Lung Volume Reduction Surgery in Patients with Homogeneous Emphysema

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KEYWORDS

• LVRS • Homogeneous emphysema • Surgery for emphysema

KEY POINTS

- Lung volume reduction surgery (LVRS) offers clinical and functional benefit in hyperinflated patients with homogeneous-type emphysema. It is important to exclude patients with low diffusing capacity of the lungs for carbon monoxide or pulmonary hypertension.
- LVRS in patients with homogeneous emphysema requires more experience with LVRS than in patients with heterogenous disease with obvious target zones for resection.
- The functional benefit of LVRS in homogeneous emphysema is clinically relevant but smaller than in heterogenous emphysema.

INTRODUCTION

Lung volume reduction surgery (LVRS) improves pulmonary function, exercise capacity, quality of life, and even survival in highly selected patients with advanced emphysema.[1–4] Almost all of these studies, including the largest randomized trial comparing LVRS with medical therapy, the National Emphysema Treatment Trial, obtain their successful results from operated patients with heterogeneous emphysema morphology. The argument, that in patients with heterogeneous emphysema only nonperfused, functionless tissue is resected, is convincing. Furthermore, this target area for resection is clearly identifiable on computed tomographic (CT) scan and perfusion scintigraphy. Especially in the case of upper lobe predominant emphysema, resection and remodeling of the lung are easy and straightforward.

The idea, to resect tissue with remaining gas-exchange function in patients with poor lung function owing to homogeneously situated emphysema, is difficult to justify. Nevertheless, with respect to certain selection criteria, promising results about LVRS in patients with homogeneous emphysema are reported. The first larger study on this subgroup demonstrated significant benefit after surgery, although results are slightly inferior compared with LVRS in heterogeneous emphysema.[5] Despite this positive report, most other centers continued to exclude patients with homogeneous emphysema from their program. This negative attitude was further supported by a publication from the National Emphysema Treatment Trial (NETT), which described a very high mortality after LVRS in patients with a homogeneous morphology. However, these patients with homogeneous diffuse emphysema had a heavily destroyed (vanished) lung with very low forced expiratory values in 1 second (FEV1 <20% predicted) and a diffusion capacity less than 20% predicted. This report was misinterpreted by many physicians, which concluded that all patients experience a high mortality after LVRS.[6,7] However, it was shown that patients from the NETT with homogeneous emphysema in combination with

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FEV1 greater than 20% predicted and diffusion capacity greater than 20% predicted had a significant improvement of certain pulmonary function parameters as well.[8]

Nevertheless, lung volume reduction (LVR) in homogenous emphysema type has been avoided by most groups for a long time. With the emergence of bronchoscopic LVR techniques, new attempts to improve dyspnea also in patients with homogeneous morphology were undertaken, and the results were reported.

Therefore, this review discusses the rationale of LVR, the definition of homogeneous emphysema, the selection process, management, and outcome after LVRS as well as the bronchoscopic treatment. Outcomes are summarized, leading to a recommendation, and an attempt to stimulate other groups to offer LVRS in well-selected patients. Clinical scenarios will be used to illustrate the daily practice in the decision process and management of patients.

RATIONALE BEHIND LUNG VOLUME REDUCTION

Emphysema is a loss of pulmonary elasticity by destruction of alveolar walls and capillaries and by enlarged airways distal to the terminal bronchioles. The consequence of the latter is lung hyperinflation, which interferes with respiratory mechanics, among other physiologic changes. Primarily, the diaphragm is pressed down, and the suspension of the muscle fibers becomes almost perpendicular, which inhibits full function. Volume reduction intends to re-create the normal lung volume (total lung capacity [TLC]) and reshapes the lung to its original form.[9] LVRS allows an individual remodeling of the lungs, by selecting the target areas for resection based on emphysema morphology on CT and perfusion scans. With the gained intrathoracic space, the diaphragm might return to its original position, and even more importantly, to its domelike shape. The residual volume (RV) is reduced, and the lung's elastic recoil is improved. The diaphragm regains more strength and work capacity, which improves breath work and decreases dyspnea.[10] In addition, airflow improves by reopening the collapsed small airways because of reinstalled pull-out forces. The same effect leads to opening of capillaries, which reduces the ventilation/perfusion mismatch and improves diffusion capacity, and hence, might decrease pulmonary hypertension.[11]

Reducing hyperinflation in emphysema treatment seems to be the most important step. In 1 randomized controlled trial, although shown with the meanwhile abandoned endobronchial coils compared with medical treatment, improvements in lung function, quality of life, and 6-minute walking distance were significantly better, when performed in patients with RV greater than 225% than in patients with RV between 175% and 225%.[12] Most concerns about LVR(S) in homogeneous emphysema might arise from the fear of resecting (or bypassing, respectively) functional tissue, which contributes to gas exchange. Obvious target areas of complete destruction for resection are lacking. Therefore, in an adequate volume resection, it is important to balance the positive effect of improved respiratory mechanics with the disadvantage of resecting functional tissue of gas exchange. LVR with endobronchial valves in homogeneous emphysema showed some positive effect, although the downside of this minimally invasive LVR technique is that consequently a whole lobe is eliminated.[13] In contrast, surgery offers a more tailored approach, as the "homogeneous" emphysema type allows the identification often of some "intermediate" parts of destruction, when carefully assessed with appropriate imaging methods like CT in combination with densitometry.[14] In addition, in purely homogeneous emphysema, the surgeon might approach both apical parts of the upper lobes, which are usually physiologically less perfused and therefore less effective for gas exchange.

DEFINITION OF HOMOGENEOUS EMPHYSEMA

One of the major challenges of homogeneous emphysema is its definition. There are different proposals to define homogeneity in emphysema morphology. All of them were basically developed from either a surgical or an interventional point of view and are difficult to compare.

One of the first definitions of emphysema morphology, including homogeneous emphysema, was CT based and has been introduced more than 20 years ago with the intention to get a simple and practical guide for patient selection for LVRS and for comparison of results.[14] The markedly heterogeneous emphysema, including upper-lobe or lower-lobe predominance with and without the apical segments of the lower lobes, was differentiated from intermediately heterogeneous and homogeneous emphysema. Intermediately heterogeneous emphysema includes an anatomically indistinct subgroup that might look like homogeneous on the first view, but when studied carefully, several target areas of smaller size for LVRS can be identified (**Fig. 1**). Summarized with an adagium: "The longer you look to homogeneous emphysema, the more heterogeneous it becomes." The purely homogeneous emphysema

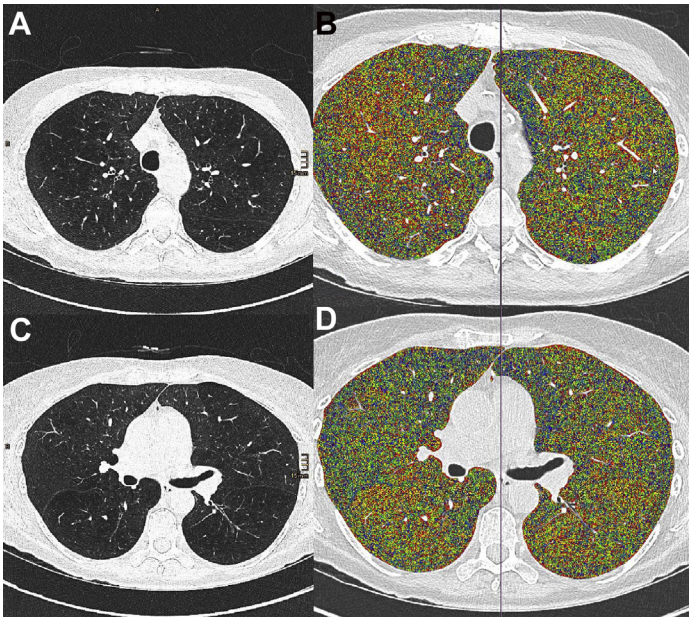

Fig. 1. Bilateral intermediate heterogeneous emphysema. Several potential target zones become obvious by densitometry. Lateral upper lobe on the right side: (*A*) axial CT scan, (*B*) densitometry, segment 6 on the right side: (*C*) axial CT scan, (*D*) densitometry.

itself, as long as CT, perfusion scintigraphy, and (if available) densitometric measurements are meticulously analyzed, offers no target area of distinct destruction (**Fig. 2**). The identification and classification of emphysema morphology are based on eye-balling slice by slice the CT scan. However, certain software applications allow density measurements that can be transferred in colored CT pictures, which might be useful for identifying different morphologies, such as pure homogeneity.[15] These so-called color-coded CT renderings offer additional aspects for the surgeon in planning target zones for LVRS.[16]

The investigators of the IMPACT trial defined homogeneous emphysema as a less than 15% difference in emphysema destruction score between target and ipsilateral lobes in a study using bronchoscopic LVR with endobronchial valves.[13] They used CT quantitative analysis software to measure volumes and destruction. These measurements regarding the density differences were performed using −910 HU as margin. In addition, less than 20% perfusion difference between both lung sides was required. For the IMPACT study, both criteria had to be met.

In the literature, some investigators use the term "diffuse" or homogeneous for any type of advanced emphysema, but are actually reporting LVRS in patients with heterogeneous emphysema; this insight might be clearer if one carefully reads the methods section of some reports.[10,17] The term diffuse emphysema should be avoided in the future.

PATIENT SELECTION

Symptomatic patients with advanced emphysema and the typical clinical signs of hyperinflation are potential candidates for LVRS. Their barrel-like chest, tendency to pause their walks and rest their arms, and their inability to eat large meals must be further assessed with pulmonary function test and body plethysmography. Facing a patient with both clinical and body plethysmographic hyperinflation at least (RV >180%, TLC >100%, RV/TLC >58) seems in the authors' experience to be the key to success. Patients with so-called dynamic hyperinflation (not obviously seen on static measurements) might be considered for LVR(S) as well, despite the current lack of scientific support. This finding needs further investigation.[18] Comorbidities and pulmonary as well as nonpulmonary risk factors must be taken into account and balanced with the risk and potential benefit.

Emphysema morphology assessed by CT and perfusion scan is of great importance for selecting patients. This selection of patients is especially important when patients have a more homogeneous pattern. In these cases, lung tissue, which still contributes to gas exchange, will be resected, or in the case of valve placement, an entire lobe is excluded. Therefore, a low CO-perfusion capacity or pulmonary hypertension is an absolute contraindication in homogeneous emphysema.

Although there is emerging evidence about successful LVRS in patients with mild to moderate pulmonary hypertension,[11] so far this combination

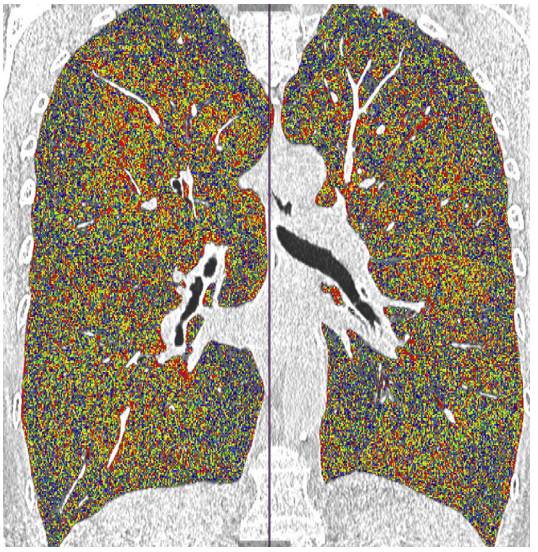

Fig. 2. Purely homogeneous emphysema without obvious target zones for LVRS (coronal densitometry).

probably needs to be restricted to patients with markedly heterogeneous emphysema. In these cases, only the nonperfused lung parts are resected, so that the elastic recoil of the parts contributing to diffusion is improved. The same shall be true for patients with very low diffusion capacity (<20%) or global respiratory insufficiency.[19] A transthoracic screening echocardiography can be advised, followed by further investigation by right-sided heart catheter when systolic pulmonary artery pressure (sPAP) is greater than 35 mm Hg.

A very low diffusion capacity was a significant risk factor for postsurgical 30-day mortality during the NETT trial, but importantly, in combination with homogeneous emphysema or FEV1 less than 20%.[6] Emphysema morphology was visually assessed by radiologists, dividing the lung into 3 zones. It remains unclear how many of the included 46 homogeneous emphysema types could have been counted as intermediately heterogeneous. They might still have profited by offering a tailored surgical approach, not just by the usual during the NETT performed upper-lobe-targeted "over-the-top," hockey-stick resection.

Other pulmonary risk factors, such as large airway disease or scarring of the parenchyma detected on CT, are absolute contraindications in these patients.

However, LVRS can be offered to every emphysema type, by careful patient selection. The decision is made based on a synopsis of patient factors, physiologic parameters, and emphysema morphology. **Table 1** lists inclusion criteria for patients with purely homogeneous emphysema.

RESULTS OF SURGICAL LUNG VOLUME REDUCTION IN HOMOGENEOUS EMPHYSEMA

Weder and colleagues[5] published the largest series on homogeneous emphysema in a single-center series of 250 consecutively operated patients, including 138 homogeneous emphysema types. From these, 82 had an intermediate morphology (see above). Results for patients with either intermediate or purely homogeneous emphysema were similar, and therefore, both were summarized as homogeneous. For the latter, 3 months after LVRS, FEV1% predicted improvement by 35% from 28 to 38, 6-minute walking distance improved from 245 to 324 m, and dyspnea score decreased from 3.5 to 1.8 ($P<.05$ for all outcomes). Median time until most values had returned to baseline was 36 months in both the heterogeneous and the homogeneous group. Thirty-day mortality was 2.4% for both groups, as well as 1-year survival was similar. Median survival after 5 years without lung transplantation was 64% in the homogeneous and 73% in the heterogeneous group. Regarding lung function in the heterogeneous group, FEV1% predicted increased from 29 to 44 (52% improvement), 6-minute walking distance from 243 to 382 m, and dyspnea score from 3.5 to 1.3.

Marchetti and colleagues[8] looked at the NETT data, comparing 85 patients with homogeneous emphysema and endobronchial coil treatment from 3 randomized trials from 2012, 2013, and 2014 with 51 patients from the NETT trial from 2003. In addition, 43 patients with medical treatment from the NETT were compared as well. Patients were matched regarding spirometry, age, and gender. LVRS patients were significantly older (64 vs 61 years, $P<.01$), had a worse baseline diffusion capacity (26.1 vs 33.4%, $P<.01$), but had a better baseline 6-minute walking distance (371 vs 311 m, $P<.01$).

The same definition for homogeneous emphysema from the NETT, as mentioned above, was applied.

At 6 months, no significant differences for FEV1 were detected between groups. There was a significant decrease in RV ($P = .002$) and TLC ($P<.001$) in both the coils and the LVRS group compared with medical therapy. The magnitude of the decline in both values was greater in the LVRS group. At 12 months, there remained a significant decline in RV ($P = .006$) and TLC ($P<.001$) compared with baseline in both groups compared with medical therapy.

Morbidity and mortality after LVRS seem still to be an issue comparing the different LVR techniques. The 90-day mortality from the NETT trial continues to be cited,[20] although carefully selected

Table 1
Inclusion and exclusion criteria for lung volume reduction surgery in patients with purely homogeneous emphysema

Criteria	Inclusion	Exclusion
Patient	Nicotine abstention >4 mo	Daily steroid intake >20 mg
Lung function	FEV <45% RV >180% TLC >100%	FEV1 <20% and/or DLCO <20%
6-min walking distance		>600 m
Gas exchange		$Paco_2$ >6.7 Pa and Pao_2 <6.0 Pa ($Paco_2$ >50 mm Hg and Pao_2 <45 mm Hg)
Pulmonary pressure		mPAP >35 mm Hg (right heart catheter)

Abbreviation: DLCO, diffusing capacity of the lungs for carbon monoxide; mPAP, median pulmonary artery pressure.

patient cohorts have shown much lower rates. The mortality of 5.2% in 511 patients[1] went down to 4.8% in 250 patients from Ciccone and colleagues,[2] to 2.4% in 250 patients from Weder and colleagues,[4] and even to 0 in 91 patients from Ginsburg and colleagues.[3] The series of Weder even included 138 patients with homogeneous emphysema, which had the same surgical mortality.

RESULTS OF BRONCHOSCOPIC LUNG VOLUME REDUCTION IN HOMOGENEOUS EMPHYSEMA

Despite initially somehow promising results, endobronchial coils for emphysema treatment have now been abandoned.[21–23] The focus has shifted toward one-way endobronchial valves, which originally have been used in heterogeneous emphysema only. The IMPACT trial randomized 43 patients with homogeneous emphysema and without collateral ventilation treated with valves versus 50 patients with medical standard care alone.[13] For the LVR group, absolute median improvement of FEV1 at 3 months compared with baseline was 100 mL. The median 6-minute walking distance improved by 23 m. From all endobronchially treated patients, 26% developed a pneumothorax with requirement for urgent chest tube treatment, and 11.5% needed some sort of revision bronchoscopy. Although difficult to compare, most studies report rates of prolonged air leak (defined as longer than 7 days) after LVRS of about 25% to 45%.[19]

SURGICAL CONCEPTS

Patient with Purely Homogeneous Emphysema

Patients with no obvious target zones on CT scan, perfusion scintigraphy, and densitometry but relevant hyperinflation might be operated bilaterally (see Fig. 2). The authors recommend a supine position with both arms raised. The operation is always initiated as video-assisted thoracoscopic surgery (VATS). With the patient in the supine position, both sides can be approached from the anterolateral position without changing the patient's position. This approach is feasible for bilateral upper-lobe "over-the-top" resections. For lower-lobe resection, the lateral decubitus position is recommended as well as lowering the placement of the ports by 2 to 3 intercostal regions.

The operation would be prematurely terminated in case the first side would need extensive adhesiolysis with consecutive unavoidable air leak.

Patient with Side Predominance and/or Intermediate (Heterogeneous) Emphysema

Lungs with intermediate emphysema morphology often require more than 1 resection area and often involve at least 2 lobes or only the middle and lower lobes (see Fig. 1). The patient is placed in the lateral decubitus position, and the VATS approach is performed as for other (ie, anatomic) resections. When the operation is planned to be bilateral and the first side is successfully done, the patient's position is changed.

In cases of unilateral disease predominance, the LVRS is performed unilaterally (Fig. 3).

Patient after Unilateral Bronchoscopic Lung Volume Reduction with Valves

Patients are referred more often for LVRS after a first primary or secondary unsuccessful LVR procedure, including endobronchial valve placement. There is so far no evidence whether these valves should be removed or not before LVRS. The authors' experience[24] points toward an

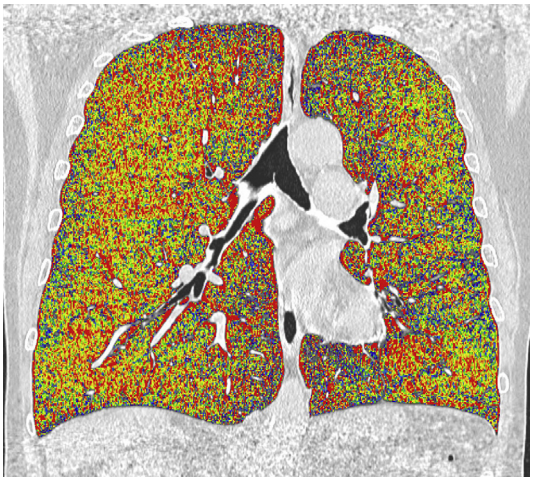

Fig. 3. Homogeneous emphysema with predominance on the right side (coronal densitometry); a unilateral procedure is suggested.

individualized approach: Valves with persistent atelectasis should not be removed and LVRS should be performed on the contralateral side. Valves without or with loss of atelectasis should be removed, as the initial target zone might be ideal for surgical resection as well (see **Fig. 3**).

SUMMARY AND RECOMMENDATIONS

Allocating patients to LVRS and selecting the adequate amount of tissue to be resected must be considered carefully in the presence of homogeneous disease. Because the main clinical effect derives from improved respiratory mechanics and because the resected tissue is still contributing to gas exchange, the presence of relevant hyperinflation is of paramount importance on 1 side. The other key element is absence of a "vanished" lung (identified by low gas exchange and/or pulmonary hypertension). These factors are the 2 key factors when considering homogeneous emphysema for LVRS.

Indication for LVRS depends on many factors, and therefore, it is impossible to give clear, straightforward recommendations that can be applied to all patients. Indication is a synopsis of clinical factors, physiologic parameters, and most importantly, the emphysema morphology assessed on CT and perfusion scan. Markedly heterogeneous emphysema includes an obvious target zone for resection. In these circumstances, by resection of only functionless, hyperinflated tissue, even borderline patients with severely impaired diffusion capacity and/or with mild to moderate pulmonary hypertension often can be accepted. In return, the exclusion criteria list is more complex and must consider the balance between reducing hyperinflation and resecting tissue, which still contributes to gas exchange.

Once the patient is suitable for LVRS, the surgeon must have a clear concept of the operation. In diffuse homogeneity, a bilateral upper-lobe "over-the-top" approach should be performed, in the authors' opinion. In cases with intermediate morphology, different imaging techniques are advisable to detect potential target zones with less function. Patients with marked side differences might profit from a unilateral approach.

CLINICS CARE POINTS

- Select patients with homogenous emphysema for lung volume reduction surgery only, when the lungs are severely hyperinflated and the diaphragm is flat.
- Diffusing capacity of the lungs for carbon monoxide must be more than 20% to 30% when lung volume reduction surgery is planned in homogenous disease.
- Remodeling of the lungs by downsizing to its predicted volume is best done at the upper lobes by resecting a hockey-stick piece.
- The lungs must be semi-inflated in order to estimate the volume you want to resect during video-assisted thoracoscopic surgery.

DISCLOSURE

W. Weder: Astra Zeneca: Advisory Board & Speaker, Covidien (Medtronic): Teaching Grant & Speaker.

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