ASSESSMENT OF DIAPHRAGM'S FUNCTION.
A METHODOLOGICAL STUDY AND A CLINICAL STUDY

PROTOCOL VERSION 3

COLLABORATION BETWEEN CARDIAC DISEASES, INTENSIVE CARE, ANESTHESIA AND SURGERY, CARDIOPULMONARY AND VASCULAR SURGERY AND PULMONARY DISEASES.

AARHUS UNIVERSITY HOSPITAL.

CONTENTS

BACKGROUND

Shortness of breath is a frequent symptom and can be caused by many different disorders from several different organs. Many patients experience shortness of breath as a result of heart or lung disease or as a complication of thoracic surgery. Shortness of breath is a subjective sensation and can be caused by a lack of oxygen, reduced ventilation or dysfunctional breathing muscles.

The diaphragm is the main breathing muscle. Decreased ability to contract the diaphragm causes shortness of breath. The investigation of dysfunction of the diaphragm is complicated by the fact that newly discovered shortness of breath is not specific to diaphragm dysfunction and can be caused by the many other causes of shortness of breath. Diaphragm dysfunction is therefore an overlooked cause of shortness of breath.

We want to shed more light on the function of the diaphragm. Therefore, we will do two studies. The first is a method study in which different ultrasound methods are compared with the golden standard, x-ray transillumination, in healthy, heart- and lung-diseased patients. The second study will assess the diaphragm function in patients after thoracic surgery (lung surgery and heart transplantation) and in patients where severe heart failure necessitates the need for a mechanical heart heart (Left Ventricular Assist Device, LVAD).

STUDY 1:

It is difficult to measure the function of the diaphragm. There are various examination methods to assess the function of the diaphragm. Imaging studies, such as x-rays (fluoroscopy) and ultrasound examinations, are used. X-ray examination of the chest and diaphragm during breathing is considered an older gold standard, but is not really used much in everyday clinical practice. Ultrasound has gradually become the common examination method, as ultrasound examination allows a number of advantages such as easier use, less set up and avoidance of radiation risk. There are several different methods for ultrasound determination of diaphragm function, none are sufficiently validated and there is no consensus about the optimal method. There is a need for a comparison of different methods with transillumination (golden standard) to establish a precise basis for comparison. [1]

STUDY 2:

The etiology of shortness of breath is multifactorial, and shortness of breath can be a symptom of a wide range of lung or heart diseases. In failing heart pump function, shortness of breath is one of the most frequent symptoms. Heart failure can be treated with various types of medicine, but in severe heart failure so that sufficient circulation cannot be maintained, heart transplantation may be the only treatment. Shortage of transplant organs results in waiting time for transplantation. Therefore, an LVAD has been developed that can maintain adequate blood circulation as either temporary treatment before heart transplantation or as definitive treatment in patients who cannot undergo regular heart transplantation. The LVAD is implanted in the thorax and helps pump blood from the left ventricle into the aorta. The LVAD is located on top of the left hemidiaphragm and can therefore inhibit the movement of the diaphragm. Thereby, the LVAD can give rise to shortness of breath, and in patients who have concurrent heart failure, it can thus be difficult to assess whether shortness of breath is due to heart failure or reduced diaphragm function. Treatment that these conditions are different.

Heart transplantation entails a complete replacement of the heart. Due to the close relationship with the phrenic nerve, this can be damaged during the operation and thus result in reduced diaphragm function.

Some diseases, e.g. Cancer of the lung, mediastinum and esophagus requires thoracic surgery. Nerves to the diaphragm can be damaged during the operation and thereby cause reduced diaphragm function, which can lead to shortness of breath. Pleural effusion is common after thoracic surgery and also manifests as shortness of breath. In addition, patients often have other competing diseases such as chronic obstructive pulmonary

disease (COPD) or heart failure, which can also cause shortness of breath. This results in complex diagnostic conditions and complicates the investigation of shortness of breath after thoracic surgery.

HYPOTHESIS/AIM

1. To compare the precision of different ultrasound examination methods for assessing diaphragm function compared with X-ray translucency.
2. Investigate whether LVAD implantation, heart transplantation and thoracic surgery affect diaphragm function.

TITLES

1. Precision of sonographic measures of diaphragm function.
2. The role of diaphragm mobility in heart failure requiring LVAD, heart transplant and thoracic surgery.

METHOD

DESIGN

STUDY 1:

Methodology study. Different ultrasound methods for evaluating diaphragm function are compared with transillumination of the diaphragm.

STUDY 2:

Prospective, observational study of diaphragm function before and after thoracic surgery types that may affect diaphragm function.

SETTING

All studies are carried out at Aarhus University Hospital as a collaboration between Heart Diseases, Lung Diseases, Cardiopulmonary and Vascular Surgery, Anesthesia and Surgery and Intensive Care.

PARTICIPANTS

STUDY 1:

Participants are divided into 3 categories: 1/3 healthy, 1/3 lung medicine patients and 1/3 patients who have had a heart transplant or LVAD implanted. Everyone over 50 years.

STUDY 2:

Patients who must undergo lung surgery or surgery for oesophageal cancer with interventions in the chest cavity at Cardiopulmonary and Vascular Surgery as well as patients with severe heart failure who must undergo heart transplantation or LVAD and/or are scheduled for this.

INCLUSION AND EXCLUSION CRITERIA

STUDY 1:

Inclusion criteria:

- Completed informed consent
- 1 of the following:
    - Quick control person
    - Disease in the lungs: COPD or Idiopathic Pulmonary Fibrosis.
    - Disease of the heart that has led to a heart transplant or LVAD

Exclusion criteria:

- Known diaphragm dysfunction
- Neuromuscular disease
- Pleural effusion. Discovered during the investigation
- Pneumothorax. Discovered during the investigation
- Healthy group only (1/3): Significant comorbidity affecting heart or lung function (hypertension and mild valvular disease without symptoms is ok), including diagnosed COPD.
- Only healthy group (1/3) and lung disease group (1/3): Previous operation in the thorax

STUDY 2:

Inclusion criteria:

- Completed informed consent.
- One of the following:
    - Planned LVAD implantation / Heart transplant
    - Planned surgery for lung cancer/esophageal cancer. For lung cancer, the planned operation must be the removal of one or more lung lobes.

Exclusion criteria:

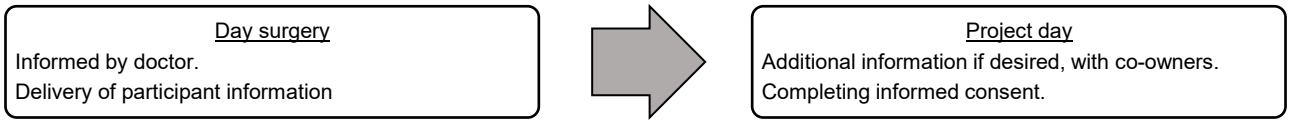
- Known diaphragm dysfunction
- Neuromuscular disease
- Pleural effusion (over 1 cm)
- Pneumothorax

RECRUITMENT

STUDY 1:

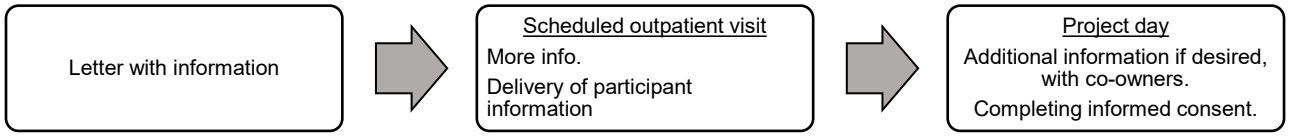
FAST GROUP:

Patients who are to be operated on in day surgery at Aarhus University Hospital. In the course of surgery (before or after, when patients are awake and capable), patients are informed about the project by a doctor associated with the trial. It is ensured that the information can be conveyed in an undisturbed single room. Participant information is provided. On the project day (a later date), if there is a desire for this, there will be the possibility of a follow-up interview with the possibility of the participation of co-chairs. The reflection time will thus be >1 day. Written consent is then secured. Patients have the option of withdrawing consent at any time without further requirements for a reason.



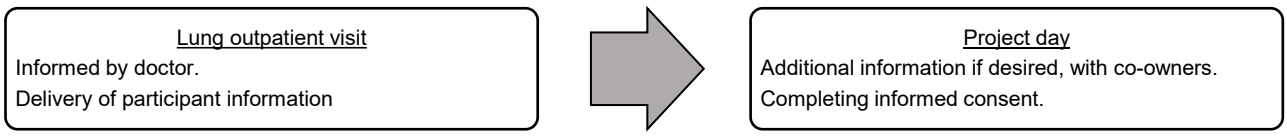
HEART TRANSPLANT RECIPIENTS/LVAD GROUP:

This patient group is checked with frequent checks after the heart transplant/LVAD. In order to ensure a stable phase, all patients who have had a heart transplant and are checked at AUH after 6 months will be invited to participate in the present project. The patients will per letter to be informed by a doctor associated with the trial about participation. The patients are invited at the next scheduled outpatient visit (as part of the transplant/LVAD check-up) to hear more about the project. It is ensured that the information can be conveyed in an undisturbed single room, where oral information is given as well as written information is provided. On the project day (a later date), if there is a desire for this, there will be the possibility of a follow-up interview with the possibility of the participation of co-chairs. The reflection time will thus be >1 day. Written consent is then secured. Patients have the option of withdrawing consent at any time without further requirements for a reason.



PULMONARY GROUP:

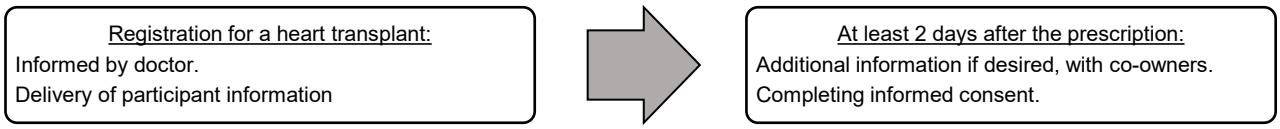
Patients who visit the COPD clinic or the Center for Rare Lung Diseases are informed about the project by a doctor associated with the trial. It is ensured that the information can be conveyed in an undisturbed single room. Participant information is provided. On the project day (a later date), if there is a desire for this, there will be the possibility of a follow-up interview with the possibility of the participation of co-chairs. The reflection time will thus be >1 day. Written consent is then secured. Patients have the option of withdrawing consent at any time without further requirements for a reason.



STUDY 2:

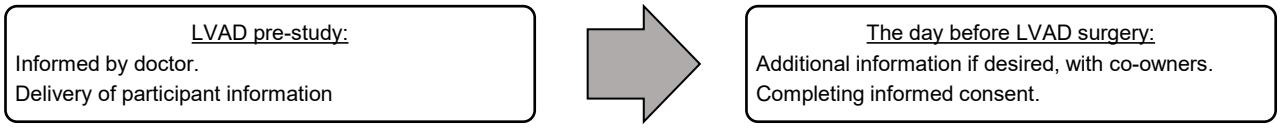
PLANNED HEART TRANSPLANTATION:

Patients who are registered on the heart transplant list, etc. imminent heart transplant, will be informed about the project at the preliminary examination for this treatment or regular check-up prior to heart transplantation, which takes place in a private room. Both oral and written information is given here. After being put on the waiting list, patients will be informed and written consent will then be secured. Relatively close to this date, there will be the possibility of a follow-up interview with the possibility of the participation of co-chairs. The reflection time will thus be >1 day.



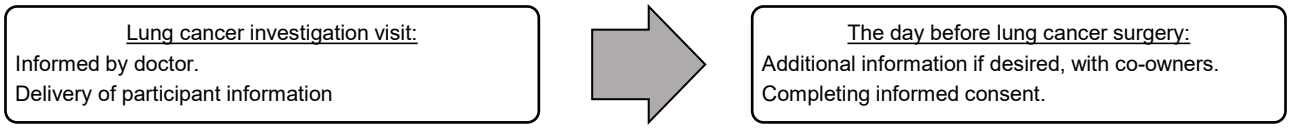
PLANNED LVAD:

Patients who have imminent treatment with an LVAD will be informed about the project during the preliminary examination for this treatment, which takes place in a private room. Both oral and written information is given here. The day before the operation, when the patients are all already admitted to optimize their cardiac condition, written consent is secured. On this day, there will be an opportunity for a follow-up interview with the possibility of the participation of co-chairs. The reflection time will thus be >1 day.



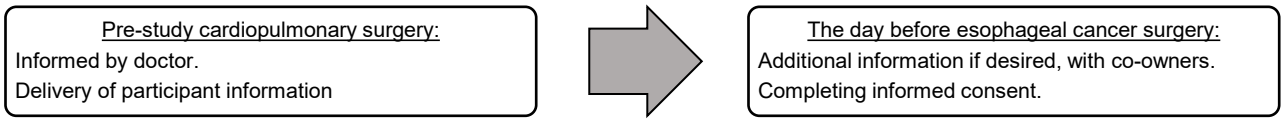
PLANNED SURGERY FOR LUNG CANCER:

The group that is to be operated on for lung cancer is informed about the project when visiting the Clinic for Lung Cancer Investigation. Conversation that takes place in a private room. Written information is provided. The day before surgery, when the patients routinely meet for the last interviews before surgery, written consent is secured. On these days, there will be the possibility of a follow-up interview with the possibility of the participation of co-chairs. The reflection time will thus be > 1 day.



PLANNED SURGERY FOR ESOPHAGEAL CANCER:

The group that is to be operated on for oesophageal cancer is informed about the project when visiting the Cardiopulmonary Surgery Clinic. Conversation that takes place in a private room. Written information is provided. The day before surgery, when the patients routinely meet for the last interviews before surgery, written consent is secured. On these days, there will be the possibility of a follow-up interview with the possibility of the participation of co-chairs. The reflection time will thus be > 1 day.



SURVEYS

STUDY 1:

In study 1, 1 lung function examination, 1 complete ultrasound examination and 1 x-ray examination are carried out.

STUDY 2:

In study 2, only lung function examination and ultrasound examination are carried out. These are made

Lung cancer: 1) the day before surgery, 2) 3 days after surgery and 3) 2 weeks after surgery.

Oesophageal cancer: 1) the day before surgery, 2) 3 days after surgery and 3) 10 days after surgery (after which most are discharged).

LVAD implantation: 1) the day before surgery, 2) 14 days after surgery and 3) 3 months after surgery.

Heart transplant: 1) in close relation to the write-up on the heart transplant list, 2) 14 days after the operation and 3) 3 months after the operation

PULMONARY FUNCTION TEST:

Lung function testing takes place by having the patient blow as hard as they can into a tube. Various endpoints are then measured automatically by a machine. 3 inhalations are made per study, of which the values from the best are used.

INSPIRATION'S PRINT:

Inspiratory pressure is measured with an electronic manometer. It consists of a mouthpiece that you breathe into and which automatically measures the pressure.

ULTRASOUND EXAMINATIONS:

The participants are examined in a standing/sitting position with ultrasound in the mid-axillary line with the liver/spleen as a reference point on the right and left side. A movie clip is saved for later analysis.

Diaphragm movement is measured in 3 different ways: M-mode, Area method and B-mode. [1] [2] [3] [4] Diaphragm thickening fraction is measured in 1 way. [5]

Normal and deep breathing is carried out.

TRANSLUCENT:

Performed only in study 1. Film clips of the movement of the diaphragm during X-ray translucency are recorded.

Transillumination, inspiratory pressure measurement and ultrasound examination are carried out simultaneously. Normal and deep breathing is carried out.

ENDPOINTS

STUDY 1:

Diaphragm movement and thickening fraction compared to the cranial movement of the diaphragm as measured by translucency (gold standard) for the following measures:

Primary endpoint:

- Movement of the right hemidiaphragm: 1. M-mode method.

Secondary endpoints

- Movement of the right hemidiaphragm by 1. Area method & 2. B-mode.
- Thickening fraction of the right hemidiaphragm: 1. B-mode.
- Inspiratory pressure

The above is assessed by correlations and Bland-Altman analysis where relevant.

Correlations are made between lung function (FEV1, FVC, FRC) and ultrasound measurement of diaphragm function (see above) as well as diaphragm function measured by transillumination.

STUDY 2:

Change over time of:

Primary endpoint

- M-mode method of diaphragm movement (ultrasound, only on the right hemidiaphragm).

Secondary endpoints

- Area method for diaphragm movement (ultrasound and transillumination for LVAD patients).
- B-mode method of diaphragm movement (ultrasound).
- Lung function (FEV1, FVC, FRC).

STRENGTH CALCULATION

STUDY 1:

There is no data available for test-retest variance within ultrasound methods or fluoroscopy. It is therefore not possible to make a power calculation of how the spread in the comparison of two methods will be (Limits of agreement with Bland-Altman analysis). The starting point is therefore the bias (absolute difference in mean value) between an ultrasound method (m-mode method) and transillumination. As this is a methodological study, greater requirements are set than in study 2 (see below) for which bias can be detected. Assuming equal variation for the two methods, a detection of bias of 10% (SD 36%, own data for M-mode method) will require 92 participants (power 0.8 and alpha 0.05). Due to uncertainty about SD on the screening method, it is desired to include 100 participants.

STUDY 2:

LUNG/OESOPHAGEAL CANCER PATIENTS:

Data from own research shows diaphragm movement of 6.65mm (SD 2.38) (M-mode method). At a power of 0.9 and alpha 0.05, 36 patients are needed (before-after situation) to show a 20% change that is considered clinically relevant. In order to compensate for drop-outs and an unknown diaphragm movement in particular lung surgery patients, it is desired to include 50 patients.

LVAD/HTX PATIENTS:

A pragmatic approach is desired. It is desired to include all patients who are operated on with the implantation of an LVAD/Heart transplant over 2 years (approx. 40 patients).

SUMMARY OF DESIRED NUMBER OF INCLUDED PATIENTS

STUDY 1:

We want 100 patients (34 healthy, 33 pulmonary medicine patients and 33 patients who have had a heart transplant/LVAD) included, distributed equally between the 3 groups to compensate for drop-outs and increase power.

STUDY 2:

It is desired to include 50 lung/oesophagus patients with the same reasoning as above. Regarding LVAD/heart transplant patients, it is desired to include all patients who are recommended for surgery over 2 years (approx. 40 patients)

DATA REGISTRATION

The following demographic data are recorded: sex, height, weight, age and comorbidity. Demographic data is obtained from Region Midt's EPR system as well as anamnestic data. Consent to the trial gives the trial group and any accounting body the right to obtain information in the patient record regarding conditions that are relevant to the trial and for control purposes.

Data is registered in Case-Report-Form in RedCAP, which is administered by Aarhus University. The Danish Data Protection Authority's rules are followed and all personally identifiable data is deleted at the end of the study.

DATA ANALYSIS

STUDY 1:

Movement is measured continuously (centimeters or square centimeters) and calculated as a mean with standard deviation for the various ultrasound measurements. Correlation between diaphragm movement and sex, age, BMI is analyzed with multivariable analysis of variance, MANOVA.

The different measurement methods are compared individually with the golden standard with the paired T-test (Wilcocon's test if non-parametric). The 0 hypothesis is that there is no difference between the index method and the golden standard. Data is also depicted with a Bland-Altman plot and correlation between the index test and the golden standard.

STUDY 2:

Participants act as their own controls and before/after differences are analyzed with or univariate ANOVA for repeated measurements.

BLINDING

Analysis of ultrasound films is performed blinded to data for translucency in study 1.

RISKS AND DISADVANTAGES

STUDY 1 & 2:

Ultrasound examination, lung function examination and manometry are without risks.

STUDY 1 ONLY:

Transillumination with X-rays includes irradiation. Based on an expected radiation time of a maximum of 1 minute (closer to 30 s), the accumulated radiation dose is estimated to be 0.1-1 mSievert. This would theoretically increase the lifetime risk of developing serious cancer by <0.01%.

Patients will have to attend the hospital on a day when they would not otherwise have to attend. Participation in the experiment takes approx. 30 minutes.

No compensation or inconvenience allowance will be paid to trial participants.

ETHICAL CONSIDERATIONS

STUDY 1:

Ultrasound examinations and lung function examination are without any kind of risks or discomfort for the participants and the examinations do not contain any ethical considerations.

The participants will be X-rayed. The radiation dose is minimal and the expected, accumulated dose of 0.1-1mSievert must be compared to being exposed to approx. 3 mSv for background radiation annually. The expected radiation dose corresponds to an increased risk of serious cancer of 1 in 100,000. If it turns out that there is good correlation and agreement between ultrasound methods and fluoroscopy, there will be no need for fluoroscopy in the future if dysfunction of the diaphragm muscle is suspected, and future patients will therefore be spared radiation. [6] It will also be possible to reduce the radiation dose employees are exposed to. In study 1, only subjects aged ≥50 years are included in order to minimize the risk of developing cancer secondary to the experiment. There have been no studies in which the radiation dose during fluoroscopy is indicated, as it depends on the apparatus and method. In this study, we record the total radiation dose, and the total radiation dose is closely monitored.

STUDY 2:

The ultrasound examinations are performed independently of LVAD implantation or surgery for lung/oesophageal cancer. The examinations are carried out at already planned clinic visits in order to reduce the burden on the patients.

Overall, we believe that the clinical potential of the study outweighs the risks and disadvantages that the patients are exposed to.

ECONOMIC CONSIDERATIONS

The group listed below, all employed at Aarhus University Hospital, has taken the initiative for the experiment. All costs for equipment, personnel and utensils are covered by the departments involved and their respective research sections, and the experiment has not received any money from outside. None of the researchers involved have personal, financial interests in the experiment.

BIOBANK

A biobank will not be established

LAW AND PERMITS

The Act on the processing of personal data will be complied with.

Studies 1 and 2 require approval from the Scientific Ethics Committee.

Studies 1 and 2 require approval from the Danish Data Protection Authority.

Both studies are registered in ClinicalTrials.org.

Both trials only include the use of CE marked equipment and therefore do not require approval from the Danish Medicines Agency.

COMPENSATION

The trial is covered by the patient reimbursement

PUBLICATION

Results, positive, negative or inconclusive, are sought to be published in peer-reviewed medical journals. Likewise, results will be disseminated at scientific congresses.

RESEARCH GROUP

Søren Helbo Skaarup, doctor, Lung diseases. Aarhus University Hospital.

Brian Bridal Løgstrup, senior physician, Heart diseases. Aarhus University Hospital.

Morten Bendixen, senior physician, Heart, Lung and Vascular Surgery. Aarhus University Hospital.

Thomas Birkelund, ward physician, Intensive Care Unit. Aarhus University Hospital.

Peter Juhl-Olsen, department physician, clinical associate professor, Anesthesia and Surgery. Aarhus University Hospital.

AUTHORSHIP

Qualification for authorship requires participation in study design and concept development, data collection, data processing, interpretation of data and participation in manuscript writing. All authors must approve the manuscript.

PERSPECTIVE

STUDY 1:

The first study will identify the optimal research method. This makes it much easier and safer to examine future patients, as you want to avoid X-rays.

STUDY 2:

The second study will focus on a probably overlooked cause of shortness of breath in patients with severe heart failure and in patients undergoing thoracic surgery, which will be able to optimize treatment and avoid unnecessary examinations and treatment.

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ASSESSMENT OF DIAPHRAGM'S FUNCTION.
A METHODOLOGICAL STUDY AND A CLINICAL STUDY

Protocol summary

Doctors responsible for the project:

Søren Helbo Skaarup, doctor, Lung diseases. Aarhus University Hospital.

Brian Bridal Løgstrup, senior physician, Heart diseases. Aarhus University Hospital.

Morten Bendixen, senior physician, Heart, Lung and Vascular Surgery. Aarhus University Hospital.

Thomas Birkelund, ward physician, Intensive Care Unit. Aarhus University Hospital.

Peter Juhl-Olsen, department physician, clinical associate professor, Anesthesia and Surgery. Aarhus University Hospital.

Test site:

Aarhus University Hospital

BACKGROUND & PURPOSE

We want to do two studies, both of which deal with the function of the diaphragm muscle.

The diaphragm muscle is the most important muscle for breathing. Poor functioning of the breathing muscle causes shortness of breath, but shortness of breath can be caused by many other conditions. It can be diseases of the heart, lungs or following operations in the chest. Furthermore, with the current examination methods, it is difficult to examine and assess the function of the diaphragm muscle, as there are different ways of examining the muscle, of which the established method (X-ray fluoroscopy) is both difficult and associated with radiation for both patients and examiners.

In the first study, we will compare different examination methods to assess the diaphragm muscle. X-rays have been used and are considered the best method, perhaps mostly for historical reasons. With an ultrasound examination, however, the function of the diaphragm muscle can also be assessed, and ultrasound is completely risk-free. The connection between X-ray recordings and the various ultrasound examination methods has not been investigated. We want to examine a number of healthy people, as well as patients with heart and lung diseases. The purpose is to examine exactly how newer ultrasound methods perform compared to the classic examination method, X-ray fluoroscopy.

In the second study, we will investigate changes in the function of the diaphragm muscle in patients undergoing surgery in the chest cavity. During surgery in the chest cavity, you get close to and often affect the nerve that controls the diaphragm muscle. It is unclear whether this can cause lasting or short-term (days) effects on the diaphragm. In the study, the patients' function of the diaphragm muscle is measured before and after surgery. The aim is to elucidate the extent to which different types of surgery (lung cancer, oesophageal cancer, heart transplantation and insertion of an artificial heart pump (LVAD) affect the function of the diaphragm.

METHOD, DESIGN & RESEARCH METHODS

DESIGN

STUDY 1:

Methodology study. Different ultrasound methods for assessing diaphragm function are compared with x-ray fluoroscopy.

STUDY 2:

Observational study. Patients who are to have surgery in the chest cavity have their lungs scanned with ultrasound before and after surgery.

SETTING

All studies are carried out at Aarhus University Hospital as a collaboration between Heart Diseases, Lung Diseases, Cardiopulmonary and Vascular Surgery, Anesthesia and Surgery and Intensive Care.

PARTICIPANTS

STUDY 1:

Participants are divided into 3 categories: 1/3 healthy, 1/3 lung medicine patients and 1/3 patients who have had a heart transplant or LVAD implanted. Everyone over 50 years.

STUDY 2:

Patients who must undergo lung surgery or surgery for esophageal cancer with interventions in the chest cavity at Heart, Lung and Vascular Surgery, as well as patients with severe heart failure who must undergo heart transplantation or LVAD implantation.

INCLUSION AND EXCLUSION CRITERIA

STUDY 1:

Inclusion criteria:

- Completed informed consent
- 1 of the following:
    - Healthy control person over 50 years of age
    - Lung disease: Smoker's lungs or stone lungs

- Disease of the heart that has led to a heart transplant or implantation of an LVAD.

Exclusion criteria:

- Known dysfunction of the diaphragm
- Chronic nerve or muscle disease
- Fluid in the lung cavity. Discovered during the investigation
- Air in the lung cavity. Discovered during the investigation
- Only group healthy (1/3): Significant disease affecting heart or lung function (high blood pressure and mild heart valve disease without symptoms is ok), including diagnosed smoker's lungs.
- Only healthy group (1/3) and lung disease group:

STUDY 2:

Inclusion criteria:

- Completed informed consent.
- One of the following:
  - Planned LVAD implantation / Heart transplant
  - Planned surgery for lung cancer/esophageal cancer

Exclusion criteria:

- Known dysfunction of the diaphragm
- Chronic nerve or muscle disease
- Fluid in the lung cavity. Discovered during the investigation
- Air in the lung cavity. Discovered during the investigation

SURVEYS

STUDY 1:

In study 1, 1 lung function examination, 1 complete ultrasound examination and 1 x-ray examination are carried out.

STUDY 2:

In study 2, only lung function examination and ultrasound examination are carried out. These are made

Lung cancer: 1) the day before surgery, 2) 3 days after surgery and 3) 2 weeks after surgery.

Oesophageal cancer: 1) the day before surgery, 2) 3 days after surgery and 3) 10 days after surgery (after which most are discharged).

LVAD implantation: 1) the day before surgery, 2) 14 days after surgery and 3) 3 months after surgery.

Heart transplant: 1) in close relation to the write-up on the heart transplant list, 2) 14 days after the operation and 3) 3 months after the operation

PULMONARY FUNCTION TEST:

Lung function testing takes place by having the patient blow as hard as they can into a tube. Various endpoints are then measured automatically by a machine. 3 inhalations are made per study, of which the values from the best are used.

INSPIRATORY PRESSURE:

Inspiratory pressure is measured with an electronic manometer. It is a mouthpiece that you breathe into and which automatically measures pressure.

ULTRASOUND EXAMINATIONS:

The participants are examined in a standing/sitting position with the liver/spleen as a reference point on the right and left side. A movie clip is saved for later analysis.

Normal and deep breathing is carried out.

X-RAY REVIEW:

Only carried out in study 1. Film clips are recorded of the movement of the diaphragm during X-ray translucency.

RISKS AND DISADVANTAGES

STUDY 1 & 2:

Ultrasound examination, lung function examination and manometry are without risks.

STUDY 1 ONLY:

Transillumination with X-rays includes irradiation. Based on an expected radiation time of a maximum of 1 minute (closer to 30 s), the accumulated radiation dose is estimated to be 0.1-1 mSievert. This would theoretically increase the lifetime risk of developing serious cancer by <0.01%.

Patients will have to attend the hospital on a day when they would not otherwise have to attend. Participation in the experiment takes approx. 30 minutes.

No compensation or inconvenience allowance will be paid to trial participants.

ETHICAL CONSIDERATIONS

STUDY 1:

Ultrasound examinations and lung function examination are without any kind of risks or discomfort for the participants and the examinations do not contain any ethical considerations.

The participants will be X-rayed. The radiation dose is minimal and the expected, accumulated dose of 0.1-1mSievert must be compared to being exposed to approx. 3 mSv for background radiation annually. The expected radiation dose corresponds to an increased risk of serious cancer of 1 in 100,000. If it turns out that there is a good correlation between ultrasound methods and fluoroscopy, there will be no need for fluoroscopy in the future if dysfunction of the diaphragm muscle is suspected, and future patients will therefore be spared

radiation. [6] It will also be possible to reduce the radiation dose employees are exposed to. In study 1, only subjects aged ≥50 years are included in order to minimize the risk of developing cancer secondary to the experiment, as it takes many years from exposure to radiation to developing cancer. In this study, we record the total radiation dose, and the total radiation dose is closely monitored.

STUDY 2:

The ultrasound examinations are performed independently of LVAD implantation or surgery for lung/oesophageal cancer. The examinations are carried out at already planned clinic visits in order to reduce the burden on the patients.

Overall, we believe that the clinical potential of the study outweighs the risks and disadvantages that the patients are exposed to.

ECONOMIC CONSIDERATIONS

The group listed below, all employed at Aarhus University Hospital, has taken the initiative for the trial. All costs for equipment, personnel and utensils are covered by the departments involved and their respective research sections, and the experiment has not received any money from outside. None of the researchers involved have personal, financial interests in the experiment.

BIOBANK

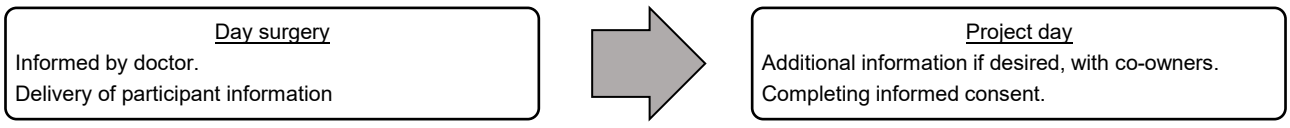
A biobank will not be established

RECRUITMENT

STUDY 1:

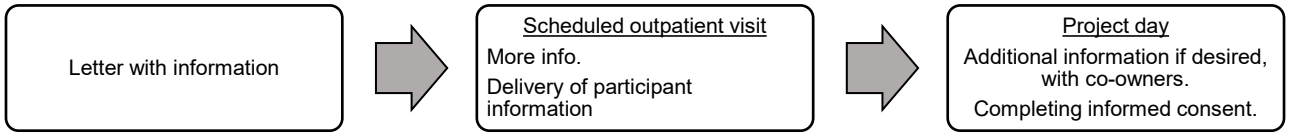
FAST GROUP:

Patients who are to be operated on in day surgery at Aarhus University Hospital. In the course of surgery (before or after, when patients are awake and capable), patients are informed about the project by a doctor associated with the trial. It is ensured that the information can be conveyed in an undisturbed single room. Participant information is provided. On the project day (a later date), if there is a desire for this, there will be the possibility of a follow-up interview with the possibility of the participation of co-chairs. The reflection time will thus be >1 day. Written consent is then secured. Patients have the option of withdrawing consent at any time without further requirements for a reason.



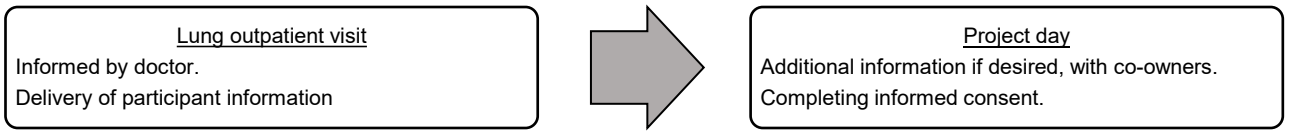
HEART TRANSPLANT RECIPIENTS/LVAD GROUP:

This patient group is checked with frequent checks after the heart transplant/LVAD. In order to ensure a stable phase, all patients who have had a heart transplant and are checked at AUH after 6 months will be invited to participate in the present project. The patients will per letter to be informed by a doctor associated with the trial about participation. The patients are invited at the next scheduled outpatient visit (as part of the transplant/LVAD check-up) to hear more about the project. It is ensured that the information can be conveyed in an undisturbed single room, where oral information is given as well as written information is provided. On the project day (a later date), if there is a desire for this, there will be the possibility of a follow-up interview with the possibility of the participation of bystanders. The reflection time will thus be >1 day. Written consent is then secured. Patients have the option of withdrawing consent at any time without further requirements for a reason.



PULMONARY GROUP:

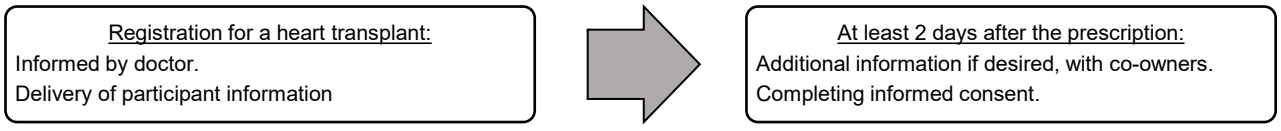
Patients who visit the COPD clinic or the Center for Rare Lung Diseases are informed about the project by a doctor associated with the trial. It is ensured that the information can be conveyed in an undisturbed single room. Participant information is provided. On the project day (a later date), if there is a desire for this, there will be the possibility of a follow-up interview with the possibility of the participation of co-chairs. The reflection time will thus be >1 day. Written consent is then secured. Patients have the option of withdrawing consent at any time without further requirements for a reason.



STUDY 2:

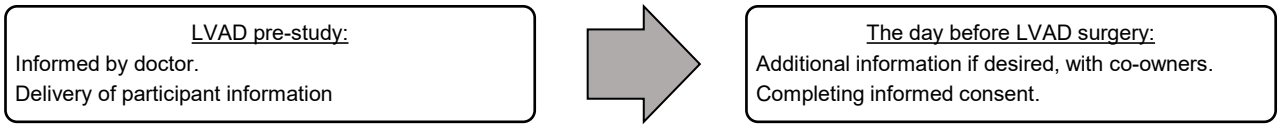
PLANNED HEART TRANSPLANTATION:

Patients who are registered on the heart transplant list, etc. imminent heart transplant, will be informed about the project at the preliminary examination for this treatment or regular check-up prior to heart transplantation, which takes place in a private room. Both oral and written information is given here. After being put on the waiting list, patients will be informed and written consent will then be secured. Relatively close to this date, there will be the possibility of a follow-up interview with the possibility of the participation of co-chairs. The reflection time will thus be >1 day.



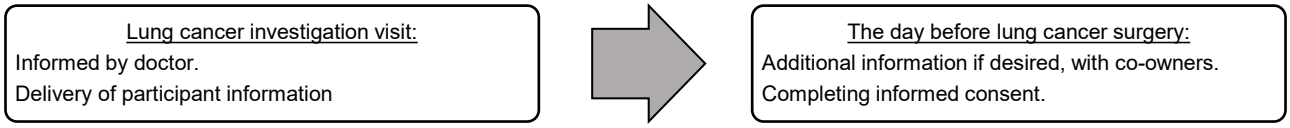
PLANNED LVAD:

Patients who have imminent treatment with an LVAD will be informed about the project during the preliminary examination for this treatment, which takes place in a private room. Both oral and written information is given here. The day before the operation, when the patients are all already admitted to optimize their cardiac condition, written consent is secured. On this day, there will be an opportunity for a follow-up interview with the possibility of the participation of co-chairs. The reflection time will thus be >1 day.



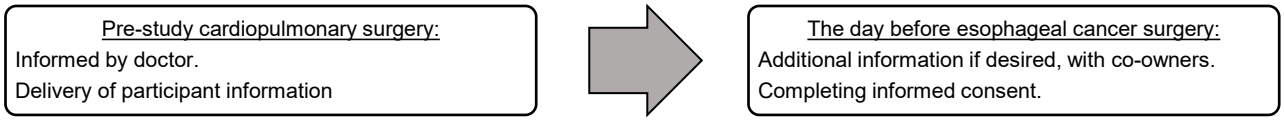
PLANNED SURGERY FOR LUNG CANCER:

The group that is to be operated on for lung cancer is informed about the project when visiting the Clinic for Lung Cancer Investigation. Conversation that takes place in a private room. Written information is provided. The day before surgery, when the patients routinely meet for the last interviews before surgery, written consent is secured. On these days, there will be the possibility of a follow-up interview with the possibility of the participation of co-chairs. The reflection time will thus be > 1 day.



PLANNED SURGERY FOR ESOPHAGEAL CANCER:

The group that is to be operated on for oesophageal cancer is informed about the project when visiting the Cardiopulmonary Surgery Clinic. Conversation that takes place in a private room. Written information is provided. The day before surgery, when the patients routinely meet for the last interviews before surgery, written consent is secured. On these days, there will be the possibility of a follow-up interview with the possibility of the participation of co-chairs. The reflection time will thus be > 1 day.



PUBLICATION

Results, positive, negative or inconclusive, are sought to be published in an international journal. Likewise, results will be disseminated at scientific congresses.