Influence of chest physiotherapy on mulitple breath washout in children with cystic fibrosis

Christian Voldby,Kent Green,Susanne Rosthøj,Thomas Kongstad,Lue Philipsen,Frederik Buchvald,Marianne Skov,Tania Pressler,Per Gustafsson,Kim G. Nielsen

Abstract

It is presumed that early detection and treatment of the chronic lung diseases cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) are crucial for improving the prognosis. Mucus stagnation and secondary infections and inflammation in the airways causes progressive lung damage from infancy in CF and PCD, which again causes early death in CF and reduced pulmonary function in PCD. Early detection of ongoing lung damage will facilitate early intervention with intensive treatment, enhance disease surveillance and further improve preventive treatment. This will improve quality of life for patients with both CF and PCD and likely improve survival in CF.

Pulmonary function is an important marker of prognosis and effect of treatment, but current pulmonary function tests do not register the earliest damages in the lungs in school children – and are inappliccable for infants and toddlers due to requirements for good coorporation. For this reason there is a demand for more sensitive methods that can be used in all age groups. Gas washout – multiple breath inert gas washout (MBW) – is a method that meets these criteria and seems promising for detection of minimal lung damage prior to debut of clinical symptoms and detection by other methods.

MBW is for the first time in Denmark established in the Pediatric Pulmonary Service at Copenhagen University Hospital, where a recently established ”Respiratory Physiology Lab for Children” offers a wide range of methods to detect lung disease in children.

Aim:

The aim of the Ph.D.-project is to investigate:

- Reliability of results conducted from MBW measurements under different standardized conditions (reproducibility), including establishment of a Danish reference material for children.
- Whether MBW can be used as a marker of early lung disease compared to conventional lung function methods in the chronic lung diseases CF and PCD.
- Whether MBW can be used as a relevant outcome to detect interventions in basic CF treatment.

The Ph.D.-project will generate a new and more aggressive approach to surveillance and

treatment of patients with CF and PCD with an overall aim to reduce morbidity and mortality and improve quality of life. Furthermore, it is expected that this project will generate new knowledge that can be used in the more common lung diseases asthma and COPD, which affects 10% and 15% of children and adults, respectively.

Citation: Christian Voldby,Kent Green,Susanne Rosthøj,Thomas Kongstad,Lue Philipsen,Frederik Buchvald,Marianne Skov,Tania Pressler,Per Gustafsson,Kim G. Nielsen Influence of chest physiotherapy on mulitple breath washout in children with cystic fibrosis. **protocols.io**

dx.doi.org/10.17504/protocols.io.jsjcncn

Published: 08 Sep 2017

Protocol

Overview

Step 1.

This is a description of the study protocol ”Influence of chest physiotherapy on multiple breath washout in children wit cystic fibrosis'. This is a methodological substudy in the Ph.D. protocol ”Ventilation distribution as an early marker of lung disease in children with cystic fibrosis and primary ciliary dyskinesia” (point 1.1.3. in the Ph.D.-protocol).

Here, we present a compromised version of the original Ph.D. protocol, e.g. summary, abstract, aims etc. However, the parts from the original Ph.D.-protocol that has no relevance for the mentioned/present substudy *and* study protocols and related results that have not yet been published are censured/removed here. Thus, all specifics regards the substudy ”Influence of chest physiotherapy on multiple breath washout in children wit cystic fibrosis'.

Summary

Step 2.

It is presumed that early detection and treatment of the chronic lung diseases cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) are crucial for improving the prognosis. Mucus stagnation and secondary infections and inflammation in the airways causes progressive lung damage from infancy in CF and PCD, which again causes early death in CF and reduced pulmonary function in PCD. Early detection of ongoing lung damage will facilitate early intervention with intensive treatment, enhance disease surveillance and further improve preventive treatment. This will improve quality of life for patients with both CF and PCD and likely improve survival in CF.

Pulmonary function is an important marker of prognosis and effect of treatment, but current pulmonary function tests do not register the earliest damages in the lungs in school children – and are inappliccable for infants and toddlers due to requirements for good coorporation. For this reason there is a demand for more sensitive methods that can be used in all age groups. Gas washout – multiple breath inert gas washout (MBW) – is a method that meets these criteria and seems promising for detection of minimal lung damage prior to debut of clinical symptoms and detection by other methods.

MBW is for the first time in Denmark established in the Pediatric Pulmonary Service at Copenhagen University Hospital, where a recently established ”Respiratory Physiology Lab for Children” offers a wide range of methods to detect lung disease in children.

The aim of the Ph.D.-project is to investigate:

- Reliability of results conducted from MBW measurements under different standardized conditions (reproducibility), including establishment of a Danish reference material for children.
- Whether MBW can be used as a marker of early lung disease compared to conventional lung function methods in the chronic lung diseases CF and PCD.
- Whether MBW can be used as a relevant outcome to detect interventions in basic CF treatment.

The Ph.D.-project will generate a new and more aggressive approach to surveillance and treatment of patients with CF and PCD with an overall aim to reduce morbidity and mortality and improve quality of life. Furthermore, it is expected that this project will generate new knowledge that can be used in the more common lung diseases asthma and COPD, which affects 10% and 15% of children and adults, respectively.

Participants

Step 3.

10 children with cystic fibrosis.

Inclusion criteria

Step 4.

Positive sweat test and/or the presence of two CF mutations. Age: 5-18 years.

Exclusion criteria:

Step 5.

Current upper or lower airway infection. Fuchs criteria >2.

Primary endpoints:

Step 6.

Absolute values for LCI, Scond and Sacin.

Secondary endpoints:

Step 7.

FEV1 and sRaw.

Proportion of microorganisms in mucus.

Design

Step 8.

3 visits 1 month apart.

1. visit: 10 AM: 3 technical acceptable MBW measurements with no prior chest physiotherapy. That is: Participants cannot perform chest physiotherapy at home prior to visits, including use of a PEP-mask or participating in strenuous physical activity. 2 PM: 3 technical acceptable MBW measurements with no prior chest physiotherapy. Participants cannot perform chest physiotherapy or participate in strenuous physical activity between measurements.
2. visit: 10 AM: 3 technical acceptable MBW measurements with no prior chest physiotherapy. That is: Participants cannot perform chest physiotherapy at home, prior to visit including use of a PEP-mask or participating in strenuous physical activity. 2 PM: 3 technical acceptable MBW measurements with prior chest physiotherapy supervised by a trained chest physiotherapist performed within 1 hour before measurements.
3. visit: 10 AM: 3 technical acceptable MBW measurements with prior chest physiotherapy supervised by a trained chest physiotherapist performed within 1 hour before measurements. 2 PM: 3 technical acceptable MBW measurements with prior chest physiotherapy supervised by a trained chest physiotherapist performed within 1 hour before measurements.

- At each visit a sample of mucus is collected and sent for microbiological investigation.
- At each visit an initial clinical assessment using the Fuchs criteria is performed. At each visit auscultation of the lungs and vital signs are measured: respiration frequency, heart rate, blood pressure and oxygen saturation.

Informed consent:

Step 9.

An informed consent will be signed by all participants or their guardians prior to participation.

Statistical method

Step 10.

Demographic data will be reported as mean/median values, standard deviation (SD) and range or confidence intervals depending on the normal distribution.

Reproducibility of each MBW measurement is found by calculating the coefficient of variation (CV) as follows: 100 x SD/mean of the 3 MBW runs per visit. The variability is found using Bland-Altman plot.

Pearson’s or Spearman’s test will be used to calculate the correlation between different variables for data that are normal distributed. T-tests are used to test normal distributed data. Non-normal distributed data will be compared using paired non-parametric tests. Statistical analyses will be performed using *SAS version. 9.1.3*.

Perspective

Step 11.

LCI measurements in children and adolescents with CF and PCD may become an important addition to current lung function tests as well as a new method to monitor progression of airway disease in seemingly asymptomatic patients in children below 5 years of age. Furthermore, the method may prove more sensitive than current lung function tests in detecting the effect of existing and

potentially upcoming treatments. Similar approaches have previously shown to be able to improve survival and prognosis. Additionally, the results may form the basis for better monitoring of other more common chronic lung diseases like asthma and COPD, which affects 10% and 15% of children and adults, respectively.

Adverse events, risks, disadvantages, etc.

Step 12.

Adverse events, risks, disadvantages, etc.

MBW and other physiological lung function tests (performed in this project) are all non-invasive methods with no discomfort for the patients and all methods are already regularly performed or offered to all patients that adhere to the Pediatric Pulmonary Service, Copenhagen University Hospital.

There are no expected risks related to the collection of biological material (that is) mucus. However, collection of mucus from larynx using suction may cause discomfort. The fingertip may become sore after blood samples taken from the fingertip.

Thus, there are no expected risks for the patients participating in any of the substudies and in the opinion of the investigators the advantages of participating in the project exceed the disadvantages and the risk of possible adverse events.

Ethical aspects

Step 13.

Collection of mucus from patients with CF and PCD are routinely performed at all outpatient control visits, and are thus not extraordinarily performed in this project. Patients will be treated with antibiotics according to the department's normal guidelines according to microbiological test results and/or clinical symptoms. Collection of biological material will be performed according to the department's usual guidelines, where biological material (mucus) will be destroyed immediately after it has been cultured, that is within 1-2 days. Thus, the mucus will not be stored, only microbiological results will be stored, and no personally identifiable biological material will be stored.

The intervention studies will not be classified as clinical trials according to the rule about trials in which the medical product is used as a tool to investigate physiological responses. For this reason, registration of this protocol in EudracT and in the Danish Medicine Agency as well as GCP (Good Clinical Practice)-monitoring is not deemed necessary.

There will not be used placebo or control treatments in this project.

All results – positive and negative findings – will be submitted for publication in international peer-reviewed journals primarily or partly focused on pediatric pulmonology.

For all participants in the above mentioned studies, including both healthy subjects and subjects with CF and PCD, participation will contribute to clarify whether MBW can be used as a lung functions test in children and adolescents to diagnose and/or to exclude progression in lung disease in the patients themselves and in other patients with the same lung disease before debut of symptoms. Early detection of lung damage in children and adolescents with CF and PCD is important to maintain a stable pulmonary function in later stages of life, and participation in the project will be of great value

for the individual patients with both CF and PCD. Participation in the project will likely be an advantage for each patient with either PCD or CF, since he/she will be followed more closely than usual with more examinations and tests at the Pediatric Pulmonary Service at Copenhagen University Hospital as long as he/she is enrolled in the project. It is deemed an advantage for healthy controls participating in the study that he/she will be thoroughly examined by a doctor at the Pediatric Pulmonary Service at Copenhagen University Hospital.

Furthermore, by participating, both healthy controls and patients will help us expand our knowledge about MBW, which prospectively might be an advantage for themselves and other patients with different lung diseases such as asthma or COPD.

It is deemed that possible disadvantages and the risk of possible adverse events are easily compensated by the advantages of participating in this project.

This project was approved by The Danish National Committees on Biomedical Research Ethics for the Capital Region of Copenhagen with the following protocol no: H-1-2010-042.

This project was approved by the Danish Data Protection Agency on 20th of May 2010.

All participants and their parents or guardians will provide a written informed consent prior to participation.

Recruitment

Step 14.

Recruitment of healthy participants will take place by oral request and by posters at selected schools and day care centres. Recruitment of patients with CF or PCD will take place during regular outpatient control visits at the Pediatric Pulmonary Service at Copenhagen University Hospital. Parents and patients will be informed that they can bring a counsellor at the information conversation. Parents and patients who show interest in participation will be invited to an information visit where they will be thoroughly informed orally under quiet conditions with time for questions and receive written information for participants. A person with knowledge about the project and who also possesses the necessary pedagogical communicative skills will inform minors. The information visit will take place in one of the usual consultation rooms at the Pediatric Pulmonary Service at Copenhagen University Hospital with the possibility of locking the door. The written informed consent will not be collected until at least 14 days of reflection time has passed from the information visit.

Oral request and subsequent oral and written information will be performed by the primary investigator or by staff who have been trained in the protocol by the primary investigator.

All participants and their parents or guardians will provide a written informed consent prior to participation.

There will not be given any remuneration to any participants. Payment for transportation will be covered by the parents.

Practical execution

Step 15.

LCI measurements are only performed a few places in the world due to the expensive equipment. Equipment has been purchased by external funds and the method is already established at the Pediatric Pulmonary Service at Copenhagen University Hospital. The measurements will be performed by experienced medical laboratory technologists and by the primary investigator, who have all completed a course in Sweden (at docent chief physician Per Gustafsson), where the method have already been established and applied for many years.

Several experienced scientists, who have published scientific work regarding PCD and CF will act as associated collaborators to enhance the execution of the project. The Ph.D.-project will take place in an already established research environment, where two Ph.D.-theses were completed in 2010, and where all supervisors/collaborators have comprehensive research experience.

Both patient populations are unique and well described in the literature regarding management of clinical control visits, microbiological collection and evaluation of lung functions tests. All clinical data in this project will be collected prospectively and documented in already established databases. The CF and PCD populations at the Pediatric Pulmonary Service at Copenhagen University Hospital are among the largest and clinically most well controlled in the world. Furthermore, the treatment regimen of CF patients at the Pediatric Pulmonary Service at Copenhagen University Hospital is among the best in the world.

The Pediatric Pulmonary Service at Copenhagen University Hospital is responsible for the regional treatment of CF patients in Denmark (approximately 300 patients) as well as diagnostics and treatment of all Danish patients with PCD (approximately 100 patients).