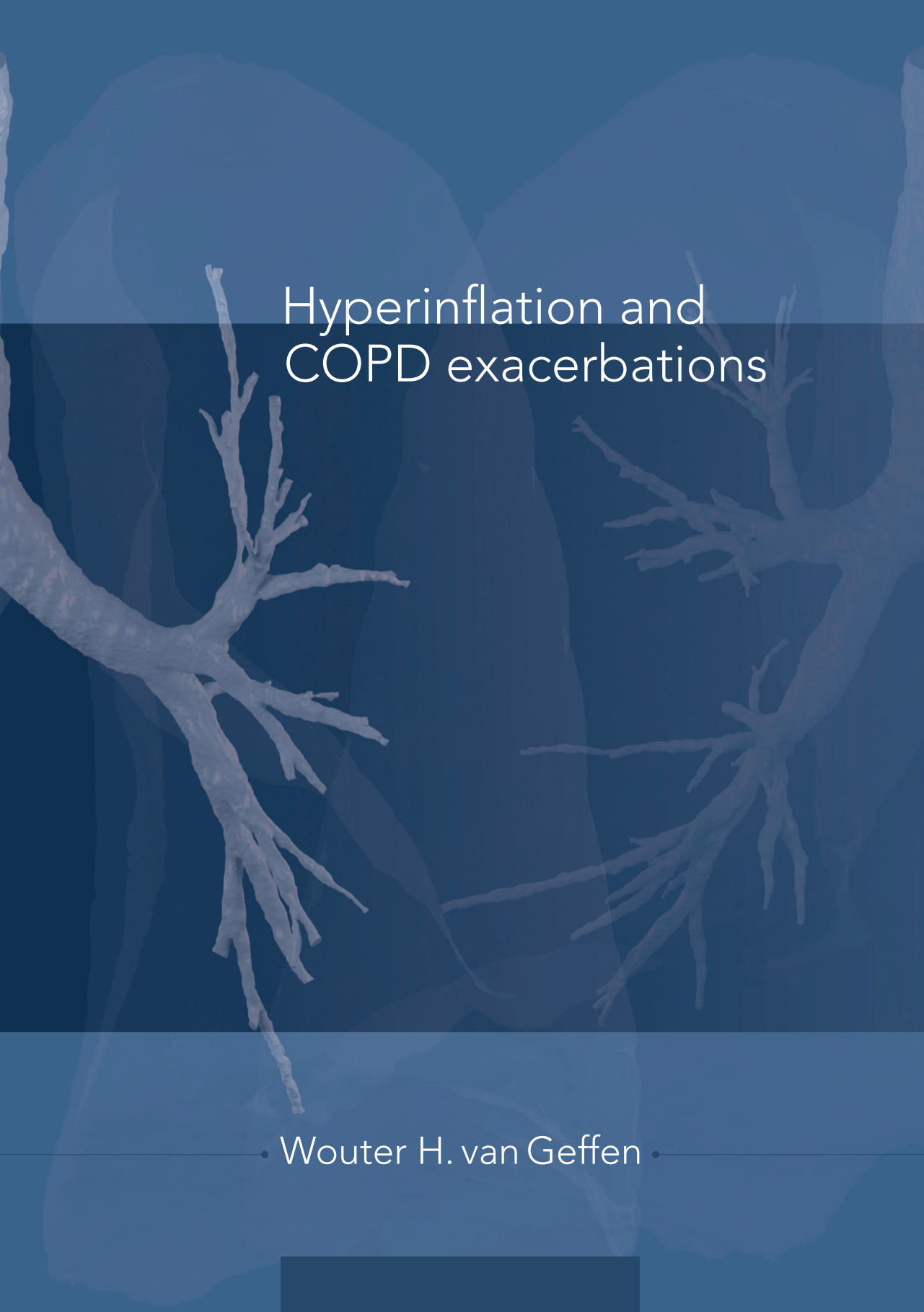
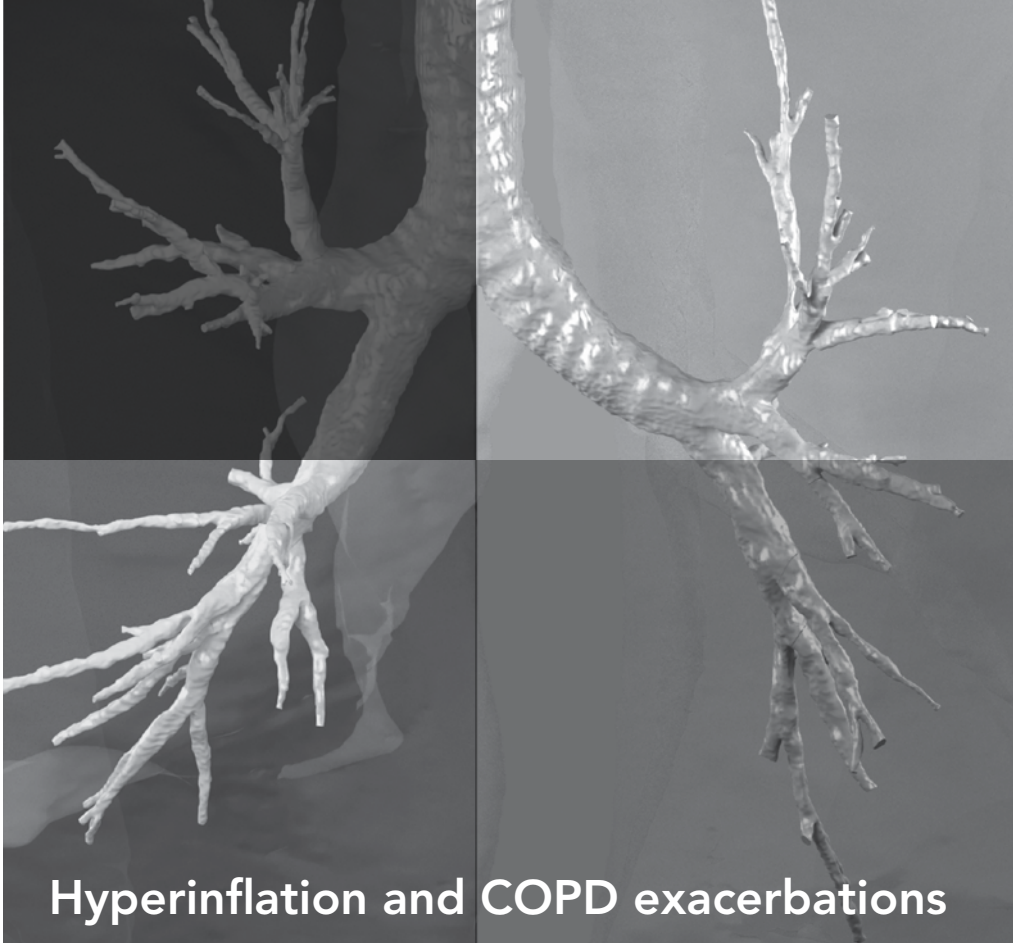


Hyperinflation and COPD exacerbations

Wouter H. van Geffen



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Colofon

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Wouter H. van Geffen
Rijksuniversiteit Groningen

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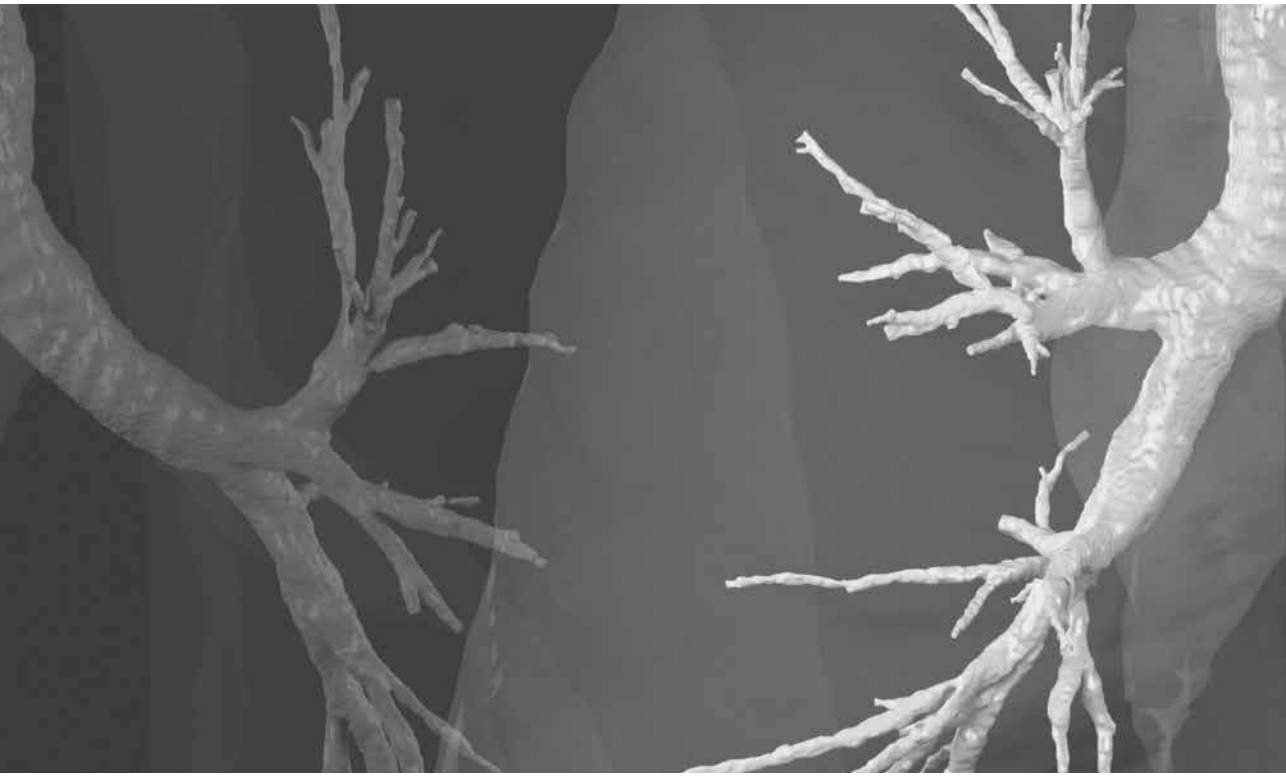
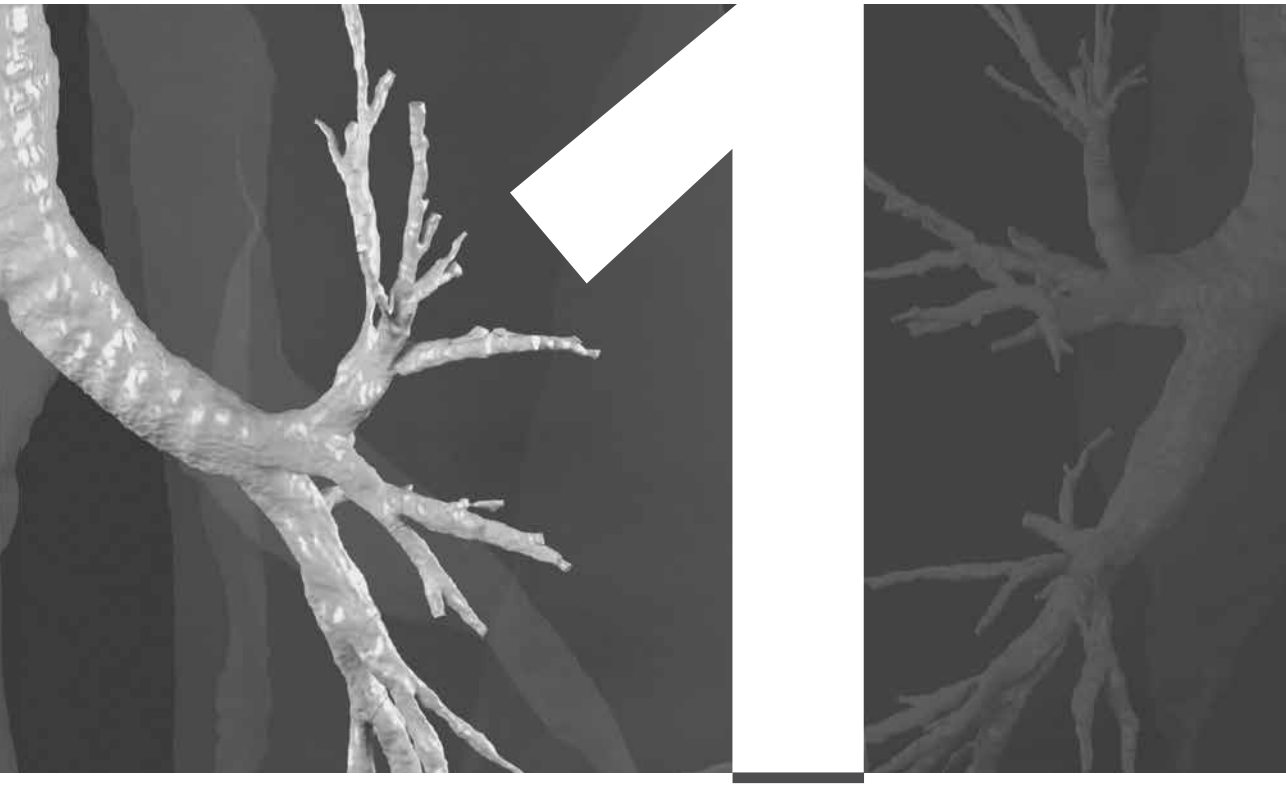


CHAPTER



1 Introduction

Definition and classification of COPD

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of death worldwide.[1, 2] COPD patients can suffer from symptoms like dyspnea, cough and mucus production. Additionally, a reduced exercise capacity, a reduced quality of life and comorbidities are associated with COPD.[1] The leading international guideline, the Global Initiative for Chronic Obstructive Lung Disease GOLD, defines the disease as follows:

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[1]

Chronic airflow limitation is the defining characteristic of COPD. This limitation is caused by a mixture of small airways disease and parenchymal destruction caused by chronic inflammation. Additionally, fibrotic changes, damage of the larger airways, recurrent infections, hyperinflation and pulmonary hypertension are often observed.[1] The relative contributions from inflammation, airway disease, and parenchymal destruction vary from person to person and even within patients between lung lobes.[3-6] This results in multiple different phenotypes of COPD. A clear differentiation of phenotypes can be useful for research purposes, but also in daily practices to assess possibilities for additional treatment.[4-7]

Definition and classification of COPD exacerbations

All patients with COPD can suffer from episodes with worsening of respiratory symptoms, called exacerbations. COPD exacerbations are defined as an acute worsening of respiratory symptoms that results in additional therapy.[1, 8] The currently used definition is the result of much debate and lack of full consensus and can be criticized for not being very precise. Contributing to this, it is clear that the spectrum of exacerbations is quite heterogeneous, in causes, severity, and treatment. In clinical trials, multiple different definitions are used, potentially leading to bias and complicating the interpretation and comparison of the results. Till today the diagnosis of an exacerbation relies exclusively on clinical assessment of the patient. A tool or biomarker that allows a more precise etiologic diagnosis would be desirable.[8, 9] COPD exacerbations are important to patients and to society: they are the main driver of quality of life in COPD, of survival, and of costs. Although exacerbations consist of a heterogeneous spectrum of pathobiological changes compared to stable COPD, including inflammation, respiratory infections, bronchoconstriction and hyperinflation, especially the severe exacerbations are treated mostly all in the same way.[10-12]
The treatment consists of bronchodilators, commonly short-acting administered via nebulizer, steroids, oxygen and antibiotics. This treatment has remained largely unchanged for years.[1, 10]
In recent years new technologies, such as improved inhalers, long acting bronchodilators, bronchoscopic lung volume reduction and imaging techniques have become available to assess and treat the COPD patient in a stable state.[1] Unfortunately, they did not yet change the practice of the treatment in the hospital of the severe exacerbation of COPD. Most knowledge about exacerbations is available about prevention, or was done in mild and moderate exacerbations, only a few attempts have been made to study severe exacerbations.[13-15]
These more severe exacerbations, however, are especially important, since they are associa-

ted with hospital admissions, loss of quality of life, and excess mortality. Lack of knowledge of these severe exacerbations could be caused by difficulties studying these patients. In mild and moderate exacerbations different changes of the lung have been detected; perhaps these apply to severe exacerbations as well. Understanding mechanisms of exacerbations might lead to more targeted and perhaps novel future treatments. [13, 15]

Changes during COPD exacerbations

Symptoms

The most prominent changes from stable state occur in symptoms. Several different symptoms are associated with exacerbations. These were used as the first tool to phenotype exacerbations 30 years ago.[16] The Anthonisen criteria based phenotyping especially on dyspnea, and change in sputum volume and purulence. As minor symptoms, wheeze, cough, sore throat or anxiety and chest pain are often reported. These symptoms can used for assessing patient reported outcome measurements (PRO). Several standardized questionnaires have been developed such as the Exact-pro, COPD assessment test (CAT) and the Clinical COPD Questionnaire (CCQ).[17-19] For now, they yield promising results in diagnosing often otherwise unreported COPD exacerbations in a research setting. However, these tests have not been really shown to reflect changes in lung function parameters, nor to differentiate between respiratory infections and other causes of increased dyspnea.

Respiratory infections

Respiratory infections are estimated to trigger approximately 70 percent of the exacerbations, of which a viral etiology is the most frequent. The remaining 30 percent are due to anxiety, hyperinflation, environmental pollution, pulmonary embolism, or have an unknown etiology.[1, 20] The different triggers cause different inflammatory processes. Viral, bacterial and eosinophilic inflammation are the most important to distinguish because of the therapeutic consequences.[11] For bacterial infections antibiotics are prescribed. However the need for antibiotics is under continuous investigation.[21] There are many reasons to be restrictive with antibiotics, among others because of increasing antibiotic resistance, their adverse effects, and the difficulty in distinguishing bacterial infections from viral infections for which antibiotics have limited use. In patients with viral infections, especially influenza antiviral agents, isolation to prevent in-hospital-spread of viruses can be considered.[22] Corticosteroids are also often prescribed, but are most effective in the exacerbated COPD patients who have an eosinophilic inflammation.[23, 24]

Since the cause of the exacerbation at least partially determines the treatment, distinguishing viral from bacterial and from non-infectious causes of exacerbations is important. To date, conventional culture of sputum is the most important diagnostic tool for bacterial infections; for viral pathogens serology has its place and more recently PCR detection techniques on nasopharyngeal swabs or sputum have made an entrance. However, these techniques are time consuming, expensive and/or require an extensive infrastructure. Thus, the search for tools to facilitate quick personalized treatment decisions is ongoing.

Hyperinflation and pulmonary function

Traditionally, stable COPD patients are monitored by pulmonary function tests (PFT) and especially the forced expiratory volume in 1 second (FEV_1). However, especially during exacerbations changes in FEV_1 are marginal and correlate poorly with patient reported

complaints such as dyspnea or with response to medication.[13, 18] Another feature of exacerbations is hyperinflation.[13-15] Hyperinflation is entrapment of air in the lungs during expiration, causing the lungs to hyperinflate.
This might be caused by increased obstruction of the airways during an exacerbation of COPD. One could hypothesize that changes in hyperinflation are more important during exacerbations than obstruction as defined by changes of FEV_1. Data about static hyperinflation during exacerbations is available, and we know now that static hyperinflation increases during exacerbations, although this has not been investigated in depth during severe exacerbations.[13, 15] One could question if the trapped air in hyperinflated patients is evenly distributed over both lungs and lobes in all patients. Perhaps the distribution of the hyperinflation is different in different types of exacerbations. A potential tool to assess this is functional respiratory imaging (FRI) with the aid of CT scans. The importance of dynamic hyperinflation is well known. In stable state we have already learned that it is closely related with symptoms and exercise limitations.[25-28] Data about dynamic hyperinflation during exacerbations has not been reported before. One could hypothesize that exercise or tachypnea induced hyperinflation is further increased during an exacerbation compared to stable state, resulting in dyspnea or other symptoms. The metronome paced dynamic hyperinflation is a test to assess this.[29]

Treatment of COPD exacerbations

Treatment of exacerbations of COPD consists of several different therapies. Corticosteroids, oxygen, antibiotics and bronchodilators are commonly used.[1, 10] The benefit of short-acting bronchodilators during exacerbations has been clearly established in improving symptoms and to a lesser degree pulmonary function. To deliver these, nebulizers are frequently used, especially in the acute setting, and many patients seem to benefit from them.[1] However, evidence is lacking to support the choice for nebulizers. This is an interesting observation, since nebulizer use is currently limited to short-acting long-acting bronchodilators whereas long-acting bronchodilators could be preferable because of generally greater bronchodilation, more improvement of hyperinflation, and a longer duration of action. Before actively advocating the use of long-acting medication, more information about the value of nebulizers versus optimal delivery by pMDI, and of short-acting versus long-acting in this setting is required.
Another option to improve the hyperinflation in stable COPD is lung volume reduction. Bronchoscopic techniques as endobronchial valves and endobronchial coils are now used to reduce lung volume and hyperinflation.[30] In selected patients this proved to be useful, however it is associated with severe adverse events as pneumothorax. The potential of this new technique and the balance with adverse events in the acute setting has not been tested.

This thesis

The goal of this thesis is to find new tools and new pathways to improve the diagnosis and treatment for severe exacerbations. We hypothesize that increased hyperinflation is relevant during exacerbations of COPD and is associated with increased symptoms. We will explore the treatment of hyperinflation in stable COPD with the perspective of a potential treatable trait in severe exacerbations. Furthermore we will test whether it is possible to quickly detect with modern point-of-care techniques the origin of the respiratory infection causing so many of these exacerbations.

In chapter two we will assess static and dynamic hyperinflation in relation with symptoms during severe exacerbations of COPD.

In chapter three we will assess whether the new point-of-care technique of an electronic nose can be used to detect viral and bacterial infections in the setting of an exacerbation of COPD.

In chapter four we will assess the heterogeneity of changes in the airways and lung volume during exacerbations of COPD.

In chapter five we will discuss the role of hyperinflation during exacerbations and its potential as treatable trait in exacerbations.

In chapter six we will assess the optimal mode of delivery of bronchodilators during acute exacerbations of COPD.

In chapter seven we will assess and discuss the bronchoscopic treatment of hyperinflation in stable COPD patients.

In chapter eight we will assess a potential predictor of pneumothorax, the most prominent complication of bronchoscopic treatment of hyperinflation by endobronchial valves in stable COPD.

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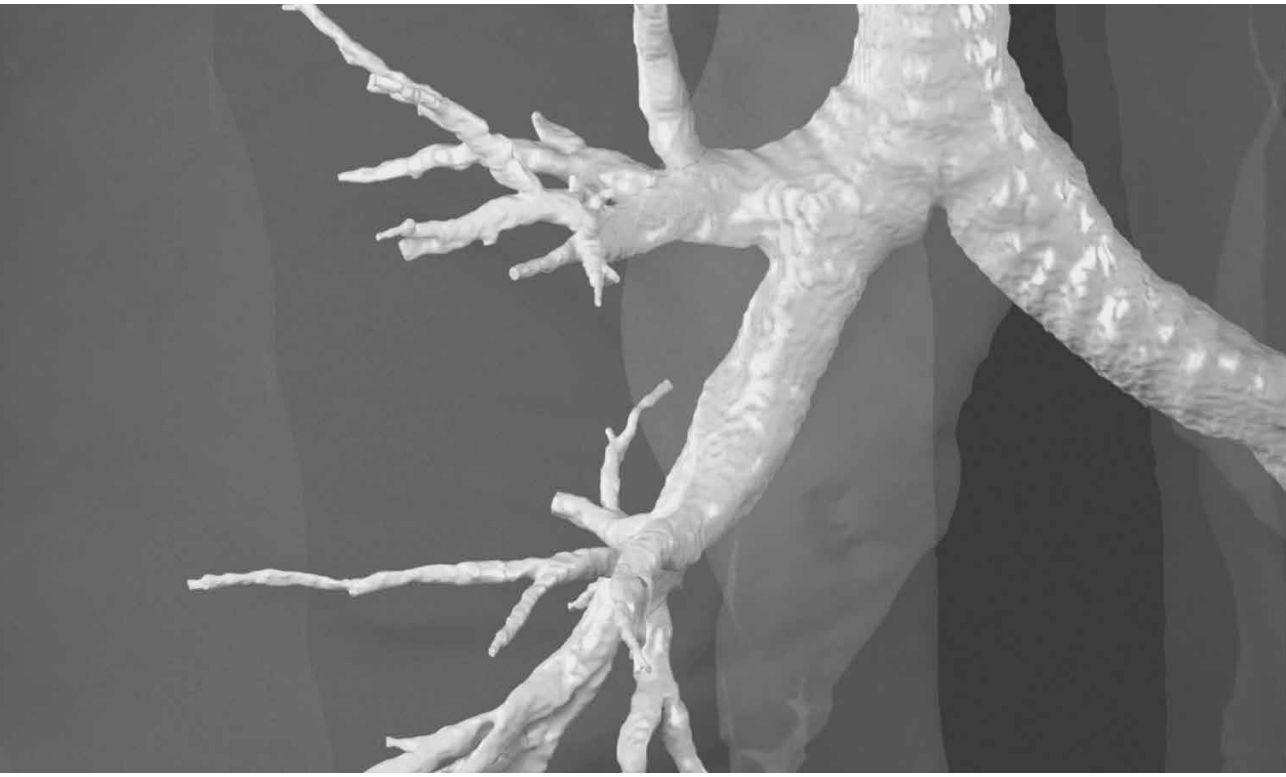

CHAPTER

2

Static and dynamic hyperinflation during severe acute exacerbations of chronic obstructive pulmonary disease

Wouter H. van Geffen and Huib A.M. Kerstjens

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ABSTRACT

Rationale

Static hyperinflation is known to be increased during moderate exacerbations of COPD (AECOPD), but few data exist in patients with severe exacerbations of COPD. The role of dynamic hyperinflation during exacerbations is unclear.

Methods

In a prospective, observational cohort study, we recruited patients admitted to hospital for an AECOPD. The following measurements were performed upon admission, and again after resolution (stable state) at least 42 days later: inspiratory capacity (IC), body plethysmography, dynamic hyperinflation by metronome-paced IC measurement, health-related quality of life and dyspnea.

Measurements and main results

Forty COPD patients were included of whom 28 attended follow-up. The IC was low at admission (2.05±0.11L) and increased again during resolution by 15.6±23.1% or 0.28±0.08 L (mean±SEM, $p < 0.01$). Testing of metronome-paced changes in IC was feasible, and it decreased by 0.74±0.06L at admission, similarly to at stable state. Clinical COPD Questionnaire was 3.7±0.2 at admission and improved by 1.7±0.2 point ($p < 0.01$), and the Borg dyspnea score improved by 2.2 ±0.5 points from 4.4±0.4 at admission ($p < 0.01$).

Conclusions

Static hyperinflation is increased during severe AECOPD requiring hospitalisation compared with stable state. We could measure metronome paced dynamic hyperinflation during severe AECOPD but found no increase.

INTRODUCTION

COPD (chronic obstructive pulmonary disease) is currently the fourth leading cause of death and predicted to become the third by 2020.[1] Chronic airflow limitation is the defining characteristic of COPD. This limitation is caused by a mix of small airways disease and parenchymal destruction caused by chronic inflammation.[1]

Important in the clinical course of COPD are episodes with worsening of respiratory symptoms from the stable state and beyond normal day-to-day variations, which require additional treatment.[1] These exacerbations are associated with viral or bacterial airway infections in the majority of cases. Most exacerbations are of mild or moderate severity; only about 4% is categorized as severe.[2] Severe exacerbations require hospital admission and are associated with increased mortality, morbidity, and health care costs.[3-5]

Apart from classification by severity (level of care) and infectious cause, little has been done to categorize exacerbations of COPD. Lopez-Campos and Agusti proposed a dual axes system for categorising and thereby for treating exacerbations, classifying exacerbations on an axis of severity and of infectious or eosinophilic inflammation.[6] We believe that hyperinflation is another important component.[7] Hyperinflation is a better predictor of symptoms than most of our physiological parameters, and also is a predictor of mortality in stable state.[8,9] Furthermore different treatment strategies can be considered for hyperinflated patients.

Static hyperinflation is caused by entrapment of air during expiration, due to peripheral airway obstruction. This can be observed especially by destruction of alveolar attachments to small airways when the disease becomes more severe. Hyperinflation is characterized by increased functional residual capacity (FRC) and reduced inspiratory capacity (IC), resulting in increased dyspnea and limitation of exercise capacity.[1,10-12] During tachypnea and exercise, hyperinflation can increase further, and this is called dynamic hyperinflation. Dynamic hyperinflation is at least partly caused by a shortening expiration time thus preventing patients to exhale completely thereby causing air trapping.[13-15] Dynamic hyperinflation of the lungs is known to limit exercise capacity in stable COPD and to impact on the perception of dyspnea.[10,16,17]

Only a few groups have attempted to study the course of hyperinflation during exacerbations. Parker et al. included 7 hospitalized patients and 13 out patients with moderate exacerbations.[18] They measured dyspnea and lung volumes with plethysmography. They found that after resolution of the exacerbation some COPD patients showed an increase in inspiratory capacity (therefore decrease of hyperinflation) and improvements in dyspnea. Stevenson et al studied admitted patients.[19] They measured symptoms with a BORG score and volumes with spirometry but lacked direct measurements of hyperinflation for instance with body plethysmography. Although both studies reported dyspnea changes in subgroup analyses, these studies did not analyse the temporal relation between changes in symptoms and changes in hyperinflation. These two studies provide a strong direction of thoughts regarding static hyperinflation. However, they did not completely answer the question whether and to what degree static hyperinflation is present during severe acute exacerbations of COPD and whether increased static hyperinflation is associated with more symptoms. Moreover, they did not assess dynamic hyperinflation.

This study was designed to confirm the presence of static hyperinflation in severe acute exacerbations and to analyse this in more depth with body plethysmography. Secondly, this study was aimed to assess dynamic hyperinflation. Furthermore we hypothesized that improvement in dyspnea and quality of life during and after admission for an acute COPD exacerbation is closely related to changes in both static and dynamic hyperinflation.

METHODS

Subjects

Patients admitted with an acute COPD exacerbation were eligible for the study. The inclusion criteria we employed were: 40 years or older, doctor's diagnosis of COPD based on an incompletely reversible airflow obstruction defined as: 1) a post-bronchodilator forced expiratory flow in one second (FEV_1)/forced vital capacity (FVC)< 70% and 2) post-bronchodilator FEV_1< 80% predicted. An exacerbation was defined as a worsening of respiratory symptoms from the stable state and beyond normal day-to-day variations, which requires additional treatment. Excluded were patients with an X-ray confirmed pneumonia, an indication for (non) invasive ventilation, admission to an intensive care unit, unstable angina pectoris or other clinically important cardiac co-morbidity requiring admission to a cardiology ward. Additionally, we excluded patients who received any investigational new drug within the last 4 weeks prior to admission. In concordance with the Dutch law and approved by our ethics committee (Medisch Ethische Toetsingscommissie Universitair Medisch Centrum Groningen), informed consent was obtained verbally within the first 24 hours of admission, and written informed consent was obtained in the first 48u after the patient had had time and energy to read the paperwork. Data of patients who did not finally provide written informed consent were excluded from the study.

Design

This trial was registered in the WHO approved International Clinical Trials Registry Platform, the Netherlands Trial Registry (NTR 4600). The study was conducted in the emergency room and pulmonary ward of a university teaching hospital in the Netherlands. Participants were tested after inclusion, prior to discharge, and after discharge in stable state at day 42 or later. Patients were allowed entry into the trial only once. Baseline characteristics were obtained, including X-ray, medication use, differential blood count, cultures and swabs for viral polymerase chain reaction. Treatment according to local guidelines included steroids (between 30-40 milligrams of prednisolone), antibiotics, antivirals, oxygen, and bronchodilators, all as needed. Individual doses of each were titrated, and the decisions about admittance and discharge were made by the treating physician who was not involved with the study team.
The primary outcomes were the changes in static hyperinflation (as measured by inspiratory capacity via spirometry(IC)) during resolution of the COPD exacerbation, and changes in health-related quality of life (HR-QoL; primary: Clinical COPD Questionnaire(CCQ)) and dyspnea (BORG score)).
The secondary outcomes were the changes in dynamic hyperinflation (as measured by inspiratory capacity during the metronome paced dynamic hyperinflation test) during resolution of the COPD exacerbation, changes in HR-QoL by COPD assessment test (CAT) and modified medical research council dyspnea score (mMRC), changes in other static hyperinflation volumes such as functional residual capacity (FRC), residual volume(RV), total lung capacity (TLC), as well as changes in FEV_1 and FVC during the resolution of the exacerbation.

Procedures

Spirometry was performed on working days during admittance, post medication; no pre-bronchodilator lung function was attempted. Once during admission and once in stable state a body plethysmography (Jaeger MasterScreen, CareFusion) was performed as per ATS/ERS criteria.[20] When measuring static hyperinflation the lung function technician aimed to measure the volumes at an elastic recoil pressure of the respiratory system of zero.

Metronome paced hyperinflation was performed once during admission and stable state. Subjects were requested to breathe at a metronome paced frequency of 40/min during 30 seconds. Before increased pacing and immediately afterwards an IC maneuver was performed. Subjects were coached to maintain as much as possible a stable tidal volume. After at least 2 minutes this measurement was repeated. Acceptability criteria of <150ml and/or <5% were used (Oxygon Jaeger, CareFusion).
Pulmonary function testing during acute exacerbations is difficult for both patients and staff. If patients failed to produce a reliable value the test was disregarded and was treated as missing value.
The diagnosis of an infection was established if the either the culture or nose swab tested positive. The swab used a polymerase chain reaction (PCR) with primers for the 15 most common respiratory viruses in the Netherlands with a cutoff cycle threshold of 40.

Statistical Analyses

Data was analysed with IBM SPSS 24. Normally distributed data with 2 time points was assessed with paired t tests. Variables with multiple time points were first assessed by ANOVA to obtain an f ratio. If the f ratio indicated a significant difference, a paired t test was performed to assess the difference between admission and stable state. Unpaired t tests were used to compare unpaired means. Bivariate correlations by Pearson were calculated to assess correlations between two variables.
No formal power calculation was deemed possible since no relevant data were identified adequately reflecting our target population. Based on previous studies we anticipated drop-outs; our ambition to perform reliable measurements based on the ATS/ERS criteria would only increase that. Aiming to measure a difference of 100 ml of change in IC, we roughly estimated the necessity of 25 evaluable patients. This estimated sample size was approved by the ethics committee.

RESULTS

From September 2014 till April 2016 patients admitted to the respiratory ward from our tertiary university hospital with an acute exacerbation of COPD were recruited. Forty-four patients provided their verbal informed consent upon admittance, forty-one of them provided written informed consent within the first 24 hours; one of these developed a pneumothorax and had to be excluded from the analysis, leaving 40 subjects included. Of 12 patients, no follow-up was obtained largely due to not being in stable state or not able to attend the follow up. A flowchart of the study is provided in Figure 2.1. Baseline characteristics are provided in Table 2.1.

Figure 2.1 Flowchart of the trial

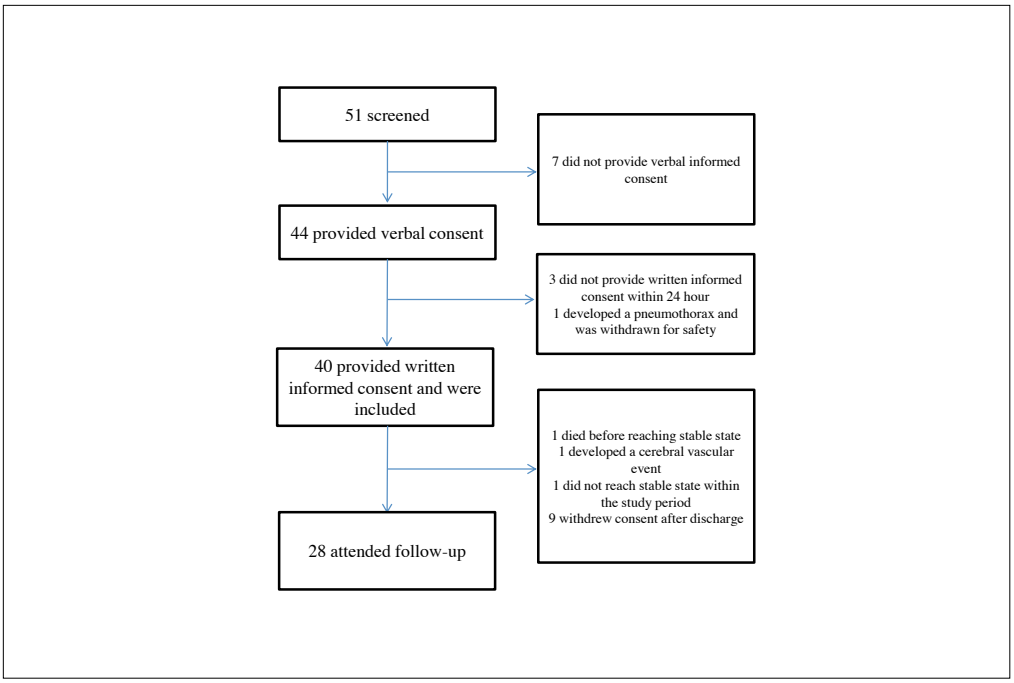


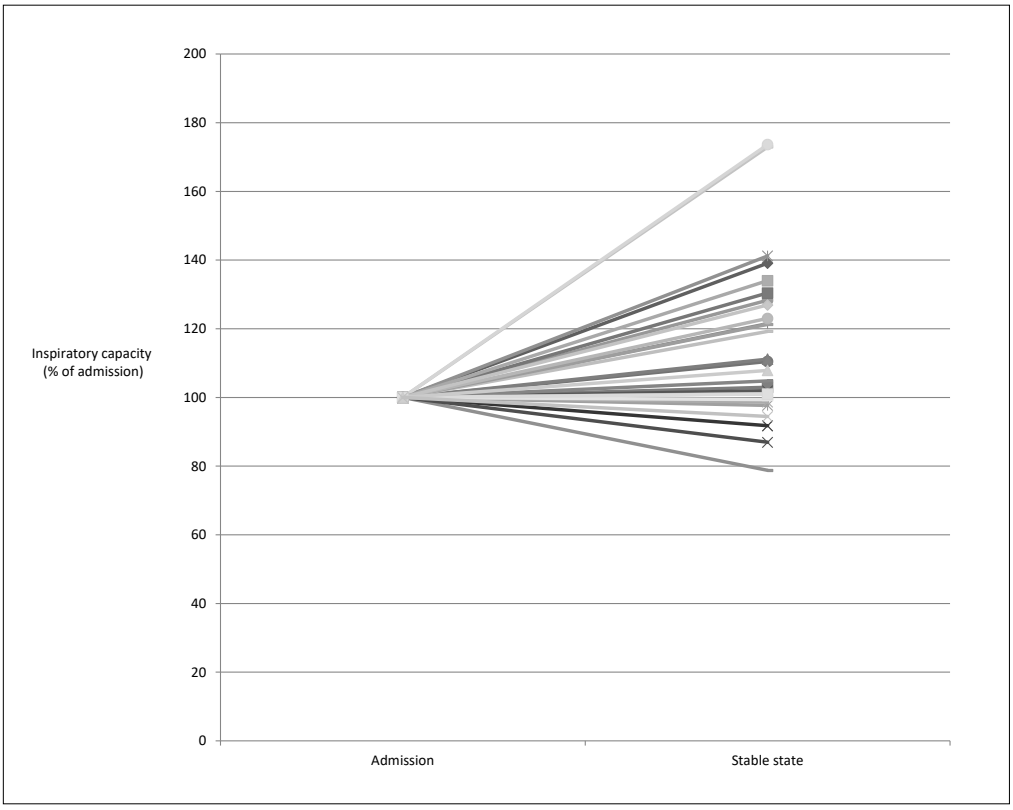
Table 2.1 Baseline characteristics

Characteristics	Value (SD)
Number of Patients	40
Age, yr	66 (10)
Sex, % male	52.5
Former smoker, %	70
Current smoker, %	30
Number of pack-years	49 (35)
Body mass index, kg/m2	24.9 (4.8)
Post-bronchodilator FEV1 (% predicted) in stable state	51 (18)
Post-bronchodilator FEV1 (liters) in stable state	1.3 (0.6)
Viral infection, %	47.5
Bacterial infection,%	42.5
Blood Eosinophils, 10E9/L	0.15 (0.19)
Blood Neutrophils,10E9/L	8.6 (3.7)
pH on admission	7.43 (0.04)
PaO2 (kPa) on admission	8.6 (2.1)
PaCO2 (kPa) on admission	5.4 (1.0)
Antibiotics % of usage during admission	62.5
Antiviral medication % of usage during admission	7.5
Days to discharge	5 (2)
6 month Readmission rate %	40

Values are presented as mean (SD) unless stated otherwise

The primary endpoint, change in static hyperinflation measured by inspiratory capacity, showed an improvement of 0.28±0.08 Liter, or 15.6±23.1% (mean±standard error of the mean (SEM)) from admission to stable state (p<0.01). This was accompanied by an improvement in CCQ of -1.7±0.2 points and in BORG score of -2.2±0.5 points. No correlation between the change in IC and change in CCQ (r= 0.12, p=0.58) or change in BORG (r=-0.2, p=0.36) was found. The relative changes in the inspiratory capacity of each individual participant are plotted in Figure 2.2.

Figure 2.2 The relative changes in the inspiratory capacity of each individual participant



Y axis: *percentage of inspiratory capacity change for each individual within this study.*

Of the secondary endpoints, static hyperinflation, measured as change in FRC by bodyplethysmography, improved significantly by 334±102ml (p<0.01). RV decreased significantly by 501±140ml, or as percentage predicted 22±6 % (p<0.01). As expected, TLC did not change during the resolution of the exacerbation. Dynamic hyperinflation (as measured by change in inspiratory capacity during a metronome paced test) did not change significantly during the recovery from the exacerbation. Symptoms improved during the resolution of the exacerbation in all questionnaires (*Table 2.2*). The change in dynamic hyperinflation did not correlate with the change in symptoms.

Table 2.2 Recovery from severe acute exacerbations of chronic obstructive disease measured at admission, discharge and in stable state.

	Admission		Discharge		Stable state		Change		
	Subjects n	mean±SD	*Subjects n*	mean±SD	*Subjects n*	mean±SD	*Subjects n*	mean±SD	
Spirometry									
FEV1 (L)	*39*	1.05±0.52	*37*	1.10±0.52	*28*	1.35±0.57	*28*	0.28±0.37	*
FVC (L)	*36*	2.61±0.85	*36*	2.98±0.85	*28*	3.29±0.88	*26*	0.58±0.68	*
Static Hyperinflation									
IC (L)	*36*	2.06±0.65	*34*	2.13±0.67	*28*	2.40±0.70	*27*	0.28±0.41	*
IC (% predicted)	*36*	74±20	*34*	76±20	*28*	88±20	*27*	10±17	*
IC relative to admission (%)	*36*	100±0	*31*	104.4±17.8	*27*	115.6±23.1	*27*	15.6±23.1	*
FRC (L)			*28*	4.86±1.64	*25*	4.36±1.29	*22*	-0.33±0.48	*
RV (L)			*28*	3.76±1.34	*25*	3.09±1.08	*22*	-0.50±0.66	*
TLC (L)			*28*	6.82±1.72	*25*	6.72±1.47			
Dynamic hyperinflation									
IC after metronome (L)			*25*	1.3±0.59	*25*	1.48±0.50			
IC change after metronome (L)			*25*	-0.74±0.31	*25*	-0.82±0.43			
Symptoms									
CCQ	*39*	3.7±0.9	*38*	2.7±1.0	*25*	1.9±1.1	*25*	-1.7±1.1	*
BORG	*39*	4.4±2.2	*38*	2.7±1.7	*25*	1.7±1.7	*25*	-2.2±2.4	*
mMRC	*39*	3.4±1.0	*38*	3.2±0.9	*25*	2.4±1.3	*25*	-1.1±1.2	**
CAT	*25*	26.2±7.0	*25*	20.8±6.0	*25*	16.5±9.0	*25*	-8.1±8.1	*

Data are presented as mean ± standard deviation.: p<0.01 significant improvement from admission to stable state by paired t-test. ** Significant improvement from admission to stable state by non parametric Wilcoxon rank test. CCQ: Clinical COPD Questionnaire; BORG: Borg dyspnea score; mMRC: modified medical research council; CAT: COPD assessment test; IC: inspiratory capacity; FRC: functional residual capacity; RV: residual volume FEV_1: forced expiratory flow in one second; FVC: forced vital capacity; TLC: total lung capacity.*

Table 2.3 Differences between patients with additionally increased hyperinflation during their exacerbation versus the patients without additional hyperinflation; increased hyperinflation was defined as a difference in IC of at least 100 mL between exacerbation and stable state.

	Additional hyperinflation (IC change >100 ml)		No additional hyperinflation (IC change <100 ml)		
	Number	Mean±SD	Number	Mean±SD	
Number of patients	15		12		
Sex (number of males)	8		6		
Admission time (days)		4.87±1.68		5.00±1.91	
Age (yr)		65.87±5.79		62.92±9.48	
BMI		27.11±3.58		22.82±5.06	*
Packyears		55.42±39.23		49.00±41.18	
pH (kPA)		7.42±0.05		7.44±0.03	
PaCO2 (kPA)		5.43±0.85		5.35±0.63	
PaO2 (kPA)		7.82±2.94		8.61±3.69	
Neutrophils admission (10e9/L)		8.26±1.75		9.41±2.86	
Eosinophils admission (10e9/L)		0.10±0.06		0.27±0.29	*
Postive viral PCR	8		5		
Postive bacterial culture	4		7		*
Lungfunction					
FEV_1 in stable state (L)		1.43±0.66		1.24±0.48	
Change in FEV_1 (L)		0.40±0.26		0.18±0.44	
IC during admission (L)		2.10±0.72		2.12±0.53	
IC stable state (L)		2.68±0.74		2.03±0.49	*
Change in IC (L)		0.58±0.28		-0.09±0.18	*
FRC plethysmograph admission		4.63±1.56		4.70±1.55	
FRC plethysmograph stable		4.23±1.29		4.64±1.32	

**P<0.05 in unpaired T tests. ** P<0.05 non parametric independent sample test. Data are presented as mean ±standard deviation. BMI: body mass index; PCR: polymerase chain reaction; IC: inspiratory capacity; FRC: functional residual capacity; RV: residual volume FEV_1: forced expiratory flow in one second; FVC: forced vital capacity; TLC: total lung capacity; CCQ: Clinical COPD Questionnaire; BORG: Borg dyspnea score; mMRC: modified medical research council; CAT: COPD assessment test.*

We compared patients with additional hyperinflation during the exacerbation with patients without additional hyperinflation (Table 2.3). The additionally hyperinflated group was defined as those patients whose inspiratory capacity improved 100 milliliters or more after recovery. The hyperinflated group had larger ICs and lower mMRC dyspnea scores (both significant) in stable state and additionally tendencies for greater improvement in mMRC and Borg dyspnea scores (both non-significant) during resolution. Interestingly, the group without additional hyperinflation during exacerbation, had a higher number of eosinophils in peripheral blood at admission and a lower BMI.
No difference in dynamic hyperinflation between the groups was detected. Subdividing the groups based on IC/TLC above or below 0.25 (instead of on decreased IC), yielded similar results, independent of whether exacerbation or stable state data were used.

An exacerbation is often associated with a viral or bacterial airway infection. To assess the hyperinflation in relation to these infections, hyperinflation was analyzed in the subgroups based on the presence or absence of a viral or bacterial infection (Table 2.4). A significant change in static hyperinflation was observed in patients with a culture positive bacterial infection, where no change was detected in the group without bacterial infection, these changes however did not statistically differ from one another (P=0.32). No difference was found in change in hyperinflation in patients with versus without a viral infection.
No difference in dynamic hyperinflation was observed between any of the subgroups.

Table 2.4 Differences in hyperinflation between exacerbations with and without a viral or bacterial infection.

	Static Hyperinflation					Dynamic Hyperinflation		
	IC admission (L)	IC discharge (L)	IC stable State (L)	IC change (L)	P value	DH admission (IC change in L)	DH stable State (IC change in L)	P value
Bacterial infection	2.3 ± 0.7	2.5 ±0.7	2.7 ±0.8	-0.4	<0.01*	-0.8 ± 0.3	-1.0 ± 0.5	0.4
No Bacterial infection	2.0 ± 0.5	2.0 ± 0.6	2.1 ± 0.5	-0.2	0.29	-0.7 ± 0.3	-0.7 ± 0.3	0.9
Viral infection	2.1 ± 0.7	2.3 ± 0.7	2.4 ± 0.7	-0.2	0.02*	-0.8 ± 0.3	-0.8 ± 0.3	1.0
No viral Infection	2.0 ± 0.6	1.9 ± 0.6	2.4 ± 0.7	-0.3	0.03*	-0.7 ± 0.3	-0.8 ± 0.5	0.2

Data are presented as mean ±standard deviation. p value: Difference between admission and stable state by paired t-test

DISCUSSION

This study showed a more complete picture of the course of static and dynamic hyperinflation in patients hospitalized for acute severe exacerbations of COPD, and its resolution towards stable state. Static hyperinflation is increased during acute severe exacerbations compared with stable state. We were able to measure dynamic hyperinflation during the exacerbation, but found no further increase (above the increase in static hyperinflation). No correlation between change in hyperinflation and symptoms was found.
COPD exacerbations are the main cause for admissions of COPD patients and hospital related mortality and morbidity in COPD patients is high. Nevertheless, little is known about the physiology of such exacerbations,[3,21-24] and there is not really a universally accepted clinical definition of a COPD exacerbation nor of strict criteria when to admit.[3,25] Although efforts have been made to better define and prevent exacerbations in several recent trials, the treatment of an exacerbation in the hospital has remained mostly unchanged for the last 2 decades.[1,26-29]

Two previous studies assessed static hyperinflation in the setting of an acute exacerbation of COPD. Our results in in-patients are in line with the results of the study of Parker (n=20), who studied mostly outpatients with less severe exacerbations than in the current study.[18] The study of Stevenson (n=22) did study the same group of patients as the current study, but provided only the change in inspiratory capacity as measured by spirometry, without the confirmation of body plethysmography. Our data confirm their results and extend them with additional measurements.[19]
Assessment of dynamic hyperinflation has not been described before in the setting of an acute severe exacerbation of COPD to our knowledge. Patients were measured in this trial with a metronome paced test aimed at changes in inspiratory capacity during tachypnoea.[12,30]

No changes in dynamic hyperinflation between the exacerbation and stable state were found. Multiple explanations are possible for this result. It could indicate that patients with an exacerbation severe enough to require admission, are limited by something else than hyperinflation, e.g. airway resistance, mucus, hypercapnia or a change in ventilation/perfusion ratio. Another explanation could be that admitted patients already have a severely decreased inspiratory reserve capacity before admission and hardly have any room for further deterioration, as opposed to patients who do not need admission and in whom past data have shown decreasing ICs during exacerbations. Another explanation lies in the breathing frequency and tidal volume during the metronome paced dynamic hyperinflation test. Due to ethical and practical concerns we imposed a frequency of 40, with a stable tidal volume during both tests. An alternative would have been to double their breathing frequency, which we deemed impossible for patients during severe exacerbations of COPD. A further increase in breathing frequency could have allowed to find an additional dynamic hyperinflation component.

Next, measurement of static hyperinflation depends on being able to measure at zero elastic recoil level.[13] Although every attempt was made to achieve this, it is more difficult to achieve during severe exacerbations. If this elastic recoil cannot be achieved for the first FRC of the dynamic measurement, i.e. before increasing the breathing frequency, dynamic hyperinflation (decrease in IC) during metronome pacing will be underestimated. Finally, one could discuss whether the test used in the current trial is the optimal standard to detect dynamic hyperinflation.[13,31] Based upon ethical arguments, the study team chose not to perform the more commonly used and better validated exercise test during the acute distress of severe exacerbation requiring admission.

Hyperinflation might provide a target for therapeutic strategies in patients with severe exacerbations. Patients admitted with a severe exacerbation of COPD are most commonly treated with short acting bronchodilators via nebulizers. Long-acting bronchodilators, both anticholinergics and beta-2-mimetics, have been shown in stable state to provide larger reductions in hyperinflation compared to short-acting bronchodilators, alongside greater increases in flows.[32-37] Long-acting bronchodilators however are not commonly available via nebulizers. A recent Cochrane review showed that after several decades of treatment with nebulizers, there is still no evidence to favour nebulizers over regular pressurised metered dose inhalers (pMDI)with good instruction.[26] New studies should shed light on the potential of combined long-acting bronchodilators on reduction of hyperinflation during severe exacerbations requiring hospitalisation. Such a trial could compare combined long-acting

bronchodilators in currently available pMDI or DPI versus short acting bronchodilators by nebulizer, the latter being usual care in many hospitals. Based on the finding that hyperinflation is increased during exacerbations, we can speculate that the long acting bronchodilators provide an early treatment for impending hyperinflation-predominant exacerbations of COPD, thus preventing some of them.[38,39] Other strategies such as rehabilitation and non-invasive ventilation have been shown to reduce hyperinflation, while cognitive-behavioural strategies and perhaps even bronchoscopic lung volume reduction interventions could be further investigated as treatment of hyperinflation in selected patients during an acute event.[7,40]

Interestingly, patients who did hyperinflate during an exacerbation of COPD had higher ICs during stable state and fewer symptoms (CCQ, mMRC and BORG) both in stable state and during exacerbations. In other words, they had a better preserved inspiratory reserve capacity. This could perhaps also explain the lack of correlation between decrease in IC (worsening of hyperinflation) and increase in symptoms. One could argue that patients who do not hyperinflate during an exacerbation, are those patients who in stable state already have a flow limitation and are less able to increase their IC. This could result in more symptoms both during and after the exacerbation. This explanation is supported by the non-significant observation that symptoms improve more during resolution in patients with additional hyperinflation during exacerbations.
Increased static hyperinflation was found in patients with a bacterial or viral infection. The patients without a cultured bacterial infection showed no increased static hyperinflation during their exacerbations. These changes however do not significantly differ. This might suggest that the presence or absence of increased hyperinflation is related with an infectious origin, however more research and a larger sample size would be necessary before drawing conclusions from this subgroup analysis.

This study has several strengths but also weaknesses that should be considered. A strong point of the study was that treatment decisions as bronchodilator dose and discharge were made by the treating physician without influence from the trial team and without influence by the study measurement results. Another strong point of the trial is that we excluded patients with pneumonia. This will make the results from the trial more applicable towards exacerbations, since pneumonia might influence lung volumes. Patients who were in such distress that (non) invasive ventilation was required were also excluded in order to prevent bias due to inability to perform reliable pulmonary function tests. A weakness of the study is that has been performed in only one center, potentially limiting the applicability of its results. Due to the severity of the exacerbation and disease, a relative high number of patients was not able or willing to provide reproducible pulmonary function tests, or attend follow-up. Especially the intensive tests including the static and dynamic hyperinflation tests and spirometry repeatedly during the hospitalization were quite a burden on patients.

Static hyperinflation turned out to be an important feature of severe acute exacerbations of COPD in our population. We believe this supports discussions whether he occurrence of hyperinflation should be incorporated in a new definition, since it is a common but not universal finding and opens a path towards a more precision medicine strategy in treatment. To our surprise changes in hyperinflation were not directly correlated with symptoms although hyperinflated patients showed lower changes in symptoms. There must be other

factors as well. Perhaps a model incorporating hyperinflation, along with the current parameters of inflammation and respiratory infections will help to work on a future definition.

In summary, this study measured changes in static and dynamic hyperinflation during acute severe exacerbations of COPD requiring hospital admittance. The increases in static hyperinflation were anticipated based on two earlier studies, only partially performed in hospital with less severe exacerbations. They have now been confirmed with body plethysmography. We were bold enough to attempt at measuring dynamic hyperinflation during acute exacerbations in the hospital setting, but could not find a further increase up and above the change in static hyperinflation already induced by the exacerbation.

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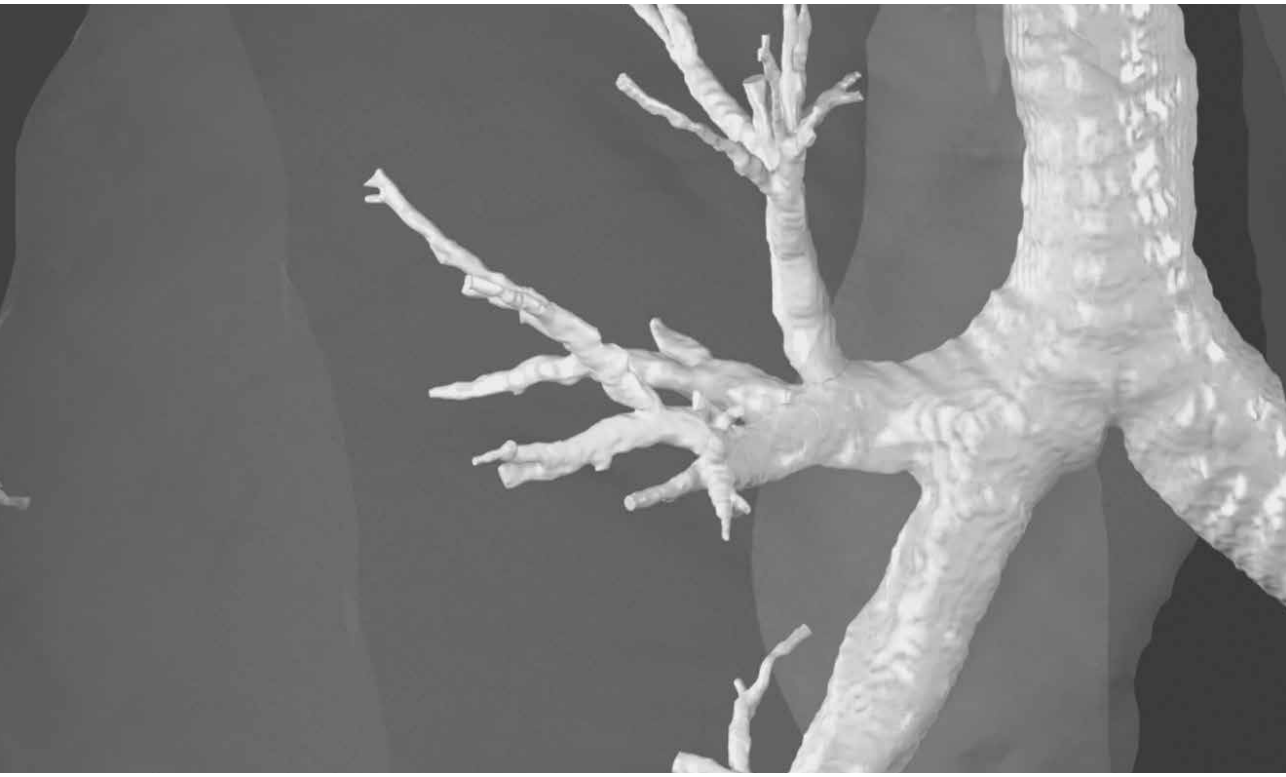

CHAPTER

3

Diagnosing viral and bacterial respiratory infections in acute COPD exacerbations by an electronic nose: A pilot study

Wouter H. van Geffen, Marcel Bruins and Huib A.M. Kerstjens

Adapted from *J Breath Res.* 2016;10(3):036001
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ABSTRACT

Background

Respiratory infections, viral or bacterial, are a common cause of acute exacerbations of chronic obstructive pulmonary disease (AECOPD). A rapid, point-of-care, and easy-to-use tool distinguishing viral and bacterial from other causes would be valuable in routine clinical care. An electronic nose (e-nose) could fit this profile but has never been tested in this setting before.

Methods

In a single-center registered trail (NTR 4601) patients admitted with an AECOPD were tested with the Aeonose® electronic nose, and a diagnosis of viral or bacterial infection was obtained by bacterial culture on sputa and viral PCR on nose swabs. A neural network with leave-10%-out cross-validation was used to assess the e-nose data.

Results

43 patients were included. In the bacterial infection model, 22 positive cases were tested versus the negatives; and similarly 18 positive cases were tested in the viral infection model. The Aeonose was able to distinguish between COPD-subjects suffering from a viral infection and COPD patients without infection, showing an area under the curve (AUC) of 0.74. Similarly, for bacterial infections, an AUC of 0.72 was obtained.

Conclusion

The Aeonose e-nose yields promising results in "smelling" the presence or absence of a viral or bacterial respiratory infection during an acute exacerbation of COPD. Validation of these results using a new and large cohort is required before introduction into clinical practice.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the 3rd cause of death worldwide.[1] A significant part of the morbidity and mortality cases, and of the costs of COPD is related to exacerbations. The most common causes of these exacerbations appear to be respiratory infections, by viral or bacterial origin.[2] However, differences in inflammatory status, level of hyperinflation, and anxiety contribute as well.[3,4] The mainstream of medical treatment consists of bronchodilators, which can be administered by nebulizers or inhalers, and corticosteroids.[2] The need for antibiotics is under continuous investigation and discussion.[5] There are many reasons to be restrictive with antibiotics, among which increasing antibiotic resistance, their adverse effects, and the difficulty in distinguishing between bacterial infections, and viral infections in which case antibiotics should not be administered.[3]

This leads to an important clinical challenge: to quickly distinguish between viral, bacterial, and non-infectious causes of exacerbations. Bacterial culture of sputum is the most important diagnostic tool for bacterial infections; for viral pathogens serology is commonly used, and more recently, PCR is applied in some hospitals. However, these techniques are time consuming, expensive and/or require an extensive infrastructure. So the search for improved screening tools to make important treatment decisions continues. Preferably, these tools should support decisions preventing in-hospital-spread of viruses as well.[6] Such a screening tool needs to be easy-to-use, patient friendly, quick, and preferably fit for point-of-care testing. It will be even more useful in settings with limited or no microbiological support.
An electronic nose, (e-nose) could become this new screening tool. An e-nose measures volatile organic compounds (VOC's). A large number of VOCs is present in exhaled breath.

Electronic noses can be based on several different technological principles, e.g. sensor arrays consisting of conducting polymers, quartz-microbalance based sensors, nanomaterial-based sensors, and colorimetric sensors. [7,8]

In the Aeonose®, metal-oxide sensors are used. Using this specific technology, it has been feasible to distinguish between tuberculosis infections and other lung diseases.[9]

E-noses using other techniques have been capable of diagnosing bacterial sinusitis and ventilator-associated pneumonia.[10,11] E-noses have been used to distinguish between asthma and COPD, and more recently in more advanced trials in profiling stable COPD and Asthma.[8,12-14] It is also possible now to identify whether patients are suffering from an exacerbation of COPD or not.[15]

So far, electronic noses have not been tested in the setting of acute exacerbations of COPD, especially not from the viewpoint of choosing treatment guided by possible etiologies of the exacerbation. In contrast to some other e-noses, the recently developed handheld Aeonose® is easy-to-use, patient friendly, and quick. Collection bags are not required. Besides this, calibration models can be transferred to other Aeonose devices removing the need for calibrating e-noses individually.[16] This enables point-of-care testing, opening up the possibility of a tool being used for daily practice in exacerbation treatment.
This trial was designed to assess the Aeonose for rapid, easy-to-use, patient friendly, discrimination between causes of exacerbations of COPD. The hypothesis tested is that using this

e-nose, it is feasible to detect the presence of a viral or bacterial cause of acute exacerbations of COPD.

METHODS

This trial was registered in the WHO approved International Clinical Trials Registry Platform, the Netherlands Trial Registry (NTR 4601).

The study was conducted in the emergency room and pulmonary ward of our university teaching hospital in Groningen (The Netherlands).

Subjects

Patients diagnosed with COPD by current GOLD standards were screened.[2] The main criteria used were postbronchodilator forced expiratory volume in one second < 80% predicted and postbronchodilator forced expiratory volume in one second/forced vital capacity < 0.70. All patients were former or current smokers.

All were diagnosed with an acute exacerbation of COPD and hospitalized. The diagnosis was made based on the GOLD definition of an acute event characterized by worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.[2] During the first days of their hospital stay, sputum cultures, nose brush for PCR for viral respiratory infections, and exhaled breath analysis by Aeonose were obtained. Blood cultures were taken if deemed necessary by the treating physician.

Participants needed to fit the inclusion criteria: a diagnosis of COPD, a confirmed COPD exacerbation, admission to the pulmonary ward, and a sputum bacterial culture and nose swab for viruses. Subjects were excluded if they suffered from lung cancer, respiratory insufficiency requiring ventilation, or if they could not adequately hold the Aeonose during the test themselves. Patients with a pneumonia confirmed by chest radiograph were excluded as well. Patients were treated during their admission with bronchodilators, corticosteroids, and supplemental oxygen. Besides this, most were also treated with antibiotics. All participants provided informed consent before performing study procedures and after being informed on the purposes and details of the investigation. Based on earlier pilot studies for different indications with this e-nose, a sample size of 40 subjects was chosen.

Primary Endpoints

The ability to ascertain the presence of a respiratory bacterial infection during an acute exacerbation of COPD by Aeonose.

The ability to ascertain the presence of a respiratory viral infection during an acute exacerbation of COPD by Aeonose.

Decision rules

Decision rules were agreed upon and followed by the study team regarding the issue whether participants suffered from a bacterial -, a viral -, or no respiratory tract infection.
The diagnosis viral infection was established if the nose swab was tested positive by a polymerase chain reaction (PCR). Primers for the 15 most common respiratory viruses in the

Netherlands were used. A viral infection was established negative if the test result were negative with a cutoff cycle threshold of 40. The diagnosis bacterial infection was established if either blood or sputum culture was positive for a bacterial pathogen. A bacterial infection was established negative if the test result showed negative. Patients suffering from both bacterial and viral infections were allowed to be included.

Spontaneous sputum samples were cultured on sheep blood, chocolate, and MacConkey agar plates at 35°C for 48 hours in 5% CO2. Sputum culture was considered positive if the cultured microorganisms are potentially pathogenic, the growth density in the culture is high (semi quantitative), the number of squamous epithelial cells is <25, and the number of the leukocytes in the Gram-stained preparation of the sputum sample is >15 per high power field (100 × 10). This corresponds with the Geckler and Bathoorn group. [17,18]

The Aeonose

The Aeonose (The eNose Company, Zutphen, the Netherlands) is a handheld device (Figure 3.1) using 3 metal-oxide sensors (AMS Premstaetten, Austria), which consist of different metals that allow for various interactions with volatile compounds. These include carbon monoxide (AS-MLC), nitrogen dioxide (AS-MLN), and volatile organic compound (AS-MLX) sensors. Over these sensors, exhaled air is guided. At the sensors surfaces, redox reactions can occur. These reactions lead to conductivity changes that are measured. The sensors are exposed to a sinusoidal temperature cycle between 280° C and 340° C thus providing information on the temperature dependence of the redox reactions as the conductivity is measured 32 times during each cycle. The temperature profile consists of two consecutive cycles lasting 20 seconds in total, thus resulting in 64 values every 20 seconds for each of the 3 sensors. This leads to a conductivity pattern for the VOCs present in the exhaled breath.
In order to achieve data reproducibility, temperature control of the sensors is within approximately 1 °C.

Patients are asked to breath normally in and out through the device during 5 minutes.
No collection bags are required so exhaled VOCs are analyzed in real-time.
During the first two minutes, no measurements are recorded and this period of time is used for clearing the lungs with filtered air. During the next three minutes, conductivity values of exhaled air are recorded. After these five minutes, the patient can stop breathing through the Aeonose, and the device starts regenerating the sensors by flushing with air. After this, a Tenax® tube is heated and VOC's released are guided over the sensors. Then the sensors are regenerated with air. In that way, a full measurement takes 15 minutes, and during 12 minutes conductivity values are recorded. The disposable mouthpieces are equipped with a HEPA-filter to provide hygiene. This mouthpiece also contains a carbon filter to ensure the patient does not inhale volatiles that could disturb the measurement. A nose clamp is used to make sure the subject is breathing through the mouth.
The Aeonose weighs 650 grams. Note that the Aeonose measures an integrated breath profile, not a specific VOC in the exhaled breath.

The main objective of this device is to classify the measured conductivity pattern of a subject. Therefore, it is necessary to train the Aeonose by exposing it to the breath of a series of well-diagnosed individuals according to the groups of the protocol. In that way, the Aeonose

can learn to distinguish between groups. The methodology for achieving this is described in the next section.

Figure 3.1 The Aeonose in use.

Statistical analysis

As described in literature the evaluation of data from sensor arrays like the Aeonose contains several steps.[7,19] This trial followed the steps of those articles, including data acquisition, data pre-processing, data reduction, and training of an Artificial Neural Network (ANN).

As conductivity values are recorded for 12 minutes as described above, each patient's measurement comprises of thousands of records. The temperature control described above enables proper reproducibility of the results. However, even for sensors produced on the same wafer, thickness and aging differences cause slight variations between sensors and Aeonoses over time. In order to cope with this phenomenon, the data were scaled, and multiple noses were used.[16]

As the matrix size is too large for classification, and in order to avoid so-called voodoo-analyses, the data were scaled and then compressed using a Tucker3 solution.[20,21] This resulted into a vector of 11 components per patient.

The vectors generated in the study, combined with a classifier value (either bacterial or viral) were used for training a back-propagating Artificial Neural Network (ANN) and investigate if the ANN would be able to distinguish between the two groups. In order to make sure that classification results are based on actual differences between subjects, and not on data coincidences or over-fitting of data, so-called leave-10%-out cross-validation was applied.

In practice, this means that 10% of data is left out, and an ANN is trained using the remaining 90%. With the ANN model found, the remaining 10% of data are analyzed. In the next step, another 10% of data of the total dataset are left out, and the remaining 90% is used for training a second ANN followed by classifying 10% of data left out previously. This process is being followed for 10 times, so all data are classified once based on training another part of the dataset. So the results shown in the next section are constructed from 10 separate ANN's.

For this data analysis, proprietary software was used, developed in-house at The eNose Company.

RESULTS

During the trial, 72 patients were screened. Based on the inclusion and exclusion criteria 25 patients were not eligible, largely due to patients' inability to provide sputa for culture. Therefore, 47 patients were assessed. 4 participants were excluded for technical reason. (Figure 3.2). So, 43 patients were included. Detailed baseline characteristics of the 43 patients are presented in Table 3.1.

Figure 3.2 Flowchart of patient inclusion.

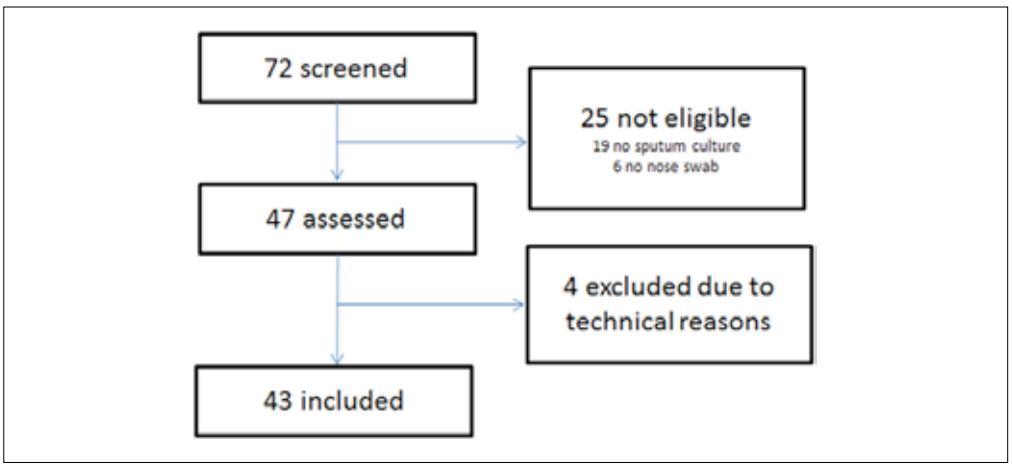


Table 3.1 Patient characteristics

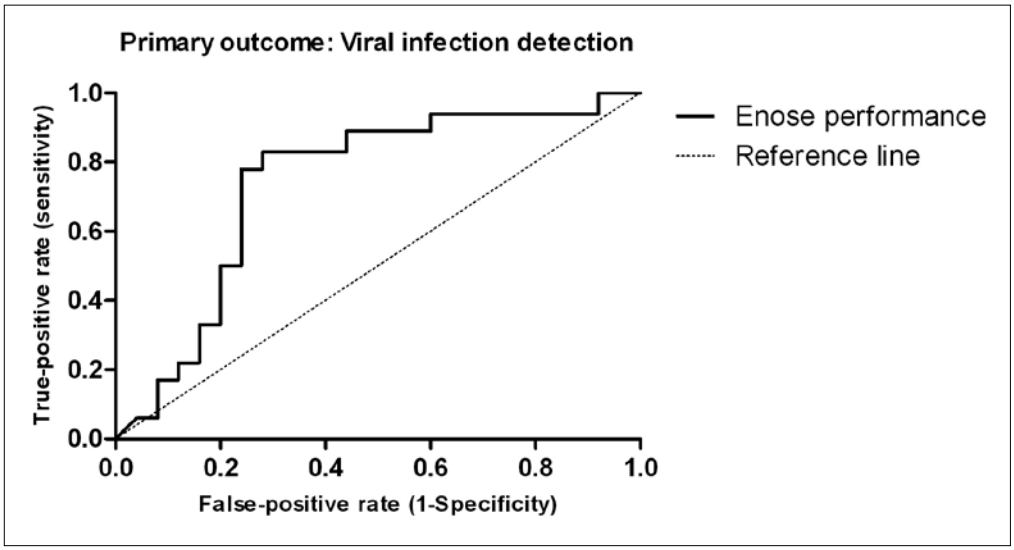
	All patients	Bacterial infection	Without bacterial infection	All patients	Bacterial infection
N	43*	22	21	18	25
Sex F/M	18/25	8/14	10/11	10/8	8/17
Age	67±11	66±12	68±11	66±10	68±12
Classification of severity of airflow by GOLD I/II/III/IV	2/18/13/10	1/8/6/7	1/10/7/3	2/6/7/3	0/12/6/7
Current smokers/ex-smokers/never smokers	20/23/0	10/12/0	10/11/0	10/8/0	10/15/0
Pack years	44±21	43±25	44±19	45±20	43±20
Number of participants treated with systemic steroids before breath pattern measurement	37	19	18	18	19
Number of participants treated with antibiotics before breath pattern measurement	26	13	13	12	14

** 9 patients had both a bacterial and a viral respiratory tract infection, 12 patients had no infection.*
Results are shown as mean ± SD.

Viral infections

Data was analyzed using an ANN as described before, and a receiver operating curve (ROC) was created to assess the Aeonose performance for this indication. The group with a viral infection was tested versus the group without a viral infection. An area under the curve (AUC) of 0.74 was found. Based on the ROC curve, a sensitivity of 83% and a specificity of 72% can be achieved. (Figure 3.3).

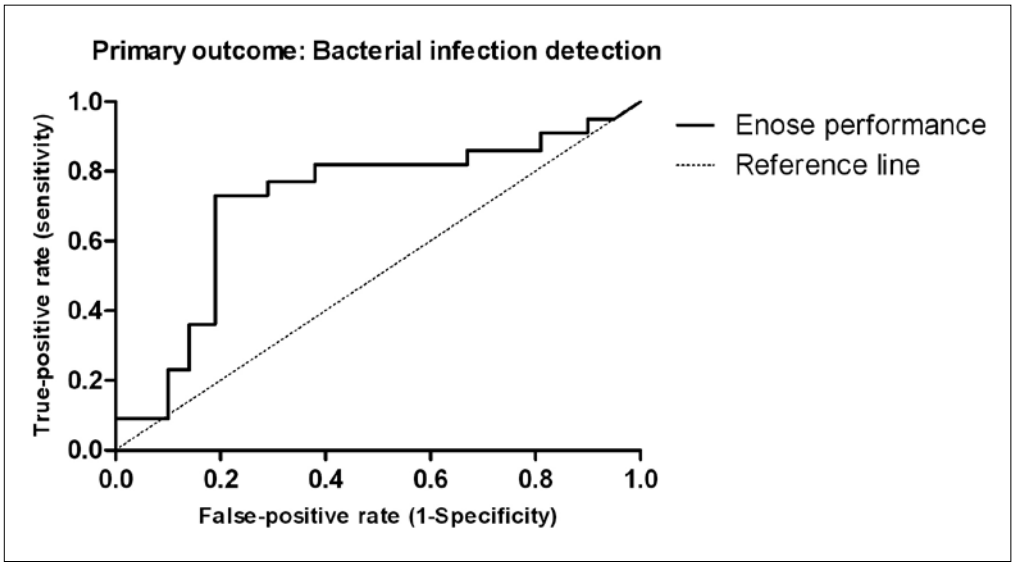
Figure 3.3 ROC curve of association between exhaled-breath patterns and viral infections during AECOPD.



Bacterial infections

Similarly, for bacterial infections, data was analyzed and a receiver operating curve (ROC) was created to assess the Aeonose performance. The group with a bacterial infection was tested versus the group without a bacterial infection. This model has an AUC of 0.72. A sensitivity of 0.73 and a specificity of 0.76 was can be achieved. (Figure 3.4).

Figure 3.4 ROC curve of association between exhaled breath patterns and bacterial infections during AECOPD.



DISCUSSION

The electronic nose tested, the Aeonose, was able to detect the presence or absence of a viral or bacterial respiratory infection during an AECOPD with a promising accuracy.
To our knowledge, this is the first registered prospective trial assessing the cause of AECOPD by e-nose technology. Like phenotyping stable COPD, the recognized importance of phenotyping exacerbations of COPD is growing as well. [4,22-24] One of the most important differences between exacerbations may be the cause. Several phenotypes have been identified already. [23,25-27] This trial shows the potential of the e-nose in phenotyping AECOPD.

Important treatment decisions in exacerbation treatment are taken every day, and are usually only partially based on phenotypes. Important questions that arise daily include: are antibiotics required? Are antiviral treatments required? Should this patient be isolated during hospital stay from other patients or sent home to prevent in-hospital-spread of viruses? Is the potential harm by drugs (antibiotics) outweighed by the expected benefit?
Current tools like viral serology, viral PCR and bacterial cultures have a classical role in answering these questions. However, these are not easily available, costly, and most importantly, test results become available with a considerable delay. It would be advantageous not having to wait for 1-3 days for results to become available. One could assume that clinicians will be happy for day-to-day care with tools like the Aeonose when proven to work reliably and cost-effectively.

The Aeonose has additional advantages making it an even more interesting tool to fill the earlier described gap in exacerbation treatment: the Aeonose is easy-to-use, no collection bags are required, and it is patient friendly because it can be used by the bedridden patient, and patients can maintain their regular breathing frequency. Measurements are inexpensive and, as opposed to the current standard by culture or viral PCR, no microbiology department is needed.

Within the field of obstructive airways diseases, e-nose technology has proven its use already in distinguishing asthma from COPD, in profiling stable disease, and in finding exacerbations.[14,15] These results, using an e-nose based on metal-oxide sensors, confirm earlier studies for different infections for other diseases or circumstances.[9,28-31] Several different sensor techniques were used in those earlier trials. It would be interesting to investigate whether these results are specific for the e-nose technique used, or can be achieved as well with e-noses based on arrays of conducting polymers, quartz microbalance sensors, nanomaterial-based sensors or colorimetric sensors.

The design of the pilot study has several limitations, of which sample size is one, leaving no possibility within the pilot to validate the results and to assess reproducibility in a second cohort. To address this, a leave-10%-out cross-validation was performed. The next step is to perform a confirmation study in a large blinded cohort to assess accuracy of the prediction. This method propagated by the STARD statement and recently by Bikov et al to assess e-nose technology, is probably the right way forward.[7,32] Another future step is to test the system for detection of individual pathogens, which will require a much larger sample size.

In the Dutch health care system patients are often treated with antibiotics often prior to referral to the hospital. Therefor the use of antibiotics was registered thoroughly, but not excluded. Effects of antibiotics can be swift, especially in infections with S. pneumonia. This would have the effect of lowering the AUC, which was now 0.72. We had considered including only patients without prior antibiotics, but this would render the setting less clinically relevant. Our reasoning was: when a patient with a COPD exacerbation visits the hospital and a decision needs to be made regarding the presence of infection, all-comers are the group of interest.

This trial is a first step towards a fast, patient friendly, point-of-care, and low-cost assessment of the cause of infections in AECOPD. Worldwide, assessment of bacterial and viral infections is not performed in most practices and clinics due to financial and logistical limitations. When confirmed, these results would be a valuable tool. This could lead to a decreased use of antibiotics and antiviral medication. This will have to be tested in further trials assessing treatment algorithms to adequately and personally target the administration as well as the withholding of antibiotics. Also, and perhaps increasingly important, a contribution could be made to rational and efficient patient isolation management to prevent in-hospital-spread of infections, especially viruses.

In summary: the e-nose tested, the Aeonose, holds a promise a quick point-of-care tool to assess the presence or absence of a viral or bacterial respiratory infection during an AE-COPD, and now needs to be confirmed.

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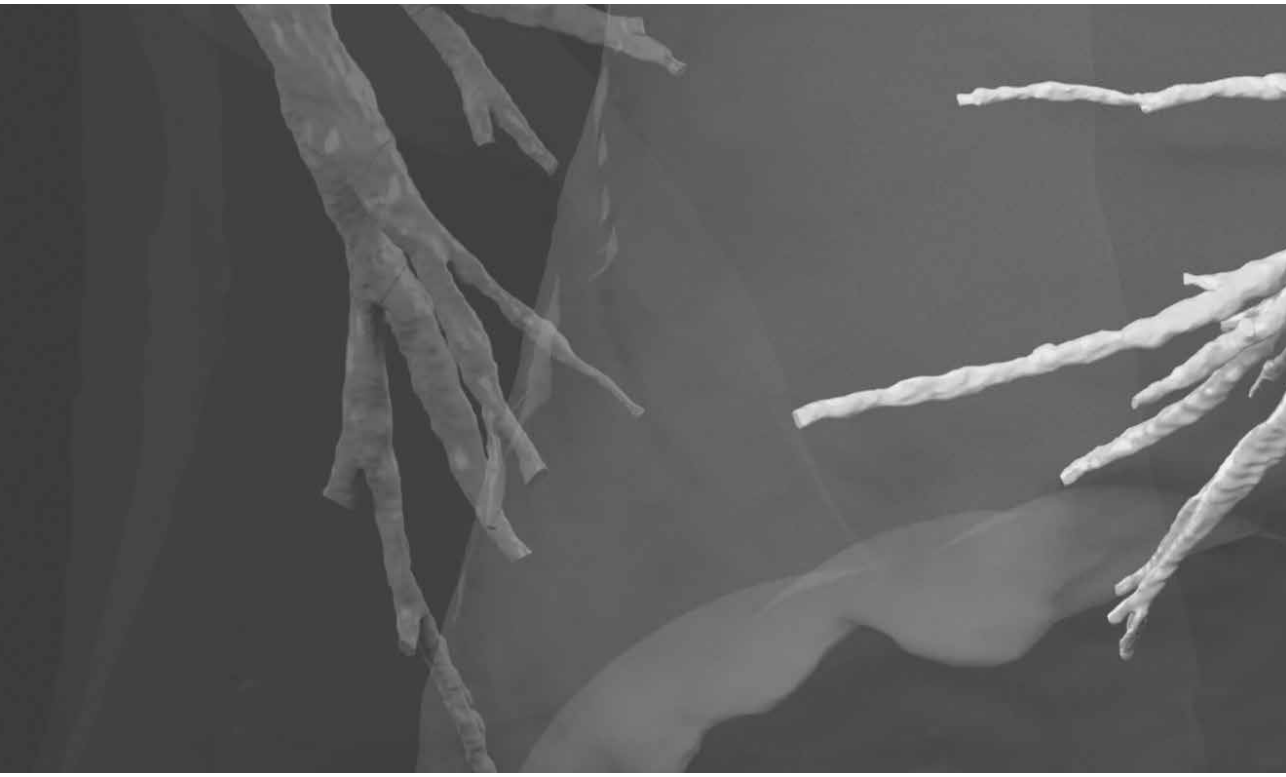

CHAPTER

4

Functional respiratory imaging: Heterogeneity in acute exacerbations of COPD

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ABSTRACT

Background

Exacerbations of COPD are a major burden to patients and yet little is understood about heterogeneity. This contributes to the current persistent one-size-fits all treatment. To replace this by more personalized, precision medicine, new insights are required. We assessed heterogeneity of exacerbations by functional respiratory imaging in three-dimensional models of airways and lungs.

Methods

Multicenter trial of patients with an acute exacerbation of COPD who were assessed by functional respiratory imaging, pulmonary function tests and patient reported outcomes, both in the acute stage and during resolution.

Results

Forty-seven patients were assessed. Functional respiratory imaging analyses showed significant improvements in hyperinflation (a decrease in total volumes at FRC of -0.25±0.61 liter, p=<0.01), airway volume at TLC (+1.70±4.65 liter, p=0.02), and airway resistance. As expected, these improvements correlated partially with changes in quality of life and in conventional lung function test parameters. Patients with the same changes in pulmonary function differ in regional disease activity measured by FRI.

Conclusion

Functional respiratory imaging is a useful tool to get a better insight in exacerbations of COPD, and significant improvements in its indices can be demonstrated from the acute phase to resolution even in relatively small groups. Functional respiratory imaging clearly visualizes the marked variability within and between individuals in ventilation and resistance during exacerbations and is a tool towards assessment of the heterogeneity of COPD exacerbations.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease with an enormous personal and societal burden. A considerable proportion of the morbidity, mortality and costs of this disease is related to exacerbations of COPD.[1] Relatively little is known about exacerbations, and the quest to effectively prevent and manage them continues. Medical treatment of acute exacerbations routinely consists of steroids, bronchodilators, antibiotics, additional oxygen, and sometimes assisted ventilation. Currently a one-size-fits-all treatment for acute exacerbations is conducted in most clinics. We and many others believe that this should urgently be replaced by more personalized, precision medicine.

Some tools to more adequately monitor the start and resolution of an exacerbation have been developed. Progress is definitely being made in the field of patient reported outcome measurements (PROMs), such as the Exact-pro, COPD Assessment Test (CAT), and Clinical COPD Questionnaire (CCQ).[2,3] Traditionally COPD patients are monitored by pulmonary function tests such as the forced expiratory volume in 1 second (FEV_1). However, especially during exacerbations, changes in FEV_1 are small and correlate poorly with patient reported complaints such as dyspnea and with the response to medication.[4-6] Both clinicians and researchers struggle with this issue on a daily basis. Therefore, new and more informative correlates of diseases severity and response are eagerly awaited to allow individualized therapy especially during exacerbations. A model for a differential approach depending on the inflammatory status has been developed, where eosinophilic inflammation and bacterial infections help guide therapy. However, this does not address viral infections.[7,8]

Furthermore, we believe that hyperinflation, which has been shown to be important in guiding therapy in stable state, should also be addressed during acute exacerbations.[1,9-12] Hyperinflation is caused by trapping of air during expiration, due to peripheral airway obstruction. Hyperinflation increases functional residual capacity in such a way that inspiratory capacity decreases, resulting in increased dyspnea and limitation of exercise capacity.[5,10,13-15] Some data about hyperinflation during exacerbations is available, showing that it increases.[5,15] Whether the increase in hyperinflation during exacerbations is specifically caused by changes in the peripheral airways and decreased expiratory time at times of greater demand remains unknown. Hyperinflation during exacerbations has been studied mostly by inspiratory capacity, yielding limited data, on aggregated level only. The result of this measurement is driven by several more regional factors, contributing differently between patients. Insightful knowledge of changes in hyperinflation during exacerbations is currently lacking, which is most mechanistically unsatisfactory, and hampers the development of personalized treatment.

Next to hyperinflation, increased airway resistance has been observed in exacerbations.[5,16,17] Airway resistance correlates with dyspnea and recovery and stable state bronchodilator response.[5,16,17] Until this point, heterogeneity of airway resistance has not been measured in exacerbations, although a technique to measure this, have been developed in stable state of COPD. [18] Clinical consequences of regional differences in airway resistance thus far are not available, perhaps since this technique has been developed only recently.
This promising new computational technique to better understand the mechanisms of acute exacerbations is called functional respiratory imaging (FRI).[18] Based on high resolution com-

puted tomography (HRCT) scans, three-dimensional models of airways and lung models are extracted and used for computational fluid dynamics simulations. The technique has been extensively tested in stable COPD and other diseases and is clinically validated.[18-21] One of the core features of FRI is that local measurements of lobar volumes, airway volumes and airway resistances can be performed while for instance the FEV_1 incorporates the whole respiratory system into a single number. The usefulness of FRI has been proven in assessing hyperinflation, airway resistance, and airway diameter during stable state of COPD, but no data are available in the acute setting.[20,22,23]

This study was designed to test whether FRI has additional value on top of assessing conventional lung function tests and patient reported outcomes in the monitoring of patients with an exacerbation of COPD. We hypothesized that it is feasible to measure functional respiratory imaging also in the setting of acute exacerbations of COPD, and that changes in FRI parameters correlate with changes in lung function parameters and patient reported outcomes during resolution of COPD exacerbations, especially for FEV_1 and hyperinflation. The inherent regional aspects of FRI should allow detection of heterogeneity in exacerbating COPD patients.

METHODS

The trial was designed as an international multicenter prospective cohort study. The study was funded by FLUIDDA NV Belgium and by GlaxoSmithKline with an unrestricted educational grant. Patients were recruited from 3 hospitals in Belgium, Italy and the Netherlands. Protocols and patient information were all approved by the designated medical ethics committees (Comite voor medische Ethiek, Universiteit Ziekenhuis Antwerpen, Comitato Etico (per la sperimentazione clinica dei medicinali) dell'Azienda Ospedaliero Universitaria Careggi, and Medische Ethische Toetsingscommissie (METc), Universitair Medisch Centrum Groningen). The trial is registered as NCT01684384 at www.clinicaltrials.gov.

Patients were recruited at the start of an exacerbation, when written informed consent was obtained. Treatment of the exacerbation was applied as usual care, according to the global initiative on obstructive lung disease (GOLD) guidelines, and consisted at least of additional bronchodilation and systemic corticosteroids.[24]
A patient was eligible for inclusion only if all of the following criteria applied; ≥ 40 years old, COPD with post-bronchodilator $FEV_1/FVC < 70\%$ and post-bronchodilator FEV_1<80%pred as documented in the last 5 years, a COPD exacerbation defined as an acute change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day to day variations, and that necessitated the administration or doubling of systemic corticosteroid treatment.

Patients were excluded from participation if any of the following criteria applied: pregnant or lactating females, patients diagnosed with asthma, patients with pneumonia as defined radiologically at the start of the exacerbation, a history of or presence of lung cancer and an indication for non-invasive ventilation, patients who were unlikely to comply with the protocol or unable to understand the nature, scope and possible consequences of the study were excluded as well, as were patients who had received any investigational new drug within the last 4 weeks prior to visit 1. Due to the recommendations of the medical ethics committee in the Netherlands patients with a weight more than 110kg were excluded, in the Netherlands only.

MEASUREMENTS

Patient reported outcomes

All measurements detailed below were obtained within 5 days of the start of the exacerbation, and repeated at stable state, i.e. day 42 provided the exacerbation had resolved as judge by their physician. Otherwise, the stable state measurements were postponed.
Health related quality of life and dyspnea score were measured by validated patient reported outcome measures (PROMs): the Saint George's Respiratory Questionnaire (SGRQ), Clinical COPD Questionnaire (CCQ), COPD Assessment Test (CAT), and Modified Medical Research Council (MMRC) Dyspnea scale.[3,25]

Lung function

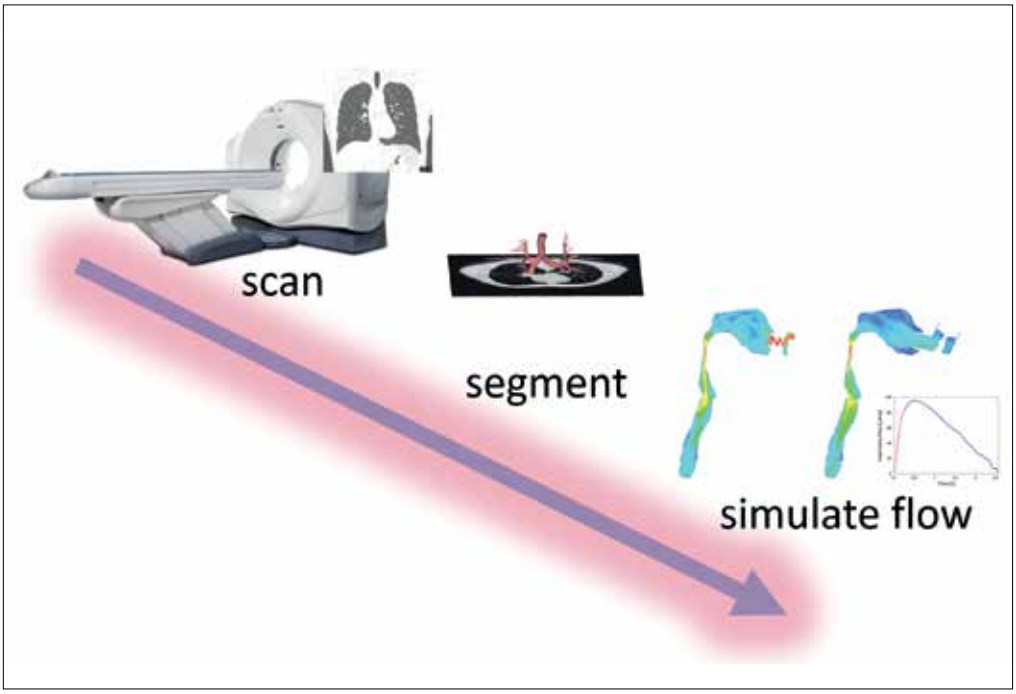
Forced expiratory volume in 1 second (FEV_1), inspiratory capacity (IC), forced expiratory vital capacity (FVC), residual volume (RV) total lung capacity (TLC) by plethysmography, functional residual capacity (FRC) and airway resistance (Raw) were measured at both visits, according to the recommendations of the ERS guidelines with the accompanying reference values [26]. All lung function tests were repeated, until three technically acceptable measurements had been made, with a maximum of 8 measurements. There was no withholding of bronchodilator treatment for the lung function measurements.

Computed tomography

During the exacerbation, and in a clinical stable state, HRCT scans at functional residual capacity (FRC) and total lung capacity (TLC) during breath hold were performed. In order to make sure that the scans were taken at the correct lung function level, FRC and TLC were ensured by lung function technician coaching with the aid of a spirometer. Specific CT settings are reported in the online supplement.

Post-processing of the CT data included segmentation of the airway tree (Mimics, Materialise, Leuven, Belgium). Three-dimensional models of airways and lung models were extracted from scan and were used for computational fluid dynamics simulations. Functional respiratory imaging (FRI), a clinically validated computational workflow, was used to perform measurements of lobar volumes (iVlobe), a parameter for lung hyperinflation. FRI was also used to assess airway volumes (iVaw) and airway resistances (iRaw) (Figure 4.1). The small i designates "imaging". FRI has the potential to measure all these parameters at all lobes, different airway generations and time points. We predefined the most important parameters: changes from exacerbation to stable state in the total score of both lungs for the parameters iVlobe, iVaw, and iRaw. Based on the clinical relevance for each FRI parameter, measurements at FRC or TLC level were selected.

Figure 4.1 Overview of the FRI concept.



Patients are first scanned. Then the CT images are segmented, and the rendering of the airways is calculated. Then a 3d model of the lung is developed. Finally, flow is simulated in this model using CFD techniques.[18]

Analyses

Study outcomes

The primary goal was to assess, during the resolution of an exacerbation, the strength of the association between change in lung function and change in parameters measured by Functional Respiratory Imaging. The secondary goal was to assess the strength of the association between the changes in the same functional respiratory imaging parameters and SGRQ, CAT, MMRC and CCQ.

Statistical analyses

A power calculation was based on an estimated correlation coefficient of 0.7 for the primary objectives with 95% confidence intervals 0.52 - 0.80. The number needed to achieve 80% power with alpha 0.05 was 50 subjects (2-sided sample size calculation for a Pearson correlation analysis derived by Power and Precision 4.0 (Biostat, USA)).

Analyses were performed using R 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria). All continuous variables (imaging based volumes and CFD based resistances, lung function parameters and PROMs) were tested for normality using Shapiro-Wilk W tests and transformed if necessary and successful.

Paired Student`s t-tests were used to evaluate the changes of these parameters from exacerbation to recovery. These tests were also used to check for the segmentation reproducibility of the FRI measurements. Two-sided testing was performed.
Correlations between the continuous variables (the changes) were examined using multiple regression analysis techniques. ANOVA was used to fit the model, and goodness-of-fit statics were performed. A p-value smaller then 0.05 was defined as statistically significant.
Parameters are reported as mean ± standard deviation for descriptive statistics and +/- standard error of the mean for evaluative statistics.

RESULTS

Between October 2012 and August 2014 a total of 54 patients were enrolled in this trial, 38 in Belgium, 6 in the Netherlands, and 10 in Italy. The main patient characteristics of the recruited patients are presented in Table 4.1. Forty seven were evaluable due to 7 dropouts (3 participants died, 3 withdrew consent, 1 was lost to follow up). All participants were Caucasian.

Table 4.1 Patient characteristics (n=47)

Patient characteristics	
Sex M/F	27M/20F
Age (years)	68.0±9.9
Obstructive GOLD stage 2/3/4	19/22/6
Current smokers / Ex-smokers / Never smokers	13/33/1
Pack years	46.5±22.2
Treatment in outpatient setting / hospital setting	9/38
Days between exacerbation and stable state measurements	55.1±22.7

Results are shown as mean ± SD. Demographics presented were measured during screening and the lung function data presented in this stable was measured at stable state

Changes from exacerbation to stable state

Parameters of FRI improved from the acute phase to resolution of the exacerbation (Table 4.2 and Figure 4.2 and 4.3). A significant improvement was seen in hyperinflation, i.e. a decrease in total volumes (iVlobe, total) at FRC of -0.25±0.61 liter (p=<0.01,). Similarly, airway volumes (iVaw, total) at TLC increased, 1.70±4.65 liter (p=0.02), though not at FRC.

The airway resistance (iRaw) both at FRC and TLC level decreased significantly during recovery (Table 4.2).
Significant improvements were also seen in FEV_1, IC, FRC (Table 4.2), as well as in airway resistance measured by plethysmography. Patients reported significant improvements in health related quality of life (SGRQ, CCQ, and CAT). All improvements were greater than the minimal clinical important difference, and therefore also clinically significant.

Table 4.2 Change from exacerbation to stable state in lung function and functional respiratory imaging parameters

Parameter	At exacerbation	At stable state	Mean change	Significance
FEV_1 (liter)	1.15±0.43	1.31±0.50	0.16±0.25	<0.01 *
FEV_1 (% predicted)	45.92±15.05	51.89±16.83	5.97±9.15	<0.01 *
$iVaw_{FRC}$ (ml)	34.78±14.20	36.28±12.87	1.50±7.65	0.19
$iVaw_{TLC}$ (ml)	54.79±16.05	56.49±16.32	1.70±4.65	0.02*
FRC (liter)	4.83±1.31	4.62±1.17	-0.22±0.58	0.01 *
$iVlobe_{FRC}$ (L)	5.01±1.18	4.75±1.10	-0.25±0.61	<0.01*
TLC (liter)	6.72±1.42	6.74±1.30	0.02±0.60	0.81
$iVlobe_{TLC}$ (L)	6.47±1.18	6.49±1.14	0.02±0.41	0.76
RAW (kPa*s/L)	0.71±0.24	0.63±0.34	-0.10±0.29	0.04 *
$iRaw_{FRC}$ (kPa*s/L)	0.11±0.13	0.06±0.08	-0.04±0.12	0.03*
$iRaw_{TLC}$ (kPa*s/L)	0.04±0.03	0.04±0.02	-0.01±0.02	0.03*
IC (liter)	1.96±0.59	2.20±0.73	0.14±0.27	<0.01 *
RV (liter)	3.87±1.23	3.66±1.02	-0.21±0.76	0.07
TCO(mmol/min/kPa)	3.52±1.50	3.53±1.63	0.06±0.67	0.54
Patient reported outcomes				
SGRQ	62.18±15.31	48.60±20.51	-14.62±18.88	<0.01 *
CCQ	3.40±1.20	2.41±1.30	-1.00±1.45	<0.01 *
CAT	24.06±7.81	18.23±8.13	-5.83±11.28	<0.01*
mMRC	3.11±1.15	2.43±1.17	-0.67±1.23	<0.01*

*Values are shown as mean ± SD. * denotes p-value <0.05*
*FRI: measurements by functional respiratory imaging, iVlobe: volumes, iVaw: airway volumes, iRAW: airway resistances, FEV_1: forced expiratory volume in 1 second, IC: inspiratory capacity, TLC: total lung capacity, FRC: functional residual capacity, RV: residual volume, RAW: airway resistance, TCO: transfer factor for carbon monoxide, SGRQ: the Saint George's Respiratory Questionnaire, CCQ: Clinical COPD Questionnaire, CAT: COPD Assessment Test, mMRC: modified medical research council dyspnea scale. Correlations are reported as p and r. * denotes p-value <0.05*

Figure 4.2 Variability in changes from exacerbation to stable state in iVlobe volumes at TLC in individual patients (8 patients randomly selected). The scale represents the percent change in volume of the different lung lobes at TLC. Red represents an increase in volume while blue represents a decrease.

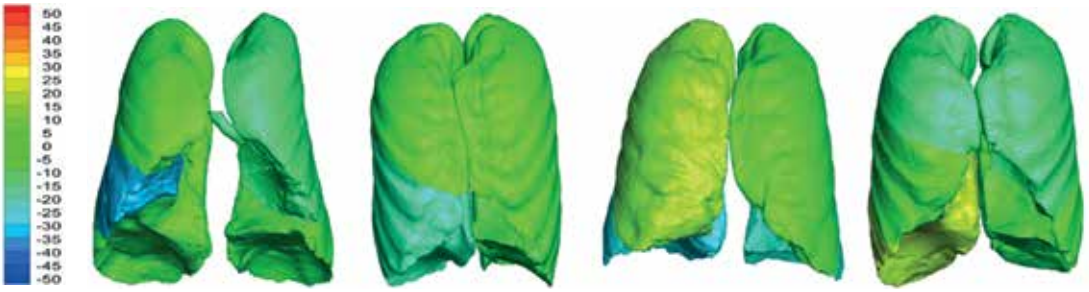
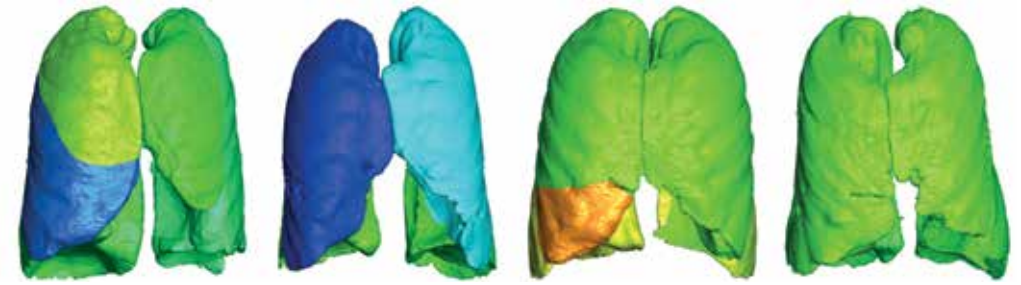


Figure 4.3 Variability in changes from exacerbation to stable state in siRaw at TLC in individual patients (8 patients randomly selected). The scale represents the percent change in resistance of the different airway branches at TLC. Red represents an increase in resistance while blue represents a decrease.



Correlations of FRI parameters with lung function and patient reported outcome measurements

The strength of the association between the changes from exacerbation to stable state in conventional lung function parameters (FEV_1, and IC and RAW) and change in parameters measured by functional respiratory imaging (change iVaw, iVlobe and iRaw) was assessed. Change in FEV_1 correlated with siVaw (FRC) (p=0.02, R=0.34). The change in RAW measured by plethysmography correlated with change in RAW measured by FRI (iRaw, p=0.04). The changes in FEV_1, sRAW and IC were not correlated with the changes iVaw, siRaw and iVlobe. The changes in CCQ and CAT correlated with changes in FRI based specific airway resistance (siRaw), Changes in mMRC correlated with siVaw. By contrast, the changes in PRO's did not correlate significantly with changes in iVlobe or iVaw (Table 4.3).

Table 4.3 Correlation between change in functional respiratory imaging parameters and change in classical pulmonary function tests and in quality of life, from exacerbation to stable state

Change in Pulmonary function parameter or Patient reported outcome	Change in Functional respiratory imaging parameter (level of measurement)	R	p-value
Primary endpoints			
FEV_1 (liter)	iVlobe (FRC)	0.26	0.08
FEV_1 (liter)	iVaw (TLC)	0.21	0.16
FEV_1 (liter)	siVaw (FRC)	0.34	0.02*
IC (liter)	iVlobe (FRC)	0.35	0.06
IC (liter)	iVaw (TLC)	0.09	0.62
IC (liter)	siVaw (FRC)	0.05	0.78
RAW	iRaw(FRC)	0.33	0.04*
sRAW	siRaw(TLC)	0.13	0.42
Secondary endpoints			
SGRQ	FEV_1 (liter)	0.24	0.11
SGRQ	iVlobe (FRC)	0.14	0.38
SGRQ	iVaw (TLC)	0.12	0.45
SGRQ	siVaw (FRC)	0.17	0.26
SGRQ	siRAW (TLC)	0.28	0.07
CCQ	FEV_1 (liter)	0.20	0.17
CCQ	iVlobe (FRC)	0.24	0.11
CCQ	iVaw (TLC)	0.12	0.41
CCQ	siVaw (FRC)	0.14	0.34
CCQ	siRaw(TLC)	0.36	0.01*
CAT	FEV_1 (liter)	0.38	0.01*
CAT	iVlobe (FRC)	0.26	0.08
CAT	iVaw (TLC)	0.26	0.08
CAT	siVaw (FRC)	0.17	0.24
CAT	siRaw(TLC)	0.42	<0.01*
mMRC	FEV_1 (liter)	0.31	0.04*
mMRC	iVlobe (FRC)	0.12	0.45
mMRC	iVaw (TLC)	0.17	0.25
mMRC	siVaw (FRC)	0.36	0.01*
mMRC	siRaw(TLC)	0.30	0.045*

*FEV_1: forced expiratory volume in 1 second, IC: inspiratory capacity, Raw: airway resistance, SGRQ: the Saint George's Respiratory Questionnaire, CCQ: Clinical COPD Questionnaire, CAT: COPD Assessment Test, FRI: measurements by functional respiratory imaging, iVlobe: volumes, iVaw: airway volumes. iRaw: airway resistances. siVaw: specific airway volumes corrected for volumes. siRAW: specific airway resistances corrected for volumes. Correlations are reported as p and r. *denotes p-value <0.05*

FRI measures versus global patient changes

We have taken a deeper look at two patients from within this trial. Both were female GOLD Stage III COPD patients, age 57 and 62 years and a smoking history of 35 and 20 pack-years (from now on we will refer to these as patient 1 and patient 2, respectively). Both patients present similar FEV_1 values at baseline (39.0%pred and 40.5%pred) as well as a similar change in FEV_1 after recovering from an exacerbation (3.0%pred and 2.1%pred). Even though the spirometry measurements are the same for both patients, FRI parameters show clear differences between the two patients. A detailed overview of the FRI parameters can be found in Table 4.4 and Figures 4.4 and 4.5.

At baseline, patient 1 is clearly hyperinflated, with a total lung volume of 140.6%pred at TLC and 201.1% pred at FRC in opposition to patient 2 (95.4%pred at TLC and 118.5%pred at FRC. When looking at changes in the FRI parameters, the increase in FEV_1 is mainly associated with a decrease in lobar volume (6.1% at TLC and 28.3% at FRC) for patient 1, and only partially with change in resistance. On the other hand, patient 2 has a slight increase in lobar volume (1.4% at TLC and 4.9% FRC), particularly in the upper lobes, but here the increase in FEV_1 can be linked to larger airway volumes at FRC (+95.72%) and a corresponding drop in resistance (-90.80%).

These results suggest that functional respiratory imaging is a technique able to differentiate between patients with comparable spirometry measurements. Therefore, FRI may result in more precise diagnosis and treatment, particularly in heterogeneous diseases such as COPD.

Table 4.4 Changes in functional respiratory imaging parameters from exacerbation to stable state in 2 individual patients with similar changes in classical pulmonary function tests

Parameter	**Patient 1**		**Patient 2**	
	Baseline	Change	Baseline	Change
FEV_1	0.82L	+7.32%	0.77L	+9.09%
iVaw FRC	32.41 mL	-6.29 %	7.37 mL	+95.72%
iVaw TLC	42.20 mL	+14.79%	29.13 mL	+3.06%
FRC	4.86L	-9.88%	2.92L	+12.67%
iVlobe FRC	201.13 %pred	-28.33 %	118.52 %pred	+4.87 %
TLC	6.22L	-0.96%	4.59L	+3.92%
IVlobe TLC	140.62 %pred	-6.14 %	95.35 %pred	+1.43 %
Raw	0.441 kPa.s/l	+20.18%	1.060 kPa.s/l	-18.96%
iRaw FRC	0.05 KPas/L	+5.51 %	0.17 Kpas/L	-89.90%
iRaw TLC	0.09 Kpas/L	-51.35 %	0.05 Kpas/L	-0.82%

Measurements by functional respiratory imaging, iVlobe: volumes, iVaw: airway volumes. iRaw: airway resistances. FEV_1: forced expiratory volume in 1 second, TLC: total lung capacity, FRC: functional residual capacity, Raw: airway resistance

DISCUSSION

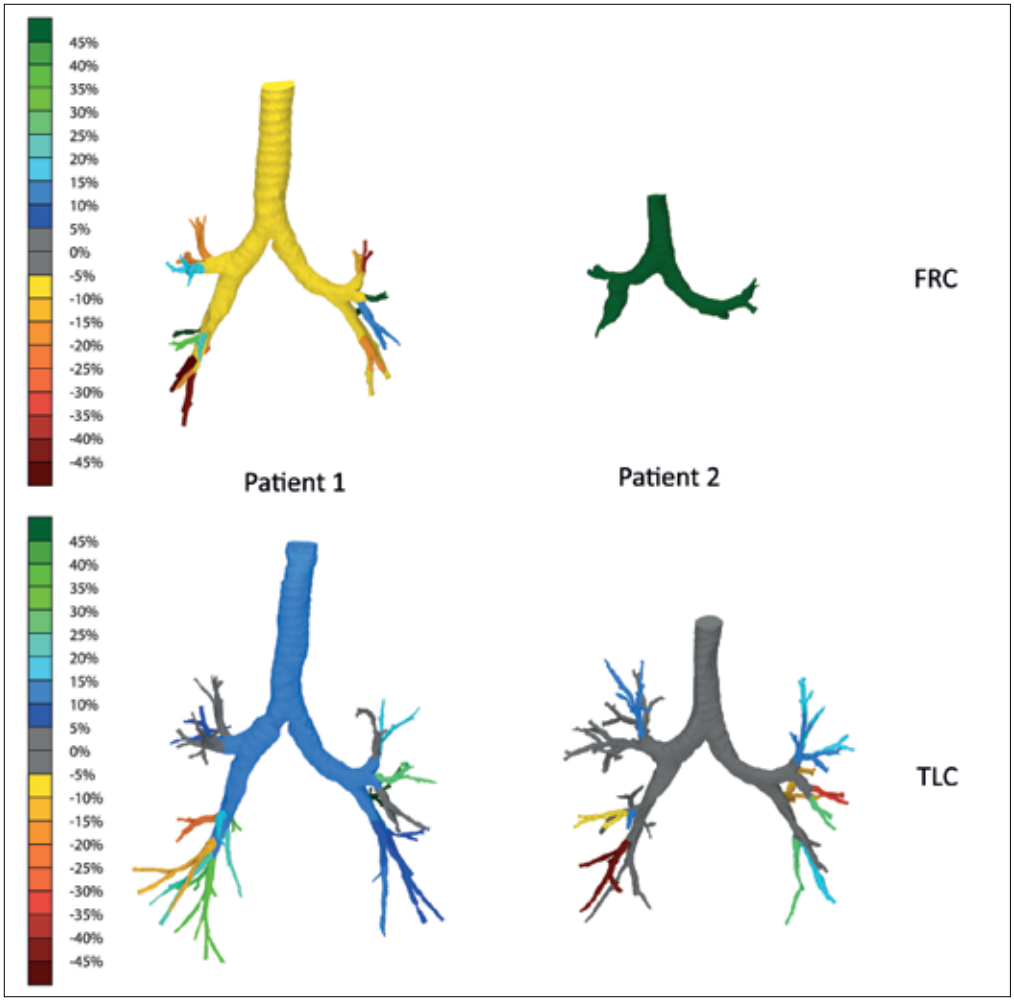
We show that functional respiratory imaging is feasible in the acute setting of COPD exacerbations. It is able to demonstrate significant differences between exacerbation and stable state. The changes in functional respiratory imaging correlate partially with changes in conventional lung function parameters and quality of life. It clearly visualizes regional heterogeneity within patients and large differences between patients.
FRI allows individualized measurements of patients with an AECOPD and among others visualizes the marked differences between patients. It does not measure a pulmonary function test with CT, but it measures different parameters. The parameters, hyperinflation, airway diameter and air resistance, specifically of the lungs, and segments within the lungs, are measured without bias from the oropharynx, e.g. cough and oxygen masks. Importantly, the FRI parameters improve after recovery of the exacerbation. Since a CT scan can be performed during an acute event, even when conventional pulmonary function testing is not well possible, these findings might influence treatment decisions in the future, both for the group of acute exacerbations, and for individuals.

Next to the feasibility of FRI during exacerbations, this study also showed the ability to measure different regions of the lung during COPD exacerbations. One could have thought that volume and resistance changes during exacerbations were evenly distributed throughout the lung, however as our study shows in a small group marked changes between different regions. Next, changes in FEV_1 after an exacerbation are not always determined by changes in the larger airways, but can also be driven by changes in the smaller airways, and that this influence is different in different subjects. To gain a more complete overview about this heterogeneity and its clinical implications, a larger sample size study with a treatment algorithm is required. However one could imagine that this new described intra-patient heterogeneity of the lung function can be of interest for future practitioners, since treating different lung regions might require different strategies.[12] Could regional guided treatment be of use during exacerbations as well? Are those exacerbations with increased airway resistance the ones requiring a more frequent, higher dosed nebulizer treatment, such as asthma?

Thus far, no specific therapies for local differences in resistance have made it into daily clinical practice. During exacerbations, the presence and magnitude of effects of bronchodilators on resistance is not routinely assessed at all. FRI allows for measurement of airway resistance at several levels, and has the potential to demonstrate and visualize differences between severity and location of individual patients. It was not possible to detect whether changes are caused by mucus, airway wall thickening, muscle contraction or other causes. Differences between the individuals can be expected to be high, and cluster analysis of larger patient groups will help to identify the best strategy based on airway resistance during exacerbations.

This study shows the feasibility of measuring FRI parameters during exacerbations and compared the results to stable state. In clinical routine, the feasibility of lung function testing in patients admitted with an exacerbation of COPD is limited due to several reasons such as staff attendance, the absence of plethysmography and the clinical condition of the patient.

Figure 4.4 Change in airway volume



FRI images of 2 patients displaying the changes in airway volume. The scale represents the percent change in volume of the different airway branches at the different lung levels. Green represents an improvement, while red represents a worsening. The airway volume is the volume of the lumen of the airways and does thus represent the volume of air inside the airways. The airways are measured starting from the trachea at the top of the sternum up to the point where no distinction can be made between the intraluminal and alveolar air. This is where the airway diameter is around 1 – 2 mm. One can infer that an increase in airway volume means bronchodilation has occurred. [18]

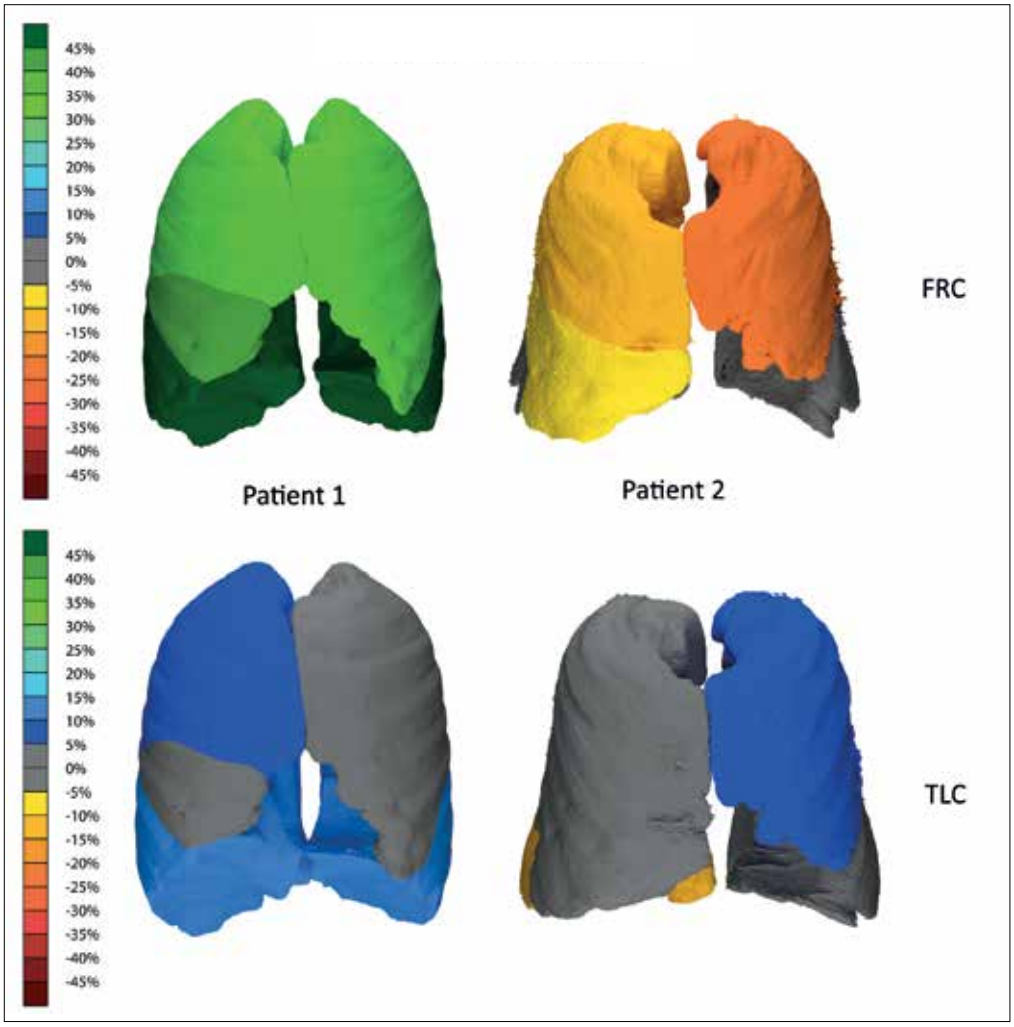
Since a CT scan can be performed during an acute event, even in patients in severe respiratory distress when conventional pulmonary function testing is not well possible, FRI might have a specific future role in clinical assessment of COPD exacerbation. Costs and radiation however need to be considered.

FRI could be used to assess the parameters of increased hyperinflation during the exacerbation. Then FRI could aid in individualizing treatment, above all of the bronchodilators. In patients who after initial bronchodilation show persistent hyperinflation, the effect of additional bronchodilation should be examined. Based on the distribution of the hyperinflation, bronchodilator device selecting may be performed. For instance, regular nebulizers in case of central hyperinflation, and PMDI's with spacer in more peripheral hyperinflation. Another potential strategy could be the selection of the type of bronchodilator. In stable COPD long-acting bronchodilators have replaced short-acting bronchodilators in patients with a more severe hyperinflation. We speculate that during exacerbations, FRI can be used to treat patients with more hyperinflation with long-acting bronchodilators compared with the current standard treatment of short-acting bronchodilators in less hyperinflated patients.[6] Additionally, different physiotherapeutic strategies e.g. to regulate breathing next to sputum evacuation can be considered for this group. And, in the long run, perhaps non-invasive lung volume reduction techniques, currently tested only in stable, though severely obstructed patients, could perhaps one day be attempted, as guided by FRI. [27,28]

It would be of great clinical importance if FRI measurements can also aid in delineating the absence of hyperinflation and small airways dysfunction, a markedly different phenotype of exacerbation. Some of these patients suffer predominantly from fear and should be reassured and treated for their anxiety, as opposed to more bronchodilators. The latter, by inducing tachycardia and giving false hopes might even augment fear. We speculate that FRI especially in combination with other biomarkers like eosinophilia, or viral and bacterial diagnosis will allow more precise assessments in acute exacerbations, potentially unlocking precision treatment.

This study has several strengths and weaknesses that should be mentioned. It has been performed in different centers, in different countries each with their own local radiologic and pulmonary function equipment making the applicability of its results broader: it is feasible in several different clinical settings. The correlations between the standard pulmonary function measurements and the FRI measurements were relatively low, which should not be a surprise given the difficulty of assessing them during exacerbations. During exacerbations, all measurements, including classical lung function, will be more variable than during stable state, lowering all correlations. At current, the variability in all these tests, including spirometry, during exacerbations is largely unknown and should be examined. The usefulness of all tests to adequately guide clinical decisions should be assessed, as much of the FRI measurementw as of for instance FEV_1, which is not routinely performed during acute exacerbations probably for good reason. Survival, hospital re-admission, length of stay, and to response to therapy should be considered as endpoint in future trials assessing treatment strategies.

Figure 4.5 Change in lobe volume



FRI images of 2 patients displaying the changes in lobar volume. The scale represents the percent change in volume of the different airway branches at the different lung levels. Green represents an improvement, while red represents a worsening.

CONCLUSION

In summary, we have shown for the first time that functional respiratory imaging based on HRCT measurements is feasible also in patients with an acute exacerbation of COPD. During the resolution of the exacerbation, the parameters indeed improve considerably. The changes do correlate to some degree with changes in conventionally measured parameters like change in FEV_1, resistance, and hyperinflation, as well as with patient reported outcomes, but also provide additional information. The technique clearly visualizes the marked variability within and between individuals in ventilation and resistance during exacerbations. Information about regional differences in patients, and heterogeneity between patients can now be obtained.

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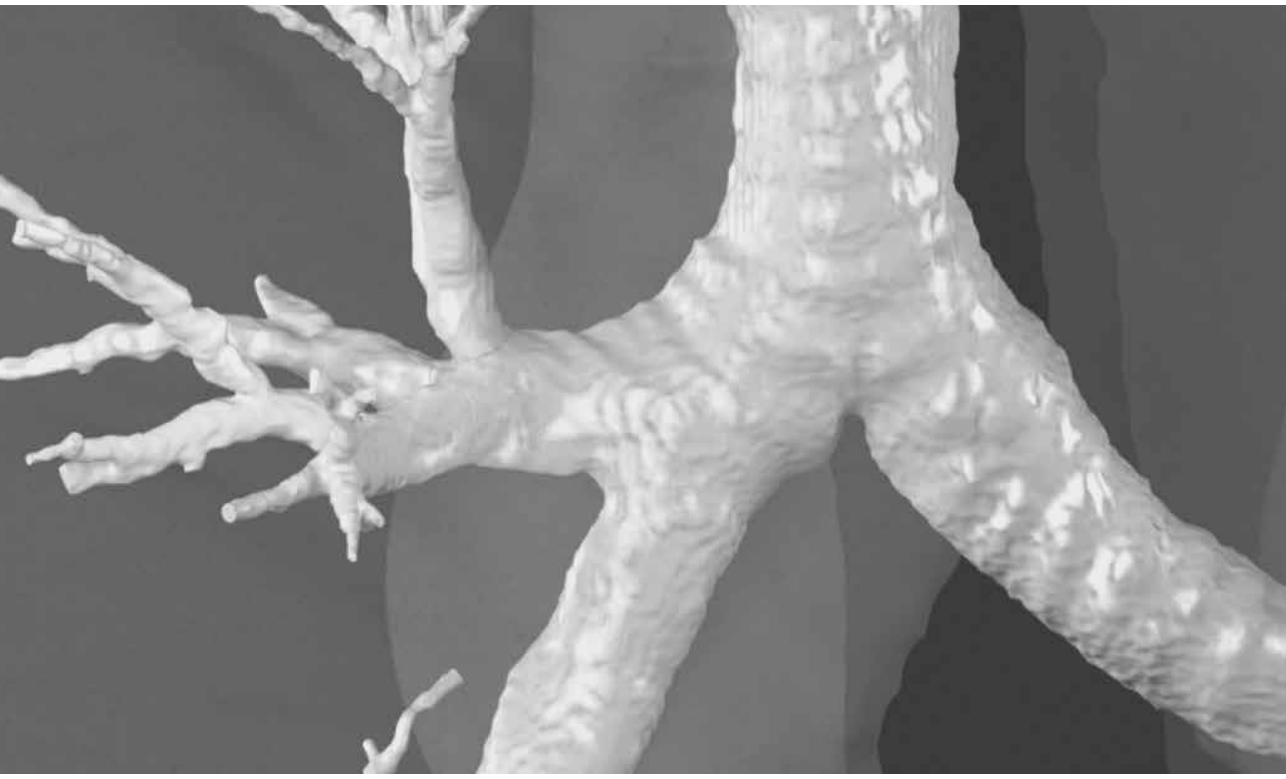

CHAPTER

Hyperinflation in COPD exacerbations

Wouter H. van Geffen, Huib A.M. Kerstjens, Dirk-Jan Slebos

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We welcome the Viewpoint by Jose Luis Lopez-Campos and Alvar Agusti.[1] As intended, we believe it will spark a useful discussion about the causes and treatment of exacerbations of chronic obstructive pulmonary disease (COPD) - a specific problem that has a huge effect on quality of life, with high economical costs and for which clinical guidance is sparse.

Lopez-Campos and Agusti propose a two-axes system for categorising and treating COPD exacerbations. The axes (steroid sensitive inflammation and bacterial infection) proposed could well prove useful, and, as suggested by the authors, should be studied prospectively to see whether they fit many patients and whether the proposed treatments suffice.

We regularly see patients with COPD exacerbations who do not fit well into this system. These patients are dyspnoeic, with hyperinflated lungs, and without an infectious or eosinophilic pattern, and are nevertheless frequently treated by prednisolone and even antibiotics, thereby having potentially more side-effects than beneficial effects.

We would therefore like to add hyperinflation as an additional axis to the proposed system. Hyperinflation is a characteristic of exacerbations in many patients.[2] The severity of hyperinflation varies between individual patients and also regionally in the lung and is related with (regional) bronchus obstruction.[3] Static hyperinflation, which further increases during exacerbations, is very relevant to understand the cause of increased dyspnoea, probably the most central presenting symptom of exacerbations.[4] In these patients with greatly increased hyperinflation, increased anxiety is also an important reason for presentation at exacerbation, and this too can be linked to changes in hyperinflation, either as a cause of hyperinflation or contributing to its further increase.

To render an additional axis relevant in any grading system, the axis should also have therapeutic consequences. Most patients are prescribed mainly shortacting bronchodilators during exacerbations. In many hospitals, longacting bronchodilator treatments might even be ceased in favour of nebulisations, inevitably with shortacting bronchodilators. Not only are the effect of both β-2-adrenergic and anticholinergic shortacting bronchodilators generally smaller than that of their longacting counterparts but also their duration of action is shorter. In other words patients have increased residual bronchoconstriction, and quicker recurrence of bronchoconstriction, leading to increased hyperinflation, dyspnoea, and anxiety. When the hyperinflation axis is dominant, more emphasis should be placed on optimum bronchodilation and deflation. This switch towards longacting bronchodilators has long been made in stable COPD.[4]

In stable-state COPD, important improvements are being made to reduce hyperinflation and improve dyspnoea by personalised non-pharmacological strategies, such as rehabilitation programmes, non-invasive ventilation, cognitive-behavioural strategies, surgical lung volume reduction, and, more recently, bronchoscopic lung volume reduction interventions.[5, 6] Although speculative, we might consider some of these innovative advances in deflating lungs of individual patients with a predominantly hyperinflated phenotype during exacerbations too.

We believe that an additional axis of hyperinflation and associated treatment will improve individualised care of patients with exacerbations. As the authors suggest, the system should be discussed and tested.

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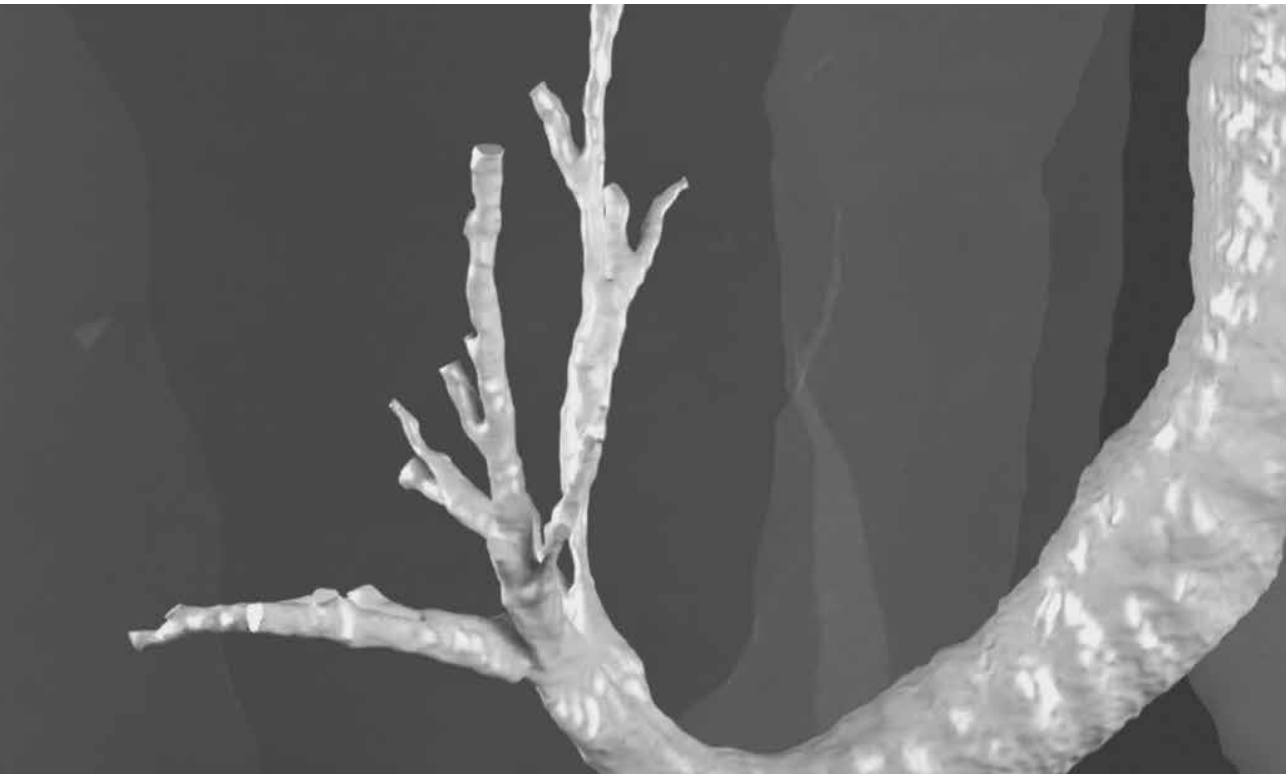

CHAPTER

Bronchodilators delivered by nebuliser versus pMDI with spacer or DPI for exacerbations of COPD

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ABSTRACT

Background

Bronchodilators are a central component for treating exacerbations of chronic obstructive pulmonary disease (COPD) all over the world. Clinicians often use nebulisers as a mode of delivery, especially in the acute setting, and many patients seem to benefit from them. However, evidence supporting this choice from systematic analysis is sparse, and available data are frequently biased by the inclusion of asthma patients. Therefore, there is little or no formal guidance regarding the mode of delivery, which has led to a wide variation in practice between and within countries and even among doctors in the same hospital. We assessed the available randomised controlled trials (RCTs) to help guide practice in a more uniform way.

Objectives

To compare the effects of nebulisers versus pressurised metered dose inhalers (pMDI) plus spacer or dry powder inhalers (DPI) in bronchodilator therapy for exacerbations of COPD.

Search methods

We searched the Cochrane Airways Group Trial Register and reference lists of articles up to 1 July 2016.

Selection criteria

RCTs of both parallel and cross-over designs. We included RCTs during COPD exacerbations, whether measured during hospitalisation or in an outpatient setting. We excluded RCTs involving mechanically ventilated patients due to the different condition of both patients and airways in this setting.

Data collection and analysis

Two review authors independently assessed studies for inclusion, extracted data and assessed the risk of bias. We report results with 95% confidence intervals (CIs).

Main results

This review includes eight studies with a total of 250 participants comparing nebuliser versus pMDI plus spacer treatment. We identified no studies comparing DPI with nebulisers.
We found two studies assessing the primary outcome of 'change in forced expiratory volume in one second (FEV_1) one hour after dosing'. We could not pool these studies, but both showed a non-significant difference in favour of the nebuliser group, with similar frequencies of serious adverse events. For the secondary outcome, 'change in FEV_1 closest to one hour after dosing': we found a significant difference of 83 ml (95% CI 10 to 156, P = 0.03) in favour of nebuliser treatment. For the secondary outcome of adverse events, we found a non-significant odds ratio of 1.65 (95% CI 0.42 to 6.48) in favour of the pMDI plus spacer group.

Authors' conclusions

There is a lack of evidence in favour of one mode of delivery over another for bronchodilators during exacerbations of COPD. We found no difference between nebulisers versus pMDI plus spacer regarding the primary outcomes of FEV_1 at one hour and safety. For the secondary outcome 'change in FEV_1 closest to one hour after dosing' during an exacerbation of COPD, we found a greater improvement in FEV_1 when treating with nebulisers than with pMDI plus spacers.

A limited amount of data are available (eight studies involving 250 participants). These studies were difficult to pool, of low quality and did not provide enough evidence to favour one mode of delivery over another. No data of sufficient quality have been published comparing nebulisers versus DPIs in this setting. More studies are required to assess the optimal mode of delivery during exacerbations of COPD.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is one of the most important respiratory diseases and the third leading cause of death worldwide.[1] It is generally caused by exposure to smoke or pollution. It is characterised by lung function decline and is associated with a decreased quality of life. Patients with COPD may have episodes with worsening of respiratory symptoms that require additional treatment.[2] These COPD exacerbations are the main driver of quality of life and survival in COPD. Exacerbations consist of a heterogenous spectrum of pathobiological changes compared to stable COPD, including inflammation, infection and hyperinflation.[3-5] Exacerbations account for between 34% and 70% of all costs incurred in COPD.[6]

Description of the intervention

Bonchodilation is important in the medical treatment of COPD, both in stable state and during exacerbations.[7] The choice of drug, dose and device all contribute to the success of inhaled medication in their own way, but remarkable differences exist in the prescribing habits of individual clinicians in all of these areas.

The inhaled bronchodilators used in COPD are short-acting beta2-agonists (SABA), long-acting beta2-agonists (LABA), and short-and long-acting anticholinergics. These are administered through various devices.[7]

Many clinicians choose to treat patients with nebulisers, especially in the acute setting, and many patients claim to benefit from them.[8] However, evidence supporting this choice from systematic analysis is lacking, and the available data are frequently biased by the inclusion of asthma patients.[9-12]

This Cochrane review will assess the evidence available on nebulised bronchodilator treatment versus delivery by pressurised metered dose inhalers (pMDI) with spacer or by dry powder inhalers (DPI) for acute exacerbations of COPD. We published our planned strategy and methods earlier as a protocol.[13]

How the intervention might work

Prior research has clearly established the benefit of bronchodilation in treating patients with COPD. Several systematic reviews have shown this for bronchodilators in a stable state of COPD.[14, 15] During exacerbations, experts also recommend the use of bronchodilation.[7] Hence, bronchodilators are common in treatment of COPD exacerbations all over the world. However, less is known about the best mode of delivery for these treatments, especially during exacerbations. Important features known to affect the deposition include particle size, choice of the device, respiration pattern and inhalation technique. During exacerbations of COPD, nebulisers, as well as pMDIs and DPIs, have been shown to be useful in delivering medication into the lungs.[16, 17] However, there are differences between device types, which may lead to differences in efficacy. For instance, the use of nebulisers is more time-consuming compared with pMDI/DPI, and patients require a better technique to inhale their bronchodilators by DPI and especially pMDI without spacer. Due to the nature of exacerbations, the best choice of a delivery method for bronchodilators may differ from stable state.

Why it is important to do this review

Although there is consensus on the use of bronchodilators, there has been little attention to the mode of delivery. As a consequence, wide variations in practice exist between and within countries and even among doctors in the same hospital. We assessed the available RCTs to help guide practice in a more uniform way.

OBJECTIVES

To compare the effects of nebulisers versus pressurised metered dose inhalers (pMDI) plus spacer or dry powder inhalers (DPI) in bronchodilator therapy for exacerbations of COPD.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) of both parallel and cross-over designs.

Types of participants

We included studies in participants with an exacerbation of COPD receiving treatment at home, in the clinic or in hospital. We excluded RCTs involving mechanically ventilated patients due to the different condition of both patients and airways in this setting. We also excluded people with asthma from our analysis.

Types of interventions

We included trials comparing a bronchodilator medication by nebuliser with the same bronchodilator medication by either pMDI (with or without spacer) or DPI. We allowed co-interventions including inhaled steroids.

Types of outcome measures

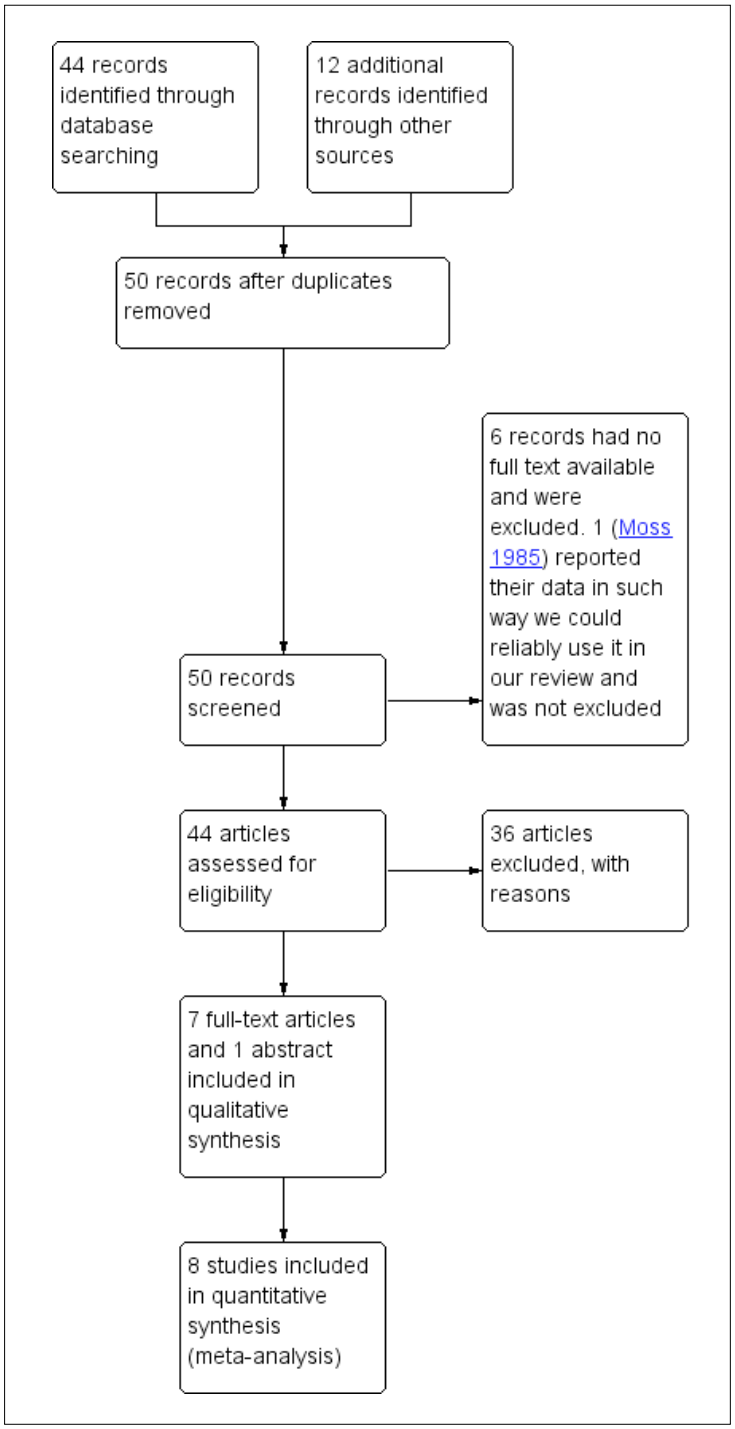
Primary outcomes

1. Change in forced expiratory volume in one second (FEV_1), one hour after dosing
2. Serious adverse events

Secondary outcomes

1. Change in peak FEV_1
2. Change in FEV_1 closest to one hour after dosing
3. Change in FEV_1 at other time points during the first 24 hours after dosing
4. Change in dyspnoea score during the first 24 hours after dosing
5. Change in quality of life on the first day of dosing
6. Admission rates
7. Time in hospital emergency department
8. Length of hospital stay
9. Change in oxygen saturation
10. Hospital readmission in 30 days
11. Adverse events/side effects

Figure 6.1 Study flow diagram



Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the Information Specialist for the Cochrane Airways Group. The CAGR contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts. We searched all records in the CAGR up to 1 July 2016.

We also searched ClinicalTrials.gov (clinicaltrials.gov) and the World Health Organization (WHO) trials portal (who.int/ictrp/en/). We searched both databases from their inception 1 July 2016, and we imposed no restriction on language of publication.

Searching other resources

We checked reference lists of all primary trials and review articles for additional references. We searched for errata and retractions from included trials published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed) to 1 July 2016.

Data collection and analysis

Selection of studies

Two review authors (WG and HK) independently screened titles and abstracts for inclusion of all the potential trials identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. Based on the consensus reached, we retrieved the full texts for assessment. Two review authors independently screened the full-text records and identified trials for inclusion. We reported the reasons for excluding the ineligible trials in a 'Characteristics of excluded studies' table. We resolved any disagreements through discussion or, if required, we consulted a third review author. We identified and excluded duplicates and collated multiple reports of the same trial so that each trial rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 6.1).

Data extraction and management

We used a data collection form, which we piloted on one included study, to record trial characteristics and outcome data. Two review authors extracted the following trial characteristics from included trials.

1. Methods: trial design, total duration of trial, details of any 'run-in' period, number of trial centres and location, trial setting, withdrawals and date of trial.
2. Participants: N, mean age, age range, sex, severity of condition, diagnostic criteria, baseline lung function, smoking history, and inclusion and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial and notable conflicts of interest of trial authors.

Two review authors extracted outcome data from the included trials. We noted in the 'Characteristics of included studies' table if outcome data was not reported in a usable way. We resolved disagreements by consensus or by involving a third review author. One review author, WG, transferred data into Review Manager (RevMan 2014). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the trial reports. A second review author checked the papers' trial characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies
Two review authors assessed risk of bias for each trial using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[18] We resolved any disagreements by discussion or by involving a third review author. We assessed the risk of bias according to the following domains.
1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as either 'high', 'low', or 'unclear' and provided a quote from the trial report or a justification for our judgment in the 'Risk of bias' table. We summarised the 'Risk of bias' judgements across different trials for each of the domains listed. We considered blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient- reported pain scale). Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' summary (Figure 6.2).

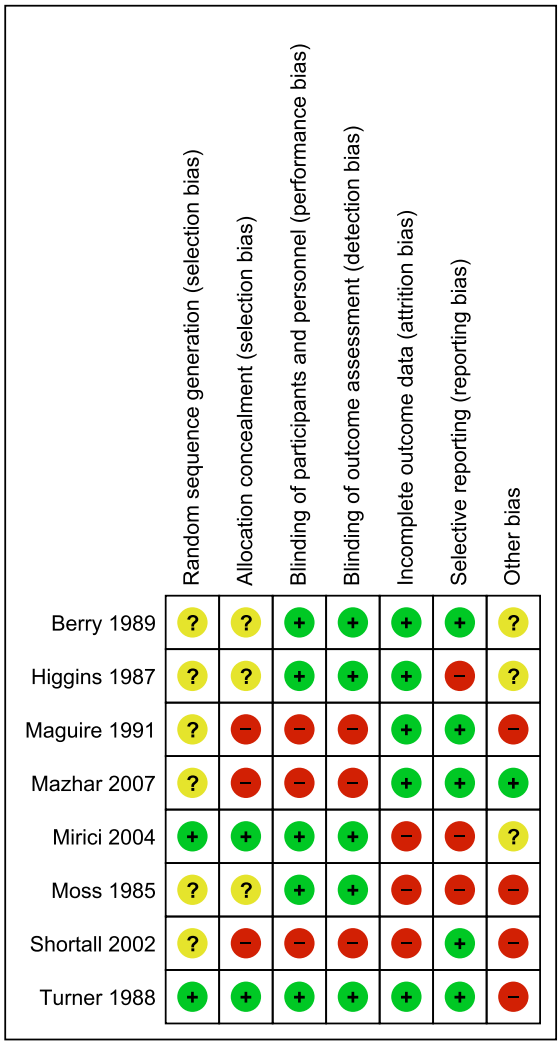
When considering treatment effects, we took into account the risk of bias for the trials that contributed to that outcome.

Assessment of bias in conducting the systematic review
The review was conducted according to the published protocol[13], and we report any deviations from it in the 'Differences between protocol and review' section.

Measures of treatment effect
We analysed dichotomous data as odds ratios (OR) and continuous data as mean difference (MD) or standardised mean difference (SMD). We entered data presented as a scale with a consistent direction of effect. To analyse the cross-over trials included in Analyses 1.1, 2.2 and 2.3, we used the generic inverse variance (GIV) method.

We undertook meta-analyses only where it was meaningful to do so, that is, if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense.

Figure 6.2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



We narratively described skewed data reported as medians and interquartile ranges.

For these studies, we expected to have to standardise the results of the studies to a uniform scale before combining them. The SMD expresses the size of the intervention effect in each study relative to the variability observed in that study. However, we could not use the SMD due to the cross-over design of some of the included studies. In the studies where this was the case, we decided to present the data as a mean difference only.

Unit of analysis issues
If we had identified both cluster RCTs and individual RCTs, we planned to synthesise the acquired data. We planned to combine the results if we only detected a little heterogeneity

between the trial designs, and we considered bias based on the choice of randomisation unit to be unlikely. Otherwise, we would have adjusted the sample sizes or standard errors using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions.[18]

Dealing with missing data
When we thought missing data could introduce serious bias, we explored the impact of including such studies in the overall assessment of results by performing a sensitivity analysis. The studies we examined for the primary outcomes mostly had relatively short-term outcomes. We found some missing data for the primary outcomes. In the case of Turner[12], we managed to obtain original data, and we were able to calculate some of the missing data. We did not impute or extrapolate existing data.

Assessment of heterogeneity
We used the I^2 statistic to assess heterogeneity among the studies in each analysis. Where we identified substantial heterogeneity, we have reported it and explored possible causes.

Assessment of reporting biases
Had we been able to pool more than 10 studies, we would have created and examined funnel plots to explore possible small trial and publication biases. However, we did not reach a pool of 10 studies.

Data synthesis
We used a random-effects model and performed a sensitivity analysis with a fixed-effect model. We used the standard deviations to standardise the mean differences to a single scale and compute trial weights.

Subgroup analysis and investigation of heterogeneity
We planned to analyse data according to bronchodilators used,mechanism (anticholinergic or beta-adrenergic), and short-acting versus long-acting beta2-agonists, analysing subgroups separately for SABA, LABA, SAMA, LAMA, and SABA/LAMA combinations. We also planned to analyse the data from single dose trials in the primary outcomes, and to analyse a subgroup of multiple treatment (doses) trials for the primary and secondary outcomes. However, due to the small number of studies included in our review, subgroup analyses (e.g. for dose or device) were underpowered. Therefore, we decided to assess all data pooled.

Sensitivity analysis
We assessed the risk of introducing bias due to missing data through a sensitivity analysis of our primary outcomes by comparing Berry and Mazhar with the other studies assessed as being at low risk of bias.[19, 20]

'Summary of findings'
We created a 'Summary of findings' table using both the primary and secondary outcomes. We used the five GRADE considerations (trial limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence as it relates to the trials contributing data to the meta-analyses for the prespecified outcomes. We used

methods and recommendations described in Section 8.5 and Chapter 12 of Higgins, using GRADEpro software.[18, 21] We detailed all decisions to downgrade or upgrade the quality of trials in the 'Summary of findings' table footnotes and made comments to aid readers' understanding of the review where necessary.

RESULTS

Description of studies

Results of the search

We found 1082 records from the Cochrane Airways Group Specialised Register. After scanning titles and abstracts, we selected 44 for full-text review. In addition, we identified 277 records from ClinicalTrials.gov (clinicaltrials.gov) and 80 from the WHO trials portal (www.who.int/ictrp/en/). Of these, we selected only one additional ongoing study (NCT02291016), with no available data. We found 12 additional references through other sources. We analysed those 56 articles in detail, as reported in Figure 6.1.

Included studies

See the 'Characteristics of included studies' for full details. We identified eight studies with an appropriate design to evaluate our predefined outcomes. A total of 250 participants with COPD were randomised to doses of aerosol with an inhaler plus spacer or a nebuliser treatment. Six out of the eight included studies reported excluding participants experiencing the most severe exacerbations, using criteria such as pH < 7.30 kPa, inability to perform spirometry or stand unsupported, respiratory failure or requiring mechanical ventilation. We identified no studies reporting on dry powder inhaler versus a nebuliser. We included studies with single or multiple dose and cross-over designs. The studies took place in hospital settings in the United States,[12, 19, 22-24] the United Kingdom,[20, 25] and Turkey.[26] The studies used different beta2-agonists, anticholinergics, pMDIs, spacers and nebulisers. We noticed a difference in dosage ratio between the pMDI/spacer and nebuliser in the studies. This ratio varies from 1:1 in Higgins to 1:11.5 in Maguire.[22, 25]

Excluded studies

See the 'Characteristics of excluded studies' table in the orginal publication for full details. Most commonly, we excluded studies in the ventilation setting, studies without an appropriate comparator to answer our hypothesis and studies mixing results for asthma and COPD.

Risk of bias in included studies

See Figure 6.2 for the 'Risk of bias' summary. For each study, we describe the 'Risk of bias' assessment in the 'Characteristics of included studies' table. The methodological quality of the studies included varied. Most of the studies did not describe the method of sequence generation, allocation concealment, or blinding of outcome assessment. None of the included studies reported the use of an intention-to-treat analysis or a power analysis. One study did not adequately describe the use of a spacer in their manuscript.[23] However, we decided to include this study in our analysis based on the following arguments: we estimated that they did use a spacer in their study; according to our protocol, we had agreed to include studies that did not use a spacer; based on the reported trial design, we assessed this study to be of sufficient quality to be included in this analysis; and the study has been included in another meta-analysis.[27]

Allocation
Only Mirici and Turner.[12, 26] reported the use of a computer-generated list of random numbers; the other six included studies may have been influenced by selection bias. Mirici adequately described their allocation blinding, and based on the overall quality of Turner.[12, 26] We deemed the risk for selection bias due to allocation concealment methods to be low.

Blinding
Three studies were not blinded, so the risk of performance and detection bias in these studies is high.[20,22,24] The other studies were all double-blinded.

Incomplete outcome data
The risk of attrition bias was high in three of the studies using peak expiratory flow (PEF) measurements in the analysis, because FEV_1 measurements after hospitalisation were not available for all participants.[23, 24, 26] Moss was never published as a full paper.[23] Shortall reported that 4 participants of the oral/pMDI group and 12 in the intravenous/nebuliser group did not complete the trial.[24] It remains unclear why these participants dropped out and what caused the imbalance between the groups in the number of drop-outs.

Selective reporting
We observed a risk of selective reporting bias in three studies where authors described a change in FEV_1 in the methods but did not report it.[23, 25, 26] Mirici did not report FEV_1 and forced vital capacity (FVC) measurements after hospitalisation.[26] The abstract of Moss et al was not published as a full paper, leading to a high risk of reporting bias.[23]

Other potential sources of bias
An important issue to consider is a difference in dose ratio between the pMDI/spacer and the nebuliser in the studies. This ratio varies from 1:1 in Higgins to 1:11.5 in Maguire. [22, 25]

Effects of interventions

Summary of findings

Table 6.1 Summary of findings for the main comparison.

Bronchodilators delivered by nebuliser versus pMDI with spacer for exacerbations of COPD

Patient or population: participants with an exacerbation of COPD; people with asthma excluded from our analysis
Settings: treatment was allowed at home or in the clinic or hospital.
Intervention: nebuliser
Comparison: pMDI with spacer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk pMDI with spacer	Corresponding risk Nebuliser				
Change in FEV_1 1 h after dosing in ml	The mean change in FEV_1 1 h after dosing in the pMDI group was 103 ml	The mean change in FEV_1 1 h after dosing in the nebuliser group was 36 ml more (from 38 ml fewer to 110 ml more)	—	40 (1)	⊕⊖⊖⊖ Very low [a]	—
Serious adverse events	88 per 1000	88 per 1000 (17 to 348)	OR 1.00 (0.18 to 5.53)	70 (2)	⊕⊕⊖⊖ Low [b]	—
Change in FEV_1 closest to 1 h after dosing in ml	The mean change in FEV_1 closest to 1 h after dosing in the pMDI group is93 ml	The mean change in FEV_1 closest to 1 h after dosing in the nebuliser groups was 83 ml more (10 to 156 ml more)	—	126 (4)	⊕⊕⊖⊖ Low [b]	—
Change in dyspnoea score during the first 24 h after dosing	The mean change in dyspnoea score during the first 24 h after dosing–1.28 points on the Borg scale (lower score indicates reduced dyspnoea)	The mean change in dyspnoea score during the first 24 h after dosing was 0.12 points worse (0.56 better to 0.79 worse) on the Borg scale in the nebuliser groups	—	74 (2)	⊕⊕⊖⊖ Low [b]	A lower Borg score indicates reduced dyspnoea
Adverse events/side effects	56 per 1000	89 per 1000 (24 to 278)	OR 1.65 (0.42 to 6.48)	110 (3)	⊕⊕⊖⊖ Low [b]	—

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR**: odds ratio; **ml**: millilitres; **FEV_1** : forced expiratory volume in 1 second; **pMDI**: pressurised metered dose inhaler.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

a Downgraded for sample size (only one small study included in the analysis) (–2) and indirectness (e.g. older trials, so devices used may not be relevant to clinical practice today, and heterogeneity in dose between the groups) (–1)
b Downgraded for sample size of the included trials (–1) and indirectness (e.g.older trials, so devices used may not be relevant to clinical practice today and heterogeneity in dose between the groups) (–1)

Primary outcomes

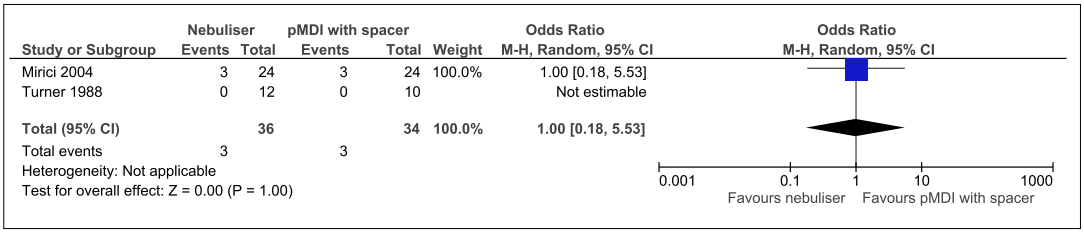
Change in FEV_1 one hour after dosing

We analysed the change in FEV_1 one hour after dosing in Berry and Mazhar.[19, 20] Due to different measurement units and the cross-over design of the studies, we could not pool them. A separate analysis of both studies showed a non-significant difference in favour of the nebuliser group. Mazhar found a mean absolute increase in FEV_1 of 4.3% ± 4.8 in the nebuliser group, compared with 2.6% ± 3.3 in the pMDI group.[20] Berry found a mean relative increase in FEV_1 of 16.7% ± 17 in the nebuliser group compared with 13.4% ± 20.5 for the pMDI group.[19] Change in FEV_1 one hour after dosing did not show a significant difference between the pDMI and nebuliser group (MD 36 ml, 95% CI −38 to 110, N = 40, Analysis 1.1).
Most other included studies reported two separate values for FEV_1 instead of a change in FEV_1 at this time point, making meta-analysis of their data impossible.

Serious adverse events

There were no significant differences in the occurrence of serious adverse events between the two delivery methods in the two trials that reported on this outcome.[12, 26] Turner reported none.[12] Mirici reported that two participants developed a pneumothorax and one participant required mechanical ventilation in the nebuliser group, and three participants developed a pneumothorax in the pMDI group[26] (Figure 6.3).

Figure 6.3 Forest plot of comparison: Primary endpoint: Nebuliser vs pMDI/DPI, outcome: Serious adverse events.



Secondary outcomes

Change in peak FEV_1

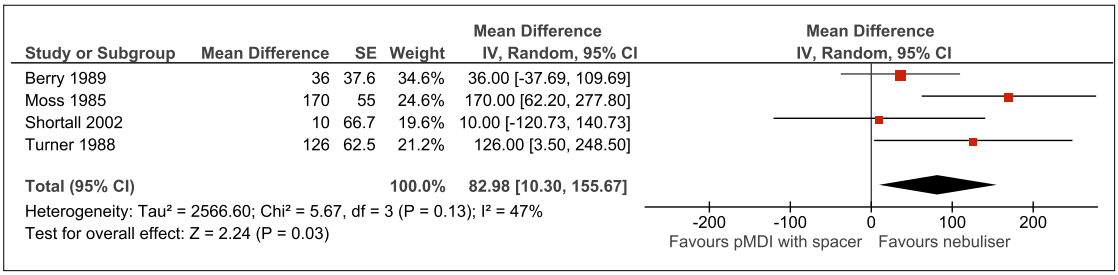
There were no data available regarding change in peak FEV_1.

Change in FEV_1 closest to one hour after dosing

We pooled reported data change in millilitres. According to our protocol, we could include cross-over designs.[13] This resulted in the fact that studies reporting a different scale of data could not be included in the meta-analysis. The forest plot shows a significant difference of 83 ml (95% CI 10 to 156, P = 0.03) in favour of the nebuliser treatment (Figure 4). If multiple time points were available, we included the time points closest to one hour of dosing. Moss measured FEV_1 at 20 minutes after the dose, while we included the measurements from Turner at a 30 minute time point.[12, 23] The measurements from Berry were performed at one hour.[19] Shortall did not report data about the timing of measurements; however, based on their trial design, we assumed they were performed at a sufficient time point to include them in this analysis.[24] Due to a different unit of reporting, we could not include data from Maguire

and Mazhar in this meta-analysis.[20, 22] However, their results also show a non-significant difference in favour of the nebuliser group. We calculated the standard error for the GIV analysis from the formula in Section 16.4.6.1 of Higgins.[18]

Figure 6.4 Forest plot of comparison: Secondary endpoint: Nebuliser vs pMDI/DPI, outcome: *Change in FEV_1 at other time points during the first 24 hours after dosing*



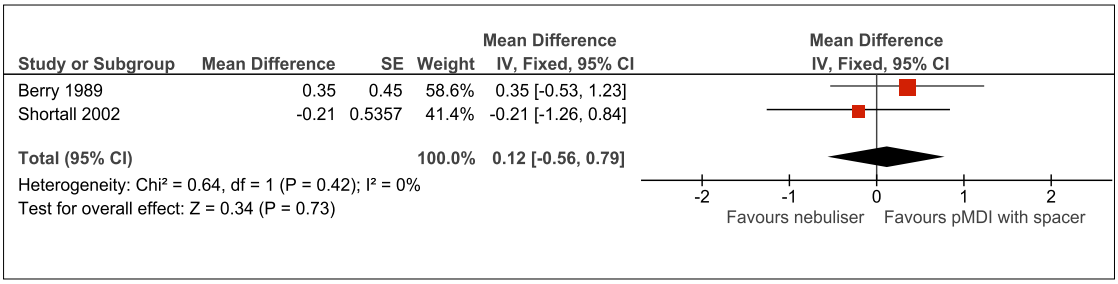
Change in FEV_1 closest to one hour after dosing

We were not able to find data about additional time points other than those reported in the analyses above. Therefore, we did not deem a separate analysis to be meaningful for this outcome.

Change in dyspnoea score during the first 24 hours after dosing

Based on data from two studies measuring dyspnoea with Borg's scale, we found no significant change in dyspnoea score.[19, 24] One additional study also used this scale, reporting no significant difference between the groups.[12] However, we were not able to obtain the raw data for this outcome to recalculate their numbers to our previously defined outcome. Based on the included data, we found a non-significant difference of 0.12 points (95% CI -0.56 to 0.79; P = 0.73) in favour of the pMDI group (Figure 6.5).

Figure 6.5 Forest plot of comparison: Secondary endpoint: Nebuliser vs pMDI/DPI, outcome: Change in dyspnoea score in the first 24 hours after dosing.



Change in quality of life on the first day of dosing

There were no data available about change in quality of life on the first day of dosing.

Admission rates

We found no significant difference in admission rate. Turner took place at the emergency department, reporting two admissions in both the pMDI and nebuliser group. [12]
We nevertheless found a non-significant difference in favour of the nebuliser group (OR: 0.80, 95% CI 0.09 to 7.00) because the nebuliser group contained slightly more participants.

Time in hospital emergency department

Although Turner was performed at the emergency department, it did not report on time in the emergency department.[12] Thus we could not extract data about this outcome.

Length of hospital stay

We found no significant difference in hospital stay in the one study reporting this outcome: Shortall reported a non-significant difference in favour of the pMDI group of 0.80 days (95% CI −1.05 to 2.65, P = 0.40).[24]

Change in oxygen saturation

Mirici reported a change in oxygen saturation at several time points after inclusion. There were no significant changes at 30 minutes after the first dose or at the other reported time points (6 h, 24 h, 48 h or 10 d).[26]

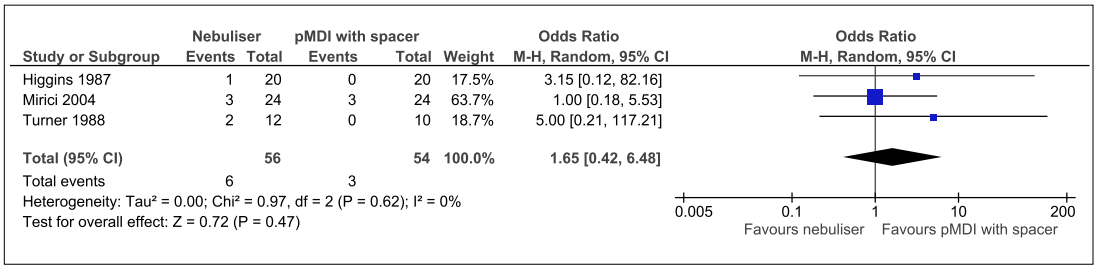
Hospital readmission in 30 days

There were no data available about hospital readmission rates in 30 days.

Adverse events/side effects

We found no significant differences between the groups concerning adverse events in the three studies reporting on this outcome.[12,25,26] Turner reported two adverse events in the nebuliser group; however, they did not explain the nature of these events.[12] One participant in Higgins developed a marked fall in saturation from 88% to 73% 15 minutes after taking the nebuliser treatment.[25] As stated earlier in the primary outcome section, Mirici reported two participants developing a pneumothorax and one participant requiring mechanical ventilation in the nebuliser group, and three participants developing a pneumothorax in the pMDI group[26] (Figure 6.6).

Figure 6.6 Forest plot of comparison: 2 Secondary endpoint: Nebuliser vs pMDI/DPI, outcome: 2.10 Adverse events/side effects.



DISCUSSION

Summary of main results

There is a lack of evidence favouring one mode of bronchodilator delivery over another during exacerbations of COPD. We found no difference between nebulisers and pMDI plus spacer regarding the primary outcomes FEV_1 at one hour and safety. The secondary outcome 'change in FEV_1 closest to one hour after dosing' showed a greater improvement in FEV_1 when treating with nebulisers than with pMDI plus spacers. A limited amount of data are available (eight studies involving 250 participants). These studies were difficult to pool. There were no available study data to enable us to include data about DPIs in our analysis.

Bronchusobstruction

The search for better parameters for acute, severe COPD exacerbations is ongoing , but for now, FEV_1 continues to be an important parameter in clinical trials for COPD exacerbations.[4] This review assessed change in FEV_1 at several time points. We found no significant differences between the pMDI and nebuliser group for a change in FEV_1 at one hour after dosing, but we could not pool the available data. The secondary outcome, 'change in FEV_1 closest to one hour after dosing', showed a greater improvement in FEV_1 in the nebuliser group than in the pMDI plus spacers group. Overall, there is a lack of evidence favouring one mode of delivery over another for bronchodilators during exacerbations of COPD with regard to bronchus obstruction.

Adverse events

Three studies reported on adverse events. [12,25,26] This is the first time the data have been pooled and assessed systematically. Adverse and especially serious adverse events might influence the device choice for physicians when treating patients with COPD exacerbations. However, with current available data in this systematic review, we found no significant differences between pMDI and nebuliser treatment. Overall, there is a lack of evidence favouring one mode of delivery for bronchodilators over another during exacerbations of COPD with regard to adverse events.

Dyspnoea and quality of life

Patient-reported outcomes are becoming more important in current practice. Patient-reported outcomes include scoring of dyspnoea and quality of life. The analysis of dyspnoea showed no significant differences between pMDI and nebuliser treatment. We did not identify any data about quality of life. Overall, there is a lack of evidence favouring one mode of delivery for bronchodilators over another during exacerbations of COPD with regard to dyspnoea and quality of life.

Clinically important outcomes

This systematic review assessed additional clinically important outcomes, used both by physicians and policymakers on a daily basis. We were surprised by the lack of data about admission rates, time in the hospital emergency department, length of hospital stay, and hospital readmission within 30 days. These are perhaps parameters that have only recently become more important, and additionally necessitate longer trials. Overall. there is a lack of evidence favouring one mode of delivery for bronchodilators over another during exacerbations of COPD with regard to these outcomes.

Overall completeness and applicability of evidence

The overall completeness of the evidence is low. Due to differences in outcome reporting we could not calculate the change in parameters from all studies. The evidence gathered related only to the comparison of nebulisers versus pMDIs. We found no studies investigating DPIs versus nebulisers using the same substance, nor studies with nebulised long-acting bronchodilators. Data about important clinical parameters, hospital readmission in 30 days, change in peak FEV_1 and change in quality of life were not available. Participants in the included studies were all treated in a hospital setting rather than at home. Turner reported on an emergency department setting, from which most participants were not admitted.[12]
We recognise that the setting in which a patient receives treatment may have an impact on the choice of treatment mode, beyond concerns solely about the efficacy of the method. The paucity of data in this review has not allowed us to comment on the effect of the trial setting on the outcomes. We noticed a lack of standardised definitions in both COPD and exacerbations, which might influence the generalisability of the findings, although this lack of standardised definitions is also present in regular clinical practice. Thus, it is not entirely clear whether our results apply to all patients who present to a hospital with an exacerbation of COPD.

Additional studies could prove useful in providing further evidence towards the difference we signalled in bronchodilator effects in favour of the nebuliser treatment. However, readers should keep in mind that the mean clinically important difference for the FEV_1 is generally reported to be 100 to 140 ml.[28, 29]
Many practitioners commonly prescribe nebulisers for the acute exacerbation of COPD. Based on the results of our review, there is no evidence to either support or refute this practice. This might influence the applicability of the evidence; however, given the lack of evidence provided in this review, it is even more important to adequately assess the individual patient, the available modes of nebulisers and the available pMDIs and spacers. There are several important differences between different types of modern nebulisers, for instance regarding inhaled dose, delivered dose and the use of the compresso.[30, 31] In the absence of good quality evidence, such an assessment might provide guidance to select the optimal treatment for each patient.

Quality of the evidence

We used the GRADE assessment to qualify the amount of evidence of the outcomes, reporting this in the Summary of findings for the main comparison. Overall the quality of the evidence was low and sometimes even lacking. The studies that were included in this review are relatively small, and we downgraded the quality of the outcomes to reflect this. Especially for the primary outcome measuring FEV_1 at one hour, we could only include one older trial [19]. We therefore downgraded the evidence for this outcome. Heterogeneity varied across individual outcomes, ranging from I2 = 0% to I2 for = 47% for change in FEV_1 (ml) closest to one hour after dosing.

The evidence was relatively old, with studies performed from at least 9 years and up to 31 years prior to this systematic review. This might influence the results, since modern nebulisers, pMDIs and DPIs may work in a different way than the ones used 30 years ago.

It is important to note the lack of standardised dose of bronchodilators between the different designs. Although actual lung deposition is generally held to be lower by nebuliser than by pMDI when using the same dose in both devices, good data are sparse. We noticed a significant variation in dose between the studies. Additionally, the type of nebuliser, compressor and pMDI used in trials will influence the actual lung deposition. [20, 30, 31] This might influence results, although it is unclear to what extent. We downgraded the quality of the evidence due to the combination of relatively old studies and dose variation.

Potential biases in the review process

A potential bias in our review process is publication bias. We found several studies reported only as abstracts. Although we tried, we could not retrieve a full data set from the study authors for several reasons. The data reported in the abstracts were not sufficient to allow recalculation for our outcomes, except in the case of the study by Moss.[23]

Agreements and disagreements with other studies or reviews

Although the data for the primary outcome did not show significant differences, this systemic review suggests for the first time that treatment with nebulisers during an exacerbation of COPD may improve FEV_1 more than pMDI with a spacer. However, it is very difficult to interpret this result correctly due to the previously discussed bias. We therefore concur with the earlier findings from Turner and Dolovich.[27, 32] They did not find significant differences and concluded that there is not enough evidence to favour a mode of delivery for bronchodilators during exacerbations of COPD. Both reviews used asthma patients in their analysis, and both focused on FEV_1 or peak flow. A systematic review in mechanically ventilated patients with a need for aerosol bronchodilator therapy found no difference in bronchodilator effects, although they were only able to pool two studies with 28 participants in total for this outcome.[33]

AUTHORS' CONCLUSIONS

Implications for practice

Due to inconclusive findings for our primary outcomes and all but one of our secondary outcomes, risk of bias, and relatively low numbers of studies and participants (eight studies involving 250 participants), the existing published data do not provide enough evidence to firmly favour one mode of delivery for bronchodilators over another during exacerbations of COPD. One secondary outcome suggests that treatment with nebulisers during an exacerbation of COPD slightly outperforms pMDI plus spacer with regard to improving FEV_1; however, this finding should be interpreted with care. Limited data about nebulisers versus pMDIs plus spacer are available. No data of sufficient quality have been published comparing nebulisers in this setting versus DPIs. We did not identify any studies of nebulised long-acting drugs. Most studies tested on one day only, in a cross-over design.

Implications for research

More studies are required to assess the optimal mode of delivery during exacerbations of COPD. In particular, data about DPIs versus nebulisers are lacking. There seems to be a larger effect on FEV_1 with the nebuliser. However, larger studies could shed more light on this and should take into account the considerable difference in the total administered dose between nebulisation and pMDI, and indeed the differences between different nebuliser designs and inhalers devices. The outcomes of these studies have traditionally focused at bronchodilating

effects. Future studies should also assess different parameters such as adverse events, dyspnoea and quality of life. Patients, both in the acute setting and even in a stable state of COPD, seem to be more satisfied with nebulised administration than can be understood from the bronchodilatory data. Further research may be required to investigate the acceptability of different drug delivery modes in patients who may be accustomed to receiving nebulised treatment during an exacerbation. In times of strain on the medical system and its costs, length of stay and time to readmission would be valuable additional parameters for trials to consider. Investigators should report data about patients with COPD, asthma or an overlap syndrome separately. Future research evaluating nebuliser treatment compared with pMDI or DPI during COPD exacerbations should report findings as a change in means with standard error or standard deviation, or studies should provide sufficient data in the study report to enable calculation of these values. This will enable a meta-analysis of the study findings. We would also advise researchers to perform a power analysis when planning any new trials.The value of long-acting bronchodilators in the treatment of exacerbations, as well as their optimal modes of delivery, is totally unknown but would be valuable to study, especially since they have been shown to reduce hyperinflation and improve dyspnoea in stable state and are the standard of care after discharge.[4]

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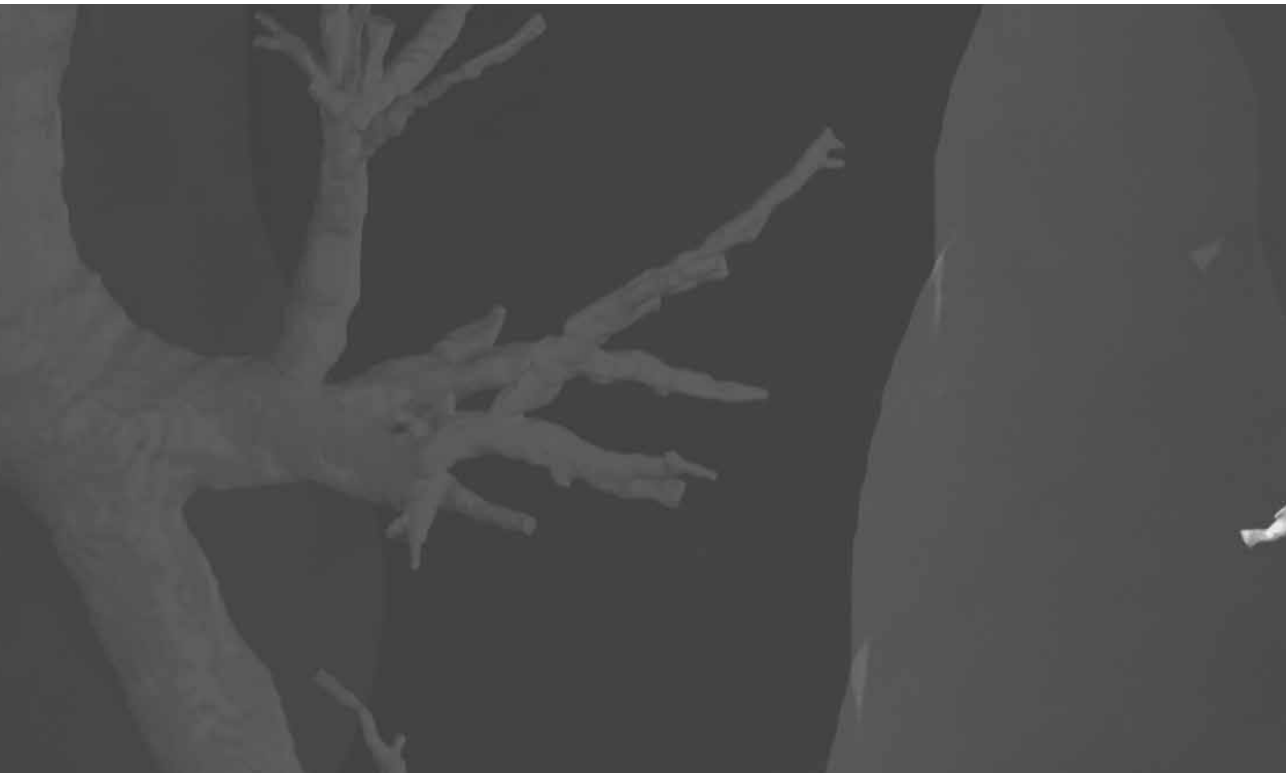

CHAPTER

Emerging bronchoscopic treatments for chronic obstructive pulmonary disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is aprogressive lung disease characterized by pathophysiological factors including airflow limitation, hyperinflation and reduced gas exchange. Treatment consists of lifestyle changes, lung rehabilitation and pharmacological therapies such aslong acting beta-2-agonists (LABA) and long acting muscarinic antagonists (LAMA). More recently bronchoscopic treatments are emerging for COPD. Among them endobronchial valves (EBV) and endobronchial coils (EBC), next to endobronchial stents, sclerosing agents, targeted lung denervation and liquid nitrogen metered cryospray. In this review we aim to summarise the new emerging bronchoscopic treatments and their effects sizes compared with lung rehabilitation and pharmacological therapies.

INTRODUCTION

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[1] COPD is the third leading cause of death worldwide.[2]

COPD is an umbrella term for airflow limitation due to parenchymal destruction (emphysema) and (small) airways disease with inflammation and fibrosis. The relative contribution of airway disease, parenchymal destruction and other changes vary from person to person and even between lung lobes. This results in multiple different phenotypes [3-6], most distinctly chronic bronchitis and emphysema.Episodes with worsening of respiratory symptoms and anxiety, exacerbations, further contribute to the decrease in quality of life and survival in COPD. These exacerbations are associated with infections and hyperinflation and usually require additional therapy.[7,8]

Pathophysiology

Bronchus obstruction

COPD is characterized by a chronic airflow obstruction. This can be detected with spirometry. The spirometry then shows a decreased forced expiratory flow in 1 second (FEV_1) and a reduced ratio between the FEV_1 and the forced vital capacity (FVC).
Bronchus obstruction and inflammation were the first factors to be treated in COPD. Bronchus obstruction was treated with bronchodilators and inflammation was treated with first oral corticosteroids and later inhaled corticosteroids. [1,9]

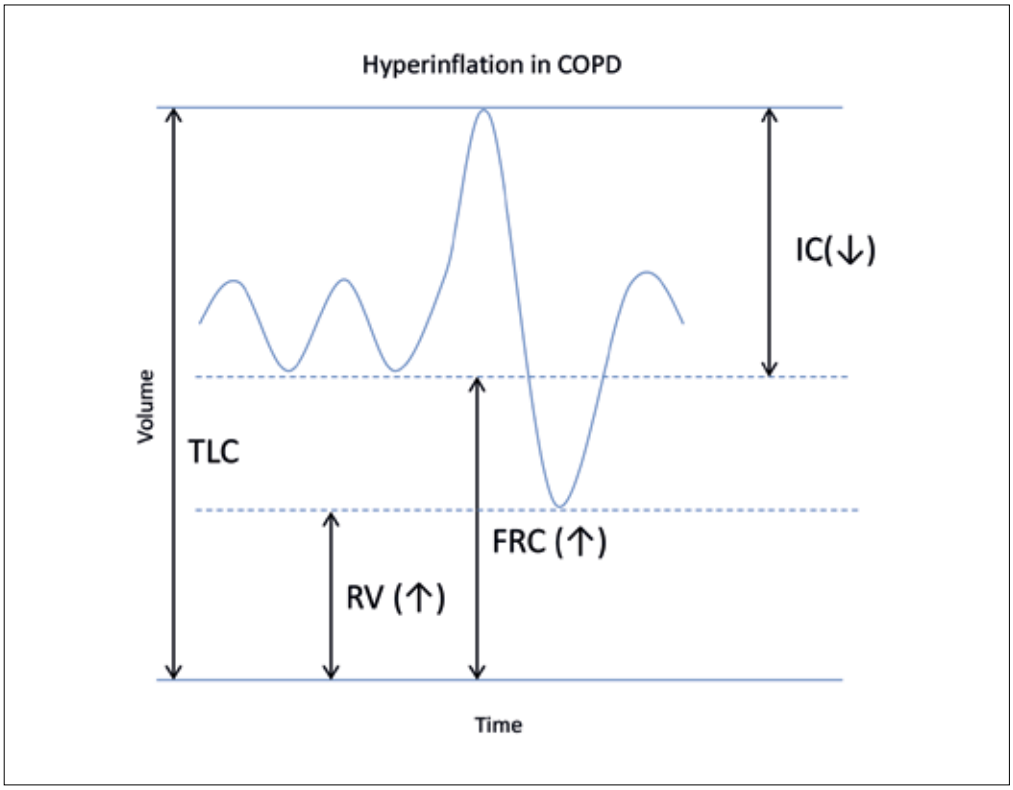
Hyperinflation

Hyperinflation is entrapment of air in the lungs during expiration, causing the lungs to hyperinflate. Hyperinflation is caused by bronchus obstruction. This phenomenon is frequently present in COPD, both in stable state, during exercise, and during exacerbations.[10-12] Hyperinflation causes symptoms such as increased dyspnea and limited exercise capacity due to a decreased inspiratory capacity (IC), increased functional residual capacity (FRC) and increased residual volume (RV). These changes in lung volumes are accompanied by a decrease in FEV_1 in most hyperinflated COPD patients (Figure 7.1).[13] Hyperinflation usually has an important dynamic component, since during exercise, hyperinflation increases further.[14,15] Hyperinflation is a predictor of mortality in stable state.[16]

Gas exchange limitations

The main gasses to be influenced in COPD are oxygen and carbon dioxide. These gasses are important for the metabolism of all living cells of the human body. Abnormalities in their transfer can result in hypercapnia and hypoxia in COPD. Gastransfer is influenced by the entrance of gasses in the alveoli, by the pulmonary vascular system and their ratio (ventilation/perfusion ratio). Additionally the number of alveoli, the amount of haemoglobin in the blood and the membrane separating air and blood in the alveoli are all influencing gas exchange.[1,17,18]

Figure 7.1 Hyperinflation in COPD



Schematic volume time curve showing change in lung volumes in hyperinflated COPD patients. Arrows indicate the direction changes.IC: inspiratory capacity; FRC: functional residual capacity; RV: residual volume ; TLC: total lung capacity

Specific treatment mainly aimed to influence the gas exchange is not in common use. Long-term oxygen does not provide symptom or survival benefit.[19] Thus far it is not possible to recreate destroyed alveoli. Stem cells, originating from the embryonic mesoderm although seem safe to administer. However thus far they didn't improved gas exchange but where used for their antiinflammatory effects.[20] Vasodilators do not improve and may even worsen gas exchange.[1,21,22]

Pharmacological treatment

Bronchodilators are the cornerstone of therapy for stable COPD. Two major classes of bronchodilators are advocated in guidelines, β2-agonists and muscarinic antagonists. Bronchodilators are mainly administered via inhalers, most commonly by pressurized metered-dose inhalers or dry powder inhalers.[23] The first substances worked for a short period of time and are therefore called short-acting bronchodilators. Long acting bronchodilators are especially useful in treating hyperinflation.[24] Their benefit however is still limited. Their effects are most commonly measured via changes in FEV_1. The most commonly accepted minimal clinical important difference for FEV_1 is 100 milliliters. The median increase in trough FEV_1 in COPD patients treated with LABAs is 99ml. For LAMAs this is a median change of 104 ml.[25]

When LAMAs are combined with a LABA, the FEV_1 increases further by 60 ml.[26]
Quality of life in COPD is most commonly measured via the St George's Respiratory Questionnaire (SGRQ). The minimal clinical important difference for regular COPD patients difference is considered to be four.[27] LABA show an improvement in SGRQ of 2.29 points; LAMAs with 2.63 points. When LAMAs are combined with a LABA the SGQR improves further by 1.34 points.[26] Although lung rehabilitation should not be perceived as pharmacological treatment and does not primarily aim to improve FEV_1, it is a very important treatment for COPD patients. Lung rehabilitation improves quality of life measured by SGRQ with 6.89 points.[28] Inhaled corticosteroids in COPD are aimed to reduce airway inflammation. Treatment with inhaled corticosteroids alone does not conclusively modify long-term decline of FEV_1 or mortality in COPD.[1,29]

With the perception that hyperinflation is an important contributor to symptoms and to morbidity, came the idea that targeted treatment of hyperinflation is an important goal and therefore a treatable trait. Hyperinflation can be reduced with long-acting bronchodilators, and the following personalized non-pharmacological strategieshave been shown to be able to reduce hyperinflation and improve dyspnea: rehabilitation programs, non-invasive ventilation, cognitive-behavioural strategies, and specific lung volume reduction interventions.[10,15]

Lung volume reduction surgery

The first lung volume reduction was performed by surgery, and already as early as 1957.[30] As the name suggests, lung volume reduction surgery (LVRS) reduces lung volume, by removing the most destructed and hyperinflated part of the lung.[31,32] LVRS can be done unilaterally and bilaterally. Reduction of the volume of hyperinflated COPD patients reduces exertional breathlessness at a given workload. This is attributed to a combination of reduced thoracic hyperinflation, reduced breathing frequency, and reduced mechanical constraints on lung volume expansion.[33,34] The largest surgical lung volume reduction trial (The 'NETT trial') assessed 1218 patients with severe emphysema who underwent pulmonary rehabilitation.[35] These patients were randomly assigned to undergo lung volume reduction surgery or to receive continued medical treatment only. The trial showed no survival advantage for surgery over medical therapy. The highly invasive surgical technique was associated with increased morbidity and mortality, especially in patients with either a FEV_1 or diffusion capacity below 20% of predicted, and in patients treated in the lower lobes of the lung. A subgroup analysis showed a survival advantage for patients with both predominantly upper-lobe emphysema and low base-line exercise capacity. These results severely limit the applicability of LVRS. These results also led to creative new approaches such as full lobar resections by VATS and so called "non-cutting" techniques, both aiming at reducing post surgical prolonged airleak complications.[36,37]

Bronchoscopic treatments

Since the NETT trial and its ambiguous results, much less invasive bronchoscopic treatment options for achieving lung volume reduction in patients with the predominantly emphysema disease phenotype have been developed, aimed at improving quality of life and reduction of mortality and morbidity both by deflation itself, while evading much of the mortality and morbidity associated with surgery.[35,38] Different technologies have been tested, with most

of them still being performed in clinical trials only, though some of them have already made it in into clinical practice in some European countries.[38] Due to the different mechanisms of action of the different bronchoscopic treatments it is important to carefully phenotype patients who might benefit from each bronchoscopic treatment. We will discuss the different technologies separately.

Endobronchial Stents

Airway bypass is a bronchoscopic treatment whereby transbronchial passages through the walls of the more central airways into the lung parenchyma are created to release trapped air. These passages are supported with paclitaxel drug eluting stents to facilitate the mechanics of breathing with an aim of lung volume reduction.

This technology was tested in a multicenter randomised, double-blind, full sham bronchoscopy controlled trial, the EASE trial.[39] 208 patients were treated and the control group consisted of 107 patients. Patients with severe hyperinflation were included (FEV_1 below 50% predicted or 1Liter, RV >180% predicted).All patients had pulmonary rehabilitation before the procedure. Although the patients improved considerably initially after the procedure, the trial failed to show any longer lasting superiority of airway bypass for the primary endpoints (FVC and mMRC) and FEV_1. Also quality of life measured by the SGRQ nor the 6-minute walk test showed a lasting benefit for the patients treated with this technique. It is noteworthy that the sham control patients did not show any placebo effect on SGRQ. The therapy failed because the majority of the airway stents showed no (lasting) patency due to either obstruction by mucus, fibrotic tissue, the next bullae, or simply dislocated.

Valves

One-way endobronchial and intrabronchial valves are devices designed to prevent air from flowing into the most damaged lobe of the lungs. Whilst prevented to enter the lobe, air is able to exit the lobe thus creating a resorption atelectasis of the target lobe. This atelectasis causes lung volume reduction and thus reduces hyperinflation. The first randomized trial assessing endobronchial valves in 2010 showed only a relatively small benefit in favour of the valves.[40] Included patients all had heterogeneous emphysema, a predicted FEV_1 between 15 and 45% and a residual volume of more than 150% predicted. Post hoc analysis of this trial, and the results of the European part of the VENT trial showed big differences between responders and non responders.[41] A better response was associated with a complete fissure on the chest CT scan, and a complete occlusion of the lobe. Recently, a single center, sham controlled RCT showed that when the completeness of the fissure is deemed present assessed on HRCT before the procedure, the responder rates increase and a significant benefit in symptoms and FEV_1 ensues.[42] Exacerbations and pneumothoraces were increased in the treated group, and two patients in the treatment arm died during follow-up.

The Stelvio study also included patients which complete fissures on the HRCT.[43] The completeness of the fissure in the target lobe was confirmed with an actual measurement of the collateral flow by the Chartis system during bronchoscopy. The use of this system resulted in an even better responder rate in the treated patients than preceding studies. The Stelvio trial included patients with both heterogeneous and homogenous emphysema. The patients showed an increase in FEV_1 of 140 ml compared with placebo on top of maximum bronchus

dilatation. Their quality of life measured by the SGRQ improved with 14.7 points compared with placebo.

After post-hoc data using endobronchial valves showed promise in treating homogeneous emphysema patients, a group that has no surgical alternative, the Impact trial was designed to prospectively assess the usefulness of endobronchial valve treatment in patients with homogenous emphysema.[44] The results confirmed the earlier found beneficial effect of the endobronchial valves. The most common adverse events in this trial were pneumothoraces (26%) and exacerbations of COPD requiring hospitalization (16%). An advantage of this therapy is that valves can be removed if patients do not benefit from the treatment.

The trials testing intrabronchial valves in patients with occlusion of the whole target lobe in patients with complete fissures are currently awaited. An earlier trial treating patients without complete occlusion did not show results comparable with the endobronchial valves yet.[45-47]

Endobronchial Coils

Endobronchial coils are shape-memory nitinol devices delivered bronchoscopically into the airways. They induce lung volume reduction by contraction of lung parenchyma. Patients are most commonly treated bilaterally with a total of approximately 11 coils per lung. The first pilot studies with this technique were published in 2010 and 2012.[48,49] Since then the technique has been tested in several randomized controlled trials and coils are now used commercially in some European countries. Three randomized controlled trials have been published with a total of 231 patients in the treated group and 230 in the standard medical care group.[50-52] Those treated with coils showed an improvement in 6-minute walk distance, FEV_1 and symptoms measured by SGRQ compared with the patients who received standard care. The largest of these trials, the RENEW trial showed an improvement in FEV_1 in patients treated bilaterally of 130 ml from baseline, they did not report a between group difference in millilitres, SGRQ improved with 8,9 points after 6 months compared with placebo.[50] The REVOLENS trial reported a difference of 90 ml between the treatment and placebo group[52] on top of maximum bronchus dilatation. Treatment was associated with more adverse events, mainly COPD exacerbations (28%), pneumonia (20%) and pneumothorax (10%). Once placed, endobronchial coils cannot be removed.[50]

Sclerosing agents

Two different techniques aimed at sclerosing the most the diseased part of the lung have been tested. The sclerosis causes a lung volume reduction effect in the treated part of the lung. The results of the techniques are irreversible.[38]

The first technique is known as bronchoscopic thermal vapour ablation. This technology works by locally applying steam to induce a permanent fibrosis and atelectasis. The Step-up trial randomised patients with upper lobe predominant emphysema only. A total of 46 patients was randomised to vapour therapy and 24 to standard care.[53] Treated patients improved in FEV_1(11% at 6 months), quality of life (9.7 points in SGRQ at 6 month) and exercise capacity (31 meter in the 6 minute walk test compared with the untreated group). The most common side effects were an increased rate of exacerbations and pneumonitis in the treated patients.

The second technique uses a lung sealant called Aeriseal. This is a solution mixed by air which is delivered by bronchoscope at a diseased part of the lung. The technique was first published in 2009 and was tested with an aim of lung volume reduction in advanced, upper lobe predominant emphysema.[54,55]

The Aspire trial is the only randomized trial assessing this technique, however the sponsor ran out of financial resources and therefore the trial was terminated prematurely. Data from the trial has been published for a follow-up period up to 6 month.[56]
The few patients who were treated showed an increased response rate in FEV_1, symptoms and 6 minute walk test. The low numbers in the treated patient group diminished further by 2 deaths and over 40% of the patients had to be admitted at the hospital with serious adverse events due to severe inflammatory responses. Because of its great potential to specifically target interlobar emphysemateous areas, its use has been redefined and efforts are underway to more carefully use this device using slowly increasing dosages and repeat bronchoscopies.(NCT 02877459)

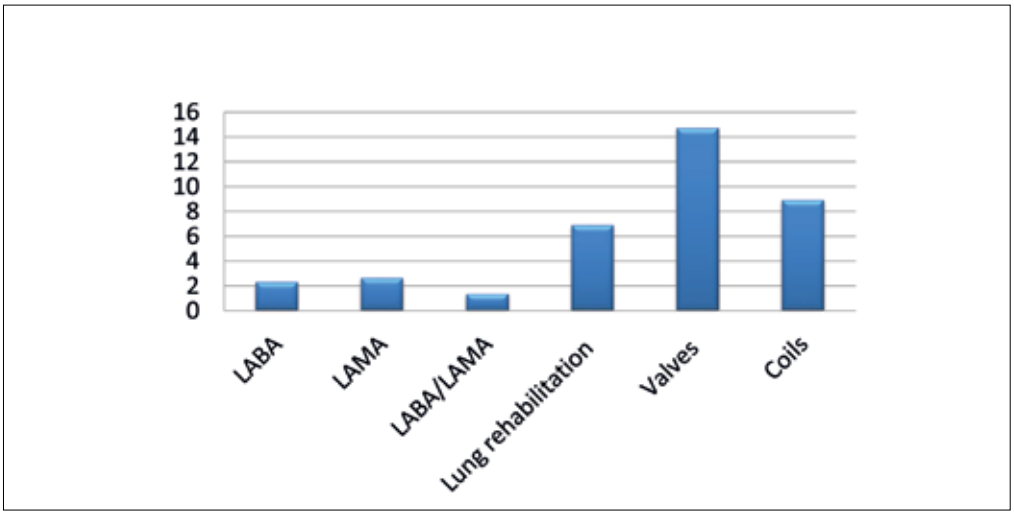
Targeted Lung Denervation
In 2015 a pilot study performed in South Africa and the Netherlands was performed with a system to elicit targeted lung denervation.[57] This system is designed to disrupt parasympathetic pulmonary nerves surrounding the main bronchi using a special RF-energy releasing system, thereby decreasing the release of acetylcholine in the airways, resulting in a permanent anti-cholinergic effect. Twenty-two patients were treated, showing feasibility of the intervention. The trail showed a better outcomes for the highest RF energy dose used. One year changes from baseline in the 20 W dose compared to the 15 W dose were: FEV_1 (+11.6% ±32.3vs +0.02%±15.1, p=0.324), submaximal cycle endurance (+6.8 min±12.8 s 2.6 min±8.7, p=0.277), and St George's Respiratory Questionnaire (−11.1 points±9.1 vs -0.9 points ±8.6, p=0.044). The adverse event analysis showed that 59% of the patients developed a COPD exacerbation in the first year. The first randomized sham controlled trial assessing this technology is currently underway (ClinicalTrials.gov identifier: NCT02058459).

Liquid Nitrogen Metered Cryospray
Liquid Nitrogen Metered Cryospray is a method designed to bronchoscopically deliver liquid nitrogen to the central airways in such an way that is leads to a cryoablation depth of 0.1 to 0.5mm for the treatment of chronic bronchitis. This treatment is intended to induce a regenerative airway tissue healing effect, by initially destroying the hyperplastic goblet cells and excess submucous glands by cryo necrosis. After treatment rapid rejuvenation of normal epithelium occurs, without scarring occurs, a hallmark of cryoablation, and it is thus a potential future treatment for chronic bronchitis.[58,59] The first in human trials testing this system and its hypothesis are currently underway (NCT02106143, NCT02483052, and NCT02483637).

Concluding remarks

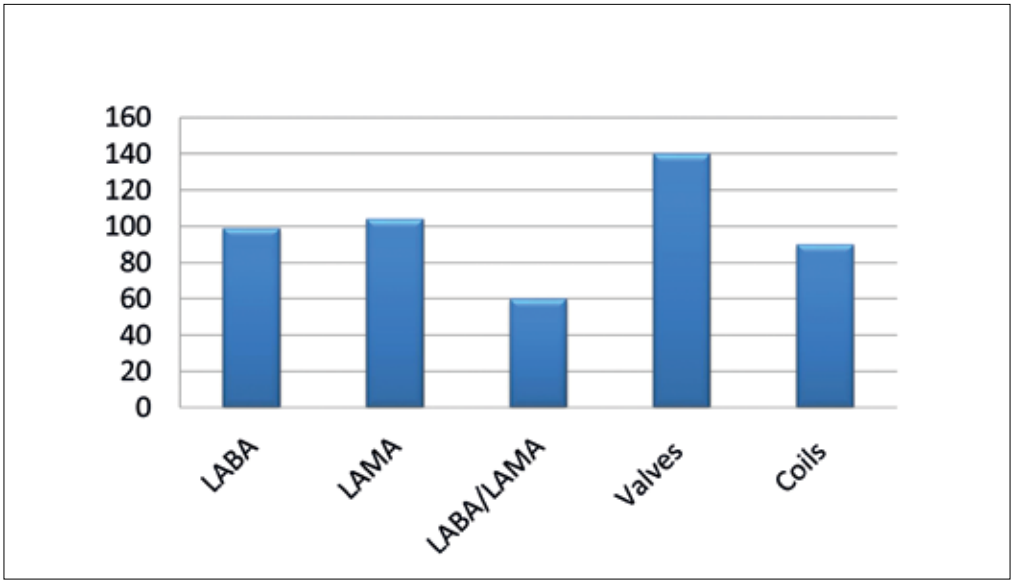
Different emerging bronchoscopic treatments for COPD have been tested recently, most of them with an aim of lung volume reduction in hyperinflated emphysema patients. Most of the evidence has been collected for the use of endobronchial valves and endobronchial coils. In highly selected patients these therapies do show benefit both in quality of life (Figure 7.2), and in lung function (Figure 7.3).

Figure 7.2 Improvement in SGRQ



Effect sizes of different therapeutic options in COPD on quality of life as measured withthe SGRQ.Y axis: Improvement in SGRQ in points. X axis Different therapeutic options. LABA: long acting beta-2-agonists, LAMA: long acting muscarinic antagonists. Effect size for LABA/LAMA is the additional effect when a LAMA is combined with a LABA. Effect sizes for rehabilitation, valves and coils are on top of maximum bronchodilation. Compiled from the following references: [25,26,28,43,50]

Figure 7.3 Improvement in FEV_1



Effect sizes of different therapeutic options in COPD with FEV_1.Y axis: Improvement in FEV_1 in millilitres. X axis Different therapeutic options. LABA: long acting beta-2-agonists, LAMA: long acting muscarinic antagonists. Effect size for LABA/LAMA is the additional effect when a LAMA is combined with a LABA. Effect sizes for valves and coils are on top of maximum bronchodilation. Compiled from the following references: [25,26,43,52]

Although the bronchoscopic procedures can be regarded as minimally invasive, serious adverse events have been observed. The occurrence of pneumothoraxes, especially with successful valve placement, and increase in infectious and inflammatory events when using coils probably being the most important.

More research is need to better select the patients who will benefit from the different treatments. Also additional research is needed to better predict and treat the procedure related adverse events. More therapies are being developed and the existing are being developed further. The fast development of these bronchoscopic treatments will extend the therapeutic arsenal of the respiratory physician for patients with COPD.

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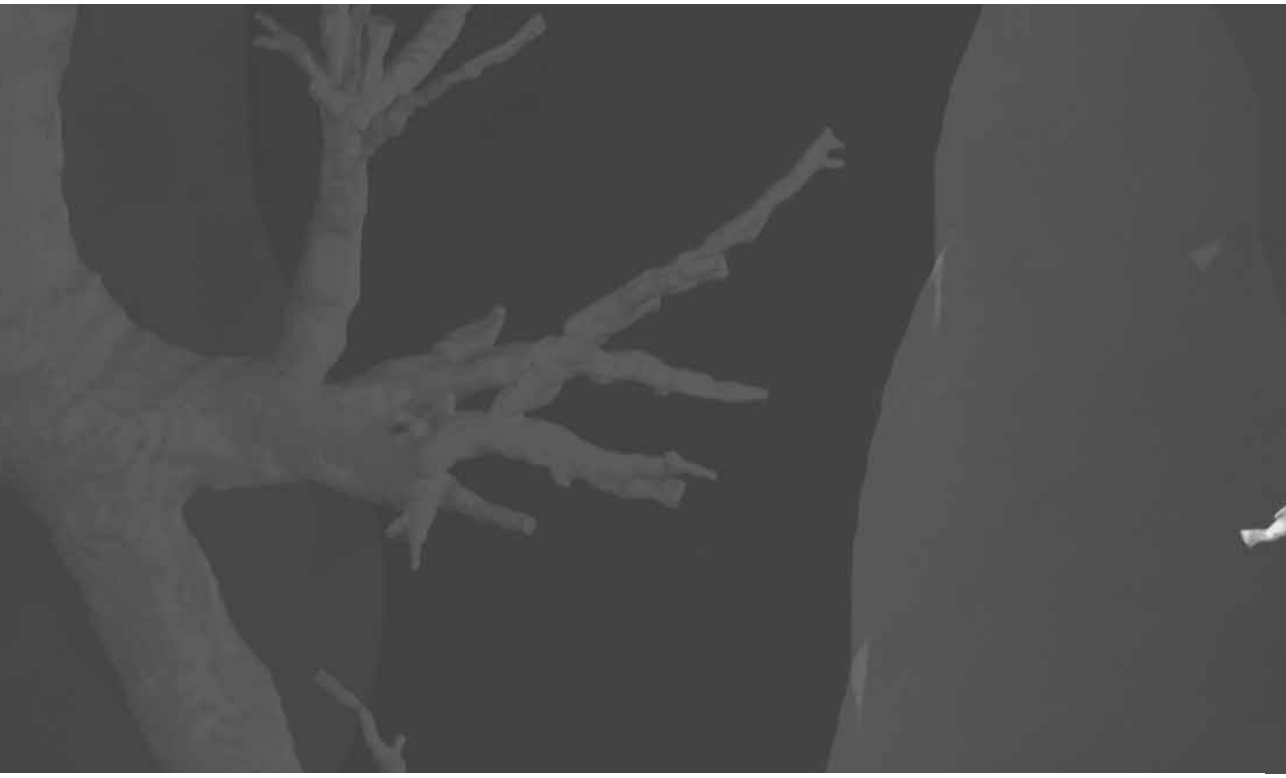

CHAPTER

8

Pleural adhesions assessment as a predictor for pneumothorax after endobronchial valve treatment

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ABSTRACT

Background

Pneumothorax after bronchoscopic lung volume reduction using one-way endobronchial valves (EBV) in patients with advanced emphysema occurs in approximately 20% of the patients. It is not well known which factors predict the development of a pneumothorax.

Objective

To assess whether pleural adhesions on pre-treatment HRCT scans are associated with pneumothorax occurrence after EBV treatment.

Methods

HRCT scan analyses were performed on all patients who received EBV treatment in a randomized controlled trial. Three blinded readers scored adhesions by number and by measuring the longest axis of each pleural adhesion in the treated lung. A "Pleural Adhesions Score" was calculated by adding 1 point for each small pleural lesion (<1mm), 5 points for each medium lesion (1-5mm) and 10 points for each large lesion (>5mm).

Results

HRCT scans of 64 treated patients were assessed, of whom 14 developed a pneumothorax. Patients who developed a pneumothorax had a higher median number of pleural adhesions, 2.7 (IQR 1.9-4) compared to 1.7 (1-2.7) adhesions in the group without pneumothorax (P<0.01). The Pleural Adhesions Score in the group with pneumothorax was higher compared to the group without: 6.7 (3.7-11.2) versus 14.3 (12.4-24.1) (P<0.01). A threshold Pleural Adhesions Score of ≥ 12 was associated with a higher risk of pneumothorax (odds ratio: 13.0 (95%CI: 3.1-54.9)). A score < 12, did not rule out the occurrence of a pneumothorax.

Conclusions

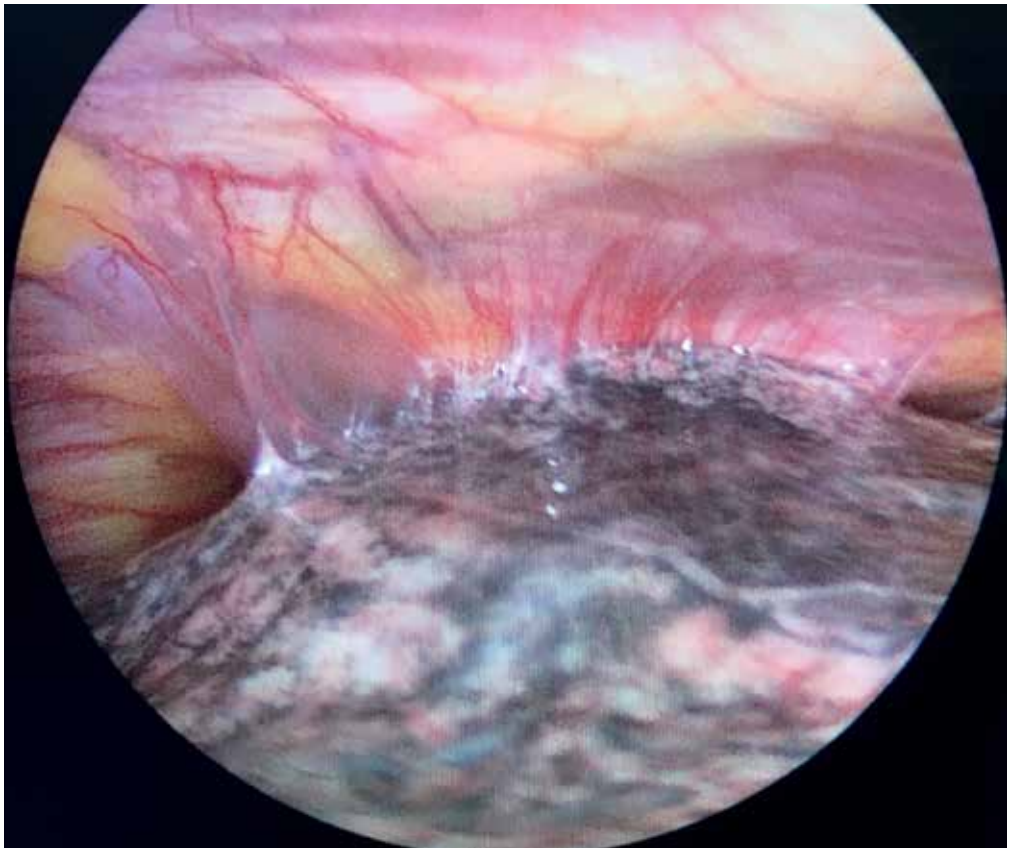
A higher number of pleural adhesions on HRCT with a subsequent higher Pleural Adhesions Score in the treated lung is associated with a higher occurrence of pneumothorax after EBV treatment.

INTRODUCTION

Bronchoscopic lung volume reduction is a rapidly developing treatment option for emphysema patients with severe hyperinflation.[1-6] Following careful selection of the right patients, lung volume reduction may lead to clinically relevant improvements in lung function, quality of life and exercise performance.[7-13] Of the available techniques, treatment with endobronchial valves (EBV) in patients without interlobar collateral ventilation, shows the best results.[14-18] However, pneumothorax after EBV treatment is a common adverse event, occurring in about 20% of the patients.[19] The severity varies, from just an asymptomatic radiologic abnormality, a pneumothorax 'ex-vacuo', up to a life threatening tension-pneumothorax.[20, 21] A reliable risk assessment for pneumothorax is therefore an important unmet need in this new treatment area. Identifying which patients are at higher risk may help informing them better about their individual risks, and lead to longer planned observation time in the hospital after treatment.

It is not well known what causes the development of a pneumothorax after EBV treatment.[19] A possible explanation is that the pneumothorax is caused by pre-existent adhesions between the treated lung and parietal pleura (see figure 8.1 for a thoracoscopic view).

Figure 8.1 Example of a pleural adhesion.



An image of a pleural adhesion, observed during a video assisted thoracoscopy.

Large volume shifts after successful EBV treatment and subsequent repositioning of the lung could subsequently rupture the visceral pleura. Whether this explanation is valid remains unknown since pleural adhesions have not been systemically assessed with this point of view before. Indeed, an earlier study showed that larger changes in volume after treatment associate with a higher risk of pneumothorax, an observation that fits with the hypothesis that pleural adhesions form a risk.[19] However, this study did not assess whether a larger volume of the target lobe is a risk factor. Other possible mechanism involve visceral pleural rupture in target and non-target lobe surfaces, rupture of bulla, or a mechanism unrelated to pleural surface rupture but due to a mismatch between lung and thoracic cage causing a 'pneumothorax ex-vacuo'. Pneumothorax related to procedure and post-procedure management might occur due to high mechanical ventilation pressures, the Chartis measurements and heavy coughing. Furthermore specific emphysema phenotype, heterogeneity of emphysema, and emphysema severity, might influence pneumothorax risk after valve therapy.

The objective of this study was to assess whether pleural adhesions on pre-treatment high resolution computed tomography (HRCT) scans are associated with pneumothorax after EBV treatment. We hypothesized that pleural adhesions are associated with the occurrence of pneumothorax in the lung treated with EBV. In addition, we hypothesized that larger volumes of the target lobes are also associated with the occurrence of pneumothorax.

MATERIAL AND METHODS

Study design

Pre-treatment HRCT scans of all patients who received EBV treatment in the STELVIO trial were analyzed.[14] In this trial 64 patients with severe emphysema and hyperinflation were treated with valves in the absence of collateral flow between the target lobe and ipsilateral non-target lobe between June 2011 and November 2014. Inclusion criteria included a post-bronchodilator forced expiratory volume (FEV_1) < 60% of predicted, total lung capacity (TLC) > 100% of predicted, and residual volume (RV) > 150% of predicted. Furthermore, the HRCT scan needed to demonstrate a target lobe with a (near-) complete interlobar fissure. The main exclusion criterion was evidence of collateral ventilation in the target lobe during Chartis measurement. Patients were randomized to receive immediate EBV treatment or standard of care. The standard of care group was treated with EBV after 6 months of follow-up. In the current analyses, the data of both groups were combined. Details of the trial, including its design, ethics, informed consent and inclusion/exclusion criteria have been published previously.[14] All patients provided informed consent and confidentiality was maintained.

All patients were observed after treatment in the hospital for at least one day. Chest X-rays were performed, directly after treatment, before discharge and when indicated in case of symptoms to assess the presence of a pneumothorax. The occurrence of pneumothorax was registered until one year after treatment for all patients.

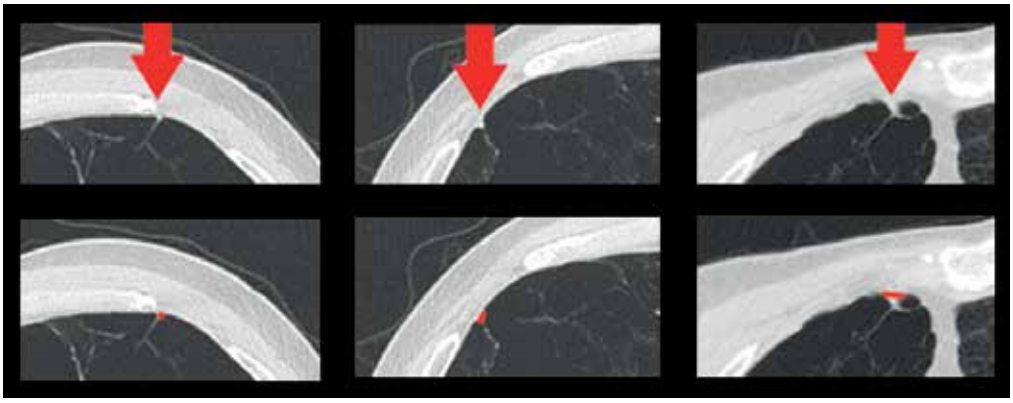
Scoring of occurrence of pleural adhesions

To identify pleural lesions, the baseline chest HRCT scan was assessed by 3 blinded readers (2 pulmonologists and a specialized chest radiologist). The readers were not informed about the later occurrence of pneumothorax during reading. The readers individually and independently assessed the number, location and size of pleural adhesions in the treated lung. They were instructed to report only lesions with pleural involvement, peripheral lung lesions without pleural involvement were therefor not reported.

Pleural adhesions score (PAS)

It was hypothesized that larger lesions produce more traction on the pleura, and therefore increase the pneumothorax risk. Therefore, the size of a pleural adhesion was measured and categorized into an arbitrary score: 1 point for each small pleural lesion (<1mm), 5 points for each medium lesion (1-5mm) and 10 points for each large lesion (>5mm, Figure 8.2). This system was developed before the assessment of the pleural lesions by the readers was completed. Afterwards, all scores in an individual patient were cumulated into the so called "Pleural Adhesions Score (PAScore)". The PAScore was also expressed per treated and untreated lobes. Finally, for each patient an average PAScore score of all 3 assessors was calculated.

Figure 8.2 Examples of a pleural adhesion.



Top row: 3 different size pleural adhesions. Bottom row: a red line indicates the measurement of each adhesion. The picture on the left was measured as <1 mm, resulting in a PAScore of 1 point, the middle was measured as 1-5mm, resulting in 5 points, and lesion on the right was measured as >5mm resulting in 10 points

Volume measurements

Quantitative volume measurements of the treated and non-treated lobes were performed on the baseline inspiratory HRCT using the Thirona Lung Quantification CT software (version 15.01, Thirona, Nijmegen, The Netherlands).[14, 22, 23]

Analyses

To assess differences between the groups of patients with and without a pneumothorax, the independent sample Mann-Whitney U tests were performed. To derive a threshold for the PAScore a receiver operating characteristic (ROC) curve was used with a sensitivity and specificity of at least 0.8. The odds ratios were calculated using logistic regression. Variation between the readers was analyzed with the intraclass correlation coefficient. A p-value <0.05 was considered significant. SPSS version 22 was used for the statistical analyses [IBM, USA].

RESULTS

The HRCTs of the 64 patients were all assessed by 3 blinded readers. Fourteen patients (22%) developed a pneumothorax after endobronchial valve treatment and 50 patients did not. Ten patients required chest tube drainage, 4 patients with a pneumothorax 'ex-vacuo' did not. The baseline characteristics of both groups are reported in table 8.1.

Table 8.1 Baseline Characteristics of the Patients

	All Patients (N=64)	Without pneumothorax (N=50)	With pneumothorax (N=14)	P value [a]
Demographic characteristic				
Female sex — (%)	67%	62%	86%	0.10
Age — yr	59 (53-65)	59 (53-64)	62 (52-68)	0.39
Body-mass index [b]	24 (22-26)	24 (22-26)	23 (22-25)	0.71
Number of pack-years	35 (23-45)	35 (22-45)	33 (24-45)	0.66
Lung function				
Forced expiratory volume in 1 sec				
Value — liters	0.79 (0.61-0.94)	0.88 (0.64-1.01)	0.71 (0.53-0.83)	0.05
Percent of predicted value	28 (24-36)	28 (25-37)	27 (23-32)	0.16
Forced vital capacity				
Value — liters	2.62 (2.00-3.21)	2.65 (2.01-3.41)	2.53 (1.85-3.03)	0.29
Percent of predicted value — %	79 (65-93)	79 (65-92)	76 (65-94)	0.81
Residual volume				
Value — liters	4.34 (3.82-5.04)	4.34 (3.81-4.89)	4.32 (3.85-5.29)	0.69
Percent of predicted value — %	214 (195-240)	209 (193-232)	224 (200-254)	0.20
Total lung capacity				
Value — liters	7.21 (6.70-8.48)	7.25 (6.62-8.60)	7.19 (6.80-7.84)	0.81
Percent of predicted value — %	131 (124-141)	130 (124-136)	141 (128-144)	0.61
Residual volume/Total lung capacity				
Ratio — %	58 (53-68)	58 (51-69)	62 (56-67)	0.07
Arterial blood gas				
PaCO2 — kPa [c]	5.0 (4.7-5.6)	5.0 (4.7-5.6)	5.2 (4.7-6.1)	0.38
PaO2 — kPa [c]	9.3 (8.0-10.2)	9.3 (8.0-10.2)	9.0 (7.5-10.7)	0.96
Exercise performance				
Distance on 6-minute walk test - m	356 (300-427)	383 (305-431)	325 (275-407)	0.13
Quality of life				
St George's Respiratory Questionnaire Total score - points [d]	58 (47-64)	58 (49-64)	57 (47-66)	0.96
Modified Medical Research Council scale - points [e]	3 (2-3)	3 (2-3)	3 (2-3)	0.14
Clinical COPD Questionnaire Total score - points [f]	2.6 (2.2-3.3)	2.6 (2.1-3.4)	2.8 (2.3-3.2)	0.81

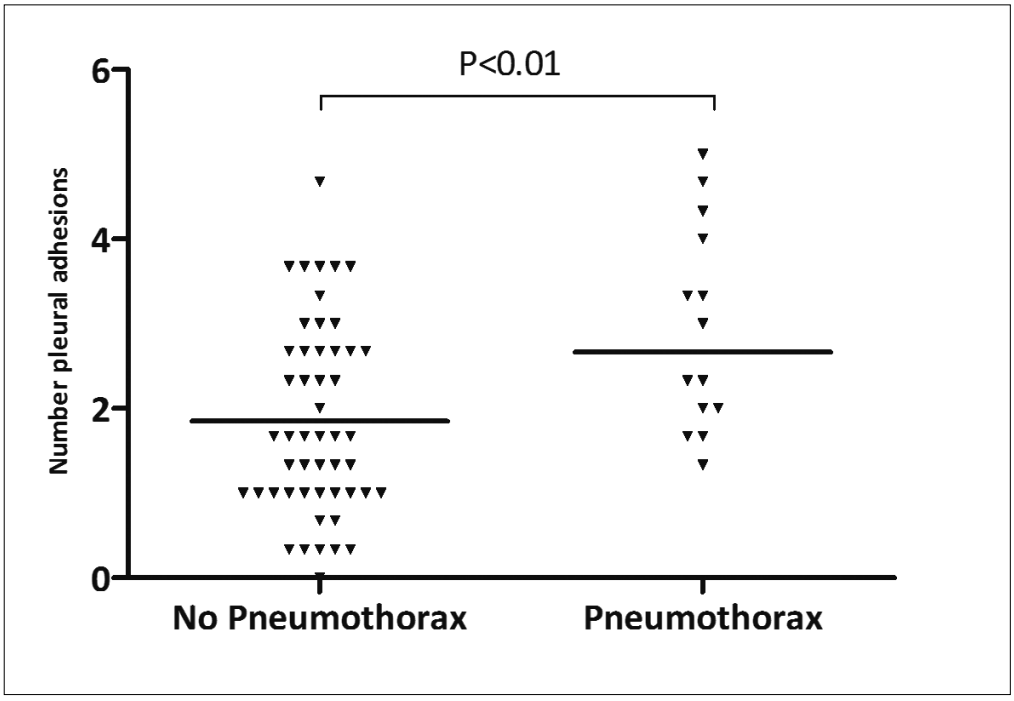
Values are presented as median (IQR) unless indicated otherwise. COPD, chronic obstructive pulmonary disease; PaCO2, partial pressure of carbon dioxide; PaO2, partial pressure of oxygen. [a] Between-group difference (non-parametric). [b] Weight in kg divided by the square of the height in m2. [c] Measurements were performed while the patient was breathing ambient air. [d] Scores range from 0 to 100, with higher scores indicating worse quality of life. [e] Scores range from 0 to 4, with higher scores indicating a greater severity of dyspnea. [f] Scores range from 0 to 10, with higher scores indicating worse function.

No statistically significant differences were observed between the 2 groups; nevertheless, the pneumothorax group tended to a slightly lower absolute FEV_1 (p=0.05) and more hyperinflation (RV/TLC ratio) (p=0.07). Due to the low number of pneumothoraces no separate analysis was performed on subgroups with different types of pneumothorax.

Pleural lesions

Participants with a higher number of pleural adhesions more often developed a pneumothorax: patients who developed a pneumothorax had a median number of 2.7 (IQR 1.9-4) adhesions compared to 1.7 (1-2.7) adhesions in patients without a pneumothorax (P<0.01, Figure 8.3 and Table 8.2). Pearson's correlation between small lesions and pneumothorax was r=0.22 and large lesions had a correlation with pneumothorax of r=0.29.

Figure 8.3



Total number of pleural adhesions in the target lung by group based on the occurrence of pneumothorax after one-way endobronchial valve treatment. Each dot represents the mean of the observed number of pleural adhesions in a single participant by 3 assessors. The Mann-Whitney U test was used to assess the difference between the groups. The horizontal line represents the median.

Table 8.2 Results of the analysis

Characteristic	All Patients (N=64)	Without pneumothorax (N=50)	With pneumothorax (N=14)	P value [a]
Pleural adhesions [b]				
Treated lobe	1.3 (0.7-2)	1.0 (0.3-2)	1.5 (1.0-2.7)	0.06
Non treated lobe	0.7 (0.3-1.3)	0.5 (0-1.3)	1 (0.6-1.5)	0.04
Total treated lung	1.8 (1-3)	1.7 (1-2.7)	2.7 (1.9-4.0)	<0.01
Pleural Adhesion Score				
Treated lobe	5.3 (2-10)	4.8 (1.5-7.9)	10 (8.3-19.5)	<0.01
Non treated lobe	1.7. (0.3-5.7)	1.7 (0-5.7)	4 (1.4-6.8)	0.04
Total treated lung	7.3 (4.3-13.7)	6.7 (3.7-11.2)	14.3 (12.4-24.1)	<0.01
Lobar volumes				
Treated lobe volume - ml	1773 (1446-2145)	1790 (1465-2150)	1720 (1378-2093)	0.66
Treated lobe volume, percentage of total treated lung volume	53 (47-61)	53 (48-62)	53 (48-60)	0.88

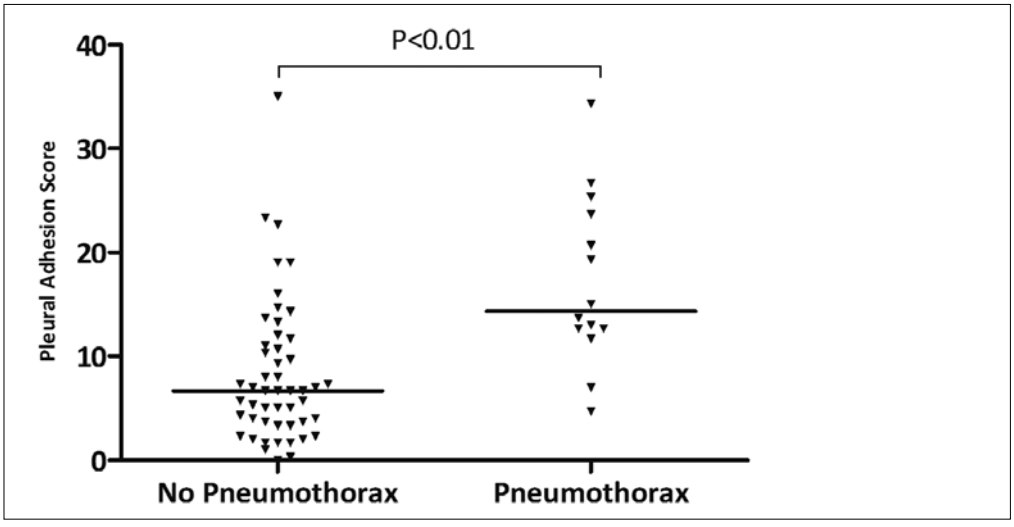
Values are median + IQR. Mean number of observed pleural adhesions by the three readers. ≠: The volume of the treated lobe as percentage of the whole volume of the treated lung.

No significant difference between both groups was found when separately assessing the number of pleural adhesions in the treated lobe. The patients who developed a pneumothorax showed more adhesions in the untreated lobe than those who did not develop a pneumothorax, respectively 1 (0.6-1.5) and 0.5 (0-1.3) (p=0.04).

Pleural Adhesion Score

The Pleural Adhesions Score [median + IQR] in the group with a pneumothorax was 14.3 (12.4-24.1) compared to 6.7 (3.7-11.2) in the group without (P<0.01, Table 8.2 and Figure 8.4).

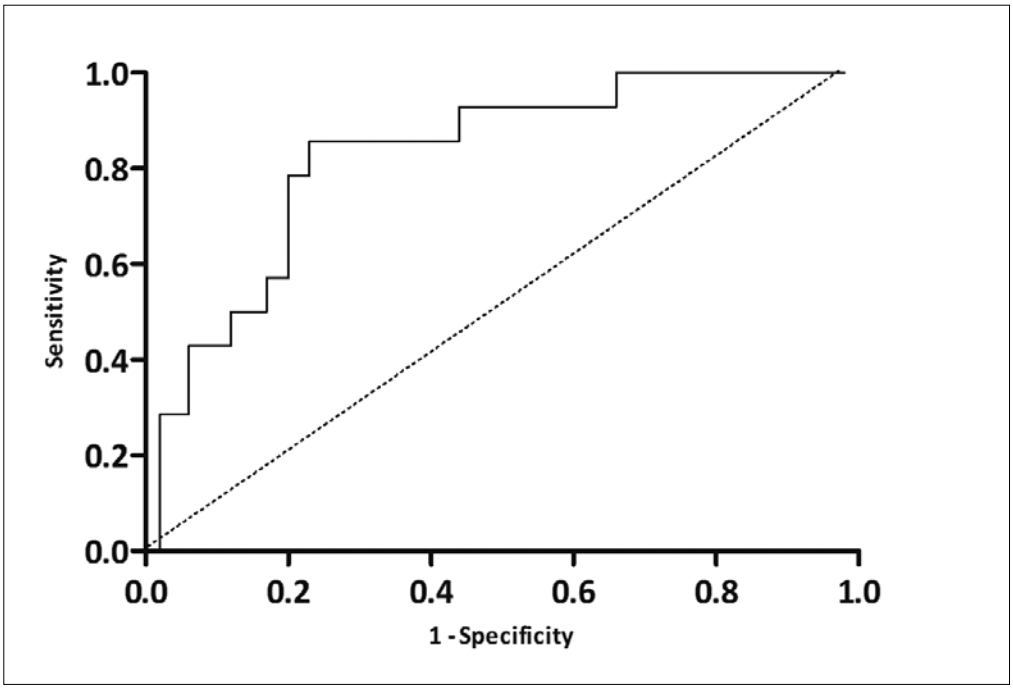
Figure 8.4



Pleural Adhesion Score in the target lung by based on the occurrence of pneumothorax after one-way endobronchial valve treatment. Each dot represents the mean of the Pleural Adhesion Score of three assessors. The Mann-Whitney U test was used to assess the difference between the groups. The horizontal line represents the median score.

Every extra point on the PAScore was associated with a higher pneumothorax risk: per point an odds ratio of 1.2 (95%CI: 1.1-1.3, P<0.01). From the ROC curve, an area under the curve (AUC) of 0.83 was calculated (Figure 8.5).

Figure 8.5



Receiver operating characteristic curve of the Pleural Adhesion Score for pneumothorax. Solid line: Pleural Adhesion Score, dotted line: reference line. Area under the Curve: 0.81

From the ROC curve a threshold Pleural Adhesions Score of ≥ 12 was derived to achieve a-sensitivity and specificity of both 0.8. A score above this threshold showed a markedly higher risk for pneumothorax (odds ratio: 13.0 (95%CI: 3.1-54.9)). However, 3 patients with a PAScore < 12 developed a pneumothorax after treatment. The negative predictive value of the PAScore was 93%, the positive predictive value was 48%. Analysis of the individual PAScores of the 3 readers showed an intraclass correlation coefficient of 0.46.

Volumes

No difference in volumes of the individual target lobes or target lobe to total lung ratio was detected between both groups (Table 8.2). In 51 patients it was possible to measure the change in total lung volume after EBV treatment with CT volume measurements. Eight of these developed a pneumothorax. No difference between the groups in target lobar volume reduction was detected, however this finding should be interpreted with care since we could not measure in 6 of the pneumothorax patients.

Location

Thirty-six patients were treated in the upper lobes of whom 9 patients developed a pneumothorax (25%), whereas 5 out of 28 lower-lobe treated patients developed a pneumothorax (18%) (P=0.43)

DISCUSSION

Our analysis of the presence of pleural adhesions on the pre-treatment inspiratory HRCT scans from all patients treated with one-way endobronchial valves in the STELVIO trial[14] showed that a higher number and larger sized pleural adhesions in the treated lung was associated with a higher occurrence of a pneumothorax after treatment .

Endobronchial valve treatment has been shown to be a very effective treatment for patients with severe emphysema without collateral ventilation[14]. However, both the STELVIO trial and the BeLieVeR-HIFi trial demonstrated that about 20% of the treated patients develop a pneumothorax early after treatment.[14, 16] Although a pneumothorax after EBV treatment is nowadays considered to be part of the treatment, for these patients, the occurrence of a pneumothorax can be a serious complication that associates with higher morbidity, prolonged hospital admissions, chest tube insertions, additional bronchoscopies, treatment failure, and rarely even death.[14, 16, 19, 20] Better patient selection and prediction of pneumothorax risk therefore is of great importance. Our results showed that pleural adhesions assessment may identify patients at risk. As a next step, the PAScore should be prospectively studied, perhaps combined with video-assisted thoracoscopy results and a multi-variate analysis. In our view a high PAScore, and therefore a higher pneumothorax risk, could lead to a number of measures to be taken. First, a prolonged observation period in the hospital could be considered, although it remains difficult to predict when it is safe to discharge patients. Second, a more intensive observation with repeated X-thorax could be considered. Third, bed rest and cough reduction might be attractive, as Herzog at al. demonstrated that such a regimen reduces the occurrence of early pneumothorax from 25% to 5%.[24] Even more speculative is to perform prophylactic interpleural drainage in patients at high risk for life threatening pneumothoraxes or surgical removal of the adhesions prior to treatment. Finally, the risk of a higher PAScore could be discussed between the physician and patient who is a candidate for bronchoscopic volume reduction treatment.

This study observed a higher PAScore in the treated lobe compared with the untreated lobe. Both study design and sample size however did not allow reliable analysis of associations between the severity of the pneumothorax and the distribution of the pleural adhesions. However one would expect that a more severe pneumothorax with a larger air leak is caused via lesions in the untreated lobe.
Next to the pleural adhesions we hypothesized that the volume of the treated lobe at baseline on HRCT could correlate with pneumothorax occurrence. In the analysis by Gompelmann et al change in volume after treatment of the target was related to the pneumothorax risk.[19] The present study could not assess the change in lung volume after the procedure in relation with pneumothorax occurrence. From a post hoc view one might argue that this change in volume is more associated with pneumothorax occurrence, however we aimed to predict the risk before starting the treatment. At baseline, in our study the median target lobar volume was not significantly different between both groups, an observation that per-

sisted when target lobar volumes were corrected for total lung volume. Furthermore, we observed a trend that patients in the group who developed a pneumothorax were more often treated in the upper lobes, had a lower FEV_1 and more hyperinflation. This could reflect more destruction and perhaps an additional vulnerability of the tissue.

Previous data about systemic scoring of pleural adhesions is not available, perhaps because it was thought not to have clinical consequences. Only one paper was recently published, assessing pleural adhesions as a minor endpoint amongst others. They found adhesions to be slightly protective against pneumothorax. However these adhesions were not scored systematically and were analyzed by a single reader only.[25] Also since pleural adhesions were not systematically examined before as a risk factor for pneumothorax we had to develop a new scoring system. Taking into account the results of our study the PAScore appeared to be a tool to estimate this risk, with an area under the curve 0.83. However, the PAScore was the average score of 3 independent readers, who demonstrated only moderate agreement. On the other hand this inter observer agreement is comparable to the inter observer agreements of other radiological scores, for instance in interstitial lung diseases and fissure assessment.[26-28] Further optimization in quantifying pleural adhesions is clearly needed, in such a way that only 1 reader is needed to produce reliable measurements, or even better to develop quantitative CT analysis software to measure this.

Another interesting opportunity is to assess the pleura in more detail, especially in relation with the surrounding tissue, e.g. by targeted ultrasound. Cassanelli et al already showed that ultrasound is able to detect pleural adhesions.[29] Future studies might investigate whether patients with more peripheral destruction in panlobular or paraseptal emphysema and adjacent pleural adhesions are at higher risk to develop pneumothorax than patients with a more centrilobular emphysema. Another related question could be raised whether the completeness and speed of the development of the atelectasis of the treated lobe is associated with the occurrence of a pneumothorax, or that the presence of the adhesions per se is more important.

CONCLUSION

Our study showed that more extensive pleural adhesions are associated with higher risk of pneumothorax after treatment with EBV. These data, if prospectively validated, have the potential to significantly influence treatment decisions and algorithms.

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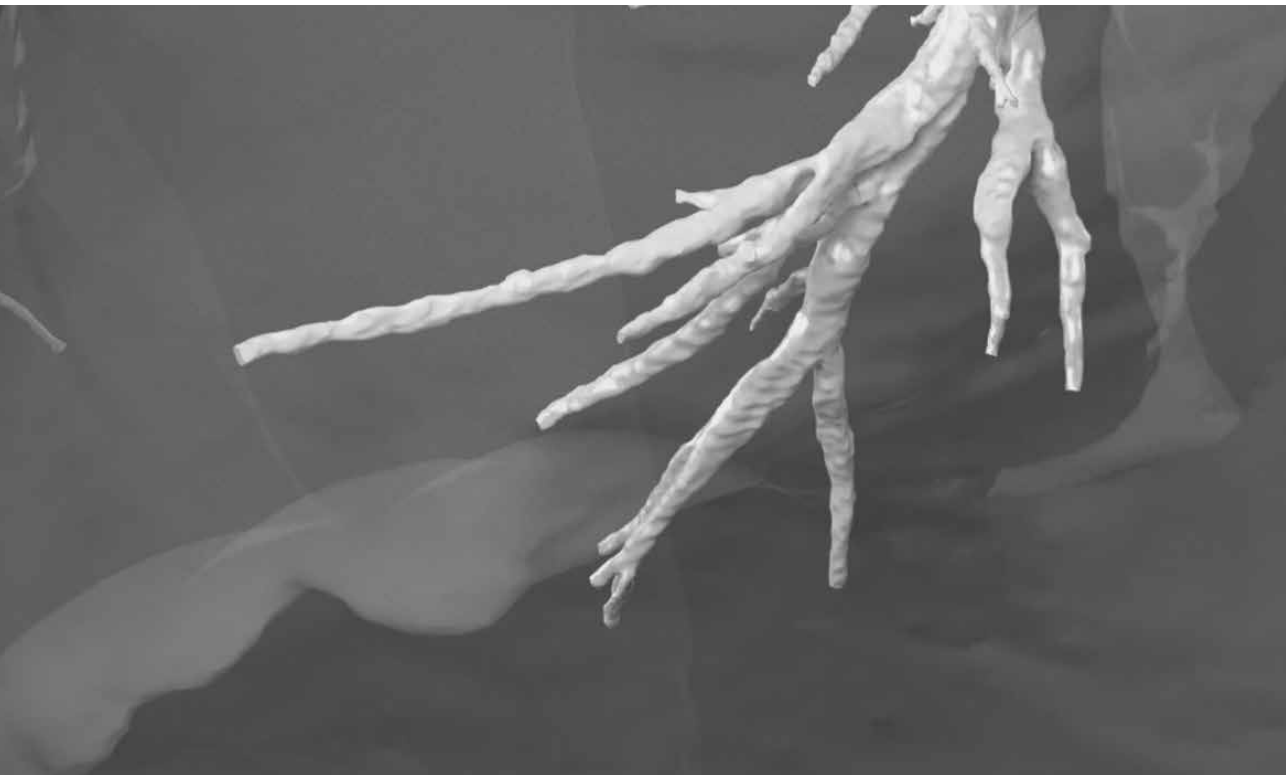

CHAPTER

9

Summary

To date, a lot is still unknown about a number of aspects around COPD exacerbations, such as heterogeneity and hyperinflation. This knowledge gap explains the current one-size-fits-all approach in treatment.[1-3] This thesis described new tools and new pathways to improve the diagnosis and treatment for severe exacerbations. We detected marked heterogeneity between patients and within single patients as well. Changes in lung function were studied, especially hyperinflation. With a perspective to address the described heterogeneity this thesis then assessed the current treatment of hyperinflation in a stable state and the potential of bringing treatments from stable state to a more personalized approach of treating COPD exacerbations.

In chapter two we described the course of static and dynamic hyperinflation in patients hospitalized for an acute severe exacerbation of COPD, and its resolution towards stable state. Static hyperinflation was increased during acute severe exacerbations compared with stable state. We could not record an increase in dynamic hyperinflation during the exacerbation. No correlation between change in hyperinflation and symptoms was found. Patients with increased hyperinflation during the admission showed less eosinophilic inflammation and less bacterial infection, and might be considered a different exacerbation phenotype.

In chapter three we assessed whether the electronic nose "Aeonose" can aid in distinguishing viral from bacterial and from other causes of COPD exacerbations. The Aeonose e-nose yielded promising results in 'smelling' the presence or absence of a viral or bacterial respiratory infection during an acute exacerbation of COPD. This trial can be considered as a first step towards a new fast, patient friendly, point-of-care, and low-cost assessment of the cause of infections in AECOPD.

In chapter four we assessed functional respiratory imaging by CT scans as a tool to get a better insight in exacerbations of COPD. Significant improvements in functional respiratory imaging indices could be demonstrated from the acute phase to resolution even in relatively small groups. Functional respiratory imaging visualized marked variability within and between individuals in lung volumes, lobar volumes, ventilation and resistance during exacerbations and is therefore a promising tool towards the assessment of the heterogeneity of COPD exacerbations.

In chapter five the role of hyperinflation during exacerbations is discussed. Patients with a predominantly hyperinflated phenotype during exacerbations could and should perhaps be treated differently. Assessment of hyperinflation and associated treatment could improve individualised care of patients with exacerbations. Hyperinflation has the potential to be a treatable trait in exacerbations of COPD.

In chapter six the current available evidence of the optimal mode of delivery for bronchodilators during exacerbations of COPD is systematically reviewed. This Cochrane review showed a lack of evidence in favor of any mode of delivery over another for bronchodilators during exacerbations of COPD. No difference was found between nebulizers versus pMDI plus spacer in the primary outcomes FEV_1 at one hour and safety. As secondary outcome we found a greater improvement in FEV_1 when treating with nebulizers than with pMDI plus spacers at all time points combined. The magnitude of the difference was, however, not clinically significant.

In chapter seven different emerging bronchoscopic treatments for COPD were assessed, most of them with an aim of lung volume reduction in hyperinflated emphysema patients. Most of the evidence has been collected for the use of endobronchial valves and endobronchial coils. In highly selected patients these therapies do show benefit both in quality of life and in lung function. Although the bronchoscopic procedures can be regarded as minimally invasive, frequent serious adverse events have been observed. The most important of these were the occurrence of pneumothoraces, especially after successful valve placement, and increases in infectious and inflammatory events when using coils.

In chapter eight predictors of pneumothorax were studied, the most prominent complication of bronchoscopic treatment of hyperinflation by endobronchial valves in stable COPD. We found that when using pre-treatment inspiratory HRCT scans from all patients treated with one-way endobronchial valves in the STELVIO trial, a higher number and larger sized pleural adhesions in the to be treated lung were associated with a higher occurrence of a pneumothorax after treatment.[4] These data, if prospectively validated, have the potential to influence treatment decisions and algorithms in stable state.

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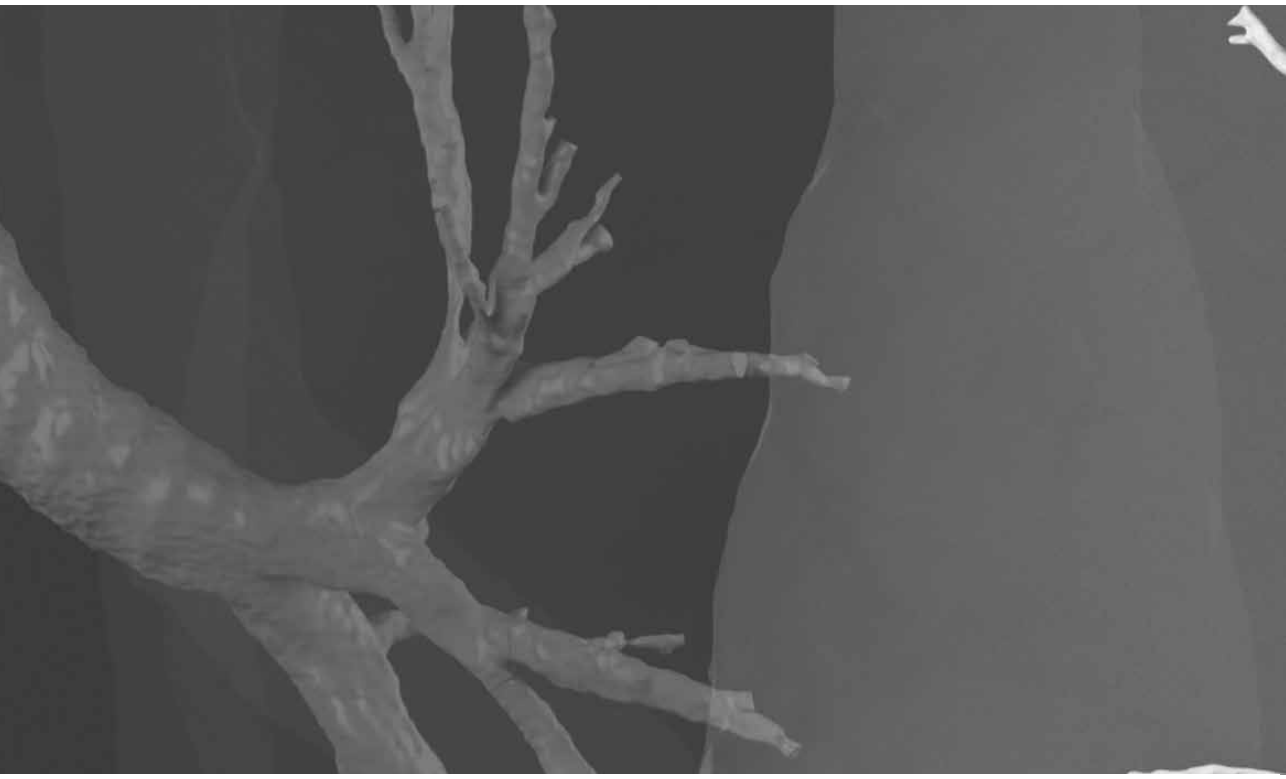

CHAPTER

10

Discussion and future perspectives

In the Netherlands alone, each year approximately 10.000 patients die due to COPD. Exacerbations of COPD are a major cause of this mortality. Additionally, they are associated with major morbidity and loss of quality of life.[1] To date, not all exacerbations can be prevented, and this thesis focused on the severe ones, those requiring hospital admissions. It is a widely held opinion that these hospital based exacerbations are treated in a stereotypic, non-individualized way. In other words, it is currently quite a routine or one-size fits all endeavor: bronchodilators, administered via nebulizers, steroids, antibiotics and additional oxygen. Phenotyping and individually tailored treatment might improve future outcome by reducing morbidity and improving quality of life. A major hurdle towards optimal treatment of exacerbations is their heterogeneity. Exacerbations differ in respect to cause, probably mechanism, and inflammatory characteristics and this should lead to differences in treatment.[2]
To help patients and physicians, future trials of treatment of COPD exacerbation should incorporate a more differentiated approach for different types of exacerbation.

Most exacerbations are deemed infectious of origin.[1] A rapid, point of care technique to quickly assess an infectious cause can be potentially useful. This would evolve into patients suffering from a viral infections to be treated differently than those patients with bacterial infections, and again differently from those with less inflammation and/or a more hyperinflation dominant exacerbation. The electronic nose tested in chapter three might have the potential to fit this profile, but needs more prospective testing before it can be used in daily practice. Such a study could involve randomization between a standard of care group treated with steroids and antibiotics (based on the non-exact Anthonisen criteria), and a group treated based on an e-nose guided strategy.[3] That strategy would lead to antibiotics only in case of actual measured bacterial infection, anti-viral medication individualized to certain amenable virus infections, and in the absence of these positive signals of infection, long acting bronchodilators in hyperinflation dominant exacerbations, for instance steroids only in eosinophilic exacerbations, and perhaps psychosocial treatment alone in yet others.

Inflammation is omnipresent, and augmented in virally or bacterially induced exacerbations. Inflammation occurs also without known contribution of infectious agents. Recently, more attention has been given to the occurrence of eosinophilic inflammation in stable state and during exacerbations.[4-6] In asthma this eosinophilic phenotype is a valuable target for personalized treatment with several anti-interleukins to prevent exacerbations, and research for additional anti-interleukins is ongoing. Early trials of anti-Il5 suggest effects also in eosinophilic COPD, even though the mechanisms might be different from asthma.[7] Trials have been presented largely in the outpatient setting that systemic corticosteroids can be safely withheld in non-eosinophilic exacerbations and extending these studies to the in hospital exacerbations would be very interesting, if not only to prevent the occurrence of side-effects of systemic steroids on to much routine use. Also, trials to reduce the inflammation during exacerbations with azithromycin are ongoing. Potentially azithromycin could be used as an addition to steroids or even as replacement in some patients.

As we showed in chapter four next to different types of increased inflammation, exacerbations are heterogeneous with respect to changes in lung volumes and airway patency. Varying degrees of hyperinflation can be detected. As anxiety is commonly associated with hyperinflation a possible route to treat hyperinflation is to treat the anxiety patient.

Such a treatment can be performed with benzodiazepines or opioids. A different way to improve current treatment is to improve the administration of optimal bronchodilators during severe exacerbations in these patients. The medication is commonly prescribed via nebulizers and all available bronchodilators that can administered by inhalation are short-acting. Newer bronchodilator compounds, both anticholinergic and beta-2-agonist, are more potent than their short-acting comparisons, and have a substantially longer duration of action. Both are quite desirable properties also during an exacerbation. However, no long-acting medication is currently available for use via nebulizers. We assessed that there is not enough evidence available to support the widespread use of nebulizers in chapter six during exacerbations. These results open up a window for a study assessing modern dual long-acting bronchodilator versus the conventional short-acting combination bronchodilators via nebulizer. Such a study should be conducted in stable state first and then repeated during exacerbations. The next step will be a subgroup analysis to find the best responders e.g. those with more hyperinflation. This subgroup will then have to be studied prospectively before the outcomes of such studies can result in a broadly accepted, more personalized bronchodilator treatment during exacerbations.

As discussed in chapter two and four hyperinflation is commonly observed in exacerbations. Next to heterogeneity between patients, exacerbations show heterogeneity in lung volumes and airway patency, even within a single patient as was shown in chapter four. This heterogeneity might have influenced previous attempts to improve personalized treatment for exacerbations. In stable state this within-patient heterogeneity is used to treat patients with hyperinflation with endoscopic techniques. We assessed some of these techniques in chapter seven. The results are excellent in selected patients with stable COPD.[8-10] From a physiological point of view there is a lot of potential to use it in exacerbations as well since hyperinflation is further increased then. For instance a future patient with an exacerbation due to hyperinflation of the right upper lobe could be treated locally. Before testing one of those techniques during exacerbations, more research is needed on a larger scale in stable disease. Safety of most procedures for endobronchial lung volume reduction are already a concern in stable state COPD, and these are likely to be of larger concern during exacerbations. Patients treated by valves experience attract a pneumothorax in up to 20% of the cases.[11] As we found in chapter eight, there might be ways to predict the occurrence of adverse events in treat, but these tools are not prospectively proven yet for use in stable state, let alone in a life-threatening situation such as a severe exacerbation of COPD. New stable diseases studies need to be designed especially with a focus on long-term outcomes and safety first. Then a study is needed to compare the nature and severity of COPD exacerbations prior treatment and afterwards. Then in the distant future a trial with lung volume reduction during exacerbations can be considered. Currently it is not certain what technique will be tested then. A future treatment can be with airway bypasses. In stable disease they showed a quick effect with a good safety profile, although mucus from exacerbations might limit their effects in an exacerbation setting.[12] With the perspective of today, endobronchial valves have the most potential, they show very good results in stable disease and can be removed after treatment of an exacerbation if needed or in the event of complications. Thus far however the complication risk is too high to expose patients with acute COPD exacerbations to such trials.

Based on our findings and the rapid development of tools to assess heterogeneity in COPD exacerbations, there is potential to improve the current treatment for severe COPD exacerbations, thus reducing morbidity, improving quality of life, costs and mortality. Research should continue in this field to actually achieve this reduction. The current Dutch healthcare policy aims to reduce the number of COPD exacerbations and related health care costs. This should be encouraged, and future policy updates should include an aim to reduce mortality as well.

Concluding remarks

In this thesis the heterogeneity of COPD exacerbations was assessed, and as a logical sequitur, leads for a more personalized treatment of exacerbations. All this was done to oppose to the current one-size fits all approach. One of the targets for a differentiated approach is hyperinflation. Before a personalized approach can be actually used in daily practice some interesting and feasible trials lay ahead. Patients with frequent severe exacerbations eagerly await and welcome a better prognosis and good outcomes and so many are prepared to contribute to the studies. The treatment for COPD exacerbations of the future is within reach.

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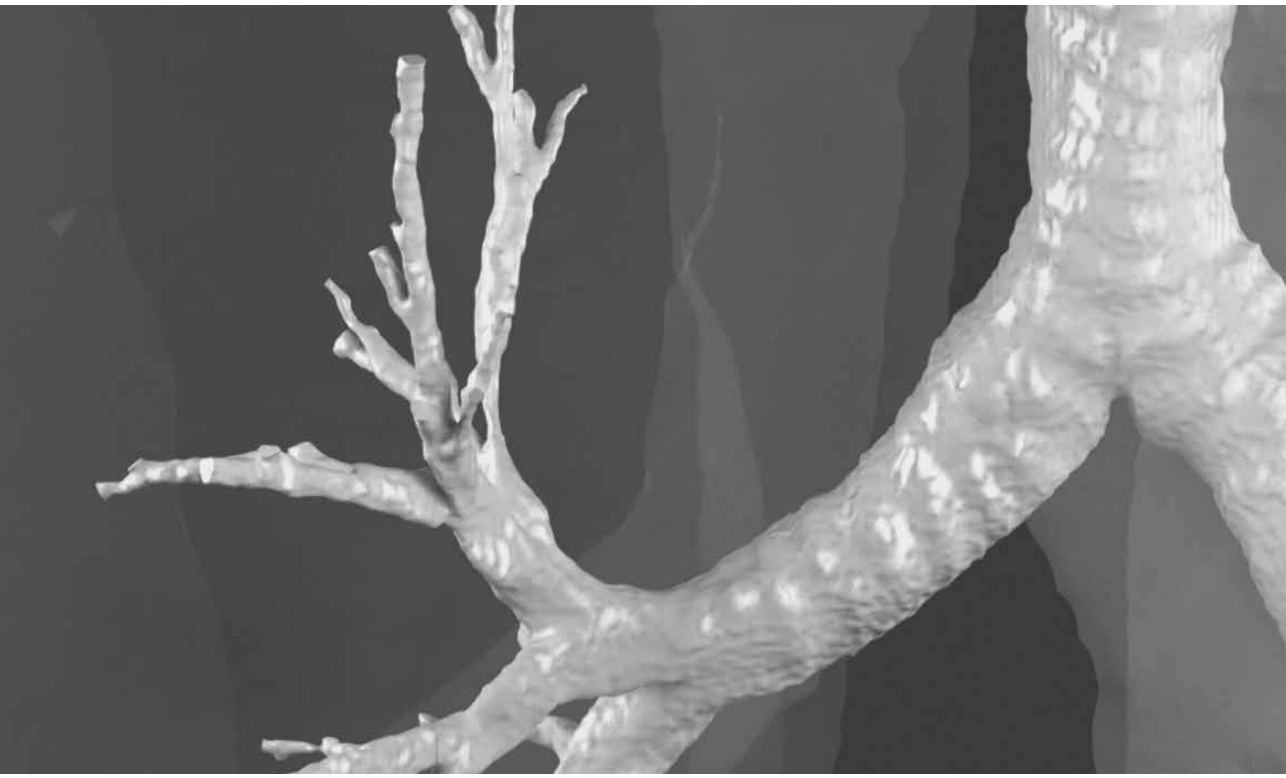
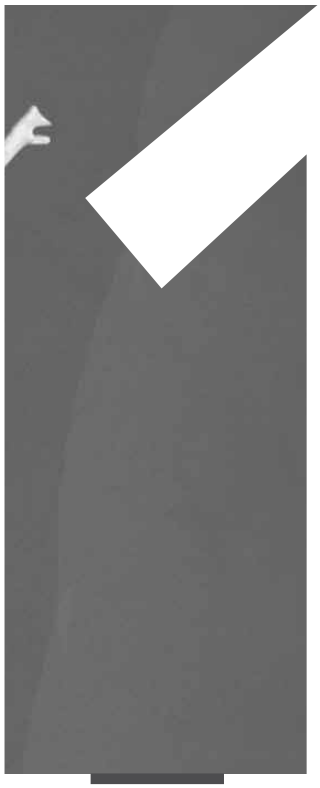


CHAPTER



Nederlandse samenvatting

COPD (chronic obstructive pulmonary disease) is een veel voorkomende chronische longziekte. De afkorting COPD betekent in het Nederlands: chronische obstructieve longziekte. Het woord obstructief duidt hier op een belemmering van de uitademing. In Nederland alleen al overlijden aan COPD jaarlijks ongeveer 10.000 mensen. Patiënten met COPD hebben last van kortademigheid en hoesten. Dit heeft tot gevolg dat veel COPD patiënten zich minder kunnen inspannen en een lagere kwaliteit van hun leven ervaren.

Alle COPD patiënten kunnen last hebben van een periode van plotselinge toename van de klachten waarvoor ze op dat moment extra behandeling nodig hebben. Een dergelijke periode wordt een longaanval (ook wel "exacerbatie") genoemd. Voor de meer ernstige vormen moeten patiënten in het ziekenhuis worden opgenomen. Deze ernstige longaanvallen leiden tot veel meer symptomen, lange termijn schade, meer sterfte en hoge zorgkosten. De behandeling wordt veelal voor alle typen patiënten en soorten longaanvallen hetzelfde uitgevoerd, en is al jaren vrijwel niet verbeterd. Deze behandeling bestaat uit kortwerkende luchtwegverwijders via vernevelaars, extra zuurstof, prednisolon en antibiotica. Er is nog veel onbekend over longaanvallen. Dit gebrek aan kennis is wellicht de reden dat de behandeling de laatste jaren zo goed als onveranderd is gebleven.

Een van de kennishiaten betreft het fenomeen hyperinflatie. Deze hyperinflatie ontstaat doordat COPD patiënten teveel lucht vasthouden na een uitademing waardoor de long zich zelf opblaast. Van deze hyperinflatie was bekend dat bij een stabiele COPD patiënt dit klachten van kortademigheid en een beperkt inspanningsvermogen geeft. Bij een patiënt met stabiel COPD kan hyperinflatie worden behandeld met langwerkende luchtwegverwijders, revalidatie, niet invasieve beademing en longvolumereductie. Het is bekend dat hyperinflatie toeneemt tijdens milde longaanvallen, maar of het voorkomt tijdens ernstige exacerbaties is niet bekend. Als hyperinflatie ook bij ernstige aanvallen voorkomt zou een hierop gerichte behandeling effectief kunnen zijn.

Dit proefschrift heeft als doel om de kennis en behandeling van longaanvallen te verbeteren. Hiervoor werden nieuwe technieken en behandelingen onderzocht, de meeste hiervan gericht op hyperinflatie.

In hoofdstuk twee beschrijven we het voorkomen van hyperinflatie tijdens ernstige COPD longaanvallen. We vonden dat hyperinflatie in een rusttoestand (statische hyperinflatie) was toegenomen tijdens een longaanval in vergelijking met de periode daarna wanneer patiënten weer hersteld waren. De mate van hyperinflatie getest bij snel geforceerd ademen (dynamische hyperinflatie) veranderde niet tijdens een longaanval in vergelijking met de stabiele situatie van de patiënt na de longaanval.

In hoofdstuk drie onderzochten we of een elektronische neus (Aeonose) kan helpen bij het maken van onderscheid tussen een longaanval veroorzaakt door een virale infectie, een bacteriële infectie of een andere oorzaak. De elektrische Aeonose laat potentie zien want de neus lijkt onderscheid te kunnen maken tussen de aan- en afwezigheid van een bacteriële of virale luchtweginfectie tijdens een longaanval. Voordat de neus in de praktijk gebruikt kan worden zijn er nog meer onderzoeken nodig.

In hoofdstuk vier bestudeerden we met functionele respiratoire beeldvorming, CT scans gemaakt bij patiënten tijdens en na een longaanval. We konden hiermee duidelijke verschillen meten tussen de aanval en stabiele fase na het herstel van de aanval. Ook konden we verschillen tussen patiënten onderling en zelfs in individuele patiënten tussen verschillende longgebieden observeren. Functionele respiratoire beeldvorming geeft de mogelijkheid om totale longvolumes, volumes van longkwabben, de ventilatie en weerstand van de longen te meten en verschillen hierin te detecteren tussen de aanval en de stabiele fase daarna.

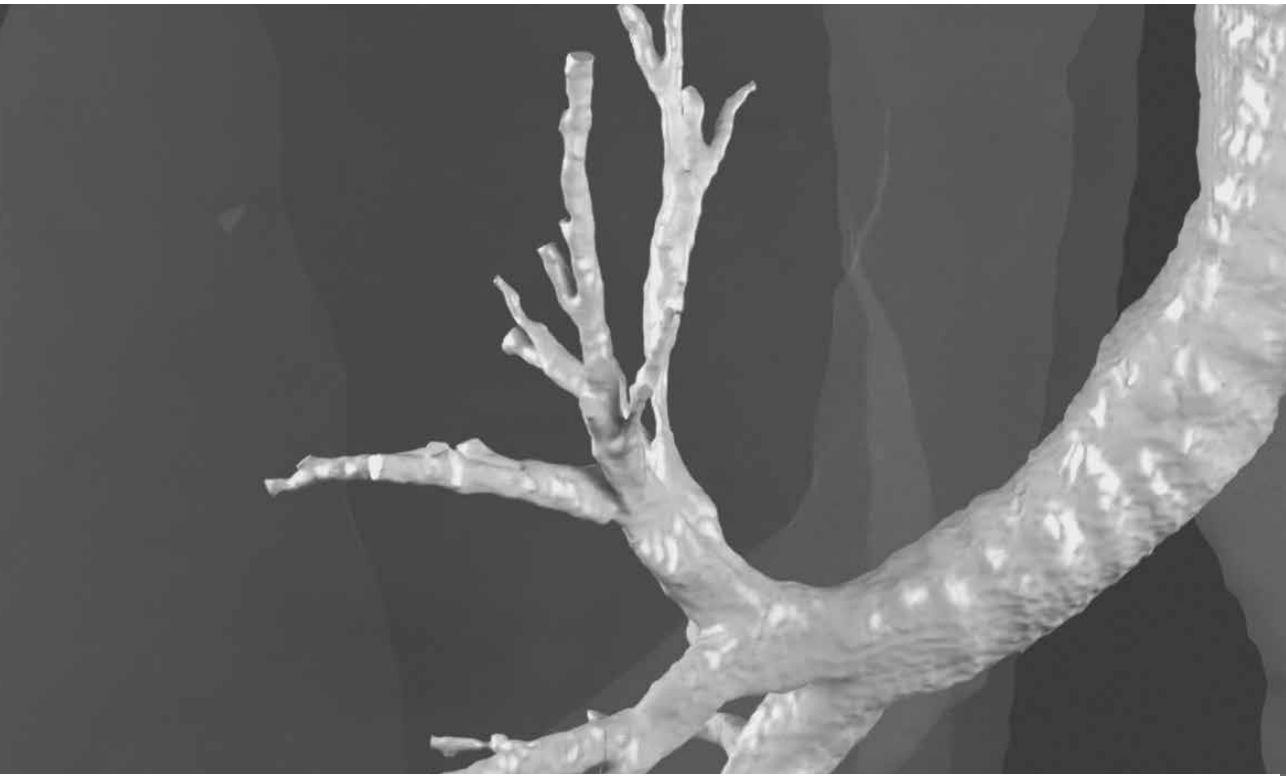
In hoofdstuk vijf bediscussiëren we de rol van hyperinflatie tijdens COPD longaanvallen. Patiënten met een longaanval met vooral hyperinflatie kunnen en zouden misschien wel anders behandeld moeten worden dan nu het geval is.

In hoofdstuk zes worden door middel van een systematische meta-analyse alle beschikbare onderzoeken gebundeld om te onderzoeken wat de beste manier van afgifte voor luchtwegverwijders is tijdens COPD longaanvallen. Deze Cochrane review laat zien dat er eigenlijk maar heel weinig onderzoek naar is gedaan. Er is onvoldoende over bekend, dus men kan niet zeggen dat de huidige manier van vernevelen beter of slechter is dan luchtwegverwijders via een normale inhalator. Als er gekeken wordt naar het effect op longfunctie van een inhalator en een vernevelaar 1 uur na toediening, is er geen verschil. Als de verschillende meetmomenten van de verschillende studies gebundeld worden is er klein voordeel voor de vernevelaar, maar dat verschil is niet klinisch relevant.

In hoofdstuk zeven worden verschillende bronchoscopische behandelingen voor COPD besproken. De meeste van deze behandelingen zijn speciaal ontwikkeld voor COPD patiënten met hyperinflatie. Er is inmiddels veel kennis over endobroncheale ventielen en coils. Deze behandelingen zijn effectief in een uiterst geselecteerde groep patiënten. Ze laten gunstige effecten zien op onder andere longfunctie en kwaliteit van leven. Echter hoewel deze technieken als minimaal invasief worden beschouwd zijn er toch veel bijwerkingen. De meest belangrijke hiervan is het optreden van een klaplong na de behandeling met ventielen.

In hoofdstuk acht wordt het optreden van klaplongen onderzocht, de belangrijkste complicatie van een longvolumereductie behandeling met ventielen. Gekeken werd of het optreden van een klaplong na plaatsing van ventielen voorspeld kon worden. We analyseerden hiervoor de CT scans van COPD patiënten voor de start van longvolumereductie behandeling. Hieruit bleek dat patiënten met meer en grotere pleurale afwijkingen in de behandelde long vaker een klaplong ontwikkelden na een ventiel behandeling.

Mede op basis van onze resultaten denken we dat de toekomstige behandeling van ernstige longaanvallen persoonlijker zou moeten worden en daardoor waarschijnlijk beter kan worden. Een van de mogelijkheden om de behandeling te verbeteren is het richten van de behandeling op hyperinflatie. De potentiële effecten hiervan zijn het zeker waard: minder morbiditeit, een betere kwaliteit van leven, minder sterfte en minder maatschappelijke kosten. Om deze kwaliteitswinst te realiseren is meer onderzoek nodig. Patiënten met COPD en vooral degenen die een ernstige longaanval hebben doorgemaakt wachten met smart op een betere behandeling en prognose. Een nieuwe behandeling voor longaanvallen is binnen bereik.



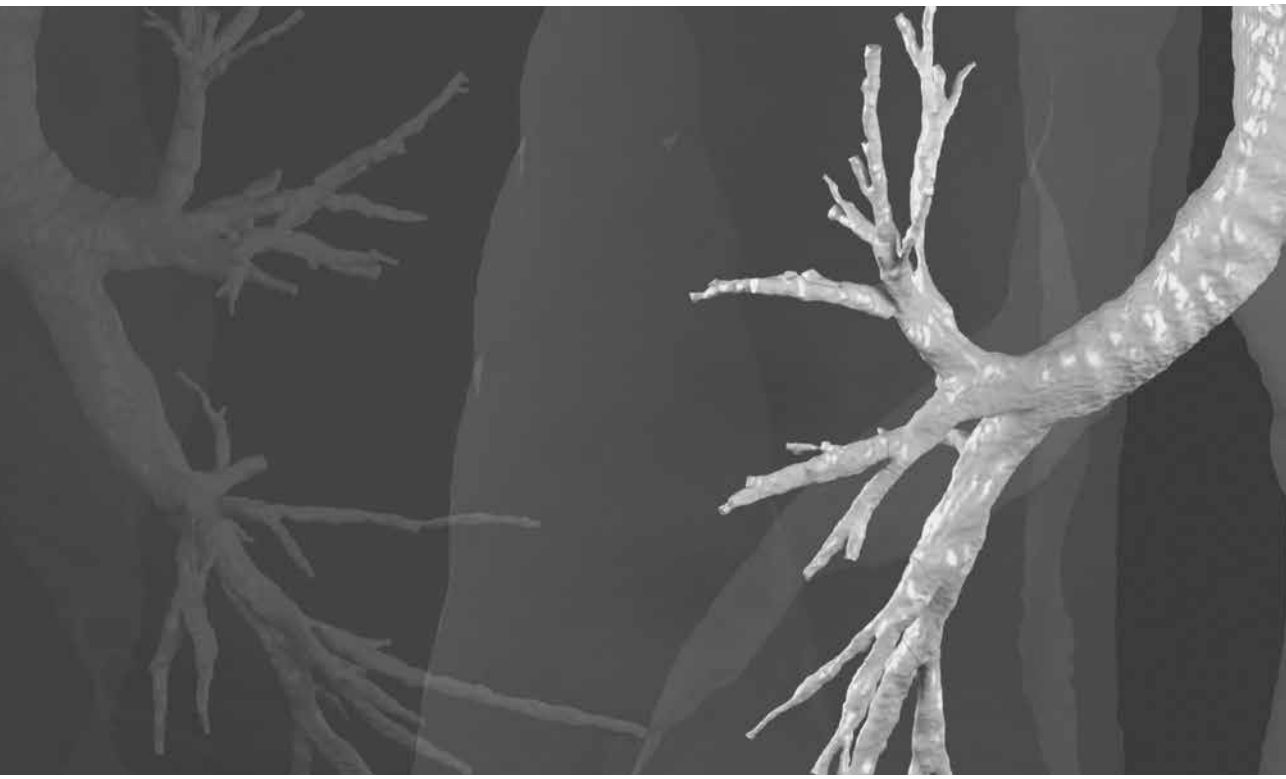
CHAPTER

Curriculum Vitae

Wouter van Geffen werd geboren in 1985 te Groningen. In 2003 rondde hij zijn VWO op het Praedinius Gymnasium af en startte met de studie Geneeskunde aan de Rijksuniversiteit Groningen.

In 2009 begon hij met de opleiding tot longarts bij prof. dr. H.J.M Groen en dr. D.J. Slebos in het Universitair Medisch Centrum Groningen. In 2015 studeerde hij af als de op dat moment jongste longarts van Nederland. Hierna was hij werkzaam bij prof. dr. H.A.M. Kerstjens in het Universitair Medisch Centrum Groningen en bij prof. dr. P.L. Shah in het Royal Brompton Hospital te Londen.

Sinds 2016 is hij werkzaam in het Medisch Centrum Leeuwarden. Voor zijn onderzoek naar COPD exacerbaties won Van Geffen prijzen van de European Respiratory Society (ERS) en het Medisch Centrum Leeuwarden (MCL). Wouter beoefent het vak van longarts in de ruimste zin, maar heeft als speciale aandachtsgebieden COPD en longkanker. Wouter woont met zijn echtgenote Fenne en hun kinderen Olivier (2016) en Maurits (2018) in Leeuwarden.



CHAPTER

Dankwoord

Onderzoek doen is fantastisch. Het is een prachtige manier om kennis te vergaren en vooruitgang te boeken in de behandeling van patiënten. Bovenal is onderzoek doen teamwork. Dit proefschrift is tot stand gekomen met de hulp van velen. Ik dank iedereen die mij in de loop der jaren heeft geholpen.
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De geheime wapens van dit proefschrift zijn zonder twijfel de researchverpleegkundigen. Jullie waren onmisbaar. Zo regelden jullie een groot deel van de logistiek, deden de testen onder moeilijke omstandigheden en straalden positieve energie uit naar onder andere de deelnemers, afdeling en longfunctieafdeling. Ontzettend bedankt!
Beste Jantien, wat was het een geschenk dat jij van D3 naar ons team toe kwam. Je wist het onderzoek een vliegende start te geven en dacht kritisch mee met zowel opzet als uitvoering. Je zette het met militaire precisie op en zorgde voor een uitstekende overdracht toen jij een prachtige vervolgstap kon maken. Zonder twijfel ben je een schoolvoorbeeld voor je studenten.
Beste Jetty, toen jij ons kwam helpen met het Enose onderzoek was ik erg blij. Jouw ervaring in het onderzoek en flexibiliteit waren van onschatbare waarde. Ook toen de inclusie langzamer liep dan gehoopt, hield je de positieve state of mind. Een prachtig hoofdstuk en een goede stap voorwaarts voor de eNose company waren het resultaat.
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Mijn mede AIOS: Wouter de Jong, Marjolein Lacor, Ries van de Biggelaar, Marieke Duiverman, Els van Kampenhout, Caroline Godfroy, Jorien Minnema-Luiting, Marlies van Dijk, Wud Al-Kailany, Jan Zijlstra, Annette Bijsmans, David Koster, Arenda Meedendorp, Chantal Koops, Yvette de Reus, Lysbert Schaap en Kor-Johan Koning. Door het teamwork van onze groep en de ruimte die jullie mij gegeven hebben is de fundering van dit proefschrift gelegd. In drukke tijden konden we het werk klaren en hielden we elkaar overeind. Ik ben blij dat jullie flexibel waren als ik dat niet kon zijn en dankbaar voor de mogelijkheden die jullie me geboden hebben door me te sparen op mijn onderzoeksdagen. Ik vond het fijn om met jullie te mogen werken en elke keer wanneer er iemand op een mooie plek terecht komt geeft dat ook mij veel voldoening. Bedankt en het ga jullie goed.
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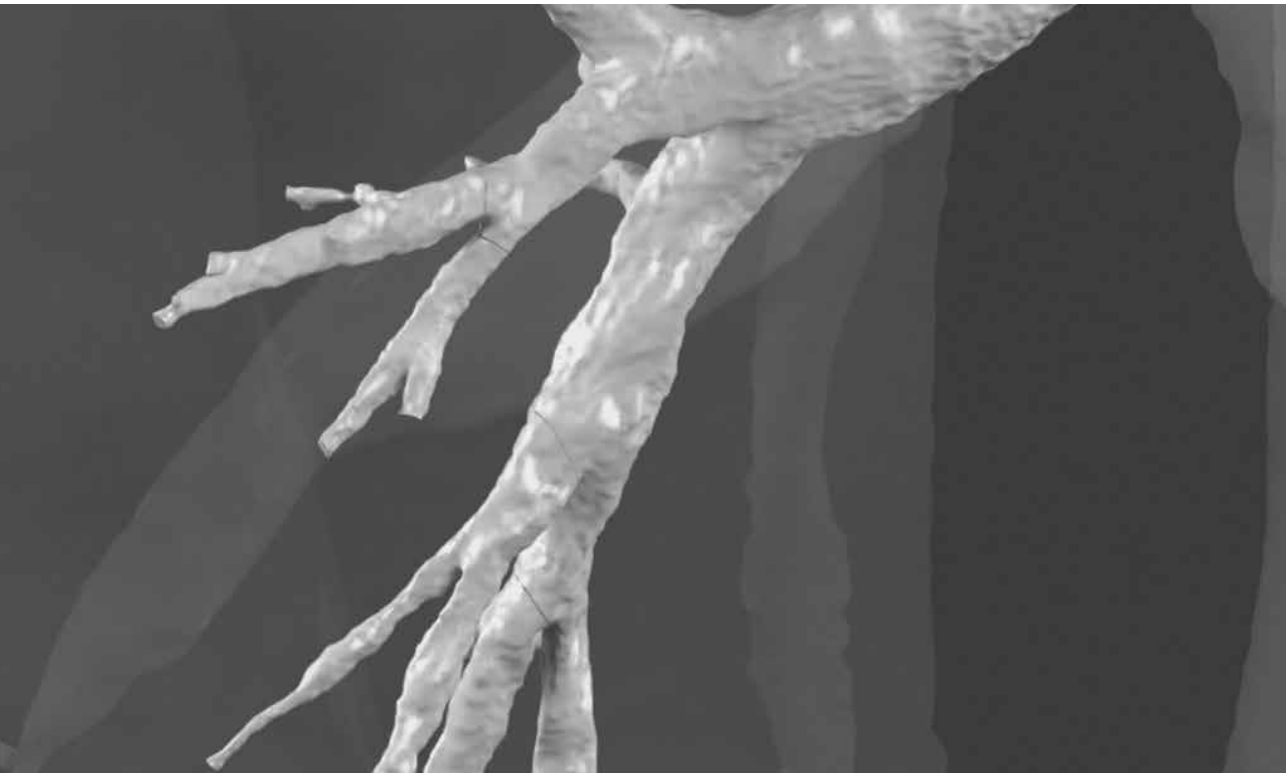

CHAPTER

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