

# Research Protocol

## Project summary

Nanoparticles are deposited in lungs almost exclusively by diffusion. The deposition of inhaled nanoparticles of a given size is dependent on the time the particle resides in the lungs as well as the diffusion distance. An apparatus for measurement of nanoparticle deposition in humans has been developed as a result of a joint project between Lund University Department of Engineering and Lund University Department of Translational Medicine. In this device, termed Airspace dimension assessment with nanoparticles (AiDA) a nanoaerosol is first generated in a container. The participant inhales maximally through a mouthpiece, holds their breath a given amount of time, and then exhales. The particle concentration in inhaled and exhaled gas is measured, and the difference is considered a measure of the deposition. As the residence time is standardized, the deposition will represent the diffusion distance in the lungs. Preliminary data has shown that the method has a high reproducibility and comparatively small interindividual differences between healthy people. Persons with obstructive pulmonary disease are expected to have a reduced deposition due to their larger diffusion distances in alveoli. Hence, we believe the method may potentially be useful for detecting emphysema.

The aim of this study is to test if this method can find early emphysema related changes. We also expect there to be a correlation between the AiDA outcomes and extent of emphysema as measured by spirometry, DLCO and computed tomography (CT) densitometry. The data collection will be conducted starting Jan 2014, and is planned to last two years.

## General information

- Funding sources
  - The Swedish Research Council (project 621-2011-3560)
  - The Crafoord Foundation,
  - The Swedish Governmental Agency for Innovation Systems (VINNOVA)
  - The ERA-NET project EuroNanoMed2
  - The Swedish Heart and Lung Foundation.
- Primary investigators:
  - Prof. Per Wollmer, MD, PhD, Inga Marie Nilssons gata 49, 20502 Malmö, Sweden, tel +46-40-331441, responsible for the medical aspects of the project
  - Ass. Prof. Jakob Löndahl, PhD, Faculty of Engineering LTH  
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Box 118, SE-221 00 Lund, Sweden +46 46-222 05 17; responsible for the technical aspects of the project
  - Dr. Laura Aaltonen, MD, Inga Marie Nilssons gata 49, 20502 Malmö, Sweden, tel +46-40-338929; responsible for the recruitment and logistics of the project
- Clinical laboratories:
  - Skåne University Hospital Malmö, Inga Marie Nilssons gata 49, 20502 Malmö
  - Ergonomics and Aerosol Technology, Design Sciences, Box 118, SE-221 00 Lund, Sweden

## **Rationale & background information**

COPD affects more than 200 million people, causing three million deaths yearly. Almost 90% of COPD deaths occur in low- and middle-income countries. Currently, COPD is diagnosed with pulmonary function tests, which are insensitive to early emphysema. Early emphysema can be diagnosed with computed tomography or other more experimental methods, such as MRI with hyperpolarized gas. These methods, however, are not easily accessible in a clinical outpatient setting. As emphysema is irreversible, early diagnosis is needed to improve patient outcomes. Hence, there is a need for a simple, readily available method to diagnose emphysema at an early stage.

Nanoparticle deposition in diseased lung is not widely studied. Löndahl et al. 2012 found reduced deposition of particles <40 nm in ten COPD-patients relative to seven controls. There have been previous attempts to use the deposition patterns of larger particles to determine airspace dimensions. These methods, however, have not become clinically available, mainly due to cumbersome measurement protocols.

We believe the Airspace Dimension Assessment could differentiate between COPD and healthy subjects. The measurement protocol is simpler than the previously suggested aerosol-based methods. Hence, we believe this method may be developed to assess early emphysema.

## **References (of literature cited in preceding sections)**

- WHO: *Global surveillance, Prevention and Control of Chronic Respiratory Diseases: A Comprehensive Approach*. Geneva: World Health Organization; 2007
- Löndahl J, Swietlicki E, Rissler J, et al. Experimental determination of the respiratory tract deposition of diesel combustion particles in patients with chronic obstructive pulmonary disease. *Part Fibre Toxicol*. 2012;9:30.

## **Study goals and objectives**

The aim of this study is to test the feasibility of the method as a way to diagnose early COPD in an unselected cross-sectional population. We also expect there to be a correlation between the particle deposition and extent of emphysema as measured by spirometry, DLCO and computed tomography (CT) densitometry. A secondary aim is to conduct a smoking subgroup analysis, we believe the method may find smoking –related changes.

## **Study Design**

This is a prospective, cross-sectional study.. The subjects consist of a random sample of participants to a general population study (Swedish CArdioPulmonary bioImage Study, SCAPIS). All data collection is carried out in Skåne University Hospital, Malmö, Sweden.

We have no medical exclusion criteria; we plan to include persons regardless of their medical status or history. The subjects perform a total of six measurements; of these at least five should be of acceptable technical quality. As the measurements will be conducted using a prototype of the instrument, the technical development and assessment will take place parallel with the measurements. A more detailed quality criteria will be made available during the study.

The expected duration of the study is two years.

## **Methodology**

The COPD subjects will undergo the AiDA-test, lung function testing with diffusing capacity of carbon monoxide, as well as computed tomography of the chest. The values will be compared to predicted values as given by European Community for Coal and Steel. The study group will undergo a CT scan of the chest. The scan will be performed at suspended full inspiration with a reduced radiation dose, generating an exposure of 120 kV / 15 mAs. An additional image at full expiration was performed, generating a similar radiation dose of 120 kV / 15 mAs. The images were reconstructed using 1.0 mm contiguous slices, with the spatial frequency reconstruction algorithms I70f, I26f and B20f (Siemens). The densitometric variables were obtained using *syngo.via* Pulmo 3D software. The software automatically separates the lungs from the other thoracic organs and vessels and abdominal organs. Before the densitometric values are analyzed, an examiner manually ensures that the computer had chosen the appropriate tissue. The extent of emphysema was estimated using a threshold technique quantifying the percentage of voxels with an x-ray attenuation value below -950 Hounsfield Units (HU). (4, 5). A total of three densitometric variables were obtained:

- CT RA-950 (%), also known as Emphysema Index (EI). This variable relies on the concept of “density mask” first described by Muller et al 1988.
- The HU value at the 15th percentile of the attenuation distribution histogram in inspiration, termed PD15.
- Mean lung density, MLD.

The control group subjects will undergo the AiDA-test and lung function analysis as detailed above. To avoid exposure to ionizing radiation, no CT will be carried out for the control group for the purpose of this study.

The above studies are carried out the same day, although for various logistic reasons it is permitted to have the various investigations be conducted within the same 30 day period.

## **Follow-Up**

The referring clinician will be notified of any incidental findings on spirometry and CT, with a follow-up suggestion if needed. Currently, no follow-up is planned after the completion of this study.

## **Data Management and Statistical Analysis**

Data will be, unless otherwise specified, given as mean, standard deviation and range. Chi-square test will be used for sex differences. The data for the recovery values will be reported as mean and intra-individual standard deviation of three technically acceptable tests. The group difference will be given as independent samples t-tests. The relationships between recovery and emphysema indices will be given as Pearson correlation. The requested level of significance will be  $p$  less than 0.05 for all statistical tests.

## **Quality Assurance**

The apparatus for pulmonary function studies is regularly calibrated.

The CT scanner detector is calibrated on a regular basis. In case of special events, such as detector change, a phantom study will be conducted to ensure HU-values are correctly calibrated.

The AiDA-apparatus is maintained daily. Standard control of particle concentration and zero check of flow meter is made at each measurement. Repeated measurements on a few control subjects are made before, after and a few times during the study.

### **Expected Outcomes of the Study**

This is an early feasibility study. We believe the emphysema group will have a lower particle recovery than controls. We also expect there to be a correlation between particle recovery and the various emphysema indices.

We believe this method may in the long term be developed to assess early emphysema. Many more studies, however, are needed in larger samples, and in samples with early emphysema. The method is comparatively simple, and it could be developed into a device to be used in clinical outpatient setting.

### **Dissemination of Results and Publication Policy**

The results will be sent to a peer-review publication with Dr. Aaltonen as the first author and Dr Wollmer as the last. Other authors to be included are Jakob Löndahl, PhD, Jonas KF Jakobsson, Eeva Piitulainen, MD PhD, Sandra Diaz MD PhD, and Sophia Zackrisson MD PhD.

### **Duration of the Project**

Data collection is planned for one year starting early 2013, another year is planned for data analysis.

### **Project Management**

HLA: study design, participant recruitment, writing the manuscript, CT protocol and interpretation  
PW: study design, data analysis and interpretation  
JL: study design, measurements  
JKFJ: AiDA – measurement, study design  
EP: participant recruitment  
SD: CT protocol and interpretation  
SZ: data analysis  
All authors: input to the protocol and data analysis.

### **Ethics**

The COPD-group will undergo a CT scan of the chest. Low radiation dose acquisition protocol is applied to minimize radiation exposure. Furthermore, the control group will not be subjected to CT. The nanoparticle exposure is less than 1 % of daily mass and number exposure compared to relatively clean urban environment (Hussein 2012). All subjects have received information about the study both in person and in writing. All subjects have signed informed consent. Any possible incidental findings will be followed up.

### **Informed Consent Forms**

A copy of the informed consent form, approved by the regional ethics committee, is attached. Upon request, an English translation will be made available.

### **Other support for the Project**

No other support has been provided other than stated under funding sources.

### **Collaboration with other scientists or research institutions**

No other research institutions or scientists are involved with this project.

### **Curriculum Vitae of primary investigators**

Per Wollmer - [http://portal.research.lu.se/portal/sv/persons/per-wollmer\(ea07c204-46dd-44d0-ac87-a19106e037e5\).html](http://portal.research.lu.se/portal/sv/persons/per-wollmer(ea07c204-46dd-44d0-ac87-a19106e037e5).html)

Jakob Löndahl -

[http://www.eat.lth.se/fileadmin/cast/user\\_upload/CV\\_English\\_research\\_short.pdf](http://www.eat.lth.se/fileadmin/cast/user_upload/CV_English_research_short.pdf)