Protocol Unilateral vs. bilateral lung volume reduction surgery

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Unilateral versus bilateral lung volume reduction surgery for patients with severe COPD

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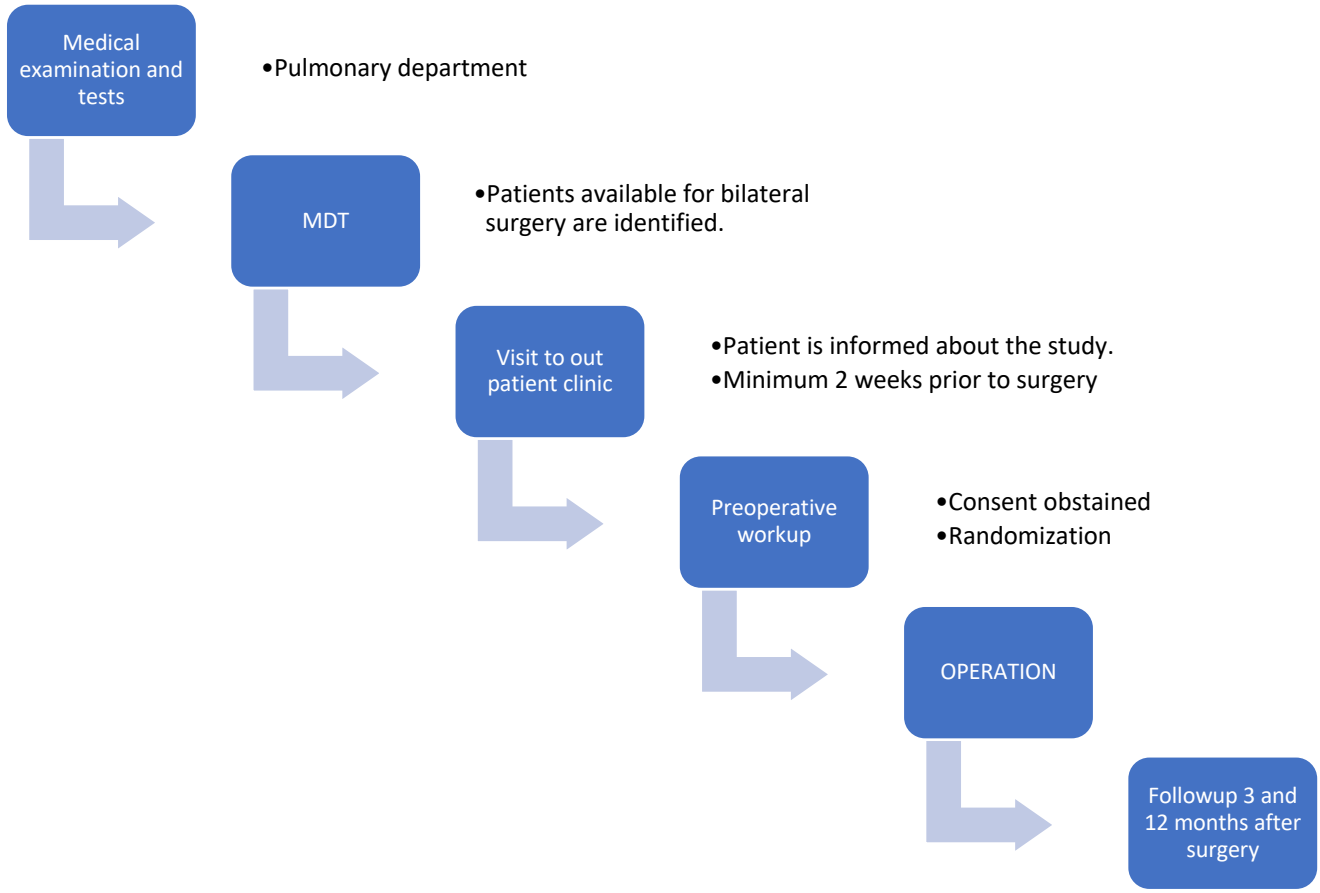
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Trial diagram



Introduction

Lung volume reduction surgery (LVRS) has proved effective in the treatment of severe emphysema in COPD. Studies have shown improving exercise capacity, lung function, quality of life and survival for 5 years[1,2] postoperatively. Efforts are continuously made to improve the treatment further, to relieve the patients' symptoms. Most LVRS in the last 20 years have been performed bilaterally in order to achieve the greatest effect possible. So far, we have performed the surgery unilaterally at our centre.

To clarify whether a uni- or bilateral approach should be preferred, a review of 746 papers was performed in the department. Conclusively seven studies investigate this topic, with a total number of patients in these 7 studies of 1461 with a range of 41 to 682. These patients have been grouped in unilateral or bilateral procedures. Details of included studies are shown in table 1 including changes in FEV1.

Article	Country	Sample size	**Δ**FEV1 (U)	**Δ**FEV1 (B)
McKenna et al [3] 1996	USA	166	210 mL	330 mL
Argenziano et al [4] 1997	USA	96	151 mL	294 mL
Kotloff et al [5]1998	USA	151	160 mL	250 mL
Serna et al [6]1999	USA	260	77 mL	274 mL
Yoshinaga et al [7] 1999	Japan	41	310 mL	400 mL
Lowdermilk et al [8] 2000	USA	682	130 mL	220 mL
Oey et al [9] 2002	UK	65	230 mL	227 mL

Table 1. Study characteristics. (U) = Unilateral. (B) = Bilateral.

This existing literature concludes, that bilateral surgery ads a greater increase in forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) than unilateral surgery, contributing to relieving dyspnoea. In the largest study by Lowdermilk et al[8] including 682 patients, the increase in FEV1 was 23% in the unilateral group and 33% in the bilateral group, compared to preoperative values.
When evaluating the improvement in physical activity, six-minute walking test (6MWT) only improved significantly in two studies [5,8], it is not included as an outcome in most studies.
A bridged LVRS also shows significant results, reoperating emphysema patients undergoing LVRS, adding to the benefits from the first LVRS [10]. Some studies show decrease in FEV1 12 months after surgery for the bilateral group[9], which is in favour of a preferring a staged unilateral approach.
The LVRS as a treatment modality also proves to be a bridging procedure to lung transplants.[11]

However, prolonging time of surgery and number of resections, performing bilateral surgery, in some studies entails increased postoperative morbidity with increased number of days in ICU[9] and more frequent need for tracheostomy[4]. Risk of prolonged air leak caused by damage to the fragile

lung tissue is a recurrent issue in LVRS. Performing surgery on both lungs might increase the risk of air leak after surgery. Risk of prolonged air leak >7 days for bilateral surgery is reported at 45%[2], widely comparable to our unpublished results for unilateral surgery with prolonged air leak > 5 days at 40%. Length of stay is consistently increased for bilateral surgery, increasing medical costs and possibly strenuous for the patient.
Conclusively the review reveals increased mortality in the bilateral surgery group in only one study[5]. The remaining studies showed not difference in mortality.
The included number of patients vary greatly in the studies and it is noted that the surgical technique varies greatly from video assisted thoracoscopic surgery (VATS) to thoracotomy or sternotomy. Furthermore, all the studies were published more than 20 years ago, before ERAS (enhanced recovery after surgery) principles were widely introduced in the cardiothoracic field. Stapler technology has similarly evolved during this period of time.
Lastly, none of the studies afore mentioned include randomization of the patients, which introduced a possible significant bias related to the preference of the individual surgeon.

Conclusively, the scope of this study is, with a randomized controlled study comparing unilateral and bilateral surgery, to compare change in lung function and physical activity, while closely monitoring mortality and morbidity in the two groups. Applying a modern ERAS and VATS approach, should unilateral or bilateral LVRS be preferred?

Objectives

1. Primary objective

The study purpose is to determine if LVRS should be performed unilaterally or bilaterally, with focus on functional outcomes, morbidity, and mortality.
Parameters measured for the two groups are:

- Lung function (FEV1) after 3 and 12 months
- In hospital 30-day mortality

2. Secondary objectives

- Lung function: FVC, DLCO, RV, RV/TLC
- CAT-score
- MRC-score
- Weight change
- 6-minute walking test
- Saint George Respiratory Questionaire
- Length of stay
- Prolonged air leak after surgery
- Rate of reoperation
- Complication rate – pneumonia, empyema, kidney failure, reintubation rate etc.

- Arterial blood gas including pO_2 and pCO_2
- Sens Motion (wristband measuring physical activity out of hospital)

Patients and materials

1. Study design

The trial is a single centre, open label, parallel group, pragmatic randomised, controlled trial with a 1:1 allocation.

All demographics and perioperative clinical variables are retrieved by an electronic healthcare software (Epic, Madison, Wisconsin).

2. Study subjects

a. Time: Start fall 2023
b. Place: Cardiothoracic Department RT 3151 and 3152, Rigshospitalet, Copenhagen.
c. Population: Patients eligible for bilateral LVRS
d. Size:

The following power calculation has been thoroughly discussed with a statistician from the Department of Biostatistics at the University of Copenhagen and approved by our collaborator Medtronic.

The research group has selected FEV1 as the primary outcome in this study. Bilateral surgery is not currently performed at our department, consequently we cannot, with our own data, provide an estimate of the difference in FEV1 between the two groups. An RCT like this has never been conducted, however retrospective observational data comparing unilateral to bilateral surgery exists. Three studies (Lowdemilk, Serna, McKenna) used a VATS approach similar to the one applied in our department, with 100% VATS procedures:

Article	**Country**	**Sample size**	**ΔFEV1 (U)**	**ΔFEV1 (B)**	**ΔFEV1**
McKenna et al [1] 1996	USA	166	210 mL	330 mL	120 mL
Argenziano et al [2] 1997	USA	96	151 mL	294 mL	141 mL
Kotloff et al [3]1998	USA	151	160 mL	250 mL	90 mL
Serna et al [4]1999	USA	260	77 mL	274 mL	197 mL
Yoshinaga et al [5] 1999	Japan	41	310 mL	400 mL	90 mL
Lowdermilk et al [6] 2000	USA	682	130 mL	220 mL	90 mL
Oey et al [7] 2002	UK	65	230 mL	227 mL	-3 mL

(U) = Unilateral. (B) = Bilateral.

Power calculation is based on a mean difference in **Δ**FEV1 between the bilateral and the unilateral group for the three studies with VATS approach at one year follow-up. For the Serna study only 2

years follow up data is available. Only the studies with 100% VATS surgeries were included. After consultation with a statistician we used a weighed mean to account for the difference in sample size between the three studies and abandoned the idea of basing the calculation on our own previous results with unilateral surgery. Based on these studies, the assumption is, that the bilateral group can achieve double reduction in **Δ**FEV1 after surgery. As this these are results of previous studies applying a surgical approach similar to ours we expect to find similar results with double reduction in **Δ**FEV1.
Studies have shown that the Minimally Clinical Important Difference (MCID) for patients with severe COPD is approximately 100ml [8]. So, we deem this estimated difference between the two groups sufficient.
Aiming for 80% power, significance level of 5 %, effect size 0.7 and drop-out 75 patients are required in each group, to show significant difference in ΔFEV1 between the two groups, based on the above-mentioned assumptions.

3 VATS studies data: Sample size 1108, 704 available for follow-up, 100% VATS

Lowdermilk, n = 682	ΔFEV1 = 0.09L Mean SD = 305L
Serna, n = 260	ΔFEV1 = 0.197L Mean SD = 0.266L
McKenna, n = 166	ΔFEV1 = 0.120L Mean SD = 0.04L
Weighted mean ΔFEV1, n = 1108	ΔFEV1 = 0.120L Mean SD = 0.256L

Two-sample t test power calculation

n = 72.41524
delta = 120
sd = 256
sig.level = 0.05
power = 0.8
alternative = two.sided

NOTE: n is number in *each* group

Conclusively, we expect to include 73 patients in each group for this study.

3. Involved personnel

Personnel	Assignment
Alberte Lund	Protocol design, primary investigator, data collection and analyses, device management, report conclusions, etc.
Kristine Jensen	Patient information and consent, protocol design, data collection, case investigation, etc.
Michael Perch, Kristine Jensen, Kåre Hornbech, Henrik Jessen Hansen, Anna Kalhauge, Jann Mortensen	Protocol design, project supervisors, consultants.
Rene Horsleben Petersen	Protocol design, project supervisor, primary consultant.

4. Selection of data

Inclusion criteria	• Usual inclusion criteria in LVRS (table 1) • Suitable target areas in both lungs • Age ≥ 18 years. • Speaks and understands Danish or English • Informed consent obtained
Exclusion criteria	• Dependent on wheelchair • Living in nursery home • Dependent on walker device • Psychiatric disorder (anxiety, depression, schizophrenia) • Simultaneous lung cancer surgery • Massive adhesions during surgery assessed by the surgeon indicating problems postoperatively • Increased risk of post-operative bleeding assessed perioperatively by the surgeon. • Perioperative decision on not doing operation on the other side (medical, surgical or anaesthesiologic problems that favours a fast termination of the surgery, decided by the team in OR). • Previous cardiothoracic surgery

	• Increased bleeding risk (e.g., preoperative INR >2, overdue discontinuation of anticoagulants according to guidelines by the Danish Society for Thrombosis and Haemostasis, known coagulopathy).

5. Allocation into groups

Allocation sequence is generated in RStudio by a biostatistician. This allocation sequence will be uploaded to REDCap for all investigators to be able to perform randomisation. Patients will be included by investigators, research nurses or surgical staff given adequate training in informed consent. Investigators, research nurses or surgical staff will access the randomization the day before surgery.
Blinding is not possible, and the study is therefore conducted as open label.
Furthermore, statistical analyses will follow a pre-specified statistical analysis plan (SAP), where comparison of primary outcome and secondary outcomes will be conducted after treatment groups have been blinded to assessors. The manuscript will be formulated based on the initial blinded analyses, thereby ensuring blinding of trialists during data analysis and manuscript drafting. Hereafter data will be unblinded and the manuscript will be finalised based on the conclusions drawn while data were still blinded.

6. Completing and interrupting the trial

We include an interim analysis half way, stopping the trial if we find significantly increased mortality in one group.
If the patient is allocated to the unilateral group, contralateral surgery can be considered after one year follow-up is completed.

7. Surgical treatment and intervention

Both unilateral and bilateral LVRS are done with a standardized 3 port VATS access. Lower ligament is freed, no graspers on the parenchyma and stapling of the selected areas with a Signia™ powered stapler with Tri-Staple™ technology (Medtronic). The reloads will not be buttressed and it will be vascular or parenchymal reloads. Two drains will be placed on the operative side and the same pain management will be applied including perioperative blocs and a pain catheter.
The unilateral procedures will be performed with the patient in a side position.
In the bilateral procedures the patient will be positioned on the back and the side to be operated on lifted by rotating the table. The surgeon is free to decide which side to deal with first.
Postoperatively the drains will be removed when there is no sign of air leakage on the digital chest drain system. Chest x-ray will be performed to secure a fully inflated lung before discharge.

8. Postoperative physical activity

Day 0: Surgery and overnight stay in recovery room.
Day 1: Patients are moved to regular surgical ward and physical therapy is initiated.
Day 1 - discharge: The patient is encouraged to physical activity after discharge within the limits of dyspnoea level and pain. Advised against heavy lifting for the first two weeks.

9. Data collection

All data will be treated confidentially and anonymized during data processing. Data will be stored in Research Electronic Data Capture (REDCap™). All data will be stored in accordance with the Danish Data Protection Agency's rules.

Preoperative clinical variables

- Medical history including lung disease, smoking history, alcohol intake etc.
- Demographic (eg. Age, gender)
- Standard questionnaire CAT = COPD assessment test, MRC-score (Medical Research Council dyspnoea score)
- Lung function tests; DLCO = Diffusion capacity of the lung for carbon monoxide; FEV1 = Forced expiratory volume in 1 second; RV = Residual volume; RV/TLC = RV-to-TLC ratio (hyperinflation); TLC = Total lung capacity.
- Blood gas analyses.
- Saint George Respiratory Questionnaire
- 6-minute walking distance including changes in heart rate and saturation.
- Sens Motion measurement of physical activity
- Echocardiographic findings: Left ventricle ejection fraction, valve diseases, gradient over valves, pulmonary pressures.
- CT-scanning (HRCT, both in- and expiratory scans): Description of emphysema and planning of target areas for surgery.
    - Automatic measurements of emphysema on lobe level.
    - Which kind of emphysema? Centrilobular, advanced conflating centrilobular emphysema, paraseptal or panlobular? Are there any bullae? Is it homogeneous or inhomogeneous? Where is the emphysema mostly located?
    - Complete/incomplete fissures between the lobes
    - Any infiltrates, atelectasis or nodules in the parenchyma?
    - The bronchial tree, wall thickness, mucus in the lumen?
    - Signs of airway collapse? Tracheobronchial malasia? Air-trapping in the parenchyma?
    - Signs of pulmonary hypertension?
    - Is the diaphragm flattened as a sign of hyperinflation?

    - Bone structure and possible signs of fractures.
- Ventilation/perfusion scintigraphy: Distribution of ventilation, perfusion and volume on lobe level.
- MDT conference decision of target areas for surgery

Operative clinical variables

- Number of resections and cartilages used
- Surgery duration
- Complications including bleeding, infection, air leak and reoperation
- Clavien Dindo classification
- Need of supplementary chest drain
- Admittance to ICU
- Length of stay
- Days with chest drain
- Prolonged air leak
- 30 days mortality rate
- Overall mortality

Clinical variables at follow up

- Lung function
- 6-minute walking test
- Saint George Respiratory Questionnaire
- Sens Motion measurement of physical activity
- CAT and MRC score
- Blood gas analyses

Statistical analysis

The continuous variables are presented as the mean (standard deviation) or median (interquartile), in accordance with the result of a normality test. The categorical variables are expressed as the number and percentage. We compare continuous variables by t-test or U-test and categorical variables by Fisher's or Chi-squared test.
If there is missing data, multiple imputation will be used. Outcomes will be expressed using odds ratios (OR) with 95% confidence intervals (CI). C-statistic will be used to evaluate the discrimination among models.
The statistical analyses are conducted using R statistical software (version 4.0, R Foundation for Statistical Computing).

Risks and benefits

Standard treatment at our department is currently a unilateral surgery approach. We expect that the benefit of bilateral surgery is the possibility of increasing lung function and physical activity for the patient even further than with unilateral surgery, reinforcing the effect of the treatment. Patients undergoing LVRS have a reduced mortality rate compared to medically treated patients, but whether the mortality is further reduced when performing bilateral surgery is unknown.

However, when applying a more comprehensive surgical procedure with increased operating time, our worry is that the rate of postoperative wound infections, pneumonia and air leak from the lung tissue will increase. Existing literature has not shown increased mortality rate or rate of complications in the bilateral group.

But due to these reasons, we will conduct an interim analysis when half of the patient cohort has been included and evaluate the rate of these complications in the two groups.

There are no benefits associated with participation in the study for each individual patient. However, conduction of this study will contribute to knowledge about the ideal treatment for this patient group and the expectation is, that this is the basis for further improvement of the treatment in the future.

If the patient decides not to participate in the study, he/she will receive unilateral surgery, which is the standard treatment at our department.

Ethical considerations

Existing literature on this topic is fault and conducted many years ago. With a bilateral approach, we expect the patients to gain a greater advance in lung function than the unilateral group, however, with a more extensive procedure the worry is that the rate of complications increases. Notably, other centres perform bilateral surgery without increased rate of morbidity and mortality, but an RCT has to our knowledge never been performed. The participants will be thoroughly informed of this existing knowledge within the field, including possible risks and benefits. Furthermore, we will inform the patients of the possible increased positive effect on lung function with bilateral surgery, but underline that these results are not guaranteed.
The trial will comply with the Declaration of Helsinki, Danish law and European law on the processing of personal data. All who contributed to this study are employed at Rigshospitalet, Copenhagen University Hospital. The present study requires approval by the Science Ethics Committee before starting up.
No compensation will be given to participants.

Information and consent

After agreement of bilateral suitable surgical targets on MDT, the patient will visit the outpatient clinic for a consultation with the surgeon. At this occasion the study will be presented to the patient by the treating surgeon. The patient will be provided with written and oral participant

information about this project. The information includes the introduction of the present study, purpose and structure, benefits and risk. The patient will be informed about his/her right to bring an assessor to the interview. (English or Danish).
The interview will be conducted by the investigators, or a person with delegated responsibility for this study, and will take place in a quiet environment suited for this purpose. Patients will be informed that participation is voluntary, and data will be collected by people who work for this project and treated confidentially. All data will be treated according to the General Data Protection Regulation and we will comply with the Danish law on data protection. Patients will be informed according to the Scientific Ethics Committee about their right to leave the study at any time without affecting their further treatment at the department. The participant will receive a flyer about the patient's rights as a participant in a clinical study and will be encouraged to read it thoroughly.
Patients will also be told what treatment they will receive if they choose to discontinue and that they at any point are allowed to evoke their consent to participate.
They will also be informed that they may be excluded from the study at the discretion of an investigator or surgeon.
The patient will be offered reflection time before informed consent is signed (one month minimum). When the patient arrives at the department for preoperative work up 1 day before surgery, informed consent will be secured and randomization can be performed. Copy of the information and signed consent statement will be provided.
It is the responsibility of the study researchers that all patients receive oral and written information, so that the patient is fully aware of all aspects of study participation and allowed to ask questions.
The trial will be registered prior to start to the international project database clinicaltrials.gov.

Budget

This project is an investigator-initiated project outgoing from the responsible investigators AL and RP. An agreement of collaboration has been reached with Medtronic, who have agreed to support this project with 2.100.000 Danish kroner. This grant covers tuition fee, salary payments and equipment. The grant is addressed to RP, the primary investigator of this project.
All data is owned by the research group, and the medical company in question has no ownership of the data or influence on publishing decisions.
HJH and RP have previously received "speaker fees" from Medtronic.

Study conduct and responsibility

The project plan and process are surveyed by PhD-student Alberte Lund. Overall responsibility for the project belongs to Professor René Horsleben Petersen.
The study will be conducted in compliance with this protocol.
No substantial deviation from the protocol will be implemented without prior review and approval from the supervisors and the Ethical committee.

No researchers involved have any conflict of interest.

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Forms/appendix

Tabel 1: Inclusion criteria for LVRS

Moderate to severe COPD with MRC score > 2
< 75 years old
17 < BMI > 30
FEV1 > 20% and < 45% of predicted
RV > 200% of predicted as a sign of relevant hyperinflation
DLCO > 20% of predicted
The patient should be in ideal medical treatment and have completed rehabilitation
A high-resolution CT < 3 months old should follow the referral to MDT
Absence of nodules suspicious of malignancy on CT scan
Absence of significant comorbidity including severe cardiovascular disease
LVEF normal
Absence of pulmonary hypertension, TI-gradient < 40 mmHg
Absence of chronic or frequent lung infections
Smoking abstinence six months prior to surgery
Assessed as sufficiently physically fit to undergo surgery and rehabilitation

COPD: Chronic obstructive pulmonary disease, *MRC: Medical Research Council dyspnea score*, *BMI: Body Mass Index*, *FEV1: Forced expiratory volume in 1 second*, *RV: Residual volume*, *DLCO: Diffusion capacity of the lung for carbon monoxide*, *MDT: Multidisciplinary Team*, *LVEF: Left ventricle ejection fraction*, *TI: Tricuspid regurgitation gradient*