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The Use of Computer Aided Lung Sound Analysis to Characterise Adventitious Lung Sounds: A Potential Outcome Measure for Respiratory Therapy

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ABSTRACT

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Doctor of Philosophy

THE USE OF COMPUTER AIDED LUNG SOUND ANALYSIS TO CHARACTERISE ADVENTITIOUS LUNG SOUNDS: A POTENTIAL OUTCOME MEASURE FOR RESPIRATORY THERAPY

by Alda Sofia Pires de Dias Marques

A barrier to assessing the effectiveness of respiratory physiotherapy has been insufficient accurate, reliable and sensitive outcome measures. Lung sounds provide useful, specific information for assessing and monitoring respiratory patients. However, standard auscultation techniques are too subjective to allow them to be used as an outcome measure. In this research, Computer Aided Lung Sound Analysis (CALSA) was used to assess whether adventitious lung sounds' characteristics could be quantified clinically and used as a new objective, non-invasive, bedside clinical outcome measure for physiotherapy alveolar recruitment and airway clearance techniques. Two experimental studies were conducted incorporating 'before-and-after' and 'repeated measures' components. Fifty four participants with productive lung disorders (cystic fibrosis and bronchiectasis) were recruited from out-patient clinics. Demographic, anthropometric, lung function, oxygen saturation, breathlessness and lung sound data were collected at baseline and after a single intervention (self-intervention in the first study and intervention applied by a physiotherapist in the second study). The intra-subject reliability of crackle frequency (*f*) within each session was found to be 'good' to 'excellent', estimated by the Analysis of Variance, Intraclass Correlation Coefficient, Smallest Real Difference and Bland and Altman 95% limits of agreement. Crackle initial deflection width (IDW) and crackle two cycles deflection width (2CD) were reliable over short time periods. The *f* of crackles increased in the majority of participants post interventions. Agreement on the number (*N*) and timing (*T*) of crackles between CALSA and a physiotherapist's auscultatory findings was found to be poor in anterior chest sites, but higher in posterior sites. Conclusion: the use of CALSA to identify the type and *f* of adventitious lung sounds collected clinically is feasible; crackle IDW and 2CD are both reliable measures but crackle 2CD is more consistent; crackle *f* was more responsive than the *N* or *T* of crackles per breathing cycle to the interventions. In future, CALSA may provide an objective and responsive tool for assessing and monitoring respiratory interventions in clinical settings.

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Declaration of authorship

I, Alda Sofia Pires de Dias Marques,

declare that the thesis entitled

The Use of Computer Aided Lung Sound Analysis to Characterise Adventitious Lung Sounds: A Potential Outcome Measure for Respiratory Therapy

and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- where I have consulted the published work of others, this is always clearly attributed;
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MARQUES, A., BRUTON, A. & BARNEY, A. (2006) Clinically useful outcome measures for physiotherapy airway clearance techniques: a review. *Physical Therapy Reviews,* 11**,** 299-307.

Signed: ……..

Date:…….

Qual o fim da vida?, foi-lhe alguém perguntar.
E ele: o sol, a lua, os céus investigar.

In *'O ilimitável Oceano'* by Eugénio Lisboa, edições quasi, 2001, p.21

To Miguel for his love, encouragement and uncomplaining sacrifice.
To all of you who physically or mentally gave a contribute
for this long and challenging journey to be possible.

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List of abbreviations

ABG - arterial blood gases
ACBT - active cycle of breathing technique
ACT - airway clearance techniques
AD - autogenic drainage
AL - anterior left
ANOVA - analysis of variance
AR - anterior right
BC - breathing cycle
BMI - body mass index
BMS - between subjects mean
Br – bronchiectasis
CALSA - computer aided lung sound analysis
CCPT - conventional chest physiotherapy techniques
CF - cystic fibrosis
CFTR - cystic fibrosis transmembrane regulator
CI - confidence intervals
CV - coefficient of variation
d – mean
Df – degrees of freedom
EMS - residual error components
F – female
f - frequency
F50 - median frequency
FET - forced expiratory techniques
FEV_1 - forced expiratory volume in the first second
FEV_1/FVC - ratio between forced expiratory volume in the first second and forced vital capacity
FEV_1pp - forced expiratory volume within the first second percentage predicted
Fmax - frequency of maximum intensity
FVC - forced vital capacity
Hz – hertz
ICC - intraclass correlation coefficient
ICF - international classification of functioning, disability and health
IDW - initial deflection width

LDW - largest deflection width

LL - lateral left

LR - lateral right

M/m – male

MAD - modified autogenic drainage

Max – maximum

MBS - modified borg scale

Min – minimum

ms – milliseconds

N – number

No. – number

$PaCO_2$ - Carbon dioxide partial pressure

PaO_2 - oxygen partial pressure

PEF - peak expiratory flow

PEP - peak expiratory pressure

PL - posterior left

PR - posterior right

PSD - power spectral density

Pt - patient or participant

QAH - Queen Alexandra Hospital

RC - repeatability coefficient

RMS - raters mean squares

RMS - sound intensity

SD - standard deviation

SDdiff - standard deviation of the difference

SE - standard error of the mean

SEM - standard error of measurement

SGH - Southampton General Hospital

SRD - smallest real difference

Stdv - standard deviation

STFT - short-time Fourier transform

T – timing

T – trachea

TEWA - time expanded waveform analysis

TLC - total lung capacity

TwoCD or 2CD - two cycles deflection width

VAS - visual analogue scale

VC - vital capacity

WHO - World Health Organization

WMS - within subjects mean square

WSSD - within subjects standard deviation

Chapter 1
Introduction

This chapter will start with a brief introduction to the motivation and justification for this research aiming to develop Computer Aided Lung Sound Analysis (CALSA) as an outcome measure for respiratory therapy. An overview of this Thesis will then be presented.

1.1. Computer aided lung sound analysis for respiratory therapy

Respiratory physiotherapy is used routinely in clinical practice as part of the management of a range of respiratory related problems associated with disorders of the respiratory system, i.e., breathlessness/dyspnoea, excess lung secretions, reduced lung volumes and low exercise tolerance.

One of the commonest respiratory problems is the difficulty with removing excessive lung secretions. Cystic fibrosis and bronchiectasis are two common respiratory disorders for which respiratory physiotherapy is essential to remove secretions and maintain function. However, 'respiratory physiotherapy' covers numerous treatment approaches and techniques, for which there is currently very little evidence regarding their effectiveness. One of the hindrances to generating the evidence is the lack of reliable, valid, sensitive and functionally relevant outcome measures (AACVPR, 2004, Oermann et al., 2001, Pryor, 1999, Robinson and Bye, 2002, Thomas et al., 1995a).

When assessing respiratory interventions it is therefore never clear if a lack of significant effect is found as a result of ineffective treatment, or from the use of an inappropriate outcome measure. Airway clearance techniques are known to have short-term effects in increasing mucus transport, but the evidence is less clear concerning long-term effects. Furthermore, when the effectiveness of these techniques is compared, no consistent differences are found in terms of their enhancement of mucociliary clearance (Main et al., 2005).

Respiratory physiotherapists currently use sputum quantity, respiratory function tests, tests of gas exchange, imaging evidence, breathlessness and standard auscultation, as outcome measures to monitor their interventions (Marques et al., 2006). However, most of these clinically available outcome measures are not specifically related to the physiotherapy intervention employed and may be affected by other factors. Standard

auscultation is often used to monitor respiratory physiotherapy interventions because it gives information about the structure and function of the lung that can not be obtained with any other simple and non-invasive method (Forgacs, 1978). It is also known that several pathological changes in the lungs produce characteristic sounds that can be detected more readily by auscultation than by any other measure (Gross et al., 2000). However, standard auscultation is a subjective process that depends on the hearing experience and the ability to differentiate between different sound patterns (Sovijarvi et al., 2000d).

Computer Aided Lung Sound Analysis (CALSA) makes use of an objective, non-invasive and bedside measurent, requiring minimal patient collaboration. The data acquired have clinical utility, can be interpreted objectively and are relevant and simple to collect, requiring only a microphone and a recording device (portable equipment) from which sounds may be transferred to a digital format for analysis. The technique has been found to be specific, reliable, and sensitive within the limited use to which it has been put to date. Although it has been used for some time to identify normal and adventitious lung sounds, it has not yet been evaluated as an outcome measure for physiotherapy. Therefore, this research aims to investigate the potential of CALSA to provide an objective, non-invasive, clinically useful measure for respiratory therapy.

1.2. Thesis overview

This Thesis starts with the literature review presented in Chapters 2 and 3. The complexity of outcome measurement and lack of evidence base in respiratory physiotherapy are addressed in Chapter 2. Chapter 3 will introduce the reader to normal/abnormal lung sounds, their respective characterisation, and CALSA as a potential outcome measure for respiratory physiotherapy. Chapter 4 describes the equipment and methodology used for the two studies conducted in this research. The measurements and results are presented in Chapter 5. Chapter 6 discusses the findings and presents the limitations of this research and recommendations for further work. The conclusions and a summary of the main areas to develop in future work are presented in Chapter 7.

Chapter 2

Respiratory physiotherapy for airway clearance

2.1. Introduction

This chapter will address the complexity of outcome measurement. The International Classification of Functioning, Disability and Health (ICF) will be introduced. The respiratory area in general, respiratory physiotherapy, and the specific research undertaken will be placed within the context of the ICF model, approaching the problem of providing an evidence base for respiratory physiotherapy. A general introduction to outcome measures and their respective measurement properties will follow. Finally, alveolar recruitment and airway clearance therapy outcome measures used in respiratory physiotherapy will be discussed.

2.2. Classifying the study

The World Health Organization (WHO) has stated that the impact of any condition can be classified using the International Classification of Functioning, Disability and Health (ICF). According to Steiner et al. (2002) in the ICF model, Functioning and Disability ('Body Functions and Structures', 'Activities' and 'Participation') are seen as an interaction between the Health Condition ('Disorder'/'Disease') and Contextual Factors ('Personal Factors' and 'Environmental Factors'). Therefore, ICF is a valuable tool in research into disability, in all its dimensions; impairments at the body and body part level (body functions and structures), person level activity limitations (activities) and societal level restrictions of participation (participation) and also provides a conceptual model and classification required for instruments to assess the social and built environment (WHO, 2002).

According to ICF classification, respiratory impairment is a loss or abnormality of psychological, physiologic, or anatomic structure or function resulting from respiratory disease, which relates to the exteriorisation of a pathological state and is usually determined by a laboratory measurement. The impairments that can be measured are: pulmonary function; dyspnoea; dysfunction of peripheral and respiratory muscles; anxiety and depression; abnormalities of nutrition and body composition (ATS, 1999b). Activity performance can also be affected by lung disease. Activity can be measured by numerous laboratory and field tests such as: incremental exercise tests; sub-maximal exercise tests; and walking tests (Bradley et al., 2001, ATS, 1999b). Impaired or limited activity can lead to restrictions in patients' ability to participate in society or fill expected

roles, e.g. reduced exercise performance during a timed walk test is a limitation of activity, but the resultant inability to maintain employment is a restriction of participation. Some aspects of participation can be measured using health status disease specific questionnaires, e.g., Chronic Respiratory Disease Questionnaire (Bradley et al., 2001, ATS, 1999b).

This Thesis is primarily concerned with measurement at the ICF classification impairment level, i.e., body functions and structures, specifically with measurements of impairments treated or managed with respiratory physiotherapy airway clearance techniques.

2.3. Evidence base in respiratory physiotherapy for airway clearance

There is a variety of methods used to help remove secretions from the lungs, some physical (like physiotherapy airway clearance techniques), and some chemical (like medications and inhalation therapies). Despite a lack of evidence for individual techniques, such methods are considered to be essential in optimising respiratory status and reducing the progression of lung disease. Chest physiotherapy plays an important role in assisting the clearance of airway secretions (Main et al., 2005), reducing the work of breathing, improving ventilation, increasing function and enabling relief of dyspnoea (Garrod and Lasserson, 2007), and is usually commenced as soon as a diagnosis is made. Individual physiotherapy advice to patients with sputum production is an appropriate component of their rehabilitation (BTS, 2001). The physiotherapist also has a role in providing advice about relaxation and breathing retraining techniques (BTS, 2001).

Airway clearance techniques (ACTs) and their application have changed with increased understanding of pathophysiology, with knowledge of, and developments in, medicine, and as result of quality assurance and evidence based research (IPG/CF, 2002). There are numerous airway clearance techniques, but, although these techniques are deemed to be essential in the management of patients with excessive secretions, systematic reviews and meta-analysis have not been produced (Alison, 2004, Jones and Rowe, 1997, Main et al., 2005). In some studies comparing different respiratory physiotherapy interventions, no significant differences in the amount of sputum or pulmonary function are found (Davidson et al., 1992, Giles et al., 1995) and similar short-term effects are achieved for each technique (Elkins et al., 2005a, Main et al., 2005, Varekojis et al., 2003). A review of 29 publications representing 15 data sets comparing conventional chest physiotherapy techniques (CCPT) with other ACTs, found no evidence that any of the newer techniques were better than CCPT in people

with cystic fibrosis (Main et al., 2005). However, this review was limited by the paucity of well-designed, adequately powered and reported, long-term trials (Main et al., 2005). Similar methodological problems had already been acknowledged by Jones and Rowe (Jones and Rowe, 1997). Methodologically sound randomised controlled trials of bronchopulmonary hygiene techniques are still required and investigation should include long-term follow-up (Garrod and Lasserson, 2007). Therefore, despite the expansion in number of treatment modalities the true value of these techniques has not yet been established and there is still little evidence supporting their efficacy, although they are popular with patients (Bradley et al., 2006, BTS, 2001, Elkins et al., 2005b, Gumery et al., 2002, Main et al., 2005, van-der-Schans et al., 2000), and are in routine clinical use.

As a result of the clinical acceptance that ACTs are effective and form part of routine care, it is becoming rare to find trials that compare ACTs with a 'no treatment' control group. Reviews of such trials have found evidence that ACTs have short-term (between 1 day and three months) effects in terms of increasing mucus transport, but that there was no convincing evidence for long-term (more than six months) effects (Gappa, 2004, van-der-Schans et al., 2000). The assessment of any impact of physiotherapy on lung disease is difficult in long-term studies, since other treatment strategies of the care package are constantly applied and modified. Randomised controlled trials assessing the effects of using physiotherapy versus the effects of not using physiotherapy on patients with cystic fibrosis (CF) have not yet been performed, but are believed to be a necessary step forward to determine primary outcome measures (Doring and Hoiby, 2004, Spencer and Jaffe, 2003). However, chest physiotherapy has been the main respiratory treatment of CF and bronchiectasis (Br) for so long that it may now be difficult for patients, their parents, physiotherapists and medical staff to consider a trial design that incorporated a 'no treatment' control group for any length of time. Many would argue that to recruit participants into a 'no treatment' group would be unethical. This explains in part why there are few long-term trials which use this design (van-der-Schans et al., 2000). Currently there is an ongoing long-term trial, MATREX, to determine the effectiveness and cost utility of manual chest physiotherapy techniques in the management of exacerbations of chronic obstructive pulmonary disease (Cross, 2005), but no findings have yet been published.

Thus, a systematic review of the research into respiratory physiotherapy for patients with excessive secretions presents substantial challenges, because of the variability of interventions, study durations and outcome measures used. The tendency to compare newer techniques with 'conventional' chest physiotherapy also presents challenges, as

a result of lack of consensus as to what 'conventional' chest physiotherapy actually comprises. However, as the focus of this Thesis is specifically on outcome measures, it is not proposed to develop these arguments here.

This research is about developing a new outcome measure for use in conjunction with ACTs. The population most likely to require such techniques comprises patients with excessive secretions. The next section will therefore describe patients with CF and Br, as good examples of this population. The incidence, prevalence and respective characterisation of these two conditions will be provided.

2.4. Cystic Fibrosis and Bronchiectasis

Cystic fibrosis is a genetic disease with incidence varying by continent. In Europe, it has been oscillating between 1/1700 (Ireland, Britain) and 1/25 000 (Finland) and in North America and Australia 1/3500. In the UK, one child in 2415 live births have CF and this disease affects 7500 children and young adults (Urquhart et al., 2005, Dodge et al., 1997). The life expectancy of a baby with CF, born in 1990, is estimated to be approximately 40 years (Jaffe and Bush, 2001). Improved survival has been attributed to better nutritional status, intensive treatment with antibiotics and chest physiotherapy (Button et al., 2003). Bronchiectasis is an acquired disease, the incidence of which is believed to have declined over the past 50 years, with prevalence being lower in higher income countries (Hacken et al., 2006). However, there are fewer reliable data about the incidence of Br in different countries (Hacken et al., 2006). The prognosis with respect to life expectancy in all patients with excessive secretions has improved, but respiratory failure remains the major cause of death (Al-Shirawi et al., 2006, Gappa, 2004, Hacken et al., 2006).

Cystic fibrosis and Br are closely related conditions. Cystic fibrosis is an inherited progressive pulmonary disease caused by an abnormality on the long arm of chromosome 7 (Spencer and Jaffe, 2003, Gappa, 2004). The pathogenesis starts with the defective gene, which results in an absent or deficient function of cystic fibrosis transmembrane regulator and this leads to imbalances in the airway environment, with alterations in the epithelial fluid layer and abnormal mucus production. A persistent and excessive inflammatory response results in airway obstruction and structural lung damage (bronchiectasis), respiratory failure and even death (Gappa et al., 2001). Bronchiectasis is a chronic and progressive lung disease, defined pathologically as irreversible dilatation of the bronchi and consequently lung damage (Evans and Greenstone, 2003). Bronchiectasis can be due to local disease (blockage of bronchial lumen by a foreign body, tumor, extrinsic compression of the bronchi) or a diffuse

process (congenital disease or association of systematic disease) (Barker, 2002). More than 50% of Br patients acquire the condition as a result of CF (AACVPR, 2004, Pasteur et al., 2000), and the rest are classified as idiopathic (Al-Shirawi et al., 2006, Pasteur et al., 2000).

Both of these pulmonary diseases are characterised by poor ciliary function, bronchial and bronchiolar obstruction and by viscous and sticky secretions, that are difficult to clear, being the ideal ground for bacteria with which the lungs become chronically colonised (Evans and Greenstone, 2003, Gumery et al., 2002). Retention of abnormal airway secretions promotes recurrent respiratory infections, cycles of inflammation, progressive lung damage with loss of pulmonary function and increased functional disability (AACVPR, 2004, Evans and Greenstone, 2003, Peterson et al., 2003, Suri et al., 2001, Davies et al., 2006). The exact mechanism of the vicious cycle of inflammation and infection that results in lung parenchymal destruction, remains unclear (Spencer and Jaffe, 2003). As a result of their excess secretions, patients with CF and Br suffer from airflow obstruction, abnormal respiratory mechanics, excess dead space, gas exchange disturbance, nutritional abnormalities and skeletal muscle dysfunction. These lead to symptoms of cough, sputum production, dyspnoea, exercise intolerance, functional impairment and impaired quality of life (AACVPR, 2004).

Physiotherapy has both rehabilitative and preventive aims for patients with these conditions. Chest physiotherapy and exercise are the primary physical methods for removing viscid and inflammatory material from the airways (Button et al., 2003, Davies et al., 2006). Airway clearance techniques are aimed at removing viscous airway secretions, compensating for impaired mucociliary clearance, and minimising the lung disease process (Abbott and Hart, 2005, Davies et al., 2006, Jaffe and Bush, 2001, Spencer and Jaffe, 2003). As stated earlier, although ACTs are an accepted treatment for these conditions, the evidence for their individual efficacy is weak. One of the primary reasons for this is the lack of objective, reliable, valid and appropriate outcome measures.

The next section will give a general overview of outcome measures and their respective properties. The outcome measures used for alveolar recruitment and airway clearance therapy in respiratory physiotherapy will then be reviewed.

2.5. Outcome measures

Outcome measures are tools that enable a health professional to undertake an evaluation of a strategy, intervention or program (CSP, 2003, Finch et al., 2002).

During rehabilitation, they are essential to evaluate/monitor patients' and intervention/programs' progress, the effectiveness of clinical practice, its immediate impact and consequences, and to determine the efficacy of new treatment strategies (Bradley et al., 2001, Finch et al., 2002). It is also well known that it is not feasible to measure all the outcomes related with a patient's condition. Therefore, the choice of outcome measures depends on what is being evaluated and the purpose of the measurement, the goals of the program and the resources and level of clinician expertise. It is desirable to choose an outcome that is most affected by the strategy, intervention or program applied to the patient, and least affected by variables outside the control of the service providers and yet still under the direct influence of therapy that is being offered (Finch et al., 2002). General health-related outcome measures include an evaluation of change in patients' impairments, activity, participation restrictions, and Health Related Quality of Life (AACVPR, 2004, BTS, 2001, Finch et al., 2002).

2.5.1. Measurement properties in outcome measures

To measure is to quantify and to determine the extent of something by comparison with a standard unit. *Measurement* means the use of a standard to quantify an observation and *Assessment* means the process of determining the meaning of measurements (Wade, 1992). Measures may be needed to define the type of patient studied, to measure various parts of the process of treatment and to measure the outcome (Wade, 1992). Therefore, process and outcome are distinct aspects of clinical interventions, and both should be measured.

Any outcome measure should relate to the underlying disease mechanisms and/or the well-being of the patient (Jones and Agusti, 2006). Choosing a suitable clinical outcome measure involves asking questions about relevance, validity, reliability, sensitivity, selectivity, specificity and simplicity; if the results can be communicated to others and are easy to interpret; if there is a better measure available or not (Wade, 1992, Jones and Agusti, 2006), and if the measure is cost-effective (Jones and Agusti, 2006). Interpretations for some of these terms, as they have been used in this Thesis, are given below.

2.5.1.1. Validity and reliability

Validity refers to whether a measure actually measures what it is supposed to, and if it is suitable for the required purpose (Wade, 1992, McDowell and Newell, 1996). Validity involves various concepts, i.e., face validity (the ability of the measure to measure what is intended); content validity (the ability of the measure to assess the domain of interest); criterion validity (the ability of the measure to measure accurately), ideally

assessed via comparison with a gold standard; accuracy, or precision, being the closeness of agreement between the result of a measurement and the conventional true value (Bowling, 2002, Miller et al., 2005b); construct validity (the ability of the measure to provide results that are consistent with theory). The latter involves convergent validity (the ability of the measure to correlate with related variables) and discriminant validity (the ability of the measure not to correlate with unrelated variables) (Bowling (2002), Finch et al. (2002), McDowell and Newell (1996)). Content and construct validity are normally explored in the behavioural sciences (Bowling, 1997), and are frequently attributes of questionnaires. Due to the nature of this research, these aspects of validity will not be explored further. Face validity was ensured by the published algorithms (Hsueh et al., 2005, Vannuccini et al., 1998) used in this Thesis and by following guidelines (e.g., computerised respiratory sound analysis guidelines see section 3.1).

Reliability is a prerequisite of validity but does not ensure validity (Finch et al., 2002). A measure is judged to be reliable when it consistently produces the same results, particularly when applied to the same subjects at different time periods when there is no evidence of change (Bowling, 1997). Therefore, a reliable measure must provide values which are consistent, with small errors of measurement. It might seem reasonable that any device that provides the smallest difference between replicate measurements would be the preferred measure. However, if the device is incorrectly calibrated it will produce results that are consistent but incorrect. For this reason a useful measure must demonstrate more than consistency. The types of reliability are test-retest reliability (level of consistency achieved during repeated measurements over time), intra-rater reliability (level of consistency achieved during repeated measurements by the same rater) and inter-rater reliability (level of consistency achieved during measurements by different raters) (Bowling, 2002, Finch et al., 2002, McDowell and Newell, 1996).

Wade (1992) defined measurement reliability as how closely two results relate to each other, influenced by variation in the patient's state, by inter-observer variability and by the variation over time if a mechanical tool is being used. All these variations can be random or non-random. However Miller et al. (2005b) defined reliability as the extent of agreement between the results of a successive measurement of the same item carried out with the same method, same observer, same instrument, same location, same condition of use, and repeated over a short space of time. This Thesis looks at the potential of a new outcome measure to be used in respiratory physiotherapy, which means that it needs to have reliability when measures are taken by different health

professionals; in different body locations and in different physical locations (e.g. hospital wards and patient's home); in patients with different conditions (e.g., different diseases and different levels of severity) but also with different environment conditions (e.g., different levels of noise); at different short spaces of time (e.g., immediately after therapy, twice per day, daily and weekly); using the same methodology (CALSA) and instrumentation (digital stethoscope).

It was not feasible in this Thesis to determine the reliability of the new measure under all these circumstances. Therefore, the initial focus was on reliability of measures over short periods of time, taken by the same rater.

Different types of data require different statistical analysis methods (Rankin and Stokes, 1998) to test reliability. In this study, where a digital stethoscope is recording lung sounds, the data are continuous. The kappa test is commonly used to assess the reliability of nominal data and the weighted kappa test is used for ordinal data, however, there is less consensus related to continuous data (Rankin and Stokes, 1998, Haas, 1991). Although used by various authors, Pearson's correlation, t-tests, coefficient of variation (CV), have been found to be inappropriate (Haas, 1991, Rankin and Stokes, 1998) for reliability studies. Pearson's correlation coefficient is inappropriate because the linear association and not agreement is measured. Therefore, it is possible to have a high degree of association without agreement. Paired t-tests assess whether there is any evidence that two related sets of data agree on average, i.e., similarity of means is assessed, but two very different sets of data can have the same mean. Coefficient of Variation (CV), which is the standard deviation divided by the mean and multiplied by 100 to give a percentage score, expresses the standard deviation as a proportion of the mean, making it unit independent (Bruton et al., 2000). However it is also not appropriate to use since it assumes that the largest test-retest differences will occur in individuals scoring the highest values on the test, i.e., the problem of expressing the error as a percentage, is that x% of the smallest observation will differ markedly from x% of the largest observation (Bland, 1997, Bruton et al., 2000).

It has been suggested (Rankin and Stokes, 1998, Chinn, 1990, Chinn, 1991) that the Intraclass Correlation Coefficient (ICC) which uses the analysis of variance (ANOVA) and Bland & Altman 95% limits of agreement should be used for reliability studies to study intra-rater (or test-retest) or inter-rater reliability. This combination provides information about both relative reliability and absolute reliability. Relative reliability is the degree to which individuals maintain their position in a sample with repeated

measurements and absolute reliability is the degree to which repeated measurements vary between individuals (Baumgarter et al., 1989).

2.5.1.2. Relative reliability

The ICC uses the mean squares from different sources of variance (ANOVA) in the equations. If the between subjects mean squares (BMS) and within subjects mean squares (WMS) is examined, a one-way ANOVA is used. When within-subjects mean squares (WMS) is divided into between-raters mean squares (RMS) and residual error components (EMS), a two-way ANOVA is used. There are six equations available (see Equations 1 to 6 below) to calculate ICC called (1,1), (2,1), (3,1), (1,k), (2,k), (3,k) according to the different study designs (Shrout and Fleiss, 1979). The first number relates to different study designs and the second number or k indicates the unit of analysis i.e. individual scores or mean scores.

In the ICC equation (1,1), each subject is assessed by a different set of randomly selected raters, and the reliability is calculated from a single measurement. This analysis uses one-way ANOVA results.

$$ICC(1,1) = \frac{BMS - WMS}{BMS + (k-1)WMS} \quad (1)$$

In the ICC equation (1,k), the calculations are performed as in equation (1), but reliability is calculated by taking an average of the k raters' measurements.

$$ICC(1,k) = \frac{BMS - WMS}{BMS} \quad (2)$$

In the ICC equation (2,1), each subject is measured by each rater, and raters are considered representative of a larger population of similar raters. Reliability is calculated from a single measurement. This analysis uses two-way ANOVA results and the variance due to the rater is included in the equation.

$$ICC(2,1) = \frac{BMS - EMS}{BMS + (k-1)EMS + k(RMS - EMS)/n} \quad (3)$$

In the ICC equation (2,k) the calculations are performed as in equation (3), but reliability is calculated by taking an average of the k raters' measurements.

$$ICC(2,k) = \frac{BMS - EMS}{BMS + (RMS - EMS)/n} \quad (4)$$

In the ICC equation (3,1), each subject is assessed by each rater, but the raters are the only raters of interest. Reliability is calculated from a single measurement. This analysis uses two-way ANOVA results but only the residual variance, not the between-raters variance, comes into the equation. This is because the between-raters variance is fixed; and it will always contribute the same amount to the within-subjects variance and does not need to be factored out.

$$ICC(3,1) = \frac{BMS - EMS}{BMS + (k+1)EMS} \quad (5)$$

In the ICC equation (3,k), the calculations are performed as in equation 5, but reliability is calculated by taking an average of the k raters' measurements.

$$ICC(3,k) = \frac{BMS - EMS}{BMS} \quad (6)$$

Equations (1,k), (2,k) and (3,k) are used when the unit of analysis is the mean measurement obtained either from more than one measurement or from more than one rater (k in this situation does not always refer to the number of raters). The reliability of the mean rating will almost always be greater than that of an individual rating.

To be able to interpret the results it is necessary to understand that an ICC of zero means no reliability and of one indicates perfect reliability. It is generally accepted that values above 0.75 represent 'excellent' reliability, values between 0.4 and 0.74 moderate to 'good' reliability and values below 0.4 represent 'poor' reliability (Fleiss, 1986). The ICC is simple to understand and calculate for any raters, data sets or mean measures and allows for fixed or random effects. However, the ICC in isolation does not give a true picture of reliability since it is just one point estimate of reliability based on one selected sample. Therefore, confidence intervals for the ICC should be reported (Rankin and Stokes, 1998). Furthermore, it can not be interpreted clinically because it gives no indication of the magnitude of disagreement between measurements.

An estimate of absolute reliability should be reported (see definition of absolute reliability in the last paragraph of the previous section), e.g., when studying repeatability: the Standard Error of Measurement and then the Smallest Real

Difference (SRD) or repeatability coefficient (Bland and Altman, 1986) and Bland & Altman 95% limits of agreement test should be presented (Eliasziw et al., 1994). A major criticism of the ICC is the influence of between-subjects variance on the ratio. If the true score variance is sufficiently large, reliability will always appear high and vice versa (Rankin and Stokes, 1998). Therefore ICC is likely to be greater in heterogeneous than in homogeneous samples. However, Bland & Altman techniques are independent of the true variability in the observations (between-subjects variation).

2.5.1.3. Absolute reliability

Bland and Altman (1986) described a series of statistical methods for assessing agreement between clinical measurements. Originally, the techniques were designed to compare two methods of measurement but can also be applied to test-retest reliability studies (Rankin and Stokes, 1998). The techniques are intended to compare two sets of measures and several stages are described allowing different ways of analysing the data:

1. First, the difference between the two measures is plotted, in a scatter plot, against the average of the two measurements. This gives visual information as to the bias and random error by examining the direction and magnitude of the scatter around the mean difference line. If all the data are consistently above or below the line, then a systematic bias exists.
2. The mean difference ($\bar{d}$) and the standard deviation of the difference (SD_{diff}) are calculated. The smaller the $\bar{d}$ and the SD_{diff} the better the agreement between the measures.
3. It is also important to estimate the 'true' value of the $\bar{d}$, which is a measure of the bias between measures and a 95% confidence interval (CI) can be calculated as:

$$CI = \bar{d} \pm 2.26(SE) \quad (7)$$

where SE means the standard error of mean and is calculated as:

$$SE = \frac{SD_{diff}}{\sqrt{n}} \quad (8)$$

where n is the number of observations. If zero does not lie within the interval it can be concluded that a bias exists between the two measures.

4. The 95% limits of agreement can be calculated as:

$$\bar{d} \pm 2SD_{diff} \quad (9)$$

The sample size should be large enough (preferably greater than 50), to allow the limits of agreement to be estimated well.

Bland & Altman techniques take longer and are more complex to interpret than a single reliability coefficient. Ideally, they require a sample set of 50 to ensure that the 95% limits of agreement are not too wide. Nevertheless, they provide useful information to complement the ICC because of a) the powerful visual representation of the degree of agreement, with easy identification of systematic bias, outliers, and any relationship between the variance in measures with the size of the mean (Rankin and Stokes, 1998), and b) the limits of agreement are in the unit of measurement giving greater clinical meaning. Because ICC and Bland & Altman techniques provide different information, both should be reported in reliability studies (Rankin and Stokes, 1998) and therefore, this is the approach followed in this Thesis.

Finally, if any measure aims to assess outcome or change, then the measure's responsiveness to change will need to be determined. This involves the concept of sensitivity to change which will be explored in the following section.

2.5.1.4. Responsiveness, sensitivity and specificity

The concepts of responsiveness or sensitivity to change, sensitivity and specificity are interrelated and there is an unresolved debate about whether they are aspects of validity (Bowling, 2002). Sensitivity has sometimes been used to refer to the characteristic of a measure being able to detect change (Wade, 1992, Jones and Agusti, 2006). It is also defined as the ability of an instrument to measure change in the state or to detect a positive result in a person who actually has a condition, regardless of whether it is relevant or meaningful to the decision maker (Jones and Agusti, 2006, Liang, 2000), i.e., is the proportion of true positives that are correctly identified by a test (Altman and Bland, 1994, Loong, 2006). Specificity is the proportion of true negatives that are correctly identified by a test (Altman and Bland, 1994, Loong, 2006). So, sensitivity and specificity are inversely related to one another. In this Thesis, responsiveness is being defined as the ability of the measure to detect change over time, e.g., any measurable changes occurring after respiratory physiotherapy interventions, sensitivity is used as the ability to detect adventitious lung sounds when

they exist (true positives) and specificity is the ability not to detect any adventitious lung sound when none exist (true negatives).

An instrument's responsiveness to change is directly related to the magnitude of change in subject scores, constituting a clinically important difference (Patten et al., 2003). The Smallest Real Difference (SRD) also known by the Repeatability Coefficient (Beckerman et al., 2001) is a measure of reproducibility (Pfennings et al., 1999) and represents the smallest change that can be interpreted as a real difference, which exceeds measurement noise and is reported in the same units of interest. This value gives a 95% range about a true change that might be expected due to measurement error, which means that 95% of the time there is confidence that any two measures taken will be within x (repeatability coefficient value) of each other. Therefore, it is expected that 95% of differences will be less than two standard deviations (Bland and Altman, 1986) and this is the definition of a repeatability coefficient adopted by the British Standards Institution (BSI, 1979).

The SRD is a linear transformation of the Standard Error of Measurement (SEM) which is the variability in measurements of the same individual, the within-subject variability (Altman and Bland, 1983, Bland and Altman, 1999, Chinn, 1990, Pfennings et al., 1999). At 95% confidence level, this interval is equal to the result value from the equation below (SEM multiplied by 1.96 is used to construct the 95% CI, $\sqrt{2}$ is used to account for the variance of two measures). Therefore, the index SRD is the smallest measurement change, that can be interpreted as real difference, i.e., beyond zero (Pfennings et al., 1999). Smaller changes to SRD index should be interpreted as measurement error and measures above will indicate a real difference in values.
The SRD is calculated as:

$$SRD = 1.96\sqrt{2}(SEM) \text{ = 2.77*SEM or WSSD} \quad (10)$$

where in reliability studies, the Within Subjects Standard Deviation (WSSD) is the same as Standard Error of Measurement (SEM) which is not the same as standard error of the mean sometimes also shortened as SEM. In this Thesis SEM has been used for Standard Error of the Measurement. The smaller the SEM or WSSD, the more reliable the measurements are. The SEM or WSSD is equal to the square root of the within subject mean square (WMS) obtained in the ANOVA table when measuring ICC.

2.5.1.5. Simplicity, interpretability and communicability

Simplicity refers to the facility with which a measure can be performed, especially if it will be used by more than one person (Wade, 1992); non-invasive techniques are generally, quicker, more convenient and acceptable for patients (Jones and Agusti, 2006).

Interpretability refers to the ease with which data generated by a measure can be understood. For a measure to be clinically useful its values must have meaning to health professionals. This includes interpretation of the value at a single point in time and change of values assessed over time (Finch et al., 2002). Some measures may be easy to perform, but more complex to analyse or interpret; some may be complex to perform yet easy to interpret.

Communicability refers to the ease with which reported results can be understood and interpreted by others (Wade, 1992, Jones and Agusti, 2006).

The most critical properties of any outcome measure are test-retest reliability, longitudinal validity/sensitivity to change and interpretability (Finch et al., 2002), because these will allow a health professional to exclude measures that would not be a strong base of information for decision making. The minimal clinically important difference and the feasibility of administration are also aspects that should be considered. The former refers to the smallest amount of measured change (effect size) that needs to occur before a clinically significant impact is noticeable. This is frequently different from the effect size that will produce a statistically meaningful difference. Feasibility of administration involves the time taken to administer the measure, and the time and difficulty the measure imposes on the person being measured (Finch et al., 2002). Finally, an ideal outcome measure should be cost-effective.

2.5.2. Outcome measures for respiratory physiotherapy - alveolar recruitment and airway clearance therapy outcome measures

In all areas of respiratory physiotherapy, one of the barriers to generating the required research evidence base has been the lack of good outcome measures. There are many doubts about the accuracy, reliability, sensitivity and validity of current measures, and their ability to reflect changes resulting from physiotherapy interventions.

Respiratory physiotherapists currently use the following outcome measures to monitor their interventions and evaluate their practice: sputum quantity, respiratory function tests, tests of gas exchange, imaging evidence, breathlessness, and standard

auscultation techniques. Most of these clinically available outcome measures are not specifically related to the physiotherapy intervention employed and may be affected by other factors (Jong et al., 2001). This means that there is no gold standard outcome measure that is specifically related to respiratory physiotherapy interventions. Most of the published respiratory physiotherapy research compares two or more active interventions rather than an active intervention versus an inactive control. In such studies it is never clear if differences are not detected because the outcome measures are not appropriate, or because the treatments being compared are equally effective/ ineffective. Although there are other more invasive or laboratory based outcome measures available, these are generally only applicable to a research setting.

The next sections provide a review of the outcome measures currently clinically available to the majority of United Kingdom physiotherapists which are related to the primary focus of this Thesis, i.e., alveolar recruitment and airway clearance techniques (some of this review has been published (Marques et al., 2006), see Appendix 1 of this Thesis).

2.5.2.1. Sputum quantity

Airway clearance implies movement and expectoration of secretions and is one of the aims of respiratory physiotherapy (Chatham et al., 2004, ACPCF, 2002). Sputum volume/weight (dry or wet) has been suggested as a convenient and useful outcome measure for reflecting the amount of secretions released from the airways (Williams et al., 2000b). Mucus is transported from the bronchial airways by mucociliary clearance, spontaneous cough or directed huffs and coughs. Subsequently it is either suctioned, expectorated or swallowed (Mortensen et al., 1991). Published studies have used sputum quantity as an outcome measure for various physiotherapy interventions (Arens et al., 1994, Olseni et al., 1994, Sutton et al., 1983, Pfleger et al., 1992).

Although sputum expectoration is relatively simple to collect and measure, it is not specific to alveolar recruitment or airway clearance, or sensitive to small differences. Its repeatability is influenced by many factors and therefore, the relevance of the measure has frequently been questioned (Braggion et al., 1995, Falk et al., 1984, Kluft et al., 1996, Mortensen et al., 1991, Oermann et al., 2001). Furthermore, sputum weight does not accurately or reliably represent sputum clearance and there is no convincing evidence that volume of sputum equates with pulmonary function (Desmond et al., 1983, Kluft et al., 1996, Thomas et al., 1995b, Williams et al., 2000a). Lack of expectoration during physiotherapy treatments does not mean that surface secretion movement is not happening, or that airway clearance has not occurred. It is very common to expectorate a few hours after a physiotherapy session, or to swallow

secretions, which means that weight of sputum expectorated during a session may seriously underestimate airways secretion clearance. Not all the mucus cleared from the lungs is expectorated (Boeck, 1984) and a significant amount may be swallowed or contaminated with saliva (Braggion et al., 1995, Falk et al., 1984, Mortensen et al., 1991, Ambrosino et al., 1995). Sputum production can therefore be both over estimated and underestimated. Therefore, even if measured very precisely, sputum quantity is considered to be an unreliable outcome measure.

2.5.2.2. Bedside respiratory function tests

If alveolar recruitment manoeuvres or airway clearance techniques are effective, then ventilation should improve, and therefore larger volumes of air should be inspired/ expired. The way that an individual inhales and exhales volumes of air as a function of time is assessed by spirometry. The typical measures are dynamic, forced vital capacity (FVC), vital capacity (VC), forced expiratory volume in one second (FEV_1) and the ratio between FEV_1 and FVC (FEV_1/FVC). Measures of maximum expiratory flow over the middle 50% of vital capacity, inspiratory capacity, and forced maximal flow during expiration or inspiration (peak expiratory or inspiratory flow) or as a function of volume (flow-volume curves), can also be made (ATS/ERS, 2002, Miller et al., 2005b, Pierce et al., 2005). Definitions are presented by Miller et al. (2005a, , 2005b). In order to have clinical utility, the dynamic lung volumes and maximum flows of any individual need to be compared with predicted values (Pierce et al., 2005), using the same reference source, anthropometric and demographic data (e.g. gender, age, height, weight) and ethnic characteristics (Harik-Khan et al., 2001).

2.5.2.2.1. Spirometry

The basic parameters used to interpret lung function are FEV_1, FVC or VC, FEV_1/FVC and also Total Lung Capacity (TLC). The assumption that the decrease of these parameters, below their relevant 5th percentiles is consistent with pulmonary problems is a useful and simple approach in clinical practice (Pellegrino et al., 2005). The flow-volume graph also provides important information to clinical practice, especially during the first second of the FVC manoeuvre. Maximal flow-volume curves are easily performed, widely available and economical. However, the inter-subject variability with FVC is greater than during VC measures.

Spirometry has been described as a cost-effective, simple, reliable, valid, bedside measure and easy to interpret (Miller et al., 2005b) when used to give evidence about specific lung function or indirect information about respiratory muscle performance (Pierce et al., 2005), and a sensitive marker of respiratory disease (Gappa, 2004). Evaluation of an individual's change in lung function following an intervention or over

time is often more clinically valuable than a single comparison with external reference (predicted) values. Spirometry based on the FVC manoeuvre is employed routinely in CF and Br patients. These diseases are characterised by both long-term and short-term fluctuations in lung function, which are related to the severity of disease, chronic bacterial infection and periodic pulmonary exacerbations (Rosenbluth et al., 2004, Braggion et al., 1995). Pulmonary function testing is frequently done in long-term management of these patients and results often affect clinical decision-making (Tauber et al., 2002).

For tracking change, FEV_1 , which has been found to be the best independent predictor of survival in CF (Espiritu et al., 2003), has the advantage of being the most repeatable lung function parameter and one that measures changes in both obstructive and restrictive types of lung disease (Pellegrino et al., 2005), being the typical primary outcome measure (Abbott and Hart, 2005). While the FEV_1 is an excellent marker of respiratory impairment at any one moment in time, the % FEV_1 at any one time is a poor prognostic marker of disease severity (Rosenbluth et al., 2004). Moreover, FEV_1 does not distinguish between the effects of chronic inflammation and acute infection on pulmonary function (Rosenbluth et al., 2004). This leads to a certain amount of uncertainty about how to use the FEV_1, e.g., as a basis for transplantation referral, or how best to predict the future course of the disease in general (Rosenbluth et al., 2004) and there have been no documented reports of improvement in FEV_1 following pulmonary rehabilitation when provided to patients with stable lung disease (CSP, 2003).

Stanbrook et al. (2004) studied the repeatability of the forced expiratory volume measurements in 21 adults with CF in a single cohort study repeating the measurements three times per day, daily, during nine consecutive days. They concluded that a new FEV_1 value that changes by at least 13% of predicted, relative to a measurement made several days previously, is likely to represent a true change in clinical status; and measurements made within the same day that differ by an absolute amount of at least 10% of predicted are likely to indicate a true clinical change, but, this needs confirmation by other studies.

However, it has been suggested that spirometry is inadequate for assessing the effectiveness of therapeutic interventions (Jones and Agusti, 2006). Lung function has been found to correlate poorly with breathlessness and other symptoms (Nishimura et al., 2002), to be inadequate to describe the impact of a disease (Jones and Agusti, 2006, Ramsey and Boat, 1994) and to be a poor prognostic marker of disease severity

(Pellegrino et al., 2005, Rosenbluth et al., 2004). In some studies, interventions have been shown to improve both exercise capacity and quality of life, with no detectable change in lung function (Bradley et al., 2001). Furthermore, the accuracy, selectivity and sensitivity of spirometry depends on many factors which are difficult to control: volume or flow transducer characteristics, use of an in-line filter, recorder, display or processor and also on individual factors, e.g., the co-operation of the patient, relationship between the patient and the technician (Miller et al., 2005b). Generally, measurements are highly dependent on patients' initial effort and motivation (Hughes and Pride, 2003). This makes them unsuitable for patients who are unwilling or unable to co-operate, or who have any pain or discomfort; such conditions pertain in a large proportion of patients requiring respiratory therapy.

Nevertheless, spirometry is widely used by respiratory physiotherapists for a range of screening, assessment and monitoring purposes (Pierce et al., 2005). Numerous short-term studies comparing different respiratory physiotherapy interventions have been unable to detect differences between treatments when using spirometry as an outcome measure, despite an increase in sputum production and changes in sputum viscoelasticity (App et al., 1998, Bellone et al., 2000, Braggion et al., 1995, Tyrell et al., 1986, White et al., 1997, Arens et al., 1994). However, in more intensive studies involving several treatment sessions each day over a period of a week or more (Homnick et al., 1998, Newton and Bevans, 1978, Cerny, 1989) and in long-term studies, around one year (McIlwaine et al., 1997, McIlwaine et al., 2001), spirometry was able to detect significant differences between physiotherapy interventions. Therefore, it is suggested that while spirometry lacks sufficient sensitivity to be used as a clinical outcome measure for assessing and monitoring respiratory physiotherapy treatments on a daily basis, it may be more useful for longer term evaluations in co-operative patients.

2.5.2.3. Tests of gas exchange

This section reviews the main two methods of assessing gas exchange: blood gas analysis which is invasive, and non-invasive oxygen saturation measurements.

2.5.2.3.1. Blood gas analysis

If ventilation improves or sputum is removed from the lungs, it would be logical to expect that oxygenation would also show improvement. Arterial blood gas analysis is the 'gold standard' test for assessment of arterial gases, i.e., oxygen and carbon dioxide. It is sensitive, specific, reliable, relevant, repeatable and easy to interpret. However, arterial blood gases are obtained invasively and the procedure is not always easily or simply performed (Ramsey and Boat, 1994). The test results reveal

information about oxygen partial pressure (PaO_2), carbon dioxide partial pressure ($PaCO_2$) and hydrogen ion activity (pH) in arterial blood, as well as calculated indices of bicarbonate concentration, base excess and oxygen saturation. Abnormal blood gases will occur as a result of many different pathological or disruptive processes, and so they are neither sensitive nor specific (ATS/ERS, 2002). They provide data for one specific moment in time, but are not usually used on a daily basis to monitor physiotherapy interventions (except for patients receiving intensive care), because of the invasive nature of the sampling process. There is only a weak association between arterial blood gases and ability to perform normal daily activity (Balfour-Lynn et al., 1998). Furthermore, research studies that have used arterial blood gases as an outcome measure for airway clearance or alveolar recruitment manoeuvres have not detected significant differences between different respiratory physiotherapy interventions (May and Munt, 1979, Mohsenifar et al., 1985).

2.5.2.3.2. Non-invasive oxygen saturation

Oxygen saturation can be assessed indirectly and non-invasively using pulse oximeters. The pulse oximeter obtains oxygen saturation values based on Beer's law. According to this law of physical chemistry the concentration of a solute in a solvent can be determined spectrographically by its light absorption (Hakemi and Bender, 2005). Pulse oximeters use a light sensor with two sources of light, red light at 660nm wavelength, which is absorbed 10 times more by deoxygenated haemoglobin and infrared light at 940nm wavelength, which is absorbed by oxygenated haemoglobin (Hakemi and Bender, 2005). The pulse oximeter senses the comparative absorption of red and infrared light, and complex signal processing is used to estimate the arterial oxygen saturation (Fluck et al., 2003, Kamat, 2002).

Pulse oximetry is simple to perform, is relevant and can be measured over time (Ramsey and Boat, 1994). It avoids technical and ethical concerns associated with arterial sampling for blood oxygen level determination (Balfour-Lynn et al., 1998, Dakin et al., 2003, Ramsey and Boat, 1994). However, the specificity, reliability and sensitivity levels of this outcome measure are variable. Pulse oximeters are unable to detect saturations below 83% with an acceptable degree of accuracy and precision and the measures obtained are influenced by factors, such as: arterial blood flow, temperature of the area where the oximetry sensor is located, fluorescent or direct sunlight, jaundice, discolouration of the nail bed, nail polish, bruising under the nail, motion artefact, intravascular dyes, and skin pigmentation (AARC, 1991, Hakemi and Bender, 2005, Schutz, 2001). Pulse oximeters are also unable to differentiate between oxygen and carbon monoxide, the presence of the latter bound to haemoglobin increases

registered oxygen saturation values (Schutz, 2001), so oximeters should not be used in patients who smoke tobacco (Hakemi and Bender, 2005).

Healthy subjects have oxygen saturation values around 97% to 99%, with 95% being clinically accepted as 'normal'. Oxygen saturation calculated by a pulse oximeter has a 95% confidence interval of ± 4% (Hakemi and Bender, 2005) which is deemed sufficiently accurate for most clinical situations (ATS, 1999b), but is insufficiently precise for research. In the oxyhemoglobin dissociation curve, an oxygen saturation of 90% is related with PaO_2 of 60 mmHg or 7.98 kPa (Schutz, 2001). Oxygen saturation does not reflect the ability to ventilate but decreased saturation correlates with advanced lung disease, substantially impaired pulmonary function and daily activities (Ramsey and Boat, 1994). Oxygen saturations are frequently measured during studies of respiratory physiotherapy interventions, but more often for monitoring purposes than as a primary outcome measure.

Respiratory physiotherapists need to know if patients develop clinically significant hypoxemia during airway clearance therapy. However, studies measuring oxygen saturation to assess physiotherapy treatments have not reported any significant differences between the interventions (Bellone et al., 2000, Hofmeyr et al., 1986, Newton and Bevans, 1978, Scherer et al., 1998, White et al., 1997). Measures of gas exchange have many of the qualities required of an ideal outcome measure, but their low sensitivity and specificity makes them less useful for assessing the effects of physiotherapy interventions.

2.5.2.4. Imaging

Respiratory conditions have been assessed by a large number of technological means such as chest radiographs, computerized tomography and magnetic resonance imaging. Chest radiographs provide a clear picture of the extent and severity of disease at a specific time, can evaluate the length, position and movement of the diaphragm and indirectly estimate lung volumes (Hughes and Pride, 2003, ATS/ERS, 2002). However, sometimes it may take one or two days to detect abnormalities that other clinical measures have already detected (Pryor and Prasad, 2008 pp. 21-23) since imaging tends to be more sensitive to advanced lung disease and relatively insensitive to early changes in airways (Ramsey and Boat, 1994). Although chest radiography is reliable, relevant, relatively simple to perform, commonly used for investigation and requires minimum cooperation (Ramsey and Boat, 1994), detailed interpretation of the resultant film is relatively complicated and subjective (Gatt et al., 2003). Nevertheless, comparisons with previous radiographs provide a measure of improvement or deterioration over time, and response to treatment.

Radiologists are able to provide physiotherapists and other clinicians with reports detailing any abnormalities detected, but such reports may not be immediately available. In addition, radiograph evaluation entails subjectivity, variability, and uncertainty even when performed by experienced radiologists (Herman and Hessel, 1975, Young and Marrie, 1994), and it has been found that the chest radiograph is the most common type of radiograph to be misinterpreted by observers (Albaum et al., 1996, Robinson et al., 1999). In some situations chest radiographs may suggest more extensive disease, in others they may underestimate the pathology present (Pryor and Prasad, 2008 pp. 21-23). Furthermore, the inherent risks associated with exposure to radiation mean that it would not be appropriate to recommend routine before-and-after radiographs specifically to assess the effects of physiotherapy.

For assessment of chest radiographic images there are various objective scoring systems for specific pathologies, e.g., the Brasfield score for CF (Brasfield et al., 1979) and recent attempts have been made to computerise analysis (Kakeda et al., 2004). However, no method has yet been universally accepted. In several studies including chest radiographs as an outcome measure to assess the effects of respiratory physiotherapy, no detectable differences were shown between interventions (Desmond et al., 1983, Falk et al., 1984, McIlwaine et al., 1997, McIlwaine et al., 2001, Tyrell et al., 1986). Other imaging techniques are available, but are no more practical for the assessment of routine physiotherapy.

2.5.2.5. Breathlessness (Dyspnoea)

Dyspnoea which is the clinical term for breathlessness or shortness of breath, is taken from the Greek word ‘dys’ meaning painful, difficult, or disordered and ‘pnoea’ meaning breathing (Rao and Gray, 2003). It is a subjective sensation, not necessarily related to respiratory rate or physical findings (ATS, 1999b), and may not reflect any underlying pathology or the level of airway obstruction (Scano et al., 2005). Nevertheless, breathlessness or dyspnoea is frequently used as an outcome measure for respiratory therapies.

Two general forms of dyspnoea assessment can be performed, rating exertional breathlessness during a specific task or rating the overall level of breathlessness during daily activities (Mador et al., 1995). Exertional breathlessness during a specific task is commonly quantified using one of two scales; the Borg scale (Borg, 1998a) and a Visual Analogue Scale (VAS). When comparing the two scales, the VAS was found to have slightly higher sensitivity and the Borg scale was found to have slightly higher repeatability (Wilson and Jones, 1989, Muza et al., 1990). Both scales have been

shown to be highly reproducible in the short term (Muza et al., 1990, Wilson and Jones, 1989, Silverman et al., 1988) and are good measures of perceptions of breathlessness during exercise in a laboratory setting, but not much is known about their responsiveness to change following any kind of intervention (Mador et al., 1995, Meek and Lareau, 2003).

The VAS does not vary systematically over time. Good levels of test retest reliability (Mador and Kufel, 1992) and construct validity (Gift, 1989) have been demonstrated. However, during sub-maximal exercise the intra-subject week-to-week variability of this measure has been reported to be wide (Mador and Kufel, 1992). A common problem of this scale is the difficulty in seeing the line and anchors, as well as forgetting how the scale is oriented. Furthermore, long term studies have found low/poor repeatability of this scale when measuring breathlessness (Adams et al., 1985, Jones et al., 1984).

The most commonly employed measure to assess breathlessness is the Borg scale (and its various modifications), first created in 1970 (Borg, 1998a); even though it was initially designed to measure the effects of perceived exertion rather than breathlessness *per se*. Despite the care that must be taken to provide consistent, specific instructions when using the scale (because subjects have been asked to rate 'severity of breathlessness', 'need to breathe' and 'effort of breathing'), extensive reports demonstrate the reliability and validity for Borg ratings of breathlessness (ATS, 1999b, Silverman et al., 1988) even during long time periods (Wilson and Jones, 1991). The Borg scale and its subsequent revisions (Borg, 1998a) have proven to be very useful clinically, as they correlate well with various physiologic parameters (McGrath et al., 2005) and are the preferred method to assess intensity of activity among those individuals who take medications that affect heart rate, pulse or respiratory system (Borg, 1998a). The Borg scale uses simple, descriptive, adjectives such as slight, moderate, and severe which are presented with numbers from 6-20 (original version) or 0-10 (Modified Borg Scale) (AACVPR, 2004).

Breathlessness measures which rate overall level of breathlessness during daily activities are different types of questionnaires and indexes: Baseline Dyspnea Index/Transitional Dyspnea Index (Mahler et al., 1984), University at California at San Diego Shortness of Breath Questionnaire (Eakin et al., 1998), Modified Medical Research Council Questionnaire (Fletcher, 1952, Fletcher et al., 1959), Dyspnea Domain of the CRQ (Weaver and Narsavage, 1992), Dyspnea components of the Pulmonary Functional Status Scale (PFSS) (Weaver and Narsavage, 1992) and Modified Pulmonary Functional Status and Dyspnoea Questionnaire (PFSDQ-M)

(Lareau et al., 1994, Lareau et al., 1998). Most of these are not frequently used by respiratory physiotherapists, because they tend to be long, and therefore time-consuming, complex to administer and difficult to score.

Assessment of breathlessness represents a useful role in the clinic and in respiratory physiotherapy but there are recognised limits associated with the assessment process (ATS, 1999a). Furthermore, the validity of such scales is difficult to assess because they are subjective and thus dependent on the accuracy of patient report. However, measures of breathlessness are useful outcome measures since reflect the patient perspective and respiratory physiotherapy can decrease dyspnoea through a variety of strategies.

Studies using a Borg scale or VAS as an outcome measure to assess airway clearance therapy before and after respiratory physiotherapy interventions (Elkins et al., 2005b, Thompson et al., 2002) or comparing interventions (McCarren and Alison, 2006) have been unable to detect any significant change in breathlessness. Only Ambrosino et al. (1995) in a short-term study have reported a significant decrease of breathlessness with airway clearance therapy treatments. However, breathlessness is a generic outcome measure influenced by many other factors and therefore, not specific to the physiotherapy treatment. Nevertheless, it should be considered since breathlessness is a very important symptom from the patient's perspective.

2.5.2.6. Auscultation

Standard auscultation via a stethoscope is an assessment tool used by many health professionals during chest examination in their clinical practice (Chen et al., 1998, Gross et al., 2000, Melbye, 2001, Pryor and Prasad, 2008 pp. 13-16) and is often used to monitor respiratory physiotherapy interventions. It provides information about the structure and function of the lung that cannot be obtained with any other simple and non-invasive method (Forgacs, 1978). Several pathological changes in the lungs produce characteristic sounds that can be detected more readily by auscultation than by radiography, e.g., pneumonia (Gross et al., 2000). Standard stethoscopes are widely available and easy to use (Loudon, 1982).

However, the literature has contradictory arguments about the value of standard auscultation in routine current practice. Some authors (Piirila and Sovijarvi, 1995, Sovijarvi et al., 2000d, Welsby and Earis, 2001) argue that auscultation is an inappropriate outcome measure because of the many differences in health professionals' personalities, hearing properties as well as in the stethoscopes. There can also be different approaches to the description of auscultatory findings,

nomenclature difficulties/semantic problems, clinical routines and inter and intra observer variability (Loudon and Murphy, 1984, Piirila and Sovijarvi, 1995). Inadequate understanding of the basic mechanisms of production of the sounds and the lack of adequate studies of clinical and physiologic correlations of the sounds themselves (Loudon and Murphy, 1984, Pasterkamp et al., 1987a, Piirila and Sovijarvi, 1995), have been aspects added to the list of problems when using auscultation. Others have argued that auscultation is an easy, rapid, effective, non-invasive, and cost-effective way of assessing the condition of the airway and breathing (Chen et al., 1998) and that despite the limitations, with appropriate training, acoustic stethoscopes should still be used (Adolph, 1998, Murphy, 2008, Weitz and Mangione, 2000).

The sound heard through a stethoscope depends on three main factors: sound present at the chest wall, perception of sound by the human ear and the acoustics of the stethoscope itself (Welsby and Earis, 2001). Therefore, standard auscultation is a subjective process that depends on the hearing experience and the ability to differentiate between different sound patterns (Sovijarvi et al., 2000d). This subjectivity has been demonstrated by research exploring the reliability to detect and describe adventitious lung sounds as discussed below.

Physiotherapists' inter-observer reliability (Aweida and Kelsey, 1990, Brooks and Thomas, 1995, Brooks et al., 1993b, Brooks et al., 1993a), intra-observer reliability (Allingame et al., 1995) and inter-group reliability (Allingame et al., 1995) when detecting adventitious lung sounds from tape-recordings were found to be 'poor' to 'fair'. Physicians' inter and intra-observer reliability when detecting added lungs sounds using a standard stethoscope was also found to be 'poor' to 'moderate' in an asthmatic population of 102 infants (Elphick et al., 2004), but 'good' in 200 people with asbestosis (Shirai et al., 1981). There was wide-ranging inter and intra-observer variability measured by kappa statistics, among different health professionals (40 people: 10 nurses, 10 residents, 10 physicians and 10 physiotherapists) when detecting wheezes in asthmatic patients via computer analysis versus audio files (Pasterkamp et al., 1987b), or versus standard auscultation (Levy et al., 2004) and clinical experience was not found to have any clear effect on the accuracy or reliability of the agreement detecting the adventitious lung sounds (Allingame, 1995, Brooks and Thomas, 1995, Brooks et al., 1993b, Mangione and Nieman, 1999). Although good agreement (amongst five physicians) has been found when detecting the presence of coarse, medium or fine crackles from an audio file, the number of undetected crackles was significant (Kiyokawa et al., 2001). All these studies can be criticised for various reasons: i) the added lung sounds came from tape-recorded lung sounds, which suffer

from interference that increases the difficulties of detecting the adventitious lung sounds (Allingame et al., 1995, Brooks and Thomas, 1995, Brooks et al., 1993b, Brooks et al., 1993a); ii) the crackles used in the audio files for detection were synthesised and not real crackles (Kiyokawa et al., 2001); and iii) the recordings were performed in quiet rooms (Elphick et al., 2004, Levy et al., 2004, Pasterkamp et al., 1987b) or in sound proofed rooms (Kiyokawa et al., 2001), and not in clinical settings; iv) the recordings or auscultation were only performed in one specific chest location, e.g., basal areas (Shirai et al., 1981). Furthermore, there are great difficulties and variations in the description of auscultatory findings. In lung auscultation, the agreement on nomenclature is better when there is only a question of the presence or absence of abnormal sounds. The agreement is poorer the more characteristics have to be taken into account, such as grading or timing sounds (Piirila and Sovijarvi, 1995). Therefore, there seems to be a consensus that the inter and intra-observer reliability of the detection of adventitious lung sounds among health professionals using tape-recorders, audio-files or standard auscultation is generally poor. This has important implications for its use as a diagnostic tool for lung disorders and confirms that it cannot be used as a gold standard (Elphick et al., 2004).

Although the use of a standard stethoscope is too subjective to provide a useful outcome measure, the sounds generated from the lungs have the potential to provide useful information as they relate directly to movement of air and secretions. Breath intensity decreases with induced bronchial narrowing (Pasterkamp et al., 1997a) and it is known that changes of lung sounds are due to several factors, e.g., when air or fluid collects in the pleural space (Chen et al., 1998) or in the presence of secretions. It is therefore, hypothesised that lung sounds recorded directly from a microphone, and their detailed analysis, could provide a potential outcome measure to detect changes in the airways.

2.6. Summary

Chapter 2 has provided an overview of the outcome measures used clinically by respiratory physiotherapists and addressed the problem of the lack of good outcome measures that are specifically related to the interventions employed (for example alveolar recruitment or airway clearance techniques) by these health professionals. The main problem with existing outcome measures is that many of these are non-specific, i.e., they will be affected by other factors beyond the therapeutic intervention. Therefore, when assessing the effectiveness of interventions, it is never clear if a lack of significant effect is found as a result of ineffective treatment, or from the use of an inappropriate outcome measure. It is clear that there is an urgent need to increase the

accuracy, reliability, and sensitivity of the outcome measures employed, or to develop new measures to assess the effectiveness of respiratory physiotherapy. In the next chapter, further details about lung sounds and their analysis will be provided.

Chapter 3

Lung sounds and computer aided lung sound analysis

3.1. Introduction

This chapter will address the proposed new outcome measure: computer aided lung sound analysis (CALSA). For better understanding of this section, it was considered relevant to explore the principles and different types of lung sounds. Therefore, a section about lung sounds will be presented containing the characterisation of normal, abnormal and adventitious lung sounds. CALSA will then be addressed, finishing with some explanations of how lung sounds can be recorded and analysed.

Recent guidelines for research and clinical practice in the field have been published by the Computerized Respiratory Sound Analysis (CORSA) project group in an European Review (Sovijarvi et al., 2000c). This report standardises instrumentation, ways of acquiring data, procedures and signal processing techniques as well as the lung sounds' nomenclature. Therefore, in this Thesis, CORSA guidelines and nomenclature will be followed.

3.2. Normal lung sounds

This section introduces some basic concepts/principles related to lung sounds (key concepts are also defined in Appendix 2 of this Thesis) and characterises normal, abnormal and adventitious lung sounds.

All sounds can be described using frequency, amplitude, starting phase and duration. Frequency, which refers to the fundamental frequency, is the number of complete cycles per second, measured in Hz, and amplitude is the degree of displacement of air molecules. Frequency and amplitude are perceived by human beings as pitch and loudness, respectively. The sounds that are heard from the lungs are complex and their origin is still not entirely clear (Kiyokawa and Pasterkamp, 2002). However, it is thought that normal lung sounds are a product of turbulent airflow, which arises as a result of the geometry of the bronchial tree. This geometry is the combination of successive generations of bronchi which bifurcate into smaller daughter bronchi, and consequently affect flow and the lung sounds. It begins in the trachea (generation n=0), which bifurcates into two main bronchi (n=1), each of which bifurcates into another two bronchi (n=2), successively repeating this scheme to arrive finally in the alveoli, where

the exchange of gases takes place. The total number of generations is usually 23 (Faistauer et al., 2005).

The degree and characteristics of turbulence depend on the dimensions of the conducting airways and the velocity of the airflow. The larger and medium airways (i.e. trachea and proximal bronchi) produce high velocity air flow, which consequently generates turbulence and hence breath sounds. In contrast, because the ratio of smaller:larger airways is so large in smaller airways and alveoli, the airflow has less velocity and hence the flow is laminar and silent. Lung sounds also change from individual to individual because airway dimensions are a function of body height (Dalmay et al., 1995). Therefore body size, age, and gender will all affect breath sounds (Pasterkamp et al., 1997a).

Sounds heard at the chest wall surface are generated within the lungs and modified by the transmission characteristics of the lung and chest wall (Welsby and Earis, 2001, Welsby et al., 2003). They differ according to the location at which they are heard and/or recorded and vary with the respiratory cycle (Sovijarvi et al., 2000b). The origin of expiratory sounds is more central than inspiratory sounds (Kiyokawa and Pasterkamp, 2002). The sounds from the proximal airways are attenuated by three components of substantially different acoustic qualities: solid tissue, airways and lung parenchyma, which act as a low pass filter, with a cut off frequency of approximately 300 Hz. Lung sounds are normally classified into three frequency bands: low (100 to 300 Hz), middle (300 to 600 Hz) and high (600 to 1200 Hz). The heart and muscle sounds are in the range of the lower frequencies <100Hz (Pasterkamp et al., 1997a), but both may contain frequency components up to 2kHz.

Higher frequency sounds do not spread as diffusely or retain as much amplitude across the chest wall as do lower frequencies (Welsby et al., 2003). Therefore, when lung tissue is consolidated, there is an increase of transmission of the higher frequencies of the central airway to the chest wall, because the filtering effect is reduced. There is also absorption of low frequencies and so, globally, less masking of the higher frequency sounds. High frequency sounds are known to travel further within the airway-branching structure, while low-frequency sounds propagate predominantly through the large airways via wall motion (Kompis et al., 2001). When recorded over the trachea, sound is not filtered and therefore the frequency spectrum contains frequency components as high as 1200 Hz. Kiyokama and Pasterkamp (2002) found that an increase in distending pressure, and hence volume, tends to decrease the amplitude of sound transmitted through the lungs. It is important to understand that frequency is

dependent on volume, which influences the transmission of lung sounds, but that normal lung sound generation is more related to airflow than lung volume, due to turbulence.

3.3. Abnormal lung sounds

3.3.1. Bronchial sounds

Breath sounds may be abnormal in certain pathological conditions of the airway or lungs. Normal breath sounds can be classified as ‘abnormal’ if heard at inappropriate locations. For example ’bronchial breathing’ involving a prolonged and loud expiratory phase with frequency components up to 600-1000 Hz (Sovijarvi et al., 2000b) is normal if heard over the trachea, but abnormal if heard at the lung periphery. This would be typically heard in the presence of lung consolidation.

3.3.2. Adventitious lung sounds

There are also added lung sounds (known as adventitious sounds) which can be continuous (wheezes) and discontinuous (crackles). The conditions for adventitious respiratory sounds may change from breath to breath in the presence of airway secretions. The presence of adventitious lung sounds is believed to indicate a pulmonary disorder (Sovijarvi et al., 2000a). Other added sounds, such as pleural rub will not be discussed in this Thesis, since they are unlikely to be affected by physiotherapy interventions.

3.3.2.1. Crackles

Crackles are discontinuous adventitious sounds. They are intermittent, non-musical and brief sounds thought to be caused by the sudden opening of abnormally closed airways (Nath and Capel, 1974, Forgacs, 1978). The first recordings of crackles were presented in the 1970s, when Forgacs theorised that pulmonary crackles were generated during inspiration as a result of sudden opening of the airways (Forgacs, 1978). Despite decades of subsequent research this theory has never been refuted. Currently, a crackle sound is believed to originate from the acoustic energy generated by pressure equalization, change in elastic stress after a sudden opening or closing of airways (Piirila and Sovijarvi, 1995, Sovijarvi et al., 2000b), or when there is inflammation or oedema in the lungs (Kiyokawa et al., 2001). The number of crackles generated depends more on inspired volume of air than on airflow rate.

Crackles are explosive and transient sounds and their frequency depends on the diameter of the airways, which is related to the pathophysiology of the surrounding

tissue. Their duration is less than 20 ms, and their frequency typically is wide, ranging from 100 to 2000 Hz (Sovijarvi et al., 2000b). This short duration and often low intensity, makes the discrimination and characterisation by standard auscultation difficult, and their detection becomes even more difficult when other breath sounds have greater intensity. Crackles may change or disappear during auscultation or during pulmonary function tests, possibly due to the effect of lung expansion (Kiyokawa et al., 2001).

The appearance of crackles may be an early sign of respiratory disease (Sovijarvi et al., 2000b) and their timing within the respiratory cycle allows direct estimation of the sound origin (Kompis et al., 2001). Smaller airways have been shown to produce late inspiratory crackles of shorter duration, high frequency crackles (fine crackles) with less than 10 ms of duration and are normally associated with restrictive pulmonary diseases. So, early inspiratory/expiratory, low frequency crackles (coarse crackles) with more than 10 ms of duration, are probably generated in larger, more proximal airways (trachea and main bronchi) and are associated with obstructive pulmonary disease. Expiratory crackles are usually much less frequent. Furthermore, as disease progresses, crackles tend to occur first in the basal areas and later in the upper zones of the lungs. Therefore, the timing of crackles in the respiratory cycle must be characterised in any analysis.

There are many other characteristics of crackles that may have a clinical significance in respiratory disorders (Kiyokawa et al., 2001). These include frequency, waveform (fine crackles may be more easily recognized than coarse crackles because their waveforms differ more clearly from those of normal breath sounds), alteration with posture/ gravity influence and change with physiotherapy manoeuvres or spontaneous cough. The number and distribution of crackles per breath should also be considered since they are associated with the process and severity of the disease in patients with interstitial lung disorders (Piirila and Sovijarvi, 1995, Sovijarvi et al., 2000b), pneumonia (Murphy et al., 2004, Piirila, 1992) and have different features between diseases, e.g., COPD, fibrosis alveolitis, Br, heart failure (Piirila et al., 1991), asbestosis (Shirai et al., 1981, Urquhart et al., 1981), pulmonary oedema (Urquhart et al., 1981), pneumonia, heart failure, asthma, COPD and interstitial pulmonary fibrosis (Murphy, 2008). Standard auscultation would be unable to assess all these parameters, but CALSA has the potential to identify patterns objectively.

3.3.2.2. Wheezes

Wheezes are continuous adventitious lung sounds. The normal wave form for breath sounds is replaced by continuous sinusoidal deflections (Murphy et al. 1977) produced

by fluttering of the airways. The mechanisms underlying their production appear to involve an interaction between the airway wall and the gas moving through the airway (Meslier et al., 1995). These oscillations start when the airflow velocity reaches a critical value, called flutter velocity, due to narrowed airways (Beck and Gavriely, 1990, Meslier et al., 1995, Sovijarvi et al., 2000b). The flutter mechanisms mainly explain expiratory wheezes, but inspiratory wheezes, which are normally associated with more severe airway obstruction and with upper airways obstruction, are not yet well explained and understood (Meslier et al., 1995). Normally, wheezes do not appear after the 7^{th} generation of the airways due to insufficient flow velocity. Wheezes are accompanied by flow limitation, but flow limitation is not necessarily accompanied by wheezes (Sovijarvi et al., 2000b). They can therefore be produced by all the mechanisms that reduce airway calibre such as: bronchospasm, mucosal oedema, intraluminal tumour or secretions, foreign bodies, or external compression (Meslier et al., 1995). The frequency of a wheeze is dependent on the mass and elasticity of the airway walls and on the flow velocity, and it is not influenced by the length or the size of the airway (Meslier et al., 1995). The dominant frequency of a wheeze range between 80-100 Hz to 500 Hz and the duration is longer than 100 ms (Sovijarvi et al., 2000b).

Wheezes, which are usually louder than the underlying breath sounds, are often audible at the patient's mouth or by auscultation over the larynx. In some patients, they may be audible at some distance from the patient (Meslier et al., 1995). They are clinically defined as more or less musical sounds and can be characterised by: frequency (mono or polyphonic); intensity; number/duration in the respiratory cycle (bronchial obstruction is directly related to the proportion of the respiratory cycle occupied by wheezing (Sovijarvi et al., 2000b)); relationship to the location and phase of respiration (Meslier et al., 1995); the presence of wheezes in both inspiratory and expiratory phases of the breathing cycle, indicates a more serious obstruction stage than their presence only in expiration; how they change with position (gravity influence) and physiotherapy manoeuvres. Wheezes are typical of bronchitis, bronchial asthma and diffuse lobular emphysema (Chowdhury and Majumder, 1982) and their number per respiratory cycle, using lung sound analysis, has been reported to be a good indicator of obstruction (Baughman and Loudon, 1985, Oud et al., 2000).

Wheezes have been charaterised as fixed monophonic, random monophonic, sequential inspiratory or expiratory polyphonic (Yi, 2004). Fixed monophonic wheezes imply hearing only one frequency, and are usually indicative of an incomplete occlusion of the bronchus (e.g., tumour). Random monophonic wheezes occur when there is widespread airflow obstruction (e.g., asthma). This specific kind of wheeze occurs

randomly across the breathing cycles, during inspiration or expiration, and is usually a result of bronchial spasm or swelling of the mucous membrane. Sequential inspiratory wheezes are typically generated when peripheral airways open and oscillate, late in inspiration. They are characterised as sequences of short, monophonic wheezes, each with a different pitch and sound intensity. Pulmonary diseases associated with sequential inspiratory wheezes include fibrosing alveolitis, asbestosis and other diffuse interstitial pulmonary diseases (Yi, 2004). Expiratory polyphonic wheezes are produced by the passage of air through many obstructed bronchial airways simultaneously (Sovijarvi et al., 2000b), creating several harmonic unrelated musical sounds and are associated with chronic obstructive bronchitis (Yi, 2004).

3.3.2.3. Squawks, Rhonchi and Stridor

Squawks and rhonchi can be considered to be a sub-group of wheezes but they have some specific characteristics. A squawk is a high frequency wheeze due to airway wall oscillation as airways open, and are mainly inspiratory. Normally their duration is between 90-320 ms (Piirila and Sovijarvi, 1995, Murphy, 2008) and rarely exceeds 400 ms (Sovijarvi et al., 2000a). The term ‘squawk’ should only be used to describe inspiratory short wheezes in patients with interstitial lung diseases that involve small airways or they should be called simply ‘short wheezes’.

Rhonchi or snores are described as continuous snoring or gurgling sounds, generally less musical than wheezes and with quite low frequency. They are mainly inspiratory due to airway obstruction, commonly heard during obstructive sleep apnoea syndrome and in cardiovascular diseases (Young et al., 1993, Meslier et al., 1990), with an intensity higher than 50 dB and a fundamental frequency between 30 and 250 Hz (Gavriely and Jensen, 1993, Meslier et al., 1990). The gurgling could be due to oscillation/flapping of secretions, or a periodic blocking/unblocking of the airway as secretions move, rather than the vibration of the walls. Clearly, there are two main ways that the airway can be blocked: oedema or excessive secretions. Some health professionals feel the sounds generated by each are different and give them different names, while others use the term, wheeze, for all.

Stridor is a very loud wheeze, resulting from a morphologic or dynamic obstruction in the larynx or trachea (Sovijarvi et al., 2000a). It occurs during inspiration when the obstruction is extrathoracic, and during expiration when it is intrathoracic, unless the obstruction is fixed, in which case, stridor may appear in both phases of respiration (Meslier et al., 1995, Sovijarvi et al., 2000a). In adults, the frequency of the stridor is usually less than 200 Hz (Charbonneau et al., 2000) and it is common in infants and

babies because of the small airway dimensions or supraglottic inflammation (laryngitis) (Sovijarvi et al., 2000a).

The reader will now be introduced to CALSA and its potential as an outcome measure for respiratory physiotherapy, which is designed to overcome the inherent problems of standard auscultation techniques, by removing the subjective component and allowing the quantification and respective analysis of lung sounds.

3.4. Computer aided lung sound analysis as a potential outcome measure

There is a great deal of information derivable from lung sounds which is not normally readily accessible even to experienced clinicians. At a single anatomical site a clinician can potentially make several observations: presence or absence of adventitious sounds, character, timing, location, and duration of adventitious sounds, duration of the inspiratory and expiratory phases. A clinician listening at ten sites has therefore at least sixty possible sets of recordable data, which exceeds the memory capacity of most people. Lung sounds interpretation is enhanced using CALSA through the efficient objective data collection and management, generation of permanent records of the measurements made with easy retrievability and through graphical representations that help with diagnosis and management of patients' suffering from chest diseases (Earis and Cheetham, 2000a, Earis and Cheetham, 2000b, Murphy, 2008, Sovijarvi et al., 2000a, Sovijarvi et al., 2000b, Murphy et al., 2004).

There is some evidence in the literature to support the hypothesis that CALSA characterising adventitious lung sounds may be a useful outcome measure, however, the reliability of the specific parameters (e.g. crackles' initial deflection width (IDW) and two cycles deflection (2CD)) of the adventitious lung sounds has not been adequately explored. The following sections therefore discuss this evidence in relation to 1) the clinical utility of lung sounds 2) the inter and intra-observer reliability of lung sounds when measured in the frequency domain and 3) the limited research into reliability of specific parameters of crackles and wheezes.

There is increasing evidence that CALSA provides clinically useful information about regional ventilation and changes within the lungs (Earis and Cheetham, 2000a, Kiyokawa and Pasterkamp, 2002). When combined with spirometry, CALSA increased the sensitivity of detection of pulmonary disease (Gavriely et al., 1994), and was able to provide early signs of lung disease that were not detected by spirometry alone

(Gavriely et al., 1994). Furthermore, as FEV_1 does not seem to reflect small changes in airway morphology in asthma, CALSA may provide a more sensitive indication of minor alterations in airway geometry (Schreur et al., 1994). Baughman and Loudon (1985) recorded the lung sounds of obstructive patients overnight and were able to detect different degrees of obstruction severity that were not revealed by any other outcome measure. Therefore, reliable and convenient bedside methods for recording and analysing acoustic signals and correlating respiratory sounds with other physiological signals (Sovijarvi et al., 2000a) are being developed.

CALSA has already been used to assess the airways' response to bronchodilators and bronchoconstrictors in children and in adults (Rossi et al., 2000). Baughman and Loudon (1984) studied the lung sounds of 20 asthmatic adult patients before and after the use of a bronchodilator, and found that the use of the bronchodilator was associated with a reduction in the proportion of the respiratory cycle occupied by wheezes from 86% to 31%, and a reduction in sound frequency from 440 to 298 Hz. In two studies involving patients with airways obstruction (22 and 17 patients respectively), Fiz et al. found changes in the frequency content of lung sound signals after the administration of bronchodilators (Fiz et al., 2002, Fiz et al., 1999). Malmberg et al. (1994) studied 11 asthmatic children (aged 10 to 14 years) and found that spectral analysis of lung sounds could be used to detect airways obstruction during bronchial challenge tests. Piirila et al. (1992) studying 11 patients with pneumonia, also found that crackles became shorter and the timing of the crackles shifted towards the end of the inspiration during the clinical course of the pneumonia. However, these studies involved a small number of participants, lung sounds were recorded in quiet or sound proof rooms and the analysis of the lung sounds was performed in the frequency domain (with the exception of the Piirila et al. study).

The number and distribution of adventitious sounds (e.g., crackles per breath) has been associated with severity of disease in patients with interstitial lung disorders (Piirila and Sovijarvi, 1995, Sovijarvi et al., 2000b) and pneumonia (Murphy et al., 2004, Piirila, 1992). Recorded crackles have also been found to differ in different diseases, allowing differentiation between conditions such as COPD, fibrosing alveolitis, Br, heart failure (Piirila et al., 1991), asbestosis and pulmonary oedema (Shirai et al., 1981, Urquhart et al., 1981), pneumonia (Piirila, 1992), pneumonia, heart failure, asthma, COPD and interstitial pulmonary fibrosis (Murphy, 2008). Furthermore, the number of wheezes per respiratory cycle has been reported as a good indicator for airway obstruction (Baughman and Loudon, 1985, Oud et al., 2000). Therefore, the author believes that analysing the waveform, number, distribution, timing, and frequency of

crackles and wheezes may have clinical significance in assessing physiotherapy interventions and potential to be used as an outcome measure. In the future, it may be possible to determine the site of many airway obstructions and to follow the effect of therapy by the analysis of respiratory sounds (Pohlmann et al., 2001, Sovijarvi et al., 1996).

Digital recordings of lung sounds have shown high inter-individual variability (using analysis of variance) when studying healthy people (Ploysongsang et al., 1991, Sanchez and Vizcaya, 2003) explained by height, gender and anatomic characteristics (Pasterkamp et al., 1997b, Ploysongsang et al., 1991, Sanchez and Vizcaya, 2003) and high intra-subject reliability in healthy people (Mahagnah and Gavriely, 1994, Ploysongsang et al., 1991, Sanchez and Vizcaya, 2003) and in 12 patients with fibrosing alveolitis (Sovijarvi et al., 1996). However, in all these studies 1) normal lung sounds' reliability was studied but not the reliability of the adventitious lung sounds, 2) the analysis was performed in the frequency domain and not in the time domain (particularly relevant for the analysis of crackles, see section 3.6.1). Furthermore, small samples, mainly of healthy people, were considered: 5 healthy men in the studies of Ploysongsang et al. (1991) and Mahagnah and Gavriely (1994), 7 healthy people for analysis of tracheal sounds and 10 healthy people for the lung sound analysis in the study of Sanchez and Vizcaya (2003) and 10 healthy men in the study of Sovijarvi et al. (1996).

Furthermore, inter- and intra-observer reliability of the specific parameters of crackles and wheezes has not been adequately determined. The only authors to explore the reliability of the detection of adventitious lung sounds were Hoevers and Loudon (1990). These authors reported on the inter-observer and intra-observer reliability of two physicians measuring crackles' parameters: initial deflection width (IDW), largest deflection width (LDW) and two cycles deflection (2CD), from a 'teaching tape'. The crackles were displayed as a waveform on a computer screen and the physicians had to identify each crackle parameter with a cursor. These researchers concluded that the agreement between physicians was higher when detecting the crackles based on their LDW and 2CD than on their IDW. Frequency of disagreement (detecting the crackles' parameters) was also higher for inter-observers than for intra-observers. However, the authors reported only the agreement between physicians and not the accuracy of their interpretation. Furthermore, the crackles used were from a 'teaching tape' but their origin is not clear (real or simulated crackles). The study from Hoevers and Loudon explored the agreement between the two physicians in detecting IDW, LDW and 2CD but not the reliability of these parameters.

Computer aided lung sound analysis is a non-invasive measure, requiring minimal patient collaboration. The data acquired have clinical utility, can be interpreted objectively, are relevant and can be collected simply, at the bedside, using only a microphone and a recording device (portable equipment) from which sounds may be transferred to a digital format for analysis. The technique has been found to be specific, reliable, and sensitive within the limited use to which it has been put to date. Although it has been used for some time to identify normal and abnormal lung sounds, it has not yet been evaluated as an outcome measure for physiotherapy. The author hypothesises that CALSA could become a convenient and reliable bedside measure to monitor and assess the effects of therapy.

The use of CALSA in this research involves electronic recordings via stethoscope and computer analysis of respiratory sounds, with the main objective of creating a system of classification that will enable automated processing of normal/abnormal lung sounds that can be assessed as a potential outcome measure for respiratory physiotherapy.

3.5. Recording computer aided lung sounds

Recording lung sounds is complex. While heart sounds can be recorded in isolation, by asking the subject to hold his or her breath for a few seconds, lung sounds can not be recorded without interference from other sounds such as from the heart, muscles or background noises. Lung sounds are spread over a wide frequency band and there are several other factors which are potential causes of pattern instability (Mahagnah and Gavriely, 1994, Dalmay et al., 1995), such as: instrumentation used, airflow rate, variations in lung volume, variations in sensor locations and attachment to the chest, electronic filters and accuracy of computational algorithms, inspiration or expiration phases and degree of voluntary control that the subject is able to exert over breathing (Dalmay et al., 1995). For all these reasons, comparisons between studies have been difficult. In order to improve this situation, the CORSA project, published several recommendations to standardise research and clinical practice in this field (Sovijarvi et al., 2000b), as mentioned at beginning of this chapter.

According to the CORSA report, respiratory sounds can be recorded in supine (for long-term) and in sitting (for short-term) position postures. For short-term recordings, the subject should be asked to sit with the hands supported on the thighs to avoid contact of the arms with the axillary areas. The microphone locations that have proved to be most relevant to characterise lung sounds are: trachea (on the sternal notch), chest posterior (right and left bases, 5 cm from the paravertebral line and 7 cm below

the scapular angle for both sides), chest anterior (right and left anterior chest, second intercostals space, mid-clavicular line) and chest lateral (right and left axillary, fourth to fifth intercostals space, mid axillary line) (Rossi et al., 2000). The type and quality of the microphone is crucial, because it represents the 'bridge' between the recording instrumentation and the subject. Air-coupled condenser microphones or piezoelectric microphones are commonly used. They can be attached and placed with a belt or rubber tape, but some researchers hold the microphone with the hand (Piirila and Sovijarvi, 1995), especially if it is connected to a stethoscope. Then, analogue signals from the microphones and from airflow transducers can be simultaneously recorded on magnetic tape, or passed directly to a computer for storage in digital form (Dalmay et al., 1995, Welsby and Earis, 2001, Welsby et al., 2003).

Another aspect that should be taken into account when recording lung sounds is the sample frequency. Normally a sampling rate of 5,512 Hz provides a sufficient frequency range. But higher frequencies may require a wider range of analysis. Peripheral airways phenomena are also associated with high frequencies. Therefore, when studying obstruction in peripheral airways, it is recommended, to use a sampling frequency higher than 11 kHz. But, if the study involves an interest in sounds between upper and peripheral airways, a sampling rate of 44.1 kHz can be adopted (Cheetham et al., 2000). The study of several fine crackles and wheezes may also require a wide range of analysis as they exhibit high frequency components (Charbonneau et al., 2000).

3.6. Computer aided lung sound analysis

Computer aided analysis of lung sound waveforms has a number of potential uses i.e. to help determine the site of airway obstruction, to aid diagnosis, as an assessment tool and to follow the effect of therapy. Clear and significant differences between the pattern of abnormal and normal lung sounds demonstrate the value of spectral analysis as an objective and quantitative measuring tool for continuous lung sounds (Mahagnah and Gavriely, 1994). However, some disparities have been found as a result of using different ways to analyse, and different graphical projections to represent the data (Dalmay et al., 1995). It is therefore important to understand how these sounds can be analysed and follow standardised procedures.

In CALSA, the frequency response band of the whole recording and signal processing equipment is of fundamental importance. The frequency response of direct mode recorders is variable and can attenuate low frequency components. High-pass filters with a cut-off frequency of 50-200Hz are used in lung sound recordings to decrease the

low frequency noise, possibly generated by muscles, large blood vessels and heart sounds (Vannuccini et al., 2000). The problem with this approach is that low frequency sounds can also originate in the lungs and may have clinical meaning. The high-pass cut-off frequency used by researchers has varied from no pre-filtration to > 50 Hz, > 75 Hz, > 100 Hz, > 200 Hz and > 600 Hz and the following bandpass filters have been applied: 50-2.000 Hz, 100-3.000 Hz, 150-300 Hz and 150-700 Hz (Earis and Cheetham, 2000a, Piirila and Sovijarvi, 1995).

The lung sounds signal may be analysed in time and in frequency domains. In the time domain, the technique, called time expanded waveform analysis (TEWA) is normally used, to allow detailed analysis of the waveforms (Charbonneau et al., 2000). However, the representation in the time domain may hide some important characteristics and therefore comparisons between different studies are difficult. The Fourier Transform is a mathematical tool that decomposes a time signal in another representation, frequency (Dalmay et al., 1995, Charbonneau et al., 2000). However, most of the studies so far have not taken into account a great deal of information contained in the signal, which can be of great importance to sound recognition and to the development of a diagnostic or outcome measure tool based on automatic lung sound diagnosis (Earis and Cheetham, 2000a, Oliveira et al., 1999). Signal analysis may be based on the use of short-term power and power spectral density, spectrograms, averaged power spectra, estimation of spectral energy distribution, flow representation, wheeze detection, crackle detection, cough detection, snoring detection and a variety of other techniques (Earis and Cheetham, 2000b). Charbonneau et al. (2000) recommended the respiratory sound analysis techniques listed in Table 1.

Recommendations for lung sound analysis	
Breath sounds	
Methods:	Periodograms, autoregressive models
Features:	Spectral slopes, quartile frequencies, octave band analysis
Presentation of result:	PSD plot, tables of parameters
Crackles	
Methods:	Time-expanded waveform analysis
Features:	Time parameters (IDW, 2CD, LDW), number of crackles and timing
Presentation of results:	Time plots, tables of parameters
Wheezes	
Methods:	Periodograms, STFT
Features:	Fundamental frequency, wheeze duration and timing, histogram of wheezing episodes, mean frequency balance between inspiratory and expiratory wheezes
Presentation of results:	PSD plot, sonogram plot, tables of parameters
Snores	
Methods:	Time-expanded waveform analysis, periodograms
Features:	Amplitude in time domain, main peak location and energy in frequency
Presentation of results:	PSD plot, tables of parameters, sound pressure level, spectrogram
Stridors	
Methods:	Periodograms: STFT autoregressive models
Features:	Fundamental frequency, duration of the event, number and location of high-frequency peaks
Presentation of results:	PSD plots, sonogram plots, tables of parameters

Table 1: Features of lung sounds and recommended respiratory sound analysis techniques. Power Spectral Density (PSD); Initial Deflection Width (IDW); Two-Cycle Duration (2CD); Largest Deflection Width (LDW); Short-Time Fourier Transform (STFT). Adapted from Charbonneau et al. (2000).

The following sub-sections will introduce some relevant aspects to aid understanding the analysis of two specific adventitious lung sounds, crackles and wheezes.

3.6.1. Crackle analysis

Murphy et al. (1989) have suggested that to identify a crackle i) the waveforms have to cross the baseline between three and sixteen times; ii) the amplitude of the largest peak has to be greater than double the amplitude of the background sound; iii) the beginning of the event needs to have a sharp deflection in either negative or positive direction and iv) the crossing of the baseline after the initial deflection has to be progressively wider.

According to Sovijarvi et al. (2000a) the Initial Deflection Width (IDW - the duration of the first deflection of the crackle), the Two Cycle Duration (2CD - the duration of the first two cycles of the crackle) and the Largest Deflection Width (LDW - the width of the largest deflection of the crackle), have also been used to classify crackles (see Figure 1 for a graphical representation of these parameters). Sometimes it is difficult to determine the exact beginning of a crackle for the measurement of IDW and 2CD. This difficulty does not arise in the measurement of the LDW, which is also a good parameter in classifying crackles (Piirila and Sovijarvi, 1995, Hoevers and Loudon, 1990). However, several sources only give mean values of IDW and 2CD durations for

fine and coarse crackles. The two most relevant are the American Thoracic Society (ATS) and CORSA. The ATS considers the mean durations for,

- Fine crackles:
    - IDW = 0.7 ms
    - 2CD = 5 ms
- Coarse crackles:
    - IDW = 1.5ms
    - 2CD = 10 ms.

The CORSA considers the mean durations for,

- Fine crackles:
    - 2CD < 10 ms
- Coarse crackles:
    - 2CD > 10 ms.

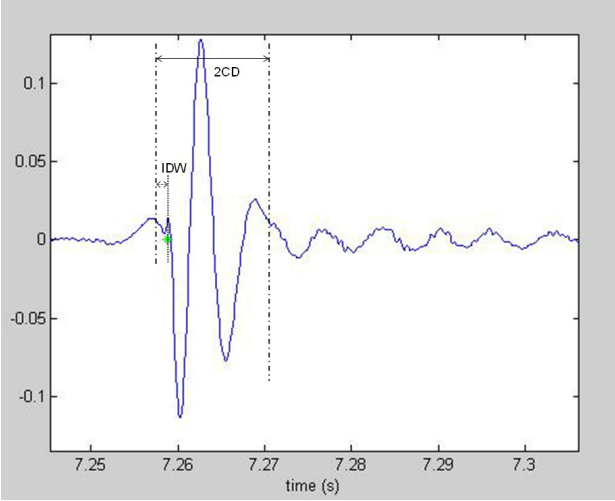


Figure 1: Plot of a crackle (time versus amplitude). Representation of the crackle Initial Deflection Width (IDW) and of the crackle Two Cycles Deflection (2CD).

Quantification of crackles can be visualised on time expanded waveform analysis where zooming in/out of the digitized waveform can be done on a computer screen. A resolution where 3 000 m represents 1 second of data is frequently recommended. This can be done manually, but it is tedious and impractical for clinical use. Therefore, different automatic methods to detect crackles have been validated (Kaisla et al., 1991, Murphy et al., 1989, Vannuccini et al., 1998). Crackles are characterised by large and rapid amplitude deviations in the time-domain signal (Yi, 2004). The primary problem is however, to establish an algorithm that will reliably identify a genuine crackle as a crackle (i.e. sensitivity), and will not label anything a crackle, when it is not genuinely a crackle (i.e. specificity). Furthermore, filtering parameters should also be taken into account when analysing crackles, since the chosen bandwidth can alter the crackles'

characteristics, in particular it can obscure the crackles' start time by obscuring the sharp corner described in criteria iii) established by Murphy et al. (Murphy et al., 1989) making the starting of the crackles more difficult to detect. Moreover, the great variability in the duration of the crackle parameters reported in the literature in similar diseases could be explained by differences in the filtering or recording methods used (Piirila and Sovijarvi, 1995). Therefore, recording sounds following CORSA guidelines (which do not recommend a specific filter) is a good step forward to increase the efficiency of the automatic detection and was adopted for this work.

3.6.2. Wheeze analysis

A consensus appears to arise from the literature that wheezes are better characterised by large and rapid amplitude deviations in the time-frequency-domain (Yi, 2004). Tools such as the spectrogram allow the visual identification even at low intensities. Therefore, CALSA allows the automatic identification of wheezes in contrast to subjective auscultation (Pasterkamp et al., 1997a). The description in the frequency domain of these sinusoidal deflections is usually performed by computing the power spectrum using Fast Fourier Transform (Meslier et al., 1995). Therefore, computer-based detection and quantification of wheezes has been developed with several algorithms that relate the amplitude of the spectral peaks of power spectra to the average lung sound amplitude (Homs-Corbera et al., 2004, Homs-Corbera et al., 2000, Hsueh et al., 2005, Shabtai-Musih et al., 1992).

However, the large variability in the predominant frequency of wheezes, the influence of the auscultation site as well as the influence of airflow on the intensity and power spectra of lung sounds, illustrate some of the difficulties encountered with automated analysis and quantification of wheezes (Meslier et al., 1995).

3.6.3. Breathing cycle analysis

As seen in previous sections related to crackles and wheezes, the timing of the adventitious sounds in the breathing cycle has clinical meaning. Therefore, the detection of the breathing cycle and respective respiratory phases is important. Normally, when a person is auscultated in a sitting position, the respiratory phases are easy to detect over the trachea or anterior part of the chest, but expiration becomes almost inaudible, when lateral or posterior parts of the chest are examined. Several methods have been proposed for the automatic detection of the breathing cycles and respective respiratory phases using different ways of analysing the signals (Hult et al., 2000, Chuah and Moussavi, 1998, Sa and Verbandt, 2002, Varady et al., 2002, Yap and Moussavi, 2001, Yi, 2004). However, of the methods involving acoustic data acquisition, only the method proposed by Chuah and Moussavi in (1998) and in (2000)

uses both tracheal and chest sounds but without pneumotachograph or plethysmography data.

Flow is usually measured directly by spirometry devices, such as a pneumotachograph, nasal cannulae connected to a pressure transducer, heated thermistor anemometry or indirectly by respiratory inductance plethysmography (detection of chest and/or abdominal movements to detect respiratory phases), strain gauges or magnetometers (Tarrant et al., 1997). From all the methods, the pneumotachograph has been considered the gold standard (Brouwer et al., 2007) and therefore the most accurate (Tarrant et al., 1997) method to assess respiratory parameters. However, one of the disadvantages of this equipment is that patients have to breathe using a mouthpiece or a face mask. This causes patients discomfort, is not practical, and changes the breathing pattern and therefore is rarely used clinically (Akre et al., 2000, Manczur et al., 1999). Furthermore, gathering breathing cycle data from non acoustic means (e.g., from pneumotachographs), may be difficult or impossible when dealing with children or with patients with some clinical neurological impairments such as cerebral palsy. Patients with respiratory problems frequently also have neurologic impairment and vice versa, or may have swallowing disorders, behaviour problems (unable to cooperate), physical deformities, or poor postural control which makes the pneumotachograph (or other kind of equipment to detect respiratory phases) a challenge, or even impossible to use. These aspects have also been acknowledged by other authors (Chuah and Moussavi, 2000, Moussavi et al., 2000, Moussavi et al., 1998, Yadollahi and Moussavi, 2006, Yadollahi and Moussavi, 2007). Breathing cycle detection without airflow measurements has been successfully achieved with an accuracy of 93% in lung sounds recorded in six places (trachea and over the chest) in 11 healthy subjects (Chuah and Moussavi, 2000, Moussavi et al., 2000, Moussavi et al., 1998). However, these researchers used six simultaneous microphones attached to the trachea and chest and the data were recorded in a respiratory acoustics laboratory and on healthy subjects. An acoustical approach to respiratory phase detection is attractive because it is objective, non invasive, relatively inexpensive, and convenient to use (Chuah and Moussavi, 1998, Chuah and Moussavi, 2000) in a clinical setting.

For an acoustical approach to be possible for detecting respiratory phases, different features must exist between the signals of the inspiration and expiration phases. Chuah and Moussavi's detection approach is based on the fact that respiratory sound intensity at the chest wall is greater in inspiration than in expiration (Chuah and Moussavi, 1998, Chuah and Moussavi, 2000). During speech, inspiration takes approximately 10% and expiration 90% of the breathing cycle, however, during tidal

breathing inspiratory phase is shorter than expiratory phase, with a ratio inspiration/expiration of about 1:2 or 40%:60% (Borden et al., 2003 pp. 57-58), and expiration is nearly silent (Sovijarvi et al., 2000a).

Tracheal breath sound signals typically have a distinct waveform. The intensity of each phase starts with a gradual increase from baseline intensity, reaches a peak close to midway, and gradually decreases back to the baseline value. However, filtering may cause some problems when the signal is minimal between the two respiratory phases because may shift the minimum of the signal and consequently yield poorer timing accuracy (Yi, 2004).

3.7. Summary

Chapter 3 has revealed that lung sounds provide useful, specific information, but that standard auscultation is too subjective to allow them to be used as an outcome measure. Therefore, in this Thesis, CALSA is proposed as an objective, non-invasive, bedside clinical measure with the potential to monitor and assess the effects of airway clearance therapy. The next Chapter will describe the equipment and methodology used during this research to assess the utility of CALSA in CF and Br patients.

Chapter 4
Equipment and Methodology

4.1. Introduction

This chapter describes the methodology used in this investigation. A general overview of the work that has been performed in this research, is provided. This is followed by the description and respective justifications of the equipment and methodology.

4.2. Research methodology

Two studies were conducted in this research. Both involved a group of patients with excessive secretions (2 pathologies, CF and Br). In the first study repeated measures were used to assess the reliability of CALSA and routine self-intervention sessions were used to test the responsiveness of CALSA. However, because the results in the first study were obtained before and after an intervention of doubtful effectiveness, it was considered necessary to explore both reliability and responsiveness further in a second study. The design of the second study was informed by the first study. In this second study, repeated measures were again used to confirm the reliability of CALSA. However, it was decided to have a physiotherapist providing the interventions to confirm the responsiveness of CALSA after a 'more effective' intervention. The second study was also designed to assess any agreement between CALSA and a physiotherapist's opinion about the number and timing of added lung sounds in the breathing cycles. Cystic fibrosis and Br participants treated themselves in different postures and as it will be seen in responsiveness to change in the results chapter (see section 5.7.2.1), crackles behaved differently in each group of participants. For this reason data from CF and Br participants were treated separately at all stages of the analysis.

4.2.1. Research aims

This research intended to investigate whether using CALSA to detect and characterise added lung sounds had any potential to be a reliable measure for physiotherapy airway clearance techniques. The specific aims were:

1. To test the methodology for recording and analysing lung sounds via a digital stethoscope in a clinical setting using a single sensor;
2. To determine the ability of CALSA to distinguish between different frequencies and types of added lung sounds;
3. To test the inter and intra-subject variability of added lung sounds recorded using a digital stethoscope;

4. To explore if the published algorithms, for assessing the sensitivity and specificity of the automatic detection of added lung sounds, are feasible to use with data collected in a clinical setting via a digital stethoscope using a single sensor;
5. To explore whether self administration chest clearance techniques had a measurable effect on recorded lung sounds;
6. To explore whether physiotherapist administrated chest clearance techniques had a measurable effect on recorded lung sounds;
7. To explore which variable(s) and/or parameter(s) of each added lung sounds would be more suitable to be used as an outcome measure for respiratory therapy;
8. To determine the ability of using CALSA to detect breathing cycles with data collected in a clinical setting via a digital stethoscope using a single sensor;
9. To explore the feasibility of identifying the number and timing of added lung sounds in the breathing cycles with CALSA;
10. To assess any agreement between CALSA and the physiotherapist's subjective opinion about the number and timing of added lung sounds in the breathing cycles.

In this research, the first study was designed to explore the first five aims and the second study was designed to confirm the results of the first study and address the last five aims.

4.3. Methodology

The protocol was submitted to the Southampton & South West Hampshire Research Ethics Committees (A) and full approval was obtained (see Appendix 3 of this Thesis) prior to recruitment. The methodology used in both studies was similar, however, in the second study participants were treated by a physiotherapist instead of applying self-interventions as in the first study.

4.3.1. Research design

A single group repeated measures design was used in both studies to assess the test-retest reliability of added lung sounds within each session using CALSA. Recordings were made from the same participants twice on the same day (at baseline and post intervention), with minimal time delay between measures. The other aims were addressed by recording ten CF participants and fourteen Br participants in the first study, at baseline and post self administration of airway clearance techniques, and seven CF participants and twenty three Br participants in the second study, at baseline and post physiotherapist administrated airway clearance techniques.

4.3.2. Research procedures

4.3.2.1. Setting and subject selection

The data collection for the first study occurred at Queen Alexandra Hospital (QAH), Portsmouth, and Southampton General Hospital (SGH). In the second study the data were all collected at QAH. Patients with a diagnosis of CF or Br aged 18 or over, who attended out-patient clinics were eligible to participate. These patients were chosen because they suffer from common respiratory disorders characterised by the presence of excessive secretions. Therefore, they are accustomed to treating themselves or being treated by a physiotherapist with airway clearance techniques. This is an essential component of their daily routine since they remove viscous airways secretions, compensate for impaired mucociliary clearance and minimize the lung disease process (Button et al., 2003, Davies et al., 2006, Jaffe and Bush, 2001, Spencer and Jaffe, 2003). This age group was chosen because adult chests generate lung sounds that are easier to detect, and because similar age groups have been used in previous studies including chest physiotherapy and sputum quantity, spirometry, oxygen saturation and breathlessness (Ambrosino et al., 1995, McCarren and Alison, 2006, Patterson et al., 2005, Thompson et al., 2002, Baldwin et al., 1994), allowing comparisons with published studies.

4.3.2.2. Recruitment

The administrator, nurse, physiotherapists and consultant respiratory physicians involved with respiratory out-patient clinics were consulted and were willing to assist with the recruitment process. Potential participants were identified via the CF or Br out-patient clinics held at QAH or SGH. Outpatient clinics were selected because the research required patients with excessive secretions who required treatment using respiratory physiotherapy techniques, but who were otherwise medically stable, and this population is more common among outpatients than inpatients. Furthermore, outpatients are more readily available, less costly, provide efficient use of staff resources and the research process is less intrusive to the family (ATS, 1999b).

A respiratory nurse and a physiotherapist at QAH and the SGH cystic fibrosis clinic administrator agreed to send out information about the studies (see Appendix 4 of this Thesis) to eligible patients who were due to attend the clinics, two weeks prior to their appointment date. Patients had time to decide if they wanted to participate in the study and had the opportunity to contact the researcher for further information. Interested participants informed the researcher, who arranged to meet them during their routine appointment time or on another day convenient to the individual.

4.3.2.3. Sample

As this research was primarily of an exploratory nature, power calculations were not deemed to be appropriate. It was therefore initially intended to recruit twenty people as a convenience sample. A similar number of patients has been used by others in research studies about physiotherapy applied to CF (Button et al., 2003, Gondor et al., 1999, McIlwaine et al., 2001, Oermann et al., 2001) and to Br (Patterson et al., 2005, Thompson et al., 2002) patients. Studies that had previously explored lung sound analysis applied to different diseases generally had fewer participants (Fiz et al., 2002, Malmberg et al., 1994a, Nath and Capel, 1974, Piirila, 1992, Rossi and Vannuccini, 1998). As the first study involved an uncontrolled intervention of unknown effectiveness, the before/after data generated were not appropriate for providing information about any anticipated effect size. It was therefore not possible to perform power calculations to determine sample size in the second study. It was intended to recruit a further thirty people as a convenience sample for the second study. This number was deemed to be adequate to provide useful information regarding responsiveness. Hopkins (2000) suggested that a sample size of 30 to 50 is required to calculate a smallest real difference that is of practical use.

Patients were included in the study if they were 1) able to give and sign informed consent; 2) diagnosed with CF or Br; 3) 18 years of age or older and 4) clinically stable for one month prior to the study (no hospital admissions, exacerbations or infections, or change in medication). Patients were excluded from the study if they had co-existing lung pathologies (defined as documented diagnosis in medical notes).

4.3.2.4. Research protocol

Patients attending a CF or Br clinic generally spend several hours at the hospital undergoing a number of tests and having appointments with various health care professionals. Data collection for this research was carried out during one of these routine attendances or at separate pre-arranged meetings with the patients.

Written informed consent (see Appendix 5 of this Thesis) was obtained before proceeding to any data collection. The researcher collected some demographic and basic anthropometric data, as well as recording information about the diagnostic criteria, past clinical history, medication, smoking habits, frequency of physiotherapy treatments and amounts of sputum expectorated. Height and weight, using indoor clothes and without shoes, were measured, with the feet together, standing as tall as possible with the eyes level looking straight ahead, as recommended by Miller et al. (2005b).

Baseline breathlessness was recorded using the Modified Borg scale (AACVPR, 2004) enlarged to a page A4 size (please see Appendix 7 for details on Modified Borg Scale). The scale was presented and read to the participants and then they ticked the appropriate number/description of the scale. The researcher then placed the flexiprobe on the index finger of the participant's non-dominant hand to collect data related to the oxygen saturation. Participants were then asked to assume the sitting position, perched on the edge of a chair without arms and covered with leather, or on a plinth (see Figure 2), in order to allow the researcher to have access to the different parts of their trunk, with a bare chest (or wearing minimal undergarments), and to support their hands on their thighs (to avoid contact between the arms and the axillary areas). This is the recommended posture for short-term recording of respiratory sounds (Rossi et al., 2000).

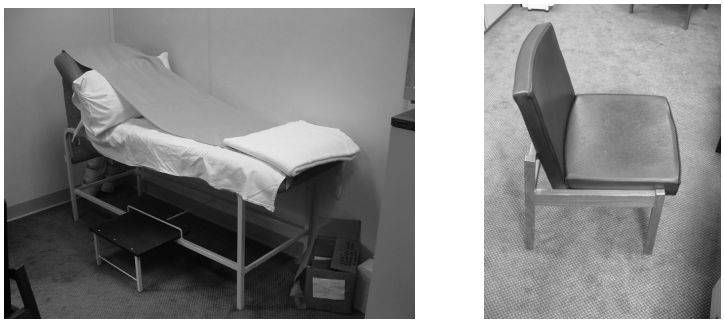


Figure 2: Examples of the plinth and chair used to position participants.

Participants' skin was marked with a pen in seven different places (see Figure 3), one centrally over the trachea (1 - on the sternal notch); two on the front of the chest (2 and 3 - right and left: in the second intercostal space, mid-clavicular line); two on the side of the chest (4 and 5 - right and left: in the fourth to fifth intercostal space, mid axillary line) and two on the back of the chest (6 and 7 - right and left bases: at 5 cm from the paravertebral line and 7 cm below the scapular angle). These locations have been reported to be the most useful for auscultation (Rossi et al., 2000). The skin was marked to ensure that the recording place after the intervention was the same used previously, to record the baseline measurements.

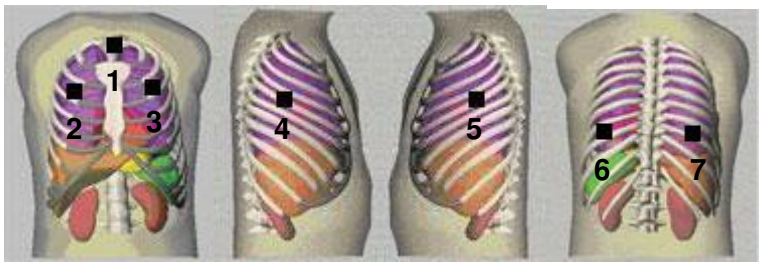


Figure 3: Diagram of the seven auscultation locations of the chest used in this research: 1 – trachea, 2 – anterior right, 3 – anterior left, 4 – lateral right, 5 – lateral left, 6 – posterior right, 7 – posterior left.

The data collection related to lung sounds was then performed using a digital stethoscope (WelchAllyn Meditron, 5079-402) over each of these places. Because the route of breathing (nose or mouth), has an effect on the intensity of the breathing sounds, the participants were all asked to breathe through the mouth during recordings, as normally as possible in the first study and slightly deeper than usual in the second study. Sufficient rests between the measurements were provided to reduce the risk of any problems of participants becoming hypocapnic (low carbon dioxide) during recordings. Nose breathing is more difficult to standardise and sufficiently high flow levels are difficult to obtain (Rossi et al., 2000). The use of a nose clip was tried but participants felt uncomfortable and therefore, it was abandoned. At each marked site the digital stethoscope recorded for 25 seconds (approximately five/six breathing cycles) and measures were repeated three times at each time point (total of 75 seconds/place). Baseline respiratory function measures were then recorded using spirometry. Measurements were repeated three times each time as recommended by Miller et al. (2005b). Participants were asked to start emptying their lungs, then to breathe in until their maximum capacity, hold their breath and then to blow through the spirometer mouthpiece as hard, as fast and as long as possible. Spirometry was not performed prior to lung sounds data collection because it is a forced manoeuvre which might move secretions and therefore, change the lung sound recordings.

These measures (breathlessness, oxygen saturation, lung sounds and spirometry) were carried out two times i.e. 1) before self-intervention in the first study and before physiotherapy intervention in the second study; 2) immediately post self-intervention in the first study and immediately post physiotherapy intervention in the second study (see Figure 4).

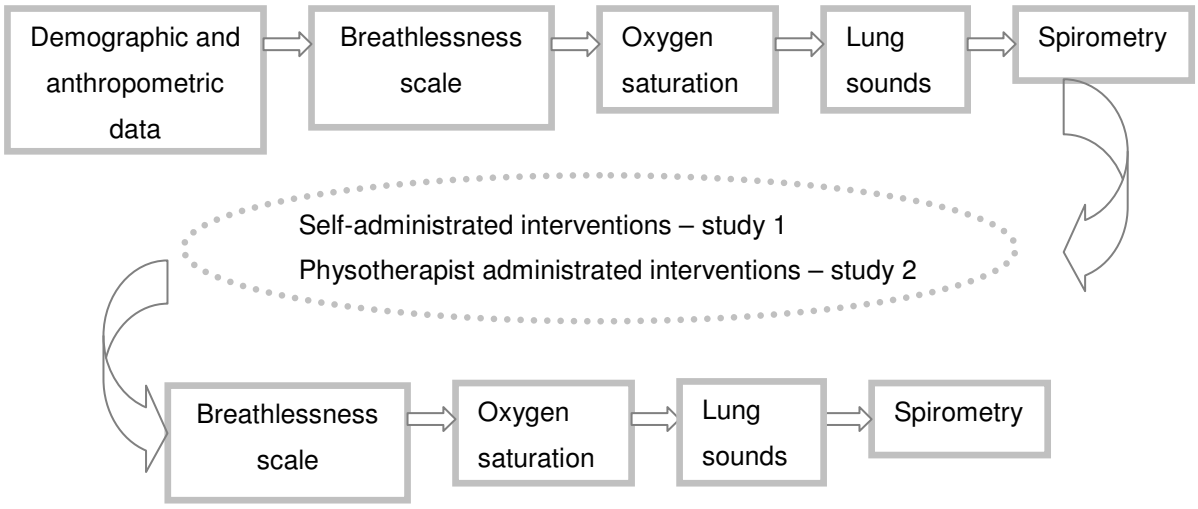


Figure 4: Sequence of data collection of both studies of this research.

In the first study some notes were taken by the researcher, during participants' self interventions to be able to describe their intervention later. In the second study, the respiratory physiotherapist performed an auscultation assessment with a Littmann Classic II standard stethoscope, at baseline and post intervention, in the same seven chest positions used to record the lung sounds with the digital stethoscope. A standard auscultation assessment chart (see Appendix 6 of this Thesis) was provided to the physiotherapist to make notes about the presence/absence of added lung sounds (type, number and timing of added lung sounds in the breathing cycles), at baseline and post the physiotherapy intervention. Some notes were taken by the respiratory physiotherapist during the intervention, to enable the researcher to describe the intervention performed. Data collection was then complete. The pen marks on participants' skin were cleaned before they left.

4.3.2.5. Airway clearance interventions

Two types of airway clearance interventions were observed in this research. In the first study, airway clearance self-interventions were carried out by the participants and in the second study airway clearance interventions were provided by a physiotherapist. This change in the methodology had the objective of participants being treated with a more 'effective' intervention in order to facilitate the assessment of CALSA's responsiveness to change.

4.3.2.5.1. Self-administrated interventions

In the first study, participants carried out their normal chest clearance intervention until either the amount of sputum expectorated reduced to nothing, or they wished to stop. Participants were asked to perform their routine treatments and therefore they were allowed to execute any airway clearance techniques in different positions and they also

could use any aid or equipment if that was part of their normal daily routine. It was estimated that this would be about 20 to 40 minutes, which was similar to the study of Baldwin et al. (1994). In practice it was 15 to 35 minutes in CF participants and between 15 and 30 minutes in Br participants. Although encouraged to continue the intervention until their chest was clear, some participants may have stopped due to time constraints i.e. another appointment, or loss of motivation.

4.3.2.5.2. Physiotherapist administrated interventions

Participants were assessed and treated according to what was considered to be 'effective' judged by the physiotherapist. Therefore, each participant had his/her own treatment and several airway clearance techniques (see Glossary of the techniques pages 248-249, at end of this Thesis) were performed. Interventions duration ranged between 20 and 25 minutes in CF and between 15 and 30 minutes in Br participants.

4.3.3. Outcome measures

In this research, the main outcome measure of interest was the findings generated using CALSA. Other measures included demographic and anthropometric variables, subjective breathlessness, oxygen saturation and lung function.

4.3.3.1. Measurement of lung sounds

Data were recorded using a digital stethoscope (WelchAllyn Meditron, 5079-402) which includes transducers (stethoscope and microphone) and is made from a chest piece (diaphragm that contains a microphone), tubing and earpieces with an acoustic seal (see Figure 5). The input from the microphone was connected to an amplifier and then, to a laptop with customised software written in Matlab (version 7.1), suitable for data acquisition as shown in Figure 6.

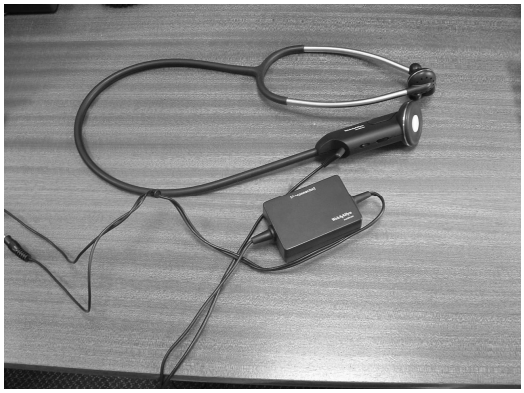


Figure 5: Digital stethoscope used for data collection.

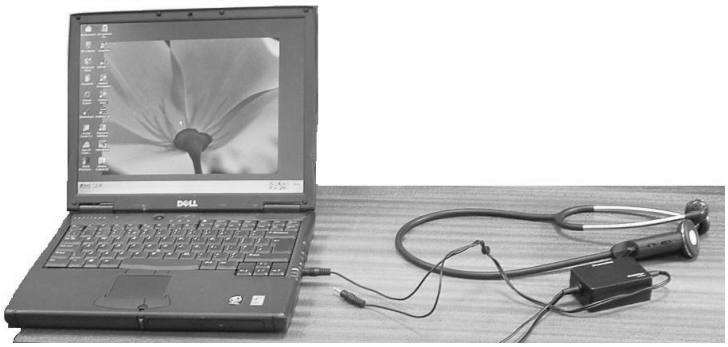


Figure 6: Digital stethoscope connected to the amplifier and then to the laptop.

The lung sound recordings were made directly by the laptop sound card (see section 4.3.2.4) following the guidelines defined by CORSA (Charbonneau et al., 2000, Earis and Cheetham, 2000a, Rossi et al., 2000) and the sampling frequency was 44.1 KHz (44.100 times per second), which is at least four times over sampling frequency (Cheetham et al., 2000). Breathing cycles were recorded for twenty five seconds each time, three times. The twenty five seconds provided the possibility of analysing five/six cycles of breathing (sometimes more) which is reported to be adequate for assessing breath sounds (Ploysongsang et al., 1991).

4.3.3.2. Measurement of demographic and anthropometric variables

Demographic and basic anthropometric data such as participant's age, height and weight were recorded because they are known to affect lung function and to be related to lung sounds (Gross et al., 2000). Date of birth information was provided by the participants. Height and weight were measured using a digital scale (SECA), previously calibrated, for use in the calculation of reference values. Body Mass Index (BMI), which is a measure of body fat and a widely accepted index to assess adiposity in adults (Dietz and Bellizzi, 1999), was calculated as weight/(height)^2.

4.3.3.3. Measurement of breathlessness

Several scales and dyspnoea indices were considered for use in this research (e.g. visual analogue scale and baseline dyspnoea index). As breathlessness was not the primary outcome of interest, a simple scoring system was deemed the most appropriate. The Borg scale is a validated subjective measure of breathlessness previously used in other studies (ATS, 1999a, Silverman et al., 1988, Wilson and Jones, 1991). Although it was originally conceived as a measure of perception of exertion during exercise, it has been used by others in 'non-exercise' research (McCarren and Alison, 2006) and therefore, it was felt to be appropriate for the research as it is simple and quick to administer. Furthermore, participants treating themselves or being treated by a physiotherapist with airway clearance techniques could be considered to be exercising. The Modified Borg scale (MBS) consists of a

vertical scale labelled 0 to 10 with corresponding verbal expressions of progressively increasing sensation intensity and the patient is instructed to scale their effort to breathe (Mador et al., 1995). Therefore, in this research, participants were instructed to grade their effort to breathe and their perception of breathlessness was recorded in Modified Borg Scale amplified to A4 size (see Appendix 7 of this Thesis).

4.3.3.4. Measurement of oxygen saturation

Measuring oxygen saturation was considered to be appropriate for this research because it is objective and could reflect the impact of the intervention, i.e., if secretions are removed, ventilation should increase and therefore, oxygenation should improve. Arterial blood gases (ABGs) acquired invasively are the gold standard measure for assessing oxygenation of the arterial blood. However, the measurement of oxygen saturation in the blood can reliably be obtained non-invasively using a probe attached to the finger, ear or nasal septum (Balfour-Lynn et al., 1998, Dakin et al., 2003). This avoids technical and ethical concerns associated with arterial sampling for blood oxygen (O_2) level determination. In general oximeters are more accurate in the higher saturation ranges and tend to over-estimate in the lower ranges (SaO_2<90%), but their accuracy is normally considered to be adequate for the majority of clinical studies. In this non-invasive research, oxygen saturation was not considered to be a primary outcome measure and the high level of accuracy provided by ABG's was not necessary. Therefore, in this research, oxygen saturation was measured with a pulse oximeter. The flexiprobe from the pulse oximeter (Sims Pneu Pac) was attached on the index finger of the participant's non-dominant hand (see Figure 7).

Figure 7: Oxygen saturation data collection.

4.3.3.5. Measurement of pulmonary function

Spirometry was performed to characterise the research participants in terms of the severity of their lung disease. Spirometry measures are how an individual inhales and exhales volumes of air as a function of time and is a reliable, valid, bedside measure, which has been used in previous research (Miller et al., 2005b) to characterise a

population's pulmonary function. The spirometer (Micro Medical Microlab 3500) was calibrated every day before starting to collect data. The ambient temperatures and time of day when the recordings took place were recorded because they are important variables in pulmonary function tests (Miller et al., 2005a). Forced Vital capacity (FVC), forced expiratory volume in one second (FEV_1), forced expiratory volume in one second % - FEV_1/FVC (FEV_1%) and peak expiratory flow (PEF) were recorded in accordance with published guidelines from the American Thoracic Society and the European Respiratory Society (Miller et al., 2005b).

4.3.4. Health and safety

A risk assessment was carried out prior to both studies and no major hazards were identified. All equipment used for measurement conformed to required safety standards for use on patients. The laptop was not connected to the mains electricity for safety reasons and the battery was used to perform the recordings. The stethoscope and pulse oximeter were disinfected before and after each participant data collection period according to the requirements of the local Trust infection control policy. During spirometry recordings each participant had his/her own mouthpiece, filter and noseclip. The researcher also used plastic gloves and washed her hands frequently in order to reduce the risk of infection transmission.

4.3.5. Anonymisation and storage of data

In this research lung sounds were recorded using a digital stethoscope. The data were digitised directly onto a laptop computer into sound files. The laptop computer was password protected and all the data were anonymised using codes. Paper records with participants' details and consent forms were kept in a locked filing cabinet and at the end of the research, data were securely stored at the University of Southampton in accordance with the policy for postgraduate research.

4.3.6. Data analysis

Different sets of data were analysed in both studies: demographic, anthropometric, subjective breathlessness, oxygen saturation, lung function and lung sounds data. All data were analysed at baseline to provide descriptive statistics. Lung sounds were also analysed for reliability at baseline and post-interventions. With the exception of the demographic and anthropometric information, the data collected post the interventions were compared to the baseline data collection (before interventions).

Normality of the distribution of all data was tested with i) descriptive analysis with Skew and Kurtosis values, ii) frequency distribution histograms, iii) normality plots (Stem and leaf, Normality Q-Q plots and box plot) and iv) Kolmogorov-Smirnov test and Shapiro-

Wilk test in SPSS version 14. It was concluded that normality could be assumed (Bland, 1997, Rasch et al., 2007). In the lung sounds data, normal distribution was found in the majority of the recording positions for the different variables studied (see an example in Appendix 8 of this Thesis). For the few data sets that presented a significant statistical value ($p<0.05$) in the Kolmogorov-Smirnov test and Shapiro-Wilk test, normality plots were analysed and small deviations from normality were found. Decisions about when to use parametric versus nonparametric tests should usually be made to cover an entire series of analyses. It is rarely appropriate to make the decision based on a normality test of one data set (Bland, 1997). Furthermore, Paired and Unpaired t-tests have been found robust enough to be used in most deviations from the normality assumptions (Bland, 1997, Rasch et al., 2007). Therefore, in this research parametric tests were found appropriate.

4.3.6.1. Analysis of the demographic/anthropometric and interventions data

Date of birth, gender, height and weight and interventions' characteristics (self-interventions or interventions provided by the physiotherapist) data were entered into SPSS version 14. Calculations of body mass index, Weight/(Height)^2 (kg/m^2) were performed. Descriptive statistics were used to characterise the participants and the interventions.

4.3.6.2. Analysis of breathlessness, oxygen saturation and lung function

Breathlessness, oxygen saturation and lung function data were also entered into SPSS version 14. The analysis was based on ordinal data collected at baseline and immediately post interventions. Breathlessness comparisons were made using the non-parametric test, Wilcoxon Signed Rank Test. The predicted values used for the lung function were based on the European Respiratory Society references (Quanjer et al., 1993) and the best of the three spirometric measures performed at baseline and post intervention was considered for analysis as recommended by Miller et al. (2005b). The comparisons (at baseline and post interventions) for the lung function and oxygen saturation variables were made using a Paired sample t-test. Means, standard deviations, confidence intervals and p values were printed out from the SPSS output and analysed.

4.3.6.3. Lung sound analysis

The lung sound files were processed using algorithms developed for this research and the potential for CALSA to be used as an outcome measure was analysed. Reliability and responsiveness to change were considered in both studies of this research. In the

second study, any agreement between CALSA and the physiotherapist's opinion about the number and timing of crackles per breathing cycle was also explored. Therefore, this section will firstly present the different steps of processing the files, and then the description of the wheezes, crackles and breathing cycles analysis. The analysis of the utility of CALSA as an outcome measure is then presented in sections 4.3.6.3.5, 4.3.6.3.6 and 4.3.6.3.7. Finally the analysis performed to assess the level of agreement between CALSA and the physiotherapist's opinion about the number and timing of added lung sounds per breathing cycle, is described.

4.3.6.3.1. Processing the lung sound files

In the first study, all sound files from the seven anatomical sites and the three repetitions in each site, were processed using algorithms written in Matlab by Dr. Anna Barney and Professor Paul White (University of Southampton).

At the start of the development of the processing algorithms, the conditioned signals were inspected manually with the goal of detecting the presence or absence of added lung sounds (crackles and wheezes). Established signal processing techniques, such as time-frequency analysis and time-scale analysis, were applied to the signal to create representations of the data that could be used to aid manual identification and these also formed the basis of the automated technique. This initial processing allowed the identification of both timing and frequency band associated with a particular added lung sound. Based on this information and in published algorithms, two programs in Matlab were written by Dr. Anna Barney (to analyse crackles) and by Professor Paul White (to analyse wheezes), for the automatic analysis, in the first study. The data were then processed by the author using these algorithms. Two files with a Matlab extension (.mat) were created for each recording, one saving the information associated with the crackles variables (number of crackles, duration of the initial deflection width (ms) and duration of two cycles deflection (ms) of each crackle) and one saving the information related with the wheezes variables (number, type, duration (ms) and frequency (Hz) of the wheezes). Then, the author, using a small application written by Dr. Anna Barney, processed the .mat files and transformed them in a .csv file in order to export the data to other applications like Excel or SPSS and continue the analysis. The data from all files were imported to SPSS version 14 for statistical analysis.

In the second study, sound files were processed by the author using a program written by a Professor Paul White's student, Julien Dolati (in his 5th year project to complete his Engineering degree). This program, entitled 'Breath Count' integrated the algorithms written for the first study by Dr. Anna Barney (to analyse crackles) and by Professor Paul White (to analyse wheezes), and allowed the breathing cycle detection

and identification of the number (*N*) and timing (*T*) of added lung sounds per breathing cycle. The processing of the data occurred in two different phases. In the first phase, the added lung sounds were detected and analysed for each file (as performed in the first study) and in the second phase, the added lung sounds were detected and analysed for each breathing cycle (analysis performed only in the second study).

In the first phase, using the 'Breath count' program, three files were generated, one file with a Matlab extension (.mat) and two files with an Excel extension (.xls), for each recording. The Excel files saved the information associated with the crackles' variables (number of crackles, duration of the initial deflection width (ms) and duration of the two cycles deflection (ms) of each crackle) and wheezes' variables (number, type, duration (ms) and frequency (Hz) of the wheezes). Due to the small number of wheezes detected only the files related to the crackles detection were imported to SPSS version 14 for statistical analysis. The analysis of crackles was made on files with 25 seconds of recorded lung sound. In each place three recordings were made. Therefore, the analysis considered 75 seconds of data in each place at baseline and post interventions.

In the second phase, analysis of the number and timing of crackles per breathing cycles was performed (this analysis was performed only in the second study). The breathing cycles automatic detection was performed also using the 'Breath Count' program. One Matlab file was created with the information related to the breathing cycles automatic detection and the crackles' characteristic parameters (IDW and 2CD) per breathing cycle. Pneumotachography is considered to be the gold standard (Brouwer et al., 2007), i.e., the most accurate method (Tarrant et al., 1997) for detection of the breathing cycles, respiratory phases and parameters (air flow and volumes), however its use has several disadvantages which have been discussed in the literature review (see section 3.6.3). Therefore, in order to explore if CALSA could be used as an outcome measure in clinical settings for physiotherapy airway clearance therapy, it was decided to record lung sound data with the digital stethoscope and try the breathing cycle detection using an algorithm without the use of a pneumotachograph.

4.3.6.3.2. Wheeze analysis

Several time-frequency domain methods for automatic analysis of wheezes have been developed (Homs-Corbera et al., 2004, Homs-Corbera et al., 2000, Hsueh et al., 2005, Shabtai-Musih et al., 1992, Qiu et al., 2005). Experimentation was required to optimise the algorithm used for the wheezes' automatic detection. However, this process was relatively easy due to details given on the process algorithms. The author chose to

follow the algorithm of Hsueh et al. (2005), because it follows CORSA guidelines, it is validated with patients' data, and a sensitivity and specificity both equal to 89% were reported when recording lung sounds not only from the chest but also from the trachea. However, this algorithm required the thresholds to be set manually which would not be practical for the amount of data that had to be analysed. Therefore, Professor Paul White wrote the algorithm and added some changes based on Qiu et al. (2005) algorithm to increase its performance.

The wheezes automatic detector program, written in Matlab, was run by the author through the data and a plot with the spectrograms was provided, which allowed the visualisation of the wheezes (see Figure 8).

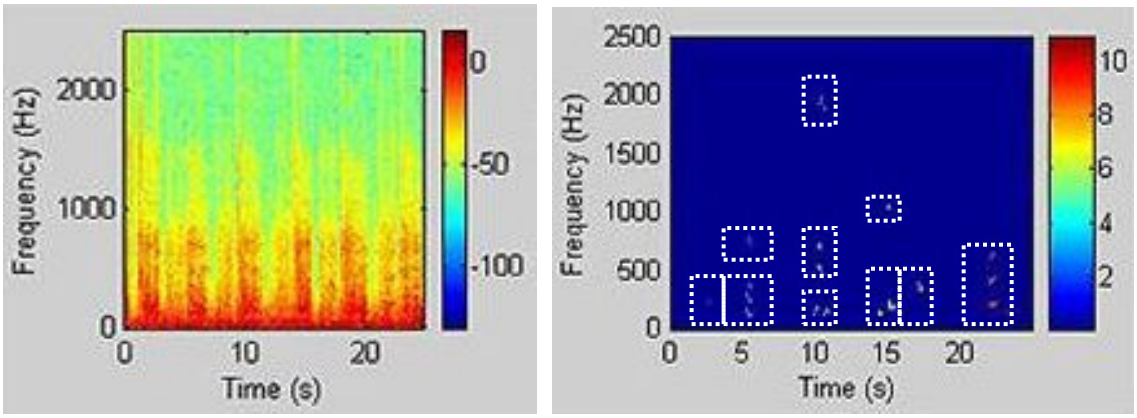


Figure 8: Examples of the different spectrograms given by the program; 1) image on the left - spectrogram without data being normalised; 2) image on the right – spectrogram provided after the final identification of the wheezes detected in the file (wheezes identified are surrounded by the dotted lines).

Information regarding the total number of wheezes per file, type (monophonic or polyphonic), characteristic frequency (Hz), duration (ms) of each wheeze was given automatically (see Figure 9).

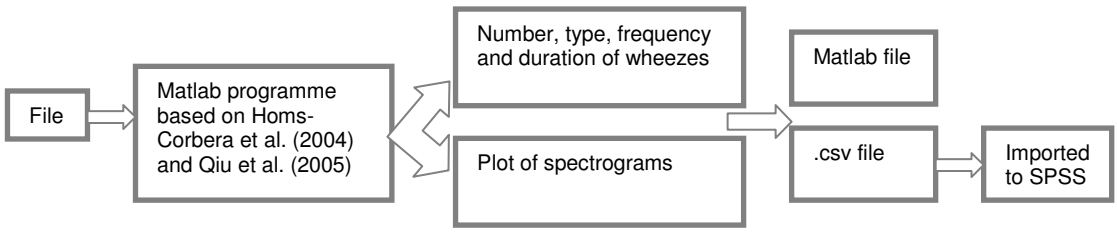


Figure 9: Sequence of wheezes data analysis.

The data were imported into SPSS version 14 for statistical analysis. Wheeze analysis was performed in the first study. However, due to the small number of wheezes

detected results were not conclusive and further analysis was performed only with the crackles' data in both studies of this research.

4.3.6.3.3. Crackle analysis

Crackles are characterised by large and rapid amplitude deviations in the time-domain signal (Yi, 2004) and are relatively easy to identify. Two main variables are used to characterise a crackle, duration of the initial deflection with (IDW) and duration of the two cycle deflection (2CD). The values are given in milliseconds. An increase or a decrease of the duration, in both variables, means that crackles become longer or shorter, and therefore the frequency value decreases or increases, respectively. A threshold of 10 ms for the 2CD variable is given by CORSA guidelines for differentiating high frequency, fine (< 10ms) from lower frequency, coarse (>10 ms) crackles. Furthermore, during respiratory disease, the involvement of different airways is associated with the crackle frequency, i.e., high frequency crackles are associated with peripheral airways and lower frequency crackles with upper airways (Kompis et al., 2001, Wodicka et al., 1992).

Crackles were identified using Murphy's (Murphy et al., 1989, Murphy et al., 1977) criteria (see section 3.6.1). Various authors have developed automatic crackle detection algorithms (Kaisla et al., 1991, Murphy et al., 1989, Vannuccini et al., 1998). Computerised respiratory sound analysis guidelines do not recommend a specific method, but they do recommend a 60 Hz to 2 kHz band-pass filter. However, with many detection algorithms, this leads to an over detection of fine crackles and under detection of coarse ones, i.e., setting the upper limit of the filter too high, 2kHz, allows noise to pass and that is erroneously detected as crackles; setting the lower limit too high, 60Hz, filters out some very low frequency crackles that should be detected.

Therefore, after data collection of the first study, selection of an analysis algorithm was carried out. This was complicated by the lack of detail in some published accounts, especially relating to selection of detection thresholds. Furthermore, the majority of algorithms published for crackles' automatic detection were validated with simulated data or with data only from the trachea region. Therefore, when these algorithms were tested with the data collected in the first study, several problems associated with the clinical setting were detected, e.g., detection of heart sounds instead of crackles. A reasonable crackles' automatic detection was also found to be very sensitive to the filtering techniques and respective thresholds used. Thus, different methods were tried until a good compromise was reached with Vannuccinni et al.'s (1998) algorithm.

The algorithm developed by Vannucinni et al. (1998) was chosen, because it uses a different kind of smoothing filter (i.e. finite impulse response filter, which belongs to Savitsky-Golay family) which smoothes the signal without so much disturbance to the location of the points where the signal crosses the baseline. Their method follows Murphy's definition of crackles, is validated using a sample of 200 inspiratory crackles recorded from 15 cryptogenic fibrosis alveolitis patients, and is reported to show a sensitivity of 84% and specificity of 89% on their test data. Furthermore, the method provides a systematic way to identify the start of a crackle (Vannuccini et al., 1998). A time-expanded waveform plot was also available to help the visualisation of the data (see Figure 10 and Figure 11).

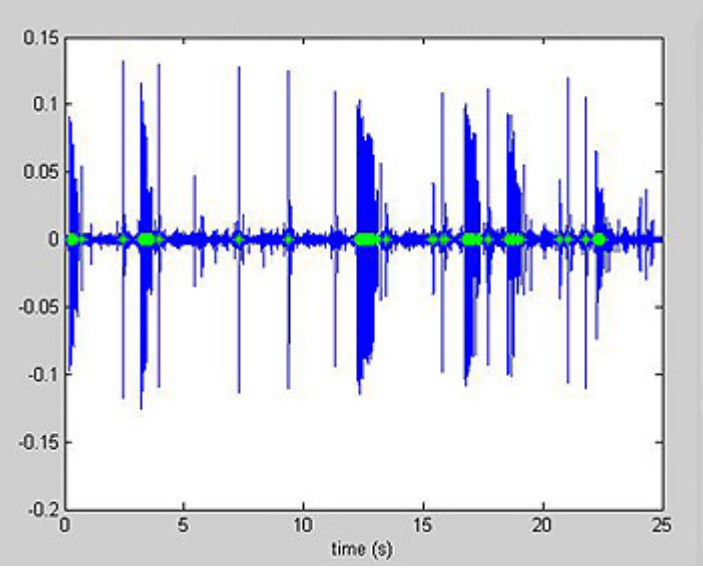


Figure 10: Plot of 25 seconds of lung sound data provided by the Matlab program, identifying the existing crackles (green dots). X axis indicates time and Y axis indicates amplitude of the signal.

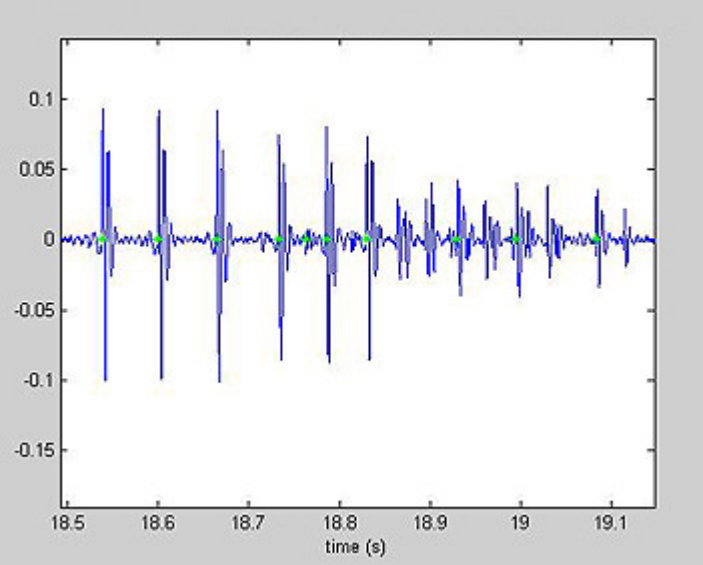


Figure 11: Close–up of 0.6 seconds of data from Figure 10 allowing better identification of the crackles (green dots). X axis indicates time and Y axis indicates amplitude of the signal.

As explained previously (see section 4.3.6.3.1), the data related with the number of crackles detected in each file, with the duration of the initial deflection width and the two cycles deflection of each crackle detected in the file was recorded in a .mat file. Then, using a small application written in Matlab, the .mat files were transformed in .csv files and the data were then exported to SPSS for further analysis (see Figure 12).

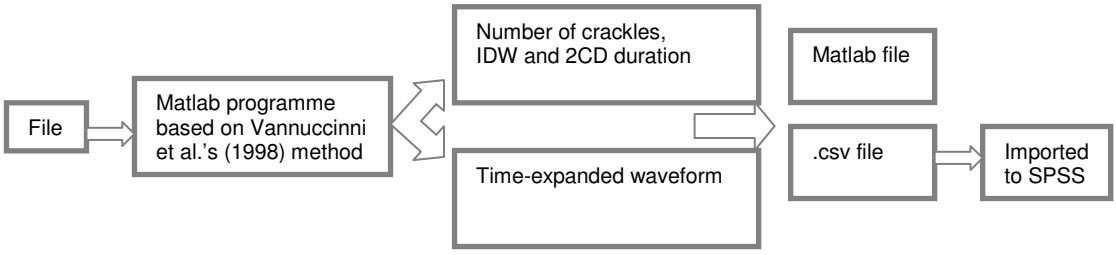


Figure 12: Sequence of crackles data analysis.

Recordings of the lung sounds were made at baseline and post interventions for each individual in both studies. In the second study, all the files were processed using the Matlab program 'Breath count'. An excel file was generated saving the information related to the number, IDW and 2CD of the crackles. The repeated lung sound recordings performed in each place per participant were analysed individually and a database with this information was built in SPSS version 14 for further analysis.

4.3.6.3.4. Breathing cycle analysis

This analysis has only been conducted on data from the second study. To detect the breathing cycles, each .wav file (raw data) was processed again using the 'Breath count' program. The data were plotted in Matlab. A maximum and minimum threshold was defined for each file by the user, i.e., the maximum threshold was the highest peak and the minimum threshold was the lowest peak, obtained across all the breathing cycles. These thresholds were then used to detect the breathing cycles within each file automatically. After the breathing cycles were detected, the crackles were plotted in the signal and a waveform with the breathing cycle detection and the crackles per breathing cycle was obtained (see Figure 13 as an example).

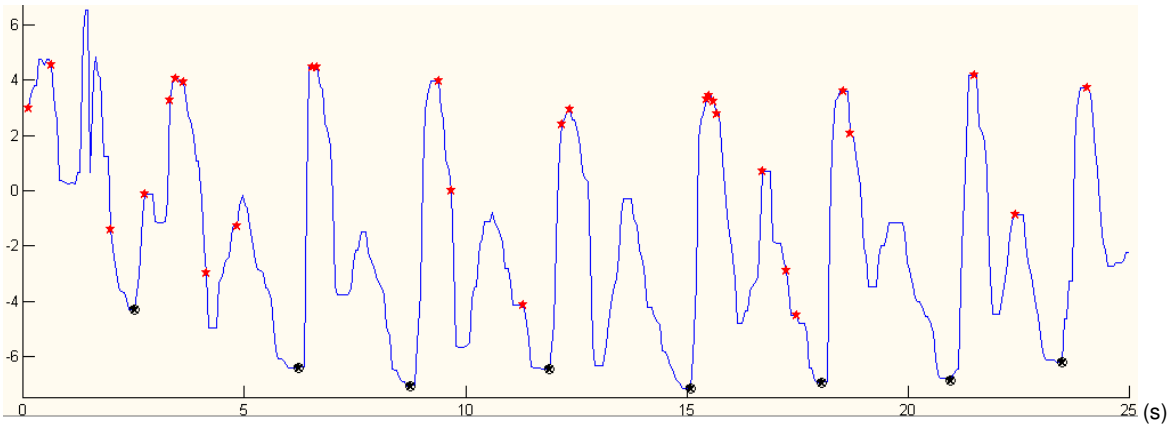


Figure 13: Example of the breathing cycles detection (black dots) with the crackles (red dots) plotted in each breathing cycle during the 25 seconds of data, at anterior right chest location of a cystic fibrosis participant.

These data were then saved and an Excel file was created with the information related to the detection of the breathing cycles and of the crackles per breathing cycle. Each Excel file contained 8 columns, with the following information:

1. First column indicates when the breathing cycle begins (seconds);
2. Second column indicates when the breathing cycle ends (seconds);
3. Third column indicates the duration of the breathing cycle (seconds);
4. Fourth column indicates the moment in the breathing cycle when each crackle occurs (seconds);
5. Fifth column indicates the IDW value (ms) of each crackle;
6. Sixth column indicates the 2CD value (ms) of each crackle;
7. Seventh column indicates the moment where the crackles occurs but in percentage of the breathing cycle;
8. Eighth column indicates the percentage of the breathing cycle occupied by crackles.

These files with the information about this type of added lung sounds detected by CALSA allowed the assessment, at baseline and post interventions, of i) the number, characteristics and timing of crackles per breathing cycle, and ii) the level of agreement between the data from the participants' auscultation charts (which were filled by the physiotherapists with the information about the type, number and timing of added lung sounds in the breathing cycles), and the data from CALSA. Detailed description of this analysis is provided in sections 4.3.6.3.6 and 4.3.6.3.8.

4.3.6.3.5. Reliability

After testing the normality of the distribution of the data and concluding that normality could be reasonably assumed, statistical testing for inter and intra-subject reliability of

CALSA using the crackles data in both studies was based first on analysis of variance. Sovijarvi et al. (1996) also used ANOVA but these authors were looking at repeatability of sound intensity, frequency of maximum intensity and median frequency of lung sounds. Computed values were compared to the 95% confidence limits calculated for each variable, making it possible to assess the likelihood that different measurements recorded in the same place were samples from a single statistical population. An identical comparison between the repeated measures post intervention for each individual was also performed.

It was considered appropriated to explore the reliability, consistency and clinical relevance of crackles. Therefore, three analyses were performed i.e. the Intraclass Correlation Coefficient (Shrout and Fleiss, 1979); Bland & Altman 95% limits of agreement (Bland and Altman, 1986) and the Smallest Real difference (SRD) or repeatability coefficient (Eliasziw et al., 1994, Bland and Altman, 1986). As previously mentioned (see section 2.5.1.3) the ICC and Bland & Altman 95% limits of agreement should both be reported in reliability studies (Rankin and Stokes, 1998) because of the different information provided (see sections 2.5.1.2 Relative reliability and 2.5.1.3 Absolute reliability in the literature review). The analysis were performed on repeated measures at baseline and post interventions.

Bland and Altman 95% limits of agreement were used to assess agreement of the lung sounds recordings across all participants but, these techniques were developed for two sets of measurements. Therefore, to simplify the model, random numbers were generated in Excel and were used to delete randomly one of the three recordings in each place. The mean of the IDW and 2CD duration of each recording, in each recording position, of each participant, was calculated. Then, a database with this information of all participants was built in SPSS. The recordings were performed by the same researcher, therefore, repeatability was examined for a single investigator. The intra-subject reliability was examined in each recording position. Therefore, the ICC was calculated using the equation (1,k) which uses the one-way ANOVA table (and for ICC calculations the three recordings were used):

$$ICC(1,k) = \frac{BMS - WMS}{BMS} \tag{11}$$

where BMS is the between subjects mean squares, WMS is the within subjects mean squares and k is the number of observers or measures (in this study k=3).

Bland & Altman 95% limits of agreement were then performed. Two new variables per each recording position across all participants were generated in the database built in SPSS; one obtained of the difference between the recording 1 and the recording 2 of the crackles' IDW or 2CD, and the other variable obtained by calculating the mean of the two recordings of crackles' IDW or 2CD. These variables were then plotted in a scatter plot for each recording position. The difference between the recordings (y axis) was plotted against the mean value (x axis). A descriptive analysis using the variable difference between the two measures was performed to obtain the mean ($\bar{d}$) and standard deviation (SD_{diff}) of the difference. The value of the mean difference was then added to the scatter plot as a solid line. This gives visual information as to the systematic bias and random error by examining the direction and magnitude of the scatter around the mean difference line. The confidence intervals for the mean difference were also measured as:

$$CI = \bar{d} \pm 2 \times (SE\,\bar{d}) \tag{12}$$

The standard error of the mean ($SE\,\bar{d}$) was calculated as:

$$SE\,\bar{d} = \frac{SD_{diff}}{\sqrt{n}} \tag{13}$$

where n is the number of subjects being analysed. The CI analysis also indicates if there is systematic bias or not. If zero is included within the confidence interval, a lack of systematic bias can be inferred. Finally, the 95% limits of agreement were calculated as the mean differences ± 2 times standard deviation of the differences:

$$\bar{d} = 2 \times SD_{diff} \tag{14}$$

and were also plotted in the scatter plot using dotted lines (upper and lower limit). Examining the plots provided an estimate of error range that relates to responsiveness that may influence the clinical acceptability.

Finally, the Smallest Real Difference, which represents the smallest change that can be interpreted as a real difference (see section 2.5.1.4), was calculated as:

$$SRD = 1.96\sqrt{2}(SEM) \quad (15)$$

The SEM was obtained by calculating the square root of the within subject mean square (WMS) values obtained in the ANOVA table performed for each recording position. These values were then used to calculate the SRD for each recording position, using Equation 15.

This approach was used for data from both studies in this research. The reliability and responsiveness to change of wheezes' characteristics was not possible to perform due to the small number of wheezes in the samples studied.

4.3.6.3.6. Responsiveness to change

The responsiveness to change was assessed using crackles' frequency data (IDW and 2CD durations). In the second study the number and timing of crackles per breathing cycle was also examined.

Frequency of crackles

Responsiveness to change was assessed by comparing the crackles' data post interventions with the baseline measurements. Comparisons between each variable in each place per participant (before and after intervention), to look at the effect of the intervention on the crackles' characteristic parameters (IDW and 2CD) were made using unpaired t-tests. Unpaired t-tests were used because the number of crackles in each file was different. Therefore, the number of events in each file to be compared, was always different (e.g., in recording 1 from lateral right position of the chest, at baseline, 50 crackles with 50 different IDW durations were detected, and was being compared with recording 1 from the same position of the chest, post intervention, where 30 crackles with 30 different IDW durations were detected) and unpaired t-test was therefore appropriate, even though the data came from the same individual.

Outputs with the number of crackles, mean, standard deviation, confidence intervals and p value from the IDW and from the 2CD of the crackles, were generated considering 75 seconds of data in each place for each recording occasion. Mean and standard deviation values were calculated for the IDW and 2CD for each dataset to use as characteristic parameters.

Baseline versus post intervention data were then analysed using the Bland and Altman 95% limits of agreement and the Smallest Real Difference. This analysis aimed to assess if there was any systematic bias in the crackles' parameters (IDW and 2CD)

after the airway clearance interventions. Therefore, using the two recordings that had been chosen for the reliability analysis, a new database was built in SPSS with the mean value of the two recordings at baseline and the mean value of the two recordings after the intervention, across all participants, in each recording position, for both variables (IDW and 2CD). Bland and Altman 95% limits of agreement and the SRD were then calculated as before.

In the second study, physiotherapist and participants were asked about the clearance of participants' lungs post intervention. Participants were grouped in three ways i.e. i) the whole group, ii) the group who considered their lungs to be clearer post intervention and iii) the group who the physiotherapist considered to have left the intervention with the lungs clearer. Therefore, the analysis was conducted considering this three groups of data separately.

Number and Timing of added lung sounds per breathing cycle

This analysis was only performed in the second study of this research. When crackles and wheezes durations and frequencies were studied different values were detected at the trachea from the other regions of the chest. It is known that trachea values should be interpreted differently from the values generated from other chest locations, due to the low pass filtering characteristics of the lungs which do not exist over the trachea region. The low pass filtering of the lungs masks the existence of high frequencies and because this filter does not exist over the trachea high frequencies are detected (shorter durations, hence high frequencies). Consequently, at trachea the lung sounds are not dependent on respiratory phases. This phenomenon has been well described by Gavriely and Cugell (1996). Therefore, sounds recorded at trachea are unlikely to be useful as an outcome measure for respiratory therapy. Furthermore, health professionals rarely use this site when auscultating respiratory patients. So, when analysing the number (*N*) and timing (*T*) of crackles per breathing cycle (BC) this site was excluded.

The *N* and *T* of crackles per BC detected post intervention in the six areas of the chest were compared with the data detected at baseline. For the purpose of this analysis each BC was divided into two phases, inspiration (40% of the total duration of each BC) and expiration (60% of the total duration of each BC) which are approximately the percentages that each phase during quiet breathing takes of the respiratory cycle (Borden et al., 2003 pp. 57-58).

However, because each individual has his/her own pattern of breathing and this (40% inspiration and 60% expiration) was just an approximation, before doing the analysis it was decided to plot histograms to show where the crackles were within the breathing cycle. The number of crackles was averaged across the three files in each recording position and was then plotted. A histogram was produced per recording position per participant, at baseline and post intervention. After analysing all the plots it was found that the best average approximation of the inspiration and expiration phases of the breathing cycle amongst the participants being studied was the same as recommended in the literature, 40% to 60% (Borden et al., 2003 pp. 57-58).

Then, each phase was divided again in two sub-phases (see , early inspiration (0-20%) and late inspiration (21-40%), early expiration (41-70%) and late expiration (71-100%). These sub-phases were created because the number and distribution of crackles within the breathing cycle has been associated with the process and severity of the disease (Murphy et al., 2004, Piirila, 1992, Piirila and Sovijarvi, 1995, Sovijarvi et al., 2000a).

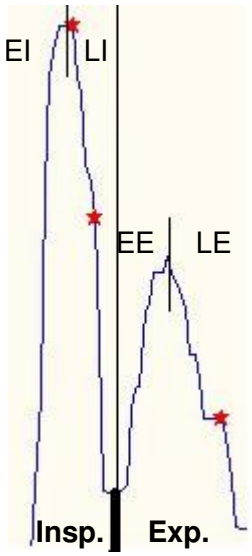


Figure 14: Representation of the phases (inspiration (Insp.) and expiration (Exp)) and sub-phases (early inspiration (EI), late inspiration (LI), early expiration (EE) and late expiration (LE)) of a typical breathing cycle analysed in this Thesis. Stars are crackles identified in the breathing cycle.

The *N* of crackles per BC and per each sub-phase of the BC detected by CALSA, at baseline and post intervention, was analysed amongst the CF participants and the Br participants separately. A database was created in SPSS version 14 with the data related to the *N* of crackles detected by CALSA in the 0-20%, 21-40%, 41-70% and 71-100% of the BCs and the total *N* of crackles per BC of each recording position. However, because the percentages chosen to divide inspiration from expiration were an approximation across all participants, a different database with the *N* of crackles

detected in the first 30% and in the last 30% of the BCs in each recording position was also created in SPSS version 14. These percentages avoided the analysis of crackles in the transition phase where there could not be absolute certainty if the crackles were inspiratory or expiratory.

After testing and concluding that normality of the data could be assumed, paired t-tests were performed to analyse differences in the number of crackles at baseline and post intervention. Because the crackles' data were averaged and normalised by the number of breathing cycles in each file; in this case, the use of paired t-test was appropriate.

4.3.6.3.7. Sensitivity and specificity of the algorithms

The signals identification was initially made manually, by inspection of the conditioned signals, with the goal of quantifying added lung sounds (crackles and wheezes) and thereafter automatically. Several algorithms were tested to perform crackles and wheezes automatic detection with the data collected in this research (Homs-Corbera et al., 2004, Homs-Corbera et al., 2000, Hsueh et al., 2005, Kaisla et al., 1991, Murphy et al., 1989, Qiu et al., 2005, Shabtai-Musih et al., 1992). A reasonable added lung sounds automatic detection was found to be very sensitive to the filtering techniques and respective thresholds used. This information was not always available in published algorithms (Kaisla et al., 1991, Murphy et al., 1989) which have limited their use with the data of this research. The algorithm from Vannuccini et al. (1998) reported a sensitivity of 84% and a specificity of 89% when detecting crackles automatically in files recorded from patients. Eighty nine per cent of sensitivity and specificity of the algorithm from Hsueh et al. (2005) to detect wheezes automatically in patients was also published. Therefore, the sensitivity and specificity of these last two algorithms were considered to be acceptable to be applied in this research, and no further assessment has been conducted.

4.3.6.3.8. Agreement between CALSA and the physiotherapist's opinion about the number and timing of the added lung sounds per breathing cycle

The analysis was performed in two different steps. First, the *N* of crackles were analysed and then the *T* of the crackles in the breathing cycles was considered. For the first step as explained above, the data from CALSA related to the *N* of crackles were averaged between the three recordings to be able to compare this with the physiotherapist's assessment. Then, a table per recording position was created, including the physiotherapist's opinion about the *N* of crackles of that specific position of the chest, of each participant, against the equivalent data from CALSA detecting crackles. Finally a 3x3 contingency table was created per recording position (see Table 2 for an example). The three columns were: no crackles were detected, between one

and six crackles were detected or more than six crackles were detected. The number of times where the physiotherapist said that no crackles were detected, one to six crackles were detected or more than six crackles were detected, amongst all participants, was counted and the total number of each column was filled on the table. The same was done for the CALSA data. The contingency table allowed the analysis of the agreement between the two different types of data.

CALSA / PHYSIO	No crackles	One to six crackles	More than six crackles
No crackles	0	18	0
One to six crackles	0	5	0
More than six crackles	0	0	0

Table 2: Example at anterior right recording position in bronchiectasis participants, of the 3x3 contingency tables created to assess the agreement between CALSA's data and the physiotherapist's opinion about the number of crackles per breathing cycle, at baseline.

As explained previously a table per recording position was created: including the *N* of crackles (previously counted by CALSA) allocated to each sub-phase of the BC, against the physiotherapist' opinion about the presence or absence of crackles in each sub-phase of the BC of each participant. A 2x2 contingency table was created per sub-phase of the BC in each recording position (see Table 3 for an example). The two columns were: no crackles were present in that sub-phase; crackles were present in that sub-phase.

The number of times the physiotherapist said that no crackles were present or that there were crackles present in each sub-phase was counted and the total number was registered in the table. The same procedure was done for the CALSA's data. The contingency table allowed the analysis of agreement between the two sets of data. This analysis was also performed separately for the CF participants and for the Br participants.

CALSA / PHYSIO	None	Early inspiration
None	7	15
Early inspiration	0	1

Table 3: Example at anterior right recording position in bronchiectasis participants, of the 2x2 contingency tables created to assess the agreement between the CALSA's data and the physiotherapist' opinion about the presence/absence of crackles per each sub-phase of the breathing cycle (early inspiration), at baseline.

A summary table is now provided to help the reader to follow the analysis that has been performed in both studies of this research (see Table 4).

Parameters	Type of analyses	Study 1	Study 2
Demographic and anthropometric	Descriptives	✓	✓
Airway clearance interventions	Descriptives	✓	✓
Physiotherapist and participants opinions about the clearance of the participants' lungs post intervention	Descriptives		✓
Breathlessness	Wilcoxon Signed Rank Test	✓	✓
Oxygen saturation	Paired sample t-test	✓	✓
Lung function	Paired sample t-test	✓	✓
Wheezes	Unpaired t-test	✓	
Reliability	ANOVA, ICC, Bland and Altman 95% limits of agreement	✓	✓
Responsiveness to change	Unpaired t-test, SRD	✓	✓
Number and Timing of crackles per breathing cycle	Paired t-test		✓
Agreement between CALSA and physiotherapist	Contingency tables		✓

Table 4: Summary of the analyses performed in each study of this research.

4.4. Summary

This chapter has described the methodology used in this research, designed to collect repeated measures data in participants with excessive secretions at baseline and post airway clearance interventions. The description of the anthropometric and demographic, breathlessness, oxygen saturation and lung function data collection and respective data analysis has been presented. The procedures of data collection of lung sounds have also been described. This included the experimentation that was required to determine the best algorithms to use for the identification of crackles and wheezes generated by excessive secretions in the airways. The processing regime, related to the lung sound data, involved signal conditioning (such as band-pass filtering and de-noising), lung sound identification and lung sound analysis. The procedure for generating reliability coefficients to assess repeatability and stability of the crackles' analysis and the responsiveness to change has also been described. Finally, a description of the analysis for assessing the agreement between CALSA and the physiotherapist's opinion about the number and timing of added lung sounds in the breathing cycles was described. The next section will present the findings from the analysis of the data.

Chapter 5

Measurements and Results

5.1. Introduction

This chapter integrates the findings of the two studies conducted in this research. The results of demographic and anthropometric variables are first presented providing a general description of the whole sample and are followed by the characterisation of the participants' airway clearance interventions, i.e., self-interventions in the first study and interventions provided by a physiotherapist in the second study. Results from breathlessness, oxygen saturation, lung function and lung sounds data, collected during the two studies, at baseline and post interventions, are then presented. The results of the lung sounds data are presented for both studies in two different pathological groups i.e. CF group (10 participants in the first study and 7 participants in the second study) and Br group (14 participants in the first study and 23 participants in the second study) due to the fact that these groups had different characteristics.

5.2. The sample

The inclusion and exclusion criteria were the same for both studies in this research. Therefore, after initially analysing the demographic and anthropometric data separately and concluding that the sample characteristics were similar at baseline, it was decided to pool the baseline data for both studies, separately for CF and Br. It was also felt to be appropriate to pool the baseline reliability analysis data (see section 5.7.1). However, due to the differences in interventions applied in each study, any data relating to outcomes post intervention have been analysed separately. Therefore, data related to gender, date of birth, height and weight (from which the Body Mass Index was calculated) are presented in Table 5 to describe the sample. The values of the forced expiratory volume within the first second percentage predicted (FEV_1 pp) are also presented in the same table to give the reader a general idea of the main characteristics of the whole sample.

Group n	Gender	Age (years) Mean ±stdv	Weight (Kg) Mean ±stdv	Height (m) Mean ±stdv	BMI (Kg/m^2) Mean ±stdv	FEV_1 pp (%) Mean ±stdv
CF-17	F-8; M-9	29.4±13.3	58.5±15.7	1.67±0.16	20.6±3.3	46.1±18.2
Br-37	F-24; M-13	61±11.2	76.7±20	1.66±0.09	27.7±5.5	78.2±18.9

Table 5: Number of cystic fibrosis (CF) participants (n=17) and bronchiectasis (Br) participants (n = 37), female (F) and male (M), mean, standard deviation (stdv), for Age, Weight, Height, Body Mass Index (BMI) (underweight < 18.5; 18.5 ≤ normal < 24.9; 25.0 ≤ overweight < 29.9; 30 ≤ obesity I < 34.9; 35 ≤ obesity II < 39.9; extreme > 40 +) and Forced Expiratory Volume in the first second percentage predicted (FEV1pp - normal > 80%) with the data from both studies pooled.

As presented in Table 5 17 CF adult patients (eight female and nine male), age range 18 to 67 years old, and 37 Br patients (24 female and 13 male), age range 25 to 83 years old were recruited for the research. The males tended to be heavier and taller than the females. In our sample, participants with Br were on average older, taller, and heavier than CF participants. On average, the BMI of CF participants was normal whereas participants with Br were generally overweight. The lung function of both groups of participants was lower than normal (80% FEV_1pp) although Br participants had better lung function than CF participants.

5.3. Characterisation of airway clearance interventions

This section will describe the airway clearance interventions in this research. In the first study 10 CF participants (CF1) and 14 Br participants (Br1) treated themselves with airway clearance interventions whereas in the second study the interventions were applied by a physiotherapist for 7 CF participants (CF2) and 23 Br participants (Br2). The same physiotherapist provided all interventions.

In each study, the participants were asked questions about their routine physiotherapy treatments and the interventions applied during each study were observed and timed (Table 6 summarises these findings). The questions asked are in Appendix 9 of this Thesis.

Airway clearance self-interventions									
No. of participants who regularly applied airway clearance self-intervention			No. of self-interventions per day					Duration of the intervention in the study (min.)	
Group	Yes	No	Zero	One	Two	Three	Four	Mean±stdv	Min-Max
CF1	10	0	0	4	6	0	0	25.5±6.4	15-35
CF2	6	1	0	3	1	2	0	21.4±2.4	20-25
Br1	11	3	3	4	7	0	0	21.8±7	15-30
Br2	19	4	0	10	8	0	1	23.7±4.3	15-30

Table 6: Frequency of cystic fibrosis (CF) and bronchiectasis (Br) participants' airway clearance self-interventions per day and mean, standard deviation (stdv), minimum (min) and maximum (max) duration (min.) of the interventions applied in the first study (CF1 n = 10; CF2 n = 7) and in the second study (Br1 n = 14; Br2 n = 23).

5.3.1. Self interventions

The majority of participants applied airway clearance self-interventions on a regular basis. Table 7 presents a description of each self-intervention performed during the first study. A glossary giving a brief description of each technique is provided at the end of this Thesis.

Group	Airway clearance self-interventions in cystic fibrosis participants and in bronchiectasis participants	No. of participants
CF1	Postural drainage in horizontal side-lying (right and left), plus Clapping, Huff and Cough	6
CF1	ACBT* followed by Huff and Cough (3 cycles) in horizontal side-lying (right and left)	3
CF1	ACBT* followed by Huff and Cough (5 cycles) in horizontal side-lying (right and left)	1
Br1	ACBT* followed by Huff and Cough (3 cycles) in sitting position	7
Br1	ACBT* followed by Huff and Cough (5 cycles) in sitting position	3
Br1	Autogenic Drainage followed by huff and cough in sitting position	1
Br1	Huff plus Cough in sitting position	3
Total		24 (10CF and 14Br)

*ACBT – Active Cycle of Breathing Techniques

Table 7: Descriptions of the cystic fibrosis (CF) and bronchiectasis (Br) participants' airway clearance self-interventions in the first study (CF1 n = 10; Br1 n = 14).

Postural drainage in horizontal side-lying (right and left), plus clapping, huff and cough was the most common self-intervention used by CF participants (6 out of 10). Four CF participants treated themselves with ACBT followed by huff and cough in horizontal side-lying (right and left). However, three CF participants used three cycles of ACBT and one participant used five cycles of ACBT. Participants with Br treated themselves mainly with ACBT followed by huff and cough. Autogenic Drainage followed by huff and

cough was also used by one Br participant and three Br participants used only huff and cough. However, it is important to note that all CF participants chose horizontal side-lying treatment positions whereas Br participants used sitting treatment positions. No participants used any equipment to perform their airways clearance techniques.

5.3.2. Interventions applied by a physiotherapist

In the second study, data were collected about the airway clearance interventions applied by a physiotherapist. The complete description of the physiotherapy interventions applied by a respiratory physiotherapist after assessing each participant of the study is provided in a table in Appendix 10 of this Thesis (page 217). A glossary giving a brief description of each technique is provided at the end of this Thesis. Several combinations of treatments were observed: ACBT with different number of cycles were applied to the majority of the participants in side-lying and/or in sitting in combination with manual techniques. The physiotherapy interventions addressed each participant's individual needs and were therefore also variable.

In the second study, the physiotherapist and participants were asked about their perceptions relating to the effectiveness of the intervention (see Appendix 11 of this Thesis). Table 8 summarise the findings related to these data.

Opinion about the effectiveness of the physiotherapy intervention						
	Physiotherapist's opinion			Participants' opinion		
Group	Lungs clearer than before	Lungs less clearer than before	Lungs the same as before	Lungs clearer than before	Lungs less clearer than before	Lungs the same as before
CF2	1	---	6	4	---	3
Br2	7	3	13	15	1	7

Table 8: Physiotherapist and participants' opinions about the effectiveness of the physiotherapy intervention, applied in the second study, on each participant (CF2 n = 7; Br2 n = 23).

The physiotherapist's opinion was that the majority of participants' lungs were unchanged post intervention. However, the opinion of the majority of the participants was that their lungs were clearer post intervention.

5.4. Breathlessness data

The breathlessness results (Modified Borg Scale) from each study are presented in Table 9.

		Modified Borg Score			Ranks (N)		
Group	Timing	Mean±stdv (Units 0-10)	Min-Max (Units 0-10)	p	Negative	Positive	Tie
CF1	Baseline	2.35±1.94	0-7	.100	2	2	6
	Post self-intervention	2.50±1.65	0-5				
CF2	Baseline	1.50±1.04	0-3	.785	2	1	4
	Post intervention	1.43±1.37	0-4				
Br1	Baseline	2.07±1.37	0-5	.414	2	1	11
	Post self-intervention	1.89±1.46	0-5				
Br2	Baseline	2.41±2.05	0-7	.020*	12	3	8
	Post intervention	1.70±1.44	0-5				

Negative Ranks – Breathlessness after < breathlessness before
Positive Ranks – Breathlessness after > breathlessness before
Ties – Breathlessness after = breathlessness before

Table 9: Means, standard deviations (stdv), minimum (min) and maximum (max) of breathlessness at baseline and post interventions and Wilcoxon Signed Ranks Test results (starred results are significant, $p<0.05$) in cystic fibrosis (CF) participants (CF1 n = 10; CF2 n =7) and in bronchiectasis (Br) participants (Br1 n = 14; Br2 n = 23) from both studies.

In each study the participants' self assessment of breathlessness at baseline and post self-interventions had a wide range both at baseline and post interventions. In the first study, after self-intervention, the majority of all participants maintained the same perception of breathlessness as at baseline. A similar finding was obtained for the CF participants in the second study. However, in the second study the majority of the Br patients perceived themselves less out of breath after the intervention applied by the physiotherapist. This result was statistically significant ($p = 0.02$).

5.5. Oxygen saturation data

Oxygen saturation results from each study are presented in Table 10.

		Oxygen saturation				
Group	Timing	Mean±stdv (%)	Min-Max (%)	P	95% CI of the difference	
					Lower	Upper
CF1	Baseline	93±2.95	89-97	.112	-.46	3.66
	Post intervention	92±2.62	87-95			
CF2	Baseline	93±4.08	87-97	.172	-2.95	.66
	Post intervention	94±2.63	89-96			
Br1	Baseline	93±2.91	86-97	.372	-2.39	.96
	Post intervention	94±2.64	87-97			
Br2	Baseline	95±2.50	88-98	.069	-0.04	1.09
	Post intervention	94±2.06	89-97			

Table 10: Means, standard deviations (stdv), minimum (min) and maximum (max) of oxygen saturation at baseline and post interventions and Paired t-test results with 95% confidence intervals (CI), in cystic fibrosis (CF) participants (CF1 n = 10; CF2 n = 7) and in bronchiectasis (Br) participants (Br1 n = 14; Br2 n = 23), from both studies.

Table 10 shows no significant differences between the oxygen saturation values at baseline and post participants' physiotherapy interventions within or between both groups of participants, in both studies of this research.

5.6. Lung function data

In this section, the lung function findings (FEV_1, FVC, FEV_1/FVC %, FEV_1 percentage predicted, FVC percentage predicted and PEF), at baseline and post interventions are reported. The results from each group of participants (first and second studies) are presented separately because of the large number of variables recorded. Table 11 reports the lung function results from the CF participants in the first study and in the second study.

Group	Timing	Lung function		p	95% CI of the difference	
		Mean±stdv	Min-Max		Lower	Upper
CF1-FVC (L)	Baseline	2.41±.84	1.14 -3.70	.570	-.20	.12
	Post self-intervention	2.46±.78	1.17-3.37			
CF1-FEV_1 (L)	Baseline	1.61±.66	.69-2.74	.450	-.05	.10
	Post self-intervention	1.59±.63	.66-2.62			
CF1-% FEV_1	Baseline	67.13±13.67	45.55-86.98	.242	-2.12	7.38
	Post self-intervention	64.50±12.74	44.79 -87.63			
CF1-FEV_1 pp	Baseline	47.20±18.60	28.04-82.94	.404	-1.20	2.72
	Post self-intervention	46.43±18.20	26.82-83.61			
CF1-FVC pp	Baseline	57.20±15.46	38.38-85.75	.111	-5.71	.70
	Post self-intervention	59.70±15.97	40.06-88.91			
CF1-PEF	Baseline	319.20±120.15	192-550	.295	-13.14	38.54
	Post self-intervention	306.50±131.93	158-560			
CF2-FVC (L)	Baseline	2.48±.90	1.40 -3.70	.242	-.12	.39
	Post intervention	2.34±.86	1.43-3.59			
CF2-FEV_1 (L)	Baseline	1.52±.78	.69-2.74	.691	-.04	.06
	Post intervention	1.51±.75	.70-2.78			
CF2-% FEV_1	Baseline	58.93±12.15	45.71-84.27	.346	-12.42	5.09
	Post intervention	62.60±15.58	48.95-84.38			
CF2-FEV_1 pp	Baseline	44.42±19.03	25.32-82.31	.850	-1.46	1.71
	Post intervention	44.29±18.51	23.40-80.57			
CF2-FVC pp	Baseline	59.33±12.16	43.88-78	.367	-3.32	7.72
	Post intervention	57.13±13.79	37.35-77.31			
CF2-PEF	Baseline	238.43±61.81	154-308	.187	-43.39	10.53
	Post intervention	254.86±76.75	147-373			

Table 11: Means, standard deviations (stdv), minimum (min) and maximum (max) of lung function at baseline and post interventions and Paired t-test results with 95% of confidence intervals (CI), in cystic fibrosis (CF) participants (n = 10 in the first study and n = 7 in the second study). Forced vital capacity (FVC); Forced expiratory volume in first second (FEV_1); FEV_1/FVC*100 gives FEV_1 percentage (%FEV_1), FEV_1 percentage predicted values (FEV_1 pp), FVC percentage predicted values (FVC pp) and Peak expiratory flow (PEF).

Table 12 presents the results from the Br participants in both studies of this research. The same key to abbreviations has been used as for Table 11..

Group	Timing	Lung function		p	95% CI of the difference	
		Mean±stdv	Min-Max		Lower	Upper
Br1-FVC (L)	Baseline	2.82±.76	1.72-3.86	.889	-.14	.16
	Post self-intervention	2.81±.83	1.76-4.25			
Br1-FEV_1 (L)	Baseline	1.82±.54	1.11-3.10	.720	-.06	.08
	Post self-intervention	1.80±.58	1.11-3.10			
Br1- % FEV_1	Baseline	65.37±11.97	43.26-84.11	.998	-4.00	4.02
	Post self-intervention	65.37±12.79	40.94-82.45			
Br1- FEV_1 pp	Baseline	75.74±17.69	52.85-118.42	.504	-1.80	3.49
	Post self-intervention	74.90±17.42	49.30-109.86			
Br1- FVC pp	Baseline	84.63±12.78	63.19-108.25	.842	-4.45	5.38
	Post self-intervention	84.16±15.07	63.84-109.78			
Br1-PEF	Baseline	257.79±106.58	104-483	.052	-.88	16.69
	Post self-intervention	249.00±109.72	101-481			
Br2-FVC (L)	Baseline	2.60±.77	1.64-4.60	.157	-.03	.15
	Post intervention	2.53±.79	1.66-4.68			
Br2-FEV_1 (L)	Baseline	1.39±.62	.59-2.74	.075	-.003	.05
	Post intervention	1.37±.63	.56-2.71			
Br2- % FEV_1	Baseline	53.76±17.08	25.87-82.88	.290	-5.41	1.70
	Post intervention	55.62±17.64	23.72-81.85			
Br2- FEV_1 pp	Baseline	59.67±28.65	21.68-133.70	.078	-.13	2.23
	Post intervention	58.62±28.84	21.03-132.04			
Br2- FVC pp	Baseline	79.66±19.91	41.80-116.16	.198	-1.09	4.94
	Post intervention	77.72±21.09	40.19-118.18			
Br2-PEF	Baseline	240.22±106.24	119-521	.176	-3.13	16.09
	Post intervention	233.74±98.74	106-506			

Table 12: Means, standard deviations (stdv), minimum (min) and maximum (max) of lung function at baseline and post interventions and Paired t-test results with 95% of confidence intervals (CI), in bronchiectasis (CF) participants (n = 14 in the first study and n = 23 in the second study).

At baseline, Br participants had higher mean lung function values than CF participants, in both studies. This difference was statistically significant for the variables FEV_1pp (p=0.001) and FVCpp (p=0.001). The mean values at baseline and post airway clearance interventions for each lung function variable were very similar within both groups of participants, in both studies. There were no statistically significant differences between the baseline and post intervention lung function data in each group of participants in either study.

5.7. Lung sound data

The results from the analysis of the lung sound data will now be presented. This section is divided into four main sub-sections examining the performance of CALSA in four areas that are essential for a robust outcome measure: i) test-retest reliability, ii)

responsiveness to change, iii) sensitivity and specificity of the algorithms and iv) validity, i.e., agreement between CALSA and the physiotherapist's opinion about the type, number and timing of the added lung sounds per breathing cycles. In the first study, data related to wheezes were analysed for the CF and Br participants. However, because a small number of wheezes were detected, results were inconclusive (see Appendix 12 of this Thesis (page 222)). Therefore, it has been decided to present only the results from the crackles' data (the complete wheezes analysis for the first study can be seen in Appendix 1 on the CD provided).

5.7.1. Reliability

The databases created for both studies, with the information from the repeated lung sound recordings performed in each place and for each participant, at baseline and post interventions, allowed the assessment of the reliability of the lung sound data. Some data files contained interference, e.g., the microphone did not make contact or the participants coughed, or the recordings were interrupted by somebody coming into the room and therefore were excluded from further analysis.

After testing the normality of the distribution of the data (see section 4.3.6.3) and concluding that normality could be assumed, the reliability analysis (inter-subject and intra-subject) was performed separately for the CF participants and for the Br participants in each study. However, because i) the inclusion and exclusion criteria were the same for both studies in this research; ii) the sample characteristics were very similar and iii) the baseline reliability results (inter-subject and intra-subject) from the second study were very similar to the baseline reliability results from the first study; it was decided to pool the data from both studies and perform the baseline reliability analysis with a single CF group (n=17) and a single Br group (n=37). The analysis of the post intervention data was performed separately for each study, because different interventions had been applied in each.

5.7.1.1. Inter-subject reliability results

Inter-subject reliability was tested in both studies, at baseline and post interventions, and with the crackles baseline data pooled from both studies. Table 13 and Table 14 show an example, at anterior right of the chest, at baseline, for the CF participants (CF1+CF2) and for the Br participants (Br1+Br2) respectively.

Variable names		Sum of Squares	df	Mean Square	F	Sig.
Crackles' Initial Deflection Width (IDW)	Between Groups	135.800	16	8.488	17.87	.001*
	Within Groups	671.793	1414	.475		
	Total	807.593	1430			
Crackles' Two Cycle Deflection (2CD)	Between Groups	5213.727	16	325.858	35.55	.001*
	Within Groups	13152.525	1435	9.166		
	Total	18366.253	1451			

Table 13: Results from the analysis of variance of the crackles' initial deflection width (**IDW**) and of the crackles' two cycles deflection (**2CD**) obtained from **cystic fibrosis** participants (n = 17), at **anterior right** of the chest, with the **baseline** data from both studies pooled (* starred results are significant, p<0.05).

Variable names		Sum of Squares	df	Mean Square	F	Sig.
Crackles' Initial Deflection Width (IDW)	Between Groups	118.207	36	3.284	6.146	.001*
	Within Groups	1212.826	2270	.534		
	Total	1331.033	2306			
Crackles' Two Cycle Deflection (2CD)	Between Groups	7055.279	36	195.980	19.27	.001*
	Within Groups	23229.624	2284	10.171		
	Total	30284.903	2320			

Table 14: Results from the analysis of variance of the crackles' initial deflection width (**IDW**) and of the crackles' two cycles deflection (**2CD**) obtained from **bronchiectasis** participants (n = 37), at **anterior right** of the chest, with the **baseline** data from both studies pooled (* starred results are significant, p<0.05).

The significant cases from the ANOVA of the inter-subject reliability analysis (of the studies separately and with baseline data pooled), showed, as might be expected, between subject variability.

Inter-subject reliability was also tested post interventions and significant cases from the ANOVA were also obtained for both variables in all the recording positions. An example at anterior right for the CF and for the Br participants, post interventions, can be seen in Appendix 13 of this Thesis (for complete analysis see Appendix 2 on the CD provided).

The analysis of variance (ANOVA) of data in the same place and timing relative to the intervention but different subjects (inter-subject reliability), for both variables, crackles' IDW and 2CD, in both studies, showed that the null hypothesis was not supported (p<0.05). Therefore, data sets from different subjects in CF and in Br participants had significantly different mean crackles' IDW and significantly different mean crackles' 2CD at the 95% level, in both studies, at baseline and post interventions.

5.7.1.2. Intra-subject reliability results

Intra-subject reliability was first calculated based on the ANOVA. The null hypothesis for the ANOVA was that all files recorded in the same place, participant and timing relative to intervention contained a set of crackles data sampled from a single statistical population. The following tables (Table 15 and Table 16) show examples of the results obtained from the ANOVA of the crackles' IDW and 2CD of the lung sound repetitions performed in all participants, in both studies at baseline. This specific example refers to the data recorded at anterior right position of the chest of a CF participant (Pt03) and a Br participant (Pt01), at baseline. Intra-subject reliability analysis was also performed post intervention. An example at anterior right post interventions of the same participants (Pt03 and Pt01) can be seen in Appendix 14 (for complete analysis see Appendix 3 on the CD provided).

Variable names		Sum of Squares	Df	Mean Square	F	Sig.
Crackles' Initial Deflection Width (IDW)	Between Groups	.042	1	.042	.090	.765
	Within Groups	19.530	42	.465		
	Total	19.572	43			
Crackles' Two Cycle Deflection (2CD)	Between Groups	.821	1	.821	.078	.781
	Within Groups	439.913	42	10.474		
	Total	440.734	43			

Table 15: Results from the analysis of variance of the crackles' initial deflection width (**IDW**) and two cycles deflection (**2CD**) of a **cystic fibrosis** participant (Pt03) at **anterior right** of the chest at **baseline** (results non significant, p>0.05).

Variable names		Sum of Squares	Df	Mean Square	F	Sig.
Crackles' Initial Deflection Width (IDW)	Between Groups	.428	2	.214	.368	.695
	Within Groups	20.935	36	.582		
	Total	21.363	38			
Crackles' Two Cycle Deflection (2CD)	Between Groups	36.218	2	18.109	1.839	.174
	Within Groups	354.543	36	9.848		
	Total	390.761	38			

Table 16: Results from the analysis of variance of the crackles' initial deflection width (**IDW**) and two cycles deflection (**2CD**) of a **bronchiectasis** participant (Pt01) at **anterior right** of the chest at **baseline** (results non significant, p>0.05).

The results from the ANOVA supported the null hypothesis (p>0.05) for the crackles' variables, in all participants (both studies) at baseline and post interventions. To continue to assess intra-subject reliability, the Intraclass Correlation Coefficient, the Bland & Altman 95% limits of agreement and the Smallest Real Difference were calculated. These calculations were performed separately, for both groups of participants, in both studies. After analysing the results from each study separately and

concluding that the results were very similar, it was decided to pool the baseline data of both studies. The post intervention data were not pooled since the interventions were different in each study and this could have affected the reliability of the measure. Therefore, the ICC, Bland and Altman 95% limits of agreement and SRD at baseline will be presented from the pooled data. The results of these calculations for the post intervention data, analysed separately for each group of participants in each study can be seen in Appendix 14 of this Thesis (for complete intra-subject reliability analysis see Appendix 3 and Appendix 4 on the CD provided).

5.7.1.2.1. Intra-subject reliability results at baseline

Results obtained from the analysis of the pooled baseline crackles data are presented in Table 17 and Table 18, providing the results from CF participants and from Br participants, respectively. The ICC is presented with the respective confidence intervals. In order to calculate the SRD or Repeatability Coefficient (RC) which is expressed in the same units as the test values (ms), the Standard Error of Measurement (SEM) had to be obtained and therefore, it is also presented. The mean and standard deviations of the differences calculated between the recordings for the crackles' IDW and 2CD are also presented in the tables and the values were used to plot the mean difference and to calculate and plot the 95% of limits of agreement (also presented in the tables) in the Bland and Altman 95% limits of agreement. The Standard Error of the mean difference ($SE\bar{d}$) was calculated to be able to obtain the 95% CI for the mean difference for both variables in the seven recording positions. These values are also presented in the tables to help the interpretation of the results. To avoid the construction of many tables the ICC, SRD and Bland & Altman 95% limits of agreement results related to each group of participants are presented in the same table, i.e., one table for CF participants and one for Br participants.

Cystic fibrosis participants – at baseline (data from both studies polled)																
	ICC (95% CI) - IDW	ICC (95% CI) - 2CD	SEM IDW (ms)	SEM 2CD (ms)	SRD IDW (ms)	SRD 2CD (ms)	$\bar{d}$ IDW (ms)	SD_{diff} IDW (ms)	$\bar{d}$ 2CD (ms)	SD_{diff} 2CD (ms)	$SE\bar{d}$ IDW (ms)	$SE\bar{d}$ 2CD (ms)	95% CI for $\bar{d}$ IDW (ms)	95% CI for $\bar{d}$ 2CD (ms)	95% LA IDW (ms)	95% LA 2CD (ms)
T	0.57(0.16;0.84)	0.92(0.78;0.97)	0.12	0.54	0.33	1.49	-0.06	0.16	-0.27	0.73	0.04	0.18	(-0.15;0.03)	(-0.67;0.13)	(-0.38;0.26)	(-1.73;1.19)
AR	0.77(0.38;0.92)	0.91(0.76;0.97)	0.18	0.68	0.50	1.89	-0.001	0.26	-0.30	0.95	0.06	0.23	(-0.14;0.14)	(-0.82;0.22)	(-0.52;0.52)	(-2.2;1.6)
AL	0.85(0.61;0.95)	0.75(0.32;0.91)	0.17	0.96	0.46	2.66	-0.070	0.23	-0.48	1.30	0.06	0.32	(-0.20;0.06)	(-1.19;0.23)	(-0.53;0.39)	(-3.08;2.12)
LR	0.84(0.58;0.94)	0.88(0.68;0.96)	0.14	0.62	0.40	1.71	-0.01	0.21	0.16	0.88	0.05	0.21	(-0.13;0.11)	(-0.32;0.64)	(-0.43;0.41)	(-1.6;1.92)
LL	0.83(0.55;0.94)	0.96(0.88;0.98)	0.21	0.46	0.59	1.29	-0.07	0.30	-0.01	0.68	0.07	0.16	(-0.23;0.09)	(-0.38;0.36)	(-0.67;0.53)	(-1.37;1.35)
PR	0.85(0.60;0.95)	0.90(0.73;0.96)	0.20	0.62	0.55	1.73	-0.01	0.29	0.03	0.91	0.07	0.22	(-0.17;0.15)	(-0.47;0.53)	(-0.59;0.57)	(-1.79;1.85)
PL	0.72(0.24;0.90)	0.94(0.84;0.98)	0.27	0.55	0.76	1.53	0.05	0.40	0.33	0.73	0.10	0.18	(-0.17;0.27)	(-0.07;0.73)	(-0.75;0.85)	(-1.13;1.79)

Table 17: Results from Intraclass Correlation Coefficient (ICC) with the 95% Confidence Intervals (CI), Standard Error of Measurement (SEM), Smallest Real Difference (SRD), Mean ($\bar{d}$) and Standard Deviation (SD) of the differences (diff.), Standard Error of the mean difference ($SE\bar{d}$), 95% Confidence Intervals for the mean difference and 95% Limits of Agreement (LA), obtained from the analysis of crackles' **IDW** and **2CD** of **cystic fibrosis** participants (n = 17), with the **baseline** data from both studies pooled.

Bronchiectasis participants – at baseline (data from both studies polled)																
	ICC (95% CI) - IDW	ICC (95% CI) - 2CD	SEM IDW (ms)	SEM 2CD (ms)	SRD IDW (ms)	SRD 2CD (ms)	$\bar{d}$ IDW (ms)	SD_{diff} IDW (ms)	$\bar{d}$ 2CD (ms)	SD_{diff} 2CD (ms)	$SE\bar{d}$ IDW (ms)	$SE\bar{d}$ 2CD (ms)	95% CI for $\bar{d}$ IDW (ms)	95% CI for $\bar{d}$ 2CD (ms)	95% LA IDW (ms)	95% LA 2CD (ms)
T	0.81(0.63;0.90)	0.95(0.90;0.97)	0.10	0.57	0.29	1.59	-0.03	0.15	-0.12	0.82	0.02	0.13	(-0.09;0.03)	(-0.42;0.18)	(-0.33;0.27)	(-1.76;1.52)
AR	0.76(0.53;0.87)	0.87(0.75;0.93)	0.16	0.84	0.46	2.33	0.060	0.23	-0.11	1.20	0.04	0.20	(-0.03;0.15)	(-0.56;0.34)	(-0.4;0.52)	(-2.51;2.29)
AL	0.78(0.57;0.89)	0.86(0.72;0.93)	0.17	0.83	0.46	2.30	0.030	0.24	-0.01	1.19	0.04	0.20	(-0.06;0.12)	(-0.45;0.43)	(-0.45;0.51)	(-2.39;2.37)
LR	0.80(0.61;0.90)	0.92(0.85;0.96)	0.16	0.71	0.44	1.97	-0.01	0.23	-0.28	0.98	0.04	0.16	(-0.10;0.08)	(-0.64;0.08)	(-0.47;0.45)	(-2.24;1.68)
LL	0.69(0.41;0.84)	0.82(0.65;0.91)	0.16	0.83	0.44	2.31	-0.02	0.22	-0.21	1.18	0.04	0.19	(-0.10;0.06)	(-0.65;0.23)	(-0.46;0.42)	(-2.57;2.15)
PR	0.72(0.45;0.85)	0.91(0.82;0.95)	0.19	0.68	0.54	1.89	-0.05	0.28	-0.17	0.96	0.05	0.16	(-0.15;0.05)	(-0.53;0.19)	(-0.61;0.51)	(-2.09;1.75)
PL	0.87(0.74;0.93)	0.93(0.87;0.97)	0.22	0.66	0.61	1.82	-0.05	0.31	-0.12	0.93	0.05	0.15	(-0.17;0.07)	(-0.47;0.23)	(-0.67;0.57)	(-1.98;1.74)

Table 18: Results from Intraclass Correlation Coefficient (ICC) with the 95% Confidence Intervals (CI), Standard Error of Measurement (SEM), Smallest Real Difference (SRD), Mean ($\bar{d}$) and Standard Deviation (SD) of the differences (diff.), Standard Error of the mean difference ($SE\bar{d}$), 95% Confidence Intervals for the mean difference and 95% Limits of Agreement (LA), obtained from' the analysis of crackles' **IDW** and **2CD** of **bronchiectasis** participants (n = 37), with the **baseline** data from both studies pooled.

Intraclass Correlation Coefficient results at baseline

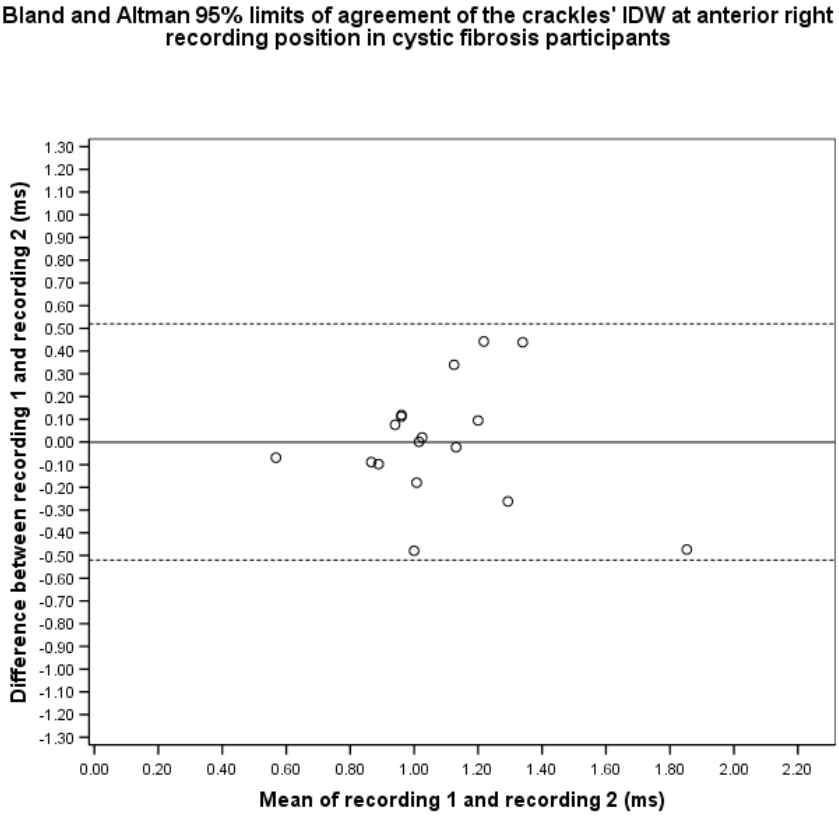
The intraclass correlation coefficient (ICC) results, shown in Table 17 and Table 18 were analysed according to Fleiss (1986) criteria, i.e., ICC values above 0.75 represent 'excellent' reliability; values between 0.4 and 0.75 represent 'moderate to good' reliability and values below 0.4 represent 'poor' reliability. In this research the ICC baseline results of the recordings from both groups of participants, were generally found to be 'excellent'. For the CF participants, the 'excellent' reliability of the crackles' IDW varied between 0.77 and 0.85 and for the crackles' 2CD varied between 0.75 and 0.96. 'Good' reliability values were found for the crackles' IDW at trachea (0.57) and at posterior left (0.72). For the Br participants the 'excellent' reliability for the crackles' IDW varied between 0.76 and 0.87, and for the crackles' 2CD between 0.82 and 0.95. 'Good' reliability values for this group of participants were also found for the crackles' IDW, at lateral left (0.69) and at posterior right (0.72).

Smallest Real Difference results at baseline

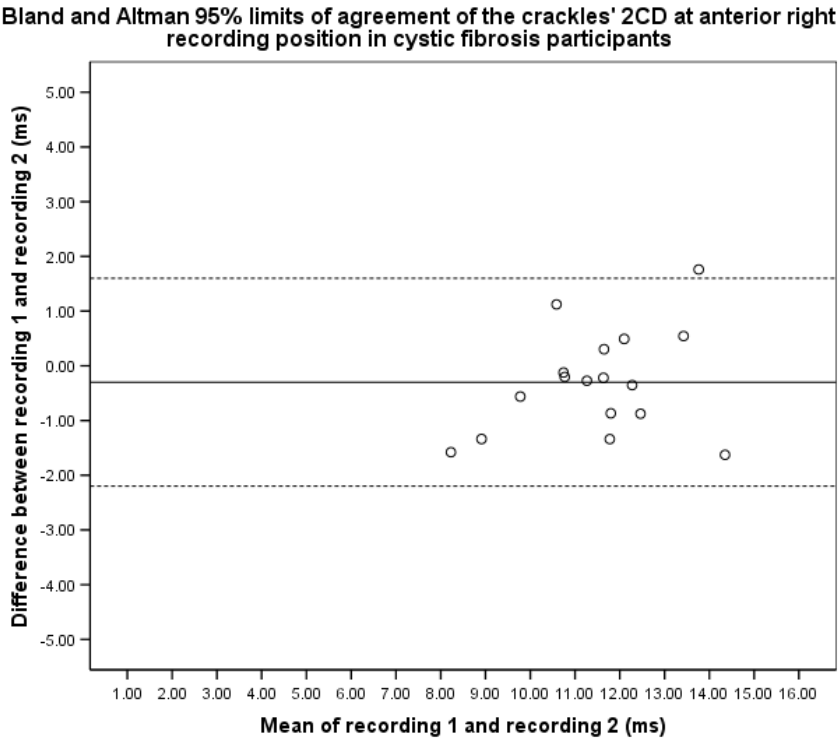
In these groups of participants the SRD measured at baseline, for both variables, was similar as shown in Table 17 and in Table 18. In CF participants, the SRD values of the crackles' IDW, ranged between 0.33 ms to 0.76 ms; and the crackles' 2CD ranged between 1.29 ms to 2.66 ms. In the Br participants, the crackles' IDW presented SRD values ranging between 0.29 ms to 0.61 ms. For the crackles' 2CD the SRD ranged between 1.59 ms to 2.33 ms. However, it is important to notice the particularly high value detected at anterior left (2.66 ms for the crackles' 2CD) in CF participants. Possible reasons for this finding will be explained in the Discussion chapter (section 6.3.1.2.2).

Bland and Altman 95% limits of agreement results at baseline

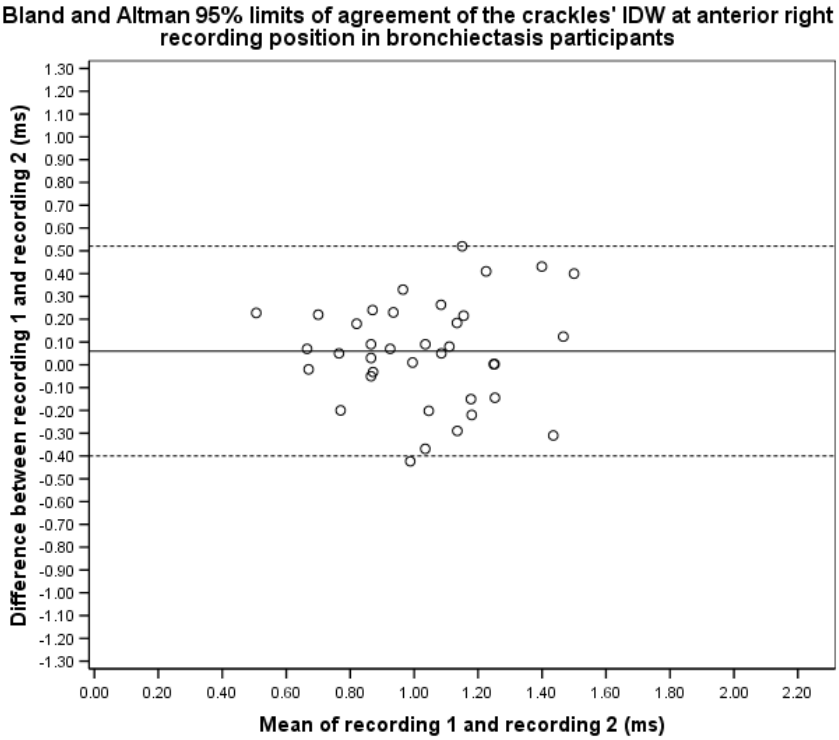
A scatter plot was produced for each variable in each recording position, with the baseline data from both studies pooled. Therefore, due to the large number of files, only one example per variable, in one recording position is provided here. Graph 1 and Graph 2 show an example of the crackles' IDW and of the crackles' 2CD in CF participants. Graph 3 and Graph 4 show an example of the crackles' IDW and of the Crackles' 2CD in Br participants. For complete analysis see Appendix 4 on the CD provided. In the graphs, the mean difference was plotted using a solid line and the 95% limits of agreement, upper and lower limits, were plotted using dotted lines. The 95% Confidence Intervals for the mean difference are also presented in Table 17 and in Table 18.



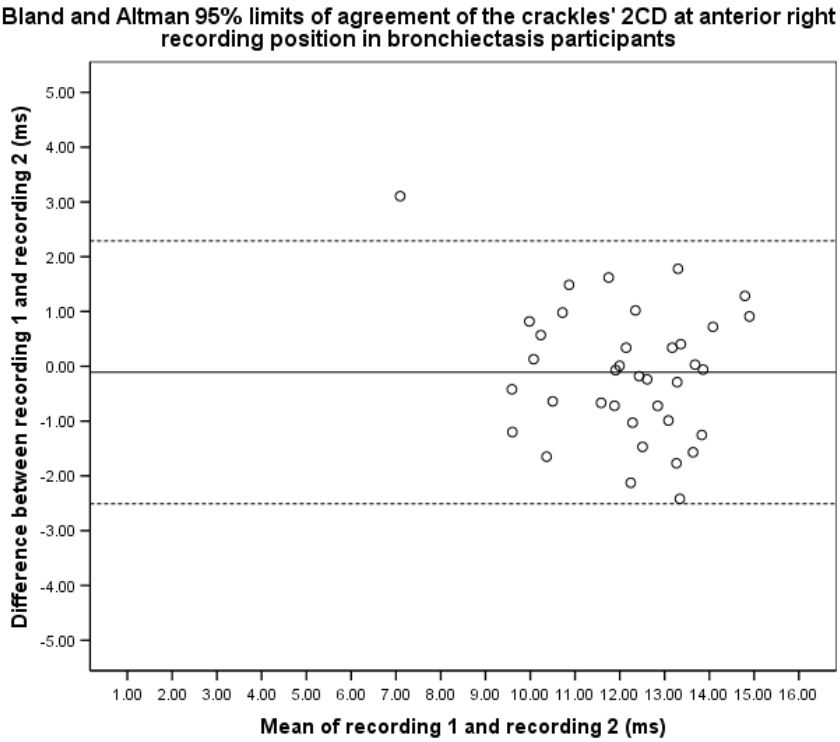
Graph 1: Results from the Bland & Altman 95% limits of agreement of the crackles' initial deflection width (**IDW**) obtained from the **cystic fibrosis** participants (n = 17) at **anterior right** of the chest, with the **baseline** data from both studies pooled.



Graph 2: Results from the Bland & Altman 95% limits of agreement of the crackles' two cycles deflection (**2CD**) obtained from the **cystic fibrosis** participants (n = 17) at **anterior right** of the chest, with the **baseline** data from both studies pooled.



Graph 3: Results from the Bland & Altman 95% limits of agreement of the crackles' initial deflection width (**IDW**) obtained from the **bronchiectasis** participants (n = 37) at **anterior right** of the chest, with the **baseline** data from both studies pooled.



Graph 4: Results from the Bland & Altman techniques of the crackles' two cycles deflection (**2CD**) obtained from the **bronchiectasis** participants (n = 37) at **anterior right** of the chest before interventions, with the **baseline** data from both studies pooled.

These plots (Graph 1 to 4) indicate that at baseline, no systematic bias was present in any of the groups, in any recording position for both variables studied (crackles' IDW and crackles' 2CD).

The reliability analysis was also performed post interventions (separately for each study as discussed previously). However, as at baseline, no systematic bias was present in any of the groups in any recording position for both variables. Therefore, it was decided to present one example at anterior right of this analysis in Appendix 14 of this Thesis (for complete analyses please see Appendix 4 on the CD provided).

In summary, this reliability section has shown that CALSA presents acceptable test-retest reliability over short periods of time. The next section will explore another aspect of developing a new outcome measure, the responsiveness to change. The results from each study will be presented following a similar structure to that used in the reliability section, i.e., in sub-sections created for the CF participants and for the Br participants.

5.7.2. Responsiveness to change

This section will present the results of estimates of responsiveness to change calculated from the analysis of the crackles data at baseline and post interventions in each study.

The null hypothesis tested with the ANOVA, i.e., that participants were comparable (inter-subject reliability) was rejected. This was tested within the two groups, CF and Br, separately in both studies. Therefore, it is acknowledged that the lung sounds measurements recorded at each place (for each variable) should not be averaged between participants for inferential statistical analysis. However, it was considered that the use of the arithmetic mean purely to illustrate a pattern that had been detected between the two groups of participants could be valuable. Therefore the data in tables 19 to 30 and in graphs 5 to 36 has been summarised in this manner. However, no inferential statistical analysis has been performed. Inferential statistics have only been performed with data from baseline and post intervention of each participant.

The crackles' frequency analysis, in both groups of participants, at baseline and post interventions, in the first and in the second study will be presented followed by the number and timing of crackles detection per breathing cycle (analysis only performed in the second study of this research).

5.7.2.1. Results from crackle frequency analysis

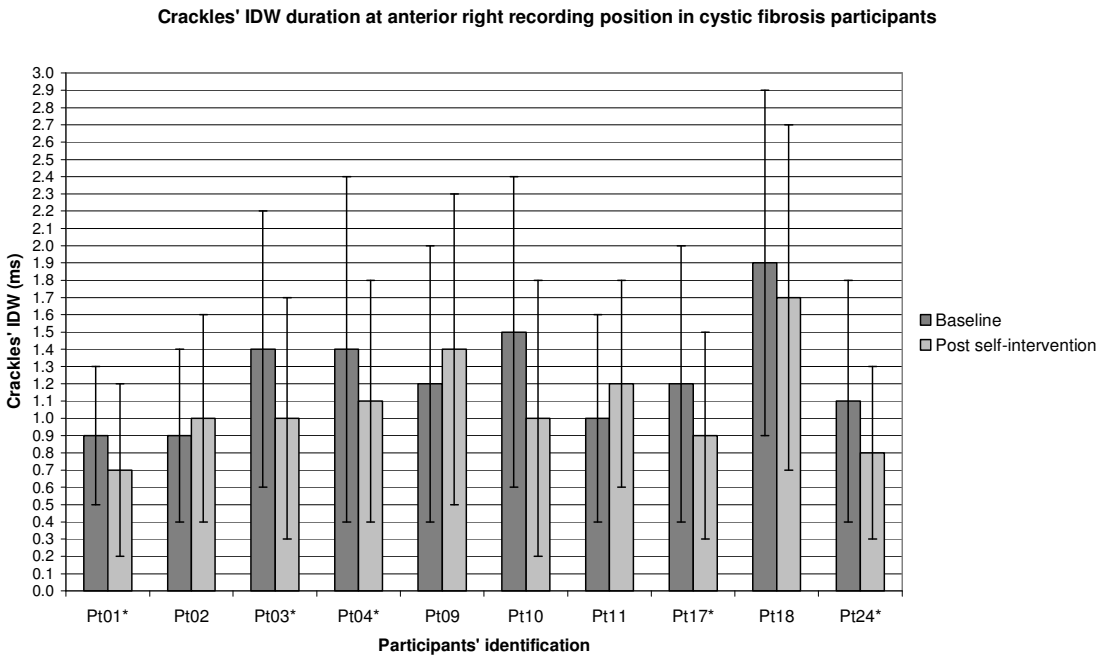
This section addresses the crackle analysis recorded from CF and Br participants in both studies of this research.

After testing the reliability of the lung sounds, the unpaired t-test was run in both studies, comparing the crackles' data post interventions with the baseline measurements, for each variable (crackles' IDW and crackles' 2CD), to assess if changes could be detected. Due to the large number of individual measurements, only a summary analysis is provided, with the main findings displayed in graphs for better visualisation of the data. However, complete analysis of the unpaired t-test results obtained from each variable studied, in each recording position, for each participant can be seen in Appendix 5 on the CD provided. Each graph, presented in the text or in the Appendix, refers to one variable, in one chest location, studied in CF or Br participants. In the x axis the participants' identification can be found and in the y axis, the crackles' initial deflection width (IDW) or the crackles' two cycle deflection (2CD) variables, in milliseconds (ms), are shown. Results will be presented for one variable, e.g., crackles' IDW, in the first study followed by the same variable in the second study, first for the CF participants and then for the Br participants at anterior right of the chest (for complete analysis please see Appendix 6 on the CD provided).

5.7.2.1.1. Crackles' frequency analysis in cystic fibrosis participants

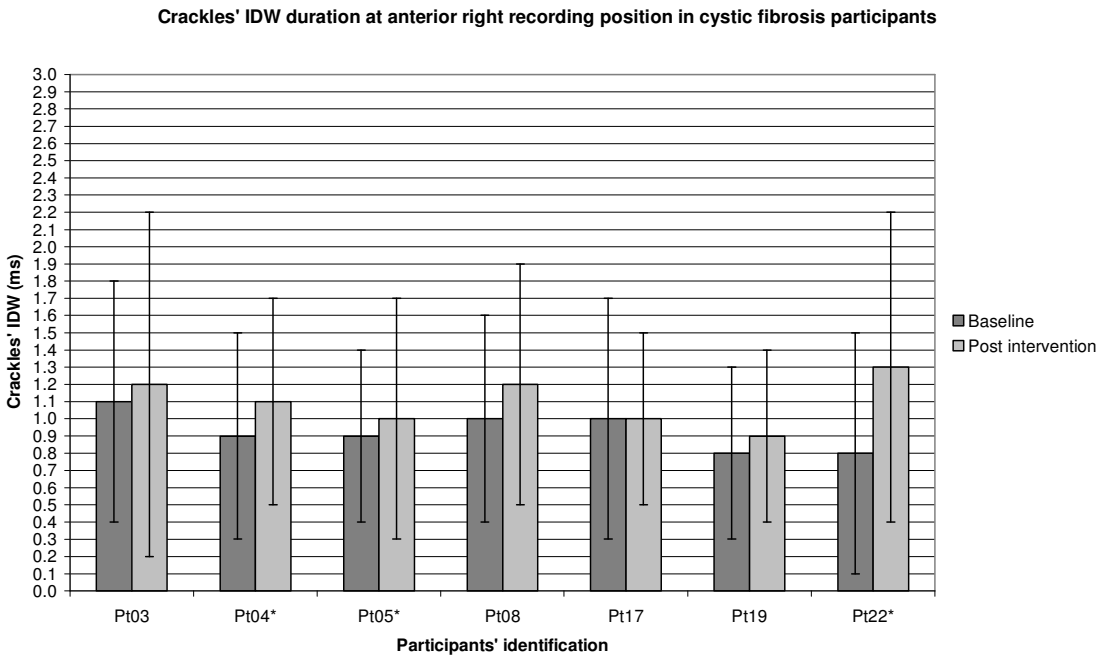
Results from the analysis of the crackles' initial deflection width (IDW) and of the two cycle deflection (2CD), at seven chest locations were analysed from 10 CF participants in the first study, and from 7 CF participants in the second study, at baseline and post airway clearance interventions.

Graph 5 and Graph 6 are examples of the analysis of crackles' IDW, recorded at anterior right of the chest which illustrates the pattern of the results found in this group of participants in each study.



Graph 5: Average data from crackles' **IDW** duration (ms) recorded at **anterior right** of the chest in **cystic fibrosis** participants (n = 10), at **baseline** and **post** airway clearance **self-intervention** (**first study**). ***** starred results are significant, $p<0.05$. Error bars represent ± standard deviation.

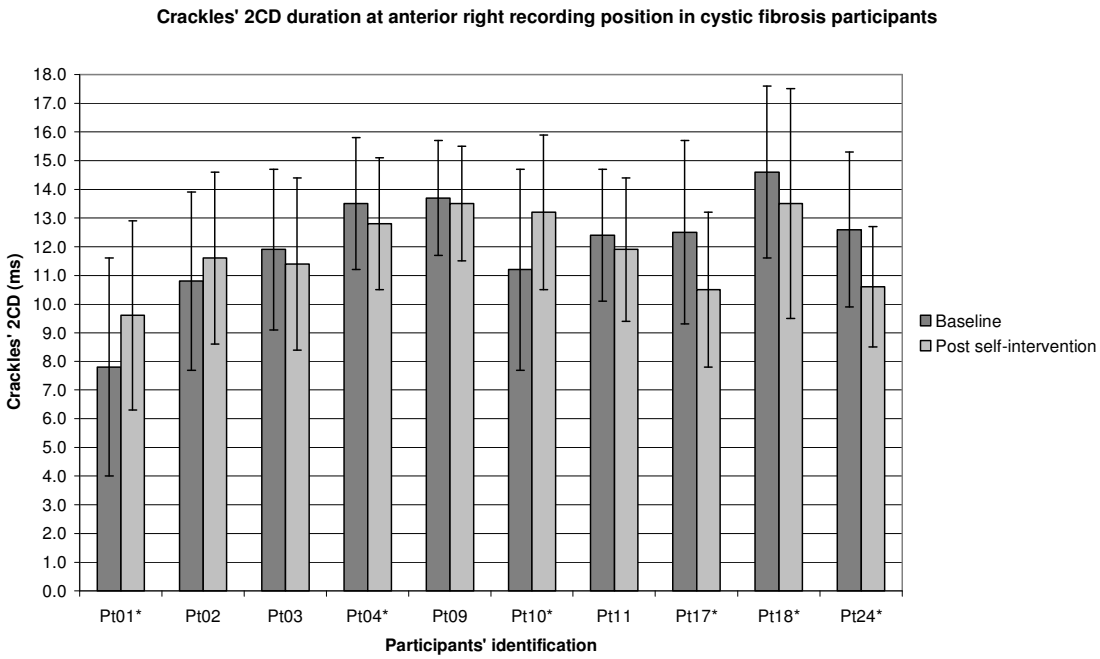
Seven participants had a decrease in duration of the crackles' IDW post self-intervention (Pt01, Pt03, Pt04, Pt10, Pt17, Pt18 and Pt24). The differences were statistically significant for the crackles' IDW in Pt01 (from 0.9±0.4 ms to 0.7±0.5 ms, $p=0.018$), in Pt03 (from 1.4±0.8 ms to 1.0±0.7 ms, $p=0.002$), in Pt04 (from 1.4±1 ms to 1.1±.7 ms, $p=0.014$), in Pt17 (from 1.2±0.8 ms to 0.9±0.6 ms, $p=0.044$) and in Pt24 (from 1.1±0.7 ms to 0.8±0.5 ms, $p=0.003$). Participant Pt02, participant Pt09 and participant Pt11 presented an increase of the duration of the crackles' IDW, post the self-intervention, but the changes were not statistically significant.



Graph 6: Average data from crackles' **IDW** duration (ms) recorded at **anterior right** of the chest in **cystic fibrosis** participants (n = 7), at **baseline** and **post physiotherapy** intervention (**second study**). * starred results are significant, $p<0.05$. Error bars represent ± standard deviation.

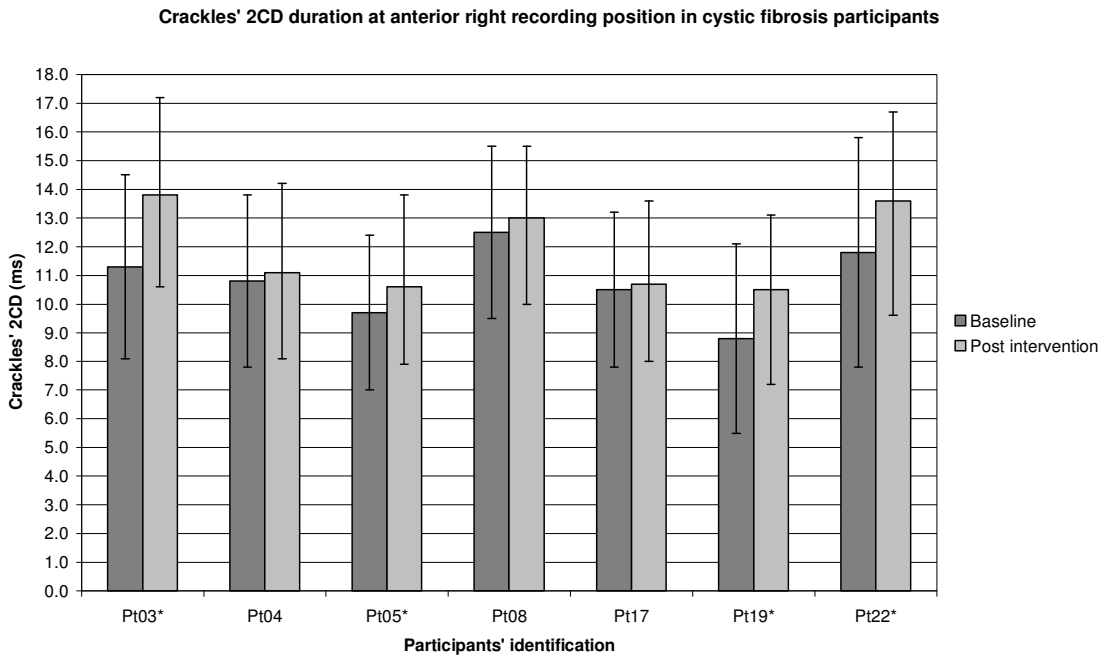
Graph 6 shows that an increase in duration of the crackles' IDW occurred in this recording position in all the seven CF participants. The differences were statistically significant in Pt04 (0.9±0.6ms to 1.1±0.6ms, $p=0.022$), in (Pt05 (IDW from 0.9±0.5 ms to 1±0.7ms, $p=0.04$) and in Pt22 (IDW from 0.8±0.7ms to 1.3±0.9ms, $p=0.003$).

Graph 7 and Graph 8 are examples of the analysis of crackles' 2CD, recorded at anterior right of the chest which illustrates the pattern of the results found in this group of participants in each study.



Graph 7: Average data from crackles' **2CD** duration (ms) recorded at **anterior right** of the chest in **cystic fibrosis** participants (n = 10), at **baseline** and **post** airway clearance **self intervention** (**first study**). * starred results are significant, $p<0.05$. Error bars represent ± standard deviation.

Seven participants had a decrease in duration of the crackles' 2CD post self-intervention (Pt03, Pt04, Pt09, Pt11, Pt17, Pt18 and Pt24). The differences were statistically significant for the crackles' 2CD in Pt04 (from 13.5±2.3 ms to 12.8±2.3 ms, p=0.020), in Pa17 (from 12.5±3.2 ms to 10.5±2.7 ms, p=0.001), in Pt18 (from 14.6±3 ms to 13.5±4 ms, p=0.031) and in Pt24 (from 12.6±2.7 ms to 10.6±2.1 ms, p=0.001). Three participants presented an increase in crackles' IDW, participant Pt01, participant Pt02 and participant Pt10. These differences were statistically significant for Pt01 (from 7.8±3.8 ms to 9.6±3.6 ms, p=0.001) and in Pt10 (from 11.2±3.5 ms to 13.2±2.7 ms, p=0.001).



Graph 8: Average data from crackles' **2CD** duration (ms) recorded at **anterior right** of the chest in **cystic fibrosis** participants (n = 7), at **baseline** and **post physiotherapy** intervention (**second study**). * starred results are significant, $p<0.05$. Error bars represent ± standard deviation.

In the second study, similarly to the crackles' IDW variable, it was observed that the duration of the crackles' 2CD increased in this recording position in all CF participants (see Graph 8). The differences were statistically significant in both variables in Pt03 (from 11.3±3.2 ms to 13.8±3.4ms, $p=0.001$), in Pt05 (from 9.7±2.7ms to 10.6±3.2ms, $p=0.017$), in Pt19 (from 8.8±3.3ms to 10.5±2.7ms, $p=0.001$) and in Pt22 (from 11.8±4ms to 13.6±3.1ms, $p=0.017$).

In summary, it was observed that in the majority of the CF participants in the first study, the duration of both crackles' variables studied decreased whereas in the second study, the duration of the same crackles' variables increased. This tendency can be better illustrated in Table 19 and Table 20 for the crackles' IDW and in Table 21 and Table 22 for the crackles' 2CD from each study. The same key was used for all the tables, i.e., T – trachea; AR – anterior right; AL – anterior left, LR – lateral right; LL – lateral left; PR – posterior right; PL – posterior left; ↑ means an increase of the crackles' duration in ms; ↓ means a decrease of the crackles' duration in ms; = means no modification of the values, comparing post airway clearance interventions with the baseline measurements of each crackles' variable in each study. The following tables (Table 19 and Table 20), summarise the results obtained from the analysis of the duration of the crackles' IDW in individual CF participants in each study.

Crackles' Initial Deflection Width (IDW)								
Code	**T**	**AR**	**AL**	**LR**	**LL**	**PR**	**PL**	**Total**
CF01	↑*	↓*	↑*	↑*	=	↑*	↓*	1=4↑ 2↓
CF02	↓*	↑	↑*	=	↑	↑	↑	1=5↑ 1↓
CF03	=	↓*	↑*	↓*	=	↓	=	3=2↑ 3↓
CF04	↑*	↓*	↑	↓*	↓*	↓*	↑*	3↑ 4↓
CF09	↓	↑	↓	↑	↓*	↓	↓	2↑ 5↓
CF10	↑	=	↑	↓	↓	↓*	↓	1=2↑ 4↓
CF11	=	↑	↓	↑	↓	↑*	↑*	1=4↑ 2↓
CF17	↑	↓*	↓*	=	↓*	↓	↓	1=1↑ 5↓
CF18	↑	↓	↓*	↓	↓	=	↓*	1=1↑ 5↓
CF24	↓*	↓*	↓*	↑*	↓	↑	↓	2↑ 5↓
Total	2= 5↑3↓	1= 4↑5↓	5↑5↓	2= 4↑4↓	2= 1↑7↓	1= 4↑5↓	1= 3↑6↓	

Table 19: Results from crackles' **IDW** duration at the seven locations of the chest in **cystic fibrosis** participants (n=10) in the **first study** (* starred results are significant, p<0.05).

Crackles' Initial Deflection Width (IDW)								
Code	**T**	**AR**	**AL**	**LR**	**LL**	**PR**	**PL**	**Total**
CF03	↑*	↑	↑	↑	↑	↑*	↓	6↑ 1↓
CF04	↑*	↑*	↓	↓*	↓*	↓	↓*	2↑ 5↓
CF05	↑	↑*	↑*	↑	↓*	↓*	↓	4↑ 3↓
CF08	↑	↑	=	↓	↑	↓*	↑	4↑ 2↓ 1=
CF17	=	↑	↑	↓*	↓	↓	↓*	2↑ 4↓ 1=
CF19	↑*	↑	↓	↑*	↑	↓	↑	5↑ 2↓
CF22	↓	↑*	↓	↑*	↑	↑	↑	5↑ 2↓
Total	5↑ 1↓ 1=	7↑	3↑ 3↓1=	4↑ 3↓	4↑ 3↓	2↑ 5↓	4↑ 3↓	

Table 20: Results from crackles' **IDW** duration at the seven locations of the chest in cystic fibrosis participants (n = 7) in the **second study** (* starred results are significant, p<0.05).

It is therefore possible to see that in the first study, the number of participants who had a **decrease** in the duration of the crackles' IDW variable is generally greater than the number who had an **increase**, post airway clearance self-intervention. In the second study an opposite tendency was found, i.e., the number of participants who had an **increase** in the duration of both variables was generally greater than the number who had a **decrease**, post physiotherapy intervention applied by a physiotherapist. The exceptions occurred for the crackles' IDW variable at anterior left region (where an equal number of participants had the crackles' duration increasing and decreasing post the intervention), and at posterior right (where the crackles' duration decreased in the majority of the participants).

Table 21 and Table 22, summarise the results obtained from the analysis of the duration of the crackles' 2CD in individual CF participants in each study.

Crackles' Two Cycles Deflection (2CD)								
Code	**T**	**AR**	**AL**	**LR**	**LL**	**PR**	**PL**	**Total**
CF01	↑*	↑*	=	↑*	↑	↓*	↓	1=4↑2↓
CF02	↓*	↑	↑*	↑	↑	↓	↑*	5↑ 3↓
CF03	↓	↓	↑*	↓	↑	↓	↓	2↑ 5↓
CF04	↑	↓*	↑*	↓*	↑	↓*	↑*	4↑ 3↓
CF09	↓	↓	↓	↓*	↓*	↓	↓	7↓
CF10	↑	↑*	↓	↓	↑	↓*	↓	3↑ 4↓
CF11	↓	↓	↓	↓	↓	↑*	↑	2↑ 5↓
CF17	↑	↓*	↓*	=	↑	↓*	↓*	1=2↑ 4↓
CF18	↑*	↓*	↓*	↓*	↓	↑	↓*	2↑ 5↓
CF24	↓*	↓*	↓*	↑	↓	↓	↓*	1↑ 6↓
Total	5↑5↓	3↑7↓	1= 3↑6↓	1= 3↑6↓	6↑4↓	2↑8↓	3↑7↓	

Table 21: Results from crackles' **2CD** duration at the seven locations of the chest in **cystic fibrosis** participants (n = 10) in the **first study** (* starred results are significant, $p<0.05$).

Crackles' Two Cycles Deflection (2CD)								
	T	**AR**	**AL**	**LR**	**LL**	**PR**	**PL**	**Total**
CF03	↑	↑*	↑*	↑	↑	↑*	↓	6↑ 1↓
CF04	↑	↑	↓	↓*	↓*	↑	↑	4↑ 3↓
CF05	↑	↑*	↑*	↓	↓*	↓*	↓	3↑ 4↓
CF08	↑*	↑	↓	↑	↑*	↓*	↓	4↑ 3↓
CF17	↓*	↑	↓	↓	↑	↓	↓*	2↑ 5↓
CF19	↑*	↑*	↓*	↑*	↑	↓	↑	5↑ 2↓
CF22	↓*	↑*	↓*	↑*	↑	↑	↓	4↑3↓
Total	6↑ 1↓	7↑	2↑ 5↓	4↑ 3↓	5↑ 2↓	3↑ 4↓	2↑ 5↓	

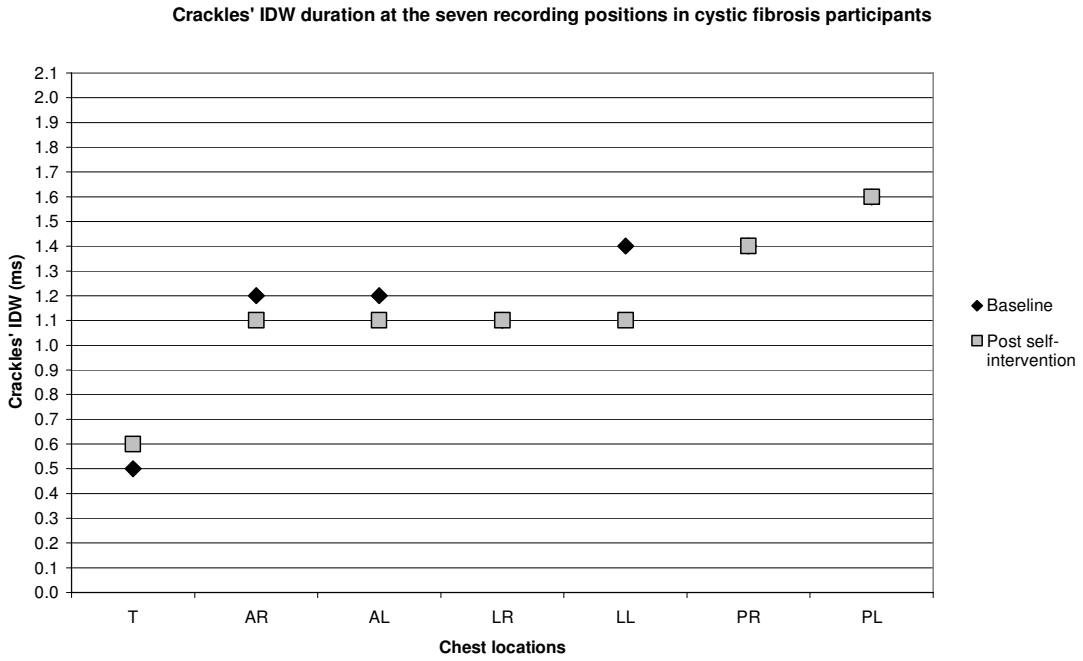
Table 22: Results from crackles' **2CD** duration at the seven locations of the chest in **cystic fibrosis** participants (n = 7) in the **second study** (* starred results are significant, $p<0.05$).

The pattern for the crackles' 2CD duration was similar to that seen for the IDW. In the first study the number of participants who had a **decrease** in the duration of the crackles' IDW variable was generally greater than the number who had an **increase** and in the second study an opposite tendency was found. The exceptions were at anterior left and posterior regions of the chest where the crackles' 2CD duration decreased in the majority of the participants.

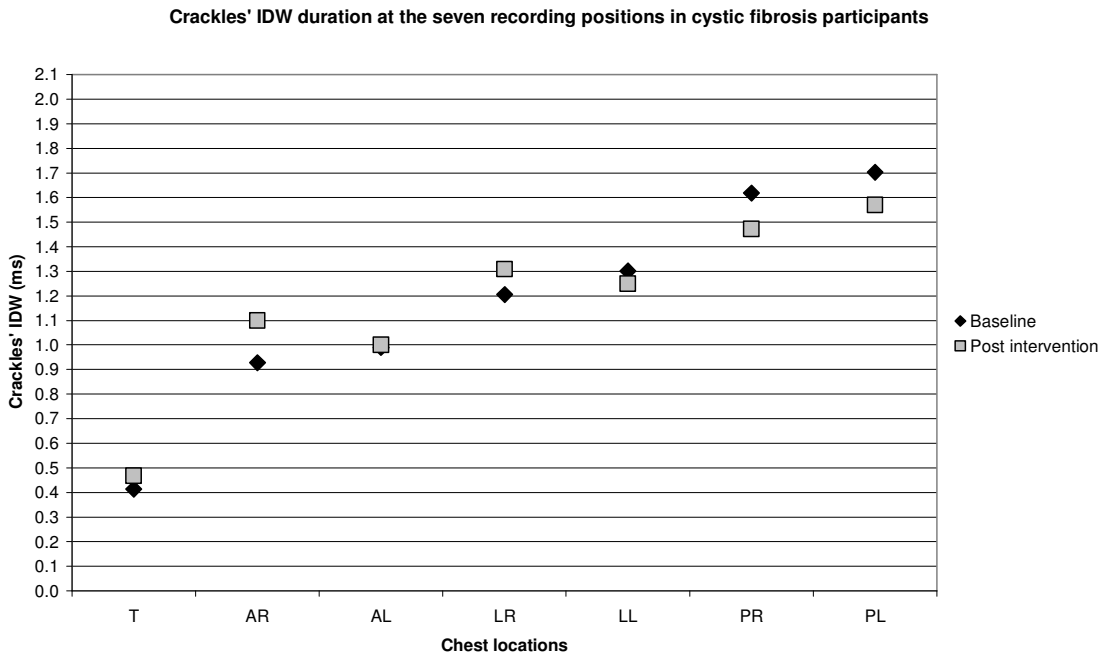
Therefore, in the CF participants, contradictory tendencies were seen in the duration of both crackles' variables in each study. In the first study, the duration of both crackles' variables decreased in the majority of participants. As shorter crackles' 2CD duration is associated with higher frequency, this suggests that the frequencies of the crackles were **increasing,** which suggests they were generated from more peripheral areas of the lungs than at baseline. In the second study, the duration of both crackles' variables increased in the majority of participants, after a physiotherapy intervention applied by a physiotherapist. As longer crackles' 2CD duration is associated with lower frequency,

this suggests that the frequencies of the crackles were **decreasing,** which suggests they were generated from more central areas of the lungs than at baseline.

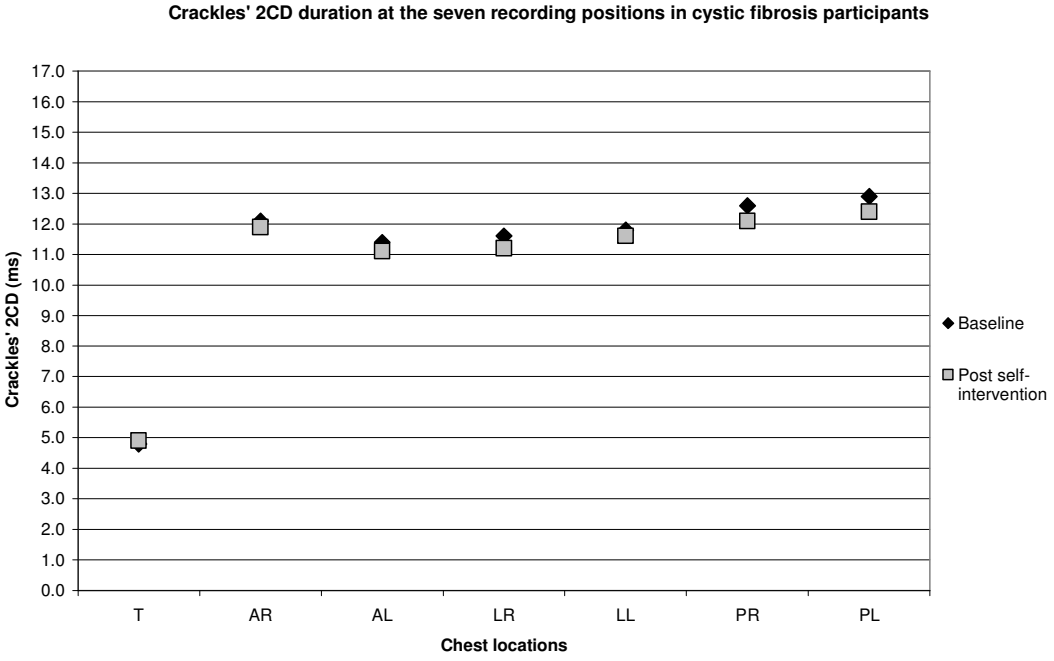
This pattern can be better visualised using the averaged data depicted in Graph 9 and Graph 10 for the crackles' IDW and the Graph 11 and Graph 12 for the crackles' 2CD, in each study. The key for the chest locations was the same in all graphs i.e. T – trachea; AR – anterior right; AL – anterior left, LR – lateral right; LL – lateral left; PR – posterior right; PL – posterior left.



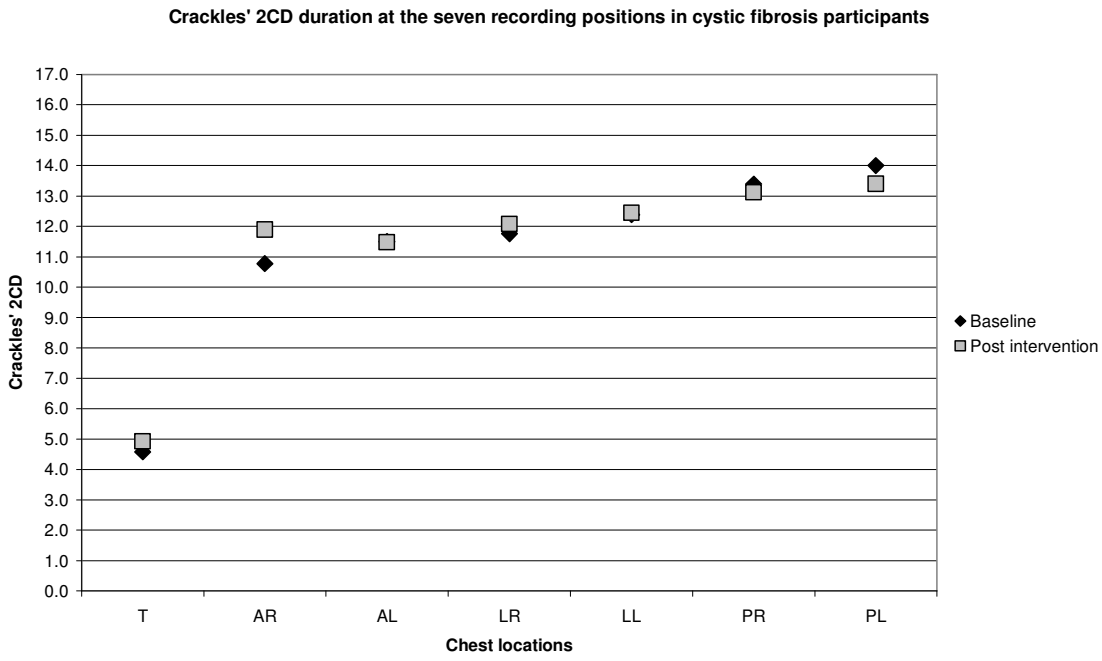
Graph 9: Results from crackles' **IDW** (ms) analysis in **cystic fibrosis** participants (n = 10) at the seven chest locations (**first study**).



Graph 10: Results from crackles' **IDW** (ms) analysis in **cystic fibrosis** participants (n = 7) at the seven chest locations (**second study**).



Graph 11: Results from crackles' **2CD** (ms) analysis in **cystic fibrosis** participants (n = 10) at the seven chest locations (**first study**).



Graph 12: Results from crackles' **2CD** (ms) analysis in **cystic fibrosis** participants (n = 7) at the seven chest locations (**second study**).

The duration of the crackles' variables, IDW and 2CD, in the first study is generally **shorter** post self-intervention whereas, in the second study it is generally **longer** post the intervention, with the exception of the posterior regions of the chest. Shorter durations mean an increase and longer durations a decrease, in the crackles' frequencies. However, it is important to note that the duration of the crackles' 2CD, in both studies, at baseline and post interventions, are values above 10 ms, which indicates that the crackles in the CF participants were more coarse, low frequency crackles than fine, high frequency crackles. The trachea values should be interpreted differently from the values generated from other chest locations. In the other chest positions there is a low pass filter due to the lung tissue. This does not apply at trachea region. Therefore the CORSA guidelines of 10 ms to differentiate fine, high (< 10 ms or > 100 Hz) from coarse, low frequency (>10 ms or < 100 Hz) crackles is not applicable for the trachea region.

5.7.2.1.2. Smallest Real Difference and Bland and Altman 95% limits of agreement in crackles' data from cystic fibrosis participants, before versus after airway clearance interventions

Bland and Altman 95% limits of agreement and the SRD were also calculated to assess if the interventions had any bias effect on the crackles' frequency. In the second study, the physiotherapist's and participants' opinions had been sought about the participants' lungs clearance post intervention, thereby providing additional information. It was therefore felt that this analysis should be performed on the data subdivided in

three ways i) with the data from all the participants, ii) with the data from participants who considered their lungs to be clearer post intervention and iii) with the data from participants who the physiotherapist considered the lungs to be clearer post intervention. The table, with all the calculations, will only be presented for the analysis performed with the data from all the participants, as an example (for complete analysis see Appendix 7 on the CD provided). Results obtained from the analysis of the crackles' IDW and 2CD before versus after interventions, in each study, in CF participants are presented in Table 23 and Table 24. Detailed descriptions of all the calculations are presented in section 4.3.6.3.5.

Cystic fibrosis participants – analysis before versus after airway clearance self-intervention (first study)														
	SEM IDW (ms)	SEM 2CD (ms)	SRD IDW (ms)	SRD 2CD (ms)	$\bar{d}$ IDW (ms)	SD_{diff} IDW (ms)	$\bar{d}$ 2CD (ms)	SD_{diff} 2CD (ms)	$SE\bar{d}$ IDW (ms)	$SE\bar{d}$ 2CD (ms)	95% CI for $\bar{d}$ IDW (ms)	95% CI for $\bar{d}$ 2CD (ms)	95% LA IDW (ms)	95% LA 2CD (ms)
T	0.12	1.77	0.33	4.91	-0.03	0.17	-0.07	2.63	0.06	0.83	(-0.15;0.09)	(-1.95;1.81)	(-0.38;0.32)	(-5.32;5.19)
AR	0.15	0.75	0.41	2.08	0.01	0.22	0.12	1.11	0.07	0.35	(-0.15;0.17)	(-0.67;0.92)	(-0.44;0.45)	(-2.11;2.35)
AL	0.29	1.32	0.79	3.66	0.09	0.42	0.60	1.86	0.13	0.59	(-0.21;0.39)	(-0.73;1.94)	(-0.75;0.92)	(-3.12;4.33)
LR	0.18	0.82	0.49	2.28	-0.05	0.26	0.29	1.19	0.08	0.38	(-0.24;0.13)	(-0.57;1.14)	(-0.57;0.46)	(-2.10;2.67)
LL	0.23	0.85	0.64	2.37	0.22	0.25	0.23	1.25	0.08	0.40	(0.04;0.40)	(-0.67;1.12)	(-0.28;0.72)	(-2.28;2.73)
PR	0.25	1.05	0.68	2.91	0.02	0.37	0.64	1.41	0.12	0.45	(-0.24;0.29)	(-0.37;1.65)	(-0.71;0.76)	(-2.19;3.47)
PL	0.33	1.21	0.92	3.35	-0.05	0.49	0.56	1.70	0.16	0.54	(-0.40;0.30)	(-0.65;1.78)	(-1.04;0.94)	(-2.84;3.96)

Table 23: Results from Standard Error of Measurement (SEM), Smallest Real Difference (SRD), Mean ($\bar{d}$) and Standard Deviation (SD) of the differences (diff.), Standard Error of the mean difference ($SE\bar{d}$), 95% Confidence Intervals for the mean difference and 95% Limits of Agreement (LA), obtained from the analysis of crackles' **IDW** and **2CD** duration (ms) of **cystic fibrosis** (CF) participants (n = 10) **before versus after** airway clearance **self-intervention** (**first study**).

Cystic fibrosis participants – analysis before versus after physiotherapy intervention (second study)														
	SEM IDW (ms)	SEM 2CD (ms)	SRD IDW (ms)	SRD 2CD (ms)	$\bar{d}$ IDW (ms)	SD_{diff} IDW (ms)	$\bar{d}$ 2CD (ms)	SD_{diff} 2CD (ms)	$SE\bar{d}$ IDW (ms)	$SE\bar{d}$ 2CD (ms)	95% CI for $\bar{d}$ IDW (ms)	95% CI for $\bar{d}$ 2CD (ms)	95% LA IDW (ms)	95% LA 2CD (ms)
T	0.08	0.58	0.23	1.60	-0.06	0.12	-0.34	0.80	0.05	0.30	(-0.16;0.04)	(-1.02;0.34)	(-0.30;0.18)	(-1.94;1.26)
AR	0.18	1.08	0.51	3.00	-0.21	0.17	-1.18	1.05	0.06	0.40	(-0.36;-0.06)	(-2.08;-0.28)	(-0.55;0.13)	(-3.28;0.92)
AL	0.12	1.19	0.34	3.31	-0.01	0.19	0.02	1.82	0.07	0.69	(-0.17;0.15)	(-1.53;1.57)	(-0.39;0.37)	(-3.62;3.66)
LR	0.33	1.15	0.92	3.19	-0.13	0.49	-0.31	1.73	0.19	0.65	(-0.55;0.29)	(-1.79;1.17)	(-1.11;0.85)	(-3.77;3.15)
LL	0.14	0.90	0.38	2.49	0.07	0.19	-0.03	1.37	0.07	0.52	(-0.09;0.23)	(-1.20;1.14)	(-0.31;0.45)	(-2.77;2.71)
PR	0.30	1.05	0.83	2.90	0.16	0.42	0.28	1.57	0.16	0.59	(-0.20;0.52)	(-1.06;1.62)	(-0.68;1.00)	(-2.86;3.42)
PL	0.33	1.02	0.92	2.83	0.13	0.49	0.53	1.45	0.19	0.55	(-0.29;0.55)	(-0.71;1.77)	(-0.85;1.11)	(-2.37;3.43)

Table 24: Results from Standard Error of Measurement (SEM), Smallest Real Difference (SRD), Mean ($\bar{d}$) and Standard Deviation (SD) of the differences (diff.), Standard Error of the mean difference ($SE\bar{d}$), 95% Confidence Intervals for the mean difference and 95% Limits of Agreement (LA), obtained from the analysis of crackles' **IDW** and **2CD** duration (ms) of **cystic fibrosis** (CF) participants (n = 7) **before versus after physiotherapy** intervention (**second study**).

Smallest Real Difference (SRD) in crackles data from cystic fibrosis participants before versus after airway clearance interventions

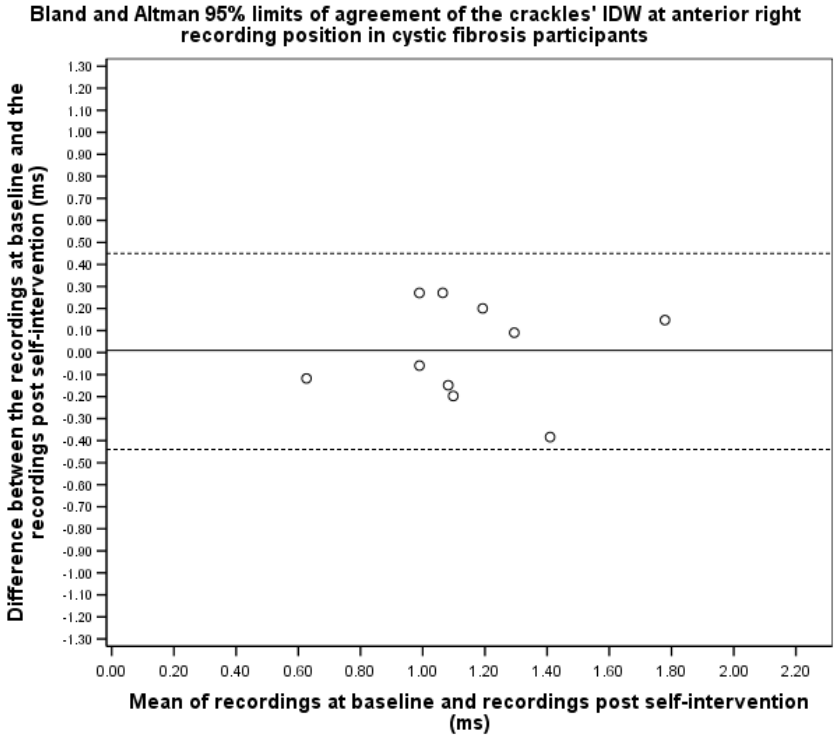
In the first study, the SRD before versus after self-intervention, for both variables analysed (crackles' IDW and 2CD), was generally higher in all recording positions than for the repeated measures taken either at baseline or post self-intervention (see Table 23). This pattern was particularly evident in the crackles' 2CD. This shows that in this group of participants the crackles duration changed after the airway clearance self-intervention.

In the second study, the SRD between data recorded before versus after intervention, for both variables analysed (crackles' IDW and 2CD from i) all participants; ii) the participants who considered their lungs to be clearer post the intervention and iii) the participants who the physiotherapist considered the lungs to be clearer post the intervention), was generally higher in all recording positions than for the repeated measures taken either at baseline or post intervention (see Table 24) for all the CF participants as an example). As in the first study, this shows that in CF participants the crackles' duration changed after the physiotherapy intervention.

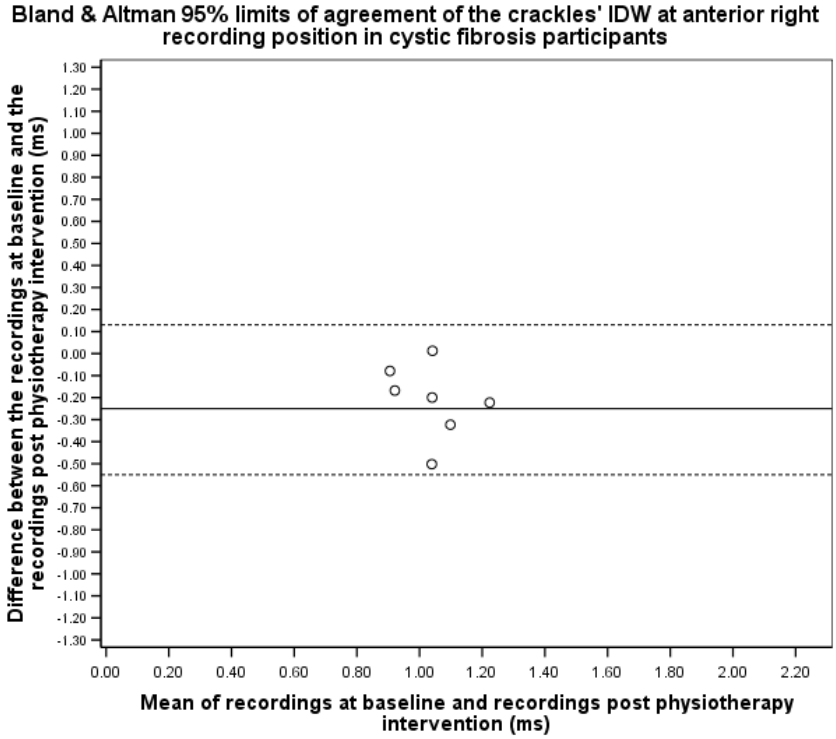
Therefore, in both studies, the differences in the duration of the crackles seen at baseline and post interventions were greater than can be attributed to error alone and suggests that this outcome measure is responsive to change.

Bland and Altman 95% limits of agreement in crackles data from cystic fibrosis participants before versus after airway clearance interventions

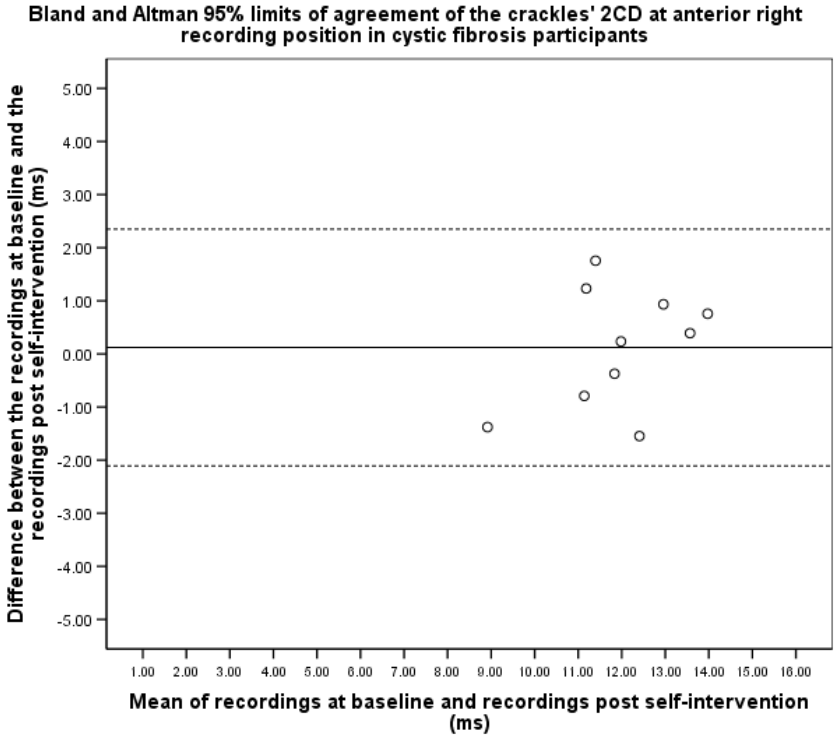
A scatter plot was produced for each variable in each recording position, for the crackles data before versus after the intervention in all the CF participants in the first study. This was also done in the second study i) with the data from all the CF participants, ii) with the data from the participants who reported their lungs to be clearer post intervention, and iii) with the data from the participants who the physiotherapist reported the lungs to be clearer post intervention. Due to the large number of graphs thereby generated, only one example is presented in this Thesis from each study (for complete analysis, please see Appendix 7 on the CD provided). Graph 13 and Graph 14 present examples for the crackles' IDW, and Graph 15 and Graph 16 give and example for the crackles' 2CD, in CF participants at anterior right of the chest in each study.



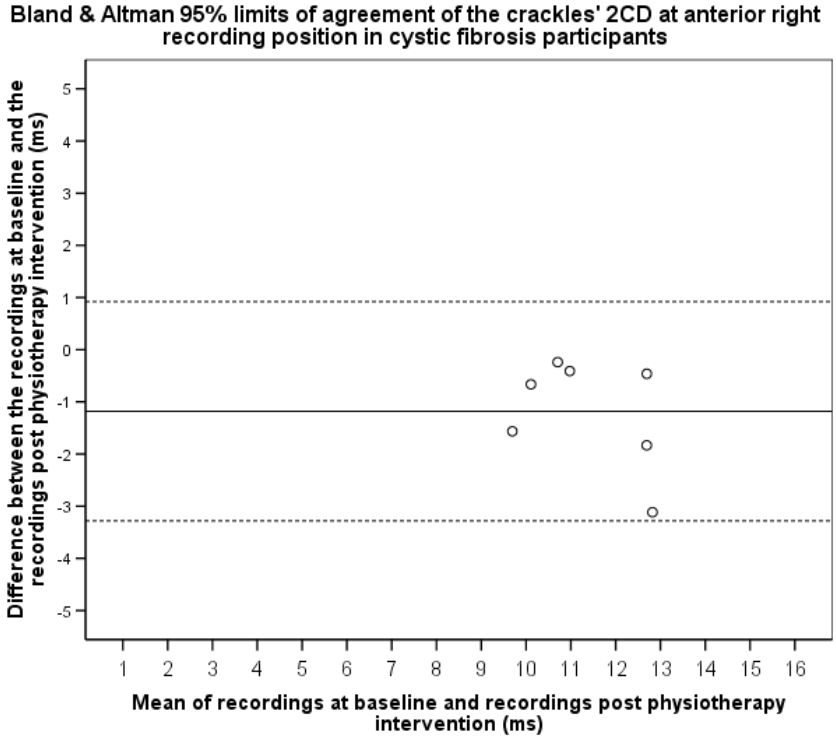
Graph 13: Results from the Bland & Altman 95% limits of agreement of the crackles' initial deflection width (**IDW**) duration (ms) obtained from the **cystic fibrosis** participants (n = 10) at **anterior right** of the chest with the data at **baseline** and **post** airway clearance **self-intervention** (**first study**).



Graph 14: Results from the Bland & Altman 95% limits of agreement of the crackles' initial deflection width (**IDW**) duration (ms) obtained from the **cystic fibrosis** participants (n = 7) at **anterior right** of the chest with the data at **baseline** and **post physiotherapy** intervention.



Graph 15: Results from the Bland & Altman 95% limits of agreement of the crackles' two cycles deflection (**2CD**) duration (ms) obtained from the **cystic fibrosis** participants at **anterior right** of the chest with the data at **baseline** and **post** airway clearance **self-intervention** (**first study**).



Graph 16: Results from the Bland & Altman 95% limits of agreement of the crackles' two cycles deflection (**2CD**) duration (ms) obtained from the **cystic fibrosis** participants (n = 7) at **anterior right** of the chest with the data **at baseline** and **post physiotherapy** intervention (**second study**).

No systematic bias was detected in any recording position for CF participants in the first study. However, some systematic bias was detected in CF participants in the second study, when the data from the participants were analysed as a single group. Systematic bias in the crackles' duration, presented the following trends:

- towards a longer duration at anterior regions (in both crackles' variables) and lateral right (for crackles' IDW only);
- ii) towards shorter durations at lateral left and posterior left of the chest (in both variables).

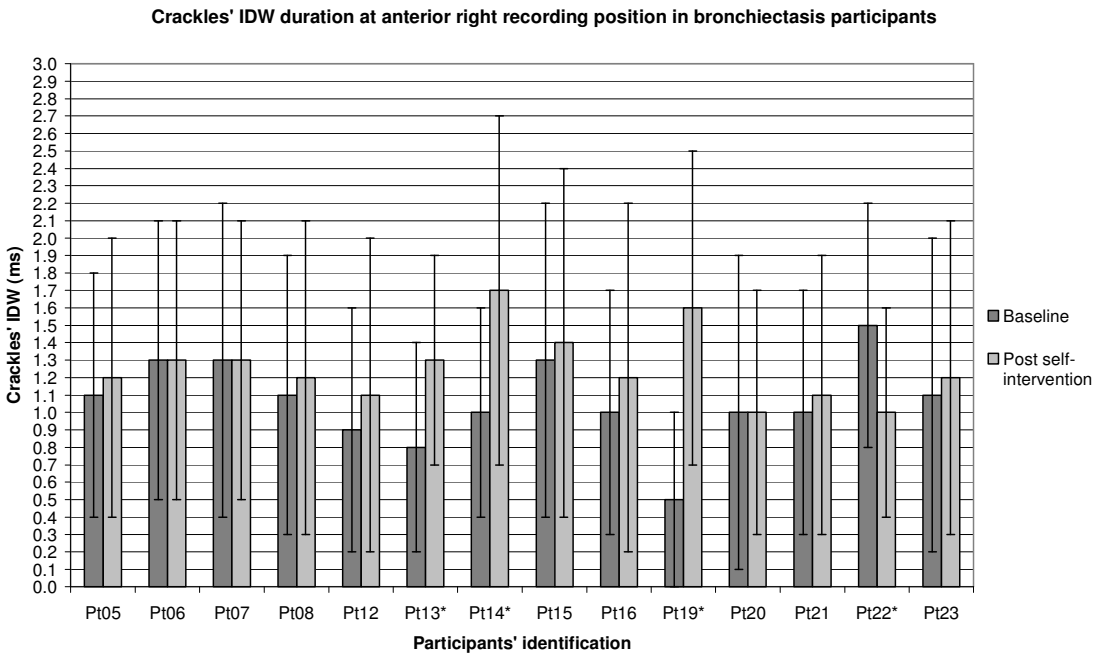
It was intended also to analyse the before versus after physiotherapy intervention with the data i) from those CF participants who reported their lungs to be clearer post intervention (n=4) and ii) from those CF participants who the physiotherapist reported the lungs to be clearer post intervention (n=1). However, the small numbers within each subgroup made this analysis unfeasible.

The next section will present the findings from the crackles' frequency analysis obtained in Br participants in both studies of this research.

5.7.2.1.3. Crackles' frequency analysis in bronchiectasis participants

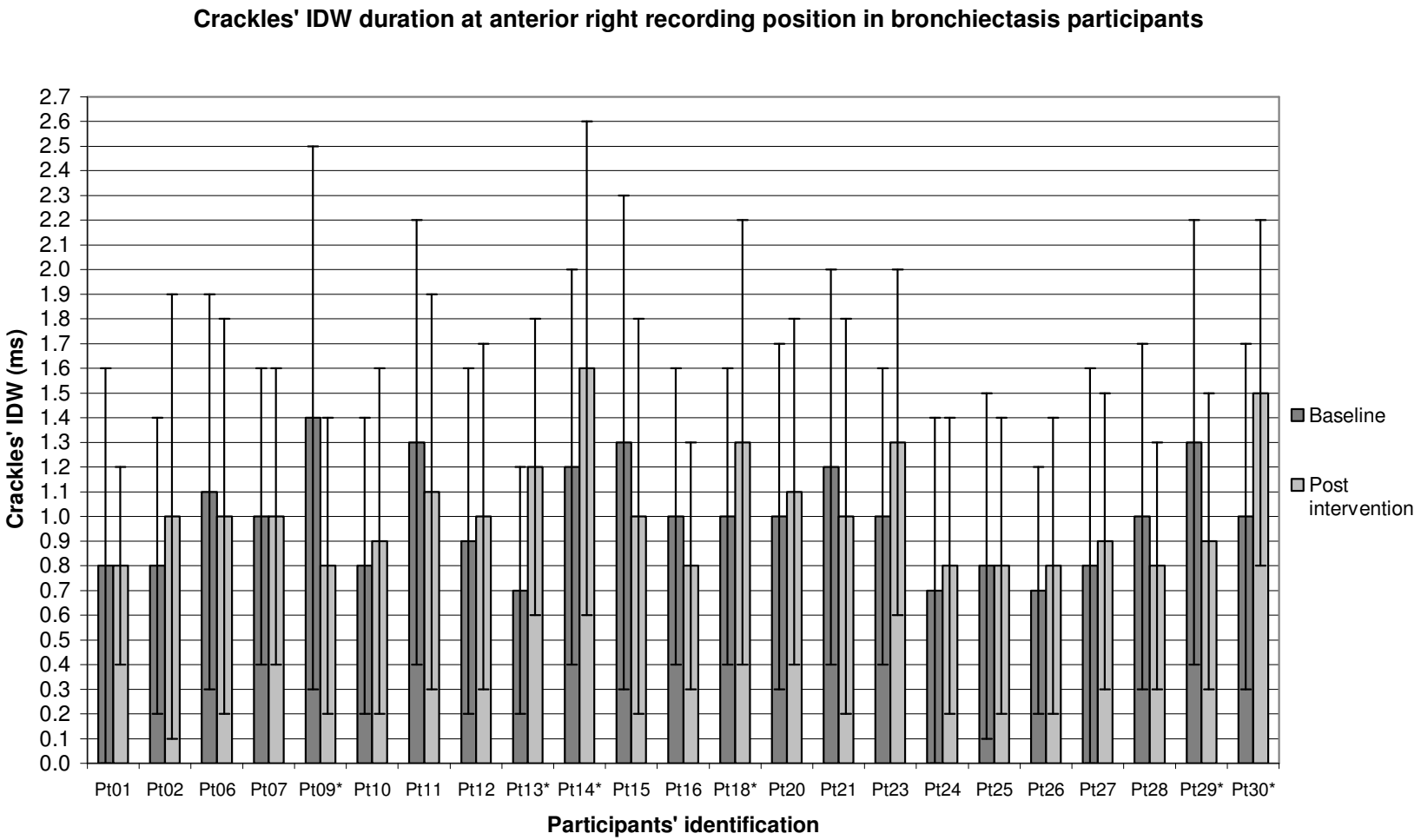
Results from crackles' initial deflection width (IDW) and two cycles deflection (2CD) at the seven chest locations were analysed in 14 Br participants, in the first study and in 23 Br participants in the second study, at baseline and post intervention. This section will present the results from the crackles' frequency analysis of Br participants in each study.

Graph 17 and Graph 18 are examples of the analysis of crackles' IDW, recorded at anterior right of the chest which illustrates the pattern of the results found in Br participants in each study. This analysis was performed for the seven chest locations across all Br participants in both studies.



Graph 17: Average data from crackles' **IDW** duration (ms) recorded at **anterior right** of the chest in **bronchiectasis** participants (n = 14), at **baseline** and **post** airway clearance **self-intervention** (**first study**). * starred results are significant, $p<0.05$. Error bars represent ± standard deviation.

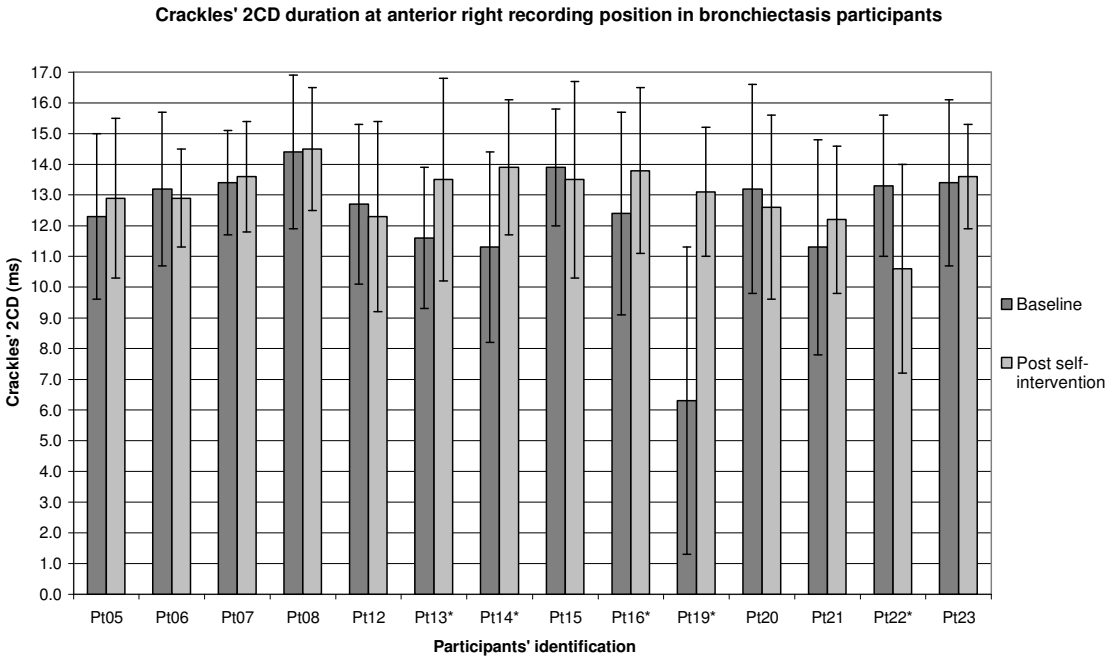
In the first study (Graph 17), the crackles' IDW **increased** in 10 participants post airway clearance self-intervention. The differences were statistically significant in three participants: Pt13 (crackles' IDW increased from 0.8±0.6 ms to 1.3±0.6 ms, p=0.001); Pt14 (crackles' IDW increased from 1±0.6 ms to 1.7±1 ms, p=0.001) and Pt19 (crackles' IDW increased from 0.5±0.5 ms to 1.6±0.9 ms, p=0.001). In three participants the duration of the crackles' IDW did **not change** post self-intervention. The duration of the crackles' IDW **decreased** in one participant (Pt22). This difference was statistically significant (crackles' IDW decreased from 1.5±0.7 ms to 1±0.6 ms, p=0.001). The non significant differences seen in the other participants' data, suggests that there was no real change, as these were likely to be within the margin of measurement error.



Graph 18: Average data from crackles' **IDW** duration (ms) recorded at **anterior right** of the chest in **bronchiectasis** participants (n = 23), at **baseline** and **post physiotherapy** intervention (**second study**). * starred results are significant, $p<0.05$.

In the second study, the duration of the crackles' IDW, **increased** in 12 Br participants post intervention (Graph 18). These differences were statistically significant in four participants: Pt13 (crackles' IDW increased from 0.7±0.5 ms to 1.2±0.6 ms, p=0.001); Pt14 (from 1.2±0.8 ms to 1.6±1 ms, p=0.008); Pt18 (crackles' IDW increased from 1±0.6 ms to 1.3±0.9 ms, p=0.006) and Pt30 (crackles' IDW increased from 1±0.7 ms to 1.5±0.7 ms, p=0.001). The crackles' IDW duration **decreased** in eight participants. These differences were statistically significant in two participants: Pt09 (crackles' IDW decreased from 1.4±1.1 ms to 0.8±0.6 ms, p=0.005) and Pt29 (crackles' IDW decreased from 1.3±0.9 ms to 0.9±0.6 ms, p=0.006). In three participants the duration of the crackles' IDW remained unchanged post intervention.

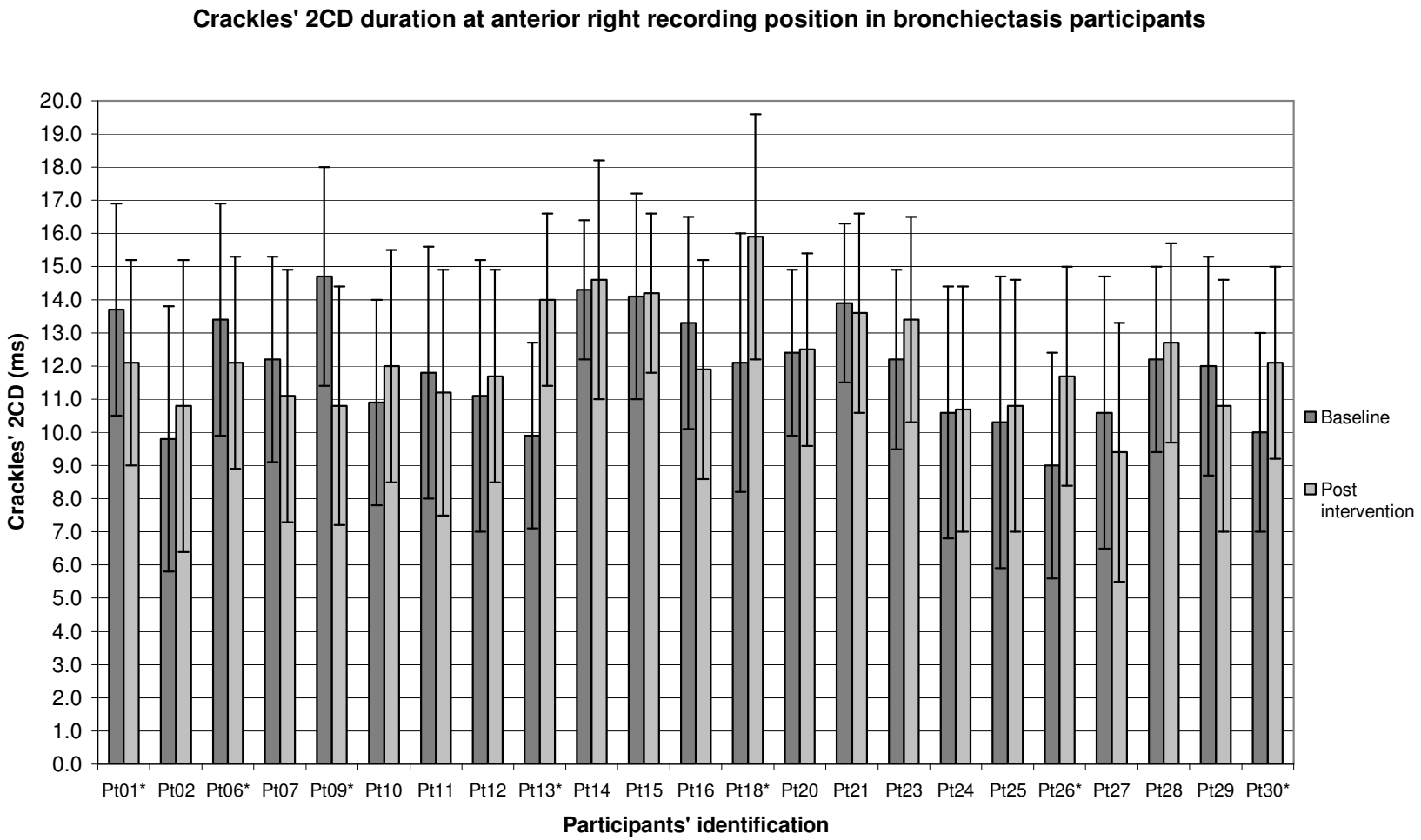
Graph 19 and Graph 20 are examples of the analysis of crackles' 2CD, recorded at anterior right of the chest which illustrates the pattern of the results found in Br participants in each study.



Graph 19: Average data from crackles' **2CD** duration (ms) recorded at **anterior right** of the chest in **bronchiectasis** participants (n = 14), at **baseline** and **post** airway clearance **self interventions** (**first study**). * starred results are significant, p<0.05.

In the first study the crackles' 2CD **increased** in nine Br participants. These differences were statistically significant for both variables in four participants: Pt13 (crackles' 2CD increased from 11.6±2.3 ms to 13.5±3.3 ms p=0.001); Pt14 (crackles' 2CD increased from 11.3±3.1 ms to 13.9±2.2 ms, p=0.001); Pt16 (crackles' 2CD increased from 12.4±3.3 ms to 13.8±2.7 ms p=0.022) and Pt19 (crackles' 2CD increased from 6.3±5 ms to 13.1±2.1 ms p=0.001). The duration of the crackles' 2CD **decreased** in five

participants. The difference was statistically significant in one participant - Pt22 (crackles' 2CD decreased from 13.3±2.3 ms to 10.6±3.4 ms p=0.001).



Graph 20: Average data from crackles' **2CD** duration (ms) recorded at **anterior right** of the chest in **bronchiectasis** participants (n = 23), at **baseline** and **post physiotherapy** intervention (**second study**). * starred results are significant, $p<0.05$.

In the second study, the crackles' 2CD **increased** in 14 Br participants. These differences were statistically significant in four participants: Pt13 (crackles' 2CD increased from 9.9±2.8 ms to 14±2.6 ms, p=0.001); in Pt18 (crackles' 2CD increased from 12±3.9 ms to 15.9±2.7 ms, p=0.001); Pt26 (crackles' 2CD increased from 9±3.4 ms to 11.7±3.3 ms, p=0.004) and Pt30 (crackles' 2CD increased from 10±3 ms to 12.1±2.9 ms, p=0.001). The duration of the crackles' 2CD **decreased** in nine participants. These differences were statistically significant in three participants: Pt01 (crackles' 2CD decreased from 13.7±3.2 ms to 12.1±3.1 ms, p=0.022); Pt06 (crackles' 2CD decreased from 13.4±3.5 ms to 12.1±3.2 ms, p=0.019) and Pt09 (crackles' 2CD decreased from 14.7±3.3 ms to 10.8±3.6 ms, p=0.001).

In summary, the majority of the statistically significant changes in the Br crackles data occurred, in both studies, in participants who had an **increase** in the duration of IDW and/or 2CD variables post intervention. Table 25 and Table 26 show the tendency towards an increase in the duration of the crackles' IDW and 2CD in Br participants in each study, post interventions. The same key was used for all the tables, i.e., T – trachea; AR – anterior right; AL – anterior left, LR – lateral right; LL – lateral left; PR – posterior right; PL – posterior left; ↑ means an increase of the crackles' duration in ms; ↓ means a decrease of the crackles' duration in ms; = means no modification of the values, comparing post airway clearance interventions with the baseline measurements.

Crackles' Initial Deflection Width (IDW)								
Code	**T**	**AR**	**AL**	**LR**	**LL**	**PR**	**PL**	**Total**
Br05	=	=	↓	↓	=	↓*	↓*	3= 4↓
Br06	↑	=	=	↓*	↑	=	↓	3=2↑ 2↓
Br07	↑*	=	=	↑	=	↑	↑*	3=4↑
Br08	↑*	↑	↑	=	↓	=	↓*	2=3↑ 2↓
Br12	=	↑	=	↑	↑	↑*	=	3=4↑
Br13	=	↑*	↑	↓*	↑	↓	↑*	1=4↑ 3↓
Br14	=	↑*	=	↑	=	↑*	↑	3=4↑
Br15	↓*	↑	↓	↓*	=	↓	↓	1=1↑ 5↓
Br16	↑	↑	↑	=	=	↑*	↑	2=5↑
Br19	=	↑*	↑*	↑*	↑	↑*	↑*	1=6↑
Br20	↑	=	↑*	↓	=	↓	↓	2=2↑ 3↓
Br21	↑	↑	↓	=	↓	↓	=	2=2↑ 3↓
Br22	↓*	↓*	↓	↑*	=	↓	↓	1=1↑ 5↓
Br23	=	=	↑	↓	↑*	↑	↑	2=4↑ 1↓
Total	6=6↑2↓	5=8↑1↓	4=6↑4↓	3=5↑6↓	7=5↑2↓	2=6↑6↓	2=6↑6↓	

Table 25: Results from crackles' **IDW** duration at the seven locations of the chest in **bronchiectasis** participants (n=14) in the **first study**. * starred results are significant, $p<0.05$.

In this Br sample, the number of participants who had an **increase** in the duration of both variables is generally greater than the number who had a **decrease** post self intervention, as shown in Table 25. However, in the first study for the crackles' IDW an exception occurs at lateral right and posterior areas.

Crackles' Initial Deflection Width (IDW)								
Code	**T**	**AR**	**AL**	**LR**	**LL**	**PR**	**PL**	**Total**
Br01	↓*	=	↑	↑	↓	↓	↑	3↑ 4↓
Br02	↑	↑	↓*	↓	↓*	↓	↑	3↑ 4↓
Br06	↑	↓	↓	↑*	↑*	↑	↑	5↑ 2↓
Br07	↓	=	↑	↓	↑	↑	↑	4↑ 2↓1=
Br09	↓	↓*	↑	↓	↑	↓*	↑	3↑ 4↓
Br10	↑	↑	↓	↑*	↑*	=	↓	4↑ 2↓ 1=
Br11	↓*	↓	↑	↑*	↑	↑	↓	4↑ 3↓
Br12	↓*	↑	↑	↑	↑	↑	↓*	5↑ 2↓
Br13	↑*	↑*	↑*	↓	↓	↑*	↑	5↑ 2↓
Br14	↑*	↑*	↑	↓	↑*	↓	↓	4↑ 3↓
Br15	↑	↓	↑	↓	↓	↑*	↓	3↑ 4↓
Br16	↑*	↓	↑*	↑	↑	↑*	↓	5↑ 2↓
Br18	=	↑*	↓	↑	↓	↑	↓	3↑ 3↓ 1=
Br20	↓*	↑	↑	↑	↓	↑	↓	4↑ 3↓
Br21	↓	↓	↑	↓	↑*	↓	↓*	2↑ 5↓
Br23	↓*	↑	↑	↑	↓	↓	↓	4↑ 3↓
Br24	↓*	↑	↑	↑	↓	↑	↓*	2↑ 5↓
Br25	=	=	↓	↓	↓*	↓	↓	6↓1=
Br26	↑	↑	↑	↑	↑	↑	↑	7↑
Br27	↑*	↑	↓	↑	↑	↓	↓	4↑ 3↓
Br28	↑	↓	↑	↑	↑	↓	↑	5↑ 2↓
Br29	↓	↓*	↑*	↓*	↑*	↑*	↓	4↑ 3↓
Br30	=	↑*	↑*	↑	↓*	↑	↓	4↑ 2↓1=
Total	10↑10↓3=	12↑8↓3=	16↑7↓	14↑9↓	13↑10↓	13↑ 9↓ 1=	8↑ 15↓	

Table 26: Results from crackles' **IDW** duration at the seven locations of the chest in **bronchiectasis** participants (n=23) in the **second study**. (* starred results are significant, $p<0.05$).

As in the first study, the number of Br participants who had an **increase** in the duration of the crackles' IDW in each recording position is generally greater than the number who had a **decrease** post intervention, as shown in Table 26. In the second study, an exception occurs at posterior left of the chest where the crackles' IDW duration decreased in 15 of the 23 Br participants. Table 27 and Table 28 show the tendency towards an increase in the duration of the crackles' 2CD in each study, post interventions.

Crackles' Two Cycles Deflection (2CD)								
Code	**T**	**AR**	**AL**	**LR**	**LL**	**PR**	**PL**	**Total**
Br05	↑	↑	↓	↑	↑	↓*	↓*	4↑ 3↓
Br06	↓	↓	↑	↓	↑	↑*	↓*	3↑ 4↓
Br07	↑*	↑	↑	↑	↑*	↓	↑*	6↑ 1↓
Br08	↑	↑	↑*	↑	↓	↑	↓	5↑ 2↓
Br12	↓*	↓	↑	↑*	↑*	↑	↑	5↑ 2↓
Br13	=	↑*	↑	↓*	↓	↓*	↑*	1=3↑ 3↓
Br14	↓	↑*	↓	↑*	↑	↑*	↑*	5↑ 2↓
Br15	↓	↓	↑	↓	↑	↓*	↑	3↑ 4↓
Br16	↑*	↑*	↑*	↑	↑	↑	↑*	7↑
Br19	↑	↑*	↑*	↑	↑	↑*	↑	7↑
Br20	↑	↓	↑	↑	↓	↓	↓	3↑ 4↓
Br21	↑*	↑	↑	↓	↑	↓*	↓	4↑ 3↓
Br22	↓	↓*	=	↑*	↓	↑	↓	1=2↑ 4↓
Br23	↑*	↑	↓	↓*	↑	↓	↓*	3↑ 4↓
Total	1=8↑5↓	9↑5↓	1=10↑3↓	9↑5↓	10↑4↓	7↑7↓	7↑7↓	

Table 27: Results from crackles' **2CD** duration at the seven locations of the chest in **bronchiectasis** participants (n = 14) in the **first study**. * starred results are significant, $p<0.05$.

In the first study, the number of Br participants who had an **increase** in the duration of the crackles' 2CD variable is generally greater than the number who had a **decrease** post self intervention (see Table 27). Because the crackles' 2CD duration is associated with the crackles' frequency, this suggests that the frequencies of the crackles **decreased**, which suggests they were being generated from less peripheral areas of the lungs, possibly as a result of mobility of the secretions to more central areas. An exception occured at the posterior areas (where the number of patients who had an increase was the same as the number of participants who had a decrease).

Crackles' Two Cycles Deflection (2CD)								
	T	AR	AL	LR	LL	PR	PL	Total
Br01	↑	↓*	↑	↓	↓	↑	↑	4↑ 3↓
Br02	↑	↑	↓*	↓	↓*	↑	↑*	4↑ 3↓
Br06	↑	↓*	↓	↑*	↑*	↑	↑*	5↑ 2↓
Br07	=	↓	↑	↓	↓*	↑	↑	3↑ 3↓ 1=
Br09	=	↓*	↓	=	↑*	↓*	↑	2↑ 3↓ 2=
Br10	↑	↑	↓	↑*	↑*	↑	↓*	5↑ 2↓
Br11	↑*	↓	↑*	↑*	↑	↑	↑	6↑ 1↓
Br12	↓*	↑	↓	↑*	↑	↑*	↓*	4↑ 3↓
Br13	↑*	↑*	↑*	↓*	↓	↑*	↑	5↑ 2↓
Br14	↑*	↑	↑	↓	↓	↓*	↓	3↑ 4↓
Br15	↓	↑	↑	↑	↑	↑*	↑	5↑ 2↓
Br16	↑*	↓	↑*	↑	↑	↓	↓*	4↑ 3↓
Br18	=	↑*	=	↑	=	↑	↑	4↑ 3=
Br20	↓*	↑	↑	↑*	↑*	↑	↓*	5↑ 2↓
Br21	↓*	↓	↓	↓*	↑*	↓	↓	1↑ 6↓
Br23	↑	↑	↓	↓*	↓	↑	↑	4↑ 3↓
Br24	↓	↑	↓	↑	↑	↑	↓*	3↑ 4↓
Br25	↓	↑	↑	↓*	↓*	↓	↓	2↑ 5↓
Br26	↑	↑*	↑*	↑	↑	↑*	↓	6↑ 1↓
Br27	↑	↓	↓*	↓	↓	↓*	=	1↑ 5↓ 1=
Br28	↑	↑	↑	↑*	↑	↓*	↑	6↑ 1↓
Br29	↑*	↓	↑	=	↑	↑*	↓	4↑ 2↓ 1=
Br30	=	↑*	=	↑*	↓*	↑	↓*	3↑ 2↓ 2=
Total	13↑6↓4=	14↑ 9↓	12↑9↓2=	12↑9↓2=	12↑9↓1=	16↑ 5↓	11↑11↓1=	

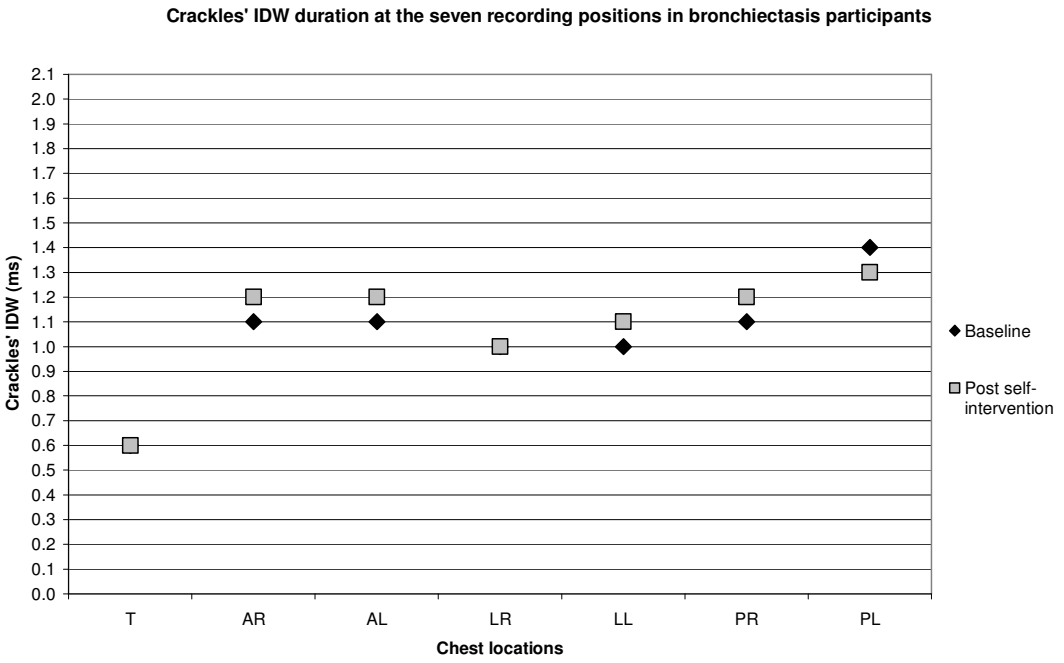
Table 28: Results from crackles' **2CD** duration at the seven locations of the chest in **bronchiectasis** participants (n = 23) in the **second study.** (* starred results are significant, $p<0.05$).

In the second study the number of Br participants who had an **increase** in the duration of the crackles' 2CD variables in each recording position is generally greater than the number who had a **decrease,** post intervention (see Table 28). This suggests that the frequencies of the crackles **decreased**. An exception occurs at posterior left of the chest, where the crackles' 2CD duration increased in 11 and decreased in 11 Br participants. A decrease in the duration of the crackles means a higher crackles' frequency (theoretically generated from more peripheral airways).

Tables 25 to 28 show which participants responded with an increase (longer duration⇔lower frequency) or a decrease (shorter duration⇔higher frequency) of crackles' duration post the interventions and in which chest areas.

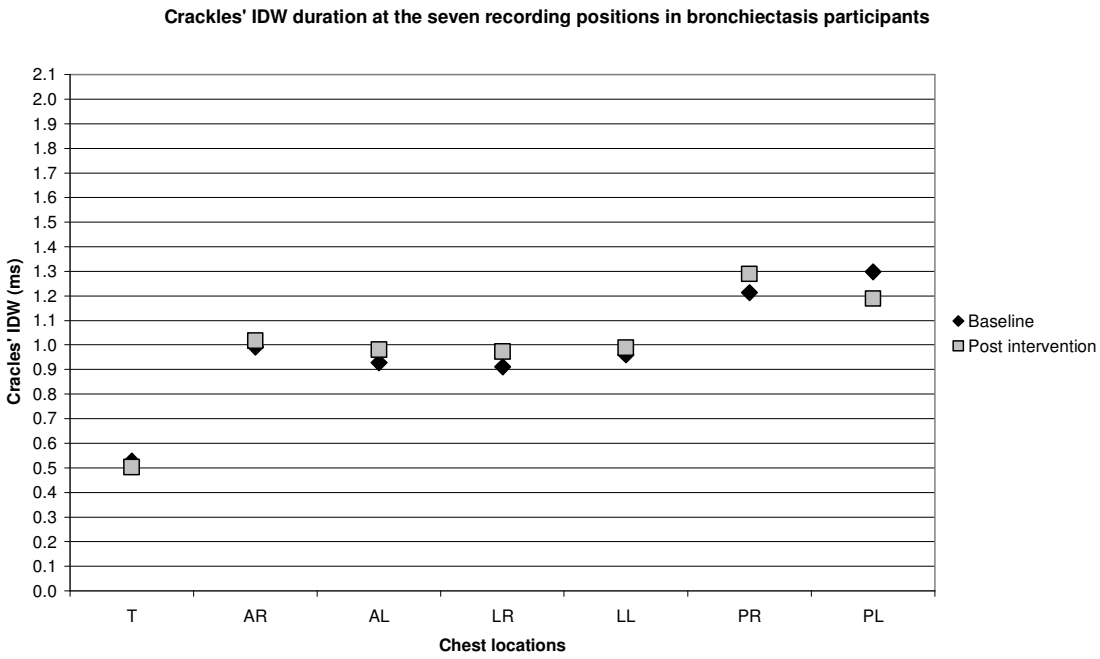
In summary, it was observed that in the majority of the Br participants in both studies, the duration of the crackles' variables (IDW and 2CD) increased. Graph 21 and Graph

22 uses the averaged data to summarise the pattern for the crackles' IDW in each study. The key for the chest locations was the same for all the graphs, i.e., T – trachea; AR – anterior right; AL – anterior left, LR – lateral right; LL – lateral left; PR – posterior right; PL – posterior left.



Graph 21: Results from crackles' **IDW** (ms) analysis in **bronchiectasis** participants (n = 14) at the seven chest locations (**first study)**.

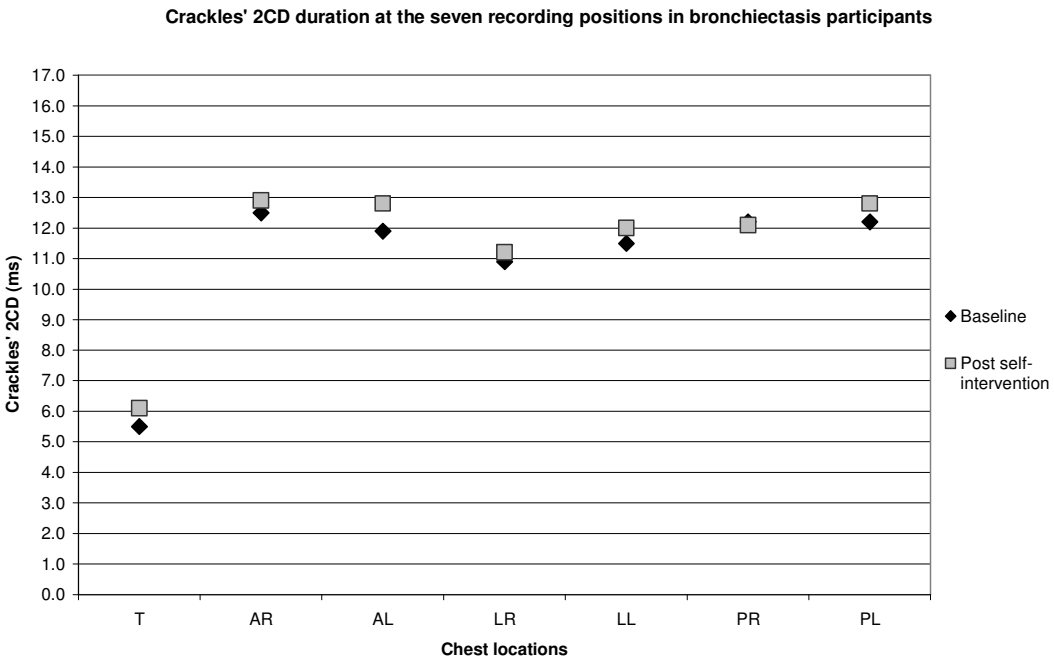
In general, in the first study the duration of the crackles' IDW variable in the Br participants is longer post airway clearance self-intervention with the exception of the posterior left recording position, as shown in Graph 21.



Graph 22: Results from crackles' **IDW** (ms) analysis in **bronchiectasis** participants (n = 23) at the seven chest locations (**second study**).

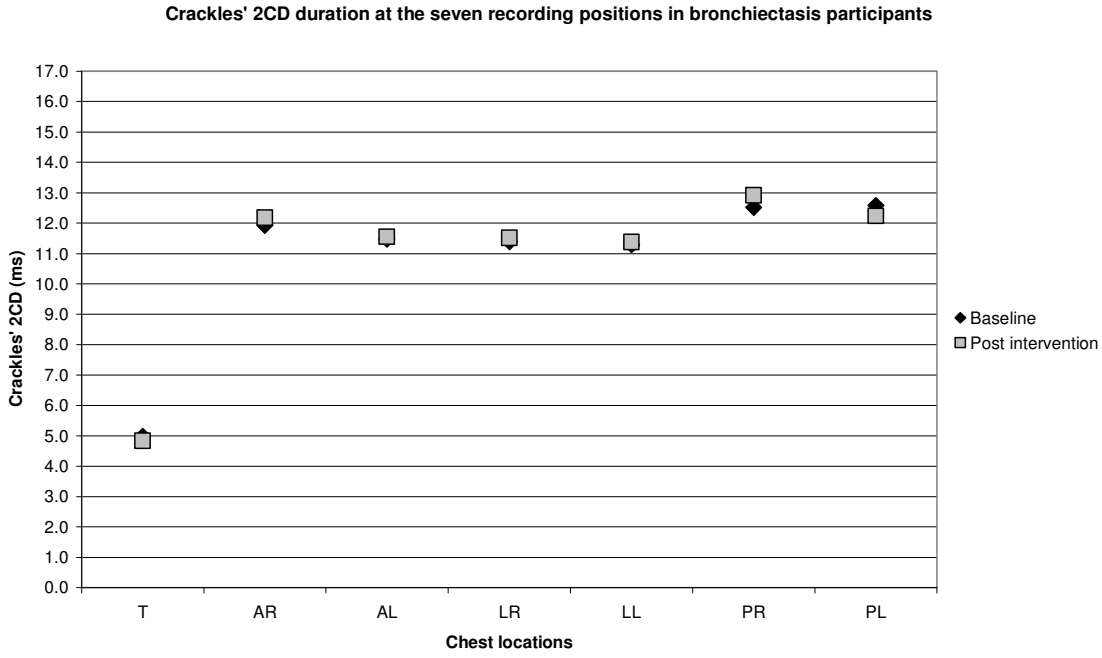
In the second study the duration of the crackles' IDW variable is again generally longer in the Br participants post intervention, with the exception at posterior left recording position, as shown in Graph 22.

Graph 23 and Graph 24 uses the averaged data to summarise the pattern for the crackles' 2CD in the bronchiectasis participants in each study.



Graph 23: Results from crackles' **2CD** (ms) analysis in **bronchiectasis** participants (n = 14) at the seven chest locations (**first study**).

In the first study, the duration of the crackles' 2CD variable in the Br participants post airway clearance self intervention was generally longer in the recording positions studied, as shown in Graph 23.



Graph 24: Results from crackles' **2CD** (ms) analysis in **bronchiectasis** participants (n = 23) at the seven chest locations (**second study**).

In the second study, the duration of the crackles' 2CD variable in the Br participants post intervention was again generally longer, with the exception at posterior left of the chest, as shown in Graph 24.

Summary of changes in crackles' frequency post intervention

The patterns found in both studies indicate a tendency towards longer durations, and hence a decrease in the crackles' frequency post intervention (in the Br participants in the first study and in both CF and Br participants in the second study). The duration of the crackles' 2CD in Br participants tended to be slightly higher than the CF participants. However, it is important to note that the crackles' 2CD variables at baseline and post interventions are generally above 10 ms in both groups. Therefore, this suggests that coarse, low frequency crackles are more frequent than fine, high frequency crackles in both pathologies studied.

5.7.2.1.4. Smallest Real Difference and Bland and Altman 95% limits of agreement in crackles data from bronchiectasis patients before versus after airway clearance interventions

As described for the CF participants, Bland and Altman 95% limits of agreement and the SRD were calculated in Br participants, in both studies, to assess the presence of systematic bias in the crackles' frequency post interventions. Results obtained from the analysis of the crackles' IDW before versus after the interventions in Br participants are presented in Table 29, for the first study and in Table 30 for the second study. Detailed description of all the calculations is presented in section 4.3.6.3.5.. In the second study, as explained for the CF participants, it was felt appropriate to perform this analysis in three different ways; i) with the data from all the participants, ii) with the data from participants who reported their lungs to be clearer post physiotherapy intervention and iii) with the data from participants who the physiotherapist reported their lungs to be clearer post intervention. The tables, with all the calculations, will be presented for the analysis performed with the data from all the participants, as an example (for complete analysis please see Appendix 7 on the CD provided). However, the results from the analysis of the three data subsets will be described in the SRD and in the Bland and Altman 95% limits of agreement sub-sections. Results obtained from the analysis of the crackles' IDW and 2CD before versus after physiotherapy interventions in Br participants are presented in Table 29, for the first study and in Table 30 for the second study.

Bronchiectasis participants – before versus after airway clearance self-interventions (first study)														
	SEM IDW (ms)	SEM 2CD (ms)	SRD IDW (ms)	SRD 2CD (ms)	$\bar{d}$ IDW (ms)	SD_{diff} IDW (ms)	$\bar{d}$ 2CD (ms)	SD_{diff} 2CD (ms)	$SE\bar{d}$ IDW (ms)	$SE\bar{d}$ 2CD (ms)	95% CI for $\bar{d}$ IDW (ms)	95% CI for $\bar{d}$ 2CD (ms)	95% LA IDW (ms)	95% LA 2CD (ms)
T	0.11	0.99	0.32	2.75	0.00	0.16	-0.29	1.42	0.04	0.38	(-0.10;0.10)	(-1.15;0.57)	(-0.33;0.33)	(-3.13;2.56)
AR	0.28	1.49	0.78	4.13	-0.10	0.40	-0.40	2.15	0.11	0.57	(-0.34;0.14)	(-1.7-;0.90)	(-0.90;0.70)	(-4.69;3.89)
AL	0.17	1.42	0.48	3.93	-0.08	0.24	-0.95	1.83	0.06	0.49	(-0.22;0.07)	(-2.06;0.16)	(-0.56;0.41)	(-4.62;2.72)
LR	0.16	1.25	0.44	3.45	0.04	0.23	0.01	1.83	0.06	0.49	(-0.10;0.18)	(-1.09;1.12)	(-0.42;0.50)	(-3.64;3.67)
LL	0.12	0.78	0.33	2.16	-0.09	0.15	-0.53	1.01	0.04	0.27	(-0.18;0.01)	(-1.14;0.08)	(-0.38;0.21)	(-2.54;1.48)
PR	0.23	1.03	0.65	2.85	-0.08	0.34	0.11	1.51	0.09	0.40	(-0.28;0.13)	(-0.80;1.02)	(-0.75;0.60)	(-2.90;3.12)
PL	0.46	1.23	1.28	3.42	0.06	0.68	0.01	1.81	0.18	0.48	(-0.35;0.47)	(-1.09;1.10)	(-1.29;1.41)	(-3.62;3.63)

Table 29: Results from Standard Error of Measurement (SEM), Smallest Real Difference (SRD), Mean ($\bar{d}$) and Standard Deviation (SD) of the differences (diff.), Standard Error of the mean difference ($SE\bar{d}$), 95% Confidence Intervals for the mean difference and 95% Limits of Agreement (LA), obtained from the analysis of crackles' **IDW** and **2CD** duration (ms) of **bronchiectasis** (Br) participants (n = 14) **before versus after** airway clearance **self-intervention** (**first study**).

Bronchiectasis participants – before versus after physiotherapy interventions (second study)														
	SEM IDW (ms)	SEM 2CD (ms)	SRD IDW (ms)	SRD 2CD (ms)	$\bar{d}$ IDW (ms)	SD_{diff} IDW (ms)	$\bar{d}$ 2CD (ms)	SD_{diff} 2CD (ms)	$SE\bar{d}$ IDW (ms)	$SE\bar{d}$ 2CD (ms)	95% CI for $\bar{d}$ IDW (ms)	95% CI for $\bar{d}$ 2CD (ms)	95% LA IDW (ms)	95% LA 2CD (ms)
T	0.13	1.17	0.36	3.23	0.03	0.19	0.05	1.69	0.04	0.35	(-0.08;0.10)	(-0.75;0.85)	(-0.35;0.41)	(-3.33;3.43)
AR	0.21	1.29	0.58	3.56	-0.02	0.30	-0.18	1.85	0.06	0.39	(-0.22;0.06)	(-1.17;0.57)	(-0.62;0.58)	(-3.88;3.52)
AL	0.14	0.75	0.38	2.08	-0.03	0.20	-0.01	1.09	0.04	0.23	(-0.19;-0.01)	(-0.71;0.31)	(-0.43;0.37)	(-2.19;2.17)
LR	0.19	1.00	0.53	2.76	-0.08	0.27	-0.12	1.44	0.06	0.30	(-0.21;0.05)	(-0.80;0.56)	(-0.62;0.46)	(-3.00;2.76)
LL	0.14	1.02	0.38	2.82	-0.04	0.20	-0.19	1.46	0.04	0.30	(-0.13;0.05)	(-0.88;0.50)	(-0.44;0.36)	(-3.11;2.73)
PR	0.24	1.01	0.67	2.80	-0.11	0.33	-0.61	1.32	0.07	0.28	(-0.27;0.05)	(-1.23;0.01)	(-0.77;0.55)	(-3.25;2.03)
PL	0.20	0.88	0.55	2.44	0.11	0.27	0.21	1.25	0.06	0.26	(-0.02;0.24)	(-0.38;0.80)	(-0.43;0.65)	(-2.29;2.71)

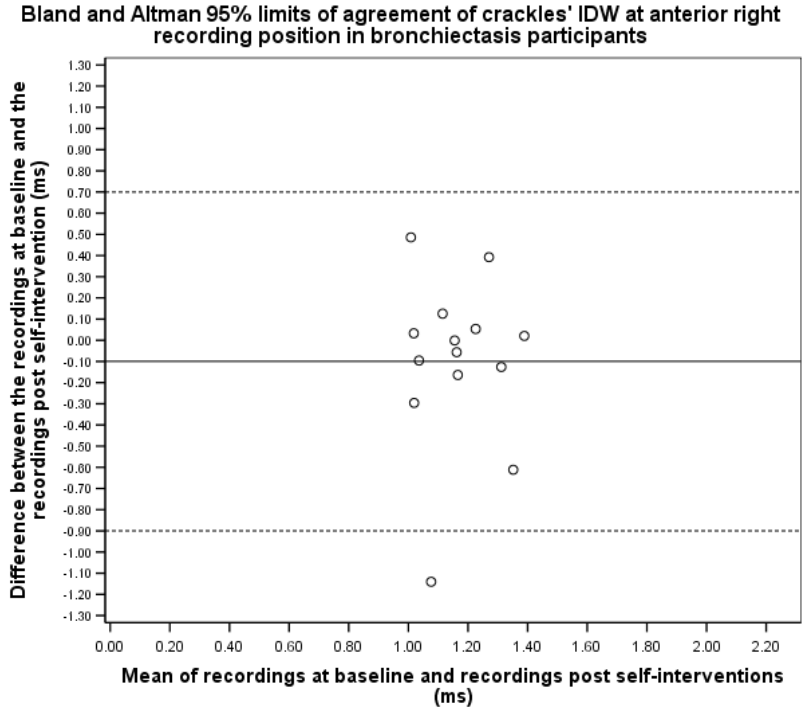
Table 30: Results from Standard Error of Measurement (SEM), Smallest Real Difference (SRD), Mean ($\bar{d}$) and Standard Deviation (SD) of the differences (diff.), Standard Error of the mean difference ($SE\bar{d}$), 95% Confidence Intervals for the mean difference and 95% Limits of Agreement (LA), obtained from the analysis of crackles' **IDW** and **2CD** duration (ms) of **bronchiectasis** (Br) participants (n = 23) **before versus after physiotherapy** intervention (**second study**).

Smallest Real Difference in crackles data from bronchiectasis participants before versus after airway clearance interventions

The SRD before versus after the interventions, in both studies, for both variables analysed (crackles' IDW and 2CD), was generally higher in all recording positions than for the repeated measures taken either at baseline or post intervention. This pattern was particularly evident in the crackles' 2CD. This shows that in Br participants, as in CF participants, the crackles duration was different post interventions. Similarly to findings for the CF participants, this change in the duration of the crackles was greater than can be attributed to error alone and therefore, suggests that this outcome measure is responsive to change.

Bland and Altman 95% limits of agreement in crackles data from bronchiectasis participants before versus after airway clearance interventions

A scatter plot was produced for each variable in each recording position, for before versus after treatment in Br participants, as shown in Graph 25 to 28. In the second study, the scatter plots were produced with the data from all participants; with the data from the participants who reported their lungs to be clearer post intervention and with the data from the participants who the physiotherapist reported the lungs to be clearer post intervention. As before, only one example is provided per study (for complete analysis please see Appendix 7 on the CD provided). Graph 25 and Graph 26 present an example for the crackles' IDW and Graph 27 and Graph 28 show an example of the crackles' 2CD, in Br participants in each study.



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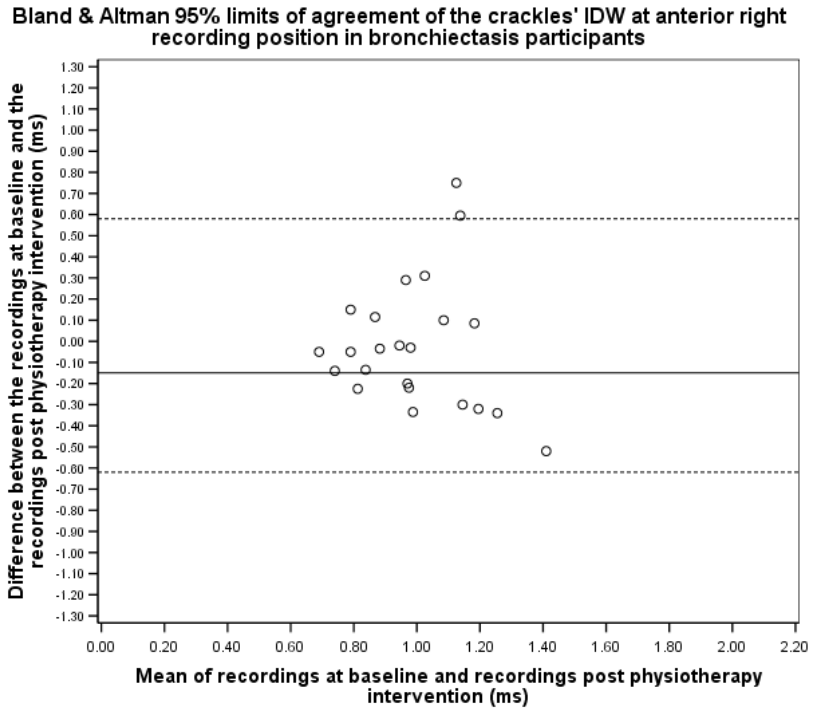
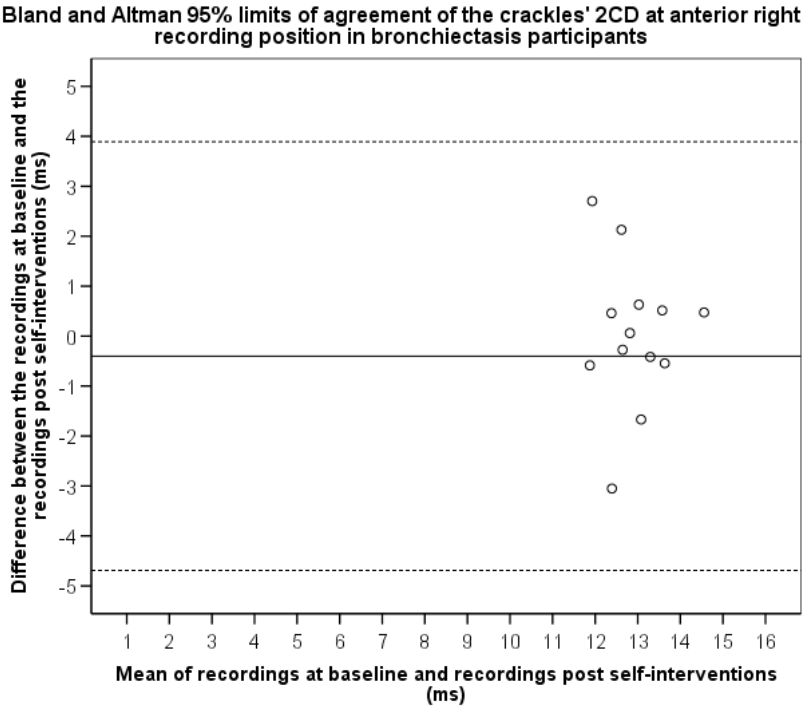
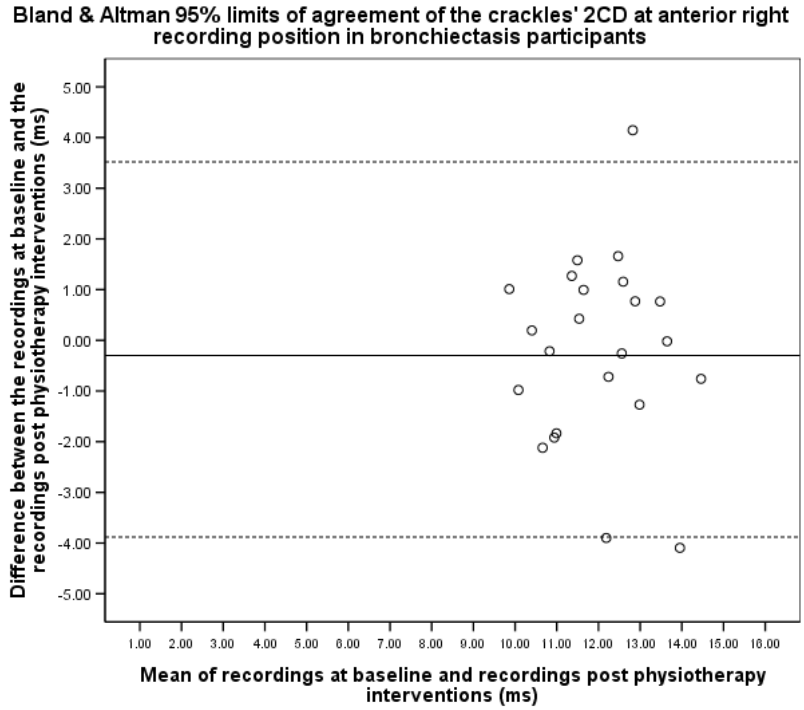
Graph 25: Results from the Bland & Altman 95% limits of agreement of the crackles' initial deflection width (**IDW**) duration (ms) obtained from the **bronchiectasis** participants (n = 14) at **anterior right** of the chest with the data at **baseline** and **post** airway clearance **self-intervention** (**first study**).



Graph 26: Results from the Bland & Altman 95% limits of agreement of the crackles' initial deflection width (**IDW**) duration (ms) obtained from the **bronchiectasis** participants (n = 23) at **anterior right** of the chest with the data at **baseline** and **post physiotherapy** intervention (**second study**).



Graph 27: Results from the Bland & Altman 95% limits of agreement of the crackles' two cycles deflection (**2CD**) duration (ms) obtained from the **bronchiectasis** participants (n = 14) at **anterior right** of the chest with the data at **baseline** and **post** airway clearance self-**intervention** (**first study**).



Graph 28: Results from the Bland & Altman 95% limits of agreement of the crackles' two cycles deflection (**2CD**) duration (ms) obtained from the **bronchiectasis** participants (n = 23) at **anterior right** of the chest with the data at **baseline** and **post physiotherapy** intervention (**second study**).

As can be seen from Graphs 25 to 28, the presence of systematic bias was detected in the Br participants post interventions in both studies when the data from all participants was considered. In the first study, systematic bias was only clearly observed in three recording positions, trachea, anterior right and anterior left of the chest (in both crackles' variables). In the second study, there was a tendency for the crackles' duration to be longer at anterior (right and left) and lateral right regions of the chest (in both variables) and to be shorter at posterior regions of the chest (in crackles' 2CD).

The analysis before versus after physiotherapy intervention was repeated with the data i) from the bronchiectasis participants who reported their lungs to be clearer post intervention (n = 15), and ii) from the participants who the physiotherapist reported the lungs to be clearer (n = 7). The objective was to verify the existence, or not, of systematic bias when only these participants were considered. Systematic bias was detected in the crackles' 2CD data from Br participants who considered their lungs to be clearer post intervention, at posterior right, and at posterior left for both variables. The systematic bias detected was in the direction of a decrease in the crackles' duration post intervention. No bias was detected in the data from participants who the physiotherapist reported the lungs to be clearer post intervention.

This section has presented the findings obtained from the crackles' frequency analysis before and after an airway clearance intervention (self-intervention in the first study and intervention applied by a physiotherapist in the second study). The next section will present the findings from the number and timing of added lung sounds per breathing cycle analysis.

5.7.2.2. Results from the Number and Timing of crackles per breathing cycle

The detection of the breathing cycles and the timing of the added lung sounds per breathing cycles have clinical significance (see section 3.6.3). The type, number (*N*) and timing (*T*) of the added lung sounds within the breathing cycle (*BC*) are essential aspects that health professionals use to assess respiratory patients. Therefore, these aspects have been explored using CALSA in the second study of this research.

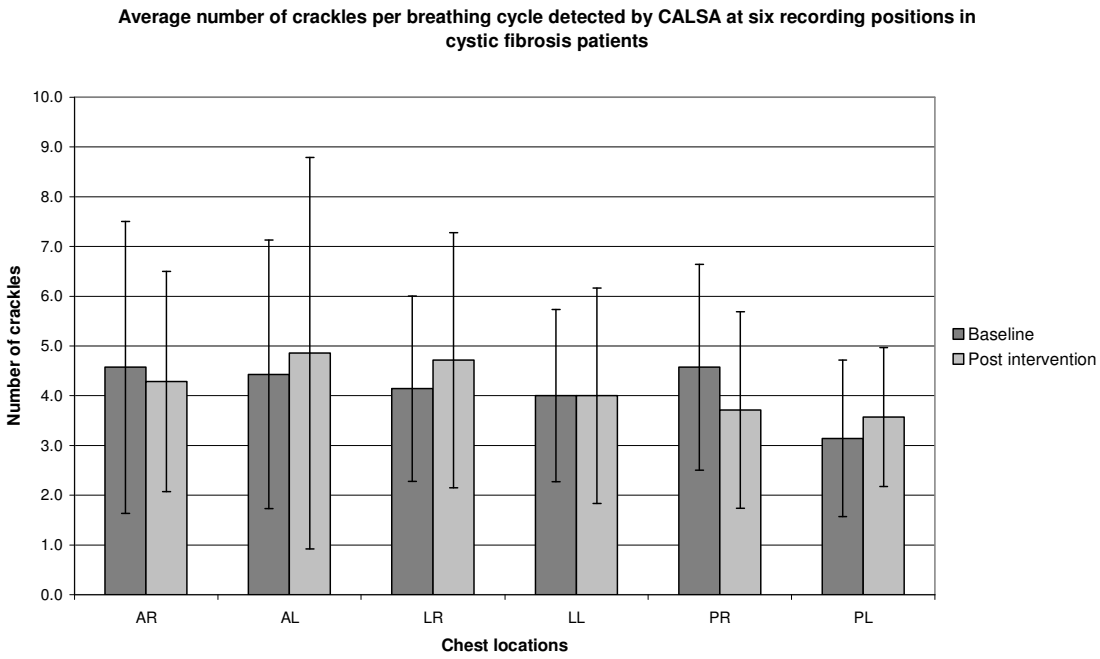
Semi-automatic detection of the breathing cycles was possible without major difficulties in all the files, in six of the seven recording positions. In the trachea recording position, because the inspiration and the expiration sounds have similar duration and amplitude, some difficulties were found. Tracheal sounds are not routinely used clinically to

assess the effectiveness of airway clearance interventions. Therefore, it was decided to analyse the *N* and *T* of the crackles per BC from the other six recording positions in the chest (see Appendix 8 on the CD provided). The time of the breathing cycle occupied by the inspiration and expiration during quiet breathing is roughly 40% and 60%, respectively. The analysis of the histograms, plotted for all the recording positions, for all participants, with the timing of the crackles per breathing cycle (see Appendix 9 on the CD provided), confirmed these percentages as a good approximation across all participants, i.e., 40% for the inspiration and 60% for the expiration. The whole breathing cycle was also divided into four sub-phases, 0-20% early inspiration, 21-40% late inspiration, 41-70% early expiration and 71-100% late expiration. The crackles detected in each sub-phase of the breathing cycles were analysed. However, as these sub-phases were artificially imposed on what is essentially a continuum, it is possible that some crackles occurring during the transition period between inspiration and expiration may have been mis-classified. It was therefore considered appropriate, as discussed in section 4.3.6.3.4, to analyse the crackles from the first and last 30% of the total breathing cycle, to avoid the transition period and be certain that the crackles were inspiratory or expiratory.

The findings from the analysis of the *N* and *T* of the crackles per BC, per sub-phase of the BC and per percentage of the *BC* at baseline and post physiotherapy intervention, will be presented first for the CF and then for the Br participants.

5.7.2.3. Number and timing of crackles per breathing cycle detected by CALSA in cystic fibrosis participants

Graph 29 shows the average number of crackles per breathing cycle detected by CALSA in CF participants in each of the six recording positions of the chest used in this study.

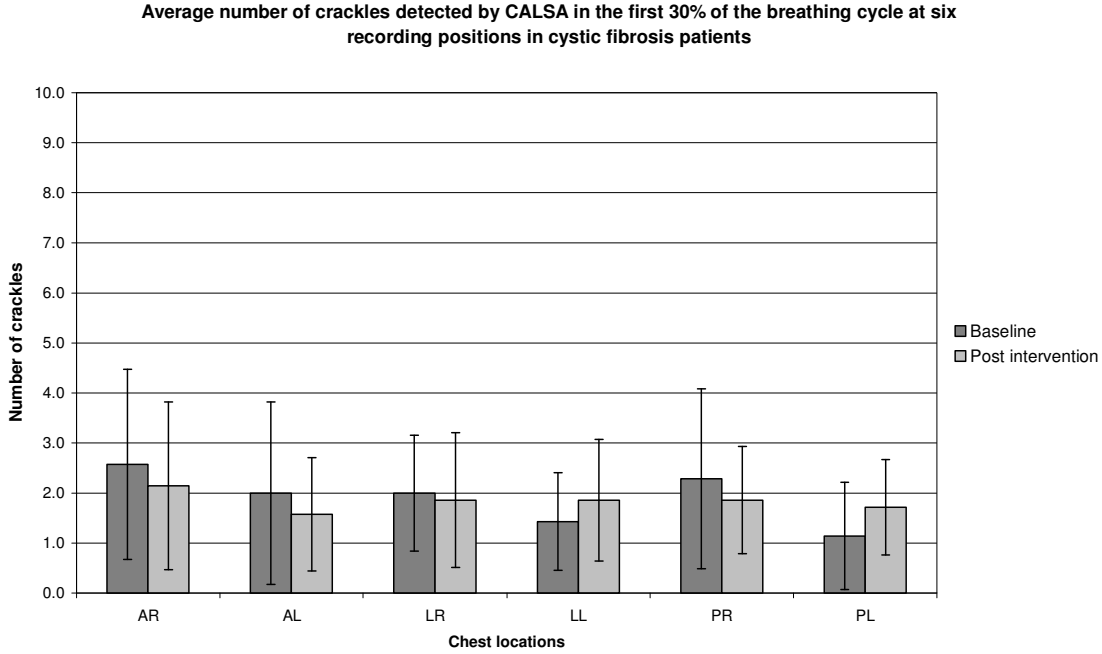


Graph 29: Average **number** of crackles per breathing cycle detected by CALSA at six positions of the chest in **cystic fibrosis** participants (n = 7) in the **second study**.

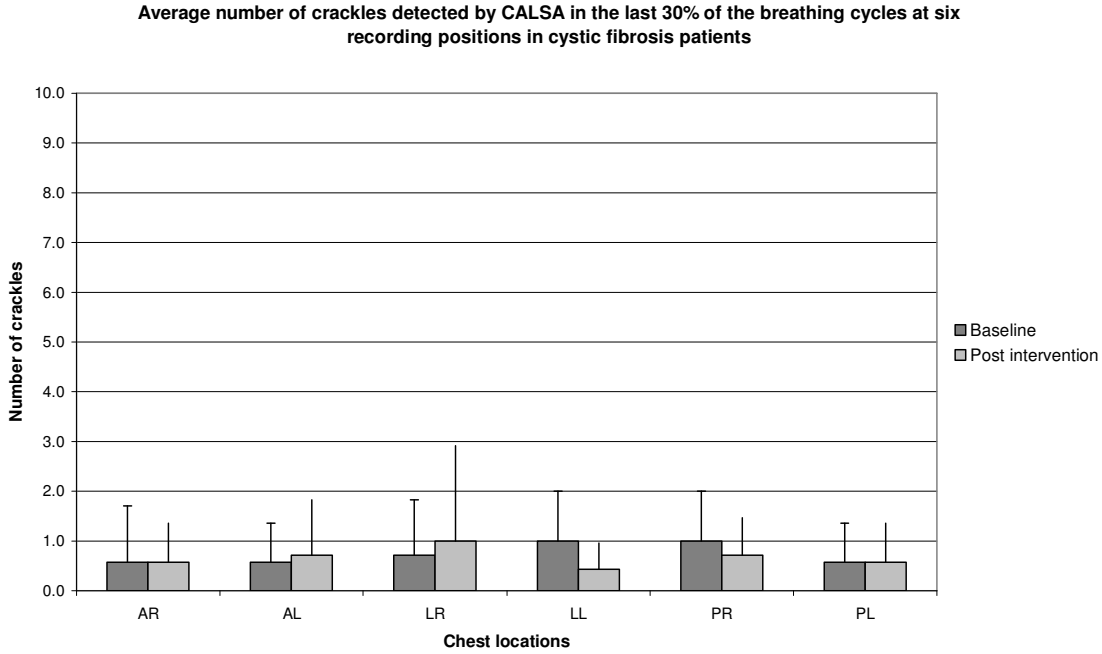
As can be observed from Graph 29 the average number of crackles per BC post physiotherapy intervention is generally slightly different to the average number at baseline. At AR and PR recording positions the average number of crackles post intervention decreased when compared to the baseline (from 4.6±2.9 to 4.3±2.2 crackles at AR and from 4.6±2.1 to 3.7±2 crackles at PR). At AL, LR and PL, the average number of crackles per breathing cycle increased post intervention (from 4.4±2.7 to 4.9±3.9 crackles at AL, from 4.1±1.9 to 4.7±2.6 crackles at LR and from 3.1±1.6 to 3.6±1.4 crackles at PL). At LL, the average number of crackles per breathing cycle was the same at baseline and post intervention. A paired t-test was used to look for statistically significant differences in the mean number of crackles detected at baseline and post intervention (see Appendix 10 on the CD provided). The differences were not statistically significant at any recording position.

It was also deemed appropriate to explore the timing of crackles within the breathing cycle. It was observed that in the CF participants the majority of crackles occurred during inspiration. As before, concerns about the potential for misclassification of crackles over the transition from inspiration to expiration led to the decision to examine the crackles from the first 30% of the BC and the last 30% of the BC, to ensure a more accurate classification of inspiration and expiration. Graph 30 and Graph 31 represent

the average number of crackles detected in the first 30% and in the last 30% of the BCs in CF participants in the second study.



Graph 30: Average **number** of crackles detected by CALSA in the **first 30%** of the breathing cycles at six positions of the chest in **cystic fibrosis** participants (n = 7) in the **second study**.



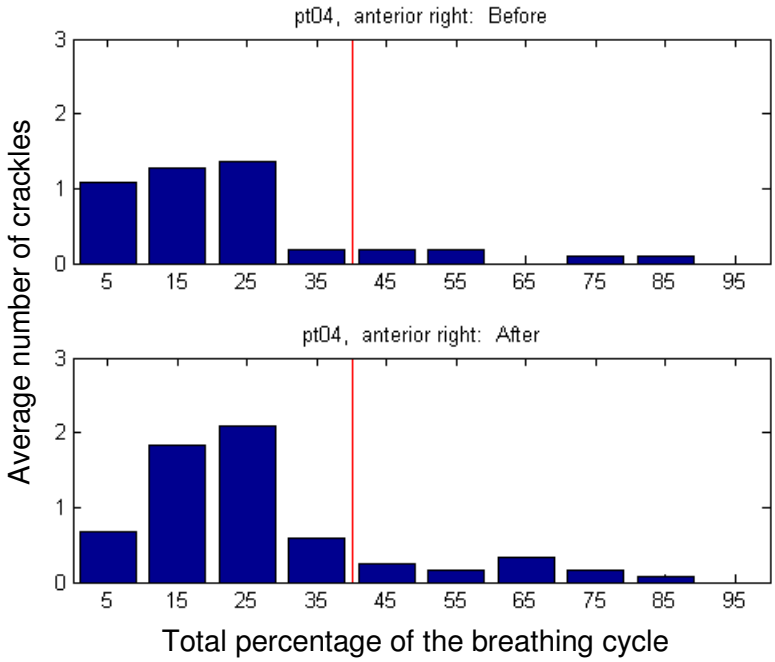
Graph 31: Average **number** of crackles detected by CALSA in the **last 30%** of the breathing cycles at six positions of the chest in **cystic fibrosis** participants (n = 7) in the **second study**.

As can be seen from the graphs above, crackles were present at baseline and post physiotherapy intervention in all six recording positions. Crackles were also present in

all four sub-phases of the BC. However, the majority of crackles were detected in the first 30% of the breathing cycle, while the last 30% of the breathing cycle was almost free of crackles. A paired t-test was used to look for statistically significant changes between the mean number of crackles at baseline and post intervention in each sub-phase of the breathing cycles (see Appendix 10 on the CD provided). No statistical significant differences were detected in any recording position for any sub-phase of the breathing cycles when comparing baseline to post intervention data.

In summary, the majority of crackles in CF participants occurred during the inspiratory phase of the *BC*. However, any difference in *N* of crackles per *BC* (or per sub-phase of the *BC*) between baseline and post intervention data did not reach statistical significance.

Histograms with the average *N* of crackles occuring within the *BC* were produced at baseline and post physiotherapy intervention, for each recording position for all participants. The objective was to analyse the transition between inspiration and expiration and to determine whether the relative *T* of the crackles post intervention was different from at baseline. An example at anterior right of the chest is provided for a CF participant.

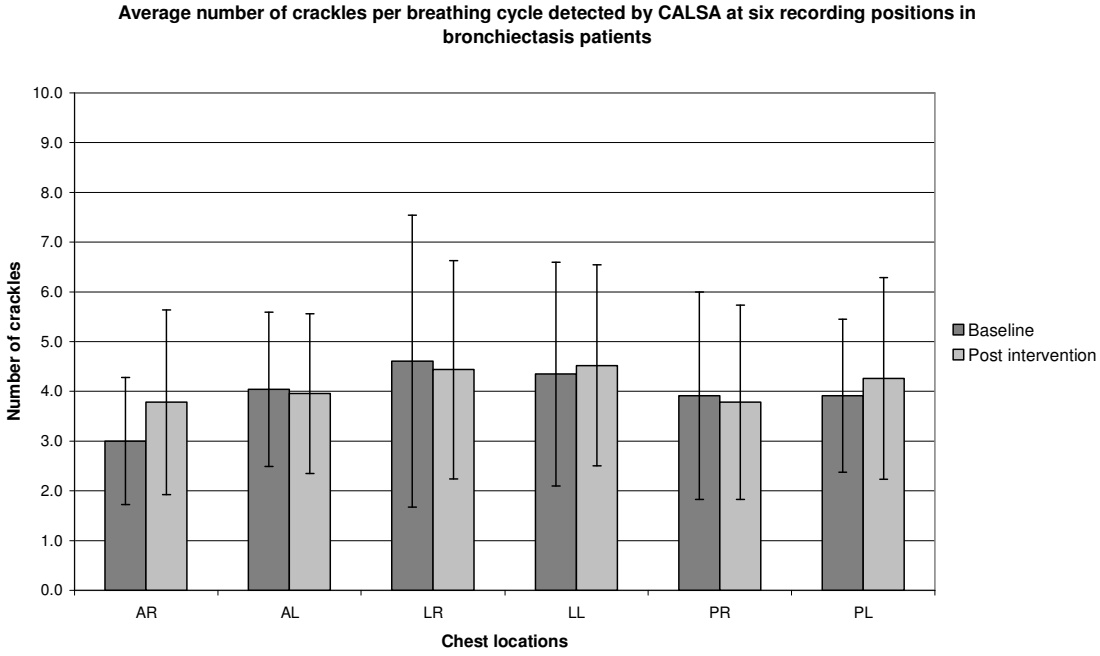


Graph 32: Histograms of the **number and timing** of the crackles per breathing cycle at **anterior right** of the chest in a **cystic fibrosis** participant (Pt04) in the **second study**. The straight line indicates 40% of the breathing cycle.

The relative *T* of the crackles per BC remained reasonably stable from baseline to post intervention. No specific pattern could be detected amongst the CF participants in the second study.

5.7.2.4. Number and timing of crackles per breathing cycle detected by CALSA in bronchiectasis participants

Graph 33 shows the average *N* of crackles per BC detected by CALSA in Br participants in each of the six recording positions of the chest.

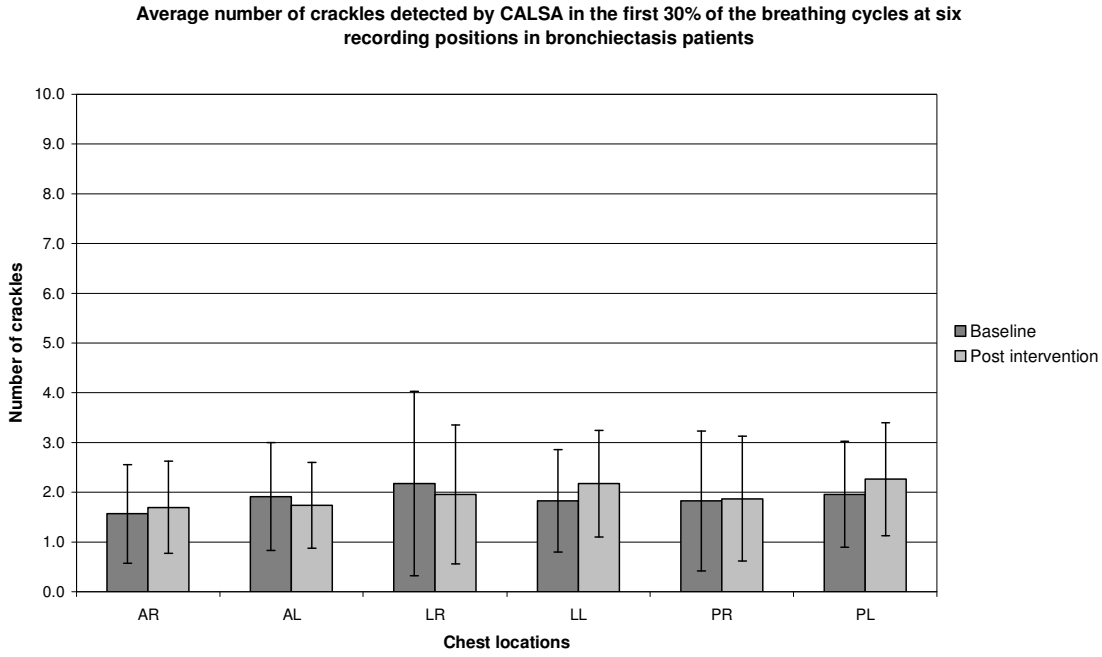


Graph 33: Average **number** of crackles per breathing cycle detected by CALSA at six positions of the chest in **bronchiectasis** participants (n = 23) in the **second study**.

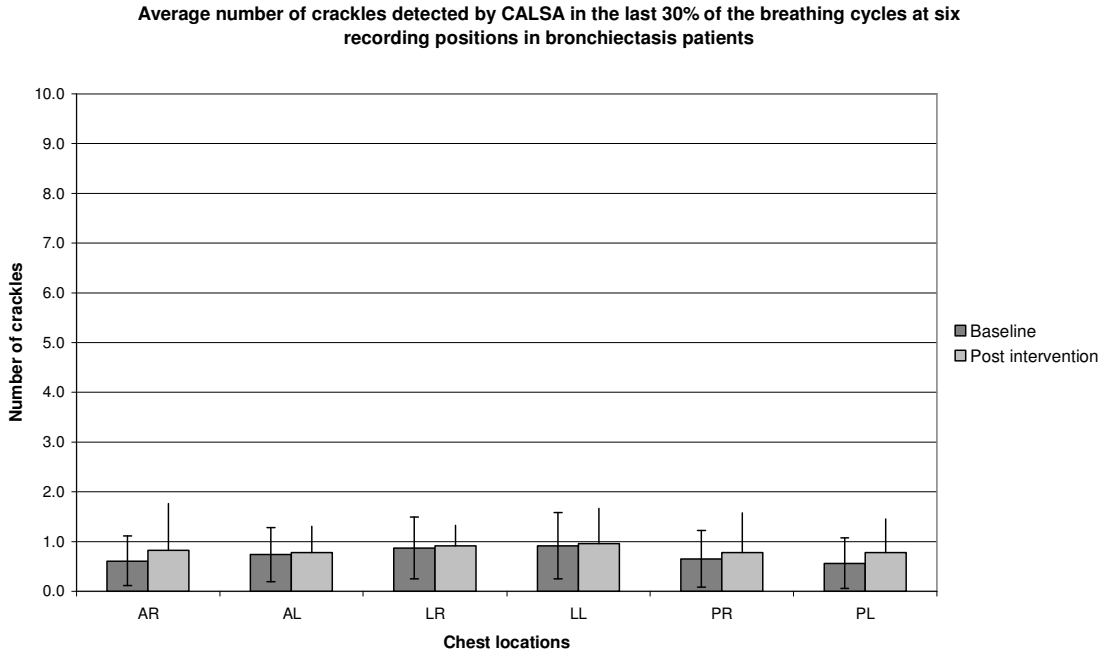
As can be observed from Graph 33, the average *N* of crackles per *BC* post physiotherapy intervention in Br participants was slightly different to the average number at baseline. The average *N* of crackles per *BC*, post intervention increased at AR (from 3±1.3 to 3.8±1.9 crackles), at LL (from 4.3±2.2 to 4.5±2 crackles) and at PL (from 3.9±1.5 to 4.3±2 crackles). The *N* decreased at AL (from 4±1.6 to 3.9±1.6 crackles), at LR (from 4.6±2.9 crackles to 4.4±2.2 crackles) and at PR (from 3.9±2.1 crackles to 3.8±2 crackles). A paired t-test was used to look for statistically significant differences in the mean *N* of crackles detected at baseline and post intervention (see Appendix 10 on the CD provided). Again, the differences were not statistically significant at any recording position.

The *T* of the crackles within the BC in each recording position at baseline and post physiotherapy intervention was analysed for the Br participants using the same process

as for the CF participants. It was again observed that the majority of crackles were inspiratory. Graph 34 and Graph 35 show the results from crackles detected in the first 30% and in the last 30% of the BCs in Br participants.



Graph 34: Average **number** of crackles detected by CALSA in the **first 30%** of the breathing cycles at six positions of the chest in **bronchiectasis** participants (n = 23) in the **second study**.

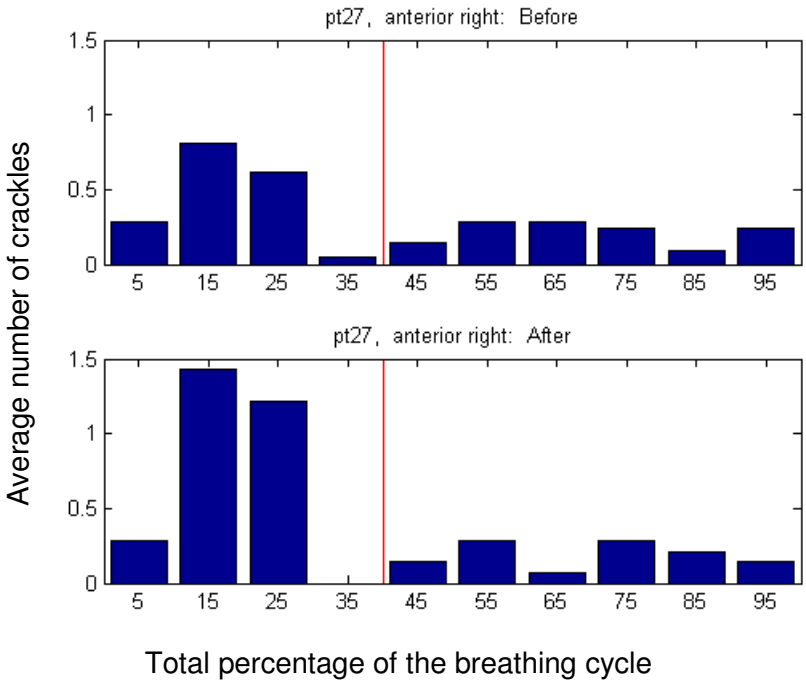


Graph 35: Average **number** of crackles detected by CALSA in the **last 30%** of the breathing cycles at six positions of the chest in **bronchiectasis** participants (n = 23) in the **second study**.

Graph 34 and Graph 35 above show that crackles were present at baseline and post physiotherapy intervention in all the six positions of the chest. Crackles were detected

throughout the *BC* in Br participants, but the majority of crackles were inspiratory. A paired t-test was used to look for statistically significant differences between the mean number of crackles at baseline and post intervention (see Appendix 10 on the CD provided). No statistically significant differences were found in any recording position in any sub-phase of the BC for the Br participants, when comparing baseline to post intervention data.

As for the CF data, histograms with the average *T* of the crackles per BC were produced at baseline and post physiotherapy intervention, for each recording position for all the Br data. An example at anterior right of the chest is provided for a Br participant in
Graph 36.



Graph 36: Histograms of the **number and timing** of the crackles per breathing cycle at **anterior right** of the chest in a **bronchiectasis** participant (Pt27) in the **second study**. The straight line indicates the 40% of the breathing cycle.

The relative *T* of the crackles per *BC* remained reasonably stable from baseline to post intervention. No specific pattern could be detected amongst the Br participants in the second study.

In summary, there were no statistically significant differences found in the *N* of crackles per *BC* (or per sub-phase of the *BC*), between baseline and post intervention in either

CF or Br participants. The *T* of the crackles per *BC* remained stable from baseline to post intervention and no pattern of change could be detected in either group.

5.7.3. Sensitivity and specificity of the algorithms

Figures relating to the sensitivity and specificity of the algorithms used in this research have been published by Vannuccini et al. (1998) and by Hsueh et al. (2005):

- 84% sensitivity and 89% of specificity detecting crackles automatically;
- 89% of sensitivity and specificity detecting wheezes automatically.

Both algorithms had previously been validated with data acquired from patients. No further analysis with the data from these two studies was performed.

After the characterisation of the sample and description of the lung function, oxygen saturation and breathlessness findings, this Chapter has presented the findings related to CALSA's potential as an outcome measure, i.e., reliability, responsiveness to change, sensitivity and specificity. The validity of CALSA has not been formally tested within this Thesis. However, comparisons have been made between the physiotherapist's subjective report of the number/timing of crackles and the CALSA data, to see if any level of agreement could be noted. These findings are presented within the following section.

5.7.4. Agreement between CALSA detecting crackles and the physiotherapist's opinion

The agreement between CALSA and the physiotherapist's opinion about the detection of the *N* and *T* of crackles per BC was analysed for each recording position. The analysis was performed separately for the CF and Br participants at baseline and post intervention.

5.7.4.1. Agreement between CALSA and the physiotherapist's opinion about the number of crackles per breathing cycle in cystic fibrosis participants

Table 31 represents the agreement between CALSA and the physiotherapist's opinion about the *N* of crackles per BC in the CF participants. Due to the difficulties with detecting the exact *N* of crackles per BC during standard auscultation, the physiotherapist was asked to complete an auscultation chart which contained three crackles' classifications i) no crackles, ii) one to six crackles and iii) more than six crackles. This is in line with current clinical practice. In Table 31 results are presented per recording position, at baseline and post intervention. On the left side, anterior left,

lateral left and posterior left results are presented, and on the right side, anterior right, lateral right and posterior right results, are presented.

Anterior Left – Baseline

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	3	1
1 to 6	0	**1**	1
>6	0	1	**0**

Anterior right – Baseline

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	4	1
1 to 6	0	**1**	0
>6	0	1	**0**

Anterior Left – Post intervention

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	4	1
1 to 6	0	**1**	0
>6	0	1	**0**

Anterior right – Post intervention

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	4	1
1 to 6	0	**1**	0
>6	0	1	**0**

Lateral Left – Baseline

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	2	0
1 to 6	0	**3**	0
>6	0	2	**0**

Lateral right – Baseline

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	2	0
1 to 6	0	**2**	1
>6	0	2	**0**

Lateral Left – Post intervention

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	2	0
1 to 6	0	**3**	1
>6	0	0	**1**

Lateral right – Post intervention

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	1	0
1 to 6	0	**3**	1
>6	0	2	**0**

Posterior Left - Baseline

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	0	0
1 to 6	0	**4**	0
>6	0	3	**0**

Posterior right – Baseline

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	1	0
1 to 6	0	**3**	2
>6	0	1	**0**

Posterior Left – Post intervention

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	0	0
1 to 6	0	**5**	0
>6	0	2	**0**

Posterior right – Post intervention

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	1	0
1 to 6	0	**4**	0
>6	0	2	**0**

Table 31: Tables related to the agreement between CALSA and the physiotherapist' opinion about the **number** of crackles per breathing cycle, in each recording position, in **cystic fibrosis** participants (n = 7), at **baseline** and **post physiotherapy** intervention (**second study**).

As can be seen from Table 31, the agreement between the physiotherapist's and CALSA's identification of the *N* of crackles per BC in CF participants is generally poor. Agreement is stronger when auscultation is performed over the posterior chest wall (lower lobes of the lungs), than when performed over the anterior chest wall (upper lobes of the lungs).

5.7.4.2. Agreement between CALSA and the physiotherapist's opinion about the number of crackles per breathing cycle in bronchiectasis participants

Table 32 represents the agreement between CALSA and the physiotherapist's opinion about the *N* of crackles present per BC in the Br participants.

Anterior Left – Baseline

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	19	1
1 to 6	0	**2**	0
>6	0	1	**0**

Anterior right – Baseline

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	18	0
1 to 6	0	**5**	0
>6	0	0	**0**

Anterior Left – Post intervention

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	20	0
1 to 6	0	**1**	1
>6	0	1	**0**

Anterior right – Post intervention

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	19	2
1 to 6	0	**1**	1
>6	0	0	**0**

Lateral Left – Baseline

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	9	0
1 to 6	0	**9**	3
>6	0	2	**0**

Lateral right – Baseline

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	4	0
1 to 6	0	**11**	3
>6	0	5	**0**

Lateral Left – Post intervention

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	12	0
1 to 6	0	**7**	2
>6	0	2	**0**

Lateral right – Post intervention

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	10	1
1 to 6	0	**8**	2
>6	0	1	**1**

Posterior Left – Baseline

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	4	0
1 to 6	0	**15**	2
>6	0	2	**0**

Posterior right – Baseline

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	5	0
1 to 6	0	**13**	4
>6	0	1	**0**

Posterior Left – Post intervention

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	5	0
1 to 6	0	**12**	4
>6	0	2	**0**

Posterior right – Post intervention

PHYSIO \ CALSA	None	1 to 6	>6
None	**0**	4	0
1 to 6	0	**17**	2
>6	0	0	**0**

Table 32: Tables related to the agreement between CALSA and the physiotherapist' opinion about the **number** of crackles per breathing cycle, in each recording position, in **bronchiectasis** participants (n = 23), at **baseline** and **post physiotherapy** intervention (**second study**).

As can be seen from Table 32,agreement about the *N* of crackles per *BC* is again poor. The pattern for higher agreement when auscultating the posterior regions is repeated in the Br participants.

5.7.4.3. Agreement between CALSA and the physiotherapist's opinion about the timing of the crackles per breathing cycle in cystic fibrosis participants

For the purposes of analysis, the BC was divided into four parts, early inspiration (0-20%), late inspiration (21-40%), early expiration (41-70%) and late expiration (71-100%). Tables of agreement at baseline and post intervention per each part of the BC, in each recording position, for the CF participants, were created (see Table 33). Due to the large number of tables thereby generated, only a summary of the findings is provided. The results obtained at anterior right of the chest are presented here as an example. The complete analysis can be seen in Appendix 11 on the CD provided.

Agreement about the relative *T* of the crackles within the BC is slightly better in late inspiration (21-40%) and in expiration than early inspiration (0-20%). Table 33 shows an example of these findings at anterior right of the chest in CF participants.

Anterior right - Inspiration Baseline

PHYSIO \ CALSA	None	Early Insp.
None	**0**	7
Early Insp.	0	**0**

Anterior right – Expiration Baseline

PHYSIO \ CALSA	None	Early Exp.
None	**3**	3
Early Exp.	1	**0**

Anterior right - Inspiration Post

PHYSIO \ CALSA	None	Early Insp.
None	**1**	6
Early Insp.	0	**0**

Anterior right - Expiration Post

PHYSIO \ CALSA	None	Early Exp.
None	**2**	4
Early Exp.	0	**1**

Anterior right - Inspiration Baseline

PHYSIO \ CALSA	None	Early Insp.
None	**1**	5
Early Insp.	0	**1**

Anterior right - Expiration Baseline

PHYSIO \ CALSA	None	Early Exp.
None	**4**	2
Early Exp.	1	**0**

Anterior right - Inspiration Post

PHYSIO \ CALSA	None	Early Insp.
None	**1**	5
Early Insp.	0	**1**

Anterior right - Expiration Post

PHYSIO \ CALSA	None	Early Exp.
None	**3**	3
Early Exp.	1	**0**

Table 33: Tables showing the agreement between CALSA and the Physiotherapist' opinion about the **timing** of crackles per breathing cycles, at **anterior right** of the chest in **cystic fibrosis** participants (n = 7), at **baseline** and **post physiotherapy** intervention (**second study**).

This pattern in which agreement is very poor in the first part of the BC and slightly better in late inspiration and expiration (where fewer crackles were detected), was observed in the data from the other regions of the chest. However, in the lateral and posterior regions CALSA and physiotherapist showed good agreement about the presence (mainly inspiratory) or absence (mainly expiratory) of crackles in a larger number of participants.

5.7.4.3.1. Agreement between CALSA and the physiotherapist's opinion about the timing of the crackles per breathing cycle in bronchiectasis participants

The same analysis was conducted for the Br participants data. Tables of agreement at baseline and post intervention per each part of the BC in each recording position were created. Again, only a summary of the findings is provided (see Table 34). The results obtained at anterior right of the chest are presented here as an example. The complete analysis can be seen in Appendix 11 on the CD provided.

Anterior right - Inspiration Before

PHYSIO \ CALSA	None	Early Insp.
None	**7**	15
Early Insp.	0	**1**

Anterior right - Expiration Before

PHYSIO \ CALSA	None	Early Exp.
None	**5**	17
Early Exp.	0	**1**

Anterior right - Inspiration After

PHYSIO \ CALSA	None	Early Insp.
None	**5**	17
Early Insp.	0	**1**

Anterior right - Expiration After

PHYSIO \ CALSA	None	Early Exp.
None	**5**	18
Early Exp.	0	**0**

Anterior right - Inspiration Before

PHYSIO \ CALSA	None	Early Insp.
None	**7**	13
Early Insp.	1	**2**

Anterior right - Expiration Before

PHYSIO \ CALSA	None	Early Exp.
None	**9**	13
Early Exp.	0	**1**

Anterior right - Inspiration After

PHYSIO \ CALSA	None	Early Insp.
None	**6**	16
Early Insp.	0	**1**

Anterior right - Expiration After

PHYSIO \ CALSA	None	Early Exp.
None	**10**	13
Early Exp.	0	**0**

Table 34: Tables showing the agreement between CALSA and the physiotherapist' opinion about the **timing** of the crackles per breathing cycles, at **anterior right** of the chest in **bronchiectasis** participants (n = 23), at **baseline** and **post physiotherapy** intervention (**second study**).

As for the CF participants data, there was very poor agreement in early inspiration with slightly better agreement in late inspiration and expiration (where fewer crackles were detected) in all regions of the chest. Again, CALSA and the physiotherapist showed better agreement about the presence (mainly inspiratory) or absence (mainly expiratory) of crackles in a larger number of participants in other recording positions.

In conclusion, the agreement between CALSA and the physiotherapist about the *N* of crackles per BC in both groups of participants was higher in data from posterior areas of the chest; agreement about the *T* of the crackles within the BC was highest after the first 20% of the cycle.

5.8. Summary

This Chapter has presented the main results from the analysis of the data collected from the two studies. In both studies, Br participants were found to be generally older and heavier compared with CF participants. Lung function and oxygen saturation

values were found to be higher in Br than in CF participants. However, Br participants perceived themselves to be more breathless than CF participants.

In the first study, from the whole sample of 24 participants, only three did not routinely treat themselves with airway clearance self-techniques. During the study, postural drainage in horizontal side lying (right and left), plus clapping, huff and cough was the most common intervention among CF participants whereas Br participants mainly treated themselves using ACBT (3 cycles) in the sitting position. In the second study, only five of the 30 participants (1 CF participant and 4 Br participants) did not treat themselves routinely with airway clearance techniques. The treatment intervention applied by the physiotherapist in the second study was adjusted to each participant's needs, with ACBT being applied to the majority of the participants in combination with manual techniques. The physiotherapist's opinion was that the majority of the participants' lungs were unchanged after the intervention. On the other hand, the majority of participants considered that their lungs were clearer after the physiotherapy intervention.

The results from the analysis of the lung sounds data of both studies have been presented in sections relating to reliability, responsiveness to change, specificity /sensitivity, and agreement between CALSA and the physiotherapist. The inter-subject reliability analysis from the ANOVA revealed that participants showed considerable inter-individual variability in crackles characteristics in both studies and in both groups of participants studied. The test-retest reliability of crackles was found to be high (as estimated by the ICC, SRD and Bland and Altman 95% limits of agreement) in both studies and in both groups of participants. The analysis comparing baseline and post intervention data indicated that the crackles data showed some responsiveness to change, i.e., the duration of the IDW and 2CD altered. The direction of this change was not consistent across both groups of participants. In the first study the duration of the crackles' IDW and 2CD in CF participants decreased, whereas in Br participants the duration of these variables increased post intervention. In the second study, the duration of the crackles' IDW and 2CD in both groups of participants increased after physiotherapy intervention in the anterior regions (upper areas of the lungs) and decreased in the posterior regions (bases of the lungs). In both studies, the analysis of the data before versus after airway clearance intervention generated high SRD values, suggesting that the change in the duration of the crackles was greater than could be attributed to error.

In the first study, the Bland and Altman 95% limits of agreement for the crackles data at baseline versus post self-intervention showed no systematic bias in the CF participants' data, but some bias in the data from the Br participants for the trachea, anterior right and anterior left recording positions was detected. In the second study the Bland and Altman 95% limits of agreement for the crackles data at baseline versus post intervention showed some systematic bias in both pathologies, i.e., an increase in crackles' duration in the upper areas of the lungs, and a decrease in recordings from the bases of the lungs in the majority of the participants. Crackles were present in the data from all the recording positions of the chest and throughout the breathing cycle, although the majority of crackles were in early inspiration. The average *N* of crackles per BC detected by CALSA remained stable from baseline to post interventions. In both groups of participants, the agreement between CALSA and the physiotherapist was generally poor. Agreement was higher in data taken from the posterior regions of the chest and from later phases of the breathing cycle.

The next chapter will discuss these findings in relation to published literature, appraise the limitations of the two studies and make recommendations for areas of future research in this field.

Chapter 6
Discussion

6.1. Introduction

The aim of this research was to explore the potential for CALSA to be used as an outcome measure for respiratory physiotherapy interventions. This Chapter will start with a discussion of the findings from the two studies relating to the non-CALSA data. This will be followed by a discussion of the CALSA findings within the context of its value as an outcome measure, and in relation to previous research. Some theories formulated by the author, relating to the CALSA findings will then be proposed. The chapter finishes with a description of the different limitations of this research and some ideas for future research in this field.

6.2. Demographic, anthropometric, breathlessness, oxygen saturation and lung function findings

The findings of the first and second studies were generally similar. Cystic fibrosis participants were generally younger and lighter than Br participants, but their clinical condition (defined mainly by the lung function values) was worse. These findings might be explained by the fact that CF is a genetic disease where several physiological systems are affected and, despite treatment, these patients still deteriorate quite significantly and quickly over time (Doring and Hoiby, 2004), whereas non-cystic fibrosis Br is more common in adults than in children where the respiratory system is affected due to local disease (blockage of bronchial lumen by a foreign body, tumour or extrinsic compression of the bronchi) and more rarely due to diffuse processes (congenital disease or association of systematic disease) (Barker, 2002, Evans and Greenstone, 2003).

However, CF participants perceived themselves as less out of breath than Br participants. Perception of breathlessness is very complex and one possible explanation for this result is that CF patients have been living with the disease since they were born, and may be ‘desensitised’ to the signals that result in other people feeling breathless. In the second study, despite both groups of participants having perceived themselves to be less out of breath after the respiratory physiotherapy intervention, differences were only statistically significant different for the Br group. This finding could be explained by the fact that in the second study a larger number of Br

participants was considered, resulting in more statistical power. However, the Modified Borg Scale used to assess the participants' level of breathlessness in this research was applied immediately post interventions in both studies, when the exertion required may have affected their breathlessness. Thus the timing of the application of the scale might have influenced this result.

The lack of statistically significant differences in either breathlessness (in the first study and in CF participants in the second study), oxygen saturation or lung function post interventions is a common finding. Numerous short-term studies (Ambrosino et al., 1995, Elkins et al., 2005b, McCarren and Alison, 2006, Patterson et al., 2005, Thompson et al., 2002) comparing different respiratory interventions for patients with excessive secretions have been unable to detect differences between treatments when using sputum weight, lung function, oxygen saturation and breathlessness as outcome measures. However, in more intensive studies (Cerny, 1989, Newton and Bevans, 1978, Homnick et al., 1998, Mulholland et al., 1994, Arens et al., 1994) involving several treatment sessions each day over a period of a week or more or in long term studies (McIlwaine et al., 1997, McIlwaine et al., 2001) improvement on these outcome measures has been reported. Therefore, the effects of respiratory physiotherapy measured by these outcome measures are conflicting. In many of these studies relatively small groups of patients are included, and this increases the risk of type II error (van-der-Schans et al., 1999). Furthermore, these studies compare two or more active interventions rather than an active intervention versus an inactive control. Therefore, it is never clear if differences are not detected because the outcome measures are not appropriate, or because the treatments being compared are equally effective/ineffective. Therefore, in the second study the author speculates that differences were found in the breathlessness measure in the Br participants due to the inclusion of a larger number of participants. In the CF group, due to the small number of participants there was insufficient statistical power to detect change.

Finally, in this research, despite lack of objective evidence of benefit (Jones and Rowe, 1997, van-der-Schans et al., 2000) all participants considered that it was important to treat themselves daily with physiotherapy airway clearance techniques.

6.3. Lung sound findings

This section will start discussing the reliability of crackles' duration (IDW and 2CD) using CALSA over short time periods and it will be followed by the discussion of responsiveness to change of crackles' duration (IDW and 2CD) using CALSA. Finally,

the sensitivity and specificity of the algorithms used by CALSA to detect the added lung sounds in this research will be discussed.

6.3.1. Reliability

This section will discuss the inter and intra-subject reliability of crackles' parameters characterised in the time domain using CALSA. This has not been previously investigated in the literature (see section 3.4).

6.3.1.1. Inter-subject reliability

As expected, the inter-subject reliability for both crackles' variables studied (IDW and 2CD) in this research was found to be low, as shown by the significant ANOVA. As well as differences in demographic and anthropometric characteristics (Pasterkamp et al., 1997a, Ploysongsang et al., 1991, Sanchez and Vizcaya, 2003), the participants had two different pathologies with varying acuity. Therefore, the hypotheses that crackles' IDW and 2CD duration would have low inter-subject reliability were accepted. Low inter-subject reliability of lung sounds has been previously reported (Ploysongsang et al., 1991, Sanchez and Vizcaya, 2003). However, comparisons are difficult because the samples studied by other researchers involved only healthy participants, and the lung sounds data were studied in the frequency domain where the spectral characteristics and patterns were analysed. In this research, lung sound data were collected from participants with excessive secretions and the reliability analysis was performed in the time domain to assess the crackles' parameters (Mahagnah and Gavriely, 1994).

6.3.1.2. Intra-subject reliability

The intra-subject reliability was found to be 'good' to 'excellent' with no systematic bias between the repeated measures at baseline or the repeated measures post interventions. Therefore, it was deemed appropriate to pool the data of both studies at baseline (since the samples characteristics, inclusion and exclusion criteria, and baseline reliability results were the same or very similar in both studies). This decision was taken because the results obtained involved a larger sample of participants and strengthened the reference values. These could be used in any future research studies in which the detection and respective duration of the crackles' IDW and 2CD are used to measure change in an individual with CF or Br following an intervention.

High intra-subject reliability of lung sounds has been reported by other authors in healthy subjects (Mahagnah and Gavriely, 1994, Ploysongsang et al., 1991, Sanchez and Vizcaya, 2003) and in healthy subjects and patients with fibrosing alveolitis

(Sovijarvi et al., 1996). However, these studies have also analysed lung sounds in the frequency domain in small samples of mainly healthy subjects. In this research crackles were analysed in the time domain and in CF and Br populations. Therefore, comparisons with previous studies are again difficult, for the same reasons.

6.3.1.2.1. Smallest Real Difference

In the absence of a gold standard to define the magnitude of minimal clinically relevant changes, the SRD can be calculated, as it provides evidence of a real change that is not attributable to 'error' or 'noise' (Beckerman et al., 2001). However, the relationship between the SRD and a clinically meaningful change is not clear.

Using as an example, the crackles' 2CD duration in CF participants at baseline, recorded at anterior right of the chest (first study), we can be 95% confident that if a patient increases the duration of this specific variable at this place by 1.89 ms, then a real change has occurred beyond measurement error (see page 85). However, does this value reflect a relevant clinical change? There is an essential difference between 'clinically relevant change' and the 'SRD'. In the opinion of Beckerman et al. (2001), the SRD is a clinimetric property of a measurement instrument, whereas 'clinically relevant change' is an arbitrarily chosen amount of change indicating which change clinicians, researchers or patients judge as affecting the clinical condition. The SRD provides information about the 'reality' of any change, but does not provide information as to whether that change is clinically meaningful.

In both studies of this research, the SRD values, over short time periods, for both variables studied (crackles' IDW and 2CD) presented a similar range of values indicating the stability of the measure in CF and Br participants. Despite the crackles' 2CD duration being longer (>10 ms) than the crackles' IDW (< 3ms), for both groups of participants in all the recording positions the SRD values were much smaller (proportionally) for the crackles' 2CD than for the crackles' IDW. The lower SRD values imply higher reliability and therefore, less change in value is required to exceed measurement error (Beckerman et al., 2001, Pfennings et al., 1999). This suggests that the crackles' 2CD is a more stable and reliable measure. Smallest real difference calculations were not found in other published studies involving lung sound analysis and therefore, comparisons with the findings of this research were not possible.

6.3.1.2.2. Sources of error using CALSA to detect crackles' duration

In the first study, a particularly high SRD value was detected at anterior left in the CF participants at baseline. This could be explained by the fact that these participants had

a catheter implanted (in the anterior region of chest below the clavicle for intravenous administration of medication) that affected the microphone positioning, so each participant had the device in a slightly different position. Therefore, in the first recordings, at baseline, the researcher had to adjust the microphone connection to the skin slightly during the recording to establish the optimum recording position, which could have affected the transmission of the added lung sounds. This difficulty did not occur post intervention due to the fact that post intervention the best place to connect the microphone was already known. The standard error of measurement was affected and consequently the SRD values. This was particularly evident on the crackles' 2CD because it was longer and easily detected.

In the second study, a higher SRD value in this specific location was not found. However, it was identified that the crackles' duration in this specific location decreased post intervention in the majority of the CF participants instead of increasing, as had occurred at the other upper and middle regions of the chest. The author speculates that: a) the reason why a higher SRD value was not found was because the researcher had acquired more experience collecting the data and had tried to find the best microphone attachment before starting the recordings; b) the reason why the crackles' duration did not increase in this area was because the secretions in this specific location did not move to more central areas. This last finding is expected since the implanted catheter makes airway clearance therapy more difficult in that specific region. Furthermore, the left lung bronchus is considerably longer, narrower (15%) and more horizontal than the right bronchus (Ellis, 2005) and because of the position of the heart, many of the major left segmental bronchi are directed more posteriorly compared to the right bronchi (Jones et al., 1999). Therefore, due to these reasons the upper area of the left lung might be more difficult to clear (Ashour et al., 1990, Rajasekaran et al., 1999, Ellis, 2005).

6.3.1.2.3. Intraclass Correlation Coefficient and Bland and Altman 95% limits of agreement

The ICC for the crackles' parameters suggested 'excellent' or 'good' reliability in almost all recording positions, in both groups of participants at baseline and post interventions. The exceptions were for the crackles' IDW duration in the first study from some locations. These findings could be explained by the fact that: i) tracheal sounds are not ideal for use as an outcome measure for respiratory therapy (see section 6.3.2 Responsiveness to change); ii) crackles' IDW duration is a more difficult measure to obtain accurately, since the duration is very short and the exact place where a crackle starts is difficult to determine (Hoevers and Loudon, 1990) increasing the measurement

error, and iii) this finding was not detected in the second study, so the researcher's technique might have improved.

However, ICCs should be interpreted with caution. As explained during the literature review (section 2.5.1.2), a major criticism of the ICC is the influence of between-subjects variance on the ratio. Therefore, an instrument can produce high ICC but reveal little information regarding the agreement between repeated measurements (Chinn, 1990, Rankin and Stokes, 1998, Bland and Altman, 1995). Bland and Altman 95% limits of agreement are independent of the true variability in the observations (between-subjects variation) and therefore, complement the ICC analysis and provide detail regarding the nature of the observed intra-subject variability (Rankin and Stokes, 1998, Bland and Altman, 1995). The reliability assessed from Bland and Altman techniques was found to be acceptable, and no consistent systematic bias was detected in any recording position of the two crackles' variables studied. Therefore, these results lead to the conclusion that the use of CALSA for characterising crackles was reproducible over short time periods.

In other studies regarding the assessment of the repeatability of lung sounds, the reliability of the spectral characteristics have been explored with analysis of variance (Sanchez and Vizcaya, 2003) or with analysis of variance and the coefficient of variation (Mahagnah and Gavriely, 1994, Ploysongsang et al., 1991, Sovijarvi et al., 1996). The use of the coefficient of variation to calculate reliability is not considered appropriate since it assumes that the largest test-retest differences will occur in individuals scoring the highest values on the test (Bland and Altman, 1995). The ICC and Bland and Altman 95% limits of agreement have been recommended as more adequate methods to assess reliability (Atkinson and Nevill, 1998, Chinn, 1990, Chinn, 1991, Rankin and Stokes, 1998). The ICC has only been used by Schreur et al. (1992) studying lung sound intensity in patients with emphysema and normal subjects and studying lung sound intensity and wheezes parameters (Schreur et al., 1994). In both studies reproducibility was found to be 'satisfactory'. However, this analysis was performed in the frequency domain where spectral characteristics were considered and the recordings were performed in a sound proofed room. Therefore, because the coefficient variation was not used in this research and the ICC and Bland and Altman 95% limits of agreement calculations were not found in published studies regarding lung sound analysis in the time domain, it was not possible to compare the results obtained in this research directly with other investigations.

6.3.2. Responsiveness to change

This section will discuss the comparisons between the analysis of the crackles' parameters at baseline versus post interventions in both studies.

6.3.2.1. Crackles' frequency at baseline and post airway clearance interventions

The most notable finding from the lung sound analysis data, in the first study, was a clear difference in the response to self-intervention between CF and Br participants. Both groups had similar baseline values for the duration of the crackles (coarse crackles). Coarse crackles were also found in Br patients by Piirila et al. (1991). However, post self-intervention, CF participants showed a trend towards shorter, higher frequency crackles. Despite this change, the post intervention crackles could still be classified as low frequency or coarse crackles (crackles' 2CD duration >10 ms or frequency <100 Hz). This probably means that the secretions post physiotherapy self-intervention were more widespread over the different regions, mainly central and middle airways of the lungs than they were at baseline. On the other hand, the Br participants showed a trend towards longer (lower frequency crackles), post self-intervention which would be associated with more central crackles, possibly as a result of mobility of the secretions to more central areas, allowing participants to cough and clear the secretions from their chest more easily than CF participants.

As the baseline measurements of the crackles' duration were similar between the two groups, the differences between the groups' responses may be due to pathology, demographic, anthropometric differences or due to the different self-interventions performed. It is known that the stage of a disease, the demographic and the anthropometric individual characteristics can affect lung sounds (Pasterkamp et al., 1997a, Ploysongsang et al., 1991, Sanchez and Vizcaya, 2003). However, the distinct modification of the parameters related to crackles in opposite directions in each group of participants post self-intervention could be related to the way participants chose to treat themselves, since there was a clear separation (CF participants treated themselves in horizontal side lying and Br participants in sitting).

The side-lying position accentuates anteroposterior expansion using the transverse excursion of the dependent chest wall. In this position, the dependent hemidiaphragm (the one that is underneath) is moved into a cephalic direction because of the compression of the viscera. This results in a greater excursion during respiration and in a greater contribution to the ventilation and gas exchange of that specific lung (Ogiwara and Miyachi, 2002, Badr et al., 2002). However, thoracic volume is decreased due to

the expansion of one hemithorax being limited by the bed. This may result in less lung volume and less elastic recoil than in other positions, e.g., sitting or standing (Badr et al., 2002). It can be argued that in side-lying the changes in lung volumes can balance themselves due to a more efficient contraction of the diaphragm (Badr et al., 2002), but the fact is that the space in the thorax is decreased. Ross et al. (1992) also showed that the distribution of ventilation was significantly less homogeneous in side-lying positions compared with supine and sitting positions. Therefore, a blockage, and /or dispersion, of secretions without a specific direction can happen more easily in side-lying than in the vertical position.

The effectiveness of self treatment techniques varies with the nature of the techniques used. Lung secretions are best cleared using forced expiratory manoeuvres which are more efficient in the central areas of the lungs (van-der-Schans, 1997). Clearance of mucus during physiotherapy is influenced by both the expiratory force and the lung volume (van-der-Schans, 1997, van-der-Schans et al., 1994). Lower expiratory force from a higher lung volume, produces higher elastic recoil pressure, resulting in a shift of the equal point of pressure in the direction of the mouth. A forced expiration started from a lower lung volume will result in a more caudal equal point of pressure (van-der-Schans, 1997). The former is appropriate for clearing centrally located secretions, while the latter is more suitable for peripherally located secretions (van-der-Schans, 1997).

It has been demonstrated that lung volumes are highest in upright positions (Clague and Hall, 1979, Jenkins et al., 1988). In sitting, lung volumes and capacities are increased compared to side lying, prone or supine, and the diameter of the main airways is slightly larger, reducing airway closure and maximising arterial oxygenation, increasing the possibility of mobilising secretions. The diaphragm fibres are in a shortened position allowing more availability for maximal expiratory efforts. Thus, coughing and other forced expiratory manoeuvres are more effective in most of the upright positions (Ogiwara and Miyachi, 2002, van-der-Schans, 1997). Furthermore, overall ventilation of both lungs is better in sitting that in any side-lying position (Jones et al., 1999). However, in sitting, due to anatomic position and the effects of gravity, the middle lobe of the right lung (compressed between the upper and the lower lobe) and posterior regions tend to be more difficult to clear.

In summary, although horizontal positions are frequently used by clinicians to encourage drainage of secretions using gravity, the sitting positions may be more effective for moving secretions from peripheral to more central airways. This could

explain the differences found in the results between the two groups of patients (a trend towards shorter, higher frequency crackles, in CF and towards longer, lower frequency crackles, in Br patients), and also the finding that Br crackles' duration did not increase at posterior and lateral right areas of the lungs, post physiotherapy self-intervention.

Based on the findings of the first study, it was therefore hypothesised that **crackles will become longer (lower frequency), post airway clearance intervention applied by a physiotherapist (second study).**

In the second study the crackles' duration changed post intervention, in similar directions in both CF and Br participants. As in the first study, both groups had similar baseline crackles' duration values. However, the crackles' duration showed a trend towards longer (low frequency) crackles, in the upper (anterior right and left) and lateral (right and left) areas of the lungs and a trend towards shorter (high frequency crackles), in the lower areas of the lungs (posterior right and left), post physiotherapy interventions. The exception found at anterior left for the CF participants, where the majority of participants did not have any increase in the crackles' duration, is probably related with the implant of the catheter, i.e., it is more difficult to mobilise secretions in that specific location of the chest. A similar finding was observed in the first study.

In summary, the hypothesis (crackles will become longer post physiotherapy intervention) was accepted at anterior and lateral areas of the chest and rejected at posterior areas of the chest, in the groups of participants studied.

In both groups of participants, in both studies, independently of the direction of the change, the post intervention crackles would still be classified as 'low frequency' (< 100 Hz $\Leftrightarrow$ > 10 ms). Therefore, the trends towards longer duration in Br participants in the first study, and in both groups of participants in the second study, probably means that the secretions post interventions were mobilised in the direction of the central and middle airways of the lungs (lower frequency crackles) and that air arrived to more peripheral airways causing the higher frequency crackles. This association between crackles frequency and the location in the airways where they are being generated has been previously investigated by Fredberg and Holford (1983) with an engineering technique called quadupole in an acoustic laboratory. This might have been explored by examining any relationship between the movement of secretions and the volume of sputum expectorated. However, because of all the problems related with the sputum weight (Kluft et al., 1996, Mortensen et al., 1991, Oermann et al., 2001), as described

in the literature review (see section 2.5.2.1.), these data were not collected by the author.

In the **first study** it was speculated that the differences found between CF and Br participants in terms of the direction of change of the crackles' duration post self-intervention (a trend towards shorter in CF participants and towards longer in Br participants), were possibly due to the position that participants chose to treat themselves. The findings of the **second study** seem to confirm that theory, since both groups were treated according to individual needs, and horizontal positions were used frequently, but the sitting position with forced expiratory manoeuvres was always included in the intervention. The differences observed between the two pathologies in the first study were not detected in the second.

The SRD and the Bland and Altman 95% limits of agreement plots were analysed to compare the data before versus after interventions in both studies. The SRD was analysed with the aim of assessing the smallest change that could be interpreted as a real change and the Bland and Altman plots were analysed to assess if there was systematic bias in the crackles' IDW and 2CD post airway clearance interventions. The presence of systematic bias would tell us if the intervention had a measurable impact on the crackles' variables being studied (IDW and 2CD). In the second study three different data subsets were analysed with the data from: i) all participants, ii) participants who considered their lungs clearer post intervention, iii) participants who the physiotherapist considered to have left the intervention with the lungs clearer. The SRD will be discussed first followed by the Bland and Altman 95% limits of agreement.

6.3.2.1.1. Smallest Real Difference before versus after intervention

The SRD values for both variables (crackles' IDW and 2CD) from the analysis of data recorded before versus after interventions were higher than for repeated measures taken either at baseline or post interventions (in both studies in both groups of participants), indicating that CALSA was able to detect the occurrence of change. Although lung sound analysis has not been used previously to measure the effect of therapeutic interventions, some authors have used it to assess pathological changes (e.g., asthma or pneumonia) or drug induced changes (e.g., bronchial changes). These authors found that acoustic analysis could detect changes during the course of airway obstruction (Fiz et al., 2002, Fiz et al., 1999, Malmberg et al., 1994a, Malmberg et al., 1994b, Rossi et al., 2000, Oud et al., 2000, Bentur et al., 2003) or disease (Murphy et al., 2004, Piirila, 1992, Piirila et al., 1991). Baughman and Loudon (1985) recorded lung sounds in asthmatic patients overnight and were able to detect different degrees

of obstruction severity that were not revealed by any other measure. Standard lung function tests, particularly FEV_1, do not seem to reflect small changes in airway morphology, but CALSA may provide a more sensitive measure to detect alterations in airway geometry (Schreur et al., 1994) and early impairment of lung periphery (Peták et al., 2006), being a promising supplement to traditional auscultation and spirometric tests (Whittaker et al., 2000). Therefore, these findings indicate that in the future it may be possible to determine the site of some airway obstructions, and to follow the effect of therapy by the analysis of respiratory sounds (Pohlmann et al., 2001, Sovijarvi et al., 1996).

6.3.2.1.2. Bland and Altman 95% limits of agreement before versus after intervention

There was no significant systematic bias (for both variables) demonstrated in the plots of data recorded before versus after intervention of the CF participants in any position, despite higher SRD values in the first study. The same was found for Br participants in the lateral and posterior regions. However, some evidence of systematic bias was detected in the trachea, anterior right and anterior left plots of Br participants, suggesting that a change has occurred. This supports the earlier finding (from previous analysis in section 5.7.2) that there was a trend towards longer (lower frequency), crackles post intervention, which means crackles being produced more in the central areas of the lungs.

The SRD values and the Bland and Altman findings in the first study have led the author to speculate that the self-intervention in Br participants mobilised secretions in the central areas, unplugging the bronchioles, allowing air to pass and generating low frequency crackles. It is presumed that change was not observed in the more peripheral airways because there was insufficient airflow arriving to those regions.

In the second study, from the analysis of the Bland and Altman plots generated for all CF and for all Br participants, systematic bias was detected in both variables (crackles' IDW and 2CD) towards an increase of crackles' duration in the upper airways (anterior regions) and towards a decrease of crackles' duration in the base of the lungs (posterior regions) for both groups of participants. The author speculates that this finding could be explained by the fact that during the respiratory physiotherapy intervention, all participants performed forced expiratory manoeuvres. The resultant increase in the flow of air in the larger airways (upper airways) could have caused the unplugging of secretions from the bronchioles and respective movement to more central airways, allowing air to pass and generating lower frequency crackles (increase

of the crackles' duration). At the same time that this occurred in the upper airways, air might have arrived to more peripheral airways, causing the decrease of the crackles' duration (higher frequency crackles). This supports the earlier finding (see analysis at the beginning of section 6.3.2.1) that there was a trend towards longer (lower frequency) crackles post intervention in the upper airways, which means crackles being produced more in the central areas of the lungs and a trend toward shorter (higher frequency) crackles which means crackles being produced by more peripheral airways.

Crackle characteristic parameters analysed using CALSA have been investigated for fibrosing alveolitis, Br, chronic obstructive pulmonary disease (COPD) and heart failure (Piirila et al., 1991), asbestos and emphysema (Piirila et al., 2000) and pneumonia (Murphy et al., 2004, Piirila, 1992). Changes over time have also been explored during the course of pneumonia (Piirila, 1992). In the Piirila's (1992) study the coarse crackle parameters (IDW and 2CD of inspiratory and expiratory crackles), presented a tendency to shorten when the patient was recovering from pneumonia, however the change was not statistically significant. This might have been due to the small number of participants involved in the study, 11 patients with pneumonia. The aim of Piirila's (1992) study was to characterise the crackles in pneumonia and to assess the change of crackles' frequency and timing in the respiratory cycle during the course of the disease but not to assess or monitor therapeutic interventions. Nevertheless, the authors found that it was possible to describe the course of a disease based on crackle parameters.

However, because in respiratory physiotherapy there is no gold standard measure (reference value for a test and used for validation of a new test) to assess the consequences of the respiratory intervention, how is it possible to know that the changes that CALSA is detecting in both studies of this research are 'real' or 'relevant' changes? There is no straightforward answer to this question. Therefore, in the attempt to address this problem in the second study, the author had i) asked the physiotherapist to perform an 'effective' intervention according to each specific participant's needs; ii) collected data regarding the physiotherapist's and participants' opinion about the clearance of the lungs post interventions and iii) analysed these results (physiotherapist's and participants' opinions) against the CALSA detecting crackles findings. These findings will now be discussed.

It was hoped that if the physiotherapist was performing an effective intervention, then she would consider that the majority of participants' lungs would be clearer post

intervention. However, although the majority of participants reported their lungs were clearer post intervention (4/7 CF participants and 15/23 Br participants), in the physiotherapist's opinion, the lungs were no clearer post intervention in the majority of the participants (6 of 7 CF participants and 13 of 23 Br participants). This could raise questions about the 'effectiveness' of the intervention that was delivered. This is discussed later in this Chapter.

Bland & Altman plots were also performed separately with the CALSA data from i) those participants who considered their lungs to be clearer post intervention and ii) those participants who the physiotherapist considered the lungs to be clearer post intervention, to see if the change detected by CALSA agreed with these judgements. This analysis was performed with a smaller number of participants and therefore, the chances of not finding a change when one existed increased. No systematic bias was detected when the plots regarding to the physiotherapist' opinion were analysed in both groups of participants, probably due to the small number of participants being considered, despite higher SRD values. However, when the plots of CALSA data from the participants who felt their lungs to be clearer post the intervention were analysed, there was a tendency to systematic bias at lateral left and posterior regions of the chest in the direction of a decrease in crackles' duration, in both groups of participants. This might have been because the number of participants who considered to have left the intervention with the lungs clearer was higher than the number of participants who the physiotherapist considered to have left the intervention with the lungs clearer.

At this point, two possibilities are present:
A) CALSA is detecting change when none has occurred or
B) The physiotherapist's and participants' opinions about the lung clearance are incorrect. These two aspects will now be developed.

A) How likely is CALSA to be detecting change incorrectly?

Ideally, to develop CALSA as a new outcome measure the results should be compared against a gold standard. However, in the absence of such, this research has established that i) repeated measures of crackles' IDW and 2CD` over short time periods are stable and reliable ii) comparisons of crackles' IDW and 2CD pre versus post intervention give higher SRD values than at baseline and a tendency to systematic bias can be detected. Therefore, it seems credible to postulate that CALSA is able to identify a real change.

B) How likely is the physiotherapist' and participants' opinion about the clearance of the lungs to be incorrect?

The physiotherapist treated the majority of participants with a well established mucociliary clearance technique known as ACBT (see section 5.3.2 for details), modifying the number of treatment cycles and the positioning and combining manual techniques according to what she considered to be the most effective intervention for that specific participant. The differences between the physiotherapist's and participants' opinions about the clearance of the participants' lungs will be explored.

Physiotherapist' opinion

What sort of differentiating criteria might the physiotherapist have used to consider the participants' lungs clearer, less clear or the same, since she was presumably performing a specific intervention that she thought to be the most effective for that specific participant?

- **Problems with the outcome measures**

As was discussed in the literature review and confirmed by the findings of both studies in this research, the current outcome measures used by respiratory physiotherapists to assess the effectiveness of the interventions do not detect changes post interventions. Therefore, physiotherapists can only use their clinical assessment ability and the use of standard auscultation to help them decide if post intervention, a patient has lungs clearer, less clear or the same. Patients are considered objectively to have their lungs clearer if they expectorate secretions and/or if after the treatment they present fewer added lung sounds. However, it is well known that secretions can be swallowed, diluted in saliva or be moved/unplugged to more central airways and be coughed later (Braggion et al., 1995, Falk et al., 1984, Mortensen et al., 1991, Ambrosino et al., 1995). Therefore, the fact that patients are not productive during the treatments does not necessarily mean that their lungs are not clearer. On the other hand because patients can expectorate a very small amount of secretions diluted in a large amount of saliva this can provide a false idea of being productive. Furthermore, due to the many differences of the health professionals' hearing properties as well as the stethoscope, standard auscultation in its current form is too subjective to be used as an outcome measure (Piirila and Sovijarvi, 1995). Therefore, respiratory physiotherapists currently have difficulties deciding whether patients' lungs are clearer, especially when working with chronic diseases like CF and Br which will always present with adventitious lung sounds.

- **Difference between effective intervention and clearance of the lungs**

An effective intervention is not necessarily an intervention producing an instant response. Some may be intended to produce a delayed response whereby the intervention can cause the movement of the secretions and the patients can cough or swallow secretions at sometime later, i.e., the treatment effects can be delayed (van-der-Schans, 1997). Therefore, assessment of outcome measures immediately post intervention may not be the optimal time to detect change.

- **Custom and practice**

It was observed that CF participants were treated on average for 21 minutes with a range between 20 to 25 minutes, and Br participants for 24 minutes with a range between 15 and 30 minutes. Typically airway clearance treatment sessions last between 20 to 30 minutes (Prasad and Main, 1998). Furthermore, the majority of participants were also treated with ACBT in conjunction with forced expiratory techniques (FET) and manual techniques. These are the most frequently used airway clearance techniques in the UK (O'Neill et al., 2002). However, no studies have clearly demonstrated that they are more effective than any other airway clearance technique (O'Neill et al., 2002, Sutton et al., 1983, Thompson et al., 2002). It was observed that the type and timing of the intervention provided across all participants was similar. As a result of the lack of evidence-based practice for airway clearance therapy, it is clinical custom for physiotherapists to apply the techniques with which they feel more comfortable. These continue until a treatment is deemed to be 'effective' or until the physiotherapist / patient becomes tired and/or unmotivated, but are generally not discontinued through reaching objective criteria. Therefore, the intervention applied in this study may not have been 'effective' as judged by objective criteria.

However, subsequent discussions with the physiotherapist who applied the intervention revealed that she was basing her reported opinion regarding lung clearance, purely on her own auscultatory findings. In patients with chronic conditions, her treatment length and content was apparently dictated by other clinical findings such as sputum production and patient perceptions. Thus, during the research intervention she continued her treatment intervention until she felt the participant had derived some 'benefit', but this was not directly related to the lung sounds heard via standard auscultation. This practice is based on her personal experience that the use of standard auscultation is not a reliable outcome measure for physiotherapy interventions applied to chronic conditions.

Due to the lack of objective criteria to assess the effectiveness of the respiratory physiotherapy treatments, physiotherapists' assessment of the patients' airway clearance is difficult. Therefore, the lack of agreement between the physiotherapist's opinion and the CALSA findings could have been anticipated.

Participants' opinion

The findings of the second study revealed some discrepancies between the physiotherapist's beliefs and the participants' beliefs. Which criteria might participants have used to describe their lungs as clearer, less clear or the same post physiotherapy intervention?

There are many reasons for participants to report that their lungs felt clearer post intervention from: i) wanting to please the physiotherapist/ researcher; ii) feeling the secretions move within the chest; iii) expectorating secretions; iv) feeling less out of breath v) feeling less 'congested'. These criteria are all subjective and therefore difficult to quantify.

One participant thought the lungs were less clear because he/she became wheezier and more out of breath during the intervention and the physiotherapist had to stop the intervention. However, another two participants reported their lungs to be 'clearer' despite having had a similar experience (feeling more wheezy and breathless and unable to complete the intervention). Therefore, the way individuals respond to their symptoms and sensations varies considerably.

Finally, these participants suffer from chronic diseases where they are used to coughing, feeling breathless and performing self airway clearance therapy on a daily basis (some of them more than once per day). Therefore, these participants might have had difficulties dissociating the consequences of one specific intervention from the consequences of their disease. Anedoctal evidence from conversations between the participants and the researcher suggests that participants felt that they breathed better (confirmed by breathlessness measures) post intervention, but knew that in a couple of hours they would be the same as they were at baseline and therefore, they did not consider that their lungs would be significantly clearer in the long term. This knowledge/ perception of their disease might have affected the way participants answered the question.

In summary, both the physiotherapist's and the participants' opinions about the airway clearance intervention are subjective opinions which lack any objective criteria to quantify or monitor change. There is also lack of a gold standard to compare against and therefore, to assess the effectiveness of these treatments is a challenge in clinical research. Since CALSA is objective, non-invasive, can be used at the bedside, and has shown reliability, stability and responsiveness to change, it seems worthwhile to pursue further research assessing its potential to be used as an outcome measure.

6.3.2.2. The number and timing of crackles detected by CALSA per breathing cycle

When crackles' and wheezes' durations and frequencies were studied, different values were detected at the trachea from the other regions of the chest. It is known that tracheal values should be interpreted differently from the values generated from other chest locations, due to the low pass filtering characteristics of the lungs which do not exist over the trachea region. The low pass filtering of the lungs masks the existence of high frequencies and because this filter does not exist over the trachea high frequencies are detected. Consequently, at the trachea the breath sounds are not dependent on respiratory phases. This phenomenon has been well described by Gavriely and Cugell (1996). Therefore, health professionals rarely use this site when auscultating respiratory patients. CALSA can distinguish respiratory phases no better at this site than humans. Therefore, when analysing and discussing the number (*N)* and timing (*T)* of crackles per breathing cycle (*BC*) this site was excluded.

6.3.2.2.1. Breathing cycle detection

In this research, the detection of the breathing cycles was performed without the use of a pneumotachograph despite this being considered the gold standard (Brouwer et al., 2007), i.e., the most accurate method (Tarrant et al., 1997) for measuring respiratory parameters. The limitations of the pneumotachograph have already been described in section 3.6.3. As a result of these limitations, to assess the potential of CALSA to be used as an outcome measure for respiratory interventions in clinical situations, it was preferred to try to identify the breathing cycles from the data recorded via the stethoscope. Breathing cycle detection without airflow measurements has been successfully achieved with an accuracy of 93% (Chuah and Moussavi, 2000, Moussavi et al., 2000, Moussavi et al., 1998). However, as explained in section 3.6.3 these researchers used six simultaneous microphones attached to the trachea and chest and the data were recorded in a respiratory acoustics laboratory and on healthy subjects. Therefore, it was not possible to use their algorithm with the data recorded in this

research in the clinical setting via one single microphone (stethoscope), so a new algorithm was developed ('Breath Count') and used in this research.

6.3.2.2.2. Number of crackles

The *N* of crackles per BC and per sub-phase of the BC (early inspiration 0-20%, late inspiration 21-40%, early expiration 41-70% and late expiration 71-100%) detected by CALSA, in both groups of participants was analysed in the second study of this research and paired t-tests were run to see if the differences were statistically significant. No statistically significant differences were found in the *N* of crackles or in the *T* of the crackles, at baseline and post intervention, in any recording position, amongst either group of participants. The *N* and *T* of crackles per BC were investigated because they are often associated with the process and severity of diseases (Piirila and Sovijarvi, 1995, Sovijarvi et al., 2000a).

In both groups of participants crackles were detected in all six areas of the chest studied and in the four sub-phases of the BC. However, the majority of the crackles were inspiratory and were mainly present in the first 30% of the BC. These findings agree with those of Piirila et al. (1991) who described crackles in Br patients as being coarse, mainly inspiratory but also detected some expiratory crackles. The number of crackles per breathing cycle has been investigated by several authors in pneumonia (Murphy et al., 2004, Piirila, 1992), and asbestosis (Piirila et al., 2000). The number of crackles per breathing cycle in Br patients has been investigated by Piirila et al. (1991) when studying crackles in patients with fibrosing alveolitis, Br, COPD and heart failure. These authors found a higher number of crackles per breathing cycle in Br patients (11.12±3.8) in posterior areas when compared with that found in this study (3.9±2.1). This could be explained by the clinical condition of the participants. Piirila et al. (1991) describe that their participants had to be treated with inhaled salbutamol preparations and received oxygen therapy before the recordings, and their participants' lung function was lower (FEV_1pp=62±20 % and FVCpp=72±12 %) than the participants' lung function in this research (FEV_1pp=76±18 % and FVCpp=85±13 %). Therefore, it seems that their population was in a more acute clinical state than the population used in this research which could explain the difference in the number of crackles.

6.3.2.2.3. Timing of crackles

It was hypothesised that the movement of secretions from smaller to larger airways, post physiotherapy intervention, would be detected by the presence of crackles earlier in the breathing cycle. Smaller airways have been shown to produce late inspiratory crackles (<10 ms ⇒ high frequency) whereas crackles in large airways tend to be

produced at the beginning of the respiratory phases (>10 ms ⇒ low frequency) (Sovijarvi et al., 2000a). It was believed that if the detected crackles' frequency decreased, then this would be coupled with a shift to their appearing earlier in the breathing cycle. The shift of the crackles in the breathing cycles has been analysed by Piirila et al. (1992) when studying the course of patients with pneumonia. Piirila et al. (1992) found a shift of crackles towards the end of inspiration in resolving pneumonia. However, in this research, when the histogram plots of the crackles detected per breathing cycle were analysed per recording position in each participant, no evidence of crackles' movement (to earlier or in any specific direction), in the breathing cycle was found when the histograms post intervention were compared with the baseline histograms. The author speculates that changes in the *T* of crackles per BC may require time to occur and therefore not be detectable so soon after the intervention. Nevertheless the hypothesis that movement of secretions to more central airways will be detected by the presence of crackles earlier in the breathing cycle has been rejected for the conditions of this study.

The study of the proportion of the breathing cycle occupied by crackles (i.e. the 'crackling period') is another parameter that has been explored to assess the course of pneumonia (Piirila, 1992). Crackles are discontinuous sounds with a rapid and explosive character, so between one crackle and another there is a period without added lung sounds making the period of interest difficult to define. The number of crackles are dependent on lung volume and Piirila (1992) measured crackling period for a controlled lung volume (2L/min). However, crackling period is a poorly defined variable because in the same period different numbers of crackles can occur. Even adopting Piirila's (1992) definition, comparisons would not be possible since in this research lung volume was not controlled. Therefore, for these reasons, it was not felt that the study of such parameter would help to develop the use of CALSA to characterise crackles as an outcome measure for respiratory therapy.

Based on the findings that 1) the crackles' frequency was both reliable and stable at baseline and post intervention; 2) the crackles' frequency changed with the intervention; 3) crackles' 2CD is a more reliable, stable (less measurement error) measure than crackles' IDW; 4) the *N* and *T* of crackles per BC did not change in a consistent direction, it would seem that using the *N* and *T* of crackles per BC to monitor effectiveness immediately post intervention might not be the most appropriate method and that crackles' frequency, especially crackles' 2CD might be a more responsive parameter.

6.3.3. Sensitivity and specificity of the algorithms

As discussed in section 4.3.6.3.7 the algorithms used for detection and parameterisation were previously published by other researchers (Hsueh et al., 2005, Vannuccini et al., 1998) and were chosen because there was sufficient detail given to implement them (in contrast to other published algorithms (Kaisla et al., 1991, Murphy et al., 1989)), so that the published specificity and sensitivity could be expected to be reproduced. Similar procedures have been adopted by other researchers studying lung sounds (Piirila et al., 2000).

6.3.4. Agreement between CALSA and the physiotherapist's opinion about the number and timing of crackles per breathing cycle

In the results section, it was observed that the agreement between CALSA and the physiotherapist's opinion about the detection of the *N* of crackles per BC was 'poor' but increased when auscultation was performed in lower areas of the chest, in both groups of participants, i.e., the agreement was almost non existent at anterior areas and improved when the lateral and posterior areas of the lungs were analysed. It was also observed, in both groups of participants that CALSA and the physiotherapist agreed more often about the *T* of the crackles in the breathing cycle, if the first 20% of the breathing cycle was not considered. Furthermore, CALSA also detected the presence of crackles in the six positions of the chest, in similar numbers, and crackles in all parts of the breathing cycles, in both groups of participants. However, the crackles were mainly inspiratory and the majority were present in the first 30% of the breathing cycle.

These findings reinforce the generally held belief that standard auscultation in its current form is problematic in the assessment of respiratory patients. Considering that crackles were present in all the six areas of the chest, in similar numbers, the fact that the physiotherapist detected crackles at lateral and posterior areas of the chest but not at anterior regions, could be explained by two reasons:

1) Standard auscultation at anterior regions of the chest might be more difficult because interferences such as heart sounds and the turbulence of the air (which is higher and noisier in the central airways (van-der-Schans, 1997)) might influence the physiotherapist's ability to detect added lung sounds. Therefore, the physiotherapist was unable to detect added lung sounds in these areas in the majority of the participants. In the posterior areas, the respiratory phases have less interference, which makes the detection of added lung sounds easier.

2) Bronchiectasis is a disease characterised by the lower areas of the lungs being affected. This knowledge might have also, subconsciously, influenced the non detection of crackles in upper areas of the lungs by the physiotherapist.

The agreement regarding the *T* of crackles in the BC improved in late inspiration and expiration and in lower areas of the chest. The majority of crackles (according to CALSA detection) were present in the first 30% of the BC, and in the first part of the BC (early inspiration), even in lower parts of the chest. However, the agreement between CALSA and the physiotherapist was poor. This might be explained by the fact that the first 30% of the BC is the most turbulent phase of the cycle and a health professional might find it difficult to differentiate the sounds and consequently to detect the crackles in this specific part of the breathing cycle. In the lower parts of the chest, less interference to sound, and a quieter expiration, make standard auscultation easier. In this region the agreement between CALSA and the physiotherapist was higher.

The agreement between two observers about the presence or absence of crackles in an asbestosis population and lung sound recordings has been explored by Shirai et al. (1981). These authors have found good inter-observer agreement and close agreement between findings on chest auscultation and sound recordings. However, the sites used to perform the recordings or the auscultation were the posterior basal chest sites. Furthermore, when added lung sound recordings in the upper and axilla areas of the chest were assessed by parents, nurse and physician versus acoustic analysis, the level of agreement was poor: only the physician agreed partially with the acoustic analysis (Levy et al., 2004). Poor agreement was also found by Elphick et al. (2004) when studying the detection of added lung sounds in the anterior right upper area of the chest performed by stethoscope examination (two observers) and acoustic analysis. The results of the research presented in this Thesis support the findings of these investigations.

In summary, the analysis and interpretation of the agreement between CALSA and the physiotherapist about the *N* and *T* of crackles per BC, highlight the fact that auscultation findings from health professionals can be misleading. Similar results have been found by previous authors (Elphick et al., 2004, Levy et al., 2004). However, because auscultation is a rapid, non-invasive way of assessing respiratory patients, the ability to detect crackles objectively using CALSA is encouraging, regarding the possibility of using this method in a clinical setting to objectify and monitor respiratory therapy interventions.

6.4. Limitations and suggestions for future research

This research had a number of limitations. Some limitations that were evident after the first study were corrected before the second study. For example, in the first study, in participants who had a catheter implanted, the best place to locate the microphone was adjusted at the same time as the baseline recordings were being performed, which affected the stability of the lung sound measurements. In the second study, the best place to contact the microphone on the participants' skin was found prior to the recordings increasing the stability of the measures. However, a number of other limitations have been identified.

Allowing participants to 'self-treat' was justifiable at the time the first study was designed, because the main focus of the study was not to investigate the effectiveness of the intervention, but to investigate the potential of CALSA as a reliable outcome measure for respiratory physiotherapy. It can be argued that intervention variability may have affected the findings. However, self-intervention was what each participant was used to applying on a daily basis and provided the opportunity to assess if CALSA could detect any change in added lung sounds. Each participant decided when to stop the intervention. It was not known whether this was due to perceived clinical changes, or due to fatigue or lack of motivation to continue. Therefore, it was felt to be important for the second study that there should be a physiotherapist performing the intervention and listening to the lung sounds. It was believed at the time that this would ensure that the intervention was 'effective' as judged by objective clinical measures.

In the second study, a physiotherapist provided an intervention according to each participant's individual needs, because it was intended to provide the most 'effective' intervention for each participant. However, the researcher assumed that providing an 'effective' intervention would mean that participants would leave the intervention with the lungs 'clearer'. These terms and their meaning were not properly discussed with the physiotherapist. Therefore, this might have influenced the poor level of agreement found between CALSA and the physiotherapist / participants in this research. In future research, definitions of all terms need to be clarified and agreed in advance.

The studies have explored the reliability and responsiveness to change of CALSA detecting and characterising crackles' IDW and 2CD when used as an outcome measure for respiratory physiotherapy interventions in a clinical setting. However, there are a number of reasons why responsiveness to change may have been affected, as

for example, convenience samples of stable CF and Br adult patients were used. This may have limited the observed responsiveness to change of the crackles' IDW and 2CD. A less stable population for example with an acute exacerbation of their respiratory condition or in a intensive care unit setting, might be expected to show greater responsiveness to treatment. Secondly, the effectiveness of the intervention of this research was uncertain (as previously discussed). Therefore, taking measurements before and after an intervention with a known physiological effect would be useful (e.g. pre/post bronchodilator, or pre/post bronchial challenge (provocation) test or pre/post tracheal suction), to confirm the responsiveness to change of crackles' frequency. Therefore, further studies are needed in order to confirm these results and also explore the reliability and responsiveness to change of CALSA in other patient populations and in other age group (children) and reliability between days.

Apart from exploring the agreement between CALSA and the physiotherapist's opinion about the *N* and *T* of crackles per BC, no validation studies have been incorporated within this research because there is no 'gold standard' against which lung sounds can be assessed. The frequency of the crackles and the place in the airways where they were being generated has been explored by other authors using an engineering technique called quadrupole (Fredberg and Holford, 1983). Smaller airways have been shown to produce late inspiratory crackles (< 10 ms $\Rightarrow$ high frequency) whereas crackles in large airways tend to be produced at the beginning of the respiratory phases (> 10ms $\Rightarrow$ low frequency) (Fredberg and Holford, 1983, Piirila and Sovijarvi, 1995, Sovijarvi et al., 2000a). Modern imaging techniques allow both static and dynamic assessment of the geometry of the airways. A future validation study might consist of comparing lung sounds with images of airways generated by these imaging techniques.

Another limitation of this research was that the individuals recruited, presented a very small number of wheezes which did not allow the analysis of wheezes as an outcome measure for respiratory therapy. It is known that more obstructive patients present wheezes in both phases of the breathing cycle (inspiration and expiration) and that the percentage of respiratory cycles affected by wheezes is related with the level of obstruction and consequently with the severity of the respiratory condition (Sovijarvi et al., 2000a). Therefore, similar studies should be conducted in wheezy representative populations (adults and children). Wheezes and crackles provide information about different aspects of lung pathology, so the ability to use both would increase the usefulness of CALSA as an outcome measure for respiratory therapy.

The manual detection of added lung sounds is a slow and laborious process. Most researchers use algorithms to detect these sounds automatically. The sensitivity and specificity of the algorithms used in this research has been previously explored (Homs-Corbera et al., 2000, Vannuccini et al., 1998), but was not specifically examined with the data collected during this research. In future studies of added lung sounds, ideally a representative sample of the data should be checked manually (visually and aurally) by large groups of health professionals, to compare with the algorithms used. This would allow people to use CALSA in a clinical setting with more confidence.

In the first study, during recordings of lung sounds, participants were allowed to breathe at their own rate and depth. Although during routine auscultation it is general practice to ask patients to breathe more deeply to amplify lung sounds, this choice was made because of the number of recordings being taken. Deep breathing for several breathing cycles can cause symptoms such as dizziness (through reduction in carbon dioxide levels). However, if the interest is in all added sounds, patients should be asked to breathe deeply during recordings. Although crackles are not dependent on airflow, wheezes are to a significant extent. Furthermore, deeper breathing might facilitate the automatic detection of the breathing cycles. The identification of the *T* of the added lung sounds per BC has a major clinical significance. In order to address the breathing cycle detection aspects in the second study, participants were asked to breathe through the mouth at their own rate but slightly deeper than normally with rest periods provided between recordings. In future studies involving breathing cycles and added lung sounds detection, participants' deep breathing is recommended because it facilitates the analysis.

Several limitations in the second study are related to the breathing cycles' detection and analysis. The recordings were performed at each anatomical site without airflow measurements, with a single microphone and in a clinical setting. Therefore algorithm development to detect the breathing cycles automatically was challenging. It was not feasible within the time available for this research to design a complete automatic detection. When the signal was plotted in Matlab the maximum and minimum thresholds per file had to be chosen manually, and then the automatic detection of the breathing cycles occurred. Another potential problem was that the breathing cycle detection algorithm had not been validated against pneumotachograph data. However, the breathing cycles' detection in each file was carefully analysed (by making a visual inspection of the detection and listening to the file), to make sure that the estimate of

the start of each cycle was reasonable. Thus, it is not apparent that any significant inaccuracy in the breathing cycles' detection exists. Finally, the method of detection and analysis of the four sub-phases of the breathing cycle (0-20% early inspiration, 21-40% late inspiration, 41-70% early expiration and 71-100% late expiration) could also be seen as a limitation of this research. These divisions were chosen as an approximation of the duration of the inspiration (early inspiration and late inspiration) and expiration (early expiration and late expiration) across all participants. However, each participant has his/her own pattern of breathing and therefore, the start and end of each respiratory phase (inspiration and expiration) might change slightly if the data from each participant were considered individually. An analysis considering the first 30% (where the majority of crackles were present) and the last 30% of the breathing cycles was performed to avoid the need to detect the transition between the respiratory phases. However, it can be argued that might have affected the analysis of the level of agreement between CALSA and the physiotherapist, since the presence or absence of crackles in each sub-phase of the breathing cycle was considered. It is not believed this analysis was significantly affected, since from visual inspection of the signal after breathing cycle detection and analysis of the histograms plots, the division of 40% for the inspiration and 60% for the expiration in each breathing cycle, seemed to be a good approximation across all participants. In order to address these limitations, in future it would be interesting to conduct a study with a group of adult and child patients (with or without respiratory pathology) where the lung sounds were recorded at the same time as pneumotachograph data were collected. This would not only allow the validation of the breathing cycle detection but also allow further signal processing work to develop more efficient ways of detecting the breathing cycles and the respiratory phases. This study would establish the accuracy of CALSA detecting added lung sounds per breathing cycle and per respiratory phase in a clinical setting.

The timing of the outcome data collection post intervention could also be considered as another limitation of this research. Because the data were collected immediately post intervention, it is not clear what impact the intervention might have had on breathlessness, oxygen saturation, lung function or on lung sound measures after a period of rest post intervention. Ideally, a third timepoint for outcome data collection is recommended (for example thirty minutes later).

Finally, the interpretation of the added lung sounds data was challenging since, while it is known that added lung sounds can be present in healthy subjects (Kraman, 1983, Murphy et al., 2004), sufficient reference values to enable the characterisation of added

lung sounds in healthy subjects do not exist in the published literature. Therefore, when analysing the lung sound data from CF and Br participants it was not possible to know when the detection of added lung sounds started to be clinically relevant. A study publishing these reference values in healthy subjects would allow conclusions about the significance of added lung sounds found in adults and children to be drawn with more confidence.

6.5. Summary

The discussion, limitations of this research and suggestions for further work have been presented with the aim of contextualising the findings as regards the meaning of this research and its continuity. The final Chapter presents the main conclusions of this research and a summary of the main priorities, in the author's opinion, for further work.

Chapter 7
Conclusions

7.1. Introduction

The overall aim of this research was to explore the potential for using CALSA as an outcome measure for respiratory therapy interventions. Two studies have been conducted to investigate the reliability and responsiveness to change of crackles' parameters identified and measured using CALSA. Validity was not formally addressed within this research, although an attempt at a surrogate for validation was sought by examining the level of agreement between the physiotherapist's opinion, the participants' opinions and the findings from CALSA.

7.2. Conclusions

This research has demonstrated that the methodology for recording lung sounds via a digital stethoscope is feasible in a clinical situation, away from protected, sound-proofed rooms. The recordings generated are adequate for analysis using standard signal processing techniques.

The type and frequency of each added lung sound were successfully identified in all the files. Therefore, using CALSA to identify the type and frequencies of the added lung sounds in data collected via digital stethoscope in a clinical setting is possible.

The inter-subject variability of crackle parameters is high, while the intra-subject variability of crackle parameters is low over short time periods, leading to the conclusion that these measures are relatively stable and reliable within individuals. Inter- and intra-subject reliability analysis was not possible with the wheezes data due to the small number of wheezes detected.

The published algorithms for assessing the sensitivity and specificity of the automatic detection of added lung sounds were found to be feasible for use with the data collected. However, as no additional calculations for sensitivity / specificity were performed, no firm conclusions about these measures can be drawn.

The measurable differences in crackle initial deflection width (IDW) and two cycles deflection (2CD) variables from pre- to post-interventions, in both studies, are larger

than any differences seen between repeated measures within the same session, leading to the conclusion that crackle' IDW and 2CD respond to change.

Both of the crackle variables (IDW and 2CD) studied provided similar results. However, the crackle 2CD variable is more reliable and stable (i.e., has less measurement error) and therefore this is the variable recommended to be used as an outcome measure.

The detection of the breathing cycles was possible using CALSA in all files. However, only semi-automatic detection was achieved within the time limit of this research (i.e., the manual threshold had to be defined). After the definition of the threshold and respective detection of the breathing cycles, the number and timing of the added lung sounds per breathing cycle using CALSA was possible in all files. Further work needs to be done on the 'Breath Count' algorithm developed for this research, but complete automatic detection seems to be feasible, even with a single sensor.

Agreement between CALSA and subjective opinions about the number and timing of crackles was generally poor, but was higher when auscultation was performed in lower parts of the chest and when the first part of the breathing cycle was not included. However, methodological limitations related to the agreement determination (i.e., the nature of 'effective treatment' was not satisfactorily defined in advance), meant that no firm conclusions can be drawn from these findings.

The information obtained during this research leads to the overall conclusion that CALSA has the potential to provide an objective, reliable and responsive tool for assessing and monitoring respiratory interventions within clinical settings. However, as outlined in the previous chapter, more work is required before CALSA can be definitively recommended and used as an outcome measure for respiratory airway clearance therapy (e.g. physiotherapy). At this point in time, the data related to lung sounds are complex and time consuming to analyse. To be clinically useful it will be essential to simplify, and increase the speed of, the analytical process. Furthermore the cost-effectiveness of implementing this outcome measure is unknown. Validation of CALSA as a responsive outcome measure is challenging because of the lack of a gold standard respiratory therapy measure with which to compare it. The data relating to responsiveness to change detected within this thesis are less convincing than the reliability data, possibly due to the relatively stable nature of the participants' conditions. Studies recording lung sounds before and after an intervention of known effect e.g. bronchoscopy intervention, pharmacology interventions, mucolytics,

bronchodilators, suction, would help in clarifying the responsiveness of the measure, and increasing understanding of the validity of CALSA in clinical settings. Nevertheless, the aims proposed at the outset for this research have been achieved.

The main priorities for further work are itemised in the next section.

7.3. Summary of the main areas for further work

Research designed to validate the use of CALSA as an outcome measure. This might be achieved by comparing lung sound findings from CALSA with imaging techniques that can model the geometry of the airways, and/or track mucociliary clearance in various populations.

Research designed to explore the reliability of adventitious lung sounds between different days is necessary to confirm the robustness of CALSA for monitoring patients over time and to assess the detection of deterioration or improvement.

Research designed to confirm the responsiveness to change of crackles' frequency. This would involve taking measurements before and after an intervention with a known physiological effect, e.g., pre/post bronchodilator, or pre/post bronchochallenge provocation test or pre/post tracheal suction.

Research designed to explore the potential for wheeze characteristics to be used as an outcome measure for respiratory therapy. This would require the collection of data from wheezy populations.

Research designed to validate the algorithm used for the breathing cycle detection. This might be achieved by comparing the algorithm findings to pneumotachograph findings, using data recorded simultaneously.

Research designed to characterise and quantify added lung sounds in healthy individuals, to create a normative database. This would require the collection of data from a large sample of healthy people in different age groups.

These are the main areas that the author considers to be essential to allow further development of the idea that CALSA can be used to characterise adventitious lung sounds in a clinical setting, and to confirm or reject the hypothesis that CALSA has the potential to be used as an outcome measure for respiratory therapy.

Appendices

Appendix 1 Publication

Physical Therapy Reviews 2006; **11**: 299–307

CLINICALLY USEFUL OUTCOME MEASURES FOR PHYSIOTHERAPY AIRWAY CLEARANCE TECHNIQUES: A REVIEW

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A lack of good outcome measures has been a barrier to the development of an evidence base for all areas of respiratory physiotherapy. Many of the clinically available outcome measures are not specifically related to the physiotherapy intervention employed and may be affected by other factors. In this paper, the outcome measures currently clinically available to UK NHS physiotherapists to assess the response to alveolar recruitment and airway clearance interventions have been reviewed. It is clear that there is an urgent need to increase the accuracy, reliability, and sensitivity of the outcome measures employed, or to develop new measures to assess the effectiveness of respiratory physiotherapy. Lung sounds provide useful, specific information, but standard auscultation is too subjective to allow them to be used as an outcome measure. Computer Aided Lung Sound Analysis (CALSA) is proposed as a new objective, non-invasive, bedside clinical measure with the potential to monitor and assess the effects of airway clearance therapy.

Keywords: Lung sounds, outcome measures, physiotherapy

There is an acknowledged need to provide all areas of physiotherapy practice with a sound evidence base. In order to achieve this, it is necessary to have objective, reliable, valid and appropriate outcome measures for research purposes. Outcome assessment is also essential to determine individual patient responses, to evaluate the overall effectiveness of an intervention, programme or service, and to make comparisons between interventions. It is, therefore, necessary to have robust outcome measures that can also be applied clinically.

The main aims of respiratory physiotherapy include: (i) increasing alveolar recruitment, thereby improving ventilation; (ii) increasing secretion removal and therefore airway clearance; (iii) decreasing work of breathing and consequently dyspnoea; (iv) increasing muscle strength and endurance to increase exercise capacity and independence in daily functioning; and (v) increasing patients' understanding of their lung condition to promote self-management. Research into airway clearance techniques was one of the priorities for research identified during the UK, Chartered Society of Physiotherapy 2002 'Priorities for Physiotherapy Research' exercise.[1,2] In this paper, we have reviewed outcome measures that address the first two related aims, *i.e.* alveolar recruitment and airway clearance techniques.

In all areas of respiratory physiotherapy, one of the barriers to the development of the required evidence base has been the lack of good outcome measures. There are many doubts about the accuracy, reliability, sensitivity and validity of current measures, and their ability to reflect clinical changes resulting from airway clearance techniques.[3–7] The American Thoracic Society[8] has suggested that there is a need either to simplify some of the current tools (without losing

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their discriminative capability or ability to detect change), or to develop new tools for respiratory interventions.

Respiratory physiotherapists use the following outcome measures to monitor their interventions and evaluate their practice: sputum quantity, respiratory function tests, tests of gas exchange, imaging evidence and standard auscultation techniques. Most of these clinically available outcome measures are not specifically related to the physiotherapy intervention employed and may be affected by other factors. There is no gold standard outcome measure that is specifically related to respiratory physiotherapy interventions. Most of the published respiratory physiotherapy research compares two or more active interventions rather than an active intervention versus an inactive control. In such studies, it is never clear if differences are not detected because the outcome measures are not appropriate, or because the treatments being compared are equally effective/ineffective. Although there are other more invasive or laboratory-based outcome measures available, these are generally only applicable to a research setting. In this paper, we have focused on reviewing only those measures currently clinically available to the majority of UK physiotherapists, and propose a potential new clinical measure, *i.e.* Computer Aided Lung Sound Analysis (CALSA). The measures have been reviewed to determine their conformity with the requirements for outcome measures recently outlined by Jones and Agusti,[9] *i.e.* relevance, sensitivity, selectivity and specificity, reliability, repeatability, interpretability, simplicity and cost-efficacy.

SPUTUM QUANTITY

Airway clearance implies movement and expectoration of secretions and is one of the aims of respiratory physiotherapy.[10] Sputum volume/weight (dry or wet) has been suggested as a convenient and useful outcome measure for reflecting the amount of secretions released from the airways.[11] Mucus is transported from the bronchial airways by mucociliary clearance, spontaneous cough or directed huffs and coughs. Subsequently, it is either expectorated or swallowed.[12] Published studies have used sputum quantity as an outcome measure for various physiotherapy interventions.[13–16] Although sputum expectoration is relatively simple to collect and measure, it is not specific to alveolar recruitment or airway clearance, or sensitive to small differences. Its repeatability is influenced by many factors; therefore, the relevance of the measure has frequently been questioned.[4,12,17–19] Furthermore, sputum weight does not accurately or reliably represent sputum clearance and there is no convincing evidence that volume of sputum equates with pulmonary function.[7,19–21] Lack of expectoration during physiotherapy treatments does not mean that surface secretion movement is not happening, or that airway clearance has not occurred. It is very common to expectorate a few hours after a physiotherapy session, or to swallow secretions, which means that weight of sputum expectorated during a session may seriously underestimate airways secretion clearance. Not all the mucus cleared from the lungs is expectorated[22] and a significant amount may be swallowed or contaminated with saliva.[12,17,18,23] Sputum production can, therefore, be both over- and under-estimated. Therefore, even if measured very precisely, the authors consider sputum quantity to be an unreliable outcome measure.

BEDSIDE RESPIRATORY FUNCTION TESTS

If alveolar recruitment manoeuvres or airway clearance techniques are effective, then ventilation should improve and, therefore, larger volumes of air should be inspired/expired. The way that an individual inhales and exhales volumes of air as a function of time is assessed by spirometry. The typical measures are forced vital capacity (FVC), vital capacity, forced expiratory volume in one second (FEV_1) and the ratio between FEV_1 and FVC. Measures of maximum expiratory flow over the middle 50% of vital capacity, inspiratory capacity, and forced maximal flow during expiration or inspiration (peak expiratory or inspiratory flow) or as a function of volume (flow–volume curves), can also be made.[24–26] In order to have clinical utility, the dynamic lung volumes and maximum flows of any individual need to be compared with predicted values,[26] using the same reference source, anthropometric (*e.g.* gender, age, height, weight) and ethnic characteristics.[27] Spirometry has been described as a cost-effective, simple, reliable, valid, bedside measure and as easy to interpret[28] when used to give evidence about specific lung function or indirect information about respiratory muscle performance,[26] and a sensitive marker of respiratory disease,[29] but is inadequate for assessing the effectiveness of therapeutic interventions.[9] Lung function correlates poorly with dyspnoea and other symptoms[30] and is inadequate to describe the impact of a disease.[9] Furthermore, the accuracy, selectivity and sensitivity of spirometry depends on many factors which are difficult to control: volume or flow transducer characteristics, use of an in-line filter, recorder, display or processor and also on individual factors, *e.g.* the co-operation of the patient; relationship between the patient and the technician.[25] Generally, measurements

are highly dependent on patients' initial effort and motivation.[31] This makes it unsuitable for patients who are unwilling or unable to co-operate, or who have any pain or discomfort; such conditions pertain in a large proportion of patients requiring respiratory therapy.

Nevertheless, spirometry is widely used by respiratory physiotherapists for a range of screening, assessment and monitoring purposes.[26] Numerous short-term studies comparing different respiratory physiotherapy interventions have been unable to detect differences between treatments when using spirometry as an outcome measure, despite an increase in sputum production and changes in sputum visco-elasticity.[13,17,32–35] However, in more intensive studies involving several treatment sessions each day over a period of a week or more,[36–38] and in long-term studies (around one year),[39,40] spirometry was able to detect significant differences between physiotherapy interventions. Therefore, it is suggested that while spirometry lacks sufficient sensitivity to be used as a clinical outcome measure for assessing and monitoring respiratory physiotherapy treatments on a daily basis, it is more useful for longer term evaluations, provided patient co-operation is not affected.

TESTS OF GAS EXCHANGE

Blood gas analysis

If ventilation improves or sputum is removed from the lungs, it would be logical to expect that oxygenation would also show improvement. Arterial blood gas analysis is the gold standard test for assessment of arterial gases, *i.e.* oxygen and carbon dioxide. It is sensitive, specific, reliable, relevant, repeatable and easy to interpret. However, arterial blood gases are obtained invasively and the procedure is not always easily or simply performed.[41] The test results reveal information about oxygen partial pressure (PaO_2), carbon dioxide partial pressure ($PaCO_2$) and hydrogen ion activity (pH) in arterial blood, as well as calculated indices of bicarbonate concentration, base excess and oxygen saturation. These provide data for one specific moment in time, but are not usually used on a daily basis to monitor physiotherapy interventions (except for patients receiving intensive care), because of the invasive nature of the sampling process.

Non-invasive oxygen saturation

Oxygen saturation can be assessed indirectly and non-invasively using pulse oximeters. Pulse oximetry is simple to perform, is relevant and can be measured over time.[41] However, the specificity, reliability and sensitivity levels of this outcome measure are variable. Pulse oximeters are unable to detect saturations below 83% with an acceptable degree of accuracy and precision and the measures obtained are influenced by many factors, such as: haemoglobin level, arterial blood flow to the vascular bed, temperature of the area where the oximetry sensor is located, fluorescent or direct sunlight, jaundice, discoloration of the nail bed, nail polish, bruising under the nail, motion artefact, intravascular dyes, and skin pigmentation.[42–44] Pulse oximeters are also unable to differentiate between oxygen and carbon monoxide; the presence of the latter bound to haemoglobin increases registered oxygen saturation values,[44] so oximeters should not be used in patients who smoke tobacco.[43] Oxygen saturation calculated by a pulse oximeter has a 95% confidence interval of ± 4%,[43] which is deemed sufficiently accurate for most clinical situations[45] but is insufficiently precise for research.

Research studies that have used arterial blood gases[46,47] or oxygen saturation[33,35,37,48,49] as an outcome measure for airway clearance or alveolar recruitment manoeuvres have not detected significant differences between different respiratory physiotherapy interventions. Thus, although measures of gas exchange have many of the qualities required of an ideal outcome measure, their low sensitivity and specificity makes them less useful for assessing the effects of physiotherapy interventions.

IMAGING

Respiratory conditions have been assessed by a variety of imaging techniques such as chest radiographs, computerised tomography and magnetic resonance imaging. Chest radiographs provide a picture of the extent and severity of disease at a specific time, but sometimes it may take one or two days to detect abnormalities that other clinical measures have already detected.[50] Although chest radiography is a very commonly used investigation and is in itself reliable, relevant and relatively simple to perform, detailed interpretation of the resultant film is relatively complicated.[51] Radiologists are able to provide physiotherapists and other clinicians with reports detailing any abnormalities detected, but such reports may not be immediately available. In addition, radiograph evaluation entails subjectivity, variability, and uncertainty even when performed by experienced radiologists;[52,53] indeed, it has been found that the chest radiograph is the most common type of radiograph to be misinterpreted by observers.[54,55] In some

situations, chest radiographs may suggest more extensive disease, in others they may underestimate the pathology present.[50] Nevertheless, comparisons with previous radiographs provide a measure of improvement or deterioration over time, and response to treatment. However, the inherent risks associated with exposure to radiation mean that it would not be appropriate to recommend routine before-and-after radiographs specifically to assess the effects of physiotherapy. For assessment of chest radiographic images there are various objective scoring systems for specific pathologies (for example, the Brasfield score for cystic fibrosis)[56] and recent attempts have been made to computerise analysis,[57] but no method has yet been universally accepted. In several studies including chest radiographs as an outcome measure to assess the effects of respiratory physiotherapy, no detectable differences were shown between interventions.[18,20,34,39,40] Other imaging techniques are available, but are no more practical for the assessment of routine physiotherapy.

AUSCULTATION

Standard auscultation via a stethoscope is an assessment tool used by many health professionals during chest examination in their clinical practice[50,58,59] and is often used by physiotherapists to monitor patients' response to respiratory interventions. However, the literature has contradictory reports about its value in routine current practice. Some authors argue that auscultation is an inappropriate outcome measure because of the differences in health professionals' hearing acuity as well as in the properties of stethoscopes. There can also be different approaches to the description of auscultatory findings, nomenclature difficulties, and inter- and intra-observer variability.[60–62] Others have argued that auscultation is an easy, rapid, effective, non-invasive, and cost-effective way of assessing the condition of the airway and breathing.[58] The sound heard through a stethoscope depends on three main factors: (i) sound present at the chest wall; (ii) perception of sound by the human ear; and (iii) acoustics of the stethoscope itself.[62] Therefore, standard auscultation is a subjective process that depends on the hearing experience and the ability to differentiate between different sound patterns.[61] Agreement between observers during standard stethoscope examination for the presence of normal or abnormal lung sounds (*i.e.* wheezes or crackles) was found to be only 'poor-to-moderate', and clinical experience was not found to have any clear effect on accuracy or reliability.[63–65] Elphick *et al.*[66] found that using computerised acoustic analysis of recorded lung sounds improved the reliability of detection for all sounds when compared to listening through a stethoscope. Therefore, although the use of a standard stethoscope may be too subjective to provide a useful outcome measure, the sounds generated from the lungs may still provide useful information, and should relate directly to movement of air and secretions. The authors believe that lung sounds recorded directly from a microphone, and their computer-aided analysis, provide a potential non-invasive bedside outcome measure that could detect changes in the airways specifically related to physiotherapy interventions.

Lung sounds

Despite an incomplete understanding of the basic mechanisms of production of lung sounds, and a lack of adequate clinical and physiological correlates of the sounds themselves,[67,68] the field has advanced in recent years. Normal lungs generate breath sounds as a result of turbulent airflow in the trachea and proximal bronchi, *e.g.* large and medium size airways. The airflow in the small airways and alveoli has a very low velocity and is laminar, and, therefore, silent. Turbulent flow characteristics are influenced by airway dimensions, which are a function of body height;[69] body size, age, gender and airflow will all affect breath sounds.[70] Sounds heard or recorded at the chest wall surface are generated from within the lungs, and are, therefore, also affected by the transmission characteristics of the lung and chest wall.[62,71] They differ according to the location at which they are heard or recorded, and vary with the respiratory cycle.[72] The geometry of the bronchi also contributes to the complexity of the thoracic acoustics[73] because it affects flow, and consequently breath sounds. Normal breath sounds are classified into three frequency bands, i.e. low (100–< 300 Hz), middle (300–< 600 Hz) and high (600–1200 Hz).[70]

Breath sounds may be abnormal in certain pathological conditions of the airway or lungs. Normal breath sounds can be classified as 'abnormal' if heard at inappropriate locations. For example, 'bronchial breathing', involving a prolonged and loud expiratory phase with frequency components up to 600–1000 Hz,[72] is normal if heard over the trachea, but abnormal if heard at the lung periphery. This would typically be heard in the presence of lung consolidation. There are also added sounds (known as adventitious sounds) which can be continuous (wheezes) or discontinuous (crackles). The presence of adventitious sounds usually indicates a pulmonary disorder.[74] Other added sounds, such as stridor and pleural rub

will not be discussed here as they are unlikely to be affected by physiotherapy interventions.

Wheezes are continuous adventitious lung sounds. The mechanisms underlying their production appear to involve an interaction between the airway wall and the gas moving through the airway.[75] The normal sound wave form for breath sounds is replaced by continuous undulating sinusoidal deflections[76] produced by fluttering of the airway walls. These oscillations start when the airflow velocity reaches a critical value, called flutter velocity, due to narrowed airways.[72,75,77] Wheezes are always accompanied by flow limitation but flow limitation is not necessarily accompanied by wheezes.[72] These can be produced by any of the mechanisms that reduce airway calibre such as bronchospasm, mucosal oedema, intraluminal tumour or secretions, foreign bodies, or external compression.[75] The pitch of the wheeze is dependent on the mass and elasticity of the airway walls and on the flow velocity and is not influenced by the length or size of the airway.[75] The dominant frequency of a wheeze is usually between 80–100 Hz and 500 Hz and the duration longer than 100 ms.[72] Wheezes can be monophonic, when only one pitch is heard, or polyphonic when multiple frequencies are heard simultaneously.[72] They are clinically defined as musical sounds and can be characterised by their location, intensity, pitch, duration in the respiratory cycle, and relationship to the phase of respiration.[75] Wheezes are typical in bronchitis, asthma and emphysema[78] and their number per respiratory cycle, using Computer Aided Lung Sound Analysis (CALSA), has been reported to be a good indicator of obstruction.[79]

Crackles are discontinuous adventitious sounds. They are intermittent, non-musical, brief sounds thought to be caused by the acoustic energy generated by pressure equalisation or change in elastic stress after a sudden opening or closing of airways.[60,72,80,81] Crackles may represent abrupt opening or closing of single airways and will frequently be heard when there is inflammation, infection or oedema in the lungs. One factor that may be affected by these conditions is the elastic recoil pressure which may increase. The appearance of crackles may be an early sign of respiratory disease.[72] Crackles tend to occur first in the basal areas of the lungs but may spread to the upper zones as disease progresses. Their character is explosive and transient and depends on the diameter of the airways, which is related to the pathophysiology of the surrounding tissue. Their duration is less than 20 ms, and their frequency content typically is wide, ranging from 100–2000 Hz.[72] This short duration and often low intensity, makes their discrimination and characterisation by normal auscultation very difficult.[82] Crackles may change or disappear during auscultation or during pulmonary function tests, possibly due to the effect of lung expansion.

Computer-aided lung sound analysis (CALSA)

CALSA is designed to overcome the inherent problems of standard auscultation techniques, by removing the subjective component and allowing the quantification of lung sounds. Digital recordings of lung sounds are simple and relevant to collect, and have shown very high inter- and intrasubject repeatability with any interindividual variability explained by height, gender and anatomical characteristics.[83] It has been claimed that the use of objective respiratory acoustic measurements is promising for detection of regional changes.[84] Lung sound interpretation is enhanced using CALSA through the generation of permanent records of the measurements made, and through graphical representations that help with diagnosis and management of patients suffering from chest diseases.[72,74,85,86]

There is increasing evidence that CALSA provides clinically useful information about regional ventilation within the lungs.[85] The number and distribution of crackles per breath has been associated with severity of disease in patients with interstitial lung disorders[60,72] and pneumonia.[87,88] Recorded crackles have also been found to differ in different diseases, allowing differentiation between conditions such as COPD, fibrosing alveolitis, bronchiectasis, heart failure,[89] asbestosis and pulmonary oedema.[90,91] Therefore, the authors believe that analysing the waveform, number, distribution, timing, and pitch of crackles and wheezes may have clinical significance in assessing physiotherapy interventions.

However, reliable and convenient bedside methods for recording and analysing acoustic signals are still being developed. Recent guidelines for research and clinical practice in the field of respiratory sound analysis have been produced (Computerized Respiratory Sound Analysis 2000) financed by the European Union.[61] There is a great deal of information derivable from lung sounds, that is not normally readily accessible even to experienced clinicians. At a single anatomical site, a clinician can potentially make several observations – presence or absence of adventitious sounds, character, timing, location, and duration of adventitious sounds, duration of the inspiratory and expiratory phases. A clinician listening at ten sites has, therefore, at least 60 possible sets of recordable data, which exceeds the memory capacity of most people. Murphy *et al.*[88] suggested that the current primary advantages of CALSA over standard auscultation are efficient objective data collection and

management, and automatic data archiving with easy retrievability.

The specificity, sensitivity and clinical utility of lung sound analysis have also been studied. CALSA has already been used to assess the airways' response to bronchodilators and bronchoconstrictors in children and in adults.[92] Baughman and Loudon[93] studied the lung sounds of 20 asthmatic adult patients before and after a bronchodilator, and found that the use of the bronchodilator was associated with a reduction in the proportion of the respiratory cycle occupied by wheezes from 86% to 31%, and a reduction in sound frequency from 440 Hz to 298 Hz. In two studies involving patients with airways' obstruction, Fiz *et al.*[94,95] found changes in the frequency content of lung sound signals after the administration of bronchodilators. Malmberg *et al.*[96] studied 11 asthmatic children (aged 10–14 years) and found that spectral analysis of lung sounds can be used to detect airways obstruction during bronchial challenge tests.

When combined with spirometry, CALSA increased the sensitivity of detection of pulmonary disease, and was able to provide early signs of lung disease that was not detected by spirometry alone.[97] Furthermore, as FEV_1 does not seem to reflect small changes in airway morphology in asthma, CALSA may provide a more sensitive indication of minor alterations in airway geometry.[98] Baughman and Loudon[79] recorded the lung sounds of asthmatic patients overnight and were able to detect different degrees of obstruction severity that were not revealed by any other outcome measure. Therefore, the possibility of using computers to aid interpretation is a further advantage of CALSA over those listed previously. In future, it may be possible to determine the site of any airway obstruction and to follow the effect of therapy by the analysis of respiratory sounds.[99,100]

The data required for CALSA have clinical utility, can be interpreted objectively and are relevant and simple to collect – requiring only a microphone and a recording device from which sounds may be transferred to a digital format for analysis. In the future, the aim should be to develop equipment and software portable enough to allow the clinician to perform a bedside measurement and to interpret the data quickly and accurately. The technique has been found to be specific, reliable, and sensitive within the limited use to which it has been put to date. Although it has been used for some time to identify normal and abnormal lung sounds, it has not yet been evaluated as an outcome measure for physiotherapy. The authors believe that in future CALSA could become a convenient and reliable bedside measure to monitor and assess the effects of therapy.

CONCLUSIONS

Clinical respiratory physiotherapists currently lack good outcome measures that are specifically related to the interventions employed (for example, alveolar recruitment or airway clearance techniques). Most of the clinically available outcome measures are not specifically related to physiotherapy interventions and may be affected by other factors. Therefore, when assessing the effectiveness of interventions, it is never clear if a lack of significant effect is found as a result of ineffective treatment, or from the use of an inappropriate outcome measure. It is clear that there is an urgent need to increase the accuracy, reliability, and sensitivity of the outcome measures employed, or to develop new measures to assess the effectiveness of respiratory physiotherapy. Lung sounds provide useful, specific information, but standard auscultation is too subjective to allow them to be used as an outcome measure. Computer Aided Lung Sound Analysis is proposed as an objective, non-invasive, bedside clinical measure with the potential to monitor and assess the effects of airway clearance therapy.

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Appendix 2 Key concepts related to lung sound analysis

Standard references were used to define these concepts (Bores, 2006, Huckvale, 2003, Sovijarvi et al., 2000a, McClellan et al., 1998).

Amplitude – is used to indicate the size of the variation in a signal, or the amount of a sinewave component present in a signal. When describing the amplitude of a sinewave component of a sound, typically a decibel scale is used, with respect to some reference amplitude.

Amplification – implies using a device capable of amplifying the magnitude of the physical quantity measured in order to better measure or observe it. The amplifier gain is the ratio of output/input magnitude.

Decibel (dB) – the decibel scale is a logarithmic amplitude scale, in which the size of a vibration is expressed in terms of its relative size to some reference vibration. To convert relative amplitude to decibels, it is satisfactory to take the logarithm of the ratio (to base 10) and to multiply by 20. Decibels are convenient to use in acoustics because many systems operate in a multiplicative manner rather than in an additive manner, e.g., a doubling of amplitude is equivalent to a change of 6 dB.

Cut-off frequency – is the frequency at which the frequency response of a filter (or other circuit) is 3 dB below the maximal value of the frequency response.

Filter – filtering is a process of selecting, or suppressing, certain frequency components of a signal. A coffee filter allows small particles to pass while trapping the larger grains. A filter does a similar thing. The filter allows the transmission of certain frequency components of the signal. In this it is similar to the coffee filter, with frequency standing in for particle size. But the filter can be more subtle than simply trapping or allowing through; it can attenuate, or suppress, each frequency components by a desired amount. This allows a filter to shape the frequency spectrum of the signal for a particular purpose. Usually, the transformation aims to remove unwanted frequency components, e.g., noise. Filters can be classified as analogue filters (e.g., implemented by operational amplifiers, resistors and capacitors) and digital filters (e.g., implemented by programmable digital hardware or software). High/Low-pass filters allow components above/below specific frequencies to pass, attenuating or stepping, all the other components.

Fourier Transform – is a procedure that allows the decomposition of a given signal in harmonic components. The Fourier Transform (FT) is a mathematical tool using integrals or sums. The Discrete Fourier Transform (DFT) is its numerical equivalent using sums instead of integrals. The Fast Fourier Transform (FFT) is a popular, computationally fast algorithm to calculate DFTs.

Frequency – number of complete cycles of vibration completed in one second. The frequency of sinewave vibrations is measured in Hertz.

Frequency domain – the space of the variable 'frequency' associated to the space of the variable 'time' by a Fourier transform (or any other frequency transformation). In the frequency domain, a signal is described by its spectrum. A signal can be studied in the time and/or frequency domain. The latter is advantageous for signals with periodic content. For example, a pure sinewave can be described by only its frequency, amplitude and phase.

Frequency resolution – is a measure of the ability to extract the frequency content of a given signal. It depends on the duration of the signal and on the sampling rate.

Frequency response – is a measure of the systems response to sinewaves of different frequencies. A frequency response graph plots the ratio of the input/output amplitudes of sinewave signals as a function of their frequencies.

Frequency spectrum – is the collection of the frequency components of a given signal.

High-pass filter – a filter that allows components above specific frequency to pass attenuating or stepping all lower-frequency components.

Initial Deflection Width (IDW) – is the duration of the first deflection in a crackle waveform (Murphy et al., 1977, Hoevers and Loudon, 1990).

Largest Deflection Width (LDW) – is the duration of the deflection of the largest amplitude in a crackle waveform (Murphy et al., 1977, Hoevers and Loudon, 1990).

Loudness - is related to the quantity of sound, and it is affected by the logarithm of the amplitude. That is why decibel is commonly used for sound analysis. Loudness is the perceptual correlate of amplitude.

Pitch - relates to the frequency of the sound as perceived by human beings. Pitch is the perceptual correlate of the fundamental frequency of an acoustical signal.

Power spectrum – is the frequency domain data representing the power distribution of a sound with respect to frequency. A power spectrum graph plots the amplitude (usually expressed in decibels) of each sinewave component against the frequency of the component.

Sampling frequency – the repetition frequency (number of times per second) at which an analogue signal is measured and converted to a digital format.

Spectrogram – graphical representation of the change of a spectrum with time. The horizontal axis is time, the vertical axis is frequency and the amplitude of the sinewaves components of the signal at any given time and frequency is displayed on a grey scale.

Timbre - it seems to be related to the overall spectral shape of the sound as perceived by human beings.

Time domain – is the natural space in which the analogue signal is represented as instantaneous amplitude versus time, i.e., by its waveform.

Time-expanded waveform – the time-expanded waveform (TEW) is the display of a signal with a time scale of ≥ 800 mm/s. From a visual inspection of such a display, it is possible to study the waveforms of normal breath sounds, tracheal sounds and adventitious sounds (crackles, wheezes) and to distinguish them from each other (Murphy et al., 1977, Sovijarvi et al., 2000a).

Two Cycle Duration (2CD) – is the time from the beginning of the initial deflection of a crackle to the point where the waveform of the crackle has completed two cycles (Hoevers and Loudon, 1990, Murphy et al., 1977).

Appendix 3 Ethics approval

NHS

SOUTHAMPTON & SOUTH WEST HAMPSHIRE RESEARCH ETHICS COMMITTEES (A)

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STA/hph
27 January 2006

Mrs Alda Sofia Marques
PhD student
University of Southampton
School of Health Professions and Rehabilitation Sciences
University of Southampton, Highfield
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Dear Mrs Marques

Full title of study: **An investigation into the use of lung sound analysis as an outcome measure for physiotherapy airway clearance techniques**

REC reference number: **06/Q1702/8**

Thank you for your letter of 20 January 2006, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The Committee has designated this study as exempt from site-specific assessment (SSA. There is no requirement for [other] Local Research Ethics Committees to be informed or for site-specific assessment to be carried out at each site.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application		14 December 2005
Application Questions A20 to A34		
Investigator CV - Mrs A Marques		14 December 2005
Investigator CV - Dr A Bruton		
Investigator CV - Professor P White		
Investigator CV - Dr A Barney		
Protocol	1	14 December 2005

Covering Letter		15 December 2005
Letter from Sponsor		02 December 2005
Peer Review		14 December 2005
Compensation Arrangements		14 December 2005
Questionnaire The Modified Borg Scale	1	15 December 2005
Letter of invitation to participant	2	20 January 2006
Participant Information Sheet	2	20 January 2006
Participant Consent Form	2	20 January 2006
Response to Request for Further Information		20 January 2006
Reply Slip	2	20 January 2006

Research governance approval

You should arrange for the R&D department at all relevant NHS care organisations to be notified that the research will be taking place, and provide a copy of the REC application, the protocol and this letter.

All researchers and research collaborators who will be participating in the research must obtain final research governance approval before commencing any research procedures. Where a substantive contract is not held with the care organisation, it may be necessary for an honorary contract to be issued before approval for the research can be given.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

06/Q1702/8	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Mr Edward Carter
Chair

Email: GM.E.hio-au.SWHRECA@nhs.net

Enclosures:
Standard approval

Copy to: Dr Martina Dorward
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SF1 list of approved sites

STA

22 March 2007

SOUTHAMPTON & SOUTH WEST HAMPSHIRE
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Mrs Alda Sofia Marques
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Dear Mrs Marques

Study title: **An investigation into the use of lung sound analysis as an outcome measure for physiotherapy airway clearance techniques**
REC reference: **06/Q1702/8**
Amendment number: **1**
Amendment date: **05 March 2007**

The above amendment was reviewed at the meeting of the Sub-Committee of the REC held on 21 March 2007.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Protocol	2	06 March 2007
Participant Information Sheet	3	06 March 2007
Notice of Substantial Amendment (non-CTIMPs)	1	05 March 2007

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

06/Q1702/8:	Please quote this number on all correspondence

Yours sincerely

Mrs Sharon Atwill
Committee Co-ordinator

E-mail: scsha.SWHRECA@nhs.net

Enclosures List of names and professions of members who were present at the meeting and those who submitted written comments

Copy to: *Dr Martina Dorward,*
University of Southampton

Appendix 4 Information sheets

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Patient Information Sheet

An investigation into the use of lung sound analysis as an outcome measure for physiotherapy airway clearance techniques

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?
Chest physiotherapy is part of the routine care for people with too many lung secretions (e.g. patients with cystic fibrosis, bronchiectasis, chest infections). However, we still know very little about how it actually works. This study is part of a PhD programme of research designed to find out if we can use lung sounds to tell us when chest physiotherapy is being effective or not. In this study we should like to record your lung sounds before, during, and after you do your own routine chest clearance exercises.

Why have I been chosen?
You have been approached because you are attending the out-patient cystic fibrosis or bronchiectasis clinic at Southampton General Hospital or Queen Alexandra Hospital and because you have a condition that means you produce a lot of sputum. We need approximately 20 people like you to take part in the study.

Do I have to take part?
It is up to you to decide whether or not to take part. If you decide to take part you will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving any reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive, now or in the future.

What will happen to me if I take part?
If you would like to take part you should contact the researcher (Alda Marques) who will answer any questions you may have (please see the end of this form for her contact details). If you still want to take part the researcher will meet you at your next out-patient appointment and you will then be asked to sign a consent form. A copy of this form will be given to you to take away. If the information is not already available in your medical notes, your height and weight will be measured, and some simple lung function tests will be carried out. For these you will be asked to blow as hard as you can through a tube for as long as possible. You will also be asked to say how easy/ hard your breathing is using a scale from 0 (very easy) to 10 (very hard). Then, a little piece of plastic will be attached to your finger tip to measure the amount of oxygen that is carried in your blood. You will be asked to keep this on your finger until the end of the measurement session.
Next, you will be asked to sit down, with either a bare chest or with you wearing minimal undergarments to allow access to your chest. The researcher will then mark

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your skin, with a pen, on 7 different places around your chest. These marks will then be used to position the end of a digital stethoscope (a special listening device, attached to a computer) to record the sounds of your lungs. We will then record your lung sounds while you breathe normally. You will then be asked to carry out your own routine chest clearance, in whatever position you prefer. Half way through you will be asked to sit up again and some more lung sounds will be recorded, before you continue with your chest clearance. When you have finished you will sit up again while more lung sounds are recorded and you will be asked to do the lung function tests again, and rate your breathlessness. Ten minutes later we will take the final lung sound recordings and you will repeat the lung function tests and breathlessness rating. The pen marks on your skin will be cleaned before you leave. None of these tests should give you any discomfort, but the lung function tests require you to blow as hard as you can. The lung sound recordings and lung function tests will add about 15 minutes to your normal self treatment time.

What do I have to do?
You are not expected to do anything different from your normal routine. This study will all take place during your routine out-patient visit. However, we should like you to bring any equipment you normally use to do your chest clearance treatments.

What are the side effects of any treatment received when taking part?
There are no side effects to taking part in this study.

What are the possible disadvantages and risks of taking part?
There are no serious disadvantages or risks in taking part in this study. However, if you have very sensitive skin, you may react to the marker pen. The researcher will ask you about any skin allergies and will check your skin condition before leaving. If you have any concerns, please contact the research supervisor (Anne Bruton – details at the end of this form).

What are the possible benefits of taking part?
There is no direct benefit from you taking part in this study. However, the information we get from this study may help physiotherapists to understand, assess and treat future patients' chest secretions.

Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Any information about which leaves the hospital will have your name and address removed so that you cannot be recognised from it. Data kept on any computer will be password protected and given a code so that you cannot be identified from it.

What will happen to the results of the research study?
The results of the study will be incorporated into a PhD Thesis and some of them may be published in a medical journal. However, if this happens you will not be identified in any report/publication. If you would like to obtain a copy of any report, please tell the researcher.

Who is organising and funding the research?

University of Southampton

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This is an unfunded PhD study organised by the University of Southampton. The researcher is jointly supervised by staff from the School of Health Professions & Rehabilitation Sciences and the Institute of Sound and Vibration Research.

Who has reviewed the study?
The study has been peer reviewed by the School of Health Professions & Rehabilitation Sciences and ethically reviewed by the Southampton & SouthWest Hampshire Local Research Ethics Committee.

Contact for further information about this study
If you would like further information you can call or write to
Alda Sofia Marques
School of Health Professions and Rehabilitation Science, Postgraduate Office, University of Southampton, Highfield, Southampton, SO17 1BJ
Telephone number: 023 8059 5906 e-mail: alda@soton.ac.uk

Anne Bruton PhD MCSP (Research Supervisor)
School of Health Professions & Rehabilitation Sciences
University of Southampton, Highfield, Southampton, SO17 1BJ
Telephone number: 023 8059 5283 e-mail: ab7@soton.ac.uk

Thank you very much for reading this information.

Appendix 5 Informed Consent

University of Southampton

School of Health Professions & Rehabilitation Sciences

Professor Roger Briggs — Head of School
University of Southampton
Highfield
Southampton
SO17 1BJ
United Kingdom
Tel +44 (0)23 8059 2142
Research Office +44 (0)23 8059 4791
Fax +44 (0)23 8059 4792
Web www.sohp.soton.ac.uk/sohp/

INFORMED CONSENT

Study number: RHM HOS0169
Patient Identification Number for this trial:
Ethics number: 06/Q1702/8

Title of Project: An investigation into the use of lung sound analysis as an outcome measure for physiotherapy airway clearance techniques

Name of Researcher: Alda Sofia Pires de Dias Marques

Please initial boxes

1. I confirm that I have read and understand the information sheet dated 6th/03/07. (version 3) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the University of Southampton where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

_____	_____	_____
Name of patient	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 6 Standard auscultation assessment chart

Subject code: ☐☐ Date: ☐☐ / ☐☐ / ☐☐☐☐

Crackles

	Before Treatment							**After treatment**						
Site	Number			Position in Cycle				Number			Position in Cycle			
	None	*Some 1-6*	*Many >6*	*Insp. Early*	*Insp. Late*	*Exp. Early*	*Exp. Late*	*None*	*Some 1-6*	*Many >6*	*Insp. Early*	*Insp. Late*	*Exp. Early*	*Exp. Late*
Trachea														
Ant right														
Ant left														
Lat right														
Lat left														
Post right														
Post left														

Wheezes

	Before Treatment							**After treatment**						
Site	Number			Position in Cycle				Number			Position in Cycle			
	None	*Some 1-2*	*Many 3+*	*Insp. Early*	*Insp. Late*	*Exp. Early*	*Exp. Late*	*None*	*Some 1-2*	*Many 3+*	*Insp. Early*	*Insp. Late*	*Exp. Early*	*Exp. Late*
Trachea														
Ant right														
Ant left														
Lat right														
Lat left														
Post right														
Post left														

In your opinion, based only on what you heard via the stethoscope after the treatment, are this patient's lungs (please tick one box)

1. Clearer than before treatment? ☐
2. Less clear than before treatment? ☐
3. The same as before treatment? ☐

Appendix 7 Modified Borg Scale

The Modified Borg Scale

Please grade your level of shortness of breath using this scale. Circle the number that better characterise your sensation of breathlessness.

0	Nothing at all
0.5	Very, Very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (maximal)

(Borg, 1998b)

Appendix 8 Examples of the normal distribution of the crackles' variables

This is an example from a Br participant, at anterior right chest position (baseline) of the crackles' Initial deflection Width (IDW).

Case Processing Summary

Variable	Number of repetitions	Cases					
		Valid		Missing		Total	
		N	Percent	N	Percent	N	Percent
IDW	1.00	40	100.0%	0	.0%	40	100.0%
	2.00	39	100.0%	0	.0%	39	100.0%
	3.00	40	100.0%	0	.0%	40	100.0%

Descriptives

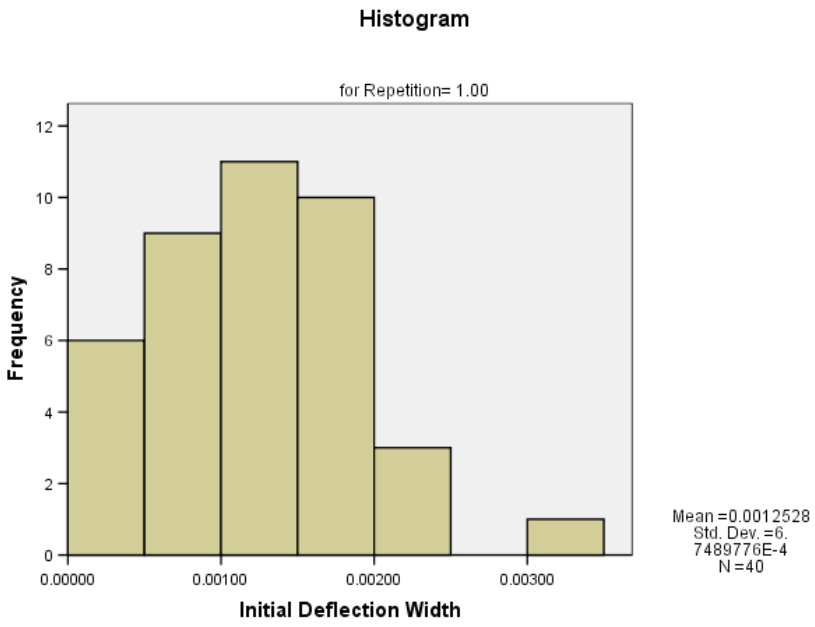
Variable	Number of repetitions			Statistic	Std. Error
IDW	1.00	Mean		.0012528	.00010671
		95% Confidence Interval for Mean	Lower Bound	.0010370	
			Upper Bound	.0014687	
		5% Trimmed Mean		.0012188	
		Median		.0013605	
		Variance		.000	
		Std. Deviation		.00067490	
		Minimum		.00023	
		Maximum		.00329	
		Range		.00306	
		Interquartile Range		.00102	
		Skewness		.574	.374
		Kurtosis		.677	.733
	2.00	Mean		.0012530	.00010227
		95% Confidence Interval for Mean	Lower Bound	.0010459	
			Upper Bound	.0014600	
		5% Trimmed Mean		.0012279	
		Median		.0012472	
		Variance		.000	
		Std. Deviation		.00063870	
		Minimum		.00011	
		Maximum		.00317	
		Range		.00306	
		Interquartile Range		.00079	
		Skewness		.552	.378
		Kurtosis		.940	.741
	3.00	Mean		.0012500	.00009789
		95% Confidence Interval for Mean	Lower Bound	.0010520	
			Upper Bound	.0014480	
		5% Trimmed Mean		.0012314	
		Median		.0012472	
		Variance		.000	
		Std. Deviation		.00061914	
		Minimum		.00011	
		Maximum		.00329	
		Range		.00317	
		Interquartile Range		.00077	
		Skewness		.563	.374
		Kurtosis		1.843	.733

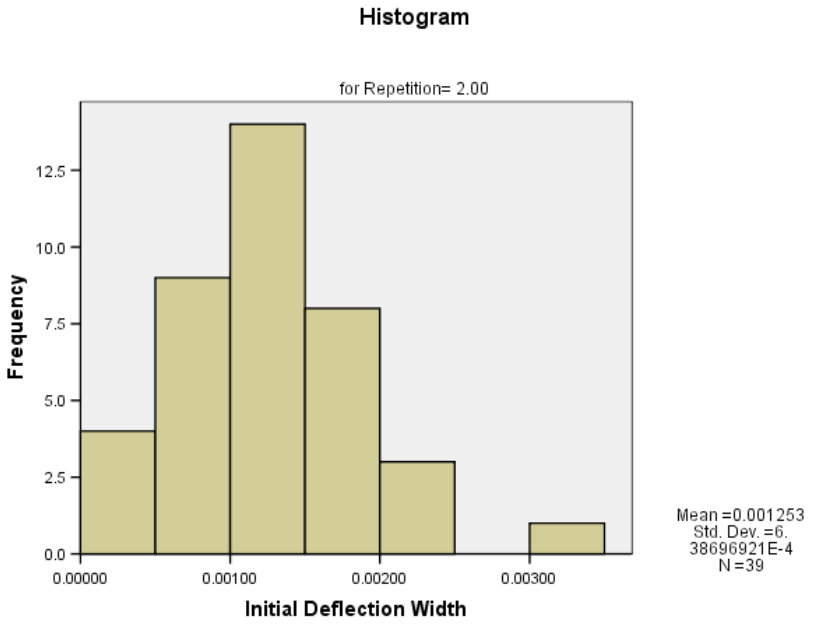
Tests of Normality

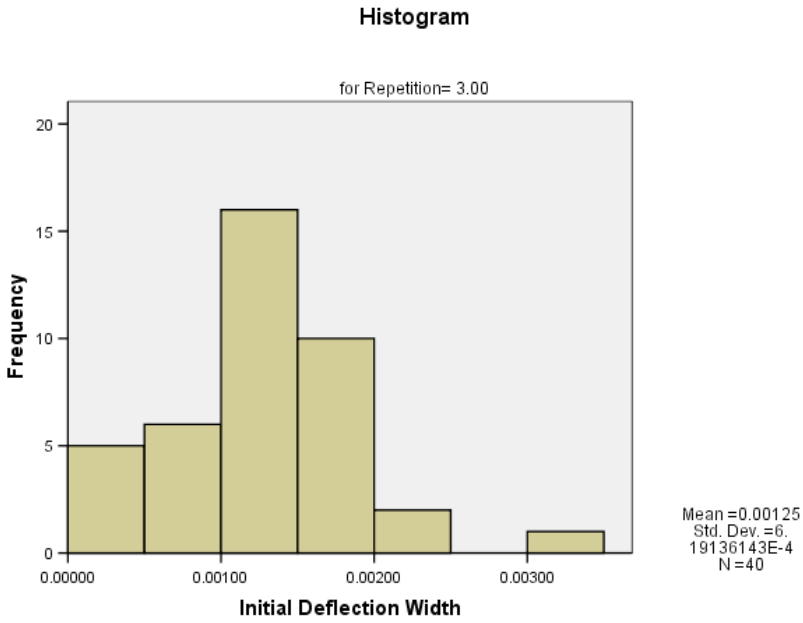
	Number of repetitions	Kolmogorov-Smirnov(a)			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
IDW	1.00	.113	40	.200(*)	.953	40	.094
	2.00	.095	39	.200(*)	.971	39	.395
	3.00	.093	40	.200(*)	.956	40	.120

* This is a lower bound of the true significance.
a Lilliefors Significance Correction

Histograms







Stem-and-Leaf Plots

Initial Deflection Width Stem-and-Leaf Plot for Repetition= 1.00

```
 Frequency    Stem &  Leaf

     6.00         0 .  223334
     9.00         0 .  556667779
    11.00         1 .  01133333444
    10.00         1 .  5557777889
     3.00         2 .  024
     1.00 Extremes    (>=.0033)

 Stem width:     .00100
 Each leaf:       1 case(s)
```

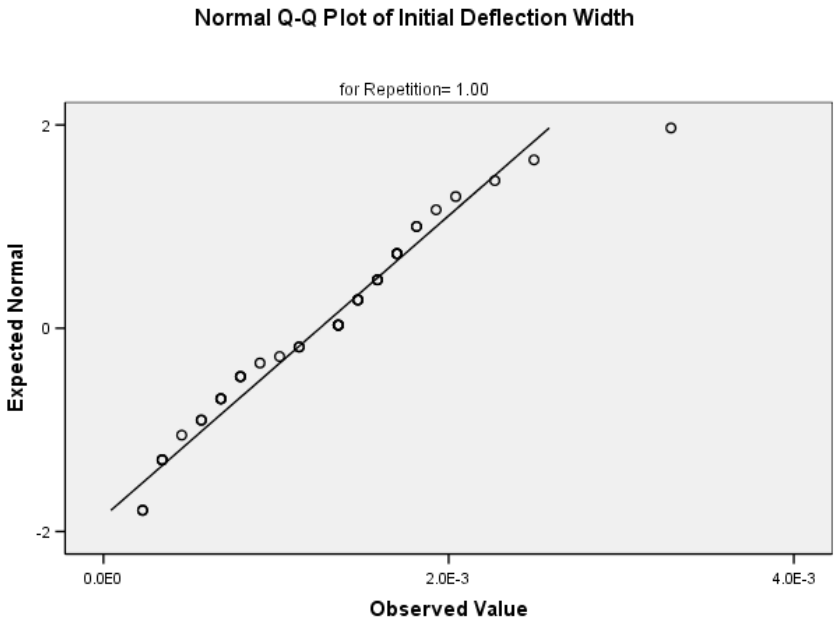
Initial Deflection Width Stem-and-Leaf Plot for Repetition= 2.00

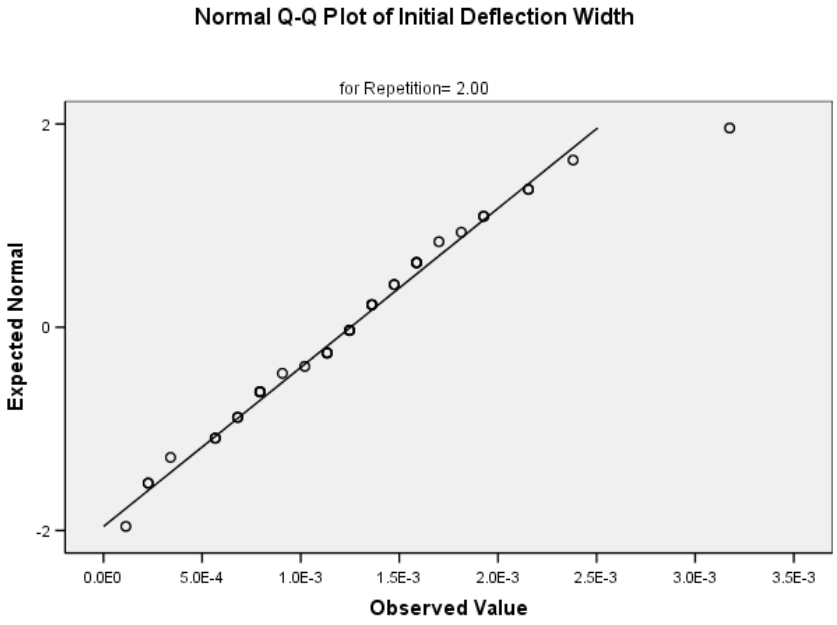
```
 Frequency    Stem &  Leaf

     4.00         0 .  1223
     9.00         0 .  556677779
    14.00         1 .  01112222333344
     8.00         1 .  55557899
     3.00         2 .  113
     1.00 Extremes    (>=.0032)

 Stem width:     .00100
 Each leaf:       1 case(s)
```

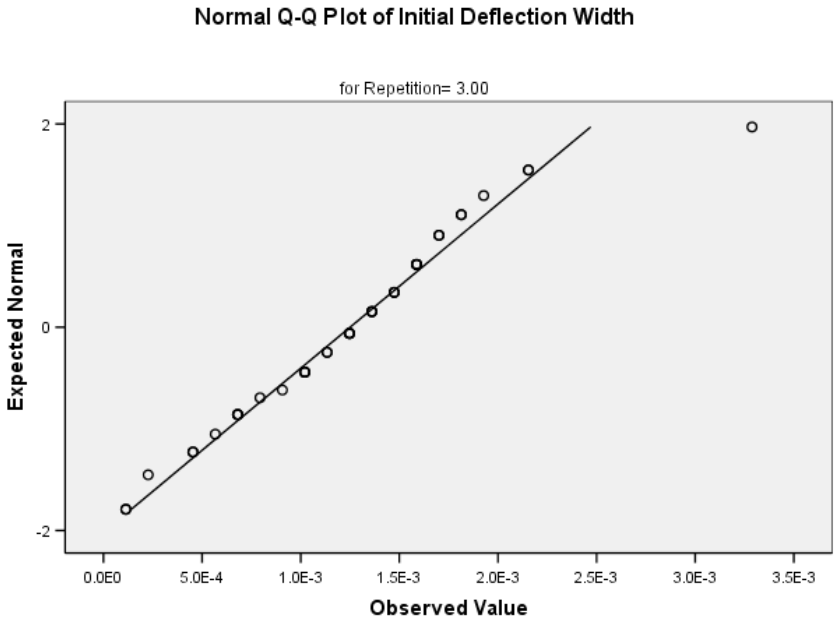
Initial Deflection Width Stem-and-Leaf Plot for Repetition= 3.00

```
 Frequency     Stem &  Leaf

     5.00        0 .  11244
     6.00        0 .  566679
    16.00        1 .  0000112222333444
    10.00        1 .  5555577889
     2.00        2 .  11
     1.00 Extremes    (>=.0033)

 Stem width:    .00100
 Each leaf:       1 case(s)
```

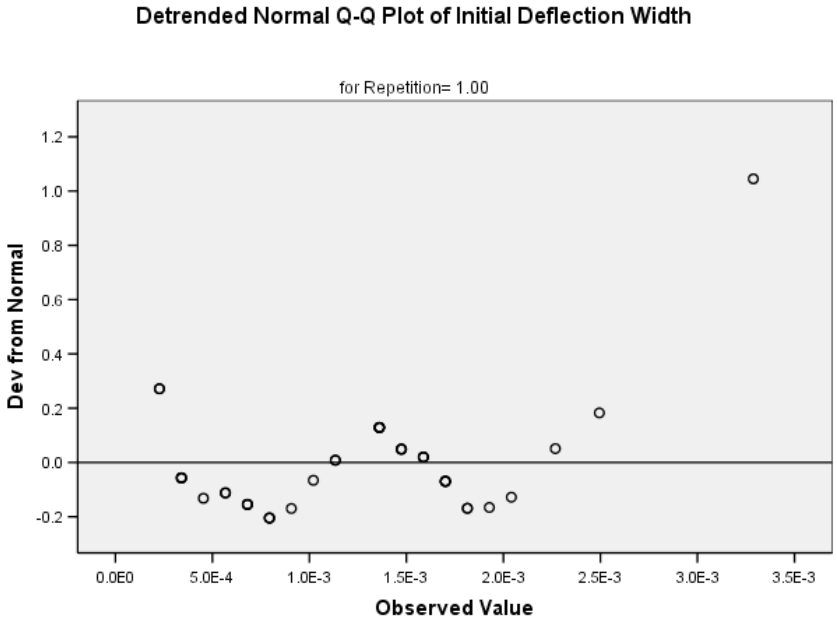
Normal Q-Q Plots

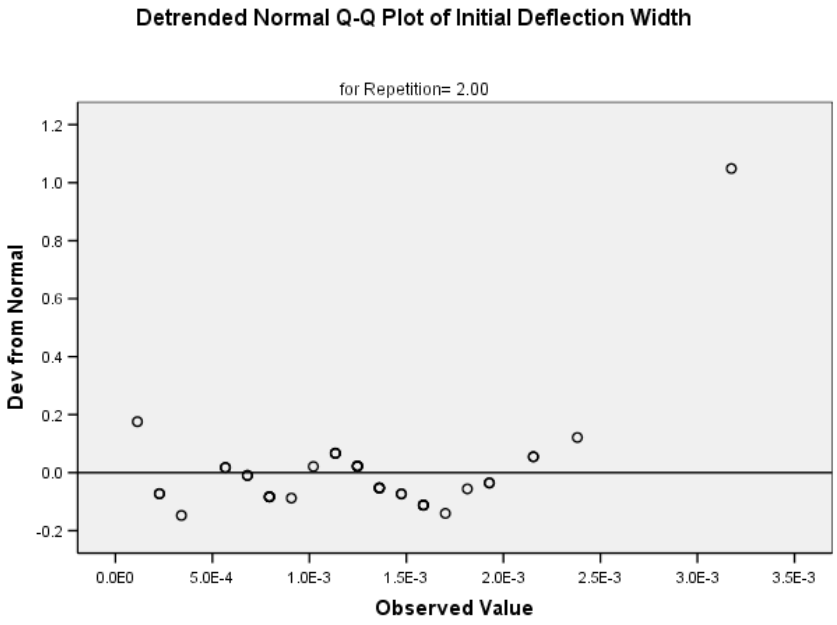


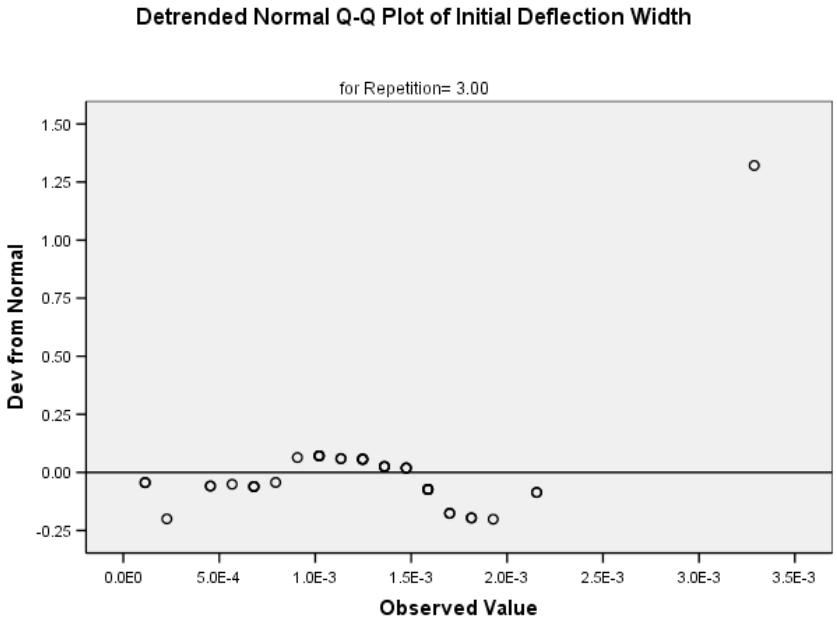

Normal Q-Q Plot of Initial Deflection Width
for Repetition= 2.00
Expected Normal
2
0
-2
0.0E0
5.0E-4
1.0E-3
1.5E-3
2.0E-3
2.5E-3
3.0E-3
3.5E-3
Observed Value

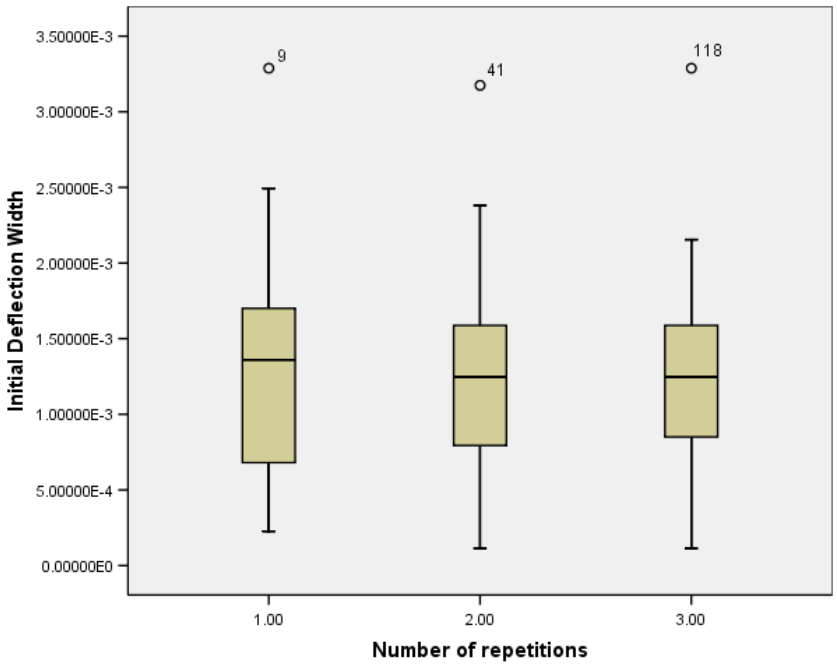

Normal Q-Q Plot of Initial Deflection Width
for Repetition= 3.00
Expected Normal
2
0
-2
0.0E0
5.0E-4
1.0E-3
1.5E-3
2.0E-3
2.5E-3
3.0E-3
3.5E-3
Observed Value

Detrended Normal Q-Q Plots






Detrended Normal Q-Q Plot of Initial Deflection Width
for Repetition= 3.00
Dev from Normal
1.50
1.25
1.00
0.75
0.50
0.25
0.00
-0.25
0.0E0
5.0E-4
1.0E-3
1.5E-3
2.0E-3
2.5E-3
3.0E-3
3.5E-3
Observed Value


Initial Deflection Width
3.50000E-3
3.00000E-3
2.50000E-3
2.00000E-3
1.50000E-3
1.00000E-3
5.00000E-4
0.00000E0
9
41
118
1.00
2.00
3.00
Number of repetitions

This is an example from a Br participant, at anterior right chest position (baseline) of the crackles' two cycles deflection (2CD).

Case Processing Summary

Variable	Number of repetitions	Cases					
		Valid		Missing		Total	
		N	Percent	N	Percent	N	Percent
TwoCD	1st recording	21	100.0%	0	.0%	21	100.0%
	2nd recording	31	100.0%	0	.0%	31	100.0%
	3rd recording	28	100.0%	0	.0%	28	100.0%

Descriptives

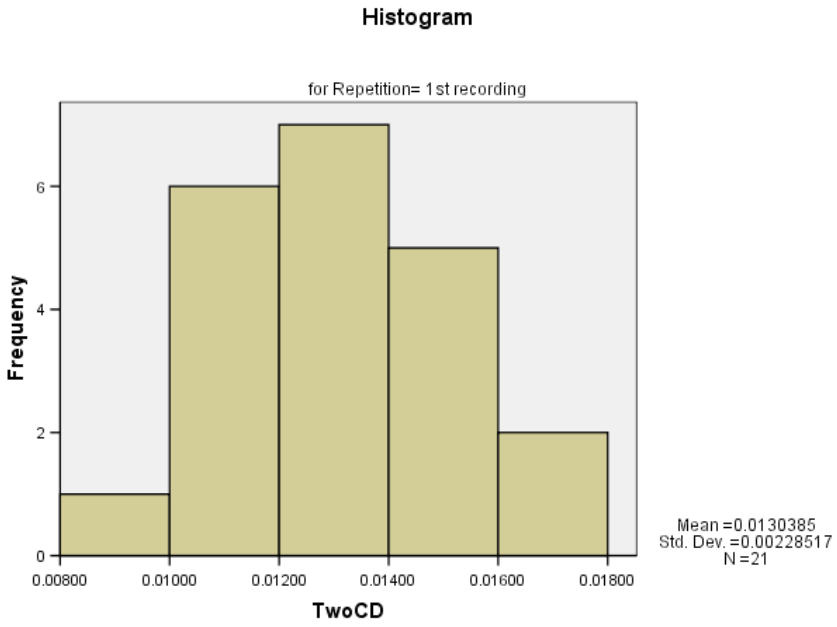
Variable	Number of repetitions			Statistic	Std. Error
TwoCD	1st recording	Mean		.0130385	.00049866
		95% Confidence Interval for Mean	Lower Bound	.0119983	
			Upper Bound	.0140787	
		5% Trimmed Mean		.0130591	
		Median		.0128120	
		Variance		.000	
		Std. Deviation		.00228517	
		Minimum		.00828	
		Maximum		.01735	
		Range		.00907	
		Interquartile Range		.00306	
		Skewness		.098	.501
		Kurtosis		-.003	.972
	2nd recording	Mean		.0123437	.00040301
		95% Confidence Interval for Mean	Lower Bound	.0115206	
			Upper Bound	.0131667	
		5% Trimmed Mean		.0123963	
		Median		.0121320	
		Variance		.000	
		Std. Deviation		.00224384	
		Minimum		.00601	
		Maximum		.01701	
		Range		.01100	
		Interquartile Range		.00272	
		Skewness		-.218	.421
		Kurtosis		1.248	.821
	3rd recording	Mean		.0118521	.00046270
		95% Confidence Interval for Mean	Lower Bound	.0109027	
			Upper Bound	.0128015	
		5% Trimmed Mean		.0119542	
		Median		.0119615	
		Variance		.000	
		Std. Deviation		.00244836	
		Minimum		.00567	
		Maximum		.01610	
		Range		.01043	
		Interquartile Range		.00357	
		Skewness		-.629	.441
		Kurtosis		.282	.858

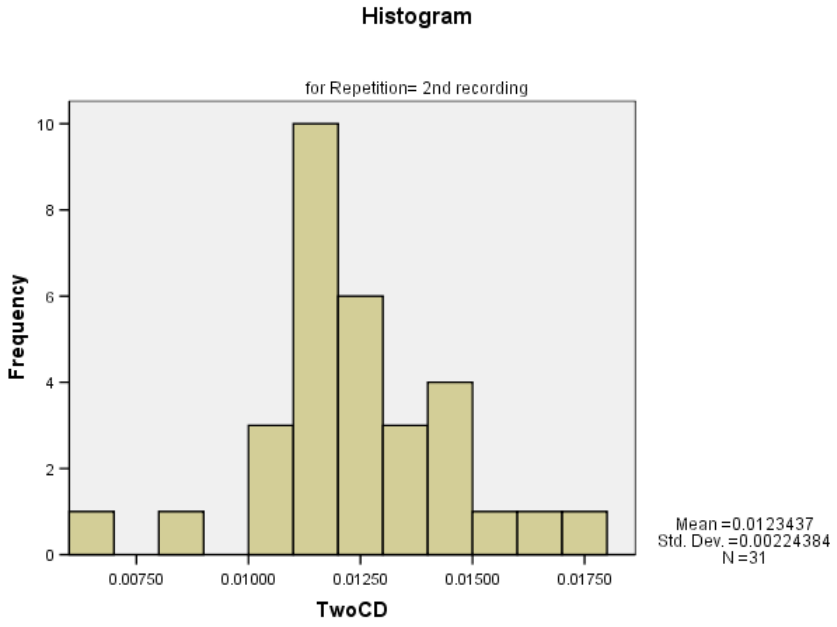
Tests of Normality

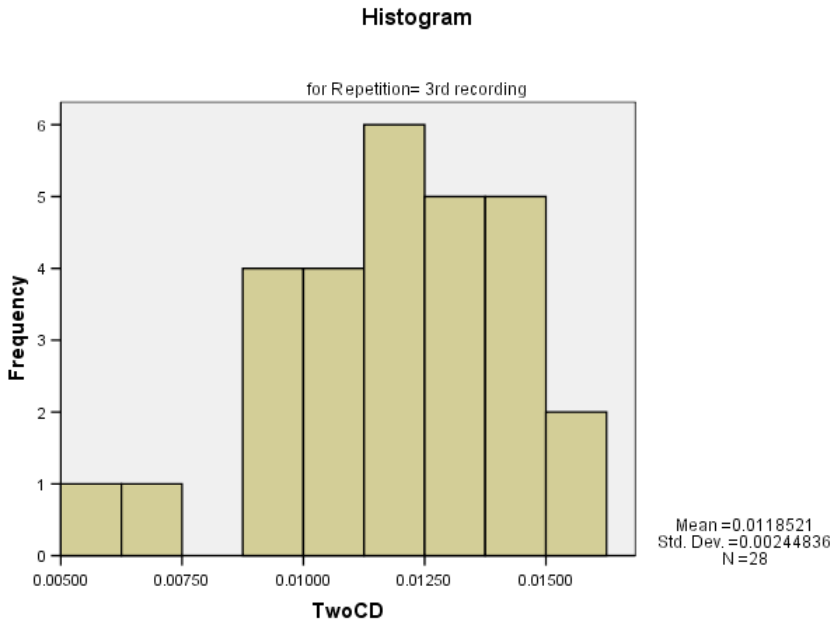
Variable	Number of repetitions	Kolmogorov-Smirnov(a)			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
TwoCD	1st recording	.091	21	.200(*)	.983	21	.964
	2nd recording	.135	31	.162	.954	31	.201
	3rd recording	.095	28	.200(*)	.966	28	.489

* This is a lower bound of the true significance.
a Lilliefors Significance Correction

Histograms







Stem-and-Leaf Plots

TwoCD Stem-and-Leaf Plot for Repetition= 1st recording

```
Frequency    Stem &  Leaf

1.00         0 .  8
16.00         1 .  0011112222233444
4.00         1 .  5577

Stem width:     .01000
Each leaf:       1 case(s)
```

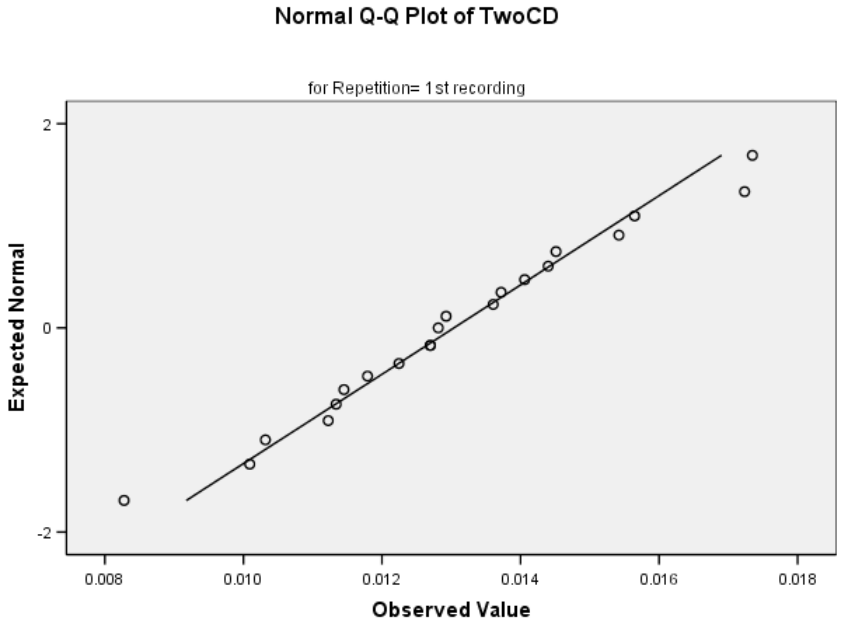
TwoCD Stem-and-Leaf Plot for Repetition= 2nd recording

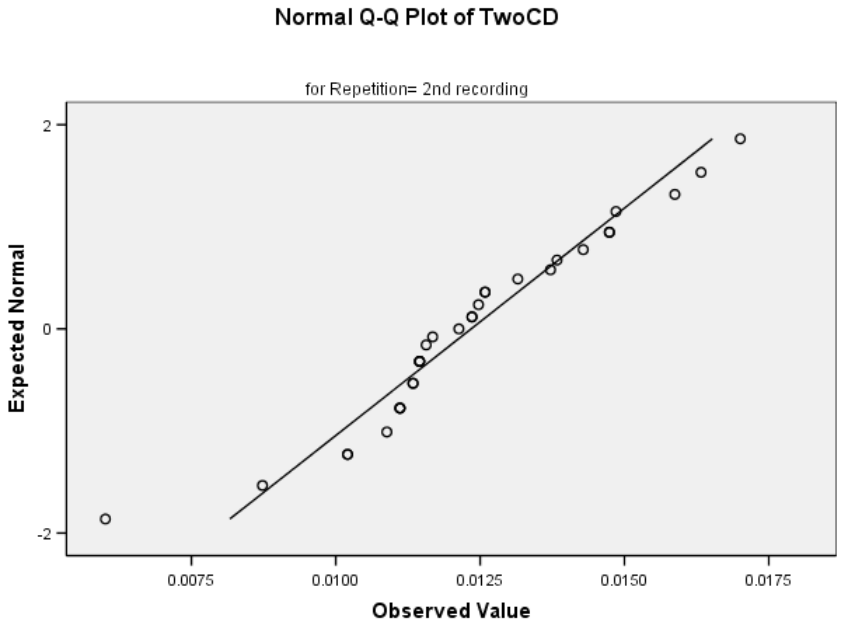
```
Frequency    Stem &  Leaf

1.00 Extremes    (=<.0060)
1.00          8 .  7
.00          9 .
3.00         10 .  228
10.00         11 .  1113344456
6.00         12 .  133455
3.00         13 .  178
4.00         14 .  2778
1.00         15 .  8
1.00         16 .  3
1.00         17 .  0

Stem width:     .00100
Each leaf:       1 case(s)
```

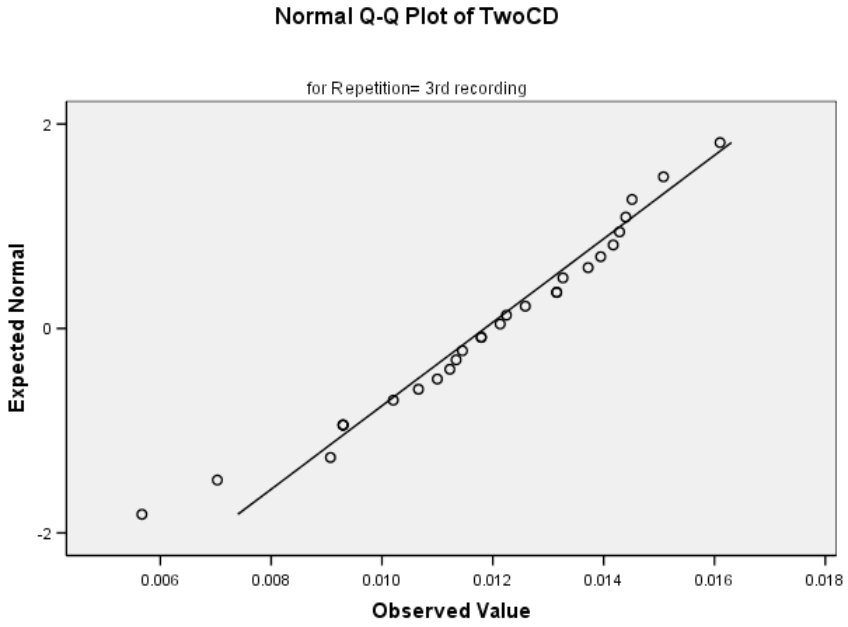
TwoCD Stem-and-Leaf Plot for
Repetition= 3rd recording

```
Frequency     Stem &  Leaf

1.00          0 .   5
1.00          0 .   7
4.00          0 .   9999
8.00          1 .   00011111
8.00          1 .   22233333
5.00          1 .   44445
1.00          1 .   6

Stem width:     .01000
Each leaf:        1 case(s)
```

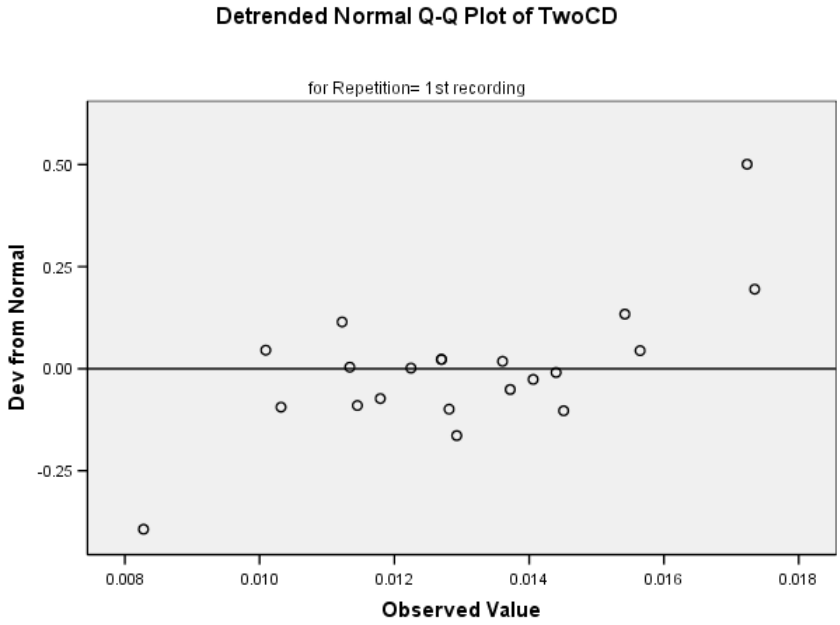
Normal Q-Q Plots

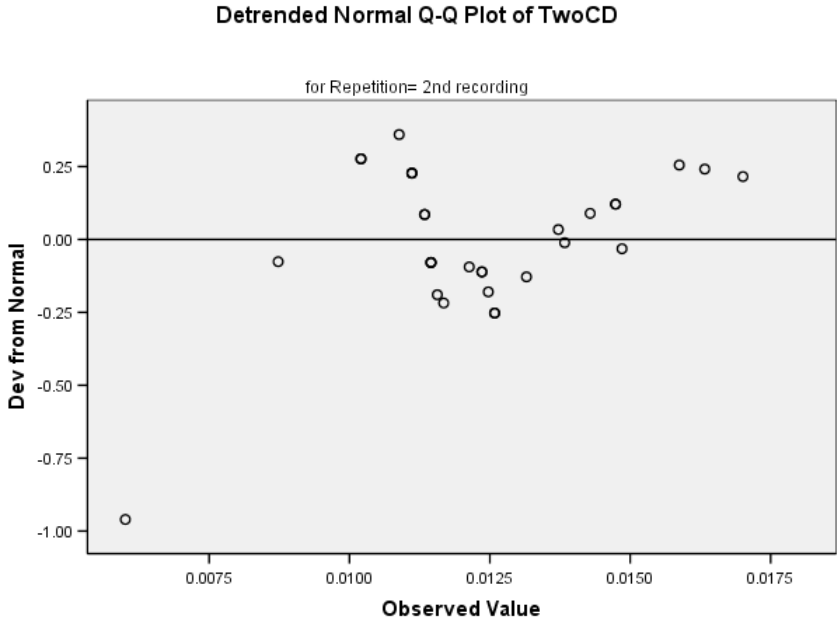


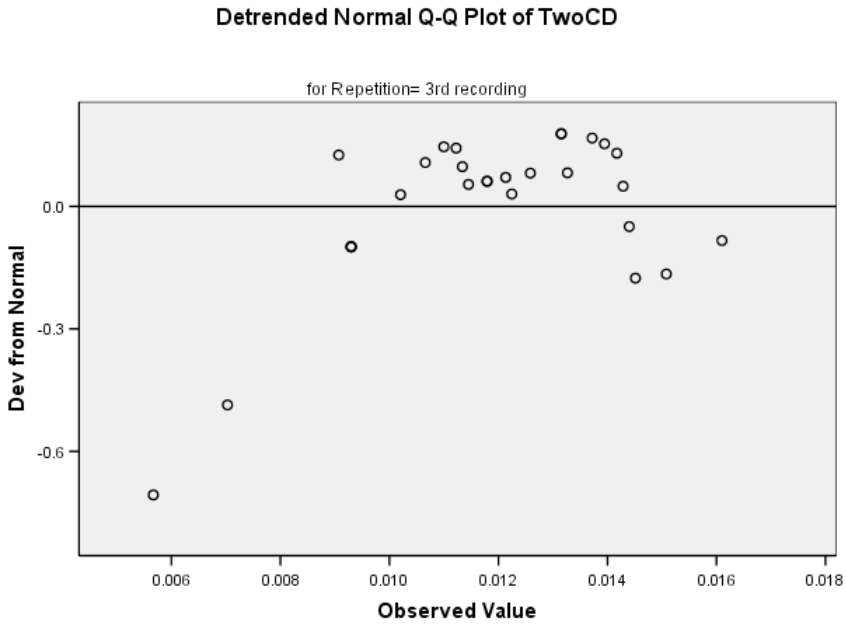

Normal Q-Q Plot of TwoCD
for Repetition= 2nd recording
Expected Normal
2
0
-2
0.0075
0.0100
0.0125
0.0150
0.0175
Observed Value

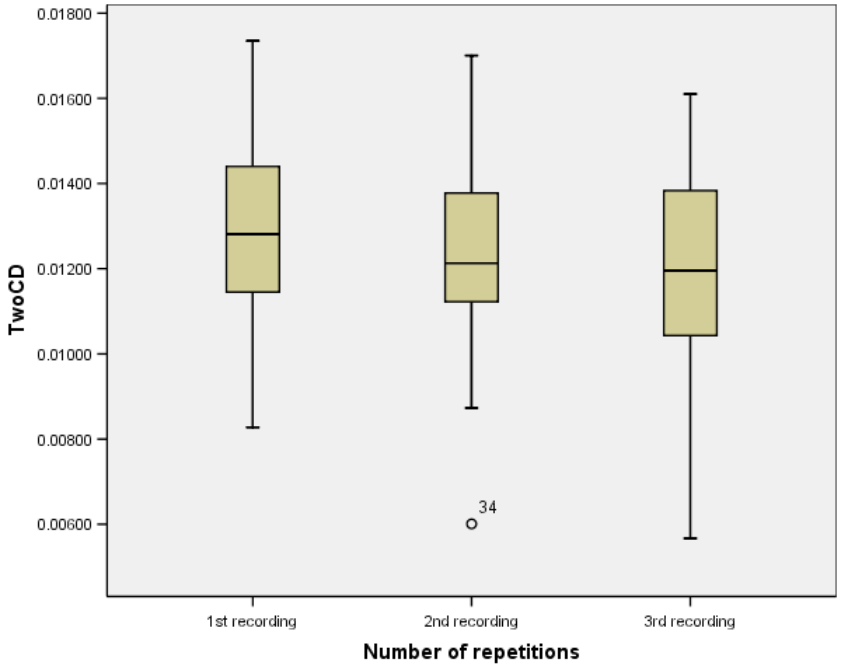

Normal Q-Q Plot of TwoCD
for Repetition= 3rd recording
Expected Normal
2
0
-2
0.006
0.008
0.010
0.012
0.014
0.016
0.018
Observed Value

Detrended Normal Q-Q Plots






Detrended Normal Q-Q Plot of TwoCD
for Repetition= 3rd recording
Dev from Normal
0.0
-0.3
-0.6
0.006
0.008
0.010
0.012
0.014
0.016
0.018
Observed Value


TwoCD
0.01800
0.01600
0.01400
0.01200
0.01000
0.00800
0.00600
34
1st recording
2nd recording
3rd recording
Number of repetitions

Appendix 9 Questions directed to the participants about their routine physiotherapy treatments

Physiotherapy treatments Yes☐ No☐

Frequency and description of physiotherapy treatments

_____

_____

_____

_____

_____

_____

_____

_____

Appendix 10 Description of the physiotherapy interventions applied by a respiratory physiotherapist

Code	Respiratory physiotherapy interventions in CF and in Br participants (second study)	No. of participants
CF	ACBT*(2 cycles) with deep inspirations and holds with mid-low lung volume huff in sitting	1
CF	ACBT*(3 cycles) with low lung volume huff in sitting	1
CF	ACBT*(2 cycles) with percussion, shaking, deep inspirations and holds with mid-low lung volume huff and cough, in side-lying (right and left)	1
CF	ACBT*(2 cycles) with percussion, shaking, deep breathing with mid-low lung volume huff, in side-lying (right and left) followed by huff in sitting	1
CF	ACBT*(4 cycles) with deep breathing and holds with mid-low lung volume huff, in side-lying (right and left) followed by 3 minutes of cough in sitting	1
CF	2 cycles of 5 diaphragmatic breathing, followed by 5 deep breaths, then percussion, and mid-low lung volume huff in side-lying (right and left), plus FEE in sitting	1
CF	4 cycles of percussion, shaking and huff in side-lying plus FEE in sitting	1
Br	ACBT*(2 cycles) followed by emphasis on huff, relaxation and diaphragmatic breathing at the end of treatment, in sitting	2
Br	ACBT*(3 cycles) with mid-low lung volume huff in sitting	5
Br	ACBT*(3 cycles) with increase deep inspirations with holds followed by mid-low lung volume huff in sitting	1
Br	ACBT*(3 cycles) with low lung volume huff in sitting	1
Br	ACBT*(4 cycles) with low lung volume huff in sitting	1
Br	ACBT*(2 cycles) with percussion in side-lying (right and left)	1
Br	ACBT*(2 cycles) with deep inspirations and mid-low lung volume huff, plus percussion and cough in side-lying (right and left)	1
Br	ACBT*(2 cycles) with percussion and shaking in side-lying (right and left) and then ACBT (3 cycles) in sitting	1
Br	ACBT*(3 cycles) with deep inspirations followed by mid-low lung volume huff in side-lying (right and left)	1
Br	ACBT*(3 cycles) with percussion in side-lying (right and left) and then ACBT (3 cycles) with low lung volume huff in sitting	1
Br	ACBT*(6 cycles) with percussion and shaking, rest and huff in side-lying (right and left)	1
Br	2 cycles, 1 minute each, of percussion, shaking and huff in side-lying (right and left) and then ACBT*(3 cycles) in sitting	1
Br	3 cycles, 1 minute each of percussion and shaking in side-lying (right and left) and huff in sitting	1
Br	3 cycles, 1 minute each of percussion, shaking and huff in side-lying (right and left) and then ACBT (3 cycles) in sitting	1
Br	6 cycles, 1 minute each of percussion, plus deep inspirations holds and sniff in side-lying (right and left), , plus FEE in sitting	2
Br	6 cycles, 1 minute each of percussion, plus deep inspirations, shaking and huff plus cough in side-lying (right and left), plus FEE in sitting	2
Total		30 (7CF and 23Br)

*ACBT – Active Cycle of Breathing Techniques; FEE – Forced expiratory exercises

Appendix 11 Question directed to the physiotherapist and to the participants about their perception of the effectiveness of the intervention

Question asked to the physiotherapist

In your opinion, based only on what you heard via the stethoscope after the treatment, are this patient's lungs (please tick one box)

1. Clearer than before treatment? ☐
2. Less clear than before treatment? ☐
3. The same as before treatment? ☐

Question asked to the participant

In your opinion, after the treatment, your lungs are (please tick one box)

1. Clearer than before treatment? ☐
2. Less clear than before treatment? ☐
3. The same as before treatment? ☐

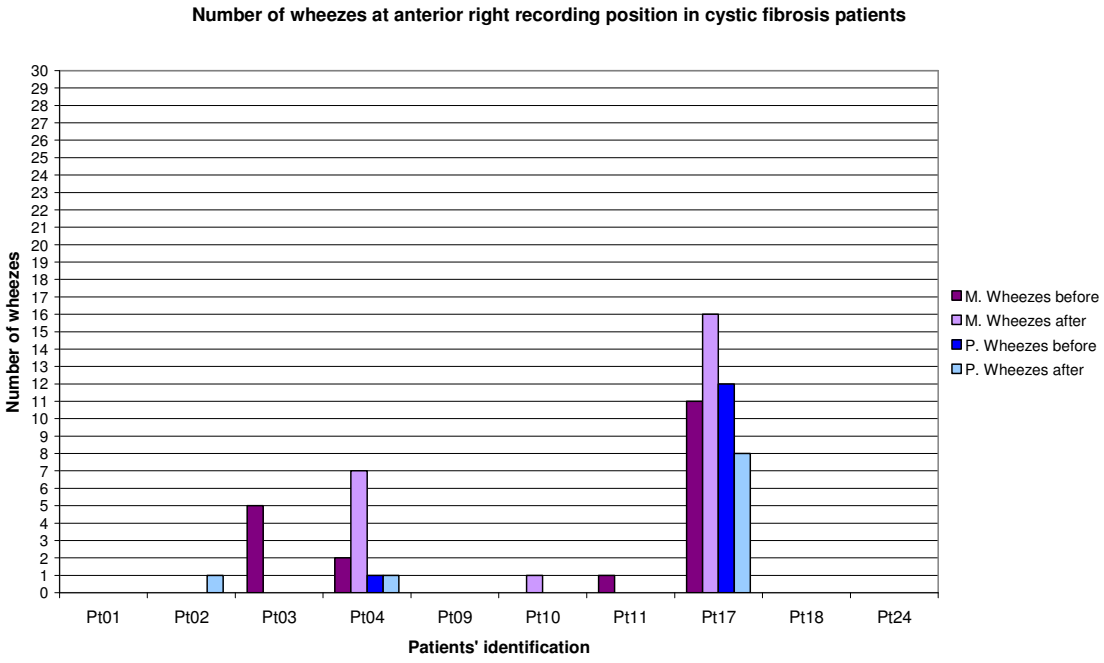
Appendix 12 Wheezes analysis

Results from wheezes analysis

This Appendix addresses the wheezes analysis recorded from CF and Br patients in the first study of this research. The number, type, duration and frequency of the wheezes in each of the seven chest locations studied, first in CF and then in Br, will be presented. However, due to the extensiveness of the results only a summary analysis is provided. The main results are exemplified with three graphs for better visualisation of the data by group of participants followed by three graphs which summarise the findings. In the x axis the participant's identification can be found and in the y axis the variable studied (number, duration (ms) or frequency (Hz) of the wheezes). The title of the graph clarifies the region of the chest which is being analysed. The complete individual results and analysis can be seen in Appendix on the CD provided, one table per patient with the number, type, duration (ms) and frequency (Hz) of the wheezes in both groups of participants.

Wheezes' analysis in cystic fibrosis participants

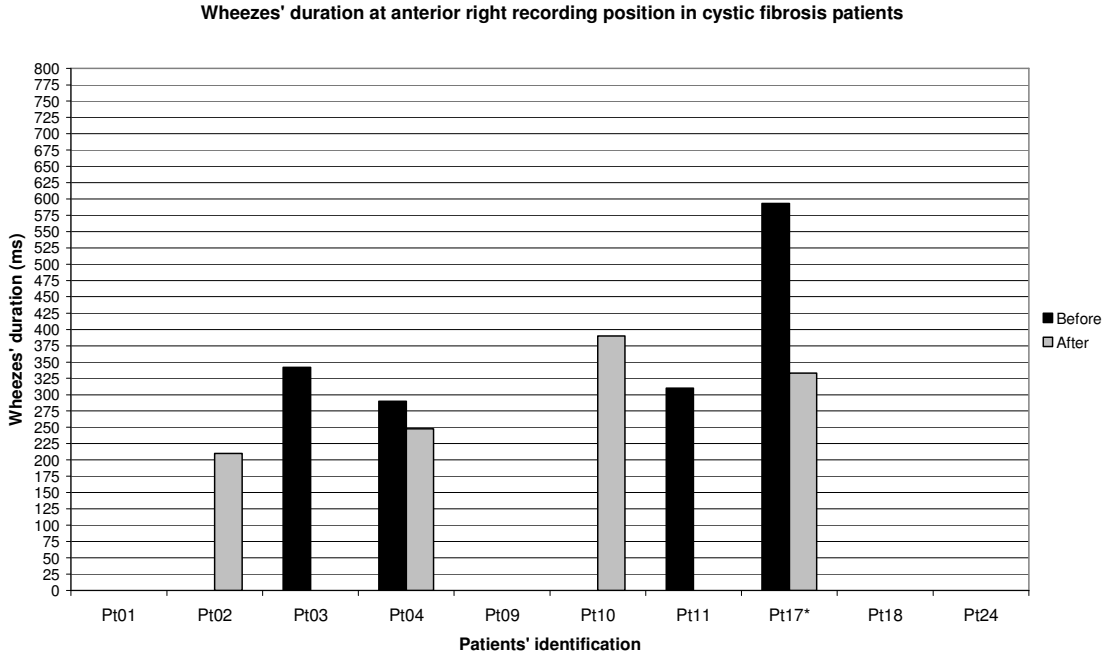
Results from the wheezes recorded in CF participants are exemplified with the data obtained at anterior right of the chest. The number of wheezes is presented in Graph 37, the wheezes' duration in Graph 38 and the wheezes' frequency in Graph 39.



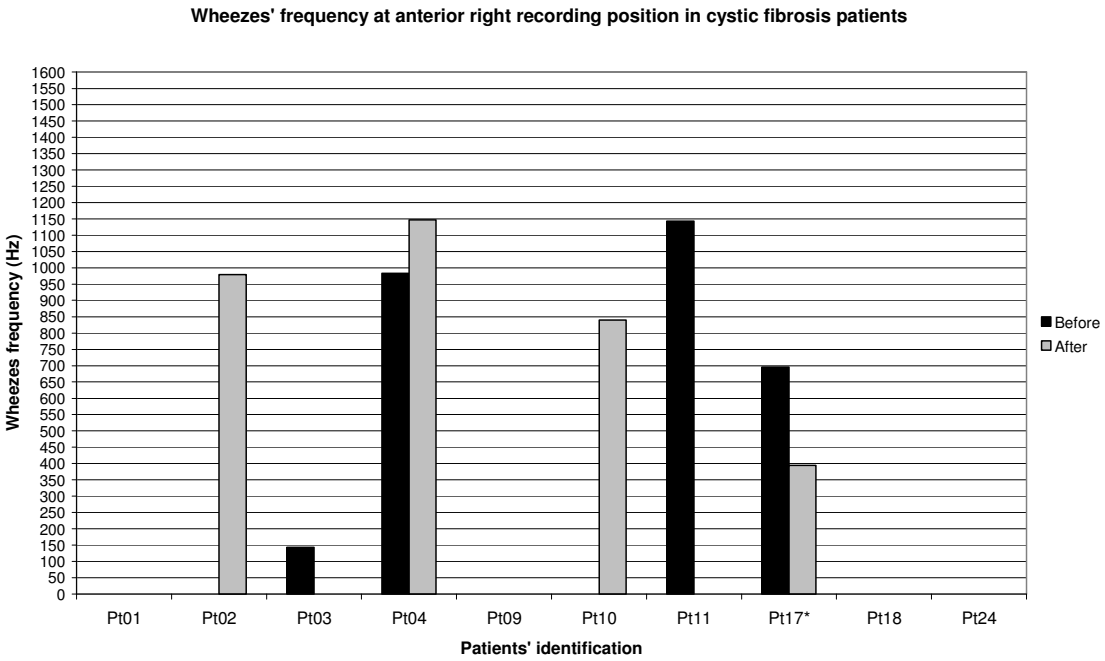
Graph 37: Number of wheezes recorded at anterior right of the chest in cystic fibrosis participants, at baseline and post self-intervention (M. - monophonic and P. – polyphonic, wheezes).

Before self-intervention four participants, Pt03, Pt04, Pt11 and Pt17, presented five, two, one and eleven, respectively, monophonic wheezes. Polyphonic wheezes were present in Pt04 (one) and in Pt17 (twelve). Post self-intervention, Pt4, Pt10, and Pt17 presented seven, one and sixteen monophonic wheezes, Pt02 and Pt04 had one and Pt17 had eight polyphonic wheezes. It is therefore, important to note that the number of monophonic wheezes increased in Pt04 and in Pt17 post self-intervention but polyphonic wheezes remained stable (Pt04) or decreased (Pt17).

The next two graphs (Graph 38 and Graph 39) present the wheezes' duration and respective frequency.



Graph 38: Wheezes' duration, recorded at anterior right of the chest in cystic fibrosis participants, at baseline and post self-intervention.



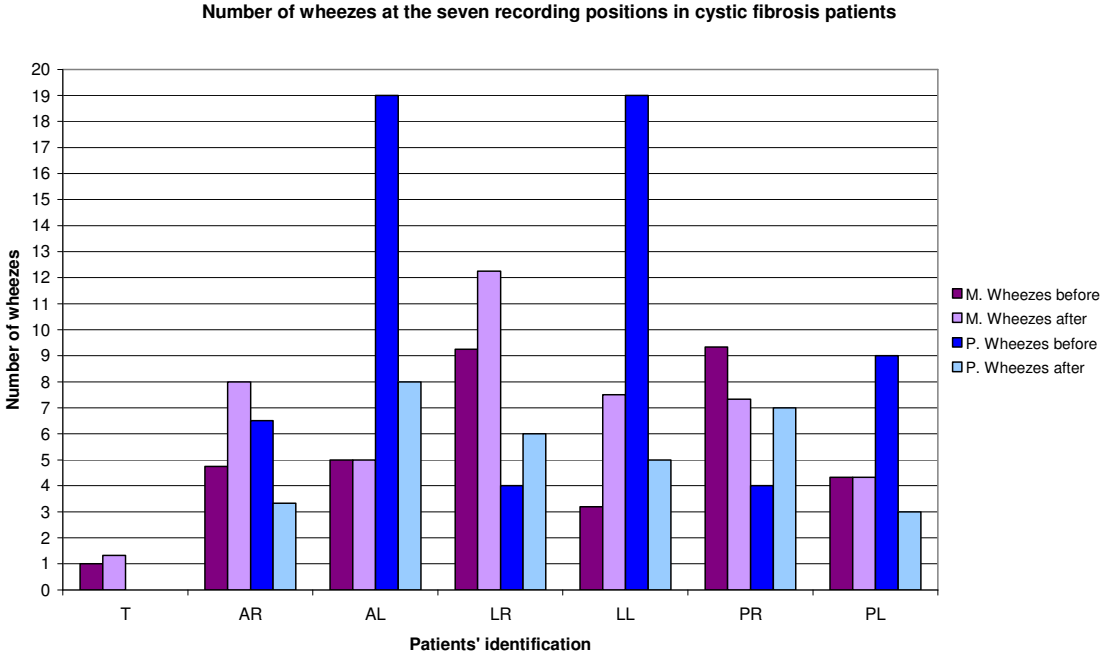
Graph 39: Wheezes' frequency, recorded at anterior right of the chest in cystic fibrosis participants, at baseline and post self-intervention.

The wheezes' duration before self-intervention varied between 290 ms in Pt04 and 593 ms in Pt17 and post treatment between 210 ms in Pt02 and 390 ms in Pt03. Participant Pt03 presented the lowest wheezes' frequency, 143 Hz (duration of 342 ms), and Pt11 the highest, 1143 Hz (duration of 310 ms), at baseline. Post self-intervention, Pt17 presented the lowest, 394 Hz (duration of 333 ms), and Pt04 the highest 1147 Hz (duration of 248 ms), frequency. Wheezes were not very common in this sample and that is the reason why there is missing data in the graphs for the majority of the participants. Only Pt04 and Pt17 presented wheezes at baseline and post self-intervention. The wheezes' duration in both participants decreased (Pt04 from 290 to 248 ms and Pt17 from 593 to 333 ms) post self-intervention. However, the wheezes' frequency increased in Pt04 (from 983 to 1147 Hz) and decreased in Pt17 (from 695 to 394 Hz). The differences were only statistically significant in Pt17 (wheezes' duration p=.015; wheezes' frequency p=.016).

Due to the extensiveness of the wheezes' analysis the creation of graphs to summarise the data was found necessary to help the interpretation of the results. For details of all the analysis performed, please refer to the Appendix on the CD. Graph 40, Graph 41 and Graph 42 were obtained by calculating the averages at baseline and post self-intervention of the variables analysed: number, duration and frequency of the wheezes detected in the CF participants. Statistics analysis of this data was not found appropriate since wheezes were not very frequent and were not always present at

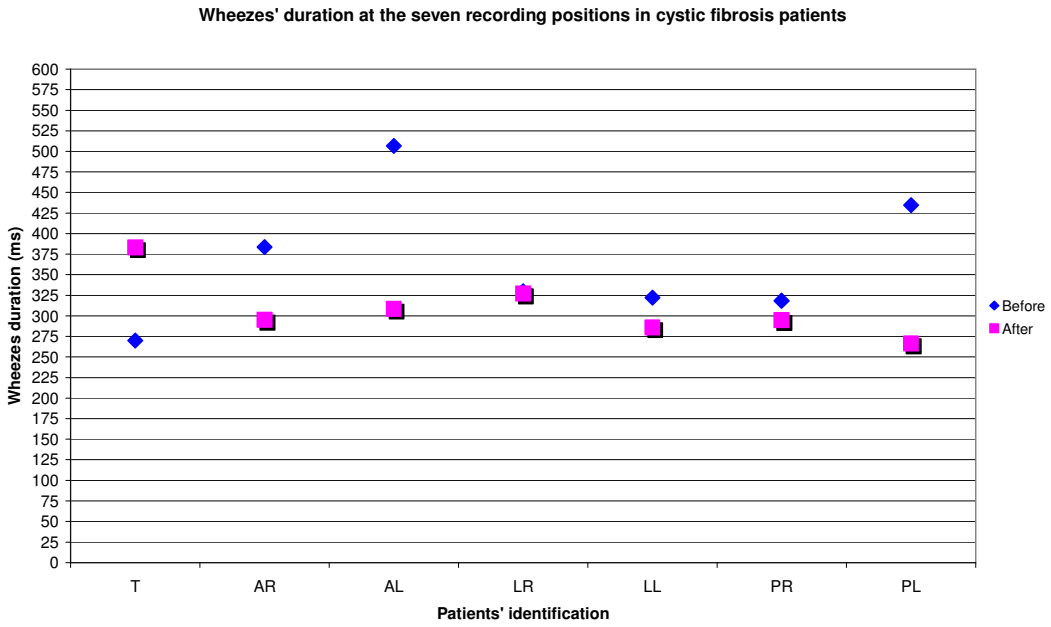
baseline and post self-intervention in the same position and when the averages were obtained across all participants.

Graph 40 shows that in this CF sample studied, very few wheezes were detected at trachea. It can also be observed that there is a tendency for the number of monophonic wheezes to increase and the number of polyphonic wheezes to decrease, post self-intervention. In the left region of the lungs more polyphonic wheezes were detected than in the right region.



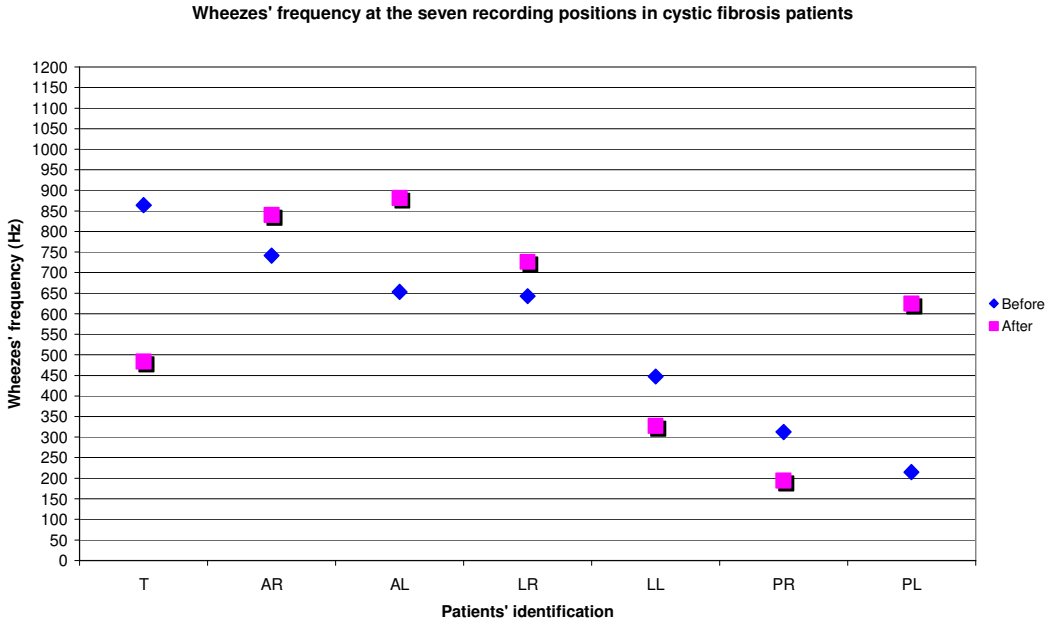
Graph 40: Number of wheezes in cystic fibrosis participants at the seven chest locations (T – trachea; AR – anterior right; AL – anterior left, LR – lateral right; LL – lateral left; PR – posterior right; PL – posterior left).

In all the chest locations with the exception of the trachea, the wheezes' duration tended to decrease post self-intervention in this group of CF participants, as shown in Graph 41.



Graph 41: Wheezes' duration analysis in cystic fibrosis participants at the seven chest locations (T – trachea; AR – anterior right; AL – anterior left, LR – lateral right; LL – lateral left; PR – posterior right; PL – posterior left).

In Graph 42, it is possible to observe that at anterior, lateral right and posterior left regions of the lungs, the wheezes' frequency tends to increase and at trachea, lateral left and posterior right tends to decrease post self-intervention. Again, it is relevant to remember that at the trachea, very few wheezes were detected.

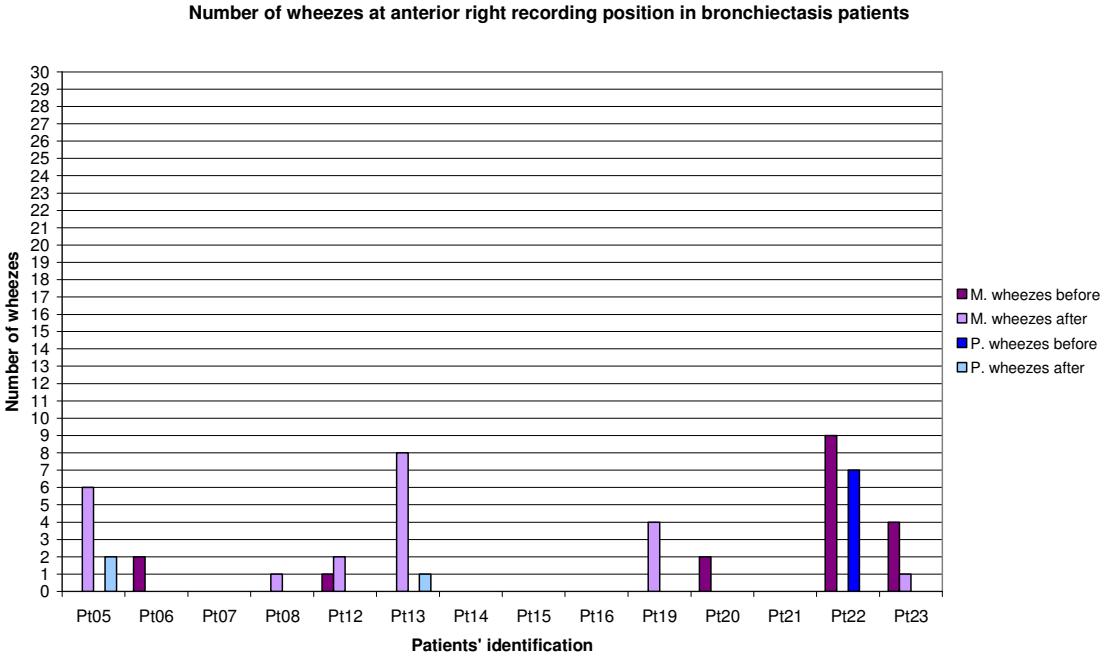


Graph 42: Results from wheezes' frequency analysis in cystic fibrosis patients at the seven chest locations (T – trachea; AR – anterior right; AL – anterior left, LR – lateral right; LL – lateral left; PR – posterior right; PL – posterior left).

Next section will present the results obtained from the analysis of the wheezes detected in Br participants in the first study.

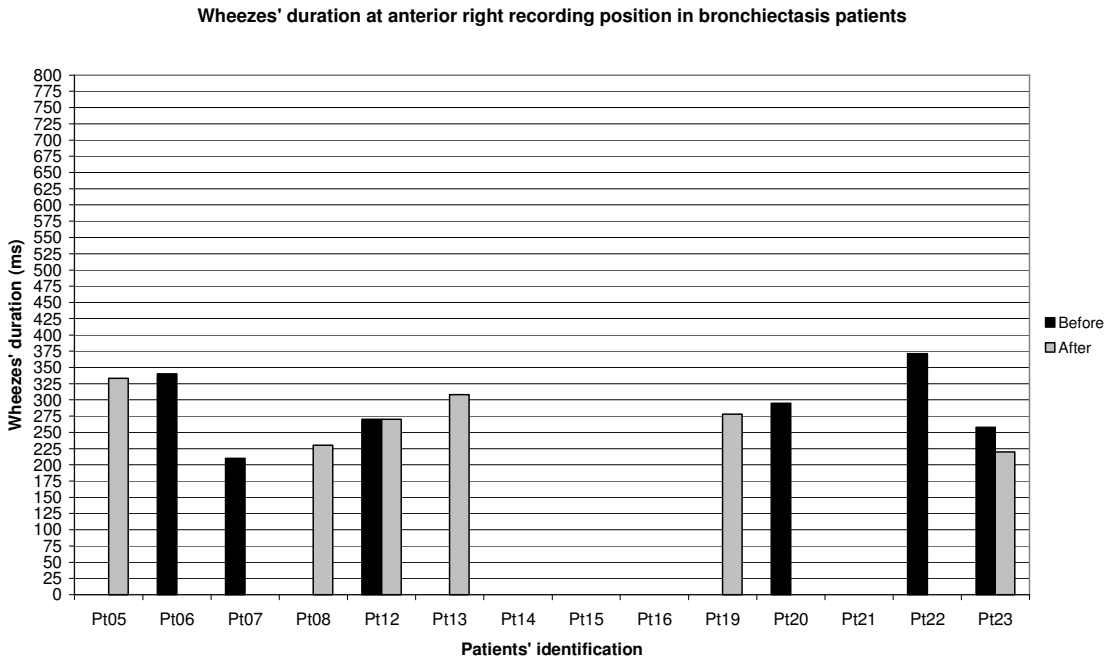
Wheezes' analysis in bronchiectasis participants

An example of the wheezes recorded in Br participants is provided using the data obtained at anterior right of the chest of this group of participants (Graph 43 for the number of wheezes, Graph 44 for the wheezes' duration and Graph 45 for the wheezes' frequency).

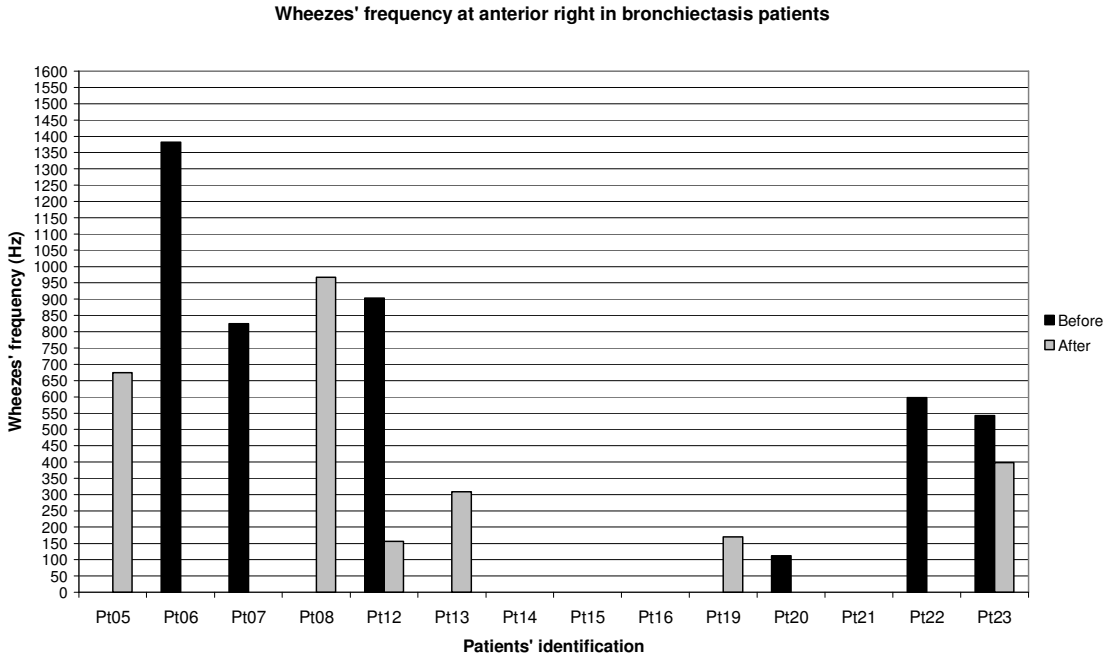


Graph 43: Number and type of wheezes recorded at anterior right of the chest in bronchiectasis participants, at baseline and post self-intervention (M. - monophonic and P. – polyphonic, wheezes).

At anterior right, wheezes were detected in the majority of the participants. At baseline, monophonic wheezes were detected in participants Pt06, Pt07, Pt12, Pt20, Pt22 and Pt23 (two, one, one, two, nine and four, respectively). Participant Pt22 also presented seven polyphonic wheezes. Post self-intervention, participant Pt05 presented six, Pt08 one, Pt12 two, Pt13 eight, Pt19 four and Pt23 one, monophonic wheezes. Two and one polyphonic wheezes were detected in Pt05 and in Pt13, post intervention. In four participants (Pt05, Pt08, Pt13 and Pt19), wheezes were detected only post self-intervention. In participant Pt12 one more monophonic wheeze was detected post self-intervention whereas the number of monophonic wheezes decreased from four to one in Pt23. The wheezes disappeared completely in Pt06, Pt07, Pt20 and Pt22 post self-intervention.



Graph 44: Wheezes' duration, recorded at anterior right of the chest in bronchiectasis participants, at baseline and post self-intervention.



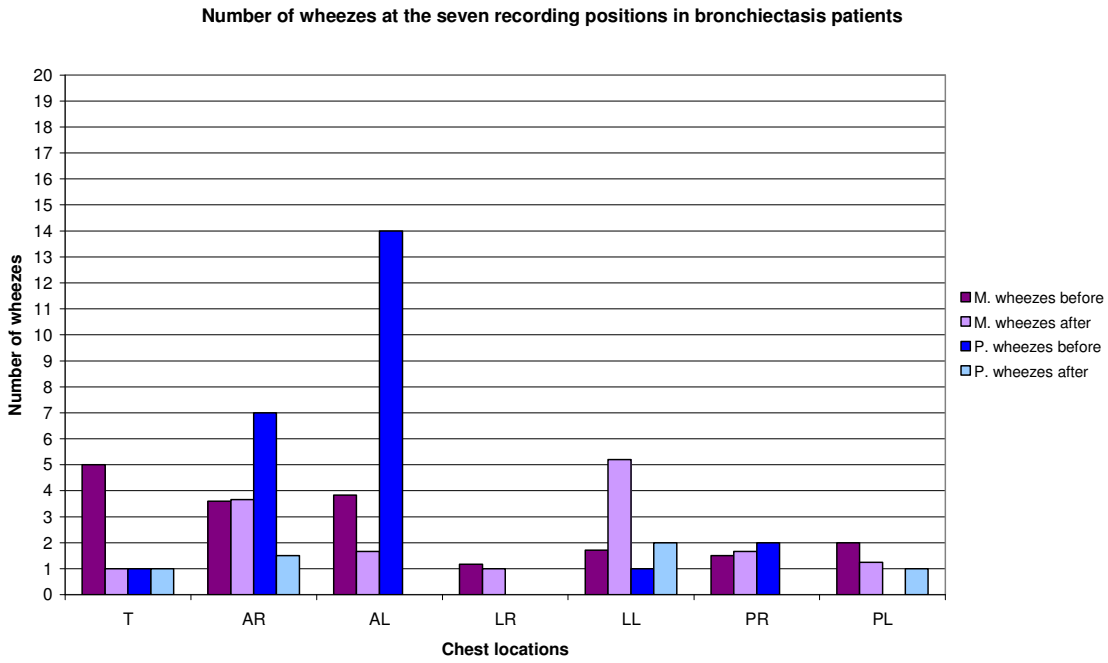
Graph 45: Wheezes' frequency, recorded at anterior right of the chest in bronchiectasis participants, at baseline and post self-intervention.

The wheezes' duration vary between 210 ms (Pt07) and 371 ms (Pt22) at baseline and between 230 ms (Pt08) and 333 ms (Pt05) post self-intervention. The wheezes' frequency varies between 112 Hz (Pt20) and 1382 Hz (Pt06) at baseline and between 156 Hz (Pt12) and 967 Hz (Pt08) post self-intervention. The wheezes' duration decreased in Pt23 and did not change in Pt12 at baseline and post self-intervention but

the frequency decreased, but not significantly, in both participants post self-intervention.

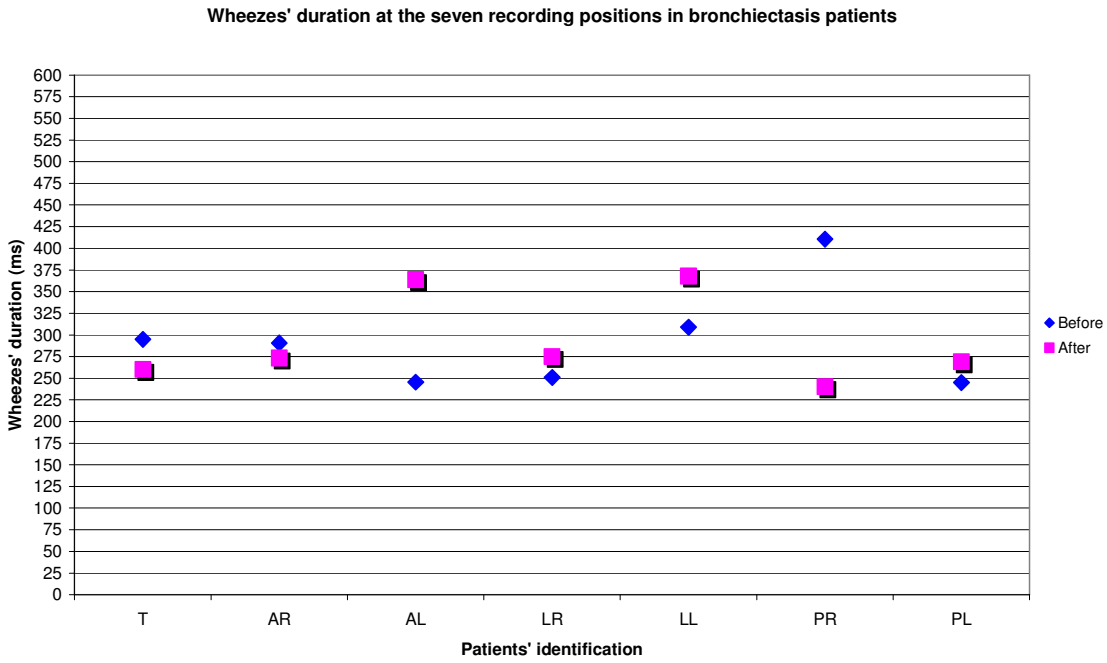
Graph 46, Graph 47 and Graph 48, show a summary of the results obtained from the number, duration and frequency of the wheezes recorded from the sample of Br participants studied.

In the sample of Br participants, the number of monophonic wheezes decreased in almost all regions of the lungs post physiotherapy self-intervention (except in lateral left and posterior right). A decrease or total disappearance of polyphonic wheezes was also detected post the self-intervention in the different chest locations (see Graph 46).

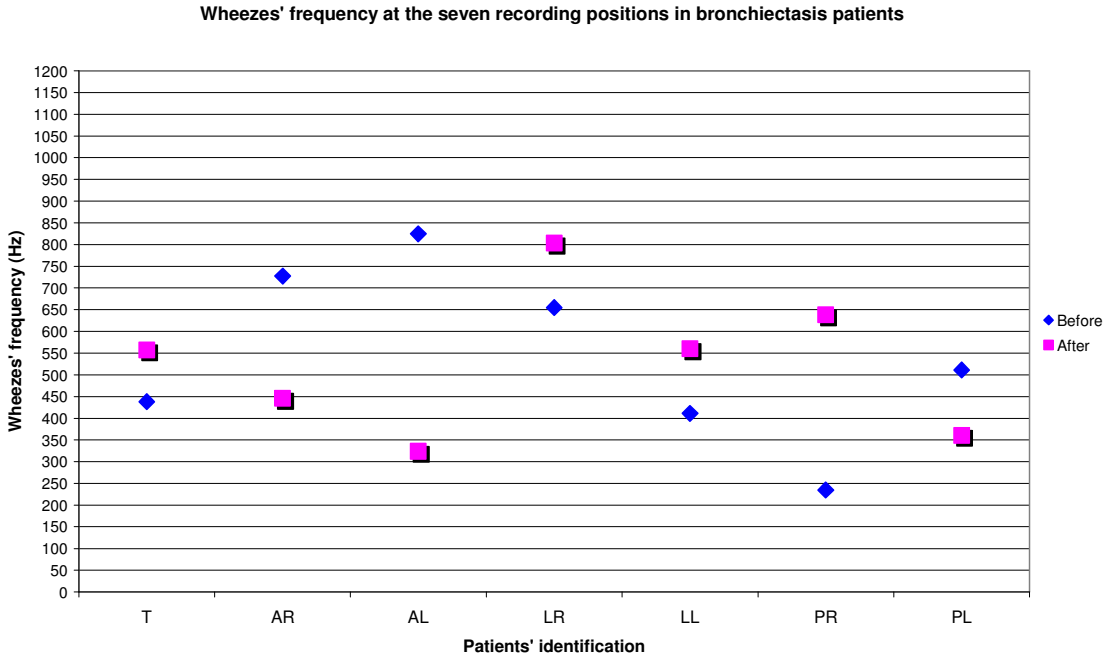


Graph 46: Number of wheezes in bronchiectasis participants at the seven chest locations (T – trachea; AR – anterior right; AL – anterior left, LR – lateral right; LL – lateral left; PR – posterior right; PL – posterior left).

The wheezes' duration seem to decrease in the upper (trachea and anterior right), and to increase in lower, chest locations, post self-intervention (see Graph 47). Upper chest locations (anterior regions), with the exception of the trachea, presented lower frequency values post self-interventions and in the other chest locations, with the exception of the posterior left, higher frequencies were detected post self-intervention (see Graph 48).



Graph 47: Results from wheezes' duration analysis in bronchiectasis participants at the seven chest locations (T – trachea; AR – anterior right; AL – anterior left, LR – lateral right; LL – lateral left; PR – posterior right; PL – posterior left).



Graph 48: Results from wheezes' frequency analysis in bronchiectasis participants at the seven chest locations (T – trachea; AR – anterior right; AL – anterior left, LR – lateral right; LL – lateral left; PR – posterior right; PL – posterior left).

Appendix 13 Inter-subject reliability analysis (post-intervention example)

Tables 35 to 38 show examples of the inter-subject reliability analysis performed post interventions, in both groups of participants, in both studies. The example presented was recorded at the anterior right of the chest. Table 35 and Table 36 show an example for the CF participants, and Table 37 and Table 38 for the Br participants, in the first study where participants applied a self-intervention and in the second study where the interventions were applied by a physiotherapist.

Variable names		Sum of Squares	df	Mean Square	F	Sig.
Crackles' Initial Deflection Width (IDW)	Between Groups	.001	9	.001	18.21	.001*
	Within Groups	.001	938	.001		
	Total	.001	947			
Crackles' Two Cycle Deflection (2CD)	Between Groups	.002	9	.001	22.14	.001*
	Within Groups	.008	904	.001		
	Total	.009	913			

Table 35: Results from the analysis of variance of the crackles' initial deflection width (**IDW**) and of the crackles' two cycles deflection (2CD) obtained from the **cystic fibrosis** participants (n = 10) at **anterior right** of the chest **post self-intervention** (* starred results are significant, $p<0.05$).

Variable names		Sum of Squares	df	Mean Square	F	Sig.
Crackles' Initial Deflection Width (IDW)	Between Groups	6.572	6	1.095	2.196	.042*
	Within Groups	258.437	518	.499		
	Total	265.009	524			
Crackles' Two Cycle Deflection (2CD)	Between Groups	941.038	6	156.840	17.17	.001*
	Within Groups	4731.594	518	9.134		
	Total	5672.632	524			

Table 36: Results from the analysis of variance of the crackles' initial deflection width (**IDW**) and of the crackles' two cycles deflection (**2CD**) obtained from the **cystic fibrosis** participants (n = 7) at **anterior right** of the chest **post physiotherapy** intervention (* starred results are significant, $p<0.05$).

Variable names		Sum of Squares	df	Mean Square	F	Sig.
Crackles' Initial Deflection Width (IDW)	Between Groups	.001	13	.001	5.123	.001*
	Within Groups	.001	1055	.001		
	Total	.001	1068			
Crackles' Two Cycle Deflection (2CD)	Between Groups	.001	13	.001	12.22	.001*
	Within Groups	.007	1015	.001		
	Total	.008	1028			

Table 37: Results from the analysis of variance of the crackles' initial deflection width (**IDW**) and of the crackles' two cycles deflection (**2CD**) obtained from the **bronchiectasis** participants (n = 14) at **anterior right** of the chest **post self-intervention** (* starred results are significant, $p<0.05$).

Variable names		Sum of Squares	df	Mean Square	F	Sig.
Crackles' Initial Deflection Width (IDW)	Between Groups	97.382	22	4.426	8.729	.001*
	Within Groups	746.450	1472	.507		
	Total	843.832	1494			
Crackles' Two Cycle Deflection (2CD)	Between Groups	3731.900	22	169.632	15.57	.001*
	Within Groups	16041.769	1472	10.898		
	Total	19773.669	1494			

Table 38: Results from the analysis of variance of the crackles' initial deflection width (**IDW**) and of the crackles' two cycles deflection (**2CD**) obtained from the **bronchiectasis** participants (n = 23) at **anterior right** of the chest **post physiotherapy** intervention (* starred results are significant, $p<0.05$).

The analysis of variance (ANOVA) of data in the same place and timing relative to the intervention but different subjects (inter-subject reliability), for both variables (crackles' IDW and 2CD), in both studies, showed that the null hypothesis was not supported ($p<0.05$). Therefore, data sets from different subjects in CF and in Br participants had significantly different mean crackles' IDW and significantly different mean crackles' 2CD at the 95% level, in both studies, at baseline and post interventions.

Appendix 14 Intra-subject reliability analysis (post intervention example)

Intra-subject reliability results post interventions (ANOVA)

The following tables show examples of the results obtained from the ANOVA of the crackles' IDW and 2CD of the lung sound repetitions performed in all participants, in both studies post interventions. This specific example refers to the data recorded at anterior right position of the chest of a CF participant (Pt03) and a Br participant (Pt01), post interventions (Table 40 and Table 40). For complete analysis see Appendix on the CD provided.

Variables names		Sum of Squares	df	Mean Square	F	Sig.
Crackles' Initial Deflection Width (IDW)	Between Groups	1.197	2	.599	.600	.552
	Within Groups	66.830	67	.997		
	Total	68.027	69			
Crackles' Two Cycle Deflection (2CD)	Between Groups	59.505	2	29.753	2.691	.175
	Within Groups	740.703	67	11.055		
	Total	800.208	69			

Table 39: Results from the analysis of variance of the crackles' initial deflection width (**IDW**) and two cycles deflection (**2CD**) of a **cystic fibrosis** participant (Pt03) at **anterior right** of the chest **post physiotherapy** intervention (p>0.05).

Variables names		Sum of Squares	df	Mean Square	F	Sig.
Crackles' Initial Deflection Width (IDW)	Between Groups	.328	2	.164	1.094	.342
	Within Groups	8.853	59	.150		
	Total	9.181	61			
Crackles' Two Cycle Deflection (2CD)	Between Groups	32.740	2	16.370	1.772	.179
	Within Groups	545.147	59	9.240		
	Total	577.887	61			

Table 40: Results from the analysis of variance of the crackles' initial deflection width (**IDW**) and two cycles deflection (**2CD**) of a **bronchiectasis** participant (Pt01) at **anterior right** of the chest **post physiotherapy** intervention (p>0.05).

The results from the ANOVA supported the null hypothesis (p>0.05) for the crackles' variables, in all participants (both studies). To continue to assess intra-subject reliability, the Intraclass Correlation Coefficient, the Bland & Altman 95% limits of agreement and the Smallest Real Difference were calculated. These calculations were performed separately, for both groups of participants, in both studies. The post intervention data were not pooled since the interventions were different in each study and could have affected the reliability of the measure. Therefore, the ICC, Bland and Altman 95% limits of agreement and SRD post intervention for each group of participants in each study will be presented.

Intra-subject reliability results post interventions (ICC, SRD, Bland and Altman 95% limits of agreement)

This sub-section will present the ICC, SRD and Bland and Altman 95% limits of agreement, in CF participants and in Br participants, in each study.

Again, to avoid the construction of many tables, the ICC, SRD and Bland & Altman 95% limits of agreement results, related to each group of participants, are presented in the same table, i.e., one table for CF participants and one for Br participants, for each study. The results for the CF participants in the first and second studies are presented in Table 41and Table 42, respectively. The results from the Br participants in the first and second studies are presented in Table 43 and Table 44 respectively.

Cystic fibrosis participants – post airway clearance self-interventions (first study)																
	ICC (95% CI) - IDW	ICC (95% CI) - 2CD	SEM IDW (ms)	SEM 2CD (ms)	SRD IDW (ms)	SRD 2CD (ms)	$\bar{d}$ IDW (ms)	SD_{diff} IDW (ms)	$\bar{d}$ 2CD (ms)	SD_{diff} 2CD (ms)	$SE\bar{d}$ IDW (ms)	$SE\bar{d}$ 2CD (ms)	95% CI for $\bar{d}$ IDW (ms)	95% CI for $\bar{d}$ 2CD (ms)	95% LA IDW (ms)	95% LA 2CD (ms)
T	0.63 (0.41;0.91)	0.96 (0.84;0.99)	0.10	0.63	0.29	1.75	0.04	0.15	0.09	0.93	0.05	0.30	(-0.07;0.14)	(-0.57;0.76)	(-0.26;0.34)	(-1.78;1.96)
AR	0.83 (0.37;0.96)	0.95 (0.81;0.99)	0.18	0.42	0.50	1.17	-0.11	0.24	-0.18	0.60	0.08	0.19	(-0.29;0.06)	(-0.61;0.25)	(-0.60;0.38)	(-1.38;1.02)
AL	0.91 (0.65;0.98)	0.91(0.68;0.98)	0.13	0.70	0.36	1.94	-0.05	0.19	-0.21	1.02	0.06	0.32	(-0.18;0.08)	(-0.94;0.52)	(-0.43;0.33)	(-2.26;1.83)
LR	0.40 (0.09;0.85)	0.50 (0.19;0.87)	0.11	0.70	0.32	1.93	0.04	0.17	0.04	1.04	0.05	0.33	(-0.08;0.16)	(-0.70;0.78)	(-0.29;0.37)	(-2.04;2.11)
LL	0.91 (0.67;0.98)	0.86 (0.46;0.96)	0.12	0.64	0.33	1.78	0.06	0.17	-0.41	0.86	0.05	0.27	(-0.06;0.18)	(-1.02;0.21)	(-0.27;0.39)	(-2.13;1.31)
PR	0.55 (0.29;0.89)	0.87 (0.51;0.97)	0.31	0.88	0.87	2.43	-0.15	0.44	-0.38	1.25	0.14	0.39	(-0.47;0.16)	(-1.27;0.51)	(-1.03;0.72)	(-2.87;2.12)
PL	0.98 (0.93;0.99)	0.97 (0.90;0.99)	0.12	0.47	0.33	1.31	0.04	0.17	-0.39	0.57	0.06	0.18	(-0.09;0.16)	(-0.80;0.01)	(-0.31;0.38)	(-1.53;0.75)

Table 41: Results from Intraclass Correlation Coefficient (ICC) with the 95% Confidence Intervals (CI), Standard Error of Measurement (SEM), Smallest Real Difference (SRD), Mean ($\bar{d}$) and Standard Deviation (SD) of the differences (diff.), Standard Error of the mean difference ($SE\bar{d}$), 95% Confidence Intervals for the mean difference and 95% Limits of Agreement (LA), obtained from the analysis of crackles' **IDW** and **2CD** of **cystic fibrosis** participants (n = 10) **post** airway clearance **self-intervention**.

Cystic fibrosis participants – post airway clearance interventions applied by a physiotherapist (second study)																
	ICC (95% CI) – IDW	ICC (95% CI) - 2CD	SEM IDW (ms)	SEM 2CD (ms)	SRD IDW (ms)	SRD 2CD (ms)	$\bar{d}$ IDW (ms)	SD_{diff} IDW (ms)	$\bar{d}$ 2CD (ms)	SD_{diff} 2CD (ms)	$SE\bar{d}$ IDW (ms)	$SE\bar{d}$ 2CD (ms)	95% CI for $\bar{d}$ IDW (ms)	95% CI for $\bar{d}$ 2CD (ms)	95% LA IDW (ms)	95% LA 2CD (ms)
T	0.78(0.14;0.96)	0.92(0.59;0.99)	0.03	0.75	0.09	2.07	-0.03	0.04	-0.25	1.11	0.02	0.42	(-0.06;0.01)	(-1.20;0.70)	(-0.11;0.05)	(-2.47;1.97)
AR	0.94(0.69;0.99)	0.93(0.65;0.99)	0.05	0.60	0.15	1.67	-0.02	0.08	-0.16	0.90	0.03	0.34	(-0.09;0.05)	(-0.93;0.61)	(-0.18;0.14)	(-1.96;1.64)
AL	0.92(0.60;0.99)	0.93(0.65;0.99)	0.10	0.63	0.28	1.74	0.04	0.15	-0.01	0.96	0.06	0.36	(-0.09;0.17)	(-0.83;0.81)	(-0.26;0.34)	(-1.93;1.91)
LR	0.95(0.73;0.99)	0.71(0.47;0.95)	0.12	0.67	0.34	1.86	-0.05	0.18	-0.49	0.88	0.07	0.33	(-0.20;0.10)	(-1.24;0.26)	(-0.41;0.31)	(-2.25;1.27)
LL	0.95(0.74;0.99)	0.85(0.21;0.97)	0.09	0.64	0.26	1.78	0.03	0.14	0.29	0.93	0.05	0.35	(-0.09;0.15)	(-0.50;1.08)	(-0.25;0.31)	(-1.57;2.15)
PR	0.84(0.17;0.97)	0.78(0.12;0.96)	0.06	0.39	0.18	1.07	0.01	0.09	-0.14	0.57	0.03	0.22	(-0.07;0.09)	(-0.63;0.35)	(-0.17;0.19)	(-1.28;1)
PL	0.88(0.38;0.98)	0.86(0.27;0.98)	0.17	0.72	0.48	2.00	-0.03	0.26	-0.31	1.05	0.10	0.40	(-0.25;0.19)	(-1.21;0.59)	(-0.55;0.49)	(-2.41;1.79)

Table 42: Results from Intraclass Correlation Coefficient (ICC) with the 95% Confidence Intervals (CI), Standard Error of Measurement (SEM), Smallest Real Difference (SRD), Mean ($\bar{d}$) and Standard Deviation (SD) of the differences (diff.), Standard Error of the mean difference ($SE\bar{d}$), 95% Confidence Intervals for the mean difference and 95% Limits of Agreement (LA), obtained from the analysis of crackles' **IDW** and **2CD** of **cystic fibrosis** participants (n = 7) **post physiotherapy** intervention.

Bronchiectasis participants – post airway clearance self-interventions (first study)																
	ICC (95% CI) – IDW	ICC (95% CI) - 2CD	SEM IDW (ms)	SEM 2CD (ms)	SRD IDW (ms)	SRD 2CD (ms)	$\bar{d}$ IDW (ms)	SD_{diff} IDW (ms)	$\bar{d}$ 2CD (ms)	SD_{diff} 2CD (ms)	$SE\bar{d}$ IDW (ms)	$SE\bar{d}$ 2CD (ms)	95% CI for $\bar{d}$ IDW (ms)	95% CI for $\bar{d}$ 2CD (ms)	95% LA IDW (ms)	95% LA 2CD (ms)
T	0.39 (0.15;0.80)	0.90 (0.69;0.97)	0.15	1.03	0.41	2.85	-0.08	0.20	0.02	1.51	0.05	0.40	(-0.20;0.05)	(-0.89;0.93)	(-0.48;0.32)	(-2.99;3.04)
AR	0.75 (0.24;0.92)	0.81(0.43;0.94)	0.17	0.64	0.47	1.77	0.04	0.25	-0.15	0.93	0.07	0.25	(-0.11;0.19)	(-0.71;0.41)	(-0.46;0.53)	(-2.00;1.70)
AL	0.70 (0.07;0.90)	0.86 (0.57;0.95)	0.18	0.62	0.51	1.71	0.05	0.26	-0.07	0.90	0.07	0.24	(-0.11;0.21)	(-0.61;0.47)	(-0.48;0.58)	(-1.87;1.73)
LR	0.90 (0.71;0.97)	0.95 (0.85;0.98)	0.13	0.79	0.35	2.18	-0.07	0.17	-0.14	1.15	0.04	0.31	(-0.17;0.03)	(-0.83;0.55)	(-0.41;0.26)	(-2.44;2.16)
LL	0.34 (0.18;0.79)	0.87(0.60;0.96)	0.20	0.70	0.56	1.95	-0.11	0.27	0.00	1.03	0.07	0.28	(-0.27;0.05)	(-0.63;0.62)	(-0.66;0.44)	(-2.06;2.06)
PR	0.88 (0.63;0.96)	0.88 (0.64;0.96)	0.16	0.71	0.46	1.96	0.07	0.23	-0.13	1.03	0.06	0.28	(-0.06;0.21)	(-0.76;0.49)	(-0.38;0.53)	(-2.20;1.93)
PL	0.66 (0.01;0.89)	0.90 (0.71;0.97)	0.27	0.79	0.74	2.18	-0.14	0.37	-0.66	0.93	0.10	0.25	(-0.36;0.08)	(-1.22;0.10)	(-0.87;0.59)	(-2.52;1.19)

Table 43: Results from Intraclass Correlation Coefficient (ICC) with the 95% Confidence Intervals (CI), Standard Error of Measurement (SEM), Smallest Real Difference (SRD), Mean ($\bar{d}$) and Standard Deviation (SD) of the differences (diff.), Standard Error of the mean difference ($SE\bar{d}$), 95% Confidence Intervals for the mean difference and 95% Limits of Agreement (LA), obtained from the analysis of crackles' **IDW** and **2CD** of **bronchiectasis** participants (n = 14) **post** airway clearance **self-intervention**.

Bronchiectasis participants – post airway clearance interventions applied by a physiotherapist (second study)																
	ICC (95% CI) – IDW	ICC (95% CI) - 2CD	SEM IDW (ms)	SEM 2CD (ms)	SRD IDW (ms)	SRD 2CD (ms)	$\bar{d}$ IDW (ms)	SD_{diff} IDW (ms)	$\bar{d}$ 2CD (ms)	SD_{diff} 2CD (ms)	$SE\bar{d}$ IDW (ms)	$SE\bar{d}$ 2CD (ms)	95% CI for $\bar{d}$ IDW (ms)	95% CI for $\bar{d}$ 2CD (ms)	95% LA IDW (ms)	95% LA 2CD (ms)
T	0.87(0.70;0.94)	0.82(0.58;0.92)	0.06	0.61	0.18	1.69	-0.01	0.09	-0.08	0.88	0.02	0.18	(-0.05;0.03)	(-0.49;0.33)	(-0.19;0.17)	(-1.84;1.68)
AR	0.75(0.42;0.89)	0.90(0.77;0.96)	0.17	0.70	0.48	1.94	0.03	0.25	-0.18	0.99	0.05	0.21	(-0.09;0.15)	(-0.65;0.29)	(-0.47;0.53)	(-2.16;1.8)
AL	0.67(0.24;0.86)	0.75(0.42;0.89)	0.14	0.70	0.40	1.95	-0.01	0.21	-0.11	1.01	0.04	0.21	(-0.11;0.09)	(-0.59;0.37)	(-0.43;0.41)	(-2.13;1.91)
LR	0.84(0.62;0.93)	0.93(0.84;0.97)	0.14	0.67	0.40	1.86	-0.08	0.19	-0.35	0.90	0.04	0.19	(-0.17;0.01)	(-0.77;0.07)	(-0.46;0.3)	(-2.15;1.45)
LL	0.76(0.45;0.90)	0.84(0.62;0.93)	0.13	0.76	0.35	2.10	-0.001	0.19	-0.53	0.95	0.04	0.20	(-0.09;0.09)	(-0.98;-0.08)	(-0.38;0.38)	(-2.43;1.37)
PR	0.91(0.80;0.96)	0.94(0.85;0.97)	0.15	0.53	0.41	1.48	-0.04	0.21	-0.14	0.76	0.04	0.16	(-0.14;0.06)	(-0.50;0.22)	(-0.46;0.38)	(-1.66;1.38)
PL	0.76(0.44;0.90)	0.85(0.64;0.93)	0.16	0.66	0.46	1.84	0.01	0.24	-0.02	0.96	0.05	0.20	(-0.10;0.12)	(-0.47;0.43)	(-0.47;0.49)	(-1.94;1.9)

Table 44: Results from Intraclass Correlation Coefficient (ICC) with the 95% Confidence Intervals (CI), Standard Error of Measurement (SEM), Smallest Real Difference (SRD), Mean ($\bar{d}$) and Standard Deviation (SD) of the differences (diff.), Standard Error of the mean difference ($SE\bar{d}$), 95% Confidence Intervals for the mean difference and 95% Limits of Agreement (LA), obtained from the analysis of crackles' **IDW** and **2CD** of **bronchiectasis** participants (n = 23) **post physiotherapy** intervention.

Intraclass Correlation Coefficient for crackles data post airway clearance interventions

The ICC results from the each study will now be presented for the CF participants and for the Br participants.

ICC for crackles data from cystic fibrosis participants post airway clearance interventions

In the first study, the crackles' IDW in CF participants, post intervention presented 'excellent' reliability values in four recording positions, ranging between 0.83 and 0.98. 'Good' reliability results were found in the other three recording positions: trachea (0.63), lateral right (0.40) and posterior right (0.55). For the crackles' 2CD the reliability was also 'excellent' (0.86 to 0.97) and was 'good' at the lateral right of the lungs (0.50).

In the second study, for the CF participants, the reliability analysis of the crackles' IDW varied between 0.78 and 0.95 ('excellent' reliability) in all the recording positions. For the crackles' 2CD reliability was 'excellent' in most of the recording positions (0.78 to 0.93) and was 'good' at lateral right of the chest (0.71).

ICC for crackles data from bronchiectasis participants post airway clearance interventions

In the first study, after airway clearance self-intervention, the ICC for the crackles' IDW was 'excellent' at anterior right (0.75), lateral right (0.90) and posterior right (0.88) areas of the lungs, was 'good' at anterior left (0.69) and posterior left (0.66), and was 'poor' in the trachea (0.39) and lateral left (0.34) regions. For the crackles' 2CD the ICC was found to be 'excellent' (0.81 to 0.95) at all recording positions.

In the second study, the ICC for the crackles' IDW, was 'excellent' in all recording positions (0.75 and 0.91) except at anterior left area where it was 'good' (0.67). For the crackles' 2CD the ICC was "excellent" at all recording positions (0.75 to 0.94).

Smallest Real Difference for crackles data post airway clearance interventions

The SRD results from each study will now be presented for the CF participants and for the Br participants.

SRD for crackles data from cystic fibrosis participants post airway clearance interventions

In the first study, the SRD values of the crackles' IDW ranged between 0.29 and 0.87 ms. For the crackles' 2CD the SRD ranged between 1.17 and 2.43 ms post intervention. The high value at anterior left was not found post intervention. Reasons for this finding were explored in Chapter 6.

In the second study, the SRD values of the crackles' IDW, in CF participants, varied between 0.09 ms and 0.48 ms. For the crackles' 2CD, the SRD ranged between 1.07 and 2.07 ms post intervention.

SRD for crackles data from bronchiectasis participants post intervention

In the first study, the SRD values of the crackles' IDW, in Br participants, varied between 0.35 and 0.74 ms. For the crackles' 2CD, the SRD range was 1.71 and 2.85 ms.

In the second study, the SRD values of the crackles' IDW, in Br participants, varied between 0.18 ms and 0.48 ms. For the crackles' 2CD the SRD range was 1.69 and 2.10 ms.

The SRD decreased for both groups of participants in the second study. It was also possible to observe that the range of the SRD values was very similar when the CF participants were compared with the Br participants in the same study. These findings indicate the stability of the measure.

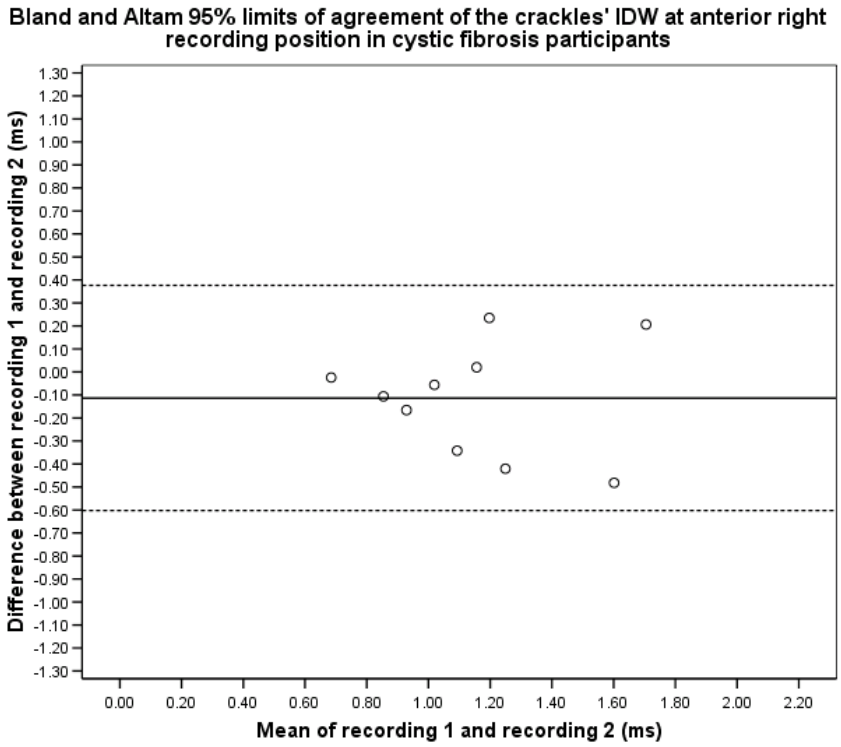
Bland and Altman 95% limits of agreement of the crackles data post airway clearance interventions

A scatter plot was produced for each variable in each recording position, post interventions, for each group of participants in each study. The example given here refers to data recorded at anterior right of the chest in CF participants and in Br participants. For the complete analysis of both groups of patients see Appendix on the CD provided. In graphs 49 to 56, the mean difference was plotted using a solid line and the 95% limits of agreement, upper and lower limits, were plotted using dotted lines. The 95% Confidence Intervals for the mean difference are also presented in the tables 41 to 44.

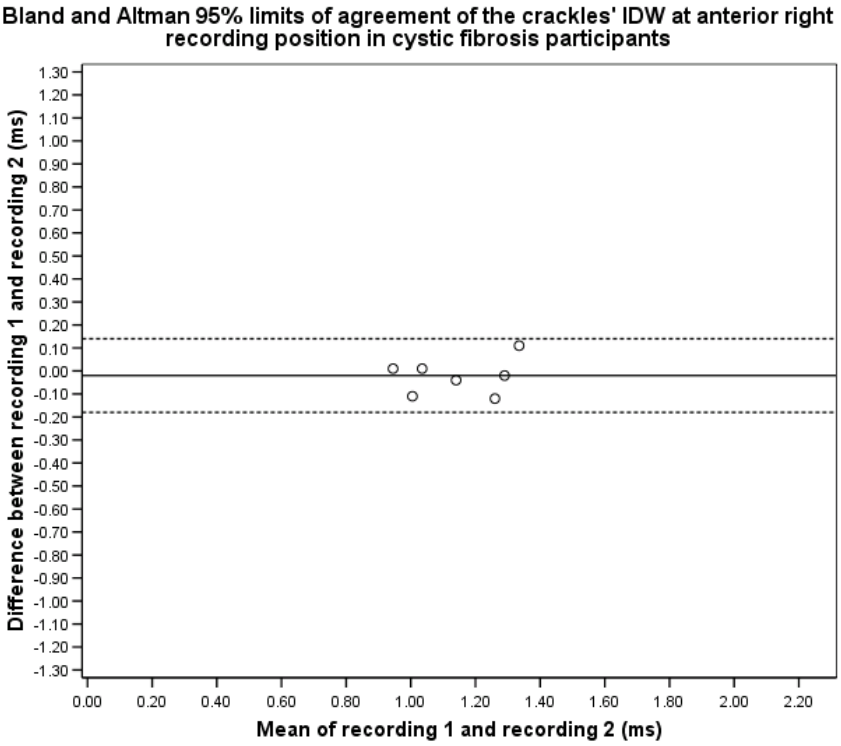
Bland and Altman 95% limits of agreement of the crackles data from cystic fibrosis participants post airway clearance interventions

Graph 49 and Graph 50 show the results for the crackles' IDW in CF participants in each study, at anterior right of the chest. Graph 51 and Graph 52 present the results for the crackles' 2CD obtained from each study.

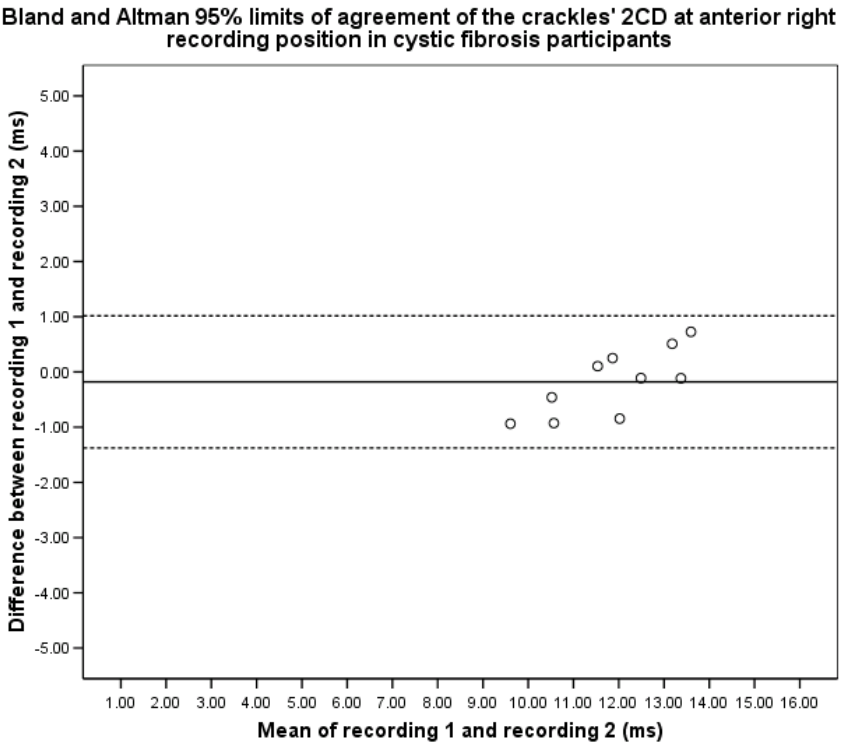
As can be observed no systematic bias was detected for the crackles' IDW or for the crackles' 2CD, in any recording position, in CF participants.



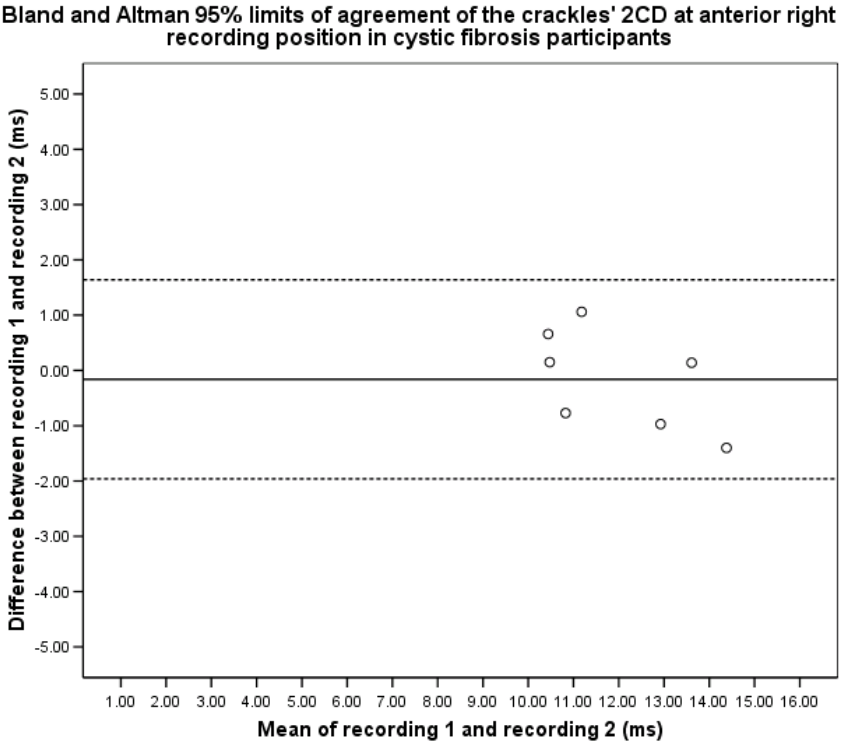
Graph 49: Results from the Bland & Altman 95% limits of agreement of the crackles' initial deflection width (**IDW**) obtained from the **cystic fibrosis** participants (n = 10) at **anterior right** of the chest post airway clearance self-intervention (**first study**).



Graph 50: Results from the Bland & Altman 95% limits of agreement of the crackles' initial deflection width (**IDW**) obtained from the **cystic fibrosis** participants (n = 7) at **anterior right** of the chest **post physiotherapy** intervention (**second study**).



Graph 51: Results from the Bland & Altman 95% limits of agreement of the crackles' two cycles deflection (**2CD**) obtained from the **cystic fibrosis** participants (n = 10) at **anterior right** of the chest post airway clearance **self-intervention** (**first study**).



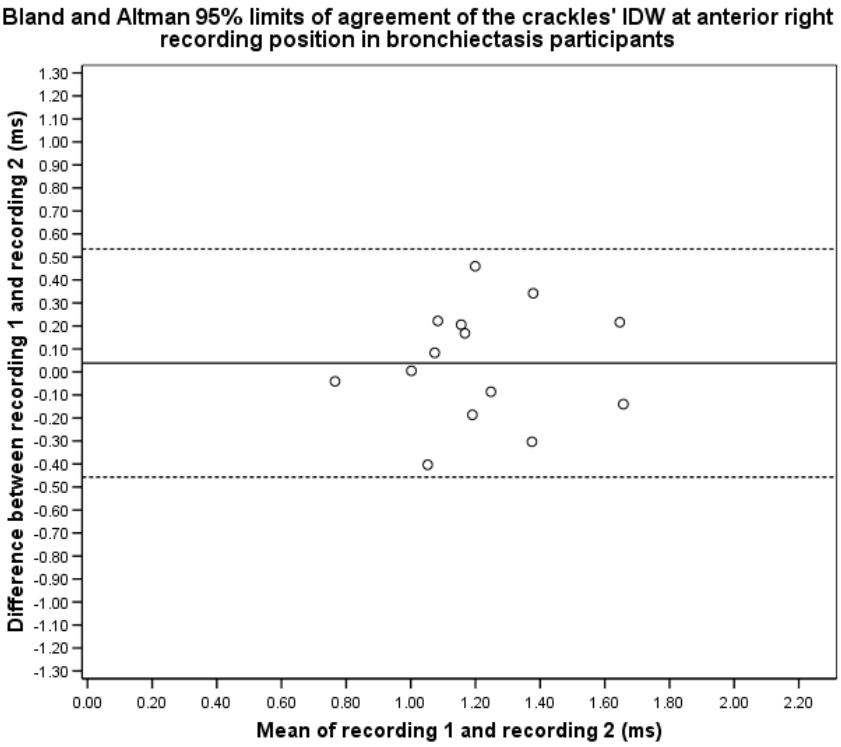
Graph 52: Results from the Bland & Altman 95% limits of agreement of the crackles' two cycles deflection (**2CD**) obtained from the **cystic fibrosis** participants (n = 7) at **anterior right** of the chest **post physiotherapy** intervention (**second study**).

Bland and Altman 95% limits of agreement in bronchiectasis participants post intervention

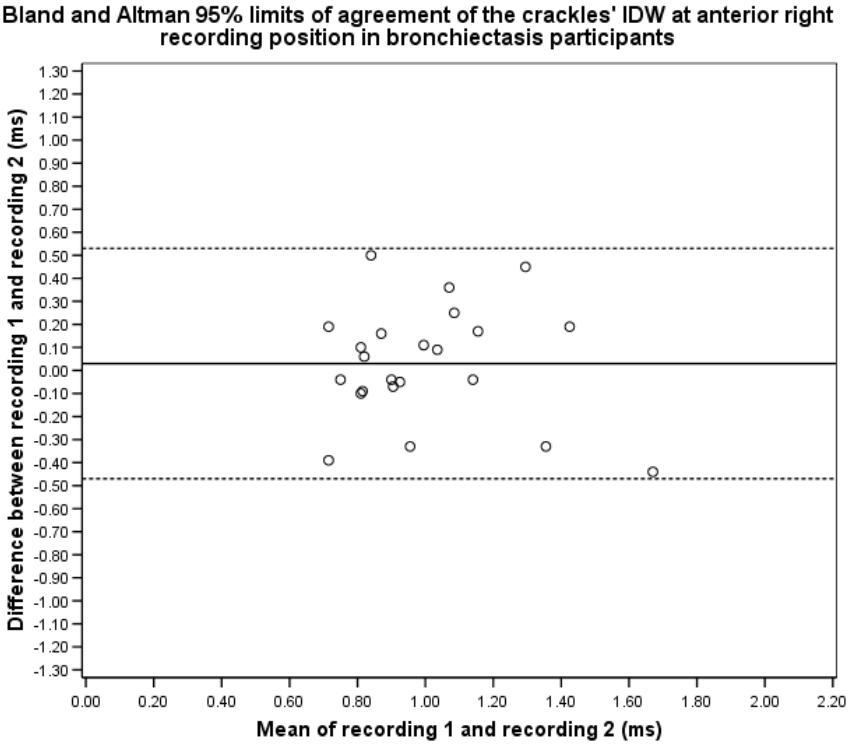
Graph 53 and Graph 54 show the results for the crackles' IDW in Br participants in each study, at anterior right of the chest. Graph 55 and Graph 56 present the results for the crackles' 2CD obtained from each study.

These plots indicate that no systematic bias was present for the crackles' IDW or for the crackles' 2CD variables in Br participants, in any recording position, in both studies.

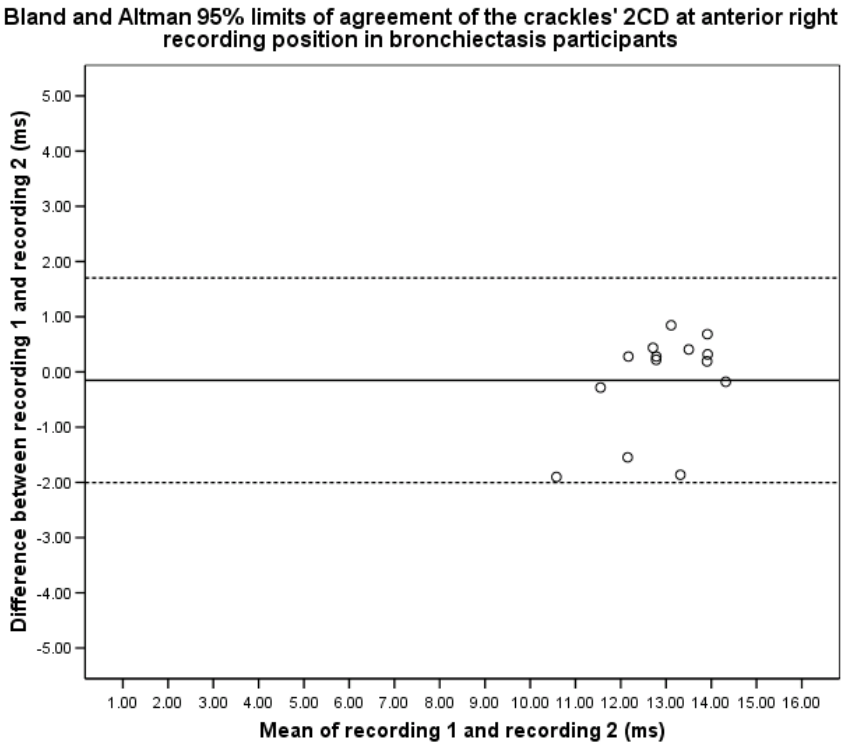
In summary, this reliability study has shown that CALSA presents acceptable test-retest reliability over short periods of time.



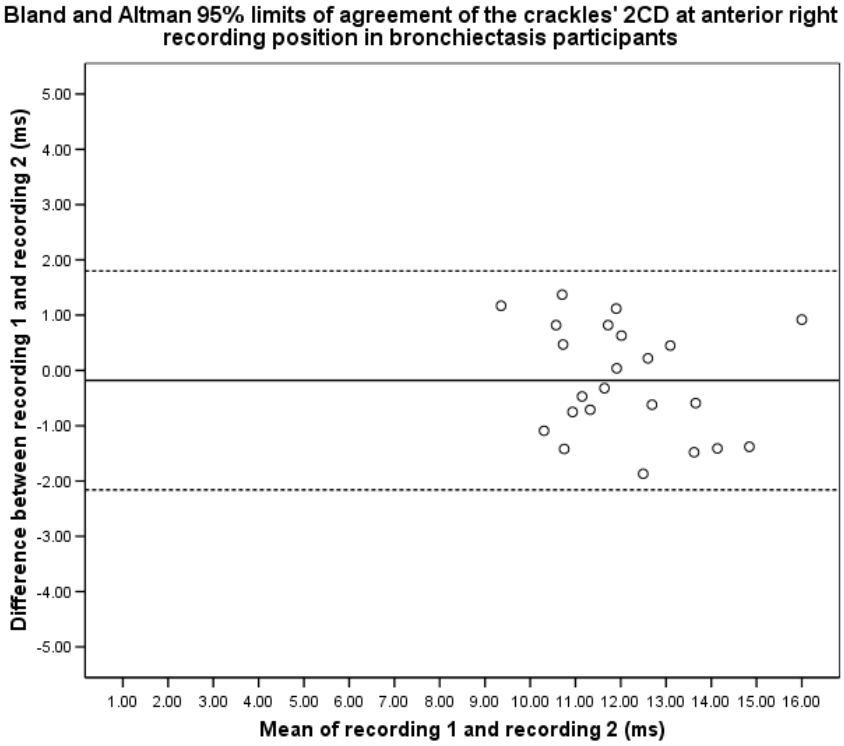
Graph 53: Results from the Bland & Altman 95% limits of agreement of the crackles' initial deflection width (**IDW**) obtained from the **bronchiectasis** participants (n = 14) at **anterior right** of the chest post airway clearance **self-intervention** (**first study**).



Graph 54: Results from the Bland & Altman 95% limits of agreement of the crackles' initial deflection width (**IDW**) obtained from the **bronchiectasis** participants (n = 23) at **anterior right** of the chest **post physiotherapy** intervention (**second study**).



Graph 55: Results from the Bland & Altman 95% limits of agreement of the crackles' two cycles deflection (**2CD**) obtained from the **bronchiectasis** participants (n = 14) at **anterior right** of the chest post airway clearance **self-intervention** (**first study**).



Graph 56: Results from the Bland & Altman 95% limits of agreement of the crackles' two cycles deflection (**2CD**) obtained from the **bronchiectasis** participants (n = 23) at **anterior right** of the chest **post physiotherapy** intervention (**second study**).

Glossary of the respiratory physiotherapy airway clearance techniques used within this research

A brief description of each technique is presented here. For more comprehensive description please refer to standard respiratory textbooks e.g. (Pryor and Prasad, 2008).

Active Cycle of Breathing Techniques (ACBT) – comprises three main components which are: breathing control, thoracic expansion exercises and forced expiration technique. Breathing control consists of gentle relaxed breathing at tidal volume using the lower part of the chest. Thoracic expansion exercises are three or four deep breaths with emphasis on inspiration, an inspiratory hold, followed by a quiet expiration. Forced expiration technique consists of one or two forced expirations with an open glottis from mid to low volume to mobilise peripheral secretions. The secretions which are already in the proximal airways can be cleared with a huff and cough at high lung volume. This technique is applied as a cycle, repeatedly, normally starting with breathing control. The length of each phase and the number of cycles is flexible and adjustable to individual needs. The Active Cycle of Breathing Techniques can be applied in sitting or used in conjunction with other techniques, e.g., postural drainage, modified postural drainage and chest clapping (percussion).

Autogenic drainage (AD) – consists of breathing in three different phases. The treatment is normally performed in sitting but can be applied in other positions. The technique involves: 1) a slow inspiration using the diaphragm and/or lower part of the chest, with the upper airways open; 2) an inspiratory hold of three or four seconds maintaining the glottis open; 3) and then an expiratory flow reaching the highest possible velocity without causing airway compression, i.e., expiration as fast as possible with an open glottis. The tidal volume breathing is carried out at different lung volume levels: low lung volume level – peripheral airways ‘unstick’ phase; mid lung volume level – middle airways ‘collect’ phase and high lung volume level – proximal airways ‘evacuate’ phase. The tidal volume breath is raised from low to high lung volume level breathing according to feedback given by auscultation or palpation of the thorax. This technique is often applied in conjunction with inhalation therapies and can also be used with oscillatory positive expiratory pressure (PEP) devices, e.g., Flutter or Cornet.

Modified Autogenic Drainage (MAD) – this is a modification of the above which gives less emphasis on the three separate phases of the breathing and is normally performed in sitting or in supine. This technique starts with a slow inspiration with an inspiratory hold. Then a fast passive expiration up to expiratory reserve volume occurs and is followed by continued active expiration into expiratory reserve volume. The length of the expiration is determined by the amount of mucus in the airways, i.e., the less mucus in the proximal airways the longer the expiration, the more mucus in the proximal airways the shorter the expiration. This technique is often used in conjunction with inhalation therapies and if the disease is severe, self applied positive expiratory pressure in the form of pursed-lip breathing can be used.

Postural drainage - this is a passive form of treatment using gravity to drain specific lobes/segments of the lungs for which eleven postural drainage positions can be used.

Modified Postural drainage – the modifications normally include, the elimination of head down positions with the lower lobes being drained in a horizontal plane, often in side-lying positions, or the use of slight tip only.

Percussion and vibration – manual techniques i.e. percussion and vibration can be included during postural drainage, as well as thoracic expansion exercises with forced expiratory manoeuvres. Percussion can be applied by a professional or self-applied and it consists in a single or double handed rhythmical chest wall percussion with a cupped hand. The rate, depth and forced of the technique should be adapted to each individual. Percussion can also be applied using a mechanical device. Vibrations are fine oscillatory pressure movements applied with the hands during the expiratory phase of the thoracic expansion exercises. The force and depth of the technique are adapted to meet individual needs.

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