Lung volume reduction surgery (LVRS) for chronic obstructive pulmonary disease (COPD) with underlying severe emphysema

Jackie Young, Anne Fry-Smith, Chris Hyde

Abstract

Background—Lung volume reduction surgery (LVRS) has recently re-emerged as a surgical option for the treatment of end stage chronic obstructive pulmonary disease (COPD) due to underlying severe emphysema. Advocates of LVRS claim that it represents a significant breakthrough in the management of this challenging group of patients while sceptics point to uncertainty about the effectiveness of the operation.

Methods—A systematic review was conducted of the evidence on the effects of LVRS in patients with end stage COPD secondary to severe emphysema.

Results—The most rigorous evidence on the effectiveness of LVRS came from case series. Seventy five potentially relevant studies were identified and 19 individual series met the methodological criteria for inclusion. The pattern of results was consistent across individual studies despite a significant degree of clinical heterogeneity. Significant short term benefits occurred across a range of outcomes which appeared to continue into the longer term. Physiological improvements were matched by functional and subjective improvements. Early mortality rates were low and late mortality rates compared favourably with those of the general COPD population. However, the entire research base for the intervention is subject to the limitations of study designs without parallel control groups.

Conclusions—LVRS appears to represent a promising option in the management of patients with severe end stage emphysema. However, until the results of ongoing clinical trials are available, the considerable uncertainty that exists around the effectiveness and cost effectiveness of the procedure will remain.

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Keywords: lung volume reduction surgery; chronic obstructive pulmonary disease; emphysema

Lung volume reduction surgery (LVRS) has recently emerged as a new surgical procedure for the treatment of end stage chronic obstructive pulmonary disease (COPD) due to underlying severe emphysema. COPD is an important cause of mortality and morbidity in the UK which has one of the highest rates in Europe. In 1995 the age standardised annual death rates were 50 per 100 000 in men and 24 per 100 000 in women. Mortality and morbidity rates rise steeply with age with most deaths occurring in elderly subjects, but with about 4% of premature deaths in the 55–65 age group attributable to COPD. Patients with COPD form a major part of the workload in both primary and secondary care, typically accounting for around 680 hospital admissions, 9600 inpatient days, and 14 200 general practice consultations a year in an average health district of 250 000 people. Very few treatment options are available for patients with end stage COPD and their management represents a considerable challenge for respiratory physicians. Most of the treatments currently available are directed generally at COPD and aim simply to improve the patient’s experience of health and well being rather than to cure the condition, and many have associated adverse side effects. A typical package of care for a patient who might be eligible for LVRS would include maximum medical therapy with inhaled or nebulised bronchodilators and steroids, supplemental oxygen, pulmonary rehabilitation, smoking cessation advice and support, early treatment of infection and management of acute exacerbations, management of anxiety and depression, and home care and social support.

LVRS involves the resection of the most functionless areas of lung in cases of diffuse emphysema and should be differentiated from procedures such as bullectomy which involve the excision of areas of lung because they are diseased. The procedure was first introduced by Dr Otto Brantigan at the University of Maryland in the 1950s and has recently been revisited by Dr Joel Cooper in St Louis who has achieved improved mortality and morbidity rates by using modern surgical developments to modify the original technique. A range of techniques and surgical approaches are currently available for LVRS. It can be performed as an open or closed procedure, unilaterally or bilaterally, and lung tissue can be excised using stapling, laser plication, or both. Current consensus is that the best technique is bilateral stapling via a median sternotomy with suture line reinforcement using bovine pericardium strips.

Advocates of LVRS claim that it represents a significant breakthrough in the management of this challenging group of patients. In the USA, despite increasing enthusiasm for the procedure among patients and surgeons, Medicare have refused to fund any further operations on...
Table 1  Inclusion and exclusion criteria

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<thead>
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<th>Inclusion</th>
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<tr>
<td>Population Patients with diffuse severe emphysema with significant functional limitation despite maximum medical therapy</td>
<td>Patients with large isolated emphysematous bullae in the presence of normal underlying compressed lung</td>
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<td>Intervention Lung volume reduction surgery (reduction pneumoplasty or pneumectomy) defined as multiple lung resections and/or excisions of diseased lung tissue to reduce lung volume. The following techniques and approaches were all included: open or closed procedure, unilateral or bilateral procedure, laser ablation, stapling or both</td>
<td>The excision of localised giant bullae</td>
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<tr>
<td>Outcomes Studies were included irrespective of which outcomes they addressed. Ideally, they would address clinical and physiological outcomes and should provide data on morbidity and mortality rates associated with the procedure</td>
<td>Studies which only considered short term outcomes, i.e. those with less than three months follow up</td>
</tr>
<tr>
<td>Duplication When several series emerged chronologically from the same source only the largest and most recent series was included</td>
<td>Studies which primarily examined the mechanism of effect of LVRS as opposed to the effectiveness of the intervention in improving patients’ symptoms, leading to the measurement of inappropriate and non-clinically important outcomes</td>
</tr>
<tr>
<td>Quality criteria (pertaining to potential sources of bias) Selection bias A consecutive case series: cases studied represented all those treated or were shown to have been selected in an unbiased way or were shown not to be significantly different from the total number treated</td>
<td>A selected case series: cases studied were a subgroup of those treated with no detail provided as to how they were selected or cases studied were a subgroup of those treated with no evidence to show that they were not significantly different from the total number treated</td>
</tr>
<tr>
<td>Attrition bias Losses to follow up of ≤ 25% or adequate management of losses to follow up, e.g. demonstration that they were not significantly different from total population; inclusion in the final analysis; or sensitivity analyses. NB. When losses to follow up arose due to cases in the series not reaching a given follow up point, studies were included if they treated cases on whom data were available as a cohort with results presented for that discrete cohort before and after the intervention</td>
<td>Losses to follow up &gt;25% and inadequate management of losses to follow up</td>
</tr>
<tr>
<td>Detection bias Prospective study design: study states that it was conducted prospectively or outcomes of interest were clearly measured before and after the intervention using predefined criteria</td>
<td>Retrospective study design: study states that it was conducted retrospectively or outcomes of interest were clearly not measured before and after the intervention using predefined criteria</td>
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</table>

the grounds that a robust research base on the effectiveness of the intervention does not exist. At the moment the procedure is not routinely funded by health authorities in the UK. Although considerable uncertainty exists about the overall balance of benefits and risks, there is a growing interest in and demand for the procedure from both clinicians and, increasingly, from patients themselves.

Existing reviews on the topic do exist but the majority are not systematic, up to date, or comprehensive in their coverage of the literature. The aim of this review is to review systematically the evidence on the effects of LVRS in patients with end stage COPD due to underlying emphysema.

Methods

SEARCH STRATEGY

A broad comprehensive search strategy was developed which was designed to identify any potentially relevant material on LVRS for COPD. The key elements of this strategy were as follows: electronic searches of MEDLINE and EMBASE using terms such as “surgery”, “emphysema”, “pneumectomy”, and “pneumoplasty”; searches of the Cochrane Library Controlled Clinical Trials Register; contacts with experts in the field to identify ongoing or unpublished research; and citation checking of all articles obtained. Full details of the search strategy are available on request from the authors. All sources were searched from 1975 onwards and no language exclusion or other limits were applied, particularly in relation to study design.

INCLUSION AND EXCLUSION DECISIONS AND QUALITY ASSESSMENT

All inclusion and exclusion decisions were made independently of the detailed scrutiny of the results of the studies, cross checked by two reviewers (JY and CH), and made using predetermined criteria which incorporated detail pertaining to the methodological quality of the anticipated studies. The final criteria used are contained in table 1.

Initially, the abstracts of all identified articles were scanned for relevance by one reviewer (JY). When abstracts were not available the full article was obtained. The inclusion and exclusion criteria were applied by one reviewer (JY) and cross checked by the other (CH). Any discrepancies were resolved by discussion.

Additional detail on methodological quality was recorded and tabulated for each of the included studies.

DATA ABSTRACTION AND ANALYSIS

The characteristics and results of the included studies were abstracted by one reviewer (JY) using a proforma. RevMan 3.1 for Windows software was used to record this information and to generate summary tables. The tabulated data were qualitatively assessed, particularly in relation to possible sources of heterogeneity. The general design, quality and clinical heterogeneity of the included studies made a formal meta-analysis inappropriate but the tabulation process enabled the identification of a range of plausible values for the likely effect of LVRS on the key outcomes of interest. When necessary the results of the individual studies were re-analysed, involving the re-calculation of certain data to facilitate comparison—for example, the conversion of all six minute walk-
LVRS for COPD with severe emphysema

Results

VOLUME OF RELEVANT MATERIAL

Initially, 198 references were identified by the formal search; 123 were excluded on the basis of the information contained in the title or the abstract and 75 full text papers were obtained, either because a decision could not be made using the available information or because they were potentially relevant for inclusion. Nineteen studies met the criteria for inclusion in the final analysis. The main reasons for exclusion were: suspicion of duplication; measurement of inappropriate or irrelevant outcomes; the evaluation of interventions other than LVRS as defined in this review; and inadequate methodological quality. Details of all excluded studies are available on request from the authors. All 19 included studies were case series but a small number of trials were also identified. All of the trials examined the effectiveness of different techniques for LVRS and not the effectiveness of the intervention as a whole and as such were not suitable for inclusion. However, where possible the individual comparison groups from these trials were included as case series in their own right.

CHARACTERISTICS OF INCLUDED STUDIES

The characteristics of the studies included in this review are shown in table 2. The key features are described below.

Intervention

Although the majority of the results reflect those of the currently preferred technique, in some studies a different operative technique or approach was used. In particular, in a number of the earlier studies laser was used to obliterate the areas of diseased lung and in a few of the more recent studies the procedure was conducted by video assisted thoracoscopy.

Rehabilitation has been shown to have an effect on exercise capacity and quality of life in patients with COPD so the estimate of effect may well be influenced by this.25 The reporting of participation in pulmonary rehabilitation was inconsistent and, when it was reported, the timing of baseline data collection in relation to preoperative rehabilitation was not clear leading to considerable ambiguity overall about whether or not the effect of LVRS and pulmonary rehabilitation was being evaluated.

One additional factor which may have had a bearing on the results, for what is essentially an experimental technique, is the level of skill and experience of the operators. An estimate of this was obtained from information on the setting of the study and the duration of the programme. Generally, the studies took place in the context of large programmes in university hospitals or specialist medical centres, although on the few occasions when this was not the case the pattern of results was fairly consistent.

Populations examined

The populations examined also varied between the individual studies in terms of their selection criteria. Generally these exhibited a high degree of selectivity. However, this is likely to be the way LVRS is going to continue to be applied in the immediate future.

Outcomes

There was more consistency between the studies in the range of outcomes that were measured. Most collected objective outcome data on both the physiological and functional aspects of the procedure using standardised assessment tools, and mortality and morbidity data were generally provided. Dyspnoea was assessed by several studies but quality of life measures were used on only a few occasions. For all of the more subjective outcomes there was considerable variation in the measurement tools used.

Study design

All of the final group of included studies were case series. Because they were selected partly on the basis of the validity assessment, there was a high degree of consistency between them in relation to their methodological quality. Most were consecutive case series of a good size which were conducted prospectively with minimal losses to follow up.

However, because they were all observational studies which did not use parallel control groups, an element of uncertainty exists about the reliability and accuracy of the reported results. The reasons for this uncertainty are explored more fully in the discussion section of this paper.

In addition to this general point, none of the studies stated that the assessment of outcomes was undertaken by independent observers, raising the specific potential for the influence of detection bias on the results.

RESULTS OF INCLUDED STUDIES

Mortality

Early and late mortality rates could be calculated for most series and these data are presented in detail for 567 patients in table 3. The interquartile range (IQR) for early mortality (defined as hospital deaths or deaths occurring within 30 days of surgery) was 0–6%, while the IQR for late mortality (defined as deaths occurring in the hospital or more than 30 days after surgery) at 3–6 months was 0–8%. Late mortality at two years was estimated as between 0% and 3%.

Lung function

Most studies collected data on a range of physiological outcomes including the forced expiratory volume in one second (FEV1). The results of the individual studies for FEV1, and FEV1 as a percentage of the predicted value are presented in table 4.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design strengths and weaknesses (n = sample size)</th>
<th>Criteria for entry to study</th>
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</thead>
<tbody>
<tr>
<td>Argenziano</td>
<td>Consecutive case series within a controlled comparison (n = 92). 75% reached the 3–6 month follow up point and were treated as a discrete cohort with 96% follow up. No information on assessment of outcomes.</td>
<td>Hyperinflation Poor diaphragmatic excursion Pulmonary perfusion and ventilation deficits Significant functional disability</td>
<td>Stapling with BPS buttressing Bilateral and unilateral</td>
<td>Pulmonary function tests Morbidity and mortality Dyspnoea</td>
<td>Baseline data: unclear when these were obtained Setting/experience: part of a 2 year programme at Columbia-Presbyterian Medical Centre, New York, USA NB. Population includes some very ill cases</td>
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<tr>
<td>Bagley</td>
<td>Consecutive case series (n = 55). 82% followed up for three months. No information on assessment of outcomes.</td>
<td>Advanced emphysema unhappy with the limits imposed by the disease Small amounts of airways inflammation Recent completion of a pulmonary rehabilitation programme RV &gt;150% of predicted PA systolic pressure &lt;50 mm Hg Smoking cessation for at least 1 year</td>
<td>Stapling with BPS buttressing Bilateral via median sternotomy 8 weeks pulmonary rehabilitation pre-op.</td>
<td>Pulmonary function tests 6 MWD Chronic Respiratory Diseases Questionnaire</td>
<td>Baseline data: 6MWD and subjective data obtained post-rehabilitation Pulmonary function test baseline data collected at various points particularly for very ill cases Setting/experience: early experience in a 320 bed community hospital in the USA NB. Results presented as numbers of patients achieving a significant improvement postoperatively</td>
</tr>
<tr>
<td>Benditt</td>
<td>Consenting cases of a consecutive series: included cases studied compared with those excluded and shown not to be significantly different (n = 21 (of 47)). 100% follow up to 3 months. No information on assessment of outcomes.</td>
<td>Evidence of emphysema on CT scan Severe airflow limitation FEV₁ &gt;15% and &lt;35% predicted TLC &gt;120% RV &gt;150% Air trapping and hyperinflation Smoking cessation for at least 3 months</td>
<td>Stapling with BPS buttressing Bilateral via median sternotomy</td>
<td>Pulmonary function tests to ATS standards</td>
<td>Baseline data: no detail on when these were obtained Setting/experience: part of a year long programme at the University of Washington in Seattle, USA</td>
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<td>Bousamra</td>
<td>Consecutive case series (n = 45). 93% followed up to 3 months. No information on assessment of outcome.</td>
<td>Marked hyperexpansion Heterogeneous emphysema Large RV Significant trapped gas volume</td>
<td>Mainly stapling Bilateral via median sternotomy or thoracotomy Pulmonary rehabilitation 6 weeks pre-op continuing post-op</td>
<td>Pulmonary function tests Dyspnoea (Mahler index), follow up inadequate 6MWD (follow up inadequate) Mortality and morbidity Pulmonary function tests Exercise testing 6 MWD Morbidity and mortality Dyspnoea (Mahler index and MMRC) Quality of life (Nottingham Health Profile and SF36)</td>
<td>Baseline data: obtained pre and post rehabilitation Setting/experience: first 45 cases treated at the Medical College of Wisconsin Hospitals, USA</td>
</tr>
<tr>
<td>Cooper</td>
<td>Consecutive case series (n = 150). 67% followed up to 6 months; 37% to 1 year; and 15% to 2 years; all treated as discrete cohorts. No information on assessment of outcome.</td>
<td>Emphysema with hyperinflation and heterogeneity Marked physiological impairment (FEV₁ &lt; 35% predicted) Marked restriction in activities of daily living despite maximal medical therapy Age &gt;75 years Acceptable nutritional status (70–130% of ideal body weight) Ability to participate in vigorous pulmonary rehabilitation programme No co-existing major medical problems that would significantly increase operative risk Willingness to undertake risk of morbidity and mortality associated with the procedure Smoking cessation for at least 6 months</td>
<td>Stapling with BPS buttressing Bilateral via median sternotomy 6 weeks pulmonary rehabilitation pre-op.</td>
<td>Pulmonary function tests Morbidity and mortality Dyspnoea (Mahler index and MMRC) Quality of life (Nottingham Health Profile and SF36)</td>
<td>Baseline data: generally obtained pre and post rehabilitation but presented separately Setting/experience: the most recent results of a large programme at Washington University, Missouri, USA which commenced in 1993</td>
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| Cordova40  | Consecutive case series (n = 69). 25 patients reached 3 months, 13 reached 1 year and 6 reached 2 years with 100% follow up and all were treated as discrete cohorts. No information on assessment of outcome. | New York Heart Association class III-IV
Evidence of airflow obstruction and hyperinflation by pulmonary function studies (i.e. post-bronchodilator FEV₁, 30% predicted)
FRC or TLC >120% of predicted
Discrepancy between helium dilution and FRC body box determination of lung volumes by >500 ml
Documented hyperinflation on chest radiograph
Diffuse emphysema documented on CT scan
Ventilation-perfusion mismatch documented in planned resected lung by VQ scan | Stapling
Bilateral via median sternotomy | Pulmonary function tests to ATS standards
Exercise testing
6MWD Quality of life (Sickness Impact Profile) | Baseline data: measurements were obtained after pulmonary rehabilitation Setting/experience: first 25 cases of 69 treated in a 2-year programme at Temple University Hospital, Philadelphia, USA |
| Criner27   | Consecutive case series (n = 3). 100% followed up for at least 3 months. No information on assessment of outcome. | Severe COPD and respiratory failure
Ventilator dependent
Poor mobility
Severe hypercapnia and cor pulmonale | Not stated
Stapling via thoracotomy or sternotomy | Pulmonary function tests to ATS standards
Arterial blood gas analysis
Bedside maximum inspired pressure and ventilation. | Baseline data: obtained 1–4 months prior to intubation (not available for one subject) Setting/experience: part of a 2 year programme at Temple University Hospital Philadelphia, USA NB. All very ill cases |
| Daniel28   | Consecutive case series (n = 26). 65% followed up to 3 months but treated as a discrete cohort (n=17). No information on assessment of outcome. | Diagnosis of COPD
No smoking for more than 1 month
Age <75 years
FEV₁, 15–35% predicted
PaCO₂ <55 mm Hg
Prednisone dosage <20 mg daily
PaO₂ <55 mm Hg by echocardiography
Commitment to preoperative and postoperative supervised pulmonary rehabilitation for 6 weeks | Stapling with BPS buttressing
Bilateral via median sternotomy
Pulmonary rehabilitation pre and post-op for 6 weeks | Pulmonary function tests to ATS standards
Arterial blood gas analysis
Bedside maximum inspired pressure and ventilation. | Baseline data: no information as to when baseline measurements were obtained Setting/experience: 1 year experience at the University of Virginia, USA |
| Eugene29   | Consecutive case series (n = 44). 91% followed up to 3 months and 86% followed up to 6 months. No information on assessment of outcome. | Severely impaired pulmonary function (FEV₁ <0.5 l)
Lifestyle limiting dyspnoea
Reduced pulmonary function (FEV₁, 20–40% predicted)
RV>250% predicted
Hyperexpansion
Diffuse bullous emphysema Target areas | Advanced age
Hypercarbia
Irreversible pulmonary hypertension
Prior operation or thoracic deformities
Significant co-morbidity
Poor patient compliance | Pulmonary function tests Dyspnoea (Borg and MMRC scores) | Baseline data: no information on when baseline data were obtained Setting/experience: part of an 18 month experience at the Western Medical Centre, Anaheim, California, USA NB. All very ill cases |
| Eugene30   | Consecutive case series (n = 28). 100% followed up to 3 months. No information on assessment of outcome. | Dyspnoea severely impairing lifestyle
Inability to work or self care
No improvement on maximal medical management
Bullous or diffuse emphysema
Hyperinflation on CT scan
Markedly low FVC and FEV₁ and high lung volumes | Not stated
Stapling with BPS buttressing
Unilateral via thoracotomy | Pulmonary function tests Dyspnoea (tool not stated) | Baseline data: no information Setting/experience: early experience (Nov 1993–July 1994) at the Western Medical Centre, Anaheim and the University of California, Irvine, USA |
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<tr>
<td>Keller31</td>
<td>Consecutive case series (n = 25). 100% followed up to 6 months. No information on assessment of outcome.</td>
<td>Established diagnosis of severe emphysema, Significant air trapping, Impaired diffusion capacity, Demonstrated distinct target areas for surgical resection, Ventilation/perfusion mismatch FEV&lt;sub&gt;1&lt;/sub&gt;, 20–30% predicted, Severe hyperinflation RV &gt;200% predicted, Heterogeneous disease, Large zones of hypoventilated and hypoperfused lung on VQ scan</td>
<td>Coronary heart disease or left ventricular failure, Chronic bronchitis, Severe hypercapnia (Paco&lt;sub&gt;2&lt;/sub&gt; &gt;55 mm Hg), Significant PA hypertension (mean &gt;55 mm Hg)</td>
<td>Stapling, Unilateral via thoracoscopy Pre-op pulmonary rehabilitation for at least 6 weeks</td>
<td>Pulmonary function tests Dyspnoea (Mahler index) Exercise testing 6 MWD (all to ATS standards) Baseline data: measurements obtained after pulmonary rehabilitation Setting/experience: first 25 cases in a series of 75 at St Louis University, Missouri, USA</td>
</tr>
<tr>
<td>Kotloff32</td>
<td>Consecutive case series within a controlled comparison. Thoracoscopic procedure (n = 40). 89% followed up for 3–6 months. Closed procedure (n = 80). 81% followed up for 3–6 months. No information on assessment of outcome.</td>
<td>Diffuse emphysema, Cessation of smoking, Carbon dioxide retention &gt;50 mm Hg, Congestive cardiac failure or oesopulmonary ( \text{End stage COPD} ), ( \text{Hypertension} ), ( \text{Left heart failure} ), ( \text{Diabetes} ), ( \text{Chronic renal failure} ), ( \text{Significant bronchospasm} ), ( \text{Severe hypercapnia} ), ( \text{Severe hypoxaemia} ), ( \text{Severe acidosis} ), ( \text{Significant PA hypertension} ), ( \text{Significant RV hypertension} )</td>
<td>Giant bullectomy, Pao&lt;sub&gt;2&lt;/sub&gt; &gt;50 mm Hg, PA systolic pressure &gt;50 mm Hg, Continued smoking, Body weight over or under 20% of ideal, Prior surgery or pleurodesis, Significant bronchospasm with wide fluctuations in FEV&lt;sub&gt;1&lt;/sub&gt;, Copious daily sputum production, Poor functional status, Severe bronchitis, Carbon dioxide retention &gt;50 mm Hg, Congestive cardiac failure or oesopulmonary ( \text{End stage COPD} ), ( \text{Hypertension} ), ( \text{Left heart failure} ), ( \text{Diabetes} ), ( \text{Chronic renal failure} ), ( \text{Significant bronchospasm} ), ( \text{Severe hypercapnia} ), ( \text{Severe hypoxaemia} ), ( \text{Severe acidosis} ), ( \text{Significant PA hypertension} ), ( \text{Significant RV hypertension} )</td>
<td>Stapling with BPS buttressing, Bilateral (some staged) via median sternotomy or thoracoscopy 6 weeks pulmonary rehabilitation pre and post-op</td>
<td>Pulmonary function tests Dyspnoea 6MWD Mortality and morbidity Baseline data: obtained after pulmonary rehabilitation Setting/experience: part of a programme at the University of Pennsylvania, USA (duration not stated)</td>
</tr>
<tr>
<td>Little33</td>
<td>Consecutive case series (n = 55). 51% followed up to 3 months and treated as a discrete cohort. No information on assessment of outcome.</td>
<td>Marked symptoms despite maximal medical management, Hyperinflation of the thorax and flattening of the diaphragm on chest radiograph, ( \text{Severe heterogeneous emphysema on CT scan} ), ( \text{Marked hyperinflation on CT scan} ), ( \text{Marked hyperinflation and hypoventilation on CT scan} ), ( \text{Large heterogeneous emphysema on CT scan} )</td>
<td>Mixed, mainly laser Unilateral via thoracoscopic ( \text{Increases open procedures and 3 resection of giant bullae} ), ( \text{No routine pulmonary rehabilitation although some did 6 weeks pre-op} ), ( \text{Current smoking} ), ( \text{Age} &lt;80 \text{ years} ), ( \text{Severe carbon dioxide retention} ) ( \text{(Paco&lt;sub&gt;2&lt;/sub&gt; &gt;55 mm Hg)} ), ( \text{Severe heart disease} ), ( \text{History of cancer in the last 5 years} ), ( \text{Ventilator dependency} ), ( \text{Presence of a lung mass} ), ( \text{Prior thoracic surgery} )</td>
<td>Pulmonary function tests Dyspnoea 6MWD Dyspnoea Mortality and morbidity Pulmonary function tests Dyspnoea (MMRC) Steroid and oxygen dependence</td>
<td>Baseline data: when pulmonary rehabilitation was undertaken baseline data were obtained after this Setting/experience: part of a wider programme at the University of Nevada, USA (duration not stated)</td>
</tr>
<tr>
<td>McKenna34</td>
<td>Consecutive case series within a controlled comparison (n = 166). 87% followed up for 6–12 months. No information on assessment of outcome.</td>
<td>Advanced generalised emphysema No bullae over 5 cm Failure of maximum medical therapy No significant coronary heart disease or psychiatric problems No life threatening illness Ability to perform pulmonary rehabilitation Smoking cessation for 6 months Steroid dosage &gt;15 mg a day No generalised osteoporosis</td>
<td>Predominately bullous emphysema Smoking, Too good physiological state Significant coronary heart disease PA pressure &gt;35 mm Hg Inability to participate in pulmonary rehabilitation Steroid dosage &gt;15 mg a day Use of multiple psychiatric drugs Significant bronchitis or asthma Previous pulmonary operation or sclerosis ( \text{Age} &lt;75 ), ( \text{PEV} &lt;30% \text{ predicted} ), ( \text{Paco&lt;sub&gt;2&lt;/sub&gt; &lt;50 mm Hg, Pao&lt;sub&gt;2&lt;/sub&gt; &gt;80 mm Hg on room air} ), ( \text{Paco&lt;sub&gt;2&lt;/sub&gt; &gt;50 mm Hg} ), ( \text{PA systolic pressure &gt;50 mm Hg} ), ( \text{Continued smoking} ), ( \text{Body weight over or under 20% of ideal} ), ( \text{Prior surgery or pleurodesis} ), ( \text{Significant bronchospasm} ), ( \text{Severe hypercapnia} ), ( \text{Severe hypoxaemia} ), ( \text{Severe acidosis} ), ( \text{Significant PA hypertension} ), ( \text{Significant RV hypertension} )</td>
<td>Stapling with BPS buttressing, Bilateral via median sternotomy or thoracoscopy 6 weeks pulmonary rehabilitation pre and post-op</td>
<td>Pulmonary function tests Dyspnoea (bolus not stated) 6MWD</td>
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Table 2 continued

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<tr>
<td>Sciurbia³⁵</td>
<td>Consecutive case series (n = 20). 100% followed up to 3 months. Outcome assessment by trained independent assessor.</td>
<td>Diffuse emphysema on the CT scan, Giant bullae, Dominant bronchiectasis, chronic bronchitis or clinical cor pulmonale, Systolic PA pressure &gt;50 mm Hg, Severe epistaxis or inability to tolerate oesophageal balloon placement, Severe dyspnoea despite maximal medical therapy, Clinically stable for 1 month pre-study FEV₁ &lt; 0.5 and RV &gt; 140% predicted after bronchodilators</td>
<td>Laser and stapling, Unilateral and bilateral Open and closed procedures, No information on pulmonary rehabilitation</td>
<td>6MWD (standardised) Dyspnoea (Mahler index) Pressure/volume relations Elastic recoil</td>
<td>Baseline data: obtained 1-4 weeks preoperatively Setting/experience: first 20 cases in the University of Pittsburgh, USA programme from October 1994 to February 1995</td>
</tr>
<tr>
<td>Snell³⁶</td>
<td>Consecutive case series (n = 20). 95% followed up to 3 months. No information on assessment of outcome.</td>
<td>Diagnosis of emphysema in patients receiving optimal management, Bronchodilator FEV₁ &lt; 40% predicted, RV &gt; 150% predicted, Apical functionless emphysematous lung on CT and VQ with relative preservation of basal lung function</td>
<td>Stapling with BPS buttressing, Bilateral via median sternotomy, 8 weeks pulmonary rehabilitation pre-op</td>
<td>Pulmonary function tests 6MWD Dyspnoea (MMRC score)</td>
<td>Baseline data: used best results obtained preoperatively Setting/experience: early experience in Australia, September 1995 to February 1997</td>
</tr>
<tr>
<td>Stammerberger³⁷</td>
<td>Consecutive case series (n = 42). 85% followed up to 3 months. 69% to 6 months (data not included). No information on assessment of outcome.</td>
<td>Severe COPD, FEV₁ &lt; 35% predicted, Considerable hyperinflation, TLC &gt;130% and RV &gt;200%, Flattened diaphragm, High motivation, No smoking for 6 months, No further improvement possible on medical management</td>
<td>Stapling Bilateral via thoracoscopy, No systematic pulmonary rehabilitation</td>
<td>Pulmonary function tests 6MWD Dyspnoea (MMRC scale)</td>
<td>Baseline data: no information Setting/experience: results of experience in Switzerland which began in Jan 1994 to Sept 1996 NB. 12MWD results halved to give 6MWD.</td>
</tr>
<tr>
<td>Zenati³⁸</td>
<td>Consecutive case series (n = 35). 86% followed up to 3 months. No information on assessment of outcome.</td>
<td>Patients who met the criteria for LVRS and lung transplantation, End stage diffuse emphysema, Severely impaired quality of life despite maximal medical therapy, Post bronchodilator FEV₁ &lt;30% predicted, Disabling dyspnoea at &lt;50 yards walking</td>
<td>Laser and stapling with BPS buttressing, Bilateral and unilateral Open and closed</td>
<td>Pulmonary function tests 6MWD Dyspnoea (Mahler index and Borg scale)</td>
<td>Baseline data: no information. Setting/experience: 18 month experience at Pittsburgh Medical Centre, USA from July 1994 to December 1995</td>
</tr>
</tbody>
</table>

6MWD = six minute walking distance; CT = computerised tomography; VQ = ventilation perfusion; BPS = bovine pericardial strips; FRC = functional residual capacity; RV = residual volume; FVC = forced vital capacity; PaCO₂, PaO₂ = arterial carbon dioxide and oxygen tensions; PA = pulmonary artery; FEV₁ = forced expiratory volume in one second; TLC = total lung capacity; MMRC = modified Medical Research Council; ATS = American Thoracic Society.
FEV1 data were available for 925 patients. At baseline the FEV1 was 0.64–0.73 l (IQR) which rose to 0.91–1.07 l 3–6 months after LVRS with a pre/post difference of 0.23–0.36 l. Two studies presented data at two years follow up; Cooper et al found a post-treatment FEV1 of 1.25 l and a pre/post test difference of 0.42 l, and Cordova et al reported a post-treatment FEV1 of 0.91 l and a pre/post test difference of 0.22 l.

FEV1, as a percentage of the predicted value was presented for 806 patients. Baseline measurements were 24–28% (IQR). In the short term these rose to 35–41% and the pre/post test difference was 9–13%. Only Cooper et al measured this in the longer term and reported post-treatment results of 36% and 42%, with pre/post test differences of 12% and 15% at one and two years, respectively.

### Six minute walking distance (6MWD)

The results of 486 patients for the 6MWD are presented in table 4. Ten studies collected data on this outcome. The unit of measurement varied across studies so, to facilitate comparison, all results were converted to metres. The baseline distance covered by study participants was 241–290 m (IQR). This rose to 306–434 m after treatment with a pre/post test difference of 32–96 m. Only Cooper et al recorded these data in the longer term with differences of 64 m and 80 m at one and two years, respectively.

### Quality of life

Only four series collected quality of life (QOL) data before and after the procedure (187 patients) and only three of these used specific measurement tools.

Bagley et al used the Chronic Respiratory Disease Questionnaire (CRQ) developed by Guyatt and colleagues, 48 Cooper et al used two well validated generic quality of life measures (the Nottingham Health Profile and the SF36), and Cordova et al used the Sickness Impact Profile.46 Full details of the QOL results are presented in table 5. Although only limited data were presented in the studies, improvements in quality of life were observed across all studies and measurement tools.

### Dyspnoea

Twelve studies measured dyspnoea before and after the intervention. A variety of measurement tools were used but only nine studies

---

### Table 4 Short and long term results of all included studies for forced expiratory volume in one second (FEV1), FEV1 as a percentage of predicted, and six minute walking distance (6MWD) in metres

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Pre</th>
<th>Post</th>
<th>Difference (p value)</th>
<th>Pre</th>
<th>Post</th>
<th>Difference (p value)</th>
<th>Pre</th>
<th>Post</th>
<th>Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argenziano66 (66)</td>
<td>0.52 (0.19)</td>
<td>0.78 (0.38)</td>
<td>0.26‡</td>
<td>22 (8)</td>
<td>34 (14)</td>
<td>12‡</td>
<td>176 (96)</td>
<td>273 (96)</td>
<td>96‡</td>
</tr>
<tr>
<td>Bagley35 (55)</td>
<td>N/A</td>
<td>N/A</td>
<td>0.19 (0.0002)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Benditt21 (21)</td>
<td>1.12‡</td>
<td>1.12‡</td>
<td>0.00‡</td>
<td>24‡</td>
<td>28‡</td>
<td>4‡</td>
<td>241‡</td>
<td>290‡</td>
<td>49‡</td>
</tr>
<tr>
<td>Boussamra45 (45)</td>
<td>0.68 (0.23)</td>
<td>0.97 (0.38)</td>
<td>0.29 (0.05)</td>
<td>26 (9)</td>
<td>40 (15)</td>
<td>14 (0.002)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cooper103 (103)</td>
<td>0.70‡</td>
<td>1.06‡</td>
<td>0.36 (&lt;0.001)</td>
<td>25‡</td>
<td>38‡</td>
<td>13‡</td>
<td>289 (101)</td>
<td>338 (101)</td>
<td>49 (0.001)</td>
</tr>
<tr>
<td>Cordova25 (25)</td>
<td>0.68 (0.19)</td>
<td>0.93 (0.29)</td>
<td>0.25 (&lt;0.001)</td>
<td>27 (8)</td>
<td>37 (12)</td>
<td>10‡</td>
<td>257 (113)</td>
<td>338 (113)</td>
<td>80 (0.001)</td>
</tr>
<tr>
<td>Criner32 (2)</td>
<td>0.41 (0.00)</td>
<td>0.90 (0.36)</td>
<td>0.49‡</td>
<td>38 (1)</td>
<td>38 (2.80)</td>
<td>0‡</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Daniel33 (17)</td>
<td>0.73‡</td>
<td>1.02‡</td>
<td>0.29 (&lt;0.0001)</td>
<td>25‡</td>
<td>36‡</td>
<td>11‡</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Eugene44 (41)</td>
<td>0.40 (0.01)</td>
<td>0.62 (0.03)</td>
<td>0.21‡</td>
<td>15‡</td>
<td>23‡</td>
<td>8‡</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Eugene25 (25)</td>
<td>0.68 (0.05)</td>
<td>0.91 (0.35)</td>
<td>0.23 (&lt;0.001)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Keller25 (25)</td>
<td>0.80 (0.33)</td>
<td>1.05 (0.41)</td>
<td>0.25 (&lt;0.001)</td>
<td>33 (8.40)</td>
<td>35 (7.90)</td>
<td>2‡</td>
<td>289 (96)</td>
<td>322 (96)</td>
<td>33 (0.01)</td>
</tr>
<tr>
<td>Kotlo40 (80)</td>
<td>0.73 (0.24)</td>
<td>1.02 (0.40)</td>
<td>0.29 (0.001)</td>
<td>27‡</td>
<td>37‡</td>
<td>10‡</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Stammberger42 (42)</td>
<td>0.80 (0.24)</td>
<td>1.18 (0.44)</td>
<td>0.38 (&lt;0.001)</td>
<td>29 (7.5)</td>
<td>41 (13)</td>
<td>12‡</td>
<td>241‡</td>
<td>290‡</td>
<td>49‡</td>
</tr>
<tr>
<td>Zenati33 (33)</td>
<td>0.64 (0.22)</td>
<td>0.97 (0.38)</td>
<td>0.33 (&lt;0.001)</td>
<td>22‡</td>
<td>35‡</td>
<td>13‡</td>
<td>273 (80)</td>
<td>306 (80)</td>
<td>33 (0.05)</td>
</tr>
<tr>
<td>IQ range</td>
<td>0.64–0.74</td>
<td>0.91–1.07</td>
<td>0.23–0.36</td>
<td>24–28</td>
<td>35–40</td>
<td>9–13</td>
<td>241–290</td>
<td>306–434</td>
<td>32–96</td>
</tr>
</tbody>
</table>

18 months to 2 years follow up

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Pre</th>
<th>Post</th>
<th>Difference (p value)</th>
<th>Pre</th>
<th>Post</th>
<th>Difference (p value)</th>
<th>Pre</th>
<th>Post</th>
<th>Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper56 (56)</td>
<td>0.69‡</td>
<td>1.03‡</td>
<td>0.34‡</td>
<td>24</td>
<td>36</td>
<td>12‡</td>
<td>354</td>
<td>418</td>
<td>64‡</td>
</tr>
<tr>
<td>Cordova39 (13)</td>
<td>0.66 (0.17)</td>
<td>0.90 (0.35)</td>
<td>0.22 (&lt;0.05)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Argenziano38 (42)</td>
<td>1.25‡</td>
<td>0.42‡</td>
<td>0.83‡</td>
<td>27</td>
<td>42</td>
<td>15‡</td>
<td>370</td>
<td>450</td>
<td>80‡</td>
</tr>
<tr>
<td>Cordova6 (6)</td>
<td>0.69 (0.20)</td>
<td>0.91 (0.37)</td>
<td>0.22 (&lt;0.12)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

VATS = video assisted thoracoscopic; MS = median sternotomy; N/A = data not available.

*Deaths measured up to and after 90 days.

+Deaths measured up to and after 90 days.

†Standard deviations/p value not given.

‡12MWD halved.

-Deaths measured up to and after 90 days.

VATS = video assisted thoracic surgery; MS = median sternotomy.

*Deaths measured up to and after 90 days.
used validated standardised tools. The most commonly used tool was the modified (American Thoracic Society) Medical Research Council of Great Britain scale (MMRC). The MMRC scale results for 403 patients are presented in table 6.

Bagley et al\textsuperscript{55} used the CRQ\textsuperscript{11} and recorded a mean improvement of 5.84 (p=0.0001). The Borg scale was used in two studies.\textsuperscript{18} In the series reported by Eugene et al\textsuperscript{29} the mean score decreased from 7.6 before surgery to 4.65 post-operatively, and Zenati et al\textsuperscript{35} reported a decrease from 3.71 to 2.4. (The extreme difference in baseline is accounted for by the fact that the patients in the study of Eugene et al\textsuperscript{29} were all very ill.) The Mahler baseline dyspnoea index (BDI) and transitional dyspnoea index (TDI) were used by a number of studies.\textsuperscript{31, 38, 39} Three studies reported scores for the functional impairment component individually\textsuperscript{31} with BDI scores of 0.83, 0.9, and 1.0, respectively, and TDI scores of 2.2, 1.65, and 1.72. Keller et al\textsuperscript{38} reported an overall baseline focal score (BFS) of 3.36 and a transitional focal score (TFS) of 6.12, and Sciurbia et al\textsuperscript{38} an overall TFS of 5.1 (p<0.001).

Length of hospital stay
Several series (668 patients) also provided information on length of stay in hospital which gives a crude indication as to resource use associated with the procedure. In those studies which reported it the IQR for length of stay was 13–18 days.

Supplemental oxygen
Several studies (487 patients) also provided data on supplemental oxygen use before and after the procedure. This provides a crude indication of resource use, quality of life, and functional ability. In the short term (3–6 months) the reduction in the percentage of patients requiring supplemental oxygen, either continuously or on exertion, was 16–42% (IQR). Cooper et al\textsuperscript{10} reported a reduction of 41% at one year and 52% at two years.

### SUMMARY OF RESULTS

The main effects of LVRS observed in unselected case series with complete follow up are outlined below:

- the pattern of results for most outcomes is fairly consistent across individual studies despite a significant degree of clinical heterogeneity;
- significant short term benefits occurred across a range of outcomes which appear to continue in the longer term;
- physiological improvements in FEV\textsubscript{1} appear to be matched by functional improvements in 6MWD and subjective improvements in dyspnoea and quality of life, although information on the latter is only available for small numbers of patients;
- operative mortality rates are low and overall mortality rates compare favourably with those of the COPD population as a whole.

### Discussion

At face value there appears to be a wealth of evidence supporting the effectiveness of LVRS. However, the review also reveals that the most rigorous available relevant research studies employ designs that make them susceptible to bias. This fact, and whether the methods of the review itself might have introduced further bias, needs to be considered before drawing final conclusions.

The systematic approach to the reviewing process which involved a clear definition of the question to be addressed; the development of a protocol; a comprehensive search strategy; clearly defined inclusion and exclusion criteria; and a detailed assessment of the quality of included studies should have minimised any bias introduced in the process of summarising the most rigorous available research literature.
Despite this, freedom from bias cannot be guaranteed. We would suggest that the greatest possible threat is from publication bias, particularly as knowledge on the impact of this is least well explored where studies other than randomised controlled trials are being reviewed. The funnel plot in figure 1 which plots sample size against the standardised mean difference for FEV₁, in the included studies acts as a crude visual check on the likelihood of missing studies. It indicates that for this outcome there are no large gaps in the data set which might be suggestive of publication bias.

The main sources of bias in the included studies relate to their lack of parallel control groups. Where outcome measurements can be made before and after an intervention, as is the case for FEV₁, 6MWD, dyspnoea score, and quality of life, the problems of interpretation are reduced but not eliminated for two reasons.

Firstly, the attribution of all or any observed change to LVRS is uncertain. Many factors other than LVRS may have influenced the difference between the pre- and post-treatment outcome measurements. Particularly important in this sense is the role of pulmonary rehabilitation. All LVRS “packages” in the included studies incorporated a component of postoperative rehabilitation and, although it was often unclear whether the pre-treatment measures were made before or after any preoperative pulmonary rehabilitation, it seems likely that in many studies the LVRS “package” would have included preoperative pulmonary rehabilitation too. Without a parallel control group it is impossible to exclude the possibility that pulmonary rehabilitation alone might have been responsible for a considerable component of the improvement in critical outcomes such as 6MWD, dyspnoea, and quality of life.

Secondly, the included studies are open to detection bias. With only one study arm it is inevitable that clinicians and patients are aware that they are on an active treatment and may tend to provide outcome measurements which conform to expectations that LVRS will result in improvement. The use of validated and standardised outcome collection methods offers some protection against this. Making the assessment of outcome independent of knowledge that a patient was part of a study testing the effectiveness of LVRS would provide further protection, but we have confirmed that this was not applied in any of the included studies.

Where outcome measurements before and after the intervention are not applicable, as in the case of mortality, the absence of a parallel control group poses much greater problems. Any comparison must rely on measurement of that outcome in an untreated group outside the study. This group may have important differences in characteristics other than treatment which could in turn account for any differences in observed outcome.

It is possible to judge that the biases identified above, and others not specifically mentioned, may not substantively alter the assessment of whether the observed impact on outcomes truly reflects the actual impact. We believe, however, that it is highly likely that they will and, further, that observed improvements in outcome will tend to be overestimates. More conservatively, it seems clear that the identified biases introduce uncertainty which widens the true range of possible size of effects on mortality, FEV₁, 6MWD, dyspnoea score, and quality of life well beyond the IQ ranges demonstrated by the review. This uncertainty is intensified when attempts are made to summate the value of the individual effects of LVRS into an assessment of overall effectiveness, and compounded further by the fact that the two effects likely to be valued most highly in assessing overall effectiveness—impact on mortality and quality of life—are those where uncertainty is greatest either because of the biases discussed or the limited number of included studies collecting data on the outcome.

However, this should not obscure the fact that LVRS, with or without pulmonary rehabilitation, has led to subjective improvements in quality of life and shortness of breath. This is consistently shown in the small number of studies that examined them. The impact on these outcomes is supported by improvements in more objectively measured physiological and functional measures such as FEV₁ and 6MWD. Improvements in these measures are also consistent across a much larger number of studies. Finally, mortality rates associated with the operation are also consistent across individual studies and compare favourably with those of untreated patients with COPD who have high mortality rates even on maximum medical management.

Based on the results of the studies included in this review the authors judge that the benefits of LVRS are likely to outweigh the risks. It seems unlikely that the biases inherent in the design of the included studies would have so exaggerated effect sizes that the research reviewed conveys overall effectiveness where it is actually completely ineffective. However, it is possible that the observed results from the most rigorous existing research, taking into account the likely biases, could actually be compatible with a true level of net benefit from LVRS which does not justify its
LVRS for COPD with severe emphysema

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20 Longhi DR, Higgins VR. Lung surgery: when less is more. Registered Nurse 1995;July:40–5.
Lung volume reduction surgery (LVRS) for chronic obstructive pulmonary disease (COPD) with underlying severe emphysema

Jackie Young, Anne Fry-Smith and Chris Hyde

Thorax 1999 54: 779-789
doi: 10.1136/thx.54.9.779

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