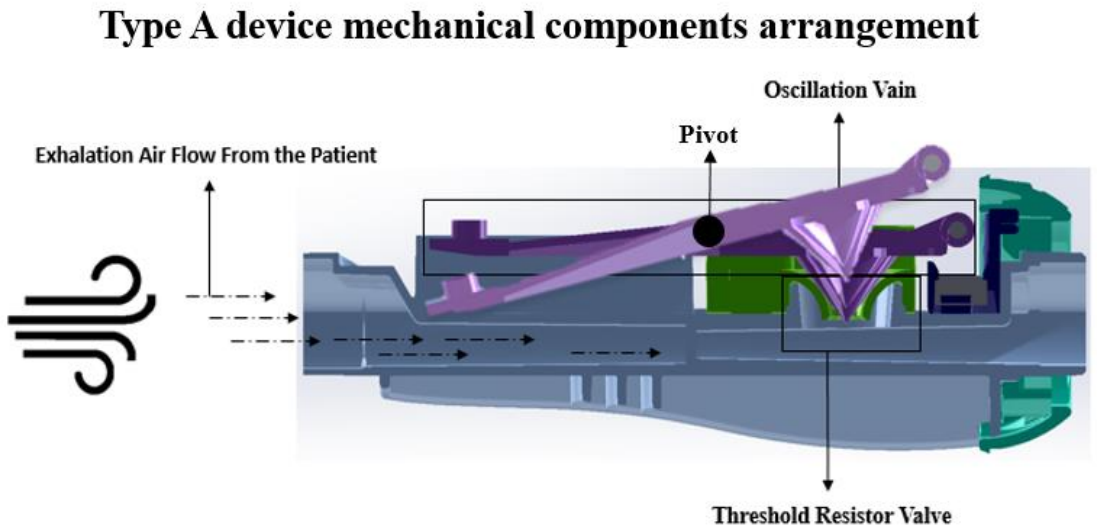


Figure 6-8 Mechanical components arrangement (threshold resistor valve and oscillation vain) employed in type A devices

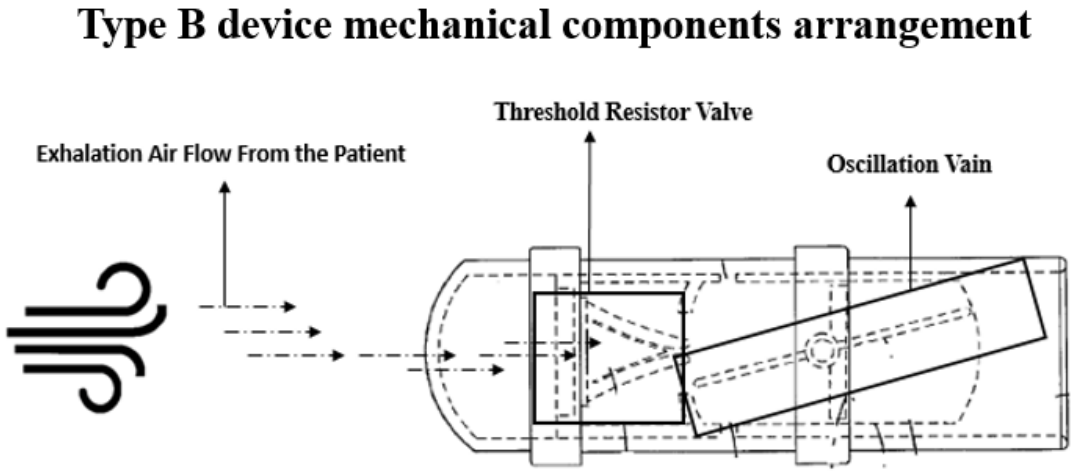


Figure 6-9 Mechanical components arrangement (threshold resistor valve and oscillation vain) employed in type B devices [68]

6.3.2.2 Flow-PEP Relationship

In term of the flow- PEP relationship, the main observation noted in our results is that this relationship is of a proportional type for all five devices under a flow range of 5 to 30 L/min. Similar results were reported in previous studies for device D [50,61], B [50,60,61] and A [55,61]. Such findings are expected as the mechanical design of these devices produces the PEP by having a resistance element (threshold valve) to the flow, hence the higher the flow, the higher the PEP produced.

6.3.2.3 Flow–Amplitude Relationship

In terms of the flow - amplitude relationship, it can be concluded that exhaling at higher flow rate with devices A, C and E will result in a larger oscillation amplitude. The same is also true for device B as long as this device is used within its intended flow rate specification. However, for device D, the clinical practice need to be aware that the flow - amplitude relationship for this device is dependent on the chosen resistance level.

The increase of the amplitude as higher flow rate can be explained by the increase in the alternating vane movement range as a result in the increase in airflow. However, in term device D, it can be speculated that such behaviour is related to the magnetic force change caused by adjustment level change, which affects the approximation of the magnet to the alternating vane.

6.3.3 Resistance Level - Pressure Wave Parameter Relationship

In terms of the relationship between the resistance levels and both the oscillation frequency and PEP parameters, for all five investigated OPEP devices, the value of these two parameters was found to increase as the resistance level increased. However, in terms of the relationship between the resistance level and the oscillation amplitude; for all type A devices, increasing the resistance levels was observed to cause the oscillation amplitude value to increase. Such results can be related to the increasing speed of the vain/counterweight set movement range Figure 6-10 with increase of flow in addition to the proximity of the magnet to the vain/counterweight that results from increasing the resistance level [60].

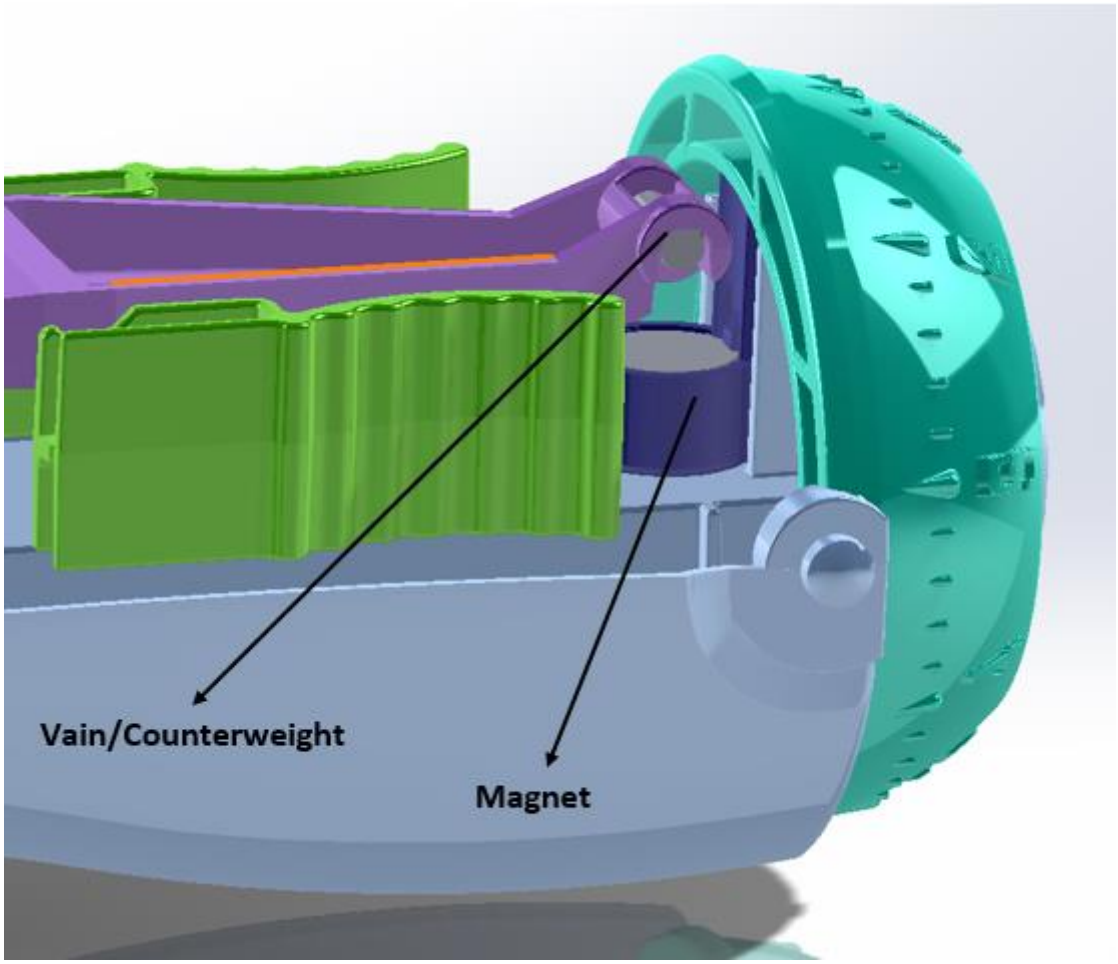


Figure 6-10 Type A devices - magnetic set approximation (created by the author)

Yet, for the device E it was observed that the highest oscillation amplitude was found to be achieved at resistance levels 3 and 4, rather than level 5. Therefore, from the perspective that a higher amplitude will result in more effective airway clearance, it is recommended that these devices are used at these resistance levels in order to generate the highest amplitude, providing that the patient is able to sustain the optimum exhalation flow required for these resistance levels.

Interestingly, the type A devices were found to require different flow rates at the same resistance levels. Therefore, respiratory therapist need to be aware of the mechanical behaviour difference for not only devices from different manufacturers but also devices from the same manufacturer. Similar observations were reported in previous work [38,61]. It can be speculated that the difference between type A devices can be related to the difference in the threshold valve dimensions and magnet approximation to the valve.

6.4 Chapter Summary

In summary, the mechanical behaviours of five OPEP devices have been characterised and described in this chapter under a unified experiment setup that includes exhalation flow ranges commonly found in the clinical practice, which allowed for a direct comparison between devices, especially devices from different manufacturers.

In this chapter:

- The mechanical behaviour of the five investigated OPEP devices was modelled. In total, 15 models were built for each of the pressure wave parameters for all five devices.
- The built models were validated by collecting a new data set. All models were found to be valid as per the change in the prediction R^2 in comparison to the model fit R^2.
- Based on the characterisation of the mechanical behaviour of the five investigated OPEP devices in this research, all five devices were found to be capable of generating pressure wave parameters within the optimum required range for effective airway clearance.
- However, the exhalation flow rate required to achieve the optimum range was found to be different for each of the pressure wave parameters and may vary from one device to another.
- Device A was observed to produce the least effective oscillation amplitude, while Device E was observed to produce the most effective oscillation amplitude out of all five devices.
- Furthermore, for patients with severe disease conditions (i.e., COPD GOLD stage 4 and severe asthma), clinicians and respiratory therapists need to be aware that the exhalation flow required to achieve oscillation frequency within the optimum range is higher for those patients.
- Device B was observed to produce PEP values exceeding 20 cmH2O at relatively low flow rates. Thus, the mechanical behaviour of this device setting needs to be precisely controlled.
- Based on the characterisation of the relation between the OPEP devices setting and the pressure wave parameters:

a- It was observed to be proportional under the flow ranges that match the device specification and is inverse relation underflow ranges outside the device specification. This can be related to the threshold resistor valves employed in OPEP devices.

b- The relation between exhalation flow and the PEP parameter was found to be always proportional. This can be related to a resistance element (threshold valve) to the flow; hence, the higher the flow, the higher the PEP produced.

c- For the frequency and amplitude relation, using OPEP devices outside their intended specification tends to result in an inverse relationship between the flow and these two parameters.

d- However, in general, for type-A devices, exhaling at higher flow rates will result in larger oscillation amplitudes. Such increase can be explained by the increase in the oscillation mechanism movement range as a result of the increase in airflow.

- The resistance level was found to have a statistically significant influence that might be valuable in fine-tuning the device to achieve the optimum pressure wave parameters.
- In addition, the exhalation flow and the resistance levels were observed to have an interdependent effect with a significant influence on the pressure wave parameters for most devices.
- For type-A devices, increasing the resistance level was found to result in an increase in the pressure wave parameters values. Such results can be explained by the increasing speed of the rocker valve movement caused by the increasing resistance level.
- However, for type B devices, increasing the resistance level was found to increase the value of the oscillation frequency and the PEP parameter. The highest amplitude values were found to be achieved at resistance levels 3 and 4.

7 CHARACTERISING AND VALIDATING THE OPTIMUM MECHANICAL BEHAVIOUR OF OPEP DEVICES FOR EFFECTIVE AIRWAY CLEARANCE

This chapter addresses the fifth objective of this research (to characterise and validate the optimum mechanical behaviour of OPEP devices for effective airway clearance). In chapter 6, the mechanical behaviours of the five OPEP devices under investigation have been characterised, and regression models to describe such mechanical behaviours have been built. In this chapter, the optimum mechanical behaviours of OPEP devices for effective airway clearance results will be presented and discussed. Validation results with clinicians and respiratory therapists will also be presented and discussed.

7.1 Introduction

When prescribing OPEP therapy for a patient, respiratory therapists and clinicians have the responsibility of choosing the appropriate OPEP device for that patient [57–59]. Also, they are responsible for optimising the use of the device to achieve effective airway clearance results [20,29,59]. However, no guidelines exist to aid clinicians and respiratory therapists in choosing the exhalation flow rate and resistance level to optimise the device's operation according to the features of each patient and the technical capabilities of each device [57]. In addition, "manufacturers' instructions for use are vague and often lack the required specifications" [54,55,61]. In a recent review, it was stressed that despite the fact that OPEP has been around for several years and is routinely used in clinical practice, the question remains as to "which settings are appropriate for optimum airway clearance results" [38].

The knowledge gap that this research is trying to address is; the appropriate OPEP device settings for producing pressure wave parameters that satisfy the optimum technical performance requirements. In chapter 3, the optimum technical performance requirements have been established through a literature review. In addition, airway clearance therapy aims guidelines that take into account these optimum technical performance requirements have been proposed.

In chapter 5, it was observed that the settings (exhalation flow and resistance levels) have a statistically significant effect on the pressure wave parameters for most of the

investigated OPEP devices. Also, the effect of the settings (exhalation flow and resistance levels) were found to have an interdependent effect on the pressure wave parameter values. In addition, chapter 5 has identified for each pressure wave parameter individually, the exhalation flow rate range required to achieve the optimum values. This knowledge is valuable for clinical practice in understanding the mechanical behaviour of OPEP devices. Nevertheless, to address the knowledge gap, there is a need to identify the OPEP device settings that achieve the optimum pressure wave parameter values simultaneously and take into account the interdependent nature of the OPEP device settings.

The optimisation problem in this research is; characterising the appropriate settings for producing pressure wave parameters that satisfy the optimum technical performance requirements for different therapy aims. The optimisation problem was solved as per the procedure described in section 4.3.3 of chapter 4. The results in this chapter will be presented in three main sections; global optimums, local optimums and validation. The global optimum results are the best OPEP device setting combinations among all possible solutions that satisfy the optimum technical performance criteria for all pressure wave parameters simultaneously. The local optimum results, on the other hand, are the best flow rates that satisfy the optimum technical performance criteria for all pressure wave parameters simultaneously at every resistance level. The validation section will present the results of validating the finds in this chapter with the target audience of clinician and respiratory therapist.

The discussion of the results will be presented in four main sections, optimum flow range, optimum resistance levels, considerations for using OPEP devices and validation results discussion.

7.2 Results

7.2.1 Mechanical Behaviour Global Optimum

Table 7-1 tabulates the combination of exhalation flow and resistance levels that satisfies the optimum technical performance criteria for different therapy aims. The table shows the pressure wave parameter values that could be achieved using these setting combinations. All decimal numbers were rounded to the nearest ten. A sample of the prediction profiler and desirability plot can be found in Appendix E.

In terms of achieving the optimum mechanical behaviour for cystic fibrosis patients, device B was found to require the least exhalation flow (13 L/min). On the other hand, device D and A were found to require the highest flow rate (25 L/min).

In terms of achieving the optimum mechanical behaviour for COPD patients, it was found that device E is unable to generate pressure wave parameters that satisfy the optimum technical performance criteria for COPD patients who are at GOLD stage 3 and 4. Yet, this device was able to produce pressure wave parameters that satisfy the optimum technical performance criteria for COPD patients at stage GOLD 2. Device B was found to require the least exhalation flow to generate the optimum technical performance for COPD patients at GOLD stages 2, 3 and 4 (16, 18 and 19 L/min respectively). While device D was found to require the highest flow level to generate the optimum technical performance for COPD patients at GOLD 2 (26 L/min). Both devices A and D were found to require the highest flow for patients with COPD at GOLD stage 3 and 4 (29 L/min).

In terms of achieving the optimum mechanical behaviour for asthma patients, device E was unable to generate pressure wave parameters that satisfy the optimum technical performance criteria for patients with severe asthma. However, this device was able to achieve the optimum technical performance for patients with mild and moderate asthma. Device B was found to require the least exhalation flow to generate the optimum technical performance for patients with mild, moderate and severe asthma (13, 18 and 19 L/min respectively). While devices A and D were found to require the highest flow level to generate the optimum technical performance for patients with mild and severe asthma (25 and 29 L/min respectively). For patients with moderate asthma, device D was found to require the highest flow (26 L/min) to generate the optimum technical performance.

In terms of the optimum mechanical behaviour for altering mucus movement, device B was found to require the least exhalation flow (13 L/min) to produce the mechanical behaviour that satisfies the optimum criteria for all pressure wave parameters simultaneously. On the other hand, device E was found to require the highest flow rate (26 L/min).

In terms of the optimum mechanical behaviour for altering mucus rheology, device B was found to require the least exhalation flow (13 L/min) to produce the mechanical behaviour that satisfies the optimum criteria for all pressure wave parameters simultaneously. On the other hand, devices D and A were found to require the highest flow rate (25 L/min).

In terms of the optimum mechanical behaviour for matching the cilia frequency, device B was found to require the lowest exhalation flow (11 L/min) to generate the optimum technical performance. However, device E was found to require the highest flow (27L/min).

Table 7-1 Global optimum mechanical behaviour for effective airway clearance for all five OPEP devices

		Therapy Aim									
		Match Patients Resonance Frequency							Alter Mucus Movement	Alter Mucus Rheology	Match Cilia Frequency
		Cystic Fibrosis	COPD			Asthma					
			GOLD 2	GOLD 3	GOLD 4	Mild	Moderate	Sever			
Device A	Flow	25	24	29	29	25	25	29	25	25	22
	Resistance Level	4	5	1	1	4	5	1	4	4	3
	Frequency	17	18	20	20	17	18	20	16	17	14
	PEP	14	15	17	17	14	15	17	14	14	11
	Amplitude	22	23	17	17	22	23	17	22	22	20
	Desirability	0.90	0.96	0.64	0.35	0.87	0.97	0.38	0.71	0.84	0.34
Device B	Flow	13	16	18	19	13	18	19	13	13	11
	Resistance Level	5	4	2	2	5	2	2	5	5	5
	Frequency	16	17	19	20	16	18	19	16	16	15
	PEP	15	16	16	17	15	15	17	14	15	12
	Amplitude	23	22	19	19	22	20	19	22	22	21
	Desirability	0.94	0.91	0.68	0.29	0.94	0.90	0.33	0.80	0.90	0.32
Device C	Flow	24	23	27	28	22	23	28	23	24	20
	Resistance Level	4	5	1	1	5	5	1	4	4	4

	Frequency	17	18	20	20	17	18	20	17	17	14
	PEP	14	14	16	17	14	15	17	13	14	11
	Amplitude	24	24	21	21	24	25	21	23	24	22
	Desirability	0.83	0.89	0.68	0.38	0.75	0.92	0.41	0.64	0.77	0.32
Device D	Flow	25	26	29	29	25	26	29	24	25	24
	Resistance Level	5	5	3	3	5	5	3	5	5	4
	Frequency	17	17	21	22	16	17	22	16	16	14
	PEP	15	16	16	17	15	16	17	14	15	12
	Amplitude	33	34	18	17	32	34	17	33	33	29
	Desirability	0.96	0.94	0.72	0.5	0.95	0.94	0.48	0.80	0.92	0.35
Device E	Flow	20	21	None	None	20	20	None	26	19	27
	Resistance Level	5	5	None	None	5	5	None	2	5	2
	Frequency	14	15	None	None	14	14	None	13	14	13
	PEP	16	17	None	None	16	17	None	17	16	16
	Amplitude	30	31	None	None	30	30	None	40	30	41
	Desirability	0.66	0.47	0.08	0.03	0.69	0.44	0.06	0.85	0.79	0.88

7.2.2 Mechanical Behaviour Local Optimum

7.2.2.1 Optimum Mechanical Behaviour for Cystic Fibrosis Patients

Table 7-2 shows the optimum OPEP device mechanical behaviour for cystic fibrosis at every resistance level. Resistance level 1 for device E was found to require the highest exhalation flow (30 L/min) to achieve the optimum technical performance criteria for cystic fibrosis patients. On the other hand, resistance level 5 for device B was found to require the least exhalation flow (13 L/min).

In terms of the exhalation flow range that satisfies the optimum criteria across all resistance levels, device E was found to have the widest exhalation flow range (20 to 30 L/min), while, both devices A and C were found to have the narrowest flow range (24-26 L/min). The exhalation flow ranges that satisfy the optimum criteria across all resistance levels for devices B and D is 13- 18 L/min and 25-29 L/min respectively.

Table 7-2 Optimum mechanical behaviour of OPEP devices for cystic fibrosis patients

	Device A					Device B				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	26	26	26	25	24	18	17	16	16	13
Frequency	18	18	17	17	18	18	18	17	17	16
PEP	14	14	14	14	14	14	14	15	16	15
Amplitude	18	18	20	22	23	18	20	20	22	23
Desirability	0.78	0.78	0.83	0.9	0.88	0.8	0.8	0.86	0.91	0.94
	Device C					**Device D**				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	25	26	25	24	24	29	28	27	27	25
Frequency	18	18	18	17	19	20	20	19	17	17
PEP	14	14	14	14	16	14	15	15	15	15
Amplitude	21	21	21	24	25	3	13	19	28	33
Desirability	0.74	0.74	0.77	0.83	0.72	0.49	0.71	0.81	0.92	0.96
	Device E									
Resistance Level	1	2	3	4	5					
Flow	30	28	27	24	20					
Frequency	14	13	12	13	14					
PEP	13	17	17	17	16					
Amplitude	27	41	46	40	30					
Desirability	0.51	0.52	0.41	0.49	0.66					

7.2.2.2 Optimum Settings for COPD Patients

Optimum Settings for COPD Patients at Stage GOLD 2

Table 7-3 shows the optimum OPEP devices mechanical behaviour for GOLD 2 COPD patients at every resistance level. Resistance levels 1 and 2 for device E were found to require the highest exhalation flow (30 L/min) to achieve the optimum technical performance criteria for COPD patients at stage GOLD 2. On the other hand, resistance level 5 for device B was found to require the least exhalation (14 L/min) to achieve the optimum criteria for those patients.

In terms of the exhalation flow range that satisfies the optimum criteria across all resistance levels. Device E was found to have the widest exhalation flow range (22 to 30 L/min). The exhalation flow ranges that satisfy the optimum criteria across all resistance levels for devices B, A, D and C are 14- 18 L/min, 24-27 L/min, 25-28 L/min and 23-26 L/min respectively.

Table 7-3 Optimum mechanical behaviour of OPEP devices for COPD patients at stage GOLD 2

	Device A					**Device B**				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	27	27	26	26	24	18	17	17	16	14
Frequency	18	18	18	18	18	15	18	18	17	17
PEP	14	14	15	15	15	18	15	15	16	16
Amplitude	18	18	20	22	23	0.86	20	20	22	23
Desirability	0.85	0.85	0.9	0.95	0.96	0.43	0.88	0.35	0.91	0.9
	Device C					**Device D**				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	26	26	25	24	23	28	27	26	27	25
Frequency	18	14	18	18	18	19	18	18	17	17
PEP	14	21	14	15	14	13	14	14	15	15
Amplitude	21	0.83	21	24	24	4	14	19	28	33
Desirability	0.83	0.83	0.85	0.9	0.89	0.43	0.64	0.73	0.92	0.96
	Device E									
Resistance Level	1	2	3	4	5					
Flow	30	30	None	27	22					
Frequency	14	14	None	14	15					
PEP	13	19	None	19	18					
Amplitude	27	43	None	43	32					
Desirability	0.13	0.12	None	0.1	0.32					

Optimum Settings for COPD Patients at Stage GOLD 3

Table 7-4 shows the optimum OPEP device mechanical behaviour for GOLD 3 COPD patients at every resistance level. For COPD patients at stage GOLD 3, it was found that for device E, no flow or resistance level combination was able to produce pressure wave parameters that satisfy the optimum criteria. Nevertheless, all type A devices were able to produce pressure wave parameters that satisfy the optimum technical performance criteria at various flow and resistance level combinations.

The resistance levels 1 and 2 for device A and resistance levels 1, 2, 3 and 4 for device D were found to require the highest exhalation flow (29 L/min) to achieve the optimum technical performance criteria for COPD patients at stage GOLD 3. On the other hand, resistance level 5 for device B was found to require the least exhalation for (15 L/min) to achieve the optimum criteria for those patients.

In terms of the exhalation flow range that satisfies the optimum criteria across all resistance levels. Device B was found to have the widest exhalation flow range (15 to 19 L/min), while, device D was found to have the narrowest flow range (27-29 L/min). The exhalation flow range that satisfies the optimum criteria across all resistance levels for devices C and A is 25-28 L/min and 26- 29 L/min respectively.

Table 7-4 Optimum mechanical behaviour of OPEP devices for COPD patients at stage GOLD 3

	Device A					Device B				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	29	29	28	28	26	19	18	18	17	15
Frequency	20	20	20	19	19	19	19	19	18	18
PEP	17	17	17	17	17	17	16	17	17	17
Amplitude	17	17	19	22	24	17	19	20	22	23
Desirability	0.64	0.63	0.62	0.54	0.61	0.50	0.68	0.48	0.39	0.36
	Device C					**Device D**				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	27	28	27	26	25	29	29	29	29	27
Frequency	20	20	20	19	20	21	21	21	19	18
PEP	16	16	16	17	17	15	16	16	17	17
Amplitude	21	21	21	24	25	2	12	18	28	34
Desirability	0.68	0.68	0.68	0.61	0.67	0.44	0.64	0.72	0.52	0.41

Optimum Settings for COPD Patients at Stage GOLD 4

Table 7-5 shows the optimum mechanical behaviour for GOLD 4 COPD patients at every resistance level. For COPD patients at stage GOLD 4, it was found that for the device E, no flow or resistance level combination was able to produce pressure wave parameters that satisfy the optimum criteria. Nevertheless, all type A devices were able to produce pressure wave parameters that satisfy the optimum criteria at various flow and resistance level combinations.

Resistance level 1 for device D device was found to require the highest exhalation flow (30 L/min) to achieve the optimum technical performance criteria for COPD patients at stage GOLD 4. On the other hand, resistance level 5 for device B was found to require the least exhalation for (15 L/min) to achieve the optimum criteria for those patients.

In terms of the exhalation flow range that satisfies the optimum criteria across all resistance levels, device B was found to have the widest exhalation flow range (15 to 20

L/min). However, the other three type A devices (D, C and A) were found to have a similar flow range; 28-30 L/min, 26-28 L/min and 27 to 29 L/min respectively.

Table 7-5 Optimum mechanical behaviour of OPEP devices for COPD patients at stage GOLD 4

	Device A					**Device B**				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	29	29	29	28	27	20	19	18	17	15
Frequency	20	20	20	19	20	19	20	19	18	18
PEP	17	17	17	18	17	17	17	18	18	18
Amplitude	17	17	19	22	24	17	19	20	22	23
Desirability	0.35	0.35	0.33	0.26	0.3	0.24	0.29	0.22	0.17	0.15
	Device C					**Device D**				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	28	28	28	27	26	30	29	29	29	28
Frequency	20	20	21	20	20	22	22	22	20	19
PEP	17	17	17	17	17	16	17	17	18	18
Amplitude	21	20	21	24	26	1	11	17	28	34
Desirability	0.38	0.38	0.38	0.32	0.36	0.29	0.43	0.50	0.26	0.18

7.2.2.3 Optimum Settings for Asthma Patients

Optimum Settings for Patients with Mild Asthma

Table 7-6 shows the optimum OPEP device mechanical behaviour for patients with mild asthma at every resistance level. Resistance level 1 for device E was found to require the highest exhalation flow (30 L/min) to achieve the optimum technical performance criteria for patients with mild asthma. On the other hand, resistance level 5 for device B was found to require the least exhalation (13 L/min) to achieve the optimum criteria for those patients.

In terms of the exhalation flow range that satisfies the optimum criteria across all resistance levels. Device E was found to have the widest exhalation flow range (20 to 30 L/min), while, device D was found to have the narrowest flow range (25-27 L/min). The

exhalation flow ranges that satisfy the optimum criteria across all resistance levels for devices B, A and C are 13- 18 L/min, 23-26 L/min and 22-25 L/min respectively.

Table 7-6 Optimum mechanical behaviour of OPEP devices for patients with mild asthma

	Device A					Device B				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	26	26	26	25	23	18	17	16	15	13
Frequency	17	17	17	17	17	17	18	17	17	16
PEP	13	13	14	14	14	14	14	14	15	15
Amplitude	19	18	20	22	23	18	20	20	22	22
Desirability	0.74	0.73	0.8	0.87	0.83	0.75	0.73	0.83	0.92	0.94
	Device C					**Device D**				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	25	25	24	24	22	27	26	26	26	25
Frequency	17	17	17	17	17	18	18	18	17	16
PEP	13	13	13	14	14	13	13	13	14	15
Amplitude	21	21	21	23	24	5	14	20	28	32
Desirability	0.69	0.69	0.72	0.79	0.75	0.32	0.5	0.58	0.87	0.95
	Device E									
Resistance Level	1	2	3	4	5					
Flow	30	28	27	24	20					
Frequency	14	13	12	13	14					
PEP	13	16	17	17	16					
Amplitude	27	41	45	40	30					
Desirability	0.54	0.58	0.48	0.54	0.69					

Optimum Settings for Patients with Moderate Asthma

Table 7-7 shows the optimum OPEP device mechanical behaviour for patients with moderate asthma at every resistance level. Resistance level 1 for device E was found to require the highest exhalation flow (30 L/min) to achieve the optimum technical performance criteria for patients with mild asthma. On the other hand, resistance level 5

for device B was found to require the least exhalation for (14 L/min) to achieve the optimum criteria for those patients.

In terms of the exhalation flow range that satisfies the optimum criteria across all resistance levels, device E was found to have the widest exhalation flow range (20 to 30 L/min), while, devices A and D were found to have the narrowest flow ranges; 25-27 L/min and 26 to 28 L/min respectively. The exhalation flow ranges that satisfy the optimum criteria across all resistance levels for device B and C are 14- 18 L/min and 23-26 L/min respectively.

Table 7-7 Optimum mechanical behaviour of OPEP devices for patients with moderate asthma

	Device A					Device B				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	27	27	27	26	25	18	18	17	16	14
Frequency	18	18	18	18	18	18	18	18	17	17
PEP	15	15	15	15	15	15	15	15	16	15
Amplitude	18	18	20	22	23	18	20	20	22	23
Desirability	0.87	0.87	0.91	0.95	0.97	0.86	0.9	0.9	0.9	0.89
	Device C					**Device D**				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	26	26	25	25	23	28	27	27	27	26
Frequency	19	19	18	18	18	19	19	19	18	17
PEP	15	15	15	15	15	14	14	14	15	15
Amplitude	21	21	22	24	25	4	13	19	28	34
Desirability	0.86	0.86	0.87	0.92	0.92	0.46	0.67	0.77	0.91	0.94
	Device E									
Resistance Level	1	2	3	4	5					
Flow	30	28	28	25	20					
Frequency	14	13	13	13	14					
PEP	13	17	17	17	17					
Amplitude	27	41	46	41	30					
Desirability	0.31	0.3	0.22	0.27	0.44					

Optimum Settings for Patients with Severe Asthma

Table 7-8 shows the optimum OPEP device mechanical behaviour for patients with severe asthma at every resistance level For patients with severe asthma; it was found that for the device E, no flow or resistance level combination was able to produce pressure wave parameters that satisfy the optimum criteria. However, type A devices were able to

produce pressure wave parameters that satisfy the optimum criteria at various flow and resistance level combinations.

Resistance level 1 for type D was found to require the highest exhalation flow (30 L/min) to achieve the optimum technical performance criteria for patients with severe asthma. On the other hand, resistance level 5 for device B was found to require the least exhalation for (15 L/min) to achieve the optimum criteria for those patients.

In terms of the exhalation flow range that satisfies the optimum criteria across all resistance levels, device B was found to have the widest exhalation flow range (15 to 19 L/min), while, device A was found to have the narrowest flow range (27-29 L/min). The exhalation flow ranges that satisfy the optimum criteria across all resistance levels for device D and C are 27- 30 L/min and 25-28 L/min respectively.

Table 7-8 Optimum mechanical behaviour of OPEP devices for patients with severe asthma

	Device A					**Device B**				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	29	29	29	28	27	19	19	18	17	15
Frequency	20	20	20	19	19	19	19	19	18	18
PEP	17	17	17	17	17	17	17	17	17	17
Amplitude	17	17	19	22	24	17	19	19	22	23
Desirability	0.38	0.38	0.36	0.31	0.35	0.29	0.33	0.28	0.23	0.21
	Device C					**Device D**				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	28	28	27	26	25	30	29	29	29	27
Frequency	20	20	20	20	20	21	22	22	19	18
PEP	17	17	17	17	17	16	16	17	17	17
Amplitude	21	21	21	24	25	1	11	17	28	34
Desirability	0.41	0.41	0.41	0.36	0.39	0.29	0.42	0.48	0.3	0.24

7.2.2.4 Optimum Settings to Alter Mucus Movement

Table 7-9 shows the optimum mechanical behaviour for altering mucus movement at every resistance level. Resistance level 1 for device E was found to require the highest

exhalation flow (30 L/min) to achieve the optimum technical performance criteria for altering mucus movement. On the other hand, resistance level 5 for device B was found to require the least exhalation for (13 L/min).

In terms of the exhalation flow range that satisfies the optimum criteria across all resistance levels, device E was found to have the widest exhalation flow range (19 to 30 L/min), while, devices A, C and D were found to have a similar flow range (23-26 L/min, 22-25 L/min and 24 to 27 L/min respectively).

Table 7-9 Optimum mechanical behaviour of OPEP devices for altering mucus movement

	Device A					**Device B**				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	26	25	25	25	23	18	17	16	15	13
Frequency	17	17	17	16	17	17	17	17	16	16
PEP	13	13	13	14	13	14	14	14	14	14
Amplitude	17	19	20	22	23	18	20	20	22	22
Desirability	0.60	0.59	0.65	0.71	0.66	0.59	0.57	0.67	0.78	0.80
	Device C					**Device D**				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	25	25	24	23	22	27	26	25	26	24
Frequency	17	17	17	17	17	18	17	17	16	16
PEP	13	13	13	13	13	12	13	13	14	14
Amplitude	21	21	21	23	24	5	14	20	29	33
Desirability	0.55	0.55	0.57	0.64	0.59	0.25	0.39	0.46	0.73	0.80
	Device E									
Resistance Level	1	2	3	4	5					
Flow	30	26	26	23	19					
Frequency	14	13	12	12	14					
PEP	13	17	16	16	15					
Amplitude	27	40	44	38	29					
Desirability	0.66	0.85	0.81	0.83	0.82					

7.2.2.5 Optimum Settings to Alter Mucus Rheology

Table 7-10 shows the optimum mechanical behaviour for altering mucus rheology at every resistance level. Resistance level 1 for device E was found to require the highest exhalation flow (30 L/min) to achieve the optimum technical performance criteria for altering mucus rheology. On the other hand, resistance level 5 for device B was found to require the least exhalation flow (13 L/min).

In terms of the exhalation flow range that satisfies the optimum criteria across all resistance levels, device E was found to have the widest exhalation flow range (19 to 30 L/min), while, devices A and D were found to have the narrowest flow ranges (24-26 L/min and 25 to 27 L/min respectively). The exhalation flow ranges that satisfy the optimum criteria across all resistance levels for devices B and C are 13- 18 L/min and 22-25 L/min respectively.

Table 7-10 Optimum mechanical behaviour of OPEP devices for altering mucus rheology

	Device A					Device B				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	26	26	26	25	24	18	17	16	15	13
Frequency	17	17	17	17	17	17	18	17	16	16
PEP	14	14	14	14	14	14	14	14	15	15
Amplitude	18	18	20	22	23	18	20	20	22	22
Desirability	0.72	0.71	0.77	0.84	0.81	0.73	0.73	0.8	0.89	0.90
	Device C					**Device D**				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	25	25	25	24	22	27	26	26	27	25
Frequency	18	18	18	17	18	18	18	18	17	16
PEP	14	14	14	14	14	13	13	14	14	15
Amplitude	21	21	21	24	24	5	14	20	28	33
Desirability	0.68	0.68	0.7	0.77	0.74	0.34	0.51	0.59	0.84	0.92
	Device E									
Resistance Level	1	2	3	4	5					
Flow	30	27	26	23	19					
Frequency	14	13	12	13	14					
PEP	13	16	16	16	16					
Amplitude	27	40	44	39	30					
Desirability	0.64	0.79	0.74	0.76	0.79					

7.2.2.6 Optimum Settings to Match Cilia Frequency

Table 7-11 shows the optimum mechanical behaviour for matching cilia frequency at every resistance level. Resistance level 1 for device E was found to require the highest exhalation flow (30 L/min) to achieve the optimum technical performance criteria for matching the resonance frequency. On the other hand, resistance level 5 for device B was found to require the least exhalation flow (11 L/min).

In terms of the exhalation flow range that satisfies the optimum criteria across all resistance levels. device E was found to have the widest exhalation flow range (19 to 30 L/min). While, device D was found to have the narrowest flow range (22-24 L/min). The exhalation flow ranges that satisfy the optimum criteria across all resistance levels for devices B, A and C are 11- 15 L/min, 19 – 23 L/min and 18-22 L/min respectively.

Table 7-11 Optimum mechanical behaviour of OPEP devices to match cilia beating frequency

	Device A					**Device B**				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	23	23	22	22	19	15	14	14	13	11
Frequency	14	14	14	14	15	15	15	15	15	15
PEP	10	10	11	11	11	10	10	11	11	12
Amplitude	19	19	20	22	22	18	20	20	22	21
Desirability	0.31	0.29	0.34	0.34	0.21	0.14	0.11	0.19	0.31	0.32
	Device C					**Device D**				
Resistance Level	1	2	3	4	5	1	2	3	4	5
Flow	22	22	21	20	18	None	23	23	24	22
Frequency	14	14	14	14	15	None	14	15	14	15
PEP	10	10	10	11	10	None	10	10	12	12
Amplitude	21	20	21	22	21	None	17	21	29	32
Desirability	0.28	0.27	0.3	0.32	0.2	None	0.14	0.16	0.35	0.29
	Device E									
Resistance Level	1	2	3	4	5					
Flow	30	27	27	23	19					
Frequency	14	13	12	13	13					
PEP	13	16	16	16	15					
Amplitude	27	41	45	39	28					
Desirability	0.58	0.88	0.80	0.85	0.80					

7.2.3 Validation Results

The optimisation results were validated with a total of four participates, two of which are clinicians and two are respiratory therapists (Table 7-12). One of the clinicians is a general practitioner while the other is an anesthesiologist. Both clinicians and respiratory therapists have over 5 years of experience. A one-hour web conference was scheduled with each participant, during which a presentation of the optimisation results findings was presented (Appendix C). The presentation was followed by asking the participants to fill in the questionnaire. The questions were presented on the screen and read out to the participants. The participants' responses to the questions were captured by the research. Also, any comments or feedback were captured by a researcher throughout the one-hour web conference.

Table 7-12 Validation participants overview

Participant Number	Job
Participant 1	Clinician - anaesthesiologist
Participant 2	Clinician - GP
Participant 3	Respiratory therapists
Participant 4	Respiratory therapists

7.2.3.1 Feasibility

Figure 7-1 shows the participants answers to the questions regarding the feasibility of the findings.

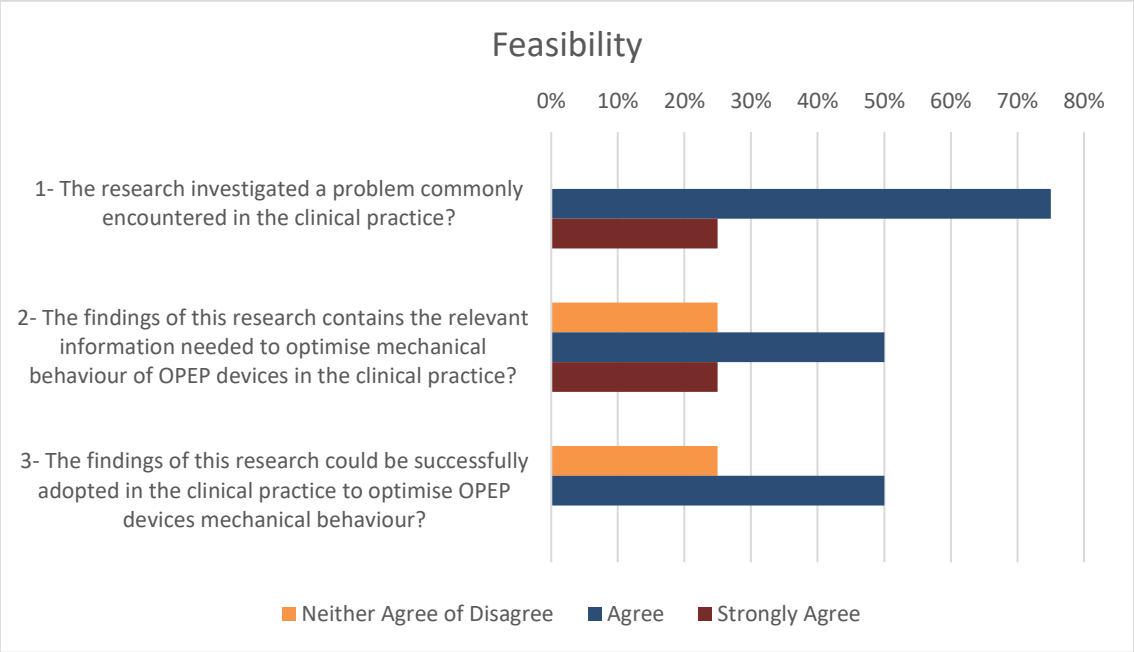


Figure 7-1 Participants answers to the results feasibility questions

All four participants (100%) responded that the problem investigated in this research is commonly found in the clinical practice. Two participants gave the following feedback.

Participant 1: "*when prescribing these devices, it is very much down to experience, as there are no "black and white" rules at the moment.*"

Participant 3: *"I give these devices for many of my patients, from experience I know that what works for one does not work for the other, it is still a trial and error practice."*

In answer to the question of whether the findings of this research contains the relevant information needed to optimise mechanical behaviour of OPEP devices in the clinical practice. Three participants (75%) responded that they agree or strongly agree. However, one participant (25%) responded that he/she neither agrees or disagrees. Three participants gave the following feedback.

Participant 1: *"I think these results definitely help put a framework around how to prescribe these devices"*

Participant 3: *"This helps eliminate or at least reduce the trial and error when prescribing these devices."*

Participant 4: "*I think this information needs to be formulated into a step-by-step guideline…. Not all respiratory therapists will have the detailed knowledge or time to apply this…*"

In answer to the question whether the findings of this research could be successfully adopted in the clinical practice to optimise OPEP devices' mechanical behaviour, three of the participants (50%) responded that they strongly agreed or agreed. One participant (25%) neither agreed or disagreed, and another (25%) disagreed. Three participants gave the following feedback.

Participant 1: "*such information is very much needed in the practice today, however, having this information in form of simple chart like the one used for evaluating the growth of newborn babies or a computer software would make it more usable and better adopted.*"

Participant 4: *"The problem, I think, is that there is too much information here. We have limited time with the patient. As I said, having this information in a step-by-step guideline or as a mobile app would make it much more practical to be adopted in practice"*

7.2.3.2 Usefulness

Figure 7-2 shows the participants answers to the questions regarding the feasibility of the findings. All four participants (100%) agreed or strongly agreed with all four questions in this section.

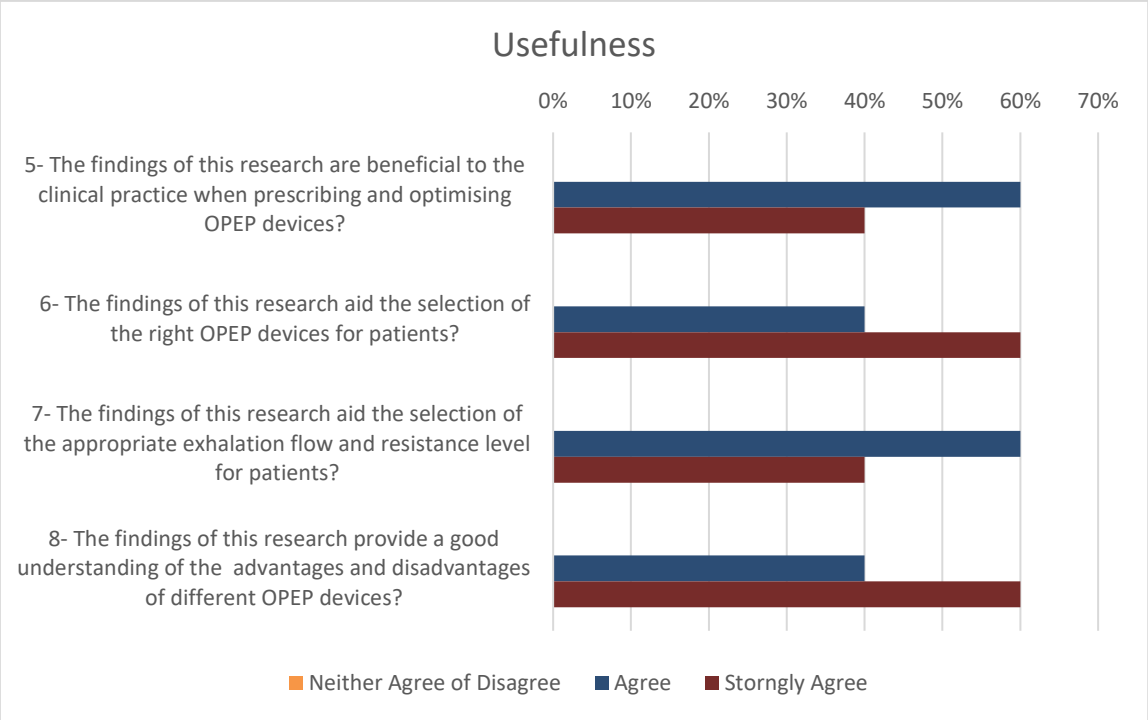


Figure 7-2 Participants answers to the results usefulness questions

In terms of whether the findings of this research are beneficial to the clinical practice when prescribing and optimising OPEP devices, Participant 2 gave the following comment: *"I think these results should be published."*

In terms of whether the findings of this research aid the selection of the right OPEP devices for patients, participants gave the following comments about this question:

Participant 1: "*the patient lung function has to be determined before prescribing an OPEP device, having this information will help in the decision-making process when choosing a device or even deciding if OPEP is the right physiotherapy method for a particular patient.*"

Participant 2: "*what I really like about these findings is that they show how these devices works for different diseases, something we know from practice and experience but this is the first time this was shown through objective evidence.*"

Participant 5: *"Often, we open a brand-new device and give it for a patient to try, only to find out that it is not suitable for them, which means we have to throw that device away*

and try another one. I think this information can help decide if a device is suitable for a patient without having to try a few options."

In terms of whether the findings of this research aid the selection of the appropriate exhalation flow and resistance level for patients, participants gave the following comments:

Participant 1: *"knowing what works for what disease is very useful."*

Participant 2: *"would be interesting to see the validation of these results in a clinical trial, also I really encourage you to publish these results."*

Participant 3: *"knowing what settings to use for different diseases is very useful."*

Participant 4*: "I actually would like a copy of these results once they are finalised."*

In terms of whether the findings of this research provide a good understanding of the advantages and disadvantages of different OPEP devices, participants gave the following comments:

Participant 1: *""these are very interesting points; I think they should be published."*

Participant 2: *"Currently, these devices are marketed as being 'fit' for different diseases. It is very interesting to see that some of the devices might not work for what they are sold for."*

7.3 Discussion

7.3.1 Flow Range Recommendations

When determining that an OPEP therapy is appropriate for a particular patient, clinicians and respiratory therapist are often faced with the question of "which device to select" [50]. The flow rate is of the utmost importance when choosing an OPEP device for a patient as well as optimisation of the mechanical behaviour of that device to achieve the therapy aim for that patients. To use an OPEP device, patients exhale into the device after taking a deep breath. The exhalation should be steady and lasts approximately 4 seconds the process is repeated for around 30 breaths [57,75]. Clinicians and respiratory therapist choose the right OPEP device to give for the patient based on their flow capabilities as

expressed by the lung function measurement for that patient [57–59]. Typically the ideal device of choice is the one the requires the least exhalation effort from the patient to generate the desired pressure wave parameters [54,55]. In addition, clinicians and respiratory therapists instruct the patient to exhale to the device at the required flow rate.

Chapter 6 has presented the results for the flow range required to achieve the optimum technical performance for each pressure wave parameter individually. Previous studies have also recommended the optimum flow rates based on this last approach [54,55,60,61]. However, the results in chapter 6 show that the optimum technical performance can be achieved using a wide range of exhalation flow if pressure wave parameters are considered individually. Yet, when it comes to producing a pressure wave that satisfies the optimum criteria for all pressure wave parameters simultaneously, the range of the flow rate for generating the optimum mechanical behaviour was found to narrows considerably for all five devices. In addition, the results of this chapter show that the exhalation flow range required to achieve the optimum pressure wave parameters simultaneously varies for the different therapy aims for each of the five investigated OPEP devices. Therefore, respiratory therapists and clinicians need to be aware of these findings when prescribing OPEP devices for patients.

Device E was found to be capable of generating the optimum mechanical behaviour for different therapy aims under a wide flow range. On the other hand, when using device A in clinical practice, the mechanical behaviour of this device must be precisely controlled as it was found to generate the optimum mechanical behaviour under a very narrow flow range. Device B was found to require the least flow to generate the optimum mechanical behaviour for different therapy aims.

It is known that the exhalation flow capabilities for COPD and asthma patients decrease with the progression of the diseases [220–222]. One of the interesting observations from the findings in this chapter is that the flow range required to produce the optimum pressure wave parameters for COPD and asthma patients tends to increase as the diseases prognosis increases. In the same vein, none of the investigated devices were able to generate all optimum pressure wave parameters for patients who are only able to sustain an exhalation flow under 12 L/min. This is probably one of the biggest shortages for

currently available OPEP devices and manufacturers need to consider designing an OPEP device that takes into account patients with severe flow limitation.

7.3.2 Resistance Level Recommendations

The results presented in this chapter show the optimum mechanical behaviour for cystic fibrosis patients is best achieved when all five devices are adjusted to a higher resistance level (resistance level 5 for devices, E, B and D, resistance level 4 for devices A and C).

Similarly, for COPD patients at GOLD stage 2, the optimum mechanical behaviour was found to be achieved when all five devices are adjusted to higher resistance level (level 4 for device B and level 5 for devices A, C, D and E). However, interestingly, for COPD patients at GOLD stage 3 and 4, the optimum mechanical behaviour was found to be best achieved by adjusting the devices to a lower resistance level (level 1 for devices A and C, level 2 for device B and level 3 for device D). These results are in agreement with results reported in previous work for device B [60].

However, for patients with mild asthma, it was found that the optimum mechanical behaviour is achieved when resistance is adjusted to a higher resistance level (level 5 for device D, B, C and E) and level 4 for device A. Adjusting resistance level on devices E, C, D and A) to level 5 was found to produce the optimum mechanical behaviour for patients with moderate asthma. However, when using device B, the optimum mechanical behaviour for those patients was found to be best achieved under resistance level 2. For patients with severe asthma, adjusting the devices to a lower resistance level was found to be best for producing the optimum mechanical behaviour (level 1 for devices A and C, level 2 for device B and level 3 for device D).

In terms of altering mucus movement and alerting mucus rheology therapy aims, it was found that for all type A devices, the optimum mechanical behaviour for these therapy aims is best achieved when the devices are adjusted to higher resistance levels (resistance level 5 for devices D and B, resistance level 4 for devices A and C). However, for device E, resistance level 2 was found to be the best for altering mucus movement, while resistance level 5 was found to be best for altering mucus rheology.

In terms of matching the cilia frequency therapy aim, there was no common theme to all devices as the best resistance level adjustment was found to vary from one device to another.

7.3.3 Considerations for Using OPEP Devices

7.3.3.1 Device E

Device E is one of the latest OPEP devices to become available in the market [223]. This is the first study to evaluate the mechanical behaviour of this device. This device was found to have superior capabilities over the type A devices as it is able to generate the optimum wave parameters at a wide range of flow rates. In addition, where there is concern of using device B for patients with severe flow limitation (because of the high-pressure levels this device can produce), device E would be the ideal choice as it requires the least flow in comparison to device D, A and C. Also, device E might result in a better airway clearance effect as it generates the highest oscillation amplitude in comparison to the type A devices.

However, the mechanical behaviour of this device has some considerations that clinicians and respiratory therapist need to be aware of when prescribing this device. The manufacturer specification for device E states that this device is suitable for patients who can sustain minimum flow rate of 10 L/min [224]. However, it was found in this research that patients need to exhale at a flow rate significantly higher than the minimum specifications to generate the optimum pressure wave parameters for different therapy aims. In addition, this research has found that, out of all five investigated devices, device E was the only device that is incapable of generating the optimum pressure wave parameters for every therapy aim. In particular, device E was unable to generate the optimum pressure wave parameters for patients with COPD stage 3 and 4, in addition to patients with severe asthma. Also, if the device is used for patients with GOLD stage 2 COPD, resistance level 3 should be avoided as the device is not capable of generating the optimum pressure wave parameters using this resistance level. Another mechanical behaviour aspect that respiratory therapist and clinicians need to be aware of when using this device is that the flow rate for generating the optimum pressure parameters varies widely for each resistance level. Therefore, when using device E, choosing the correct

resistance level relevant for the therapy aim and instructing the patient to exhale at the correct flow rate is very important.

7.3.3.2 Device B

Device B is the only device of the investigated OPEP device that is specifically labelled by the manufacturers as suitable for patients with low flow rate capabilities (less than 15 L/min) [225]. In previous work, it has been stated that the lungs of patients with very high obstruction may have resonance frequencies higher than those produced by device B [60]. In this research, this device was found to be able to generate the optimum pressure wave parameters for all therapy aims. [60] investigated the mechanical behaviour of device B under a flow range of 3-15 L/min. Hence the contrast in the results obtained can be explained by the difference in flow range used.

From the perspective that, the ideal device of choice is the one the requires the least effort from the patient to generate the desired pressure wave parameters [54,55], device B would be the ideal choice as it was found to require the least exhalation flow rate to generate the optimum pressure wave parameters for all therapy aims. Especially for children and patients with severe asthma or GOLD stage 4 COPD, where usually these lower flow rate needs are encountered [34,78].

However, there are some considerations that clinicians and respiratory therapist need to be aware of when prescribing this device. Firstly; although this device is labelled by the manufacturer to be used for patients with flow capabilities under 15 L/min, interestingly this research found that the flow range required to achieve the optimum pressure wave parameters lies between 13 and 20 L/min. Secondly; the characterisation of this device in chapter 6 has uncovered that using this device at a flow rate above 20 L/min will produce a PEP above 20cmH2O, which may results in barotrauma or increased air trapping [78], especially for patients with susceptible airways [78]. Therefore, the exhalation flow rate to this device needs to be closely monitored and controlled. In addition, prescribing this device should be limited to patients with severe exhalation flow limitation and should be avoided for patients with susceptible airways.

7.3.3.3 Device A, C and D

Device C is labelled by the manufacturer to have similar performance to device A. However; this device offers the advantage of having a port to administer nebulised medication along with the OPEP therapy [225]. This is the first study to evaluate the mechanical behaviour of this device.

The minimum exhalation flow specifications by the manufacturer for device D, A and C are 15 10 and 10 L/min respectively. All three devices were found to be able to generate the optimum pressure wave parameters for the different therapy aims. However, the flow rates required to achieve such optimum vary from one device to another

In terms of mechanical behaviour considerations that clinicians and respiratory therapist need to be aware of when using these devices. Firstly, this research found that to generate the optimum pressure wave parameters using these devices, patients need to exhale at a flow rate significantly higher than the minimum specifications by the manufacturer. Secondly, the exhalation flow required to achieve the optimum pressure wave parameters using these three devices was found to have a very narrow range. Therefore, being aware of this range and correctly performing the exhalation manoeuvre at the correct flow rate is important for effective airway clearance when using these three devices. Another observation regarding the mechanical behaviour of these three devices is that a change in the resistance level from the lowest resistance level to the highest resistance level results in a significant relative increase in the oscillation amplitude values. Therefore, choosing the highest resistance level might lead to a better airway clearance effect. The optimum pressure wave generated by device A was found to have the smallest amplitude of all devices at the optimum range. Therefore, where possible, this device should be avoided.

7.3.4 Validation Results Discussion

The findings of solving the optimisation problem were validated with two clinicians and two respiratory therapists using a questionnaire designed for this purpose. The validation focused on two main areas: the feasibility and the usefulness of the findings.

In terms of the result's feasibility, the quantitative analysis of the questionnaire data showed that the problem investigated and solved in this chapter is one that is commonly found in the clinical practice. In addition, the participants found the results presented in

this chapter to be relevant and have the potential to be adopted in practice. However, the findings presentation was questioned by two participants. It has been pointed out that there is a need for a step-by-step procedure or a software presentation of the results to allow for adoption in the clinical practice. Hence, the results need to be presented in a more usable layout. Appendix F shows a flow chart to aid health care professional in navigating to relevant findings to optimise the mechanical behaviour of OPEP devices for a particular patient.

In terms of the result's usefulness, the quantitative analysis of the questionnaire data showed that the findings were beneficial to the practice when prescribing OPEP devices. In addition, participants agreed that the results presented in this chapter have the potential to help the selection of the right OPEP devices and settings for patients. The advantages and disadvantages highlighted in this chapter were also found by the participants to give new insight that allows for better use of these devices in practice. Two participants emphasised on the need to publish these results and make the community aware of their existence. In addition, the need to validate these results in a clinical trial has been pointed out by one participant.

7.4 Chapter Summary

The optimum mechanical behaviour of OPEP devices for effective airway clearance has been identified as a knowledge gap. This research is an effort to address this gap. This chapter characterises the optimum mechanical behaviour for each of the five OPEP devices investigated for different disease conditions and airway clearance therapy aims.

In this chapter:

- It was found that the exhalation flow range required to achieve the optimum value of the pressure wave simultaneously was considerably narrower than the range required to achieve the optimum value pressure parameters individually.
- In addition, flow range required to achieve the optimum value was found to vary for all five devices and for different diseases and airway clearance therapy aims..
- Interestingly, although patients with advanced disease progression (i.e., GOLD 3 and 4 COPD, severe asthma) are known to have high exhalation flow limitations,

the exhalation flow required to achieve the optimum mechanical behaviour for those patients was to found to be higher and to increase with the disease prognosis.

- The chapter discusses the considerations the clinical practice need to be aware of when using each of the investigated OPEP devices:
  a- The type B device was found to be capable of generating the optimum mechanical behaviour under the exhalation flow range wider than the type A devices. Thus, this device might be a favourable choice for patients who exhibit flow capabilities that fall outside the exhalation flow range of type A devices.
  b- However, the clinical practice needs to be aware that device E is not able to generate the optimum mechanical behaviour for GOLD 3 and 4 COPD patients in addition to patients with severe asthma.
  c- On the other hand, out of all five investigated devices, device B was found to require the least exhalation flow to generate the optimum technical performance. Therefore, it might be the best choice for patients with severe flow limitations and children. However, the mechanical behaviours of this device need to be precisely controlled and closely monitored as it is capable of generating a PEP value above 20 cmH2O at relatively low flow rates.
  d- For devices A, C, and D, although all three devices were found to be able to generate the optimum mechanical behaviour for different disease groups and therapy aims, the exhalation flow rate required to achieve such optimum that is relatively narrow (especially for device A). Hence, the exhalation flow and resistance levels need to be precisely controlled. Furthermore, the minimum exhalation flow required to achieve the optimum technical performance was found to be significantly higher than the manufacturers' minimum specification.

8 OVERALL DISCUSSION AND CONCLUSIONS

This chapter discusses how the research aim and objectives were met. Research contributions are outlined and described. Research limitations are identified and presented. Suggestions for further work and research are put forward. Finally, the chapter finishes with the conclusion and the final thesis summary.

The identification of the optimum mechanical behaviour of OPEP devices for effective airway clearance has been identified as a knowledge gap. This gap was addressed in this research. A literature review has been conducted to identify the current "state of the art" in the field. Moreover, optimum technical performance criteria have been established. The mechanical behaviour of five OPEP devices has been characterised and extensively described. Mathematical models that describe the mechanical behaviour of these devices were built. This research has characterised the exhalation flow and resistance levels for achieving pressure wave parameters that satisfy the optimum technical performance criteria. The optimum mechanical behaviours for COPD, asthma and cystic fibrosis patients, have been characterised for each of the five investigated OPEP devices. Also, the optimum mechanical behaviours for altering mucus movement, changing mucus rheology and matching cilia frequency, have been characterised and described for each of the five investigated OPEP devices. This research discussed how these findings could be used in the clinical practice to help select the right OPEP device for patients. Also, this research discussed the advantages and considerations that clinical practices need to be aware of when using each of the investigated OPEP devices. Finally, the findings were validated with a clinician and respiratory therapist for feasibility and usefulness.

8.1 Addressing Research Aim and Objectives

The aim of the research is to characterise the optimum mechanical behaviour of OPEP devices for effective airway clearance. This aim has been addressed by the following: the optimum technical performance requirements for airway clearance by oscillation has been established through a review of the current and relevant literature using a systematic approach. The mechanical behaviours of five OPEP devices were investigated and extensively characterised. Regression models that describe the relation between the five OPEP device settings and generated pressure wave parameters have been

built. An optimisation algorithm (desirability function) was applied to the regression models to characterise OPEP device settings that satisfy the optimum technical performance criteria.

(1-**)To review the current "state of the art" in the mechanical behaviour of OPEP devices**

This research objective was met by conducting a systematic review of current and relevant literature related to the mechanical behaviour of OPEP devices (Chapter 2). The review presented and discussed the findings of previous studies that evaluated the mechanical behaviour of OPEP devices (Table 2-1). The review has identified the setting variables used in previous studies to characterise the mechanical behaviour of OPEP devices in addition to the experiment setup and equipment used. Also, pressure wave parameters relevant to the effectiveness of OPEP devices were identified in this review. Previous attempts to optimise OPEP devices' mechanical behaviour were also discussed and knowledge gap highlighted.

(2-) To review the optimum technical performance requirements for effective airway clearance by oscillation

This research objective was met by conducting a systematic review of current and relevant literature related to the technical performance required for effective airway clearance by oscillation (Chapter 3). Several theoretical perspectives regarding the mechanisms of action for airway clearance by oscillation were used as a framework for this review. The physiological effect of the pressure wave parameters on airway clearance has been described. Relevant studies were reviewed to establish the optimum pressure wave parameters for effective airway clearance by oscillation. Based on the findings of this review, optimum technical performance criteria (Table 3-8) have been proposed to guide OPEP devices' mechanical behaviour optimisation according to different disease groups and airway clearance therapy goals.

(3-) To develop and validate a system for measuring mechanical behaviour of OPEP devices

This objective was met by developing a system to measure the mechanical behaviours of OPEP devices. The capability of this system has been validated using a systematic design of an experiment capable of capturing the measurement error. Such an error was quantified using appropriate statistical tools. The acceptability of the measurement error was evaluated using the reference standard values used for this purpose and was found to be acceptable (chapter 4).

(4-)To model the mechanical behaviour of OPEP devices

This objective was met by building 15 regression models that described the relationship between the settings and pressure wave parameters of five OPEP devices (Table 6-4). To build these models, data was collected from three samples of each OPEP device using a systematic experiment design and a validated measurement system. In addition, the mechanical behaviour of the investigated OPEP devices was characterised and extensively described. The least squares method was used to find the best-fitting curve for each of the pressure wave parameters for all five devices. The significance of the models' terms was evaluated using the backward elimination method. In addition, models were verified through appropriate statistical tools (ANOVA) and the examination of the residual plot. The performance of the built models was validated by collecting new sets of data from new samples for each of the OPEP devices investigated. The capability of the models to predict the values in the data set was evaluated using prediction R2. All models were found to be valid and able to predict new values with small decreases in the R^2 value.

(5-) To identify OPEP devices optimum mechanical behaviour for effective airway clearance

This objective was achieved by characterising OPEP device settings that satisfied the optimum technical performance criteria for different therapy aims (Table 7-1) (Chapter 7). This was achieved by applying an optimisation algorithm (desirability function) to each of the 15 models built. The optimum technical performance criteria identified in Chapter 3 were used to define the optimum mechanical behaviour solution space. The

optimum mechanical behaviour for COPD, asthma, and cystic fibrosis patients has been characterised and described for each of the five investigated OPEP devices. Also, the optimum mechanical behaviour for altering mucus movement, changing mucus rheology, and matching cilia frequency have also been characterised and described for each of the five investigated OPEP devices. The optimum mechanical behaviour findings were validated for feasibility and usefulness with clinicians and respiratory therapists by using a questionnaire. The validation result showed that the findings, obtained in this research, are perceived as valid by the target audience.

8.2 Contributions to Knowledge

Three major contributions emerged from this research:

1- OPEP devices' optimum technical performance criteria
2- Comprehensive characterisation of the mechanical behaviours of OPEP devices under a unified experiment set-up and flow ranges, commonly found in clinical practice
3- Characterisation of the OPEP devices' optimum mechanical behaviours for effective airway clearance

One of the major challenges in optimising the mechanical behaviours of OPEP devices is the lack of correlation between the devices' mechanical behaviour data and the established technical performance criteria that take into account patient disease prognosis and its underlying physiological dysfunctions. The first contribution to knowledge made by this research is the proposal of technical performance criteria to guide the optimisation of OPEP devices, according to different diseases and airway clearance therapy aims. The proposed technical performance criteria relate to a patient's disease prognosis and its underlying physiological dysfunction.

The characterisation of the mechanical behaviour of OPEP devices provides valuable information to clinicians and respiratory therapists when choosing, prescribing, and optimising OPEP devices for their patients. However, previous attempts to characterise the mechanical behaviour of OPEP devices have many shortages (i.e. lack of characterisation under flow ranges commonly found in clinical practice, lack of characterisation of different OPEP devices under a unified experimental setup to allow

for direct comparison). All necessitate the need for new studies to evaluate the mechanical behaviour of OPEP devices. The second contribution to knowledge of this research is the comprehensive characterisation of the mechanical behaviour of five OPEP devices under a unified experimental setup and flow ranges commonly found in clinical practice

Currently, there are no existing guideline aid clinicians and respiratory therapists in choosing the exhalation flow rate and the resistance level to optimise the device's operation according to the features of each patient and the technical capabilities of each device. The third contribution to knowledge of this research is filling this knowledge gap by characterising the optimum mechanical behaviour of OPEP devices for effective airway clearance. Such knowledge has the potential to not only aid the clinical practice in choosing the right OPEP device for patients but also provide detailed guidance regarding the OPEP device settings to achieve the optimum technical performance for different patients and airway clearance therapy aims. This research also highlights for the clinical practise the considerations for using different OPEP devices.

8.3 Limitations

To review the optimum technical performance requirements for effective airway clearance by oscillation

This research objective was aimed at identifying the optimum technical performance criteria for mucus clearance by oscillation. The optimum pressure wave parameter values have been established by considering the mechanisms of action in airway clearance for each parameter as a framework and understanding the physiological effect for each one. However, one of the limitations encountered in this phase is the lack of clinical validation of the superiority of different mechanisms of action. Therefore, it was left to the assertion and experience of the clinician and respiratory therapist to choose which one is the best based on the optimum technical performance criteria presented in this research.

Another limitation encountered is the lack of studies investigating the optimum value of scillation amplitudes for effective airway clearance.

Development and validation of a system to measure mechanical behaviour of OPEP devices

Due to time constrain, this research did not investigate the root cause of the pressure waveform instability points found in Chapter 5 of this research,

To model the mechanical behaviour of OPEP devices

This research phase aimed to characterise the mechanical behaviour of OPEP devices and to model the mechanical behaviour of all five devices. However, because of time limitations, such characterisation was limited to five devices most commonly used in the clinical practice. Therefore, the results from this research can only be generalised to the five OPEP devices investigated in this research. Furthermore, another drawback of this research is that new samples were used for the purpose of mechanical behaviour characterisation. However, in practice, old devices may present small changes in mechanical behaviour due to cleaning and disinfection.

To identify OPEP devices optimum mechanical behaviour for effective airway clearance

This research phase aimed at characterising the optimum mechanical behaviour of OPEP devices for effective airway clearance. A drawback of these phase findings is the need for a clinical trial validation of this phase findings. Moreover, because of time limitations, the finding of this research has not been incorporated into software, which might be very useful for the clinical practice.

8.4 Future Research

To review the optimum technical performance requirements for effective airway clearance by oscillation

There is a lack of clinical validation of the superiority of different airway clearance mechanism of actions for effective airway clearance. Further research is required to establish the superiority of these mechanisms of actions in more details in a clinical trial. The findings of this research can be a starting point. The proposed optimum values for

each mechanism of action. However, the superiority of each mechanism of action might be different in in different disease groups; therefore, the design of clinical trial needs to take this consideration into account.

In addition, both experimental and theoretical research is needed to establish the optimum oscillation amplitude value for effective airway clearance.

Development and validation of a system to measure mechanical behaviour of OPEP devices

Further simulation and experimental research is required to investigate and explain the causes for pressure waveform instability points found in Chapter 5 of this research. Moreover, further simulation and experimental research are required to explain in details the difference in the mechanical behaviour observed in Chapter 6 of this research.

To model the mechanical behaviour of OPEP devices

A future research is needed to characterise and quantify the change in OPEP devices performance throughout their lifetime use, especially for device from different manufacturers

To identify OPEP devices optimum mechanical behaviour for effective airway clearance

Future OPEP devices optimisation research need to investigate the pressure wave parameters effect on airway clearance from a fluid dynamic perspective. Particularly, understanding the details of pressure wave – mucus interaction in the complex tracheobronchial tree branching. The optimum mechanical behaviour found in this research can be a starting point.

Lastly, the findings of this research need to be validated in a clinical trial. Such trial need to -at minimum- answer the question as whether the finding (optimum mechanical behaviour) of this research improve the airway results and the overall patients outcome in comparison to the current practices when using OPEP devices. In addition, the applicability of various therapy aims and their respective optimum mechanical behaviour

proposed in this research to various underlying physiological conditions and disease groups need to be confirm in clinical trial.

8.5 Conclusions

This research investigation aimed to characterise the optimum mechanical behaviour of OPEP devices for effective airway clearance.

The literature review has identified that a major limitation to characterising the optimum mechanical behaviour of OPEP devices is the lack of a technical performance criteria. This research has identified technical performance criteria for effective airway clearance. The identified criteria includes the optimum technical performance values for different disease groups and airway clearance therapy goals. In addition, a compressive summary of the physiological effect of airway oscillation has been presented in this research.

In the field of airway clearance research, along with clinical trials, device evaluations lie at the base of the evidence appraisal hierarchy. However, the methodological limitation was a major drawback in previous studies that evaluated the mechanical behaviour of OPEP devices, especially the flow range under which OPEP devices were investigated. Therefore, new studies have been encouraged. Particularly, new studies evaluating different OPEP devices. This research is the first to characterise the mechanical behaviour of two OPEP devices that have never been characterised before. Also, this is the first research to comprehensively characterise the mechanical behaviour of several OPEP devices using a validated and unified experiment setup.

Despite the fact that OPEP devices have been around for several years and are routinely used in clinical practice, the question remains as to "which settings is appropriate for optimum airway clearance results." This research provided a comprehensive characterisation of the optimum mechanical behaviour of OPEP devices for effective airway clearance. The optimum mechanical behaviour was characterised for different disease groups and airway clearance therapy aims.

In addition to the comprehensive of the optimum mechanical behaviour of OPEP devices, the findings of this research provide the following insight to respiratory therapists and clinicians when prescribing OPEP devices for patients:

- The optimum technical performance of OPEP device can be achieved using a wide range of exhalation flow if pressure was parameters were considered

individually. However, when it comes to producing a pressure wave that satisfies the optimum technical performance criteria for all pressure wave parameters simultaneously, the feasible exhalation flow range narrows considerably.

- This research found that patients need to exhale at a flow rate higher than the minimum specifications by the manufacturer in order to generate the optimum mechanical behaviour. Also, investigated OPEP devices were found to be unable to generate the optimum mechanical behaviour for patients with exhalation flow capabilities below under 12 L/min.
- The exhalation flow range required to produce the optimum mechanical behaviour for COPD and asthma patients increases as the diseases prognosis increases.
- Type B devices are capable of generating the optimum mechanical behaviour at a lower and wider range of flow rates than type A devices.
- For type A devices, changing the resistance level from the lowest resistance level to the highest resistance level increase the oscillation amplitude values generated. While for type B device resistance level 3 and 4 result in the highest oscillation amplitude.
- Type B devices have the potential to result in a better airway clearance effect as it generates the highest oscillation amplitude in comparison to the type A devices.
- Device E should not be prescribed for with severe asthma and COPD patients at GOLD stage 3 and 4 as it was found to be unable to generate the optimum mechanical behaviour for these patients.
- From the perspective that, the ideal OPEP device is the one the requires the least effort from the patient to generate the desired effect. Device B would be the ideal choice as it was found to require the least exhalation flow rate to generate the optimum pressure wave parameters.
- Prescribing Device B should be limited to patients with severe exhalation flow limitation and should be avoided for patients with susceptible airways as it was found to be capable of generating pressure level that exceeds 20 cmH2O at relatively low flow rates.

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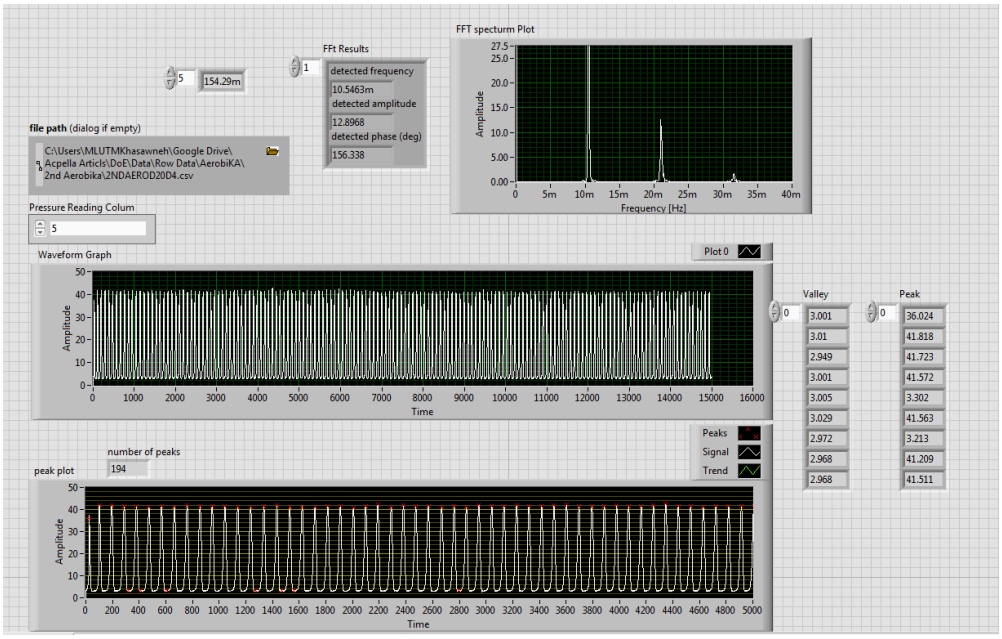
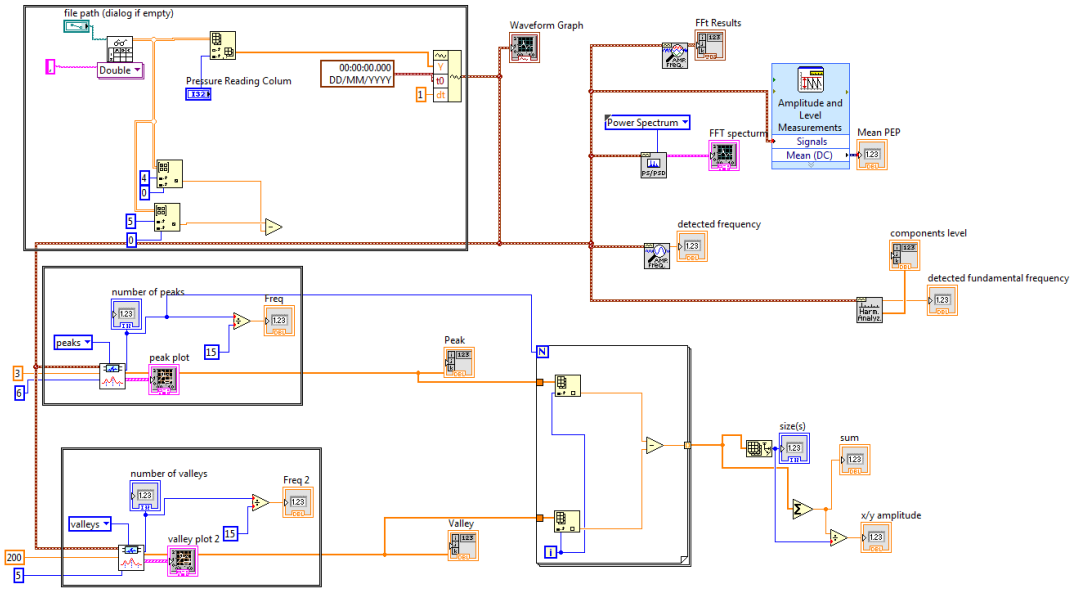
Appendix A Data Processing LabVIEW Module

A.1 LabVIEW Interface



Figure_Apx A-1 Data processing module – Interface

A.2 LabVIEW Blocks Diagram



Figure_Apx A-2 Data processing interface - Diagram

Appendix B Validation Questionnaire

Validating the characterisation of the optimum mechanical behaviour of OPEP devices for effective airway clearance

PhD Research Title: Optimising oscillatory positive expiratory pressure devices for effective airway clearance

Researcher: Mohammad Khasawneh

Supervisors: Dr. Jeffrey Alcock and Prof. Ashutosh Tiwari

The aim of this validation questionnaire is to capture the opinions and feedback of the clinicians and respiratory therapist about the characterisation of the optimum mechanical behaviour of OPEP devices.

This questions have two main section, feasibility and usefulness. The feasibility section has three questions, while the usefulness section has four questions. Please feel free make any additional comments as required

---

Name: …….

Job title: …….....

Years of Experience: ……..

Section 1: Feasibility

1- The research investigated a problem commonly encountered in the clinical practice?

Strongly Disagree	Disagree	Neither Agree Nor Disagree	Agree	Strongly Agree
☐	☐	☐	☐	☐

Any other comments:

……

……

2- The findings of this research contains the relevant information needed to optimise mechanical behaviour of OPEP devices in the clinical practice?

Strongly Disagree	Disagree	Neither Agree Nor Disagree	Agree	Strongly Agree
☐	☐	☐	☐	☐

Any other comments:

……

……

3- The findings of this research could be successfully adopted in the clinical practice to optimise OPEP devices mechanical behaviour?

Strongly Disagree	Disagree	Neither Agree Nor Disagree	Agree	Strongly Agree
☐	☐	☐	☐	☐

Any other comments:

……

……

Section 2: Usefulness

4- The findings of this research are beneficial to the clinical practice when prescribing and optimising OPEP devices?

Strongly Disagree	Disagree	Neither Agree Nor Disagree	Agree	Strongly Agree
☐	☐	☐	☐	☐

Any other comments:

……

……

5- The findings of this research aid the selection of the right OPEP devices for patients?

Strongly Disagree	Disagree	Neither Agree Nor Disagree	Agree	Strongly Agree
☐	☐	☐	☐	☐

Any other comments:

……

……

6- The findings of this research aid the selection of the appropriate exhalation flow and resistance level for patients?

Strongly Disagree	Disagree	Neither Agree Nor Disagree	Agree	Strongly Agree
☐	☐	☐	☐	☐

Any other comments:

……

……

7- The findings of this research provide a good understanding of the advantages and disadvantages of different OPEP devices?

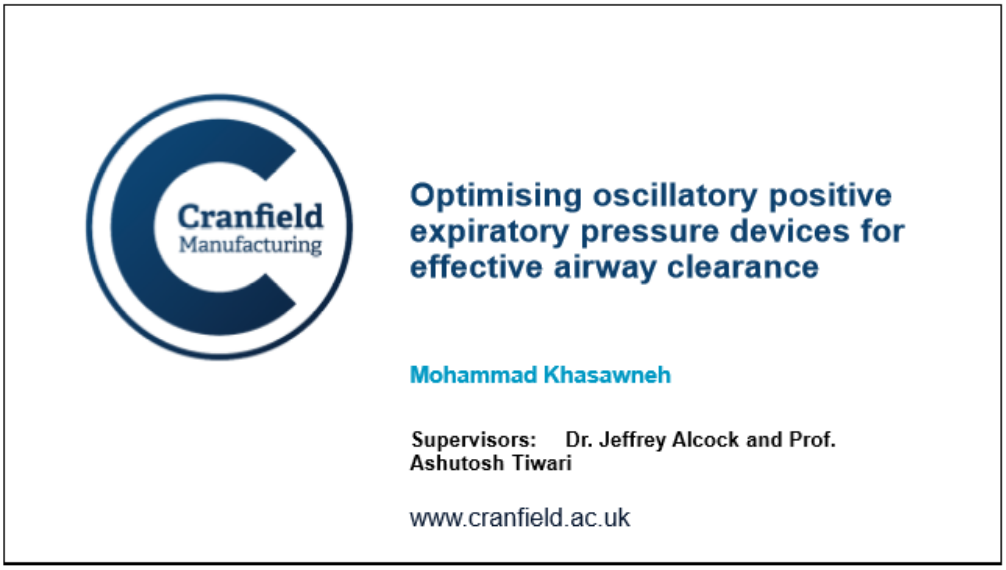
Strongly Disagree	Disagree	Neither Agree Nor Disagree	Agree	Strongly Agree
☐	☐	☐	☐	☐

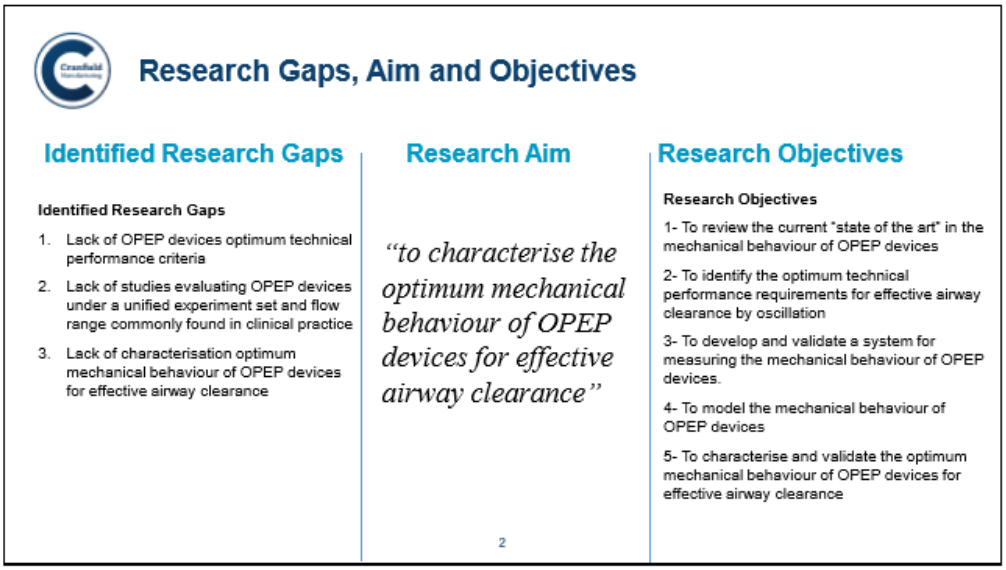
Any other comments:

……

……

Appendix C Validation Presentation

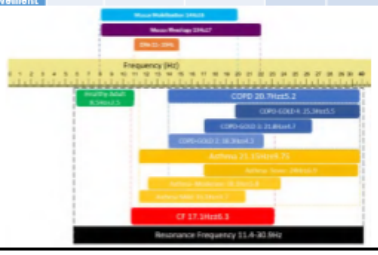




Optimal technical performance requirements for effective airway clearance by oscillation

- One of the major limitations of previous attempts to optimise the mechanical behaviour of OPEP devices is the lack of correlation between the devices' mechanical behaviour and established technical performance criteria
- The optimum pressure wave parameter values have been established by considering the airway clearance by oscillation mechanisms of action for each parameter and understanding the physiological effect for each one
- The therapy aims proposed above could be looked at in clinical practice from the two points of view; the first is "what works best for a particular patient" rather than "which one is the best". This point of view resembles one of the main principles of physiotherapy (the application of the technique must be based on the patient's respiratory dysfunction in order to result in the intended airway clearance effects
- The second point of view is; rather than thinking that "there is one mechanism of action that is responsible for the airway clearance effect", the different theoretical perspective can be thought of form the point of view that "a combination of these mechanism work together to produce the airway clearance effect". Therefore, combining more than one therapy aim as part of an OPEP device treatment plan might be most beneficial to ahcive better airway clearance results

Therapy Aim	Disease	Stage	Frequency	PEP	Amplitude
Match Resonance Frequency	Cystic Fibrosis	N/A	17.1 ± 6.3 Hz	10 - 20 cmH2O	As high as can be possibly achieved
	COPD	GOLD 2	18.3 ± 4.3 Hz		
		GOLD 3	21.8 ± 4.7 Hz		
		GOLD 4	25.3 ± 5.5 Hz		
	Asthma	Mild	16.1 ±4.7 Hz		
		Moderate	18.1 ± 5.8 Hz		
		Sever	24 ± 6.9 Hz		
Match Cilia Frequency	Any	Any	14 ± 6 Hz		
Alter Mucus Rheology	Any	Any	15 ± 7 Hz		
Alter Mucus Movement	Any	Any	13 ± 2 Hz		



3

Characterising of the Optimum Mechanical Behaviour of OPEP devices

- Device E was found to be capable of generating the optimum mechanical behaviour for different therapy aims under a wide flow range
- When using device A in clinical practice the mechanical behaviour of this device must be precisely controlled as it was found to generate the optimum mechanical behaviour under a very narrow flow range.
- Device B was found to require the least flow to generate the optimum mechanical behaviour for different therapy aims.
- The flow range required to produce the optimum pressure wave parameters for COPD and asthma patients tends to increase as the diseases prognosis increases
- None of the investigated device were able to generate all optimum pressure wave parameters for patients who are only able to sustain an exhalation flow under 12 L/min
- The optimum mechanical behaviour for cystic fibrosis patients is best achieved when all five devices are adjusted to a higher resistance level (resistance level 5 for devices, E, B and D, resistance level 4 for devices A and C).
- For COPD patients at GOLD stage 2, the optimum mechanical behaviour was found to be achieved when all five devices are adjusted to higher resistance level (level 4 for device B and level 5 for devices A, C, D and E).
- For COPD patients at GOLD stage 3 and 4, the optimum mechanical behaviour was found to be best achieved by adjusting the devices to a lower resistance level (level 1 for devices A and C, level 2 for device B and level 3 for device D).
- For patients with mild asthma, it was found that the optimum mechanical behaviour is achieved when resistance is adjusted to a higher resistance level (level 5 for device D, B, C and E) and level 4 for device A.
- Adjusting resistance level on devices E, C, D and A) to level 5 was found to produce the optimum mechanical behaviour for patients with moderate asthma

		Therapy Aim									
		Match Patients Resonance Frequency							Alter Mucus Movement	Alter Mucus Rheology	Match Cilia Frequency
		Cystic Fibrosis	COPD			Asthma					
			GOLD 2	GOLD 3	GOLD 4	Mild	Moderate	Sever			
Device A	Flow	25	24	29	29	25	25	29	25	25	22
	Resistance Level	4	5	1	1	4	5	1	4	4	3
	Frequency	17	18	20	20	17	18	20	16	17	14
	PEP	14	15	17	17	14	15	17	14	14	11
	Amplitude	22	23	17	17	22	23	17	22	22	20
Device B	Flow	13	16	18	19	13	18	19	13	13	11
	Resistance Level	5	4	2	2	5	8	2	5	5	5
	Frequency	16	17	19	20	16	18	19	16	16	15
	PEP	15	16	16	17	15	15	17	14	15	12
	Amplitude	23	22	19	19	22	20	19	22	22	21
Device C	Flow	24	23	27	28	22	23	28	23	24	20
	Resistance Level	4	5	1	1	5	5	1	4	4	4
	Frequency	17	18	20	20	17	18	20	17	17	14
	PEP	14	14	16	17	14	15	17	13	14	11
	Amplitude	24	24	20.7	21	24	25	21	23	24	22

4

Characterising of the Optimum Mechanical Behaviour of OPEP devices

- When using device B, the optimum mechanical behaviour for those patients was found to be best achieved under resistance level 2.
- For patients with severe asthma, adjusting the devices to a lower resistance level was found to be best for producing the optimum mechanical behaviour (level 1 for devices A and C, level 2 for device B and level 3 for device D).
- Altering mucus movement and alerting mucus rheology therapy aims, it was found that for all type A devices, the optimum mechanical behaviour for these therapy aims is best achieved when the devices are adjusted to higher resistance levels (resistance level 5 for devices D and B, resistance level 4 for devices A and C). However, for device E, resistance level 2 was found to be the best for altering mucus movement, while resistance level 5 was found to be best for altering mucus rheology
- In terms of matching the cilia frequency therapy aim, there was no common theme to all devices as the best resistance level adjustment was found to vary from one device to another.

		Therapy Aim									
		Match Patients Resonance Frequency							Alter Mucus Movement	Alter Mucus Rheology	Match Cilia Frequency
		Cystic Fibrosis	COPD			Asthma					
			GOLD 2	GOLD 3	GOLD 4	Mild	Moderate	Sever			
Device D	Flow	25	26	29	29	25	26	29	24	25	24
	Resistance Level	5	5	3	3	5	5	3	5	5	4
	Frequency	17	17	21	22	16	17	22	16	16	14
	PEP	15	16	16	17	15	16	17	14	5	12
	Amplitude	33	34	18	17	32	34	17	33	33	29
Device E	Flow	20	21	None	None	20	20	None	26	19	27
	Resistance Level	5	5	None	None	5	5	None	2	5	2
	Frequency	14	15	None	None	14	14	None	13	13.8	13
	PEP	16	17	None	None	16	17	None	17	16	16
	Amplitude	30	31	None	None	30	30	None	40	29.2	41

5

OPEP Devices Advantages and Considerations

Device A, C and D

Advantages

- All three devices were found to be able to generate the optimum pressure wave parameters for the different therapy aims. However, the flow rates required to achieve such optimum vary from one device to another

Considerations

- this research found that to generate the optimum pressure wave parameters using these devices, patients need to exhale at a flow rate significantly higher than the minimum specifications by the manufacturer.
- the exhalation flow required to achieve the optimum pressure wave parameters using these three devices was found to have a very narrow range. Therefore, being aware of this range and correctly performing the exhalation manoeuvre at the correct flow rate is important for effective airway clearance when using these three devices.
- Another observation regarding the mechanical behaviour of these three devices is that a change in the resistance level from the lowest resistance level to the highest resistance level results in a significant relative increase in the oscillation amplitude values. Therefore, choosing the highest resistance level might lead to a better airway clearance effect.
- The optimum pressure wave generated by device A was found to have the smallest amplitude of all devices at the optimum range, therefore, where possible this device should be avoided.

Device B

Advantages

- This device was found to be able to generate the optimum pressure wave parameters for all therapy aims..
- Device B would be the ideal choice as it was found to require the least exhalation flow rate to generate the optimum pressure wave parameters for all therapy aims.
- Especially for children and patients with severe asthma or GOLD stage 4 COPD, where usually these lower flow rate needs are encountered

Considerations

- Firstly; although this device is labelled by the manufacturer to be used for patients with flow capabilities under 15 L/min, interestingly this research found that the flow range required to achieve the optimum pressure wave parameters lies between 13 and 20 L/min.
- Secondly; using this device at a flow range above 20 L/min will produce a PEP above 20cmH2O, which may results in barotrauma or increased air trapping especially for patients with susceptible airways
- Therefore, the exhalation flow rate to this device need to be closely monitored and controlled.
- Prescribing this device should be limited to patients with severe exhalation flow limitation and should be avoided for patients with susceptible airways.

6

Device E

Advantages

- This device was found to have superior capabilities over the type A devices as it is able to generate the optimum wave parameters at a wide range of flow rates.
- Where there is concern of using device B for patients with severe flow limitation (because of the high pressure levels this device can be produce), device E would be the ideal choice as it requires the least flow in comparison to device D, A and C.
- Also, device E might result in a better airway clearance effect as it generates the highest oscillation amplitude in comparison to the type A devices.

Considerations

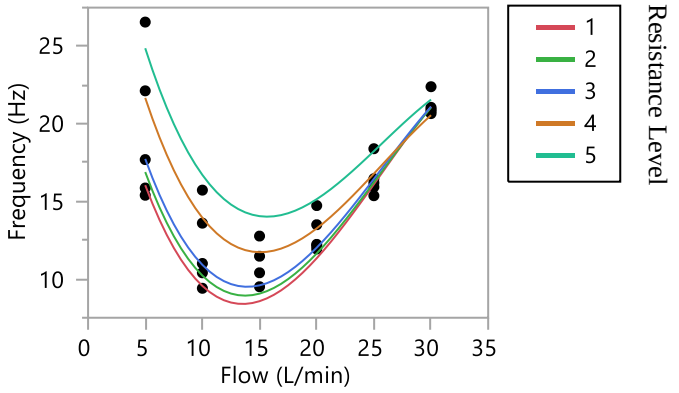
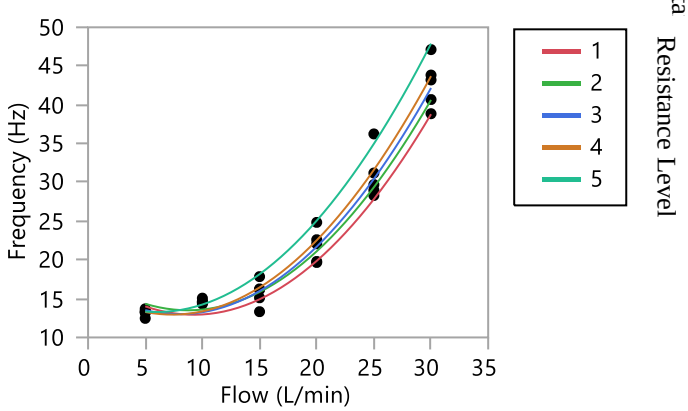
- The manufacturer specification for device E states that this devices is suitable for patients who can sustain minimum flow rate of 10 L/min. However, patients need to exhale at flow rate significantly higher than the minimum specifications to generate the optimum pressure wave parameters.
- Device E was unable to generate the optimum pressure wave parameters for patients with COPD stage 3 and 4, in addition to patients with severe asthma.
- If the device is used for patients with GOLD stage 2 COPD, resistance level 3 should be avoided as the device is not capable of generating the optimum pressure wave parameters using this resistance level.
- The flow rate for generating the optimum pressure parameters varies widely for each resistance level. Therefore, when using device E, choosing the correct resistance level relevant for the therapy aim and instructing the patient to exhale at the correct flow rate is very important.

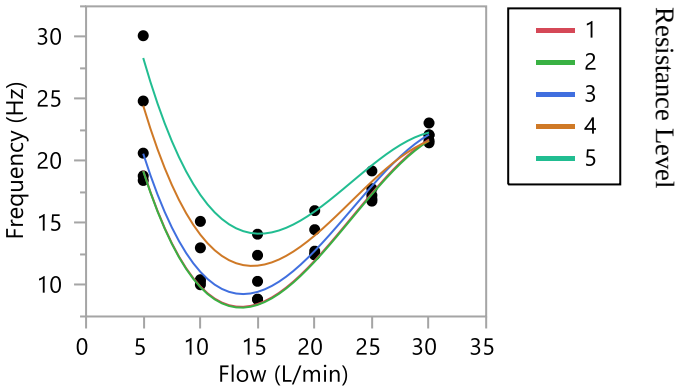
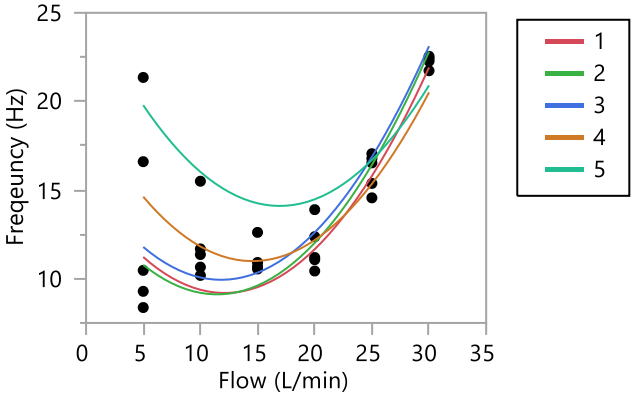
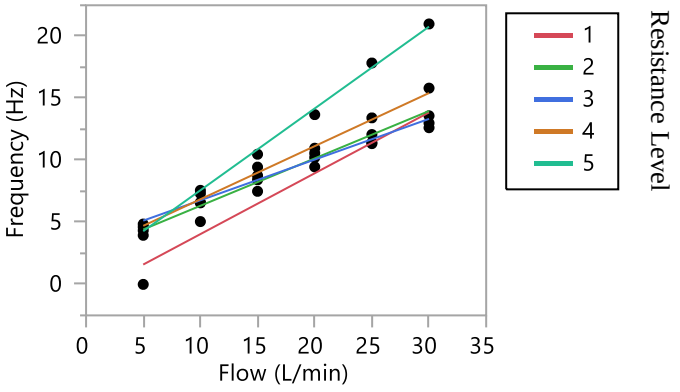
Appendix D Model Summary

D.1 Plot of the Regression Models

D.1.1 Frequency

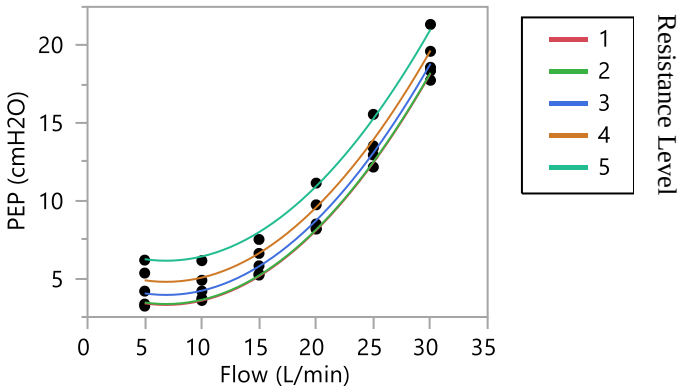
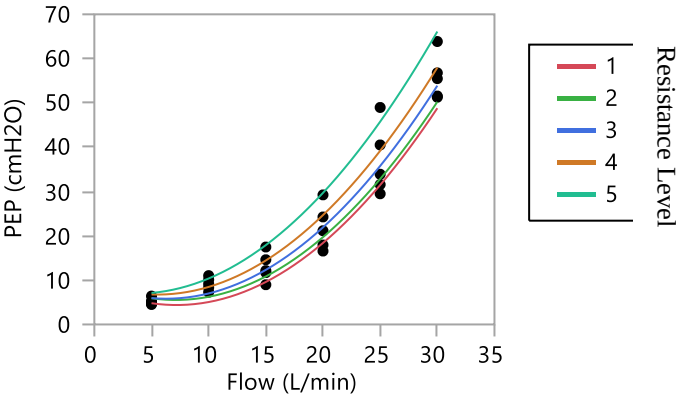
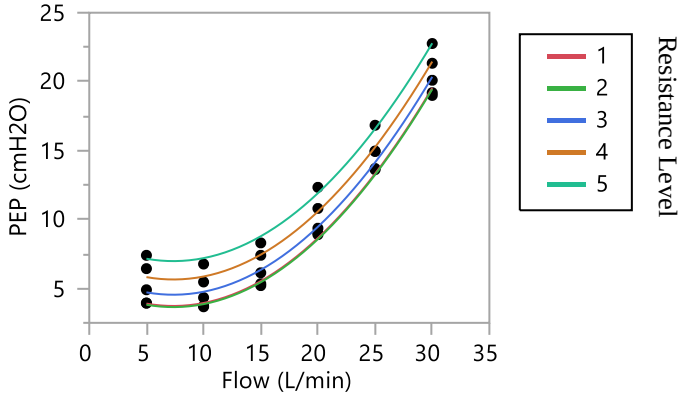
Table_Apx D.1-1 Plot of the regressions for all five devices – Frequency

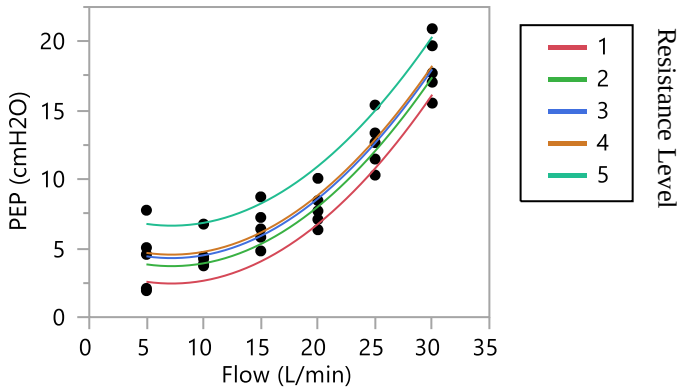
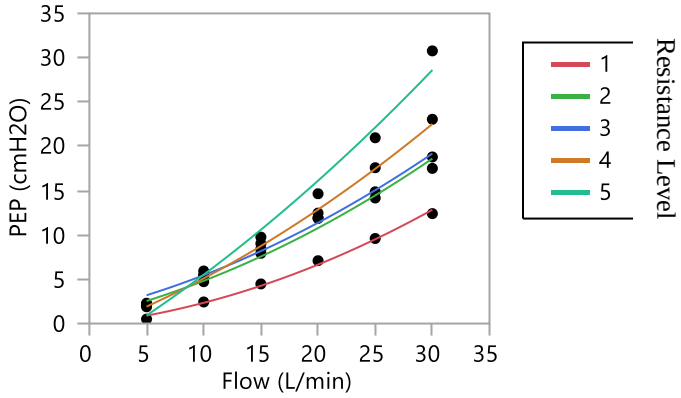
	Frequency Regression Plots
Device A	
Device B	

Device C	
Device D	
Device E	

D.1.2 PEP

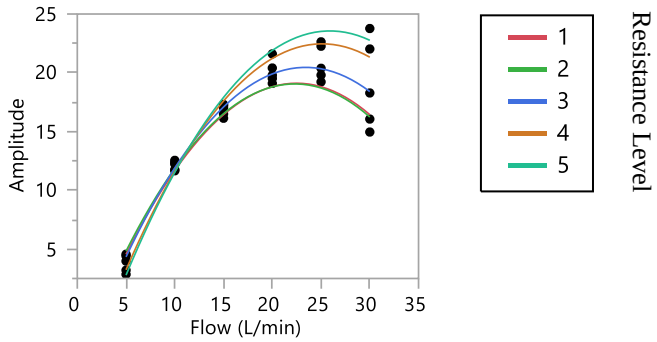
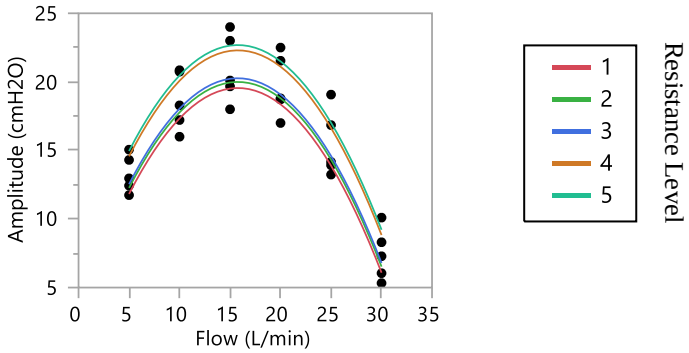
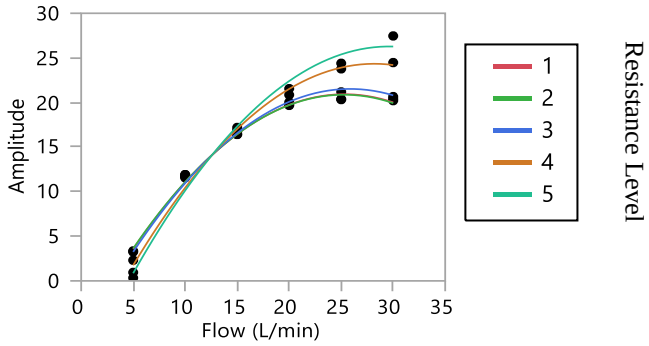
Table_Apx D.1-2 Plot of the regressions for all five devices – PEP

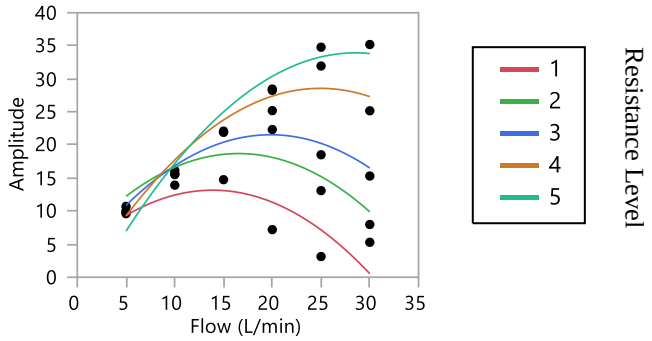
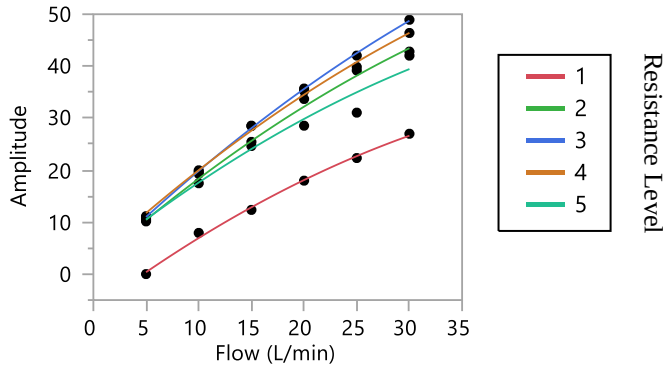
	PEP Regression Plots
Device A	
Device B	
Device C	

Device D	
Device E	

D.1.3 Amplitude

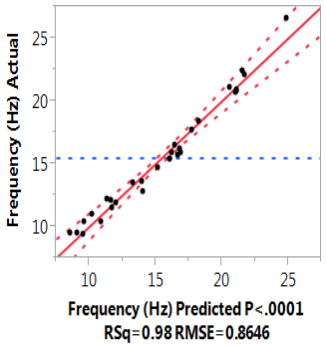
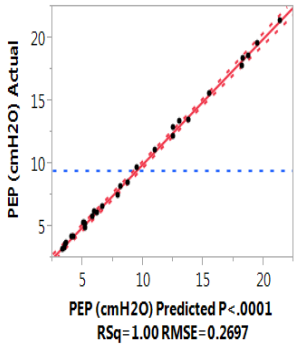
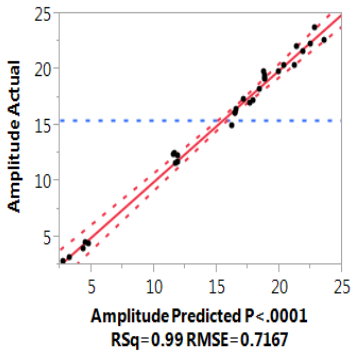
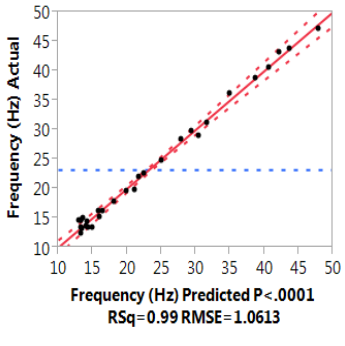
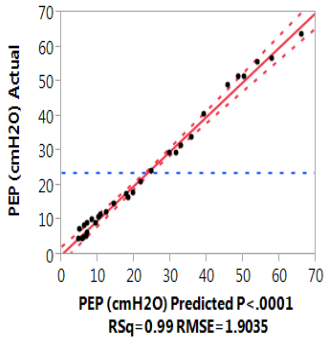
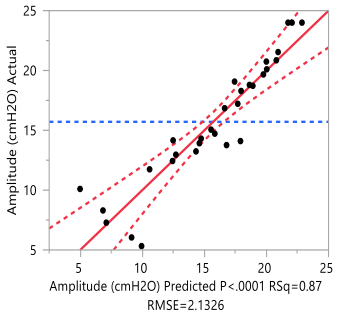
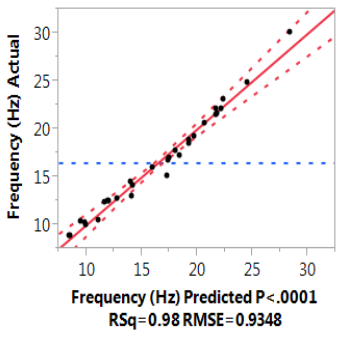
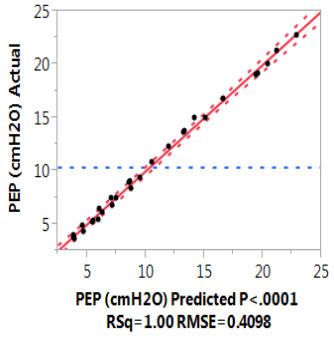
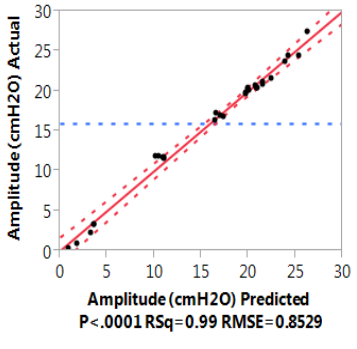
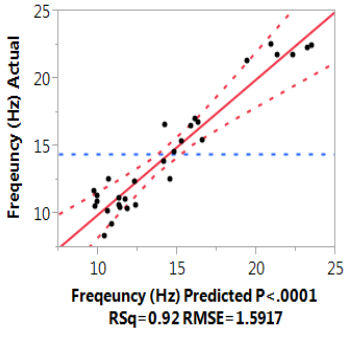
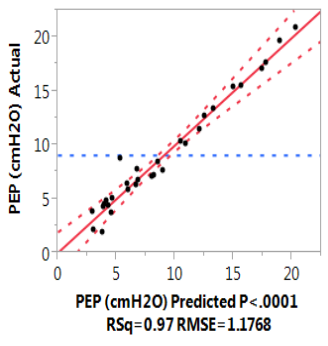
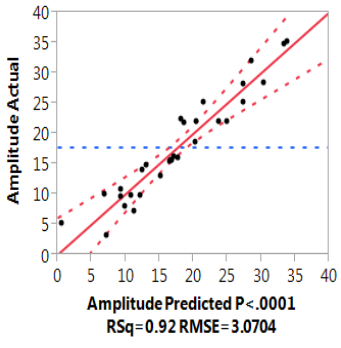
Table_Apx D.1-3 Plot of the regressions for all five devices – Amplitude

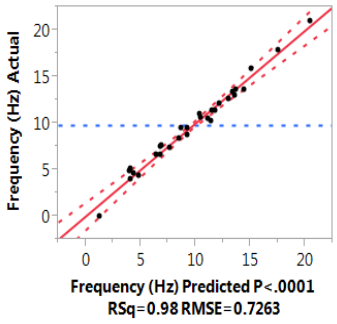
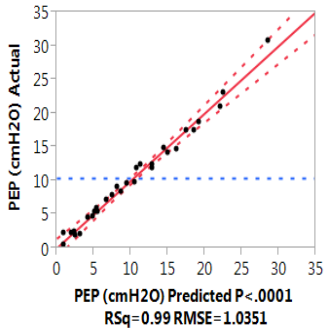
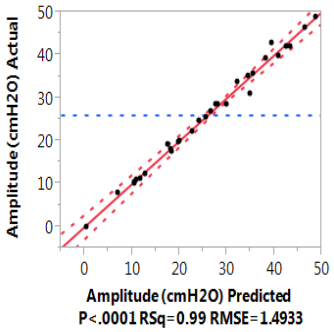
	Amplitude Regression Plots
Device A	
Device B	
Device C	

Device D	
Device E	

D.2 Model prediction Plot

Table_Apx D.2-1 A Plot of the models predictions against the experimentally collected data

	Frequency	PEP	Amplitude
Device A			
Device B			
Device C			
Device D			

Device E	 Frequency (Hz) Actual 0 5 10 15 20 Frequency (Hz) Predicted P<.0001 RSq=0.98 RMSE=0.7263	 PEP (cmH2O) Actual 0 5 10 15 20 25 30 35 PEP (cmH2O) Predicted P<.0001 RSq=0.99 RMSE=1.0351	 Amplitude (cmH2O) Actual 0 10 20 30 40 50 Amplitude (cmH2O) Predicted P<.0001 RSq=0.99 RMSE=1.4933

D.3 Regression Equations

D.3.1 Frequency Regression Equations

Table_Apx D.3-1 Regression equations for all five devices - Frequency

	Frequency Regression Equations
Device A	33.9024444426677 + -3.7348599639791 * Flow (L/min) + Match(Setting) { 1 ⇒ -4.0859555570667; 2 ⇒ -3.0592888877333; 3 ⇒ -2.0510666664; 4 ⇒ 2.7778222196; 5 ⇒ 6.4184888916; else ⇒ . } + Flow (L/min) * Match(Setting) { 1 ⇒ 0.13705142865143; 2 ⇒ 0.10114666659429; 3 ⇒ 0.06947047613714; 4 ⇒ -0.1099580950629; 5 ⇒ -0.19771047632; else ⇒ . } + Flow (L/min) * (Flow (L/min) * 0.18057915337494) + Flow (L/min) * (Flow (L/min) * (Flow (L/min) * -0.0023442469121))

Device B	-1.4701625005875 + 1.15765333333714 * Flow (L/min) + Match(Setting) { 1 ⇒ -1.76811111; 2 ⇒ -0.6814444433333; 3 ⇒ -0.32088889; 4 ⇒ 0.323555555; 5 ⇒ 2.44688888833333; else ⇒ . } + (Flow (L/min) - 17.5) * Match(Setting) { 1 ⇒ -0.1663200000229; 2 ⇒ -0.10597714288; 3 ⇒ -0.0116342859657; 4 ⇒ 0.05922285729143; 5 ⇒ 0.22470857157714; else ⇒ . } + (Flow (L/min) - 17.5) * ((Flow (L/min) - 17.5) * 0.06003666668143)
Device C	43.2242222288012 + -5.4592231054041 * Flow (L/min) + Match(Setting) { 1 ⇒ -3.7244000003733; 2 ⇒ -3.76173333224; 3 ⇒ -2.1601777749067; 4 ⇒ 2.58426666576; 5 ⇒ 7.06204444176; else ⇒ . } + Flow (L/min) * Match(Setting) { 1 ⇒ 0.11927999997943; 2 ⇒ 0.11722285716229; 3 ⇒ 0.08021333321943; 4 ⇒ -0.0950247618663; 5 ⇒ -0.2216914284949; else ⇒ . } + Flow (L/min) * (Flow (L/min) * 0.27816973552916) + Flow (L/min) * (Flow (L/min) * (Flow (L/min) * -0.0039956049397))

Device D	17.9766666679 + -1.0670047621136 * Flow (L/min) + Match(Setting) { 1 ⇒ -2.9164444464; 2 ⇒ -3.6239999977333; 3 ⇒ -2.4762222217333; 4 ⇒ 1.4506666656; 5 ⇒ 7.56600000026667; else ⇒ . } + Flow (L/min) * Match(Setting) { 1 ⇒ 0.09940952387429; 2 ⇒ 0.15276190458857; 3 ⇒ 0.12476190481714; 4 ⇒ -0.0931238094114; 5 ⇒ -0.2838095238686; else ⇒ . } + Flow (L/min) * (Flow (L/min) * 0.03987523810071)
Device E	1.74599999978667 + 0.45771428573029 * Flow (L/min) + Match(Setting) { 1 ⇒ -2.60000000152; 2 ⇒ 0.77177777828; 3 ⇒ 1.75222222268; 4 ⇒ 0.83155555568; 5 ⇒ -0.75555555512; else ⇒ . } + Flow (L/min) * Match(Setting) { 1 ⇒ 0.03289523823543; 2 ⇒ -0.0758095238103; 3 ⇒ -0.129580952376; 4 ⇒ -0.0293523810331; 5 ⇒ 0.201847618984; else ⇒ . }

D.3.2 PEP Regression Equations

Table_Apx D.3-2 Regression equations for all five devices - PEP

	PEP Regression Equations
Device A	-2.9350416677125 + 0.59264761910286 * Flow (L/min) + Match(Setting) { 1 ⇒ -1.0073333325667; 2 ⇒ -0.9506666659; 3 ⇒ -0.3640000002333; 4 ⇒ 0.48044444293333; 5 ⇒ 1.84155555576667; else ⇒ . } + (Flow (L/min) - 17.5) * ((Flow (L/min) - 17.5) * 0.02788476191057)
Device B	-17.096699998171 + 1.97218285709943 * Flow (L/min) + Match(Setting) { 1 ⇒ -3.9567777777667; 2 ⇒ -2.6778888889333; 3 ⇒ -0.8334444449333; 4 ⇒ 1.61322222223333; 5 ⇒ 5.8548888894; else ⇒ . } + (Flow (L/min) - 17.5) * Match(Setting) { 1 ⇒ -0.2115161903966; 2 ⇒ -0.1985638095566; 3 ⇒ -0.0539542858194; 4 ⇒ 0.07640761915771; 5 ⇒ 0.38762666661486; else ⇒ . } + (Flow (L/min) - 17.5) * ((Flow (L/min) - 17.5) * 0.08539047617643)

Device C	-2.866350000135 + 0.62548190474057 * Flow (L/min) + Match(Setting) { 1 ⇒ -1.1822222218667; 2 ⇒ -1.2638888892; 3 ⇒ -0.3661111113667; 4 ⇒ 0.7394444448; 5 ⇒ 2.07277777763333; else ⇒ . } + (Flow (L/min) - 17.5) * ((Flow (L/min) - 17.5) * 0.03082476190686)
Device D	-2.3892054163825 + 0.54290019045257 * Flow (L/min) + Match(Setting) { 1 ⇒ -1.8800444437667; 2 ⇒ -0.6183222219333; 3 ⇒ -0.0355444447667; 4 ⇒ 0.2161222224; 5 ⇒ 2.31778888806667; else ⇒ . } + (Flow (L/min) - 17.5) * ((Flow (L/min) - 17.5) * 0.02637861904543)

Device E	-3.2678887495738 + 0.73846971430743 * Flow (L/min) + Match(Setting) { 1 ⇒ -4.2571333330667; 2 ⇒ -0.5430777770667; 3 ⇒ 0.06581111143333; 4 ⇒ 1.0952555546; 5 ⇒ 3.6391444441; else ⇒ . } + (Flow (L/min) - 17.5) * Match(Setting) { 1 ⇒ -0.2605401904046; 2 ⇒ -0.0958792380274; 3 ⇒ -0.0988887619189; 4 ⇒ 0.08593028564114; 5 ⇒ 0.36937790470971; else ⇒ . } + (Flow (L/min) - 17.5) * ((Flow (L/min) - 17.5) * 0.00940147618414)

D.3.3 Amplitude Regression Equations

Table_Apx D.3-3 Regression equations for all five devices - Amplitude

	Amplitude Regression Equations
Device A	8.35857916594375 + 0.60339428574286 * Flow (L/min) + Match(Setting) { 1 ⇒ -0.9943333336; 2 ⇒ -0.9604444457667; 3 ⇒ -0.1221111124333; 4 ⇒ 0.79233333473333; 5 ⇒ 1.28455555706667; else ⇒ . } + (Flow (L/min) - 17.5) * Match(Setting) { 1 ⇒ -0.1282323809143; 2 ⇒ -0.1469180952857; 3 ⇒ -0.0407657143714; 4 ⇒ 0.120224762; 5 ⇒ 0.19569142857143; else ⇒ . } + (Flow (L/min) - 17.5) * ((Flow (L/min) - 17.5) * -0.0475319047636)

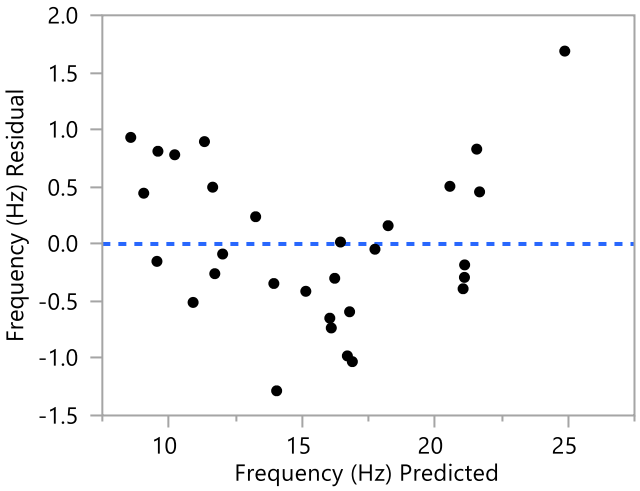
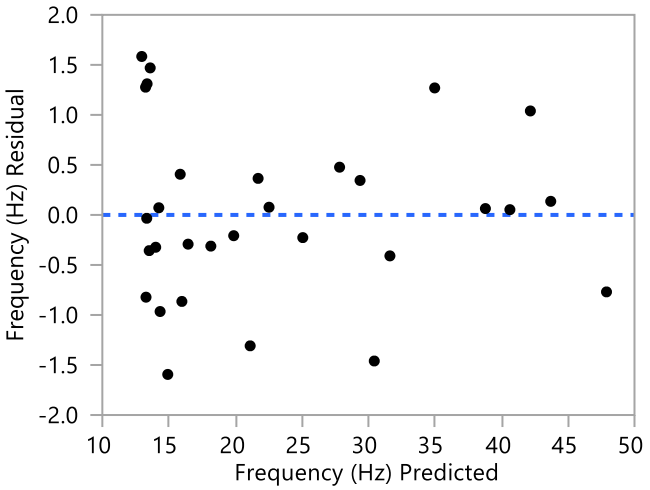
Device B	24.2761500005 + -0.2240228571314 * Flow (L/min) + Match(Resistance Level) { 1 ⇒ -2.6125555565333; 2 ⇒ -0.7669999993667; 3 ⇒ -0.4975555560333; 4 ⇒ 1.53744444463333; 5 ⇒ 2.3396666673; else ⇒ . } + (Flow (L/min) - 17.5) * ((Flow (L/min) - 17.5) * -0.06371619048) + (Flow (L/min) - 17.5) * Match(Resistance Level) { 1 ⇒ 0.16564190473143; 2 ⇒ 0.03280380961714; 3 ⇒ -0.0210057142686; 4 ⇒ -0.0928342856971; 5 ⇒ -0.0846057143829; else ⇒ . }
Device C	5.24819583294375 + 0.78517333328571 * Flow (L/min) + Match(Setting) { 1 ⇒ -0.6335555564333; 2 ⇒ -0.6485555536; 3 ⇒ -0.4035555559333; 4 ⇒ 0.54811111023333; 5 ⇒ 1.13755555573333; else ⇒ . } + (Flow (L/min) - 17.5) * Match(Setting) { 1 ⇒ -0.1278780951714; 2 ⇒ -0.1334590475429; 3 ⇒ -0.0830780952571; 4 ⇒ 0.11294095225714; 5 ⇒ 0.23147428571429; else ⇒ . } + (Flow (L/min) - 17.5) * ((Flow (L/min) - 17.5) * -0.041990952375)

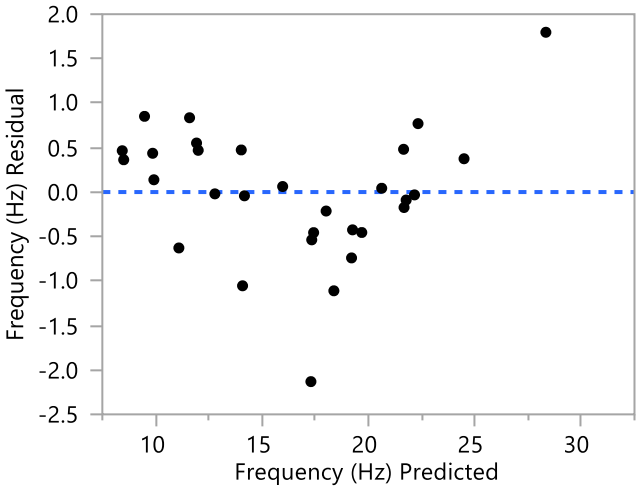
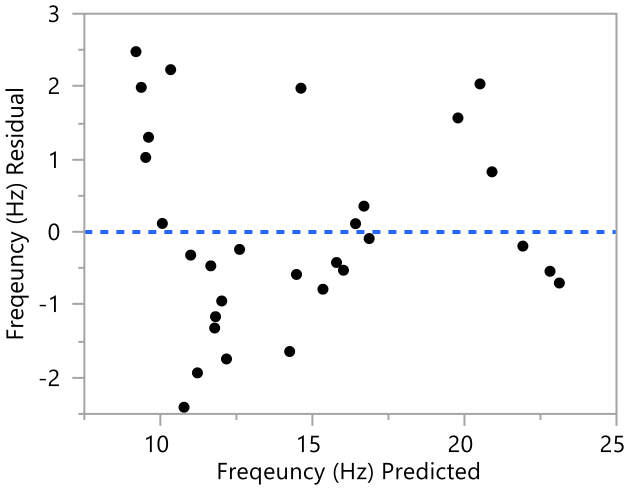
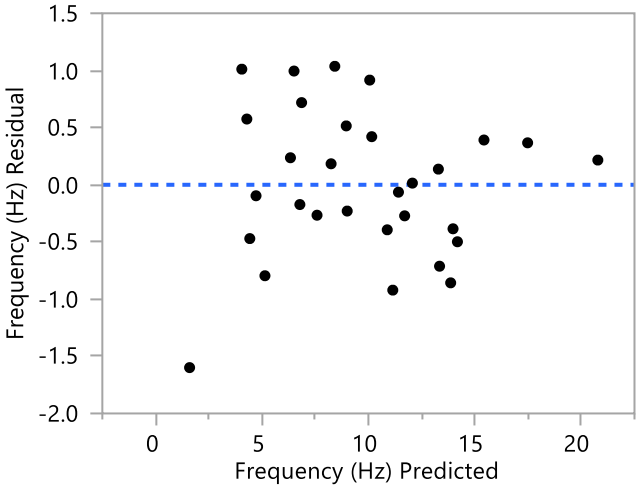
Device D	15.7619208332875 + 0.31513904762286 * Flow (L/min) + ⌊ Flow (L/min) - 17.5 ⌋ * Match(Setting) { 1 ⇒ -0.6671580952229; 2 ⇒ -0.40896761908; 3 ⇒ -0.0896342857657; 4 ⇒ 0.40636571432; 5 ⇒ 0.75939428574857; else ⇒ . } + Match(Setting) { 1 ⇒ -8.7463333343333; 2 ⇒ -2.6135555558333; 3 ⇒ 0.0136666675; 4 ⇒ 4.618111113; 5 ⇒ 6.72811110966667; else ⇒ . } + ⌊ Flow (L/min) - 17.5 ⌋ * [⌊ Flow (L/min) - 17.5 ⌋ * -0.04862428571]
Device E	4.43921666644875 + 1.28559238094971 * Flow (L/min) + Match(Setting) { 1 ⇒ -11.378333333267; 2 ⇒ 2.06888888956667; 3 ⇒ 4.99611110956667; 4 ⇒ 4.20500000123333; 5 ⇒ 0.1083333329; else ⇒ . } + ⌊ Flow (L/min) - 17.5 ⌋ * Match(Setting) { 1 ⇒ -0.2349447619726; 2 ⇒ 0.036312380936; 3 ⇒ 0.22509333350743; 4 ⇒ 0.10136000019314; 5 ⇒ -0.127820952664; else ⇒ . } + ⌊ Flow (L/min) - 17.5 ⌋ * [⌊ Flow (L/min) - 17.5 ⌋ * -0.0131866666647]

D.4 Residual Plot

D.4.1 Frequency Models Residuals Plots

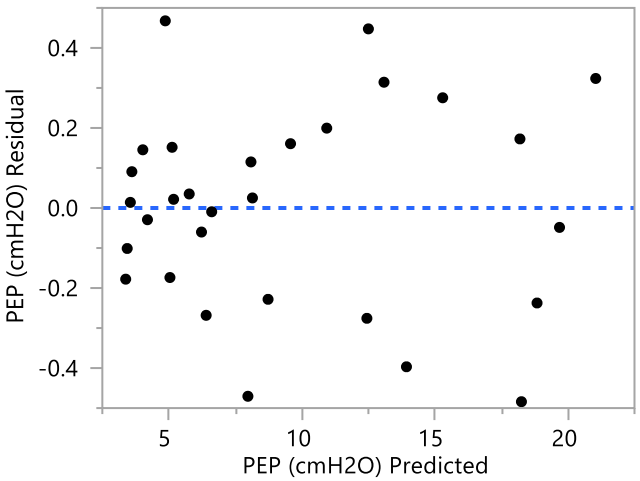
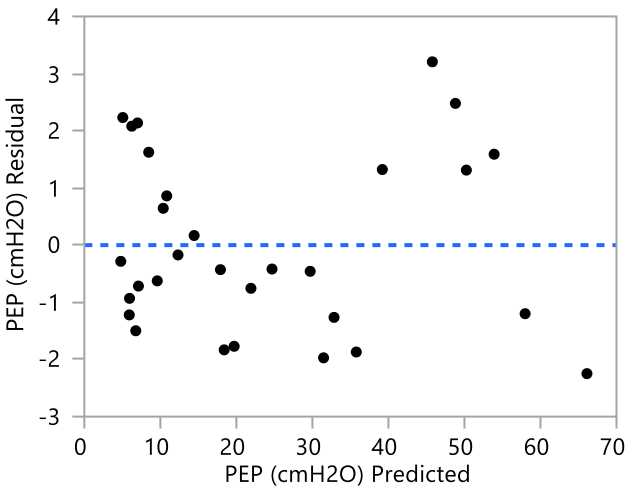
Table_Apx D.4-1 Models residual plots for all five devices - Frequency

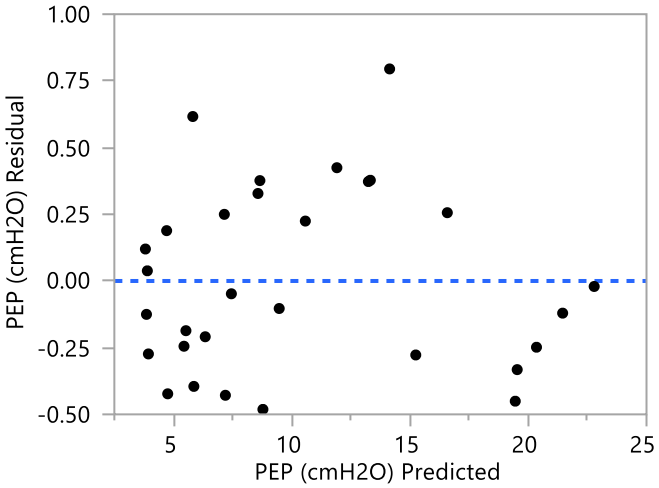
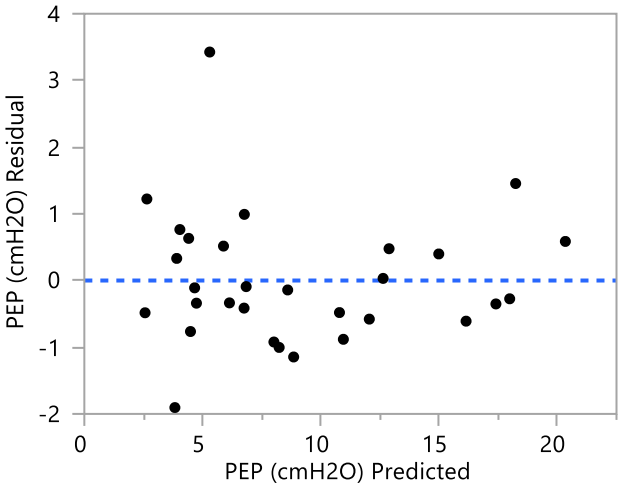
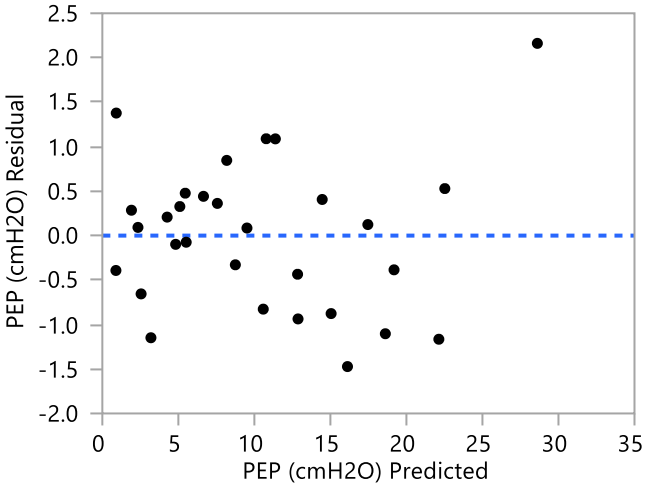
	Frequency models residuals plots
Device A	
Device B	

Device C	
Device D	
Device E	

D.4.2 PEP Models Residuals Plots

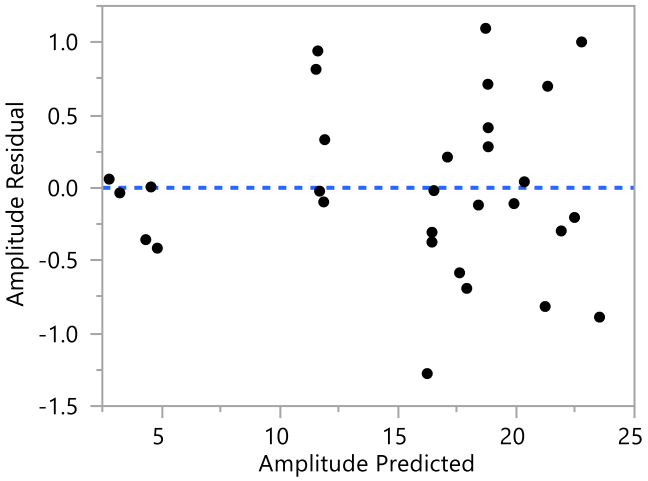
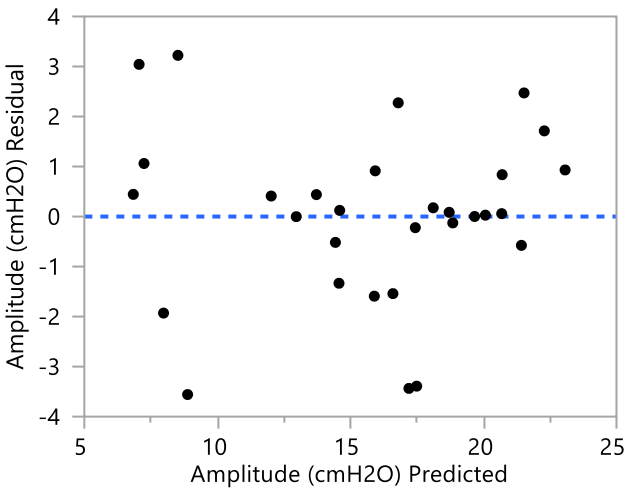
Table_Apx D.4-2 Models residual plots for all five devices - PEP

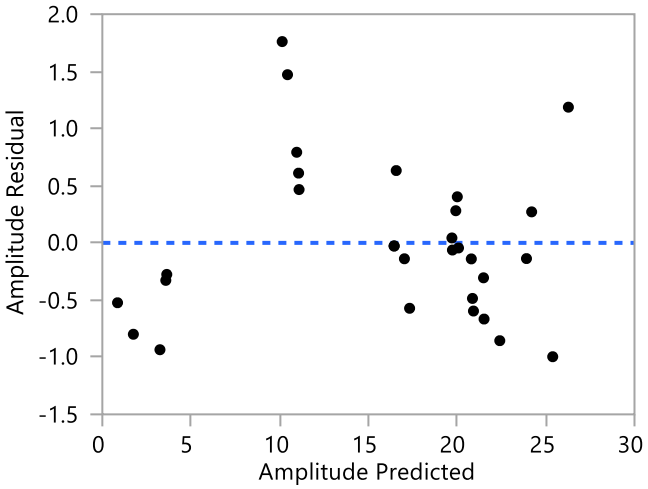
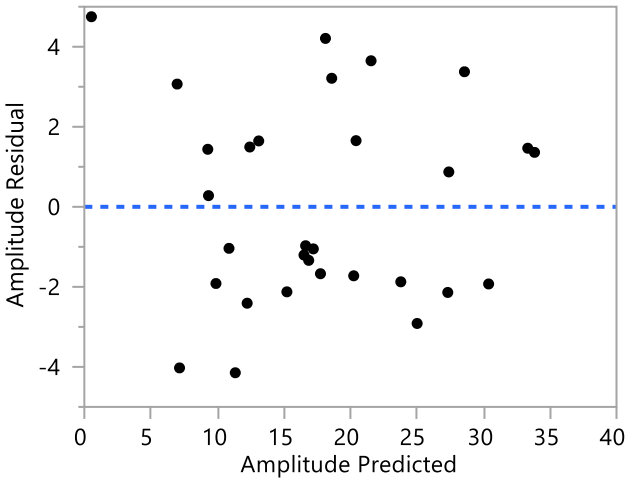
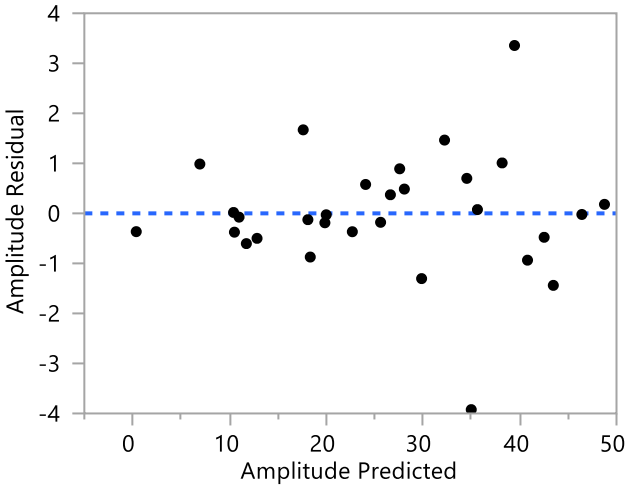
	PEP Models Residuals Plots
Device A	
Device B	

Device C	
Device D	
Device E	

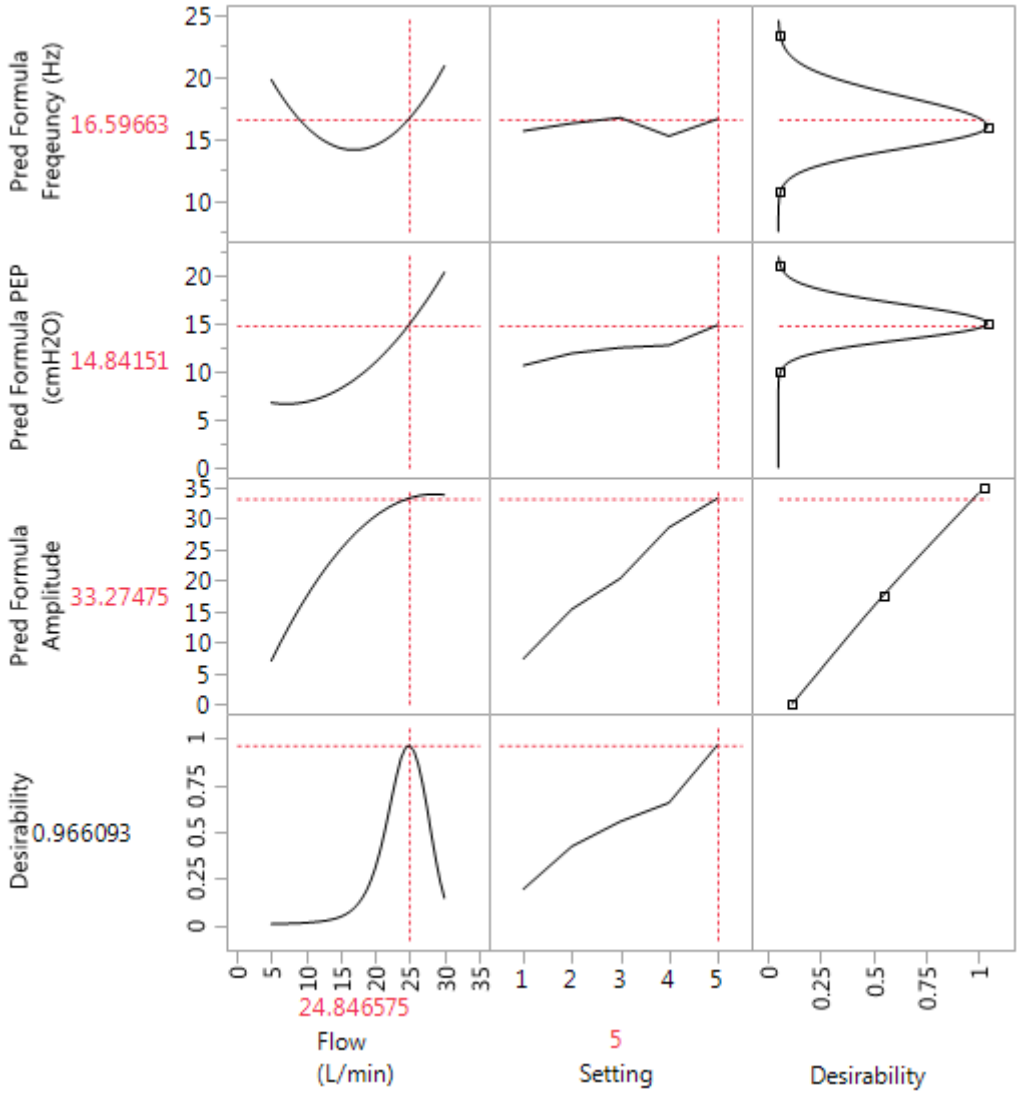
D.4.3 Amplitude Models Residuals Plots

Table_Apx D.4-3 Models residual plots for all five devices - Amplitude

	Amplitude Models Residuals Plots
Device A	
Device B	

Device C	
Device D	
Device E	

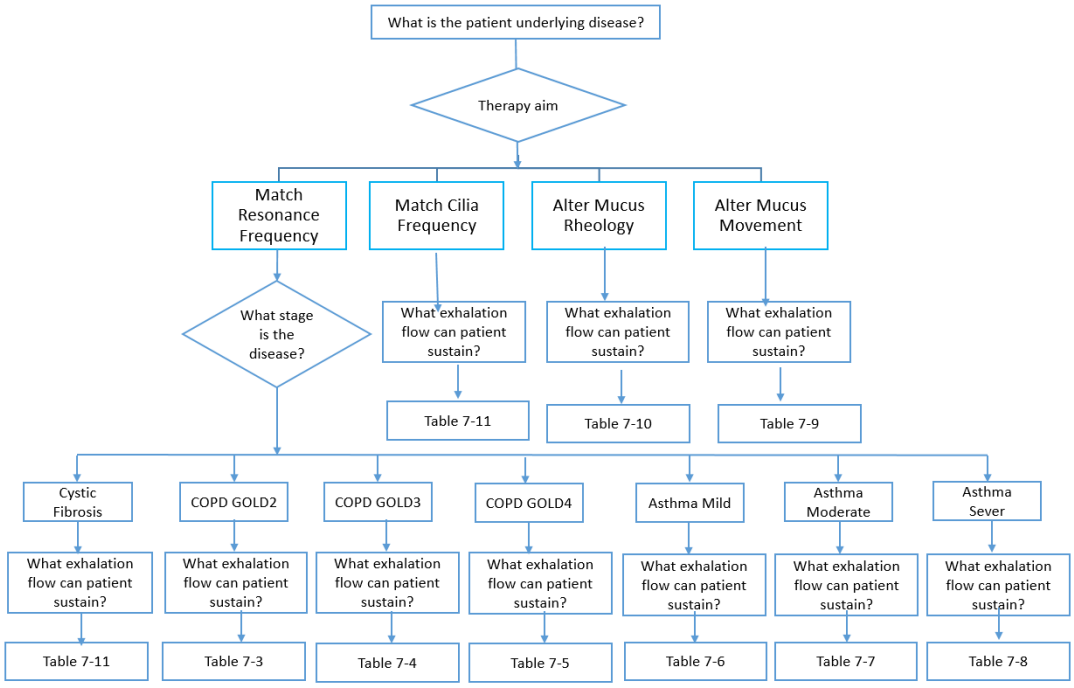
Appendix E Prediction Profiler Plots Sample



Figure_Apx E-1 Prediction profiler plot –Device D (cystic fibrosis global optimum)

Appendix F OPEP Device Optimisation Flow Chart

The flow chart in the figure below is intended to aid healthcare professional when selecting and optimising OPEP devices for patients. The process of selecting and optimising the OPPE devices relies firstly on choosing a therapy aim that matches the patient underlying disease. Secondly, it relies on choosing the device that matches the patient exhalation flow capabilities.



Figure_Apx F-1 Appendix F OPEP Device Optimisation Flow Chart