

From the Department of Clinical Science, Intervention and  
Technology, Division of Pediatrics  
Karolinska Institutet, Stockholm, Sweden

# NON INVASIVE VENTILATION IN PEOPLE WITH CYSTIC FIBROSIS

Maria Cecilia Rodriguez Hortal



**Karolinska  
Institutet**

Stockholm 2016

All previously published papers were reproduced with permission from the publisher.

Published by Karolinska Institutet.

Printed by US-AB print

© Rodriguez Hortal, 2016

ISBN 978-91-7676-463-3

Emma Tingård ®

# Non invasive ventilation in people with cystic fibrosis

## THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

**Maria Cecilia Rodriguez Hortal**

*Principal Supervisor:*

Prof. Lena Hjelte

Karolinska Institutet

Department of Clinical Science, Intervention  
and Technology

Division of Pediatrics

*Opponent:*

PhD Louise Lannefors

Gothenburg University

Sahlgrenska Hospital

Division of Occupational Therapy &  
Physiotherapy

*Co-supervisor:*

PhD Malin Nygren-Bonnier

Karolinska Institutet

Department of Neurobiology,

Care Sciences and Society

Division of Physiotherapy

*Examination Board:*

Associate Prof. Bengt Midgren

Lund Hospital of Lund

Department of Respiratory Medicine and  
Allergology

Associate Prof. Per Gustafsson

Sahlgrenska Academy

Gothenburg University, Gothenburg

Department of Pediatrics Central Hospital  
Skövde

Associate Prof. Mari Lundberg

Karolinska Institutet

Department of Neurobiology,

Care Sciences and Society

Division of Physiotherapy



To all patients with CF



## ABSTRACT

**Background:** Cystic fibrosis (CF) is the most common life shortening autosomal recessive inherited disease affecting Caucasian people. The two main clinical characteristics of CF are progressive pulmonary disease and pancreatic insufficiency. The goal of airway clearance technique (ACT) is to improve ventilation and mucociliary clearance. The overall purpose of this thesis was to evaluate and compare the effects of Non Invasive Ventilation (NIV) and positive expiratory pressure (PEP) on airway clearance, and to find out if the use of NIV during an exercise test would reduce carbon dioxide (CO<sub>2</sub>) retention compared to oxygen (O<sub>2</sub>) supplementation. To explore at what point after ACT spirometry should be performed, and to determine whether there are interindividual and intraindividual differences, were also studied. To describe the patients' experiences of using NIV as an adjunct to ACT was also a purpose. *Paper I*, a prospective study. Twenty-four patients with CF. In adult patients, mean forced expiratory volume in one second (FEV<sub>1</sub>) improved 30 min (p=0.001), 1 h (p=0.002), and 2 h (p=0.006) after physiotherapy compared to baseline; in pediatrics it improved after the session (n.s.). There were no intraindividual variations but interindividual differences were found. *Paper II*, a prospective randomized study. Thirty-two patients with CF completed a 3 month long randomized trial comparing NIV with standard PEP. There was a significant reduction in lung clearance index (LCI) following NIV compared with PEP (p=0.01). *Paper III*, a qualitative study. Eighteen patients with CF were interviewed about their experiences using NIV during chest physiotherapy. Semi-structured interviews were conducted and analyzed using qualitative content analysis. "Becoming friends with NIV" emerged as a theme and came to represent a learning process. To facilitate this learning process, different factors should be taken into account until NIV is experienced as meaningful. *Paper IV*, a prospective crossover study, compared O<sub>2</sub> supplementation and NIV during an exercise test. Eight patients with CF completed an incremental test on a treadmill (using the Bruce protocol) while comparing standard treatment O<sub>2</sub> with NIV. NIV showed a decreased rise in transcutaneous pressure of carbon dioxide (tcPCO<sub>2</sub>), maintaining the level within the normal reference values compared to O<sub>2</sub> (p=0.01).

**Conclusion:** The point at which to perform a lung function test after an ACT is different for adults and children. NIV has shown to be as effective as other ACTs. Exercise tests showed tcPCO<sub>2</sub> remaining within the normal reference values with NIV but not with PEP. All participants completed the NIV treatment without major discomfort and experienced NIV as meaningful after becoming friendly with the NIV.





## **LIST OF SCIENTIFIC PAPERS**

- I. Rodriguez Hortal, MC, Hjelte L. Time point to perform lung function tests evaluating the effects of an airway clearance therapy session in cystic fibrosis. *Respir Care*. 2014 Oct;59(10):1537-41.
  
- II. Rodriguez Hortal MC, Nygren Bonnier M, Hjelte L. Non invasive ventilation as airway clearance technique in cystic fibrosis. *Physiother Res Int*. 2016 Feb 29.
  
- III. Rodriguez Hortal, MC, Hedborg, A, Biguet, G, Nygren-Bonnier, M. Experience of using non-invasive ventilation as an adjunct to airway clearance technique in adults with cystic fibrosis – a qualitative study. *Physiotherapy theory and practice*. Pending revision.
  
- IV. Rodriguez Hortal, MC, Hjelte, L, Nygren-Bonnier, M. Non invasive ventilation (NIV) compared to oxygen supplementation during an incremental test in adults patients with cystic fibrosis. Manuscript.

# CONTENTS

<b>1. INTRODUCTION</b> .....	9
1.1 HISTORY AND EPIDEMIOLOGY.....	9
1.2 GENETICS AND PATHOGENESIS.....	9
1.3 PATHOPHYSIOLOGY.....	10
1.3.1 Respiratory System.....	10
1.3.2 Hematopoietic System.....	12
1.3.3 Gastrointestinal System.....	12
1.3.4 Endocrine System.....	13
1.3.5 Sweat Glands.....	14
1.3.6 Reproductive System.....	14
1.4 DIAGNOSIS.....	14
1.5 TREATMENT.....	15
1.5.1 Medical treatment.....	15
1.5.2 Nutrition.....	15
1.5.3 Physiotherapy and airway clearance technique.....	16
1.5.4 Noninvasive ventilation.....	18
1.6 OUTCOME.....	19
1.6.1 Lung function test.....	19
1.6.2 Single and multiple breath washout.....	19
1.7 RATIONALE BEHIND THE THESIS.....	20
<b>2. AIM</b> .....	21
<b>3. MATERIAL AND METHODS</b> .....	22
3.1 STUDY POPULATION AND DESIGN.....	22
3.2 PROCEDURE.....	23
3.3 MEASUREMENTS.....	24
3.3.1 Lung function test: spirometry and multiple breath washout.....	24
3.3.2 Exercise testing and physical function: Six minute walk test and Bruce protocol.....	25
3.3.3 Qualitative content analysis.....	25
3.3.4 Other measurements.....	26
3.4 STATISTICAL ANALYSES.....	26
3.5 QUALITATIVE ANALYSES.....	26
3.6 ETHICAL APPROVAL.....	27
<b>4. RESULTS</b> .....	28
4.1 PULMONARY FUNCTION.....	28
4.2 EXPERIENCE OF USING NIV.....	30
4.3 OTHER RESULTS.....	32
<b>5. DISCUSSION</b> .....	34
5.1 FINDINGS.....	34
5.2 METHODOLOGICAL CONSIDERATION.....	38
5.3 CLINICAL IMPLICATIONS.....	41

5.4 FUTURE STUDIES.....	42
<b>6. CONCLUSION.....</b>	<b>44</b>
<b>7. ACKNOWLEDGMENTS.....</b>	<b>45</b>
<b>8. REFERENCES.....</b>	<b>46</b>

## LIST OF ABBREVIATIONS

ACBT	Active Cycle of Breathing Technique
ACT	Airway Clearance Technique
AD	Autogenic Drainage
ASL	Airway Surface Liquid
cAMP	Cyclic Adenosine Monophosphate
CEV	Cumulative Expired Volume
CF	Cystic Fibrosis
CFRD	Cystic Fibrosis Related Diabetes
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
Cl <sup>-</sup>	Chloride
COPD	Chronic Obstructive Pulmonary Disease
DH	Dynamic Hyperinflation
DIOS	Distal Intestinal Obstruction Syndrome
DNA	Deoxyribonucleic Acid
EELV	End-expiratory Lung Volume
FET	Forced Expiratory Technique
FEV <sub>1</sub>	Forced Expiratory Volume in one second
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
HFCC	High Frequency Chest Compression
hPEP	High Positive Expiratory Pressure
ICM	Intestinal Current Measurements
LCI	Lung Clearance Index
MBW	Multiple Breath Washout
Na <sup>+</sup>	Sodium
NaCl	Sodium Chloride

NPD	Nasal Potential Difference
N <sub>2</sub>	Nitrogen
NIV	Non Invasive Ventilation
O <sub>2</sub>	Oxygen
PEEPi	Intrinsic Positive End-Expiratory Pressure
PEF	Peak Expiratory Flow
PEP	Positive Expiratory Pressure
PIF	Peak Inspiratory Flow
RV	Residual Volume
SBW	Single Breath Washout
SpO <sub>2</sub>	Peripheral Oxygen Saturation
TI	Inspiratory Time
tcCO <sub>2</sub>	Transcutaneous Pressure of Carbon Dioxide
TLC	Total Lung Capacity
VC	Vital Capacity
VT	Tidal Volume
WOB	Work of Breathing



# **1 INTRODUCTION**

Chest physiotherapy is considered a basis of care for patients with CF. The clinical picture of CF has changed over time with an increased life expectancy and increased expectations of people with CF to have a normal life. The strategies used in physiotherapy for CF have also changed dramatically over the years, moving from postural drainage and percussion toward an individualized regimen. The physiotherapist's main purpose in helping patients with CF is to manage the symptoms and progression of their condition. The daily treatment burden is still challenging.

## **1.1 HISTORY AND EPIDEMIOLOGY**

Cystic fibrosis is the most common inherited autosomal recessive life shortening disease today (1). In the late 1800s, it was referenced in a poem as “the child will soon die whose brow tastes salty when kissed”. Fanconi was the first to describe the disease in 1936, listing symptoms displaying in the pancreas and lungs, while in 1938 Andersen first mentioned cystic fibrosis of the pancreas (1, 2).

In 1948, Paul di Sant' Agnese identified an excess of sodium and chloride in the sweat of patients with CF (3), a finding which became the basis for the sweat test (4). In 1985, the gene was localized to chromosome 7. The gene was cloned in 1989 and the protein identified as the cystic fibrosis transmembrane conductance regulator (CFTR) (5). Defects in the CFTR affects ion transport in epithelial cells in the airways, sweat ducts, pancreatic ducts, intestines, biliary tree and vas deferens (6).

In Sweden, the incidence of CF is 1/5600 live-births. Of the CF population alive in 1999, 45 % were over 18 years of age. Of those born in 1991, 95 % were estimated to survive their 25th birthday (7). 614 patients were registered in the annual Swedish report in 2013, of which 64 % were adults (8).

## **1.2 GENETICS AND PATHOGENESIS**

The gene affected is located on chromosome 7, which encodes the cystic fibrosis transmembrane conductance regulator (CFTR). The CFTR corresponds to a cyclic adenosine monophosphate (cAMP) regulated chloride channel that is found in the secretory epithelial cells (9).

The major mutation is called F508del and accounts for 70 % of the disease alleles. More than 1,900 mutations have been discovered in the CF gene. Different mutations are associated with

different disease symptoms. Genotype phenotype correlation is highest for the pancreatic status. Some mutations in the CF gene do not cause any of the symptoms associated with CF (10).

A total of 306 mutations have been annotated on the CFTR2 website (11):

- CF-causing: 272
- Mutations of varying clinical consequence: 19
- Non-CF-causing: 12
- Mutations of unknown significance: 3

Many of these mutations can be divided into five classes depending on their demonstrated molecular consequences (12). Affected patients will have two copies of the mutant CFTR gene, one inherited from each parent. The normal CFTR gene is part of a family of proteins that share transmembrane transport functions. CFTR regulates the activity of chloride and sodium channels at the cell surface as well as other apical membrane channels related to ion transport (5).

### **1.3 PATHOPHYSIOLOGY**

The level of clinical complications in patients with CF is largely determined by the associated class of mutation (13).

#### **1.3.1 Respiratory System**

The hydration of the airway surface layer (ASL) fluid in the airways is regulated by the ion channels that control the amount of salt and water on the airway surfaces. The epithelia is capable of both absorbing fluid and secreting fluid, depending on the direction of the salt transport across airway epithelia. As the concentration of sodium chloride (NaCl) inside the ASL is essentially isotonic, knowing the overall amount of NaCl in the ASL is essential for determining the total fluid volume of the ASL (14).

The gene that encodes CFTR is associated with reduced chloride (Cl<sup>-</sup>) secretion and increased sodium (Na<sup>+</sup>) reabsorption, which results in reduced water content of the secretions. The periciliary liquid of the secretions is isotonic with an osmolarity that allows water to reabsorb with Na<sup>+</sup> from the lumen. This leads to reduced depth and increased viscosity of the periciliary liquid, which in turn results in a slower airway clearance and the trapping of inhaled bacteria in the thick secretion (15).

The bronchial glands consist of mucous cells (secrete mucins) and serous cells (secrete antibacterials such as lysozyme and other substances). The volume of the glands and secretory



cells are increased in CF patients. Healthy people normally produce more than 10 mL of mucus per day, which serves as a defense and protection of the lower respiratory tract (16).

The plasma exudation in CF patients is associated with decreased mucociliary transport as well as mucus plugs. The airflow obstruction arising due to retained secretions increases the work of breathing (WOB), produces ventilation-perfusion mismatch, and results in gas exchange abnormalities. Additionally, secretions retained in the airway can serve as a source of infection and inflammation. Between the production of mucus and its clearance exists an important balance that have to work perfectly in order to avoid the progression of this disease (17).

(Figure 1).

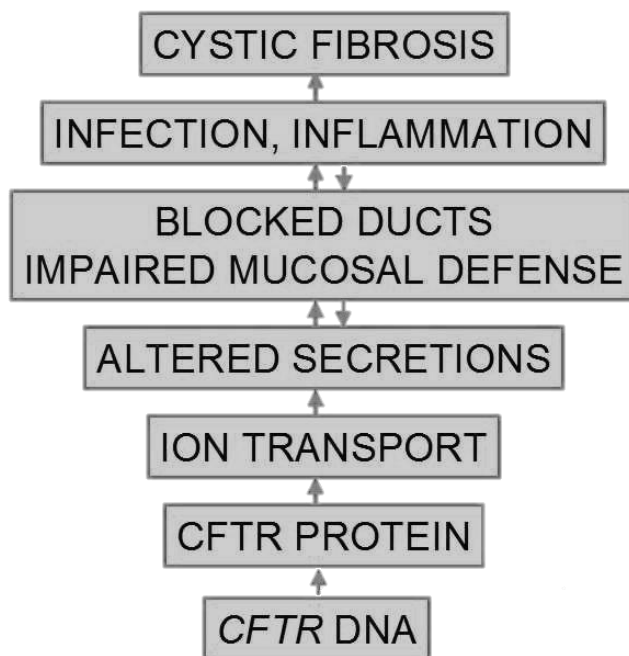


Figure 1. Pathophysiology of the CF disease

If the balance between production and clearance of secretion does not work properly, patients with CF may experience bacterial infection. *Pseudomonas aeruginosa* remains the main pathogen in adults, but other bacteria such as *Staphylococcus aureus* and *Haemophilus influenzae* have also been shown to play an important role in the lung disease. Nasal polyps are common in CF and are probably a consequence of chronic inflammation; however, their specific etiology is unclear. In patients with CF, sinonasal involvement can exacerbate lung disease, the upper airways serving as a bacterial reservoir. The decline in the amount of CFTR to bind with the bacteria contributes to the bacterial loads in the lungs (18).

As the inflammation and mucus obstruction of the airways increase, it becomes more difficult for air to pass through, leading to expansion of the alveoli and air trapping. The destruction of the pulmonary parenchyma due to chronic bacterial infection with mucus retention results in increased pulmonary arterial pressure and right-sided heart failure or cor pulmonale. The pulmonary inflammation persists and eventually becomes chronic, causing hypertrophy of the bronchial arteries and ultimately hemoptysis (13).

As the disease progresses, the FEV<sub>1</sub> decreases, and the WOB and respiratory muscle load increase. As a result, patients with CF develop a compensatory mechanism of a rapid shallow breathing pattern in an attempt to reduce this increase in load. This breathing strategy may maintain the level of minute ventilation, but alveolar hypoventilation, characterized by hypercapnia and hypoxemia, may also develop (19). The most severe respiratory signs and symptoms are due to the production of increased levels of thickened mucus that cause inflammation and obstruction of the airways (13).

Cystic fibrosis is associated with a substantial variability in phenotype (clinical picture), from severe with early lung disease to mild form (20, 21). It is described as a progressive lung obstructive disease with chronic inflammation and infections that results in tissue destruction. The end-stage of the disease is characterized by respiratory failure with severe hypoxia, pulmonary hypertension and secondary cardiac complications (22).

### **1.3.2 Hematopoietic System**

The hematopoietic system is also affected in patients with CF, characterized by iron deficiency anemia generally, and as a result of chronic hemoptysis in some cases. *Pseudomonas aeruginosa* is a common bacteria that colonizes the lungs and/or upper airways and robs iron from the host for growth purposes (13).

Iron deficiency has been reported in one third of all patients with CF. Data suggests that iron absorption is increased with exocrine pancreatic deficiency and that administration of pancreatic enzymes may impair oral iron absorption (23).

### **1.3.3 Gastrointestinal System**

There have also been findings of gastrointestinal problems in patients affected with CF, this due to the inability of the pancreas to supply digestive enzymes to the intestine. As the volume of

secreted pancreatic enzymes decreases, the pancreas secretes thick mucus that obstructs the pancreatic ducts and in such a way further shrinks the volume of enzymes that can be secreted. This situation leads to malabsorption of fat and affects absorption of the fat-soluble vitamins A, D, E, and K (24). The distal part of the CF patient's intestine may dilate and fill with fecal content. The condition manifests itself as vomiting, abdominal distention, anorexia, pain in the right lower quadrant of the abdomen, and cramping with a decrease or no change in bowel movements. The name for this condition is distal intestinal obstruction syndrome (DIOS) and is a result of deficient secretion of salt and water from the intestinal epithelium leading to dehydration of the intestinal material (25).

Some patients also present gastroesophageal reflux disease due to hypersecretion of gastric acid and hyposecretion of bicarbonate. The presence of gastroesophageal reflux disease may additionally aggravate bronchial reactivity (13). Gastroesophageal reflux has also been known to worsen respiratory symptoms (26).

Even though hepatobiliary disease is the most common non-pulmonary cause of mortality in CF, only about 33 % of CF patients present clinically significant hepatobiliary disease. The abnormal activity or absence of CFTR decreases bile fluidity, causing accumulation and precipitation of hyperviscous biliary secretions in the intrahepatic tree. Bile accumulates in the biliary ducts leading to cholangiocyte and hepatocyte injury, stimulating focal fibrosis. This in turn results in the accumulation of toxic bile acids in the liver, depletion of hepatic antioxidants, and liver cell injury. Repeated liver cell injury may activate hepatic stellate cells and lead to hepatic fibrosis and in some cases cirrhosis. Liver transplantation is restricted to patients with difficult complications of portal hypertension and/or end-stage liver failure in good nutritional state (27). Modern treatment may have had a positive influence on liver disease, seeing as how it has become less common and progressive as time has gone by (28).

#### **1.3.4 Endocrine System**

Cystic fibrosis–related diabetes (CFRD) is the most common comorbidity in CF, occurring in 20 % of adolescents and 40–50 % of adults (29). The main cause of CFRD is a reduced insulin secretion capacity combined with a variable state of insulin resistance (30). The patients displaying cystic fibrosis–related diabetes still require a high-energy diet. The glucose metabolism is affected by many factors specific to CF, like severe dehydration, administration of corticosteroids, malabsorption, chronic infection, poor nutrition, increased energy expenditure, slowed gastrointestinal transit time, and liver dysfunction (13).

### **1.3.5 Sweat Glands**

Due to the decreased functional levels of the protein CFTR, which regulates the salt content in sweat, patients with CF may experience excessive salt loss from intense heat or after extreme physical exercise (13).

### **1.3.6 Reproductive System**

Puberty is delayed in both men and women (13). Most of the men with CF are sterile due to lacking or having malformed vas deferens. However, their sperm production is normal. Advances in the field of reproductive medicine has allowed for the procurement of viable sperm and facilitated fertilization and pregnancy in CF patients (31).

Women with CF are fertile but often require more time to become pregnant. Mucus plugs in the oviduct and thicker cervical mucus result in decreased sperm movement. Although women with CF thus have reduced fertility, many of them can become mothers spontaneously (32).

## **1.4 DIAGNOSIS**

The measurement of sweat electrolyte concentrations has been the mainstay of diagnosing CF since a standardized procedure, known as the Gibson-Cooke method, was established in 1959 (4). A CF diagnosis can be made if the sweat  $\text{Cl}^-$  value is  $\geq 60$  mmol/L and the subject shows symptoms consistent with CF. A sweat  $\text{Cl}^-$  value of  $\leq 40$  mmol/L is likely to be within the normal range, and CF is considered to be unlikely though not excluded. Intermediate levels between 30 and 60 mmol/L may be associated with atypical forms of CF and should undergo extensive CFTR mutation analysis (i.e., expanded panel of CFTR mutations, evaluation for deletions or gene sequencing) (33-35). Cystic fibrosis diagnosis is made on the basis of two positive sweat tests – or a positive mutational analysis - and either a sibling or first cousin with CF, pancreatic insufficiency or lung disease, i.e. symptoms consistent with CF (33).

There are other tests used in diagnosing CF, such as nasal potential difference (NPD) analyses which provide a direct and sensitive evaluation of sodium  $\text{Na}^+$  and chloride  $\text{Cl}^-$  transport in nasal epithelial cells by assessing their bioelectric properties. Intestinal current measurements (ICM) can be used in similar ways. Rectal biopsies are used where the CFTR protein is highly expressed in the apical membrane of intestinal epithelial cells (36).

## **1.5 TREATMENT**

The three pillars of treatment are: antibiotic therapy, nutrition and airway clearance. A multidisciplinary team should work together to provide the best care to this group of patients; the care should be centralized (37).

### **1.5.1 Medical treatment**

The eradication of bacteria should be the main goal until chronic colonization has been established. When the patient has become chronically colonized, they are treated with antibiotics “on demand”, i.e. in case of slight symptoms of deterioration. Most of the antibiotics are administered intravenously. However, aerosol antibiotics have been introduced and allow the patient to achieve a high-level antibiotic concentration in the lower airways, minimizing the systemic effects (38). In order to reduce the number of hospital admissions, home intravenous antibiotic treatment was introduced in Sweden as early as 1985, enabling most patients to work or attend school while receiving the antibiotics (39).

### **1.5.2 Nutrition**

The treatment of pancreatic insufficiency with pancreatic enzyme supplementation is necessary in patients with CF who have a pancreatic insufficiency, i.e. around 85 %. Fat malabsorption leads to less absorption of the fat-soluble vitamins. Vitamins A, D, E and K should be supplemented. Patients with CF also show disturbances in their lipid metabolism, leading to low levels of essential fatty acids (40, 41). Nutritional supplements have been advocated in malnourished CF patients. Attempts to improve the nutritional status of affected children have included caloric supplements and enteral feeding, usually with elemental formulas. Aggressive nutritional therapy in CF is based on the premise that it improves pulmonary functions (42).

Nutritional supplementation is an ongoing necessity due to the patients' abnormal enterohepatic circulation of bile, increased metabolism and increased caloric demand due to severe lung disease (38). Additionally, requirements are elevated because of increased losses due to malabsorption, nitrogen losses in the feces and sputum, and a potentially altered protein metabolism (43).

### **1.5.3 Physiotherapy and airway clearance technique**

The world confederation for physical therapy (WCPT) defines physical therapists as people specialized in the developing, maintaining and restoring of people's functional abilities and ability to move throughout their entire lifespan (44). Chest physiotherapy is a treatment where the goal is to improve breathing by the indirect removal of mucus, something which is urgent in CF patients. The role of the physiotherapist working with patients with chronic lung diseases is to relieve symptoms through ACTs and preserve their physical condition and lung function through different physical training exercises (45). Chest physiotherapy has for a long time played an important role in assisting in the clearance of airway secretions and is usually commenced as soon as a CF diagnosis has been made. However, chest physiotherapy may be unpleasant, uncomfortable, and time-consuming. Early chest physiotherapy relied on techniques which required the assistance of another person, such as a physiotherapist or relative, and which included postural drainage, percussion, vibration, and shaking performed by the assistant as well as, and huffing or coughing. More recently, several self-administered alternatives to these conventional techniques have been developed. These include the active cycle of breathing techniques (ACBT), forced expiration technique (FET), autogenic drainage (AD), positive expiratory pressure (PEP), flutter, high frequency chest compression (HFCC) and exercise. Conventional chest physiotherapy includes any combination of the following: postural drainage, percussion, chest shaking, huffing, and directed coughing (46).

The airways of CF patients are plugged with a thick and sticky mucus. Therefore, clearance of secretions plays a prominent role in early therapy during the onset of the disease. Airway clearance techniques in combination with inhalation of mucolytic agents are necessary as a daily treatment. The technique is taught as soon as the diagnosis has been confirmed and is thereafter continuously evaluated. The treatment is performed twice a day, lasting from 45 minutes to one hour. Inhalation therapy has shown to improve sputum clearance. The sticky properties of the mucus are identified by different components, including free DNA, polymerized actin, and the mucins themselves, all of which are highly viscous. Cleaving free DNA into smaller pieces reduces its viscosity. Recombinant DNA technology has made it possible to produce human DNase (Pulmozyme®), a new drug developed specifically for CF which gives minimal adverse effects and gives rise to an improvement in pulmonary function and reduction in the number of exacerbations (47). Aerosol hypertonic saline solution has been shown to result in a modest increase in pulmonary function and reduction in exacerbations as

well, presumably by temporarily drawing water into the airway to dislodge the mucus (48). Some other nebulized or orally given mucolytics agents, such as thiol derivatives (Ambroxol and N-acetylcysteine), have also been used, but there is no evidence for recommending the use of either in patients with CF (49). However, oral N-acetylcysteine has shown to maintain lung function in patients with CF (50).

The airway lumen is affected in CF not only by secretions but also by airway edema, smooth muscle hypertrophy, and bronchoconstriction. The use of inhaled steroids, though never proven effective in CF in controlled clinical trials, may reduce airway edema. Bronchodilators such as  $\beta$ -adrenergic agonists, intended to relax airway smooth muscle, are administered mainly before hypertonic saline, though not all patients have responded to them in direct testing and some patients have actually shown paradoxical decreases in pulmonary function (probably because the airway wall had already been sufficiently damaged) (38).

The International Physiotherapy Group for Cystic Fibrosis (IPG/CF) (51) describes several different ACTs, all of which have been proven to be effective. Healthier patients with CF can augment mucus clearance with aerobic exercise, which stimulates deep breathing and cough (52). Positive expiratory pressure (PEP) is defined as breathing with a positive expiratory pressure of 10 to 25 cm H<sub>2</sub>O. High pressure PEP (hPEP) is a modification of the above PEP technique which includes a full forced expiration against a fixed mechanical expiratory resistance (53). Active cycle of breathing techniques (ACBT) include relaxation or breathing control, FET, thoracic expansion exercises and may also include postural drainage or chest clapping (54). Autogenic Drainage (AD) is another technique whereby the mucus is moved by airflow in different parts of the airways (55). Physical exercise increases the tidal volume (VT) with deeper breath and in this way improves the mucus clearance (46). Oscillating devices including flutter or cornet produce an oscillatory PEP effect. The thoracic oscillation provides oscillation to the chest wall (46).

The key to any device used to clear secretions is that it meets the criterion based on respiratory physiology. This criterion states: increase absolute peak expiratory flow (PEF) to move secretions towards the oropharynx. Mucus transport can be achieved by expiratory airflow during forced expiration, as well as tidal breathing. The peak expiratory flow/peak inspiratory flow ratio (PEF/PIF) needs to be 41.1 to clear secretions (56).

Airway clearance has been shown to hold short-term effects for patients with CF, but the long-term effects of no airway clearance remain unknown. However, the absence of evidence does

not necessarily imply the absence of benefit (57). Conventional chest physiotherapy is as effective as other forms of airway clearance. Patients like their independence, and therefore any technique, which they themselves can use - such as PEP - is preferred. There is not enough evidence to conclude, one way or the other, that any ACT is better or worse than any other technique (58).

#### **1.5.4 Noninvasive ventilation**

Recent years have shown NIV, as an adjunct to ACT, to help patients to clear sputum more easily than other ACTs. This remains especially true for those patients who are very ill and have difficulties expectorating sputum (58-61).

Positive pressure ventilatory assistance can be delivered in the form of inspiratory pressure support (pressure pre-set) systems, which deliver a variable volume according to a pre-set inspiratory pressure. Alternatively, a set VT (volume pre-set) system may be used, which delivers a fixed VT irrespective of the airway pressure required to generate this volume. The earliest NIV trials employed volume pre-set equipment. However, later trials have used pressure pre-set devices, primarily due to their simplicity and the comfort of the individual. The NIV machines entrain room air and allows for additional oxygen to be entrained into the ventilatory tubing, or directly into the mask (59).

The purposes of ventilation include: correct hypoxaemia and hypercapnia (type II respiratory failure), improve tidal volumes, decrease fatigue and the WOB, and treat nocturnal hypoventilation. Non invasive ventilation has been used for patients with CF since the early 1990s, when it was described as a holding treatment for patients on the transplant waiting list. Non invasive ventilation is still occasionally used as a 'bridge to transplant', but there are many other indications such as an adjunct to airway clearance therapy in CF (62). The use of NIV reduces hypoventilation and improves gas exchange by increasing minute ventilation and reducing the WOB. Clinically, NIV has also been used as an adjunct to ACTs in CF patients with moderate to severe disease. The exact mechanism by which NIV may assist airway clearance is still unclear. It has been postulated that decreased respiratory muscle fatigue and prevention of airway closure during prolonged expirations may ultimately lead to an increase in effective alveolar ventilation, better compliance with airway clearance and increased sputum clearance (63).

Many CF patients show increased energy expenditure, oxygen desaturation, fatigue and dyspnoea during chest physiotherapy. Since NIV reduces respiratory muscle work and prevents



respiratory muscle fatigue, it could thus be considered a good alternative for very ill patients who need the extra support during airway clearance (63, 64). In several studies, participants reported greater ease of expectoration, less breathlessness and less fatigue when standard chest physiotherapy treatment was assisted by NIV. Additionally, participants reported that they preferred treatment with NIV compared to standard chest physiotherapy (64, 65).

The improvements in breathlessness, fatigue and ease of expectoration may be at least partly explained by the preservation of respiratory muscle strength during NIV-assisted treatment compared to standard chest physiotherapy. This effect on respiratory muscle strength suggests that patients with CF may be able to perform airway clearance manoeuvres with less effort and/or tolerate more effective ACTs with the support of NIV, especially when it is most required during an acute exacerbation (63, 64, 66, 67).

## **1.6 OUTCOME**

Pulmonary function and exercise capacity are two outcomes to be considered with regards to the survival chances of CF patients (68). Also used are additional surrogate endpoints of lung disease, as for example chest computed tomography (69).

### **1.6.1 Lung function test**

Pulmonary function testing is a method that helps in establishing data that assists in predicting deterioration in clinical status in patients with CF.

The most common outcome measure used by physiotherapists to monitor their interventions and evaluate their practice is FEV<sub>1</sub>. The pulmonary function test most commonly performed to assess respiratory physiotherapy interventions is the forced spirometry, the volume and/or flow of air that can be inhaled and exhaled as a function of time. The procedure consists of maximal inspiration followed by a complete exhalation. First, the patient should exhale until he or she reaches the functional residual capacity (FRC), after which they should be instructed to inhale rapidly and completely. The mouthpiece should be placed in the patient's mouth and indications should be given for the patient to blow as much and as fast as possible and to keep blowing until the lungs have been totally emptied. Spirometry is a cost-effective, simple, reliable, valid and easy to interpret measure. The most commonly used pulmonary function parameter is the FEV<sub>1</sub>, followed by forced vital capacity (FVC) and ratio between FEV<sub>1</sub>/FVC. Measurements are taken considering the patient's gender, age, height, weight and race and are then compared against predicted values (70).

### **1.6.2 Single and multiple breath washout**

There are some pulmonary tests that are more sensitive than forced spirometry, such as single (SBWO) and multiple breath washout (MBWO). A nitrogen washout can be performed with a single nitrogen breath, or multiple ones. Both tests can estimate FRC and the degree of nonuniformity of gas distribution in the lungs, but the multiple breath test more accurately measures absolute lung volumes (71, 72).

Single breath washout and MBW assess ventilation distribution inhomogeneity at differing lung volumes. The most widely used is the nitrogen (N<sub>2</sub>) SBW test, which involves a vital capacity (VC) manoeuvre performed at low constant flow (400–500 mLs<sup>-1</sup>): exhalation to residual volume (RV), inhalation of 100 % oxygen gas (O<sub>2</sub>) to total lung capacity (TLC), then washout during exhalation from TLC to RV, where phase III is measured over the mid portion of the expirogram (73).

Multiple breath washout assesses ventilation distribution inhomogeneity during tidal breathing from FRC, by examining inert gas clearance over a series of breaths. Exogenous gas washout requires an initial wash-in phase. Multiple breath washout requires only passive cooperation and minimal coordination, but is more time consuming. The lung clearance index (LCI) is the most commonly reported MBW index, and is defined as the number of FRC lung turnovers required to reduce alveolar tracer-gas concentration to a given fraction of its starting concentration, 1/40 (2.5 %). LCI is calculated as the ratio of cumulative expired volume (CEV) to FRC, with CEV defined as the sum of all expiratory VT over the washout.  $LCI = CEV / FRC$  (73).

## **1.7 RATIONALE BEHIND THE THESIS**

Patients with CF need to undergo airway clearance therapy twice a day. Frequently they also need to take part in physical exercise in order to maintain their lung function. Both airway clearance therapy and physical exercise has to be performed more often as the patients deteriorate. As the disease progresses and lung function declines, the ACT increases energy expenditure, fatigue and dyspnea in the patient. Non invasive ventilation could therefore be beneficial to severely ill patients during airway clearance therapy. It is important to study the effects of NIV as an adjunct to ACT and a tool used during exercise in severely ill CF patients in order to individualize the treatment. To our knowledge, no studies have so far investigated the effects of NIV as an adjunct to ACT using high-pressure ventilation, the CF patients' experience with NIV treatment nor how NIV assisted exercise displays in CF patients.

## 2 AIM

The overall purpose of this thesis was to evaluate the use of NIV as an airway clearance treatment compared to PEP, and as ventilatory support during exercise in people with CF. Additionally, we sought to explore at what point after physiotherapy spirometry should be performed. Yet another objective was to evaluate the experience of using NIV as an adjunct to ACT.

The specific goals were to:

- Identify at what time point after a physiotherapy session spirometry should be performed in order to obtain the highest result compared to baseline, and to determine if there are interindividual and intraindividual differences in children and adults with CF. (Study I)
- Evaluate and compare the effects of NIV and PEP on airway clearance. (Study II)
- Describe adult patients' views on and experiences of using NIV as an adjunct to ACT. (Study III)
- Find out if the use of NIV during an exercise test would reduce CO<sub>2</sub> retention when compared to O<sub>2</sub> supplementation in subjects with CF. (Study IV)

### 3 MATERIAL AND METHODS

#### 3.1 STUDY POPULATION AND DESIGN

Study I was a prospective study. The criterion for inclusion was a confirmed diagnosis of CF. The exclusion criteria consisted of upper airway infection, cognitive dysfunction, the presence of nasal polyps, associated asthma, a proven inability to perform a technically acceptable lung function test and inability to stay at the clinic for the required four hours. Patients were included consecutively, drawn from the out-patient clinic at the Stockholm CF Center. Of the 28 patients screened, 24 were enrolled in the study. Of the 24 patients included, 16 were adults (mean age  $32\pm 9$  years) and 8 were children (mean age  $15\pm 2$  years).

Study II was a prospective randomized study with a control group (PEP treatment). The inclusion criteria were patients with CF at Stockholm CF Centre, over 18 years of age and with a FEV<sub>1</sub> between 20 % and 69 % of the predicted value. The exclusion criteria were the presence of a symptomatic upper airway infection, cognitive dysfunction, cardiorespiratory instability, infection with *Burkholderia cepacia complex*, gastroesophageal reflux, a history of pneumothorax or massive haemoptysis. Out of the 45 patients who met the inclusion criteria, 32 agreed to participate in the study. The mean age in the NIV group was 28 ( $\pm 11$ ) years and 33 ( $\pm 9$ ) years in the PEP group. The 13 patients who declined to participate did so because they lived too far away from the hospital.

Study III was a qualitative study applying content analysis with an inductive approach. The inclusion criteria were adults with CF being treated at Stockholm CF center, with a FEV<sub>1</sub> of 20-69 % of the predicted value or having undergone a lung transplant during the period 2012-11-01 to 2013-11-01, and adult patients who used NIV as an adjunct to ACT. The exclusion criteria were colonization of *Burkholderia cepacia* and/or Methicillin-resistant *Staphylococcus aureus* (MRSA) carriers and adults who did not master the Swedish language in speech and writing. Twenty-nine adults used NIV as an adjunct to ACT, 18 adults (aged between 20-54 years) met the inclusion criteria and agreed to participate in the study. Eleven adults who used NIV were not included for different reasons: either they did not master the Swedish language ( $n = 1$ ), were <18 years ( $n = 2$ ) or lived outside of Stockholm ( $n = 8$ ).

Study IV was a crossover study comparing NIV with O<sub>2</sub> treatment. The inclusion criteria were patients with CF at Stockholm CF center, over 18 years of age, with a FEV<sub>1</sub> between 20 and 69 % of the predicted value and who had developed alveolar hypoventilation during the physical

performance test and used oxygen supplementation during training. The exclusion criteria included the presence of a symptomatic upper airway infection characterized by fever less than one month before entering the study, cognitive dysfunction, cardio-respiratory instability, infection with *Burkholderia cepacia complex*, gastroesophageal reflux, a history of pneumothorax or massive hemoptysis. Of the 13 patients who met the inclusion criteria, 8 patients agreed to participate in the study. The mean age was 33 ( $\pm 12$ ) years. (Table 1).

Table 1. Baseline characteristics of the participants in Study I to IV.

	Study I (n=24)	Study II (n=32)	Study III (n=18)	Study IV (n=8)
Age (yrs)	26 ( $\pm 10$ )	31 ( $\pm 10$ )	34 ( $\pm 12$ )	33 ( $\pm 12$ )
Gender (male/female)	17/7	16/16	9/9	3/5
FEV <sub>1</sub> %	61 ( $\pm 30$ )	47 ( $\pm 14$ )	38 ( $\pm 9$ )	42 ( $\pm 10$ )
FVC %	70 ( $\pm 30$ )	69 ( $\pm 13$ )	63 ( $\pm 13$ )	56 ( $\pm 13$ )

FEV<sub>1</sub>: forced expiratory volume in one second. FVC: forced vital capacity.

### 3.2 PROCEDURE

Study I, the daily physiotherapy, performed by all patients, consisted of inhalation twice a day. The ACTs performed by all patients consisted of autogenic drainage, PEP and huffing maneuvers carried out in a seated position at the same time of day for two days. One physiotherapist supervised and conducted all the sessions and performed the measurements (FEV<sub>1</sub> and FVC).

In study II patients were randomized to NIV and performed their daily physiotherapy treatment with the help of bilevel PAP. The control group went through the same protocol but instead of using NIV they performed their treatment with the PEP mask. The daily physiotherapy treatment in both groups consisted of two sessions lasting 60 minutes twice a day for three months. It involved the following: inhalation, AD, huffing and NIV or PEP. NIV was administrated with a bilevel PAP device (Vivo 40, Breas, Sweden). One single physiotherapist

supervised and conducted all the monthly treatment sessions. The following tests were performed before and after the intervention: lung function test, 6-minute walk test, sputum samples, inflammatory markers (blood samples), blood gases, peripheral oxygen saturation (SpO<sub>2</sub>), heart rate and respiratory rate. Blind test leaders and nurses performed all measurements. The physiotherapist test leader instructed patients to perform the six-minute walk test and recorded the information.

Study III involved adults with CF being interviewed at Stockholm CF Center about their experiences of using NIV as an adjunct to ACT. Semi-structured interviews were conducted and analyzed in accordance with qualitative content analysis. One physiotherapist conducted the interviews and recorded the data; the interviews lasted between eight to twenty-eight minutes. A person not involved in the research group but familiar with the material transcribed the subsequent audio files.

In study IV patients were randomized to perform a maximal exercise test on a treadmill (Bruce protocol) with access to supplementary O<sub>2</sub> or NIV. After 30 minutes, they were asked to cross over to NIV or oxygen. The patients were instructed to walk on the treadmill with NIV or O<sub>2</sub> supplementation. The tests were performed on the same day with a 30 minute break (washout period) in between. The NIV device used was the same as in study II. A mask was used to administrate O<sub>2</sub> supplementation. Two physiotherapists supervised, recorded and conducted the following measurements before and after the tests: lung function test as FEV<sub>1</sub> and FVC, tcPCO<sub>2</sub>, BORG rating of perceived exertion (Borg RPE) scale, Rating of Perceived Dyspnea Scale (Borg CR-10), SpO<sub>2</sub>, respiratory rate and heart rate. Distance completed was also recorded.

### **3.3 MEASUREMENTS**

Participants were blinded to their own results throughout the whole studies.

#### **3.3.1 Lung function test: spirometry and multiple breath washout.**

In study I the lung function test was performed in a seated position at the same time of day in accordance with American Thoracic Society/ European Respiratory Society (ATS/ERS) recommendations (74). Patients performed spirometry with a portable microspirometer (MS01 Gold Standard MicroPlus, CareFusion, San Diego, California) before and immediately after their airway clearance session, as well as 30 min, 1, 2, and 3 h afterwards. Forced expiratory volume in one second and FVC were recorded as the best value out of three technically

satisfactory forced expirations. All patients performed the series of measurements on two consecutive days to identify intraindividual variations.

In study II the lung function tests included whole-body plethysmography (Sendormedics, Vmax Encore 22, USA). Static (measuring lung volume) and dynamic (measuring flow) spirometries were recorded as well, LCI obtained by MBWO nitrogen (N<sub>2</sub>). The tests were performed in accordance with American Thoracic Society guidelines (74). The technicians at the pulmonary laboratory were blinded to the physiotherapy treatment of the patients.

In study IV the lung function test was performed as in study I, before and after the test. Forced expiratory volume in one second and FVC were taken as the best value out of three technically satisfactory forced expirations. A portable microspirometer (MS01 Gold Standard MicroPlus, CareFusion, San Diego, California) was used.

### **3.3.2 Exercise testing and physical function: Six-minute walk test and Bruce protocol.**

In study II a six-minute walk test was performed in accordance with the ATS (75). Measurements taken before and after the tests measured: SpO<sub>2</sub>, Borg RPE, Borg CR-10, heart rate, all parameters recorded by the physiotherapists (76, 77).

Study IV saw the Bruce protocol test performed on a treadmill with NIV and O<sub>2</sub> supplementation. The test involved walking on a treadmill with incremental speed and gradient (78). Peripheral oxygen saturation, distance (meters), heart rate and respiratory rate were recorded before and after the test. The participants graded their perceived exertion using the Borg RPE and their dyspnea using the Borg CR-10 before and after the test.

### **3.3.3 Qualitative content analysis**

Study III covered semi-structured interviews with adult patients, conducted based on content analysis. Latent and manifest content analysis was used to analyze the data. The topics included in the interviews were: experiences of symptoms, physiotherapy treatment with NIV, attitude towards and motivation to perform the daily treatment with NIV, concerns about using NIV as a treatment as well as future treatment.

### **3.3.4 Other measurements**

Study II collected and analysed sputum cultures, blood samples for measuring arterialized capillary blood gases and inflammatory parameters, once a month.

Before each physiotherapy session, nurses blinded to the treatment of the patients measured and recorded the following: respiratory rate, heart rate and SpO<sub>2</sub> using a pulse oximeter and finger probe (Onyx vantage, Nonin, USA). Body mass index was also recorded.

Study IV measured SpO<sub>2</sub> and heart rate using a pulse oximeter with finger probe (Onyx vantage, Nonin, USA), and tcPCO<sub>2</sub> were measured and recorded during the test on the treadmill by a SenTec device (SenTec digital monitor V-Sign™ System, SenTec AG, Therwil, Switzerland) (79).

### **3.4 STATISTICAL ANALYSES**

The results of study I and II were presented as mean values with standard deviation (SD). The results of study IV were presented as median and range. In all studies the level of statistical significance was set at  $p < 0.05$ . Statistica software was used to analyse studies I and II, while study IV employed STATA.

Study I used The Student t-test to compare the paired data. Study II used ANOVA General lineal model (GLM) to make comparisons within and between the groups. Post hoc contrast was used due to the interaction between NIV and LCI being significant,  $p = 0.02$ . Study IV used the Wilcoxon signed-rank test.

### **3.5 QUALITATIVE ANALYSES**

Qualitative content analysis according to Graneheim and Lundman was chosen based on an inductive approach (80). The overall aim of the analysis was to build a model to describe the phenomenon in a conceptual form. In the present trial, both manifest and latent content meaning in the data was considered important enough to extract. Whereas manifest content means the encoding of the visible and obvious content of the text, latent content means encoding what the text talks about, the underlying meaning. Table 2 represents an example of the interpretive content analysis process from meaning unit to category.



Table 2. Example of data analysis.

Meaning unit	Condensed meaning unit	Code	Sub-category	Category
I would say that first you have to be open-minded, and you take over this first feeling that it is difficult (...) but if you go past the first moment, then you will see that it is effective. And then also to have patience, it is a boring advice. But be patient and deal with this as best you can.	Be open-minded. Be patient, and fight in the beginning of the treatment, you will see that the NIV is effective.	Be patient until the results	Tolerance before the habit	Finding the rhythm

### **3.6 ETHICAL APPROVAL**

The regional research ethics committee in Stockholm approved the studies. All participants gave their informed consent to participate. All measurements and techniques used in the different studies were already part of the existing CF treatment.

The purpose of this research was to evaluate the effects of different treatments and identify which one is the most beneficial for each individual.

The principles for medical research involving human patients were considered before, during and after the clinical trials in order to promote respect for and protect all participants' health and rights (81).

## 4 RESULTS

### 4.1 PULMONARY FUNCTION

Study I, showed that the mean FEV<sub>1</sub> in adult patients increased after each physiotherapy session, the statistically significant difference was found at 30 min (p< 0.001), 1 h (p<0.002), and 2 h (p<0,006) following physiotherapy in comparison to baseline. The mean FVC increased and was statistically significant at 30 min (p<0.02) and 2 h (p<0.04) following physiotherapy.

The mean FEV<sub>1</sub> in adult patients increased by 7 % compared to baseline (30 min after physiotherapy). In comparison to baseline, the highest by which the FVC mean was increased was 10 % (30 min after physiotherapy). The mean FEV<sub>1</sub> and FVC in pediatric patients showed no statistically significant difference compared to baseline at any point, but there was a trend towards an increase immediately following physiotherapy. The mean increase in FEV<sub>1</sub> in pediatric patients was 1 % (immediately following physiotherapy) and 2 % for FVC (immediately following physiotherapy) compared to baseline.

The study identified an interindividual variation but no intraindividual; seven adults showed peak times after 30 minutes following chest physiotherapy whereas three children showed immediately after chest physiotherapy (figure 2 and 3. Table 3).

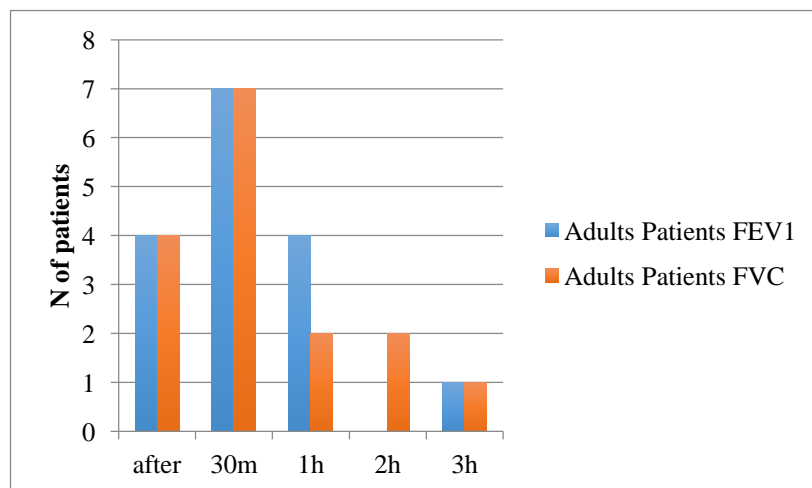


Fig 2: Number of patients peak-times. FEV<sub>1</sub> and FVC peak time adults. FEV<sub>1</sub>: forced expiratory volume in one second. FVC: forced vital capacity.

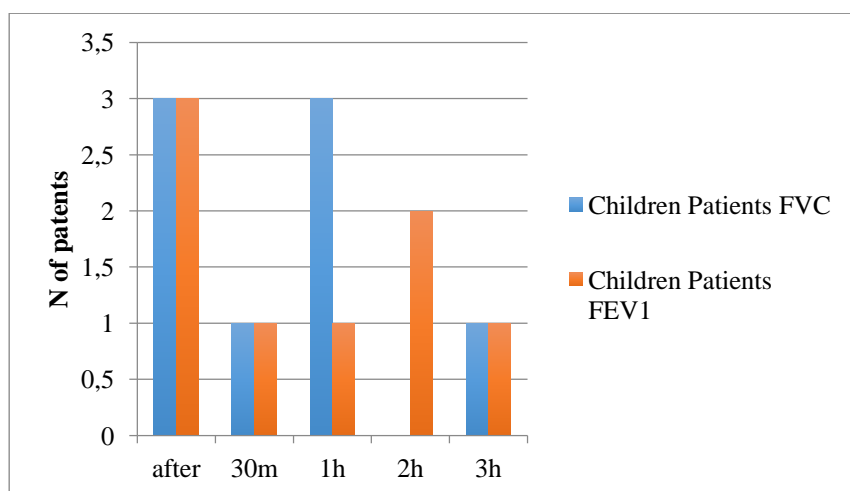


Fig 3: Number of patients peak-times. FEV<sub>1</sub> and FVC peak time children. FEV<sub>1</sub>: forced expiratory volume in one second. FVC: forced vital capacity.

Table 3. Spirometry values before and after chest physiotherapy.

	Adults	P Value	Children	p Value	Total	p Value
N	16		8		24	
FEV <sub>1</sub>	56±29		70±32		61±30	
FEV <sub>1</sub> after	58±30	.20	71±31	.69	63±30	.22
FEV <sub>1</sub> 30m	60±30	<b>&lt;.001</b>	66±32	.12	63±30	.33
FEV <sub>1</sub> 1 h	59±30	<b>&lt;.002</b>	64±30	.11	61±30	.95
FEV <sub>1</sub> 2 hrs	58±30	<b>&lt;.006</b>	68±32	.51	62±30	.26
FEV <sub>1</sub> 3 hrs	57±29	.39	67±28	.27	61±28	.51
FVC	67±27		76±37		70±30	
FVC after	69±28	.53	78±37	.12	72±31	.24
FVC 30 m	74±27	<b>&lt;0.02</b>	74±32	.46	74±28	.08
FVC 1 h	72±27	.10	75±32	.66	73±28	.22
FVC 2 hrs	72±27	<b>&lt;0.04</b>	74±31	.38	72±28	.26
FVC 3 hrs	71±27	.15	70±27	.16	70±26	.79

Values are expressed as mean% ± SD. FEV<sub>1</sub>: forced expiratory volume in the first second. FVC: forced vital capacity.

Study II showed a significant decrease in LCI following NIV treatment compared to the control group ( $p < 0.01$ ). FEV<sub>1</sub> and FVC did not change significantly following either treatment ( $p = 0.52$ ,  $p = 0.25$ ). (Table 4).

Table 4. Mean (SD) lung function parameters, LCI, 6 MWT and PCO<sub>2</sub> before and after treatment.

	NIV		PEP		p value
	Pre	Post	Pre	Post	
FEV <sub>1</sub> (l)	1.60 (±0.5)	1.54 (±0.36)	2.10 (±0.6)	2.03 (±0.6)	.98
FEV <sub>1</sub> %	43 (±12)	41 (±12)	55 (±15)	54 (±13)	.52
FVC (l)	2.82 (±0.77)	2.77 (±0.84)	3.6 (±0.9)	3.61 (±0.87)	.54
FVC%	64 (±12)	61 (±16)	78 (±13)	78 (±12)	.25
LCI	10.2 (±2.37)	9.20 (±2.55)	9.69 (±2.5)	9.76 (±2.5)	<b>&lt;.01</b>
6 MWT (m)	553 (±69)	559 (±95)	539 (±55)	553 (±77)	.76
PCO <sub>2</sub> (kPa)	5.10 (±0.73)	5.14 (±0.66)	5.22 (±0.42)	5.12(±0.53)	.08

FEV<sub>1</sub>: forced expiratory volume in 1 second, FVC: forced vital capacity, LCI: lung clearance index, 6 MWT: six minute walk test, PCO<sub>2</sub>: partial pressure of carbone dioxide.

Study IV showed that FEV<sub>1</sub> and FVC did not change significantly after treatment in either group.

#### 4.2 EXPERIENCE OF USING NIV

The results revealed six categories that were summarized in the overall theme *becoming friends with NIV* (Table 5). The six categories found were:

- *Getting a sense of control and feedback*: where the patients felt that the NIV gave them a sense of control over the disease due to being able to follow the lung volumes on the NIV display.
- *Getting support*: the patients felt that the physiotherapist offered help depending on disease status.

- *Dealing with doubts:* as NIV was perceived to be a device meant only for the most seriously ill patients, in the beginning the patients claimed not to be that sick. This fear was based upon lack of information and knowledge about the NIV.
- *Finding the rhythm:* in order to acclimatize to the NIV treatment, it was considered important to reach a level of synchronicity with the device.
- *Feeling the effects:* the ability to feel the benefits of the treatment played an important role in the experience surrounding the NIV treatment.
- *Finding their own motivation:* the motivation increased when the patients started a new treatment, while in turn the effects of the treatment increased the motivation even more.

These categories could be seen to represent different aspects that the physiotherapist should keep in mind during the implementation of NIV. The idea of becoming friends with the NIV could be deduced from all the categories, and was experienced by many of the participants in our study. To try to view the treatment as meaningful was a form of feedback given to motivate the patients to use NIV. During the time the patients learned how to use the NIV, they experienced both positive and negative feelings. This continued until they'd learned how the treatment worked. "Becoming friend with NIV" could then be seen as an individual learning process occurring until the patient is able to see the treatment as something meaningful.

The patients' experiences could be summarized as follows:

*"Yes, it felt weird at first, before, you have to learn to breathe against the device. So it was a little difficult to get used to. Now it fits like a hand into a glove. I have learned to adapt quickly to the machine's breathing ways. "* (Participant 4)

*"And it comes down to finding the melody there. I discovered that when I found the melody then it was much easier. The melody was found, I got into the right rhythm to breathe, to find that now I'll come along, now I'll breathe out here and I'll pull in and then you end up after all in some sort of symbiosis with the machine. And then, it was when it was at its best. "*(Participant 11)

Table 5. Overview of the findings: Subcategory, category and overall theme.

Subcategory	Category	Theme
Feedback of treatment Control of disease progression	Getting a sense of control and feedback	Becoming friends with NIV
Individualized treatment Alliance with the therapist	Getting support	
Fear of deterioration The machine is an obstacle	Dealing with doubt	
Tolerance before habit Practice makes perfect	Finding the rhythm	
Optimized mucus evacuation Saving time and more energy	Feeling the effects	
Something new to try Results are worth it	Finding their own motivation	

### 4.3 OTHER RESULTS

Study II found to be no difference between a standard treatment and a bilevel PAP during the six-minute walk test. The partial PCO<sub>2</sub> did not change significantly following either treatment (p=0.08), nor did the SpO<sub>2</sub> or respiratory rate. The inflammatory markers, blood gases and sputum samples analysed monthly did not show any significant deviations from the baseline data, indicating that the patients were all in stable conditions during the study (Table 4).

Study IV showed the tcPCO<sub>2</sub> increased from 4.5 kPa to 5.43 kPa (p=0.03) after NIV and from 4.84 kPa to 6.34 kPa (p=0.01) after O<sub>2</sub> supplementation; i.e. the tcPCO<sub>2</sub> increase was less in the NIV group (p=0.01). Heart rate increased from 86 to 150 (p=0.01) after NIV and O<sub>2</sub> from 97 to 153 (p=0.01) after O<sub>2</sub> supplementation. There was found to be a significant difference between the groups (p=0.04) (Table 3).

Table 6. Median (range) lung function parameters, tcPCO<sub>2</sub>, SpO<sub>2</sub>, heart rate, Borg and Borg perceived exertion before and after tests using NIV and O<sub>2</sub>.

	NIV		O <sub>2</sub>		p value
	Pre	Post	Pre	Post	
FEV <sub>1</sub> (l)	1.60 (±0.5)	1.54 (±0.36)	2.10 (±0.6)	2.03 (±0.6)	.98
FEV <sub>1</sub> %	43 (±12)	41 (±12)	55 (±15)	54 (±13)	.52
FVC (l)	2.82 (±0.77)	2.77 (±0.84)	3.6 (±0.9)	3.61 (±0.87)	.54
FVC%	64 (±12)	61 (±16)	78 (±13)	78 (±12)	.25
tcPCO <sub>2</sub>	4.5 (4-5.68)	5.43 (4.6-6.07)	4.84 (4.28-5.69)	6.34 (6.13-6.57)	<b>&lt;.01</b>
SpO <sub>2</sub>	97 (92-99)	90 (90-97)	96 (94-99)	93 (91-95)	.43
HR	86 (73-97)	150 (122-179)	97 (90-112)	153 (124-175)	<b>&lt;.04</b>
Borg RPE	6 (6-6)	15 (11-17)	6 (6-6)	15 (11-17)	.28
Borg CR-10	0 (0-2)	4.5 (3-7)	0.5 (0-3)	4 (3-8)	.51

FEV<sub>1</sub>: forced expiratory volume in 1 second, FVC: forced vital capacity, tcPCO<sub>2</sub>: transcutaneous pressure of carbon dioxide, SpO<sub>2</sub>: peripheral oxygen saturation, HR: heart rate, Borg RPE: Borg rating of perceived exertion scale. Borg CR-10: rating of perceived dyspnea scale.

## 5 DISCUSSION

The purpose of this thesis was to evaluate the use of NIV as an adjunct to ACT as compared to PEP, and as ventilatory support during exercise tests performed by people with CF. The objective was also to explore at what point after chest physiotherapy a spirometry should be performed, and to describe the experience of using NIV as an adjunct to ACT. In our studies, NIV has shown to be beneficial to patients with CF both as an ACT and during exercise tests.

### 5.1 FINDINGS

In study I the main result was the difference in FEV<sub>1</sub> in adult patients, which was dependent on amount of time following the chest physiotherapy session in question. Other main findings included patients showing different FEV<sub>1</sub> after their chest physiotherapy sessions with interindividual variations but not intraindividual variations. There was also a difference found between adult and pediatric patients.

Not taking into account the role that time plays in the period following a physiotherapy session while designing clinical and therapeutic studies may lead to underestimation as well as overestimation of outcome results. In most therapeutic studies, the individual patients perform the lung function test at the same time of day, thereby indirectly minimizing the effect of physiotherapy sessions if the physiotherapy sessions are also performed at the same time of day. Present studies normally don't consider how chest physiotherapy may affect lung function test results (82). As it may be of clinical importance, determining the individual subject's peak time following chest physiotherapy holds significant weight. In evaluating the effects of different chest physiotherapeutic sessions, the question of time as it pertains to the lung function tests should be considered. Determining which outcomes will be used in clinical trials is crucial for finding a sensitive tool to study the progress of the disease as FEV<sub>1</sub> or LCI.

Due to the progression of the disease, a more severe disease status in adult patients with CF is to be expected. In the time period following a physiotherapy session, adult patients may experience obstruction of the airways, while sputum that has not been evacuated may remain in the central airways, possibly affecting the results of the forced spirometry. This may be a possible reason for adults performing spirometry better 30 min or later following chest physiotherapy. Children may have shown better spirometry results immediately after chest physiotherapy due to experiencing lesser amounts of sputum and better lung function at baseline. The fact that pediatric patients performed somewhat worse over time might be due to having to perform 18 spirometry maneuvers during the same study period. It could very well have been difficult for the pediatric patients to remain motivated and perform at the top of their



game several times in a row.

In study II the main finding on adult patients with CF was the significant decrease in LCI identified following chest physiotherapy with assisted NIV when compared to PEP during a three month period. Both groups maintained their lung function during the course of the study period, which is in agreement with previous short-term studies done on ACTs, for example, a standard treatment involving airway clearance breathing technique had no positive effect on lung function parameters (83). On the other hand, patients did manage to maintain their FEV<sub>1</sub> and FVC, even those with severe a disease status. In our study, the treatment period was established so as to be able to evaluate the long-term (12 weeks) effects of NIV treatment. Previous studies have shown that LCI measured by multiple breath washout represents a sensitive measure of ventilation inhomogeneity. FEV<sub>1</sub> in early CF disease stages mostly reflects the proximal airways; LCI is considered to reflect abnormalities of the smaller airways, considered the site of early lung injury in CF. The lung clearance index will increase in the presence of airway narrowing caused by either inflammation or mucus plugging and has been found to be more sensitive than spirometry in the early stages of CF lung disease (84). The lung clearance index could be an efficient solution for the purpose of detecting changes in the small airways, mostly in those patients who get easily tired performing lung function tests such as the forced spirometry (85).

The improvement in LCI shown in this study could be due to the longterm effects of NIV in alveolar ventilation and the prevention of airway closure during chest physiotherapy, as has been reported in other studies (86, 87). No adverse effects were observed during the use of NIV in our study. All patients performed a six-minute walk test. Even patients with severe lung disease managed to complete a six-minute walk test (distance completed was more than 500 m) (88, 89).

Bilevel PAP offers many advantages, including decreasing the WOB, increasing FRC, improving gas exchange and improving general pulmonary function much more smoothly than PEP, seeing as how the device helps the subject. Positive expiratory pressure is a flow-dependent device so the pressure can be different during the manoeuvres. When NIV is used the patients breathe and receive support as inspiratory and expiratory pressures (pre-setted) during the breathing cycle (62).

In study III the principal finding revealed six categories that were summarized in an overall theme: *becoming friends with NIV*. From start until such a time the treatment begins to show results, there exists an interaction between the patient and the device. In keeping with the findings of previous studies, the participants had a positive experience using NIV as an adjunct to ACT (64, 65). However, the treatment required regular skill training to be useful. Patients who received feedback felt they obtained more control over their disease, while support adapted to the patient's lung condition was needed throughout the NIV treatment. The physiotherapist's implementation of NIV is both a craft and a science (90). It is essential that the physiotherapist strategically stimulates the patient's tolerance to the new therapy through information and support (91). The monitoring and evaluation procedures were important tools when adapting NIV to the status of the participants. Airway clearance technique must be monitored, reviewed and evaluated frequently in order to achieve good adherence to the daily treatment routine (92, 93). To create an alliance between the patient and the physiotherapist was shown to be necessary when a new device was introduced (94). The participants displayed some doubts about the treatment at the beginning of the NIV therapy, based on having no previous knowledge of the new device. An approach involving individualized treatment and personalized learning are thus necessary when starting a new technique (95). As shown in other studies, NIV offers participants a subjective, improved and deeper mucus clearance than previous treatment techniques could, however this could not be measured in this study (65). Motivation was an essential factor in carrying out the treatment, as was a close communication between patient and physiotherapist (96).

In the present study, to become friends with NIV constituted a learning process; during this process the participants had to learn about the new device, how it worked. They also required support from the physiotherapist. The learning process started when the NIV was introduced and continued until the patient felt comfortable with the treatment and experienced good effects. This learning process consisted of several components: continuity in learning, communication between patient and physiotherapist as well as monitoring how knowledge is received and interpreted (97). Patients' responses may in this way help guide the implementation and ongoing delivery of NIV to adults with CF, in order to improve acceptance and adherence to ACT.

In study IV the main finding was the significant decrease in elevated  $t\text{CO}_2$  after NIV compared to after  $\text{O}_2$  supplementation during an incremental test on a treadmill. Both tests were performed on the same day with an interval of 30 minutes in between. Both groups maintained the same lung function during the test period. In concordance with other studies, there was no evidence to suggest that exercise improves lung function in terms of forced spirometry (98).

As has been shown in our study, the ventilatory limitation during exercise could have been compensated by NIV assisted exercise. During exercise, minute ventilation must be maintained in order to preserve the inspiratory and expiratory flow rates, something which NIV could have done in this study. This would have been achieved by an increase in end-expiratory lung volume (EELV) and a decrease in inspiratory time (TI). Airways obstructions in CF cause prolongation of expiratory flow and, when associated with an increased breathing frequency, may result in air trapping. The consequence of air trapping is compromised functioning of the inspiratory muscles by flattening of the diaphragm and shortening the accessory and intercostal muscles. The work and O<sub>2</sub> cost of breathing are increased. More respiratory work is performed during inspiration. If the inspiratory muscles are disadvantaged or overworked, they will fatigue prematurely during progressive exercise (98). Thus ventilatory limitation during exercise in CF patients could be reduced using NIV. It has been demonstrated that assisted ventilation during training as Bilevel reduces dyspnea and increases exercise tolerance in patients with chronic obstructive pulmonary disease (COPD) (99). The expiratory flow limitation and increased respiratory frequency as described in COPD patients may reduce the expiratory time, resulting in increased end-expiratory lung volume, a condition also known as dynamic hyperinflation (DH). In such condition, tidal breathing takes place at lung volumes closer to total lung capacity (100). In concert with the DH, there is an increase in intrinsic positive end-expiratory pressure (PEEPi) and the elastic work of breathing (WOB): the final result is severe dyspnoea during physical effort which reduces the exercise tolerance (101, 102). Chronic obstructive pulmonary disease and CF are both diseases that cause chronic inflammation of the airways yet have distinct characteristics; COPD patients exhibit a reduced airway caliber, which is associated with cell damage induced by external toxic agents. Bronchiectasis in CF develops with recurrent damage to the airways, thus leading to inflammation and destruction of the muscular and elastic components of the bronchial walls (103). Since both diseases display chronic inflammation in the airways that limit exercise, the same rehabilitation programme could be used.

Non invasive ventilation can be safely used to assist in airway clearance in adults with CF, and is beneficial to those with severe bronchial obstruction and reduced inspiratory muscle strength (63, 64). After having taken part in a period of NIV-assisted training, COPD patients displayed higher mean training intensity and peak work rate than after unassisted training (104). Other studies have confirmed the benefits of performing NIV during exercise training in COPD patients (105).

The present study showed an improvement in gas exchange, probably due to an increase in VT after NIV assisted training. Non invasive ventilation improves exercise capacity by unloading respiratory muscles and therefore allowing patients to train at higher levels of exercise intensity

(99). As was described in patients with COPD, the administration of oxygen may have increased the  $ptCO_2$  in the present study. Other studies have shown that excessive oxygen administration in turn can lead to hypercapnic respiratory failure in some patients with COPD. The real explanation involves two aspects: an increased V/Q mismatch and the Haldane effect (106).

Finally, the present thesis have shown that NIV is beneficial as assisted-exercise support and as ACT in patients with CF. The results suggest that NIV should be introduced in conjunction with an explanation of its use and should be evaluated uninterrupted. When designing critical trials, one should identify and choose the most optimal time for performing the lung function tests in order to avoid overestimation and underestimation of the data, particularly if the subjects undergo chest physiotherapy. In our studies, NIV has been used as an ACT with higher inspiratory and expiratory pressure than in other studies, which represents a completely novel approach to the field (63, 64). Additionally, the application of NIV assisted exercise in CF hasn't been studied as much when compared to COPD, thus our study will promote and comprise the basis for new studies that investigate the effects of assisted ventilation during training (99).

## **5.2 METHODOLOGICAL CONSIDERATION**

In study I, the patients were chosen from an out patient CF clinic in Stockholm. Of the 28 patients screened, 24 were enrolled in the study. The patient group contained a small number of children displaying a high age variation, which may affect the result; nevertheless the characteristic of the patients studied was representative of our population. In study II, the attempt was to recruit homogenous groups representing a variation of age, gender and lung function; of the 45 patients screened, 32 were enrolled. The other 13 declined to participate because they lived too far from the hospital. Randomization was done in a stratified way in order to retain the same population regarding lung function in both groups. In study III, patients were recruited from study II, the group of patients who used NIV as an adjunct to ACT. Study IV included a variation of age, gender and lung function. Of the 13 patients eligible to participate, eight were enrolled in the study. The other five patients declined to participate, mainly due to lack of time and motivation. All participants in all the studies completed the trials.

Study I was a prospective study. Here, we used spirometry to measure FEV<sub>1</sub> and FVC, seeing as how it is still one of the most commonly used outcome parameters and - though highly technology and effort dependent - is easy to perform consecutively in an out-patient setting. Spirometry is a valid and reliable instrument for measuring lung function (107). Subjects in the study had been performing spirometry every month since they were 4–5 years of age. Forced expiratory volume in one second is certainly one of the best and widely used markers of prognosis in CF. However, the measurements lack sensitivity, particularly in mild early stages of the disease or when looking for small changes in response to an intervention (108, 109). Lung function parameters as forced spirometry have been used as end points in most therapeutic CF trials to date. However, it has been suggested that the LCI could offer a more sensitive early marker and a stronger indicator of disease progression than spirometry (110). Findings about the effectiveness of respiratory physiotherapy interventions in CF remain controversial when FEV<sub>1</sub> is considered as the outcome measure in clinical trials. The accuracy and sensitivity of spirometry depends on a variety of factors that are difficult to control and not related to the intervention itself. Therefore, spirometry might be unsuitable or its reliability affected in a number of situations, for example if patients are unwilling or unable to collaborate. Hence, this measure should only be used to characterise the pulmonary function status of patients with CF until more sensitive devices like MBWO have been established as standard (111).

The main limitation of the study was its size. The statistical power was calculated for the entire study population (children and adults) but the subanalysis was done for children and adults. As the population was distributed normally, a T-test was used. The time for performing the spirometry after ACT was chosen arbitrarily up until three hours following ACT, seeing as how the patients couldn't stay longer. Another limitation was that the subjects in the study were treated differently when it came to inhaled medications, a difference that may influence the results.

Study II was a prospective randomized study with a control group. We used spirometry and MBW to measure the lung function. One disadvantage of the LCI is that completely obstructed lung regions do not contribute to the overall measurement since the inhaled gas does not reach those regions. Therefore, in patients who have completely obstructed lung regions, LCI may lead to underestimating the disease severity; FRC levels and computer tomography should consequently be used as a complement (109). The measurements chosen, like lung function test and the six-minute walk test, are considered valid and reliable (107, 112). To measure hypercapnia, arterialized capillary blood gases were used instead of arterial blood gases, i.e. the gold standard; however, the correlation between PH and PCO<sub>2</sub> is high (113, 114). The validity of this method could be affected by the procedure or equipment used.

The study was powered for the detection of a 5 % difference in FEV<sub>1</sub>. Thus, the study population may have been too small to detect significant findings with regards to the other included parameters. The population was distributed normally, thus ANOVA was used to compare the groups. Furthermore, the present study found it ethical to involve patients with severe lung disease even when they were on a transplant list, since NIV is often used as a bridge to lung transplantation in CF patients. Some patients used NIV in their daily treatment while others had to be introduced to it, this may also affect the results. A further limitation of the study was that, it not being possible for ethical reasons, there was no control group consisting of patients with no assisted chest physiotherapy.

Study III had a qualitative design. Qualitative content analysis was chosen based on an inductive approach to analyze both manifest and latent content (80). We chose content analysis to better understand how the NIV is experienced by CF patients, as well as to be able to better describe patients' experiences and perspectives and capture their impression of the implementation of a new treatment. One of the present study's strengths was that from the very start of the analysis, the research group worked on the material. Additionally, triangulation was used to safeguard the credibility of the material. The interviews were held in connection with a scheduled visit to Stockholm's CF center to avoid extra visits. In a qualitative approach, trustworthiness is used to support the arguments' worth and is of special import when using an inductive approach (115). The results were described alongside quotations from the interviews to facilitate the reading. The criterion for trustworthiness was followed, though prior understanding could affect the interpretation of our data.

A possible weakness was that all researchers involved were physiotherapists; however one did not have any clinical experience with patients with lung diseases. The risk of researcher bias was considered. The interviewer, a physiotherapist who knew the patients but was not involved in the implementation of the treatment with NIV, may have influenced what the participants felt comfortable sharing. Knowing the researcher may have had a negative impact. Participants may have answered only what they thought the researcher wanted to hear in order to please them or avoid causing offense. Consideration should be given to the fact that the interviews were held in Swedish and all participants also lived in Stockholm. This could suggest that the results are not necessarily inclusive of the view of those from other cultures or patients living outside large cities. To minimize the risk of errors, the quotes were translated from Swedish to English by a physiotherapist whose first language is English. Another limitation lay in the fact that the interview duration was very limited, which may have affected the results. Patients with *Burkholderia cepacia* and MRSA had to be excluded seeing as there were no isolation facilities

where one could perform the interviews. Additionally, the patients' differing experiences with using NIV may have affected the results, but was taken into account before the analysis. In general, there were no differences in responses that could be traced back to how long the patients had been using the NIV.

Study IV had a crossover design. Patients who participated in this study acted as their own control subjects when comparing O<sub>2</sub> supplementation (standard treatment nowadays) with NIV treatment. The measurements chosen are considered valid and reliable. However, the study still had some limitations: the number of participants was very small with no control group. On the other hand, the power calculation suggested that eight subjects would be enough. The population was not distributed normally, which is why the Wilcoxon signed-rank test was used. The tests (Bruce protocol) were performed twice (once with NIV and once with oxygen supplementation), a fact which may have affected the results, since the subjects could have felt more familiar when the tests were performed the second time. The Bruce test is a submaximal test that is considered valid and reliable (116). The transcutaneous measurements are too valid and reliable and were used to measure hypercapnia, despite arterial blood gases being considered the gold standard (117). The results obtained during the present study may have been different if the subjects were already hypercapnic at the beginning of the test. The strength of the study was that only two physiotherapists were needed to record all the measurements, hence ensuring the data collection.

### **5.3 CLINICAL IMPLICATIONS**

The results from the present studies show that NIV can be useful as an ACT and in reducing tpCO<sub>2</sub> during an incremental exercise test in adult patients with CF. The same group of patients described having a positive experience of the new technique and would recommend its use to other groups of patients. Further results showed that spirometry as FEV<sub>1</sub> is still a useful parameter but need to be measured within a specific timeframe following ACT.

Study I showed the importance of detecting the peak value after spirometry. The practical implementation of this study is important for obtaining a reliable value following the ACT, which then may be used as an outcome in clinical trials – both considering the effect of airway clearance but also to avoid having the timeframe be a confounding factor. FEV<sub>1</sub> is still widely used as a marker of prognosis in CF, however LCI as an outcome measure has shown a rise in use in certain clinical trials involving new medication. Study II showed LCI to be more sensitive to changes than FEV<sub>1</sub> after employing NIV as an adjunct to ACT. There are still but a few studies on airway

clearance where LCI is used as an outcome. Nevertheless, it could lead to a false result in those with very low FEV<sub>1</sub> and completely obstructed airways. However, all the patients in this study were in a stable clinical condition.

The present study offers a new approach to chest physiotherapy treatment in moderate to severe CF. In study III the aim was to describe the patients' perspective on and experience with using NIV. The results offer a deeper understanding of how patients experiences using NIV as an adjunct to ACT and may help the physiotherapist in the implementation and management of NIV. The physiotherapist is considered to play a significant role in the support of people with CF. During the study, it was revealed that participants felt motivated to perform ACT when combining it with NIV. Study IV showed a decrease in the rise of ptCO<sub>2</sub> following NIV. The present study offers new treatment possibilities associated with exercise to adults with CF, thus allowing them to reach the physiological effects of physical training.

The results of our studies showed that NIV may be applied to other respiratory diseases involving affected mucociliary clearance, and as assisted-exercise to compensate for the ventilatory limitations. Our population of CF patients, of which 64 % were adults, displayed good lung function; nevertheless these patient characteristics should also be applicable to other countries.

#### **5.4 FUTURE STUDIES**

In the studies mentioned here we showed that the timeframe following the spirometry have to be taken into account when designing future clinical and pharmaceutical trials. Additionally, it suggested that LCI may be a more sensitive early marker and stronger indicator of disease progression than spirometry. Further research is needed to evaluate the completely collapsed areas not involved in the gas washout.

During a three month trial, NIV as an adjunct to ACT was shown to be a good alternative to PEP; additional long-term studies are however needed in order to evaluate the effects of NIV in airway clearance and mucus transport. Our research revealed that participants felt motivated to perform ACT when done with the help of NIV. An interesting question to be addressed in future research is what role the presented findings play in the patient's long-term adherence to treatment. Clinical experience suggests that adherence to ACT has been improved, but further research is required in order to confirm. Another issue worth further study is how children with CF experience treatment when using NIV in their ACT. In this study, only adult patients were



recruited, as this was one of the very first qualitative studies to investigate the experience of using NIV as an ACT in CF. Future studies should examine the experience of other groups of patients with lung disease in order to obtain their views on chest physiotherapy interventions with NIV, thus optimizing the treatment.

Physical training plays a significant part in the CF treatment package already, and patient survival rate is associated with fitness level. As a result, CF patients are encouraged to do physical exercise on the regular. NIV as support during exercise is effective, but more trials are needed to evaluate the long-term effects following the training period.

Another important thing to evaluate further is the use of new therapies that modifies CFTR which creates a new spectrum regarding chest physiotherapy treatment and necessity of ACT in patients with CF. The increased knowledge of how CFTR dysfunction causes lung disease has resulted in new exciting targets for treatment. New therapies are being developed to target mutant CFTR and restore CFTR function. Clinical trials testing are divided in different categories as: gene therapy, mRNA repair, and CFTR modulators (ataluren, lumacaftor, ivacaftor – others are in pipeline for phase 3 studies). How these new therapies will affect the use of chest physiotherapy for optimal treatment needs to be investigated.

## 6 CONCLUSION

This thesis has shown that:

- The optimal timeframe for performing accurate spirometry following an airway clearance session varies between individual patients. However, the individual peak time also has to be taken into account.
- For patients who are moderately to severely ill, NIV is a good alternative to PEP as an adjunct to ACT.
- "Becoming friends with NIV" emerged as the overall theme of the studies. The theme may be seen to represent an individual learning process whereas the categories stand in for different aspects that facilitate learning, and should thus be considered individually. The physiotherapist plays an important supporting role during this learning process. The patients' experience with NIV treatment as an adjunct to ACT was often seen as a meaningful one. Understanding these experiences may facilitate the physiotherapist in the work with implementing NIV. Knowing which aspects to consider will help the physiotherapist make the patient's experience of NIV a meaningful one.
- Non invasive ventilation is as good as oxygen supplementation when used by severely ill patients during an exercise test. The NIV treatment showed a decrease in the rise of tcPCO<sub>2</sub>, which kept the tcPCO<sub>2</sub> levels within the normal reference values when compared with O<sub>2</sub> supplementation.

## 7 ACKNOWLEDGMENTS

Firstly, I would like to express my sincere gratitude to my principal supervisor , Prof. Lena Hjelte, for her continued support of my PhD study and its associated research, as well as for her patience, motivating presence and immense knowledge. With her guidance I managed to make it through both the research and writing.

In addition to my principal supervisor , I would also like to thank my co-supervisor Dr. Malin Nygren-Bonnier, not only for her insightful comments, brilliant suggestions and encouragement, but also for the hard questions she asked, questions, which led me to widen the scope of my research.

Professor Claude Marcus, Head of Division of Pediatrics, CLINTEC, Karolinska Institutet, for his support and inspiration. Lisbeth Sjödin for all her help.

My sincere thanks also go out to my co-authors: Gabriele Biguet, for her invaluable support and endless assistance with the qualitative research, and Anna Hedborg for her fantastic help with the interviews and for always remaining positive and enthusiastic.

Cecilia Fridén, head of occupational therapy and physiotherapy, for providing me with the chance and the support I needed in order to complete this thesis. Li Villard, head of the Pediatric section, for all her generous support and the interest she has shown in my thesis. Åsa Dederig, former head of the functional area occupational therapy and physiotherapy for her generous support. Susanne Karlsson, Özlem Erer Dironin and Annika Luthman, all of them former head of the pediatric section, thank you for all support.

Elisabeth Berg, for her invaluable help with all manners of statistical questions.

I would like to thank my fellow physiotherapists at Stockholm CF Center, Anna Hedborg, Anna Törnberg, Kaisa Johansson and Sofia Wilhelmsson, for all the stimulating discussions, the fun we've had in the past four years and for picking up the slack when I was unable to put in an appearance.

Isabelle de Monestrol, head of the department of Cystic Fibrosis, for always being encouraging and interested in how the thesis was coming along, and for sharing her vast clinical experience of CF.

All the personnel at Stockholm CF Center, for the wonderful work they do and for making it the best place in the world to work. Special thanks goes out to Berit Widen.

All the colleagues over at the occupational therapy and physiotherapy unit, especially my "respiratory" colleagues Eeva Europe, Mats Johansson and Malin Ortfelt.

To all my friends in physiotherapy, colleagues and former colleagues. Everyone at University of Buenos Aires and my previous residence. A special mention goes out to Gabriela Naranjo, my dear colleague and friend.

My beautiful Argentinian friends: the field hockey team and all my friends from school and University. Thank you for being there for me despite the distance, and for your endless love and support.

My dear Swedish friends : the badminton league (Laura, Peti, Sofi, Maria, Emma and Ariel), Titti Harning and her family, Tindra, Dante my lovely godson, Maria Mc Lean, Silvia Malenicka and Susanne Sandström. We've laughed and cried, traveled and played, built and settled and planned and discussed almost everything throughout our lives. Thank you for being there.

Last but not least, I would like to thank all of my friends and family: my parents and my brother for supporting me throughout this writing process and life in general. Fernand, my love, for his patience, immeasurable energy and never-ending enthusiasm.

## **Funding**

Financial support through research grants from: the Swedish Cystic Fibrosis Foundation, the Freemasons´in Stockholm Childhood Foundation, the Samariten Foundation and the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet.

## 8 REFERENCES

1. Andersen DH, Hodges RG. Celiac syndrome; genetics of cystic fibrosis of the pancreas, with a consideration of etiology. *Am J Dis Child*. 1946;72:62-80.
2. Fanconi G UE, Knauer C. . Das Coeliakie-syndrom bei angeborener zystischer Pankreasfibromatose und Bronchiektasen. . *Wien Med Wchnschr* 1936 1936; 86:753-6.
3. Di Sant'Agnese PA, Darling RC, Perera GA, Shea E. Abnormal electrolyte composition of sweat in cystic fibrosis of the pancreas; clinical significance and relationship to the disease. *Pediatrics*. 1953;12(5):549-63.
4. Gibson LE, Cooke RE. A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis. *Pediatrics*. 1959;23(3):545-9.
5. Kerem B, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, et al. Identification of the cystic fibrosis gene: genetic analysis. *Science*. 1989;245(4922):1073-80.
6. Collins FS. Cystic fibrosis: molecular biology and therapeutic implications. *Science*. 1992;256(5058):774-9.
7. Lannefors L, Lindgren A. Demographic transition of the Swedish cystic fibrosis community--results of modern care. *Respiratory medicine*. 2002;96(9):681-5.
8. Zolin A ME, van Rens J et al. ECFSPR Annual Report 2013. 2016.
9. Vankeerberghen A, Cuppens H, Cassiman JJ. The cystic fibrosis transmembrane conductance regulator: an intriguing protein with pleiotropic functions. *J Cyst Fibros*. 2002;1(1):13-29.
10. Ferec C, Cutting GR. Assessing the Disease-Liability of Mutations in CFTR. *Cold Spring Harbor perspectives in medicine*. 2012;2(12):a009480.
11. Foundation C. [http://cftr2.org/mutations\\_history](http://cftr2.org/mutations_history) 2016 [Available from: [http://cftr2.org/mutations\\_history](http://cftr2.org/mutations_history)].
12. Zielenski J, Tsui LC. Cystic fibrosis: genotypic and phenotypic variations. *Annu Rev Genet*. 1995;29:777-807.
13. Grossman S, Grossman LC. Pathophysiology of cystic fibrosis: implications for critical care nurses. *Crit Care Nurse*. 2005;25(4):46-51.
14. Boucher RC. Airway surface dehydration in cystic fibrosis: pathogenesis and therapy. *Annu Rev Med*. 2007;58:157-70.
15. Saiman L. Microbiology of early CF lung disease. *Paediatr Respir Rev*. 2004;5 Suppl A:S367-9.
16. Ballard ST, Inglis SK. Liquid secretion properties of airway submucosal glands. *The Journal of physiology*. 2004;556(Pt 1):1-10.
17. Hess DR. Airway clearance: physiology, pharmacology, techniques, and practice. *Respir Care*. 2007;52(10):1392-6.
18. Hauser AR, Jain M, Bar-Meir M, McColley SA. Clinical significance of microbial infection and adaptation in cystic fibrosis. *Clin Microbiol Rev*. 2011;24(1):29-70.
19. Fauroux B. Noninvasive ventilation in cystic fibrosis. *Expert review of respiratory medicine*. 2010;4(1):39-46.

20. Zielenski J. Genotype and phenotype in cystic fibrosis. *Respiration*. 2000;67(2):117-33.
21. Geborek A, Hjelte L. Association between genotype and pulmonary phenotype in cystic fibrosis patients with severe mutations. *J Cyst Fibros*. 2011;10(3):187-92.
22. O'Sullivan BP, Freedman SD. Cystic fibrosis. *Lancet*. 2009;373(9678):1891-904.
23. Zempsky WT, Rosenstein BJ, Carroll JA, Oski FA. Effect of pancreatic enzyme supplements on iron absorption. *Am J Dis Child*. 1989;143(8):969-72.
24. Sabharwal S. Gastrointestinal Manifestations of Cystic Fibrosis. *Gastroenterology & hepatology*. 2016;12(1):43-7.
25. Colombo C, Ellemunter H, Houwen R, Munck A, Taylor C, Wilschanski M, et al. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients. *J Cyst Fibros*. 2011;10 Suppl 2:S24-8.
26. Sabati AA, Kempainen RR, Milla CE, Ireland M, Schwarzenberg SJ, Dunitz JM, et al. Characteristics of gastroesophageal reflux in adults with cystic fibrosis. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society*. 2010;9(5):365-70.
27. Parisi GF, Di Dio G, Franzonello C, Gennaro A, Rotolo N, Lionetti E, et al. Liver disease in cystic fibrosis: an update. *Hepat Mon*. 2013;13(8):e11215.
28. Lindblad A, Glaumann H, Strandvik B. Natural history of liver disease in cystic fibrosis. *Hepatology*. 1999;30(5):1151-8.
29. Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. *Diabetes Care*. 2009;32(9):1626-31.
30. Ntimbane T, Comte B, Mailhot G, Berthiaume Y, Poitout V, Prentki M, et al. Cystic fibrosis-related diabetes: from CFTR dysfunction to oxidative stress. *Clin Biochem Rev*. 2009;30(4):153-77.
31. McCallum TJ, Milunsky JM, Cunningham DL, Harris DH, Maher TA, Oates RD. Fertility in men with cystic fibrosis: an update on current surgical practices and outcomes. *Chest*. 2000;118(4):1059-62.
32. Johannesson M. Effects of pregnancy on health: certain aspects of importance for women with cystic fibrosis. *J Cyst Fibros*. 2002;1(1):9-12.
33. Farrell PM, Rosenstein BJ, White TB, Accurso FJ, Castellani C, Cutting GR, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr*. 2008;153(2):S4-S14.
34. Mishra A, Greaves R, Smith K, Carlin JB, Wootton A, Stirling R, et al. Diagnosis of cystic fibrosis by sweat testing: age-specific reference intervals. *J Pediatr*. 2008;153(6):758-63.
35. Castellani C, Massie J. Emerging issues in cystic fibrosis newborn screening. *Curr Opin Pulm Med*. 2010;16(6):584-90.
36. De Boeck K, Derichs N, Fajac I, de Jonge HR, Bronsveld I, Sermet I, et al. New clinical diagnostic procedures for cystic fibrosis in Europe. *J Cyst Fibros*. 2011;10 Suppl 2:S53-66.

37. Kerem E, Conway S, Elborn S, Heijerman H, Consensus C. Standards of care for patients with cystic fibrosis: a European consensus. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society*. 2005;4(1):7-26.
38. Davis PB. Cystic fibrosis since 1938. *Am J Respir Crit Care Med*. 2006;173(5):475-82.
39. Hjelte L, Widen B, Malmborg AS, Freyschuss U, Strandvik B. [Intravenous administration of antibiotics at home in patients with cystic fibrosis improves quality of life]. *Lakartidningen*. 1988;85(18):1614-7.
40. Fieker A, Philpott J, Armand M. Enzyme replacement therapy for pancreatic insufficiency: present and future. *Clinical and experimental gastroenterology*. 2011;4:55-73.
41. Strandvik B. Fatty acid metabolism in cystic fibrosis. *Prostaglandins Leukot Essent Fatty Acids*. 2010;83(3):121-9.
42. Levine JJ. Nutritional supplementation in cystic fibrosis: are all patients candidates for aggressive therapy? *J Pediatr Gastroenterol Nutr*. 1998;27(1):120-1.
43. Sinaasappel M, Stern M, Littlewood J, Wolfe S, Steinkamp G, Heijerman HG, et al. Nutrition in patients with cystic fibrosis: a European Consensus. *J Cyst Fibros*. 2002;1(2):51-75.
44. therapy. Twcfp. Policy statement. Description of physical therapy. 2011.
45. Garrod R, Lasserson T. Role of physiotherapy in the management of chronic lung diseases: an overview of systematic reviews. *Respir Med*. 2007;101(12):2429-36.
46. Warnock L, Gates A. Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis. *Cochrane Database Syst Rev*. 2015;12:CD001401.
47. Rubin BK. The pharmacologic approach to airway clearance: mucoactive agents. *Respir Care*. 2002;47(7):818-22.
48. Wark P, McDonald VM. Nebulised hypertonic saline for cystic fibrosis. *Cochrane Database Syst Rev*. 2009(2):CD001506.
49. Tam J, Nash EF, Ratjen F, Tullis E, Stephenson A. Nebulized and oral thiol derivatives for pulmonary disease in cystic fibrosis. *Cochrane Database Syst Rev*. 2013(7):CD007168.
50. Conrad C, Lymp J, Thompson V, Dunn C, Davies Z, Chatfield B, et al. Long-term treatment with oral N-acetylcysteine: affects lung function but not sputum inflammation in cystic fibrosis subjects. A phase II randomized placebo-controlled trial. *J Cyst Fibros*. 2015;14(2):219-27.
51. Fibrosis IPGfC. Physiotherapy in the treatment of Cystic Fibrosis. 2009.
52. Button BM, Button B. Structure and function of the mucus clearance system of the lung. *Cold Spring Harbor perspectives in medicine*. 2013;3(8).
53. Falk M, Kelstrup M, Andersen JB, Kinoshita T, Falk P, Stovring S, et al. Improving the ketchup bottle method with positive expiratory pressure, PEP, in cystic fibrosis. *Eur J Respir Dis*. 1984;65(6):423-32.
54. Pryor JA, Webber BA, Hodson ME. Effect of chest physiotherapy on oxygen saturation in patients with cystic fibrosis. *Thorax*. 1990;45(1):77.
55. FA A. Physikalische beim kindlichen Asthma bronchiale. *M Schr Kinderheilk*. 1976;124:222-4.

56. Kendrick AH. Airway clearance techniques in cystic fibrosis: physiology, devices and the future. *J R Soc Med.* 2007;100 Suppl 47:3-23.
57. Hess DR. Secretion clearance techniques: absence of proof or proof of absence? *Respir Care.* 2002;47(7):757-8.
58. Main E, Prasad A, Schans C. Conventional chest physiotherapy compared to other airway clearance techniques for cystic fibrosis. *Cochrane Database Syst Rev.* 2005(1):CD002011.
59. Moran F, Bradley JM, Piper AJ. Non-invasive ventilation for cystic fibrosis. *The Cochrane database of systematic reviews.* 2013;4:CD002769.
60. Elkins MR, Jones A, Schans C. Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis. *The Cochrane database of systematic reviews.* 2004(1):CD003147.
61. van der Schans C, Prasad A, Main E. Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis. *Cochrane Database Syst Rev.* 2000(2):CD001401.
62. British Thoracic Society Standards of Care C. Non-invasive ventilation in acute respiratory failure. *Thorax.* 2002;57(3):192-211.
63. Holland AE, Denehy L, Ntoumenopoulos G, Naughton MT, Wilson JW. Non-invasive ventilation assists chest physiotherapy in adults with acute exacerbations of cystic fibrosis. *Thorax.* 2003;58(10):880-4.
64. Dwyer TJ, Robbins L, Kelly P, Piper AJ, Bell SC, Bye PT. Non-invasive ventilation used as an adjunct to airway clearance treatments improves lung function during an acute exacerbation of cystic fibrosis: a randomised trial. *J Physiother.* 2015;61(3):142-7.
65. Stanford G, Parrott H, Bilton D, Agent P. Positive pressure--analysing the effect of the addition of non-invasive ventilation (NIV) to home airway clearance techniques (ACT) in adult cystic fibrosis (CF) patients. *Physiother Theory Pract.* 2015;31(4):270-4.
66. Fauroux B, Boule M, Lofaso F, Zerah F, Clement A, Harf A, et al. Chest physiotherapy in cystic fibrosis: improved tolerance with nasal pressure support ventilation. *Pediatrics.* 1999;103(3):E32.
67. Placidi G, Cornacchia M, Polese G, Zanolla L, Assael BM, Braggion C. Chest physiotherapy with positive airway pressure: a pilot study of short-term effects on sputum clearance in patients with cystic fibrosis and severe airway obstruction. *Respir Care.* 2006;51(10):1145-53.
68. de Jong W, van der Schans CP, Mannes GP, van Aalderen WM, Grevink RG, Koeter GH. Relationship between dyspnoea, pulmonary function and exercise capacity in patients with cystic fibrosis. *Respir Med.* 1997;91(1):41-6.
69. Loeve M, Krestin GP, Rosenfeld M, de Bruijne M, Stick SM, Tiddens HA. Chest computed tomography: a validated surrogate endpoint of cystic fibrosis lung disease? *Eur Respir J.* 2013;42(3):844-57.
70. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J.* 2005;26(2):319-38.
71. Newth CJ, Enright P, Johnson RL. Multiple-breath nitrogen washout techniques: including measurements with patients on ventilators. *Eur Respir J.* 1997;10(9):2174-85.
72. Robinson PD, Goldman MD, Gustafsson PM. Inert gas washout: theoretical background and clinical utility in respiratory disease. *Respiration.* 2009;78(3):339-55.



73. Robinson PD, Latzin P, Verbanck S, Hall GL, Horsley A, Gappa M, et al. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. *Eur Respir J*. 2013;41(3):507-22.
74. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. *Eur Respir J*. 2005;26(1):153-61.
75. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-7.
76. Borg GA. Perceived exertion: a note on "history" and methods. *Med Sci Sports*. 1973;5(2):90-3.
77. Kendrick KR, Baxi SC, Smith RM. Usefulness of the modified 0-10 Borg scale in assessing the degree of dyspnea in patients with COPD and asthma. *J Emerg Nurs*. 2000;26(3):216-22.
78. Hebestreit H, Arets HG, Aurora P, Boas S, Cerny F, Hulzebos EH, et al. Statement on Exercise Testing in Cystic Fibrosis. *Respiration*. 2015;90(4):332-51.
79. Damy T, Burgel PR, Pepin JL, Boelle PY, Cracowski C, Murriss-Espin M, et al. Pulmonary acceleration time to optimize the timing of lung transplant in cystic fibrosis. *Pulm Circ*. 2012;2(1):75-83.
80. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse education today*. 2004;24(2):105-12.
81. General Assembly of the World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J Am Coll Dent*. 2014;81(3):14-8.
82. McGarry ME, Nielson DW. Normalization of sweat chloride concentration and clinical improvement with ivacaftor in a patient with cystic fibrosis with mutation S549N. *Chest*. 2013;144(4):1376-8.
83. Braggion C, Cappelletti LM, Cornacchia M, Zanolla L, Mastella G. Short-term effects of three chest physiotherapy regimens in patients hospitalized for pulmonary exacerbations of cystic fibrosis: a cross-over randomized study. *Pediatr Pulmonol*. 1995;19(1):16-22.
84. Davies JC, Cunningham S, Alton EW, Innes JA. Lung clearance index in CF: a sensitive marker of lung disease severity. *Thorax*. 2008;63(2):96-7.
85. Subbarao P, Stanojevic S, Brown M, Jensen R, Rosenfeld M, Davis S, et al. Lung clearance index as an outcome measure for clinical trials in young children with cystic fibrosis. A pilot study using inhaled hypertonic saline. *Am J Respir Crit Care Med*. 2013;188(4):456-60.
86. Oberwaldner B, Evans JC, Zach MS. Forced expirations against a variable resistance: a new chest physiotherapy method in cystic fibrosis. *Pediatr Pulmonol*. 1986;2(6):358-67.
87. Granton JT, Kesten S. The acute effects of nasal positive pressure ventilation in patients with advanced cystic fibrosis. *Chest*. 1998;113(4):1013-8.
88. Troosters T, Gosselink R, Decramer M. Six-minute walk test: a valuable test, when properly standardized. *Phys Ther*. 2002;82(8):826-7; author reply 7-8.

89. Martin C, Chapron J, Hubert D, Kanaan R, Honore I, Paillasseur JL, et al. Prognostic value of six minute walk test in cystic fibrosis adults. *Respir Med.* 2013;107(12):1881-7.
90. Hess DR. The growing role of noninvasive ventilation in patients requiring prolonged mechanical ventilation. *Respiratory care.* 2012;57(6):900-18; discussion 18-20.
91. Yuksel H, Yilmaz O. A new model for cystic fibrosis management: control concept. *Pneumologia.* 2011;60(3):150-4.
92. Lannefors L, Button BM, McIlwaine M. Physiotherapy in infants and young children with cystic fibrosis: current practice and future developments. *Journal of the Royal Society of Medicine.* 2004;97 Suppl 44:8-25.
93. Varlotta L. Management and care of the newly diagnosed patient with cystic fibrosis. *Current opinion in pulmonary medicine.* 1998;4(6):311-8.
94. Cohen-Cymerknoh M, Shoseyov D, Kerem E. Managing cystic fibrosis: strategies that increase life expectancy and improve quality of life. *American journal of respiratory and critical care medicine.* 2011;183(11):1463-71.
95. Beresford BA, Sloper P. Chronically ill adolescents' experiences of communicating with doctors: a qualitative study. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 2003;33(3):172-9.
96. Berge JM PJ GD, Milla C. Gender differences in young adults' perceptions of living with cystic fibrosis during the transition to adulthood: A qualitative investigation. *Families, Systems, & Health* 2007;25(2):190-203.
97. Gyllensten AL, Gard G, Salford E, Ekdahl C. Interaction between patient and physiotherapist: a qualitative study reflecting the physiotherapist's perspective. *Physiother Res Int.* 1999;4(2):89-109.
98. Webb AK, Dodd ME, Moorcroft J. Exercise and cystic fibrosis. *J R Soc Med.* 1995;88 Suppl 25:30-6.
99. Ambrosino N, Cigni P. Non invasive ventilation as an additional tool for exercise training. *Multidiscip Respir Med.* 2015;10(1):14.
100. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2001;164(5):770-7.
101. Marin JM, Carrizo SJ, Gascon M, Sanchez A, Gallego B, Celli BR. Inspiratory capacity, dynamic hyperinflation, breathlessness, and exercise performance during the 6-minute-walk test in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2001;163(6):1395-9.
102. Babb TG, Viggiano R, Hurley B, Staats B, Rodarte JR. Effect of mild-to-moderate airflow limitation on exercise capacity. *J Appl Physiol (1985).* 1991;70(1):223-30.
103. Athanazio R. Airway disease: similarities and differences between asthma, COPD and bronchiectasis. *Clinics.* 2012;67(11):1335-43.
104. Hawkins P, Johnson LC, Nikolettou D, Hamnegard CH, Sherwood R, Polkey MI, et al. Proportional assist ventilation as an aid to exercise training in severe chronic obstructive pulmonary disease. *Thorax.* 2002;57(10):853-9.

105. van 't Hul A, Gosselink R, Hollander P, Postmus P, Kwakkel G. Training with inspiratory pressure support in patients with severe COPD. *Eur Respir J*. 2006;27(1):65-72.
106. Abdo WF, Heunks LM. Oxygen-induced hypercapnia in COPD: myths and facts. *Crit Care*. 2012;16(5):323.
107. Finkelstein SM, Lindgren B, Prasad B, Snyder M, Edin C, Wielinski C, et al. Reliability and validity of spirometry measurements in a paperless home monitoring diary program for lung transplantation. *Heart Lung*. 1993;22(6):523-33.
108. Que C, Cullinan P, Geddes D. Improving rate of decline of FEV1 in young adults with cystic fibrosis. *Thorax*. 2006;61(2):155-7.
109. Davies JC, Alton EW. Monitoring respiratory disease severity in cystic fibrosis. *Respir Care*. 2009;54(5):606-17.
110. Aurora P, Bush A, Gustafsson P, Oliver C, Wallis C, Price J, et al. Multiple-breath washout as a marker of lung disease in preschool children with cystic fibrosis. *Am J Respir Crit Care Med*. 2005;171(3):249-56.
111. Stocks J, Thia LP, Sonnappa S. Evaluation and use of childhood lung function tests in cystic fibrosis. *Curr Opin Pulm Med*. 2012;18(6):602-8.
112. Bellet RN, Adams L, Morris NR. The 6-minute walk test in outpatient cardiac rehabilitation: validity, reliability and responsiveness--a systematic review. *Physiotherapy*. 2012;98(4):277-86.
113. Zavorsky GS, Cao J, Mayo NE, Gabbay R, Murias JM. Arterial versus capillary blood gases: a meta-analysis. *Respir Physiol Neurobiol*. 2007;155(3):268-79.
114. Hughes JM. Blood gas estimations from arterialized capillary blood versus arterial puncture: are they different? *Eur Respir J*. 1996;9(2):184-5.
115. Elo S, Kyngas H. The qualitative content analysis process. *J Adv Nurs*. 2008;62(1):107-15.
116. Noonan V, Dean E. Submaximal exercise testing: clinical application and interpretation. *Phys Ther*. 2000;80(8):782-807.
117. Storre JH, Magnet FS, Dreher M, Windisch W. Transcutaneous monitoring as a replacement for arterial PCO<sub>2</sub> monitoring during nocturnal non-invasive ventilation. *Respir Med*. 2011;105(1):143-50.