

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

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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.¹ In 1995 the age standardised annual

death rates were 50 per 100 000 in men and 24 per 100 000 in women.² 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.³ 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.⁴

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^{5,6} 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.^{7,8} 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.⁹

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

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Table 1 Inclusion and exclusion criteria

	Inclusion	Exclusion
Population	Patients with diffuse severe emphysema with significant functional limitation despite maximum medical therapy	Patients with large isolated emphysematous bullae in the presence of normal underlying compressed lung
Intervention	Lung volume reduction surgery (reduction pneumoplasty or pneumectomy) defined as multiple lung resections and/or resections 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	The excision of localised giant bullae
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	Studies which only considered short term outcomes, i.e. those with less than three months follow up 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
Duplication	When several series emerged chronologically from the same source only the largest and most recent series was included	Studies were excluded if they had clearly originated from the same source and there were indications that their analysis included some or all of the same patients
<i>Quality criteria (pertaining to potential sources of bias)</i>		
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	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
Attrition bias	Losses to follow up of $\leq 25\%$ 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	Losses to follow up $>25\%$ and inadequate management of losses to follow up
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	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

the grounds that a robust research base on the effectiveness of the intervention does not exist.¹⁰ 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^{9 11-22} 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-

ing distances to metres and the calculation of pre/post test differences when these were not reported by the study authors. Data were summarised using additional statistics such as interquartile range to give an indication of the general size and direction of effect. The potential for publication bias was also investigated.

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.²³ 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, al-

though 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 2 Characteristics of included studies

Reference	Criteria for entry to study			Intervention	Outcomes	Additional information
	Inclusion	Exclusion				
Argenziano ²⁴	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 outcome.	Hyperinflation Poor diaphragmatic excursion Pulmonary perfusion and ventilation deficits Significant functional disability	Morbid obesity Chronic bronchitis Excessive sputum production Metastatic cancer Continued or recent smoking Less than severe functional disability	Stapling with BPS buttressing Bilateral and unilateral Mainly open procedures	Pulmonary function tests Morbidity and mortality Dyspnoea	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
Bagley ²⁵	Consecutive case series (n = 55). 82% followed up for three months. No information on assessment of outcome	Advanced emphysema unhappy with the limits imposed by the disease Small amounts of airways inflammation Recent completion of a pulmonary rehabilitation programme RV >150% of predicted PA systolic pressure <50 mm Hg Smoking cessation for at least 1 year	Recent high dose steroid use Other active medical problems	Stapling with BPS buttressing Bilateral via median sternotomy 8 weeks pulmonary rehabilitation pre-op.	Pulmonary function tests 6 MWD Chronic Respiratory Diseases Questionnaire	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 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
Benditt ¹¹	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 outcome.	Evidence of emphysema on CT scan Severe airflow limitation FEV ₁ >15% and <35% predicted TLC >120% RV >150% Air trapping and hyperinflation Smoking cessation for at least 3 months	Age >75 years Excessive daily sputum production Significant co-morbidity	Stapling with BPS buttressing Bilateral via median sternotomy	Pulmonary function tests to ATS standards	Baseline data: obtained pre and post rehabilitation Setting/experience: first 45 cases treated at the Medical College of Wisconsin Hospitals, USA
Bousamma ²⁶	Consecutive case series (n = 45). 93% followed up to 3 months. No information on assessment of outcome.	Marked hyperexpansion Heterogeneous emphysema Large RV Significant trapped gas volume	Previous major thoracic surgery Prominent component of bronchospasm Copious sputum production or congestive cardiac failure Inability to undertake pulmonary rehabilitation	Mainly stapling Bilateral via median sternotomy or thoracotomy Pulmonary rehabilitation 6 weeks pre-op continuing post-op	Pulmonary function tests. Dyspnoea (Mahler index), follow up inadequate 6MWD (follow up inadequate)	Baseline data: obtained pre and post rehabilitation Setting/experience: first 45 cases treated at the Medical College of Wisconsin Hospitals, USA
Cooper ²⁹	Consecutive case series (n = 150). 67% followed up to 6 months; 37% to 1 year; and 13% to 2 years; all treated as discrete cohorts. No information on assessment of outcome.	Emphysema with hyperinflation and heterogeneity Marked physiological impairment (FEV ₁ <35% predicted) Marked restriction in activities of daily living despite maximal medical therapy Age <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	Diffuse disease with no target areas Insufficient thoracic distension, advanced age or associated medical problems FEV ₁ too good Pleural disease Better suited to lung transplantation PaCO ₂ >55 mm Hg in association with other problems Marked kyphosis	Stapling with BPS buttressing Bilateral via median sternotomy 6 weeks pulmonary rehabilitation pre-op.	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)	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

Table 2 continued

Reference	Criteria for entry to study			Outcomes	Additional information
	Study design strengths and weaknesses (n = sample size)	Inclusion	Exclusion		
Cordova ¹⁰	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 FEV ₁ 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 Severe COPD and respiratory failure Ventilator dependent Poor mobility Severe hypercapnia and cor pulmonale	Patients with severe and refractory hypoxaemia Severe hypercapnic respiratory failure requiring mechanical ventilation Presence of severe cardiovascular disease Presence of severe pulmonary hypertension (mean Pa pressure >500 mm Hg). Severe debilitated state with total body weight <70% of ideal Presence of significant extrapulmonary end organ dysfunction expected to limit survival Psychosocial dysfunction Continued smoking	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
Criner ²⁷	Consecutive case series (n = 3). 100% followed up for at least 3 months. No information on assessment of outcome.	Diagnosis of COPD No smoking for more than 1 month Age <75 years FEV ₁ 15–35% predicted PaCO ₂ <55 mm Hg Prednisone dosage <20 mg daily Pa <55 mm Hg by echocardiography Commitment to preoperative and postoperative supervised pulmonary rehabilitation for 6 weeks Severely impaired pulmonary function (FEV ₁ <0.5 l) Lifestyle limiting dyspnoea Reduced pulmonary function (FEV ₁ 20–40%, predicted) RV >250% predicted Hyperexpansion Diffuse bullous emphysema Target areas Dyspnoea severely impairing lifestyle Inability to work or self care No improvement on maximal medical management Bullous or diffuse emphysema with hyperinflation on CT scan Markedly low FVC and FEV ₁ and high lung volumes	Not stated	Pulmonary function tests to ATS standards Arterial blood gas analysis Bedside maximum inspired pressure and ventilation. Pulmonary function tests Quality of life (tool not stated)	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 Baseline data: no information as to when baseline measurements were obtained Setting/experience: 1 year experience at the University of Virginia, USA
Daniel ²⁸	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 FEV ₁ 15–35% predicted PaCO ₂ <55 mm Hg Prednisone dosage <20 mg daily Pa <55 mm Hg by echocardiography Commitment to preoperative and postoperative supervised pulmonary rehabilitation for 6 weeks Severely impaired pulmonary function (FEV ₁ <0.5 l) Lifestyle limiting dyspnoea Reduced pulmonary function (FEV ₁ 20–40%, predicted) RV >250% predicted Hyperexpansion Diffuse bullous emphysema Target areas Dyspnoea severely impairing lifestyle Inability to work or self care No improvement on maximal medical management Bullous or diffuse emphysema with hyperinflation on CT scan Markedly low FVC and FEV ₁ and high lung volumes	Not stated	Pulmonary function tests to ATS standards 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
Eugene ²⁹	Consecutive case series (n = 44). 91% followed up to 3 months and 86% followed up to 6 months. No information on assessment of outcome.	Diagnosis of COPD No smoking for more than 1 month Age <75 years FEV ₁ 15–35% predicted PaCO ₂ <55 mm Hg Prednisone dosage <20 mg daily Pa <55 mm Hg by echocardiography Commitment to preoperative and postoperative supervised pulmonary rehabilitation for 6 weeks Severely impaired pulmonary function (FEV ₁ <0.5 l) Lifestyle limiting dyspnoea Reduced pulmonary function (FEV ₁ 20–40%, predicted) RV >250% predicted Hyperexpansion Diffuse bullous emphysema Target areas Dyspnoea severely impairing lifestyle Inability to work or self care No improvement on maximal medical management Bullous or diffuse emphysema with hyperinflation on CT scan Markedly low FVC and FEV ₁ and high lung volumes	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
Eugene ³⁰	Consecutive case series (n = 28). 100% followed up to 3 months. No information on assessment of outcome.	Diagnosis of COPD No smoking for more than 1 month Age <75 years FEV ₁ 15–35% predicted PaCO ₂ <55 mm Hg Prednisone dosage <20 mg daily Pa <55 mm Hg by echocardiography Commitment to preoperative and postoperative supervised pulmonary rehabilitation for 6 weeks Severely impaired pulmonary function (FEV ₁ <0.5 l) Lifestyle limiting dyspnoea Reduced pulmonary function (FEV ₁ 20–40%, predicted) RV >250% predicted Hyperexpansion Diffuse bullous emphysema Target areas Dyspnoea severely impairing lifestyle Inability to work or self care No improvement on maximal medical management Bullous or diffuse emphysema with hyperinflation on CT scan Markedly low FVC and FEV ₁ and high lung volumes	Not stated	Pulmonary function tests Dyspnoea (Borg and MMRC scores)	Baseline data: no information on when baseline data were obtained Setting/experience: early experience (Nov 1993–July 1994) at the Western Medical Centre, Anaheim and the University of California, Irvine, USA

Table 2 continued

Reference	Criteria for entry to study		Exclusion	Intervention	Outcomes	Additional information
	Inclusion	Exclusion				
Keller ¹	Consecutive case series (n = 25). 100% followed up to 6 months. No information on assessment of outcome.	Established diagnosis of severe emphysema Significant air trapping Impaired diffusion capacity for surgical resection Ventilation/perfusion mismatch FEV ₁ 20–30% predicted Severe hyperinflation RV >200% predicted Heterogeneous disease Large zones of hypoventilated and hyperperfused lung on VQ scan	Coronary heart disease or left ventricular failure Chronic bronchitis Severe hypercapnia (PaCO ₂ >55 mm Hg) Significant PA hypertension (mean >35 mm Hg) Giant bullectomy PaCO ₂ >50 mm Hg PA systolic pressure > 50 mm Hg Continued smoking Body weight over or under 20% of ideal Prior surgery or pleurodesis Significant bronchospasm with wide fluctuations in FEV ₁ Copious daily sputum production Poor functional status Severe bronchitis Carbon dioxide retention >50 mm Hg Congestive cardiac failure or cor pulmonale End stage COPD Inability to ambulate FEV ₁ <35% predicted despite pulmonary rehabilitation	Stapling Unilateral via thoracoscopy Pre-op pulmonary rehabilitation for at least 6 weeks	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
Kotloff ²	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.	Diffuse emphysema Cessation of smoking	Severe heart disease Severe heart disease History of cancer in the last 5 years Ventilator dependency Presence of a lung mass Prior thoracic surgery Predominately bullous emphysema Smoking Too good physiological state No significant coronary heart disease PA pressure >35 mm Hg Inability to participate in pulmonary rehabilitation Steroid dosage >15 mg a day Use of multiple psychiatric drugs Significant bronchitis or asthma Previous pulmonary operation or sclerosis Age <75 PaCO ₂ <50 mm Hg, PaO ₂ >40 mm Hg on room air	Stapling with BPS buttressing Bilateral (some staged) via median sternotomy or thoracoscopy 6 weeks pulmonary rehabilitation pre and post-op	Pulmonary function tests Exercise testing 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)
Little ³	Consecutive case series (n = 55). 51% followed up to 3 months and treated as a discrete cohort. No information on assessment of outcome.	Marked symptoms despite maximal medical management Hyperexpansion of the thorax and flattening of the diaphragm on chest radiograph Severe heterogeneous emphysema on CT scan	Mixed, mainly laser Unilateral via thoracoscopy Includes some open procedures and 3 resection of giant bullae No routine pulmonary rehabilitation although some did 6 weeks pre-op	Pulmonary function tests 6MWD Dyspnoea	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	
McKenna ⁴	Consecutive case series within a controlled comparison (n = 166). 87% followed up for 6–12 months. No information on assessment of outcome.	Advanced generalised emphysema No bullae over 5 cm Failure of maximum medical therapy or psychiatric problems No life threatening illness Ability to perform pulmonary rehabilitation Smoking cessation for 6 months Steroid dosage >15 mg a day No generalised osteoporosis	Current smoking Age >80 years Severe carbon dioxide retention (PaCO ₂ >55 mm Hg) Severe heart disease History of cancer in the last 5 years Ventilator dependency Presence of a lung mass Prior thoracic surgery Predominately bullous emphysema Smoking Too good physiological state No significant coronary heart disease PA pressure >35 mm Hg Inability to participate in pulmonary rehabilitation Steroid dosage >15 mg a day Use of multiple psychiatric drugs Significant bronchitis or asthma Previous pulmonary operation or sclerosis Age <75 PaCO ₂ <50 mm Hg, PaO ₂ >40 mm Hg on room air	Mortality and morbidity Pulmonary function tests Dyspnoea (MMRC) Steroid and oxygen dependence	Baseline data: unclear when these were obtained Setting/experience: results of a year long programme at the Lung Centre, Chapman Medical Centre, California, USA	
Miller ⁴	Consecutive case series (n = 53). 84% followed up to 6 months. No information on assessment of outcome.	Advanced generalised emphysema No bullae over 5 cm Failure of maximum medical therapy or psychiatric problems No life threatening illness Ability to perform pulmonary rehabilitation Smoking cessation for 6 months Steroid dosage >15 mg a day No generalised osteoporosis	Stapling with BPS buttressing Bilateral via median sternotomy 6 weeks pulmonary rehabilitation pre-op and post-op	Pulmonary function tests Dyspnoea (tool not stated) 6MWD	Baseline data: no information on when baseline measurements were obtained Setting/experience: early results of an 18 month programme at Emory University Medical School, Georgia, USA	

Table 2 continued

Reference	Criteria for entry to study		Intervention	Outcomes	Additional information
	Inclusion	Exclusion			
Sciurba ³⁵	Consecutive case series (n = 20). 100% followed up to 3 months. Outcome assessment by trained independent assessor.	Diffuse emphysema on the CT scan	Laser and stapling Unilateral and bilateral Open and closed procedures No information on pulmonary rehabilitation	6MWD (standardised) Dyspnoea (Mahler index) Pressure/volume relations Elastic recoil	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
Snell ³⁶	Consecutive case series (n = 20). 95% followed up to 3 months. No information on assessment of outcome.	Diagnosis of emphysema in patients receiving optimal management Bronchodilator FEV ₁ <40% predicted RV >150% predicted Apical functionless emphysematous lung on CT and VQ with relative preservation of basal lung function	Stapling with BPS buttressing Bilateral via median sternotomy 8 weeks pulmonary rehabilitation pre-op	Pulmonary function tests 6MWD Dyspnoea (MMRC score)	Baseline data: used best results obtained preoperatively Setting/experience: early experience in Australia, September 1995 to February 1997
Stammerberger ³⁷	Consecutive case series (n = 42). 85% followed up to 3 months. 69% to 6 months (data not included). No information on assessment of outcome.	Severe COPD FEV ₁ <35% predicted Considerable hyperinflation TLC >130% and RV >200% Flattened diaphragm High motivation No smoking for 6 months No further improvement possible on medical management	Stapling Bilateral via thoracoscopy No systematic pulmonary rehabilitation	Pulmonary function tests 6MWD Dyspnoea (MMRC scale)	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.
Zenati ³⁸	Consecutive case series (n = 35). 86% followed up to 3 months. No information on assessment of outcome.	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 FEV ₁ <30% predicted Disabling dyspnoea at <50 yards walking	Laser and stapling with BPS buttressing Bilateral and unilateral Open and closed No pulmonary rehabilitation	Pulmonary function tests 6MWD Dyspnoea (Mahler index and Borg scale)	Baseline data: no information. Setting/experience: 18 month experience at Pittsburgh Medical Centre, USA from July 1994 to December 1995

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.

Table 3 Mortality data from included studies

Reference (3–6 month follow up)	Early deaths (<30 days or hospital deaths)	Late deaths (≥30 days or home deaths)	Overall deaths
Argenziano ²⁴	6/92 (6%)	8/86 (9%)	14/92 (15%)
Bagley ²⁵	3/55 (5%)	3/52 (6%)	6/55 (11%)
Bousamra ²⁶	3/45 (7%)	2/42 (5%)	5/45 (9%)
Criner ²⁷	0/3 (0%)	0/3 (0%)	0/3 (0%)
Daniel ²⁸	1/17 (6%)	0/16 (0%)	1/17 (6%)
Eugene ²⁹	1/44 (2%)	11/43 (25%)	12/44 (27%)
Eugene ³⁰	0/28 (0%)	3/28 (11%)	3/28 (11%)
Keller ³¹	0/25 (0%)	0/25 (0%)	0/25 (0%)
Kotloff (MS) ³²	5/80 (6%)	6/75 (8%)	11/80 (14%)
Kotloff (VATS) ³²	1/40 (2%)	0/40 (0%)	1/40 (2%)
Little ³³	N/A	N/A	3/55 (5%)
Miller ³⁴	3/53 (6%)	2/50 (4%)	5/53 (9%)
Sciurba ³⁵	0/20 (0%)	0/20 (0%)	0/20 (0%)
Snell ³⁶	1/20 (5%)	0/20 (0%)	1/20 (5%)
Stammberger ³⁷	0/42 (0%)	3/42 (7%)	3/42 (7%)
Zenati ³⁸	0/35 (0%)	0/35 (0%)	0/35 (0%)
IQ range	0–6%	0–8%	0–11%
2 year follow up			
Cooper ³⁹	6/150 (4%)*	4/144 (3%)*	10/150 (7%)
Cordova ⁴⁰	0/25 (0%)	0/25 (0%)	0/25 (0%)

*Deaths measured up to and after 90 days.

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

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*³⁹ found a post-treatment FEV₁ of 1.25 l and a pre/post test difference of 0.42 l, and Cordova *et al*⁴⁰ 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*³⁹ 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*³⁹ 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*²⁵ used the Chronic Respiratory Disease Questionnaire (CRQ) developed by Guyatt and colleagues,⁴³ Cooper *et al*³⁹ used two well validated generic quality of life measures (the Nottingham Health Profile⁴⁴ and the SF36⁴⁵), 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

Study (n)	Mean (SD) FEV ₁			Mean (SD) % predicted FEV ₁			Mean (SD) 6MWD		
	Pre	Post	Difference (p value)	Pre	Post	Difference (p value)	Pre	Post	Difference (p value)
<i>Short term follow up 3–6 months (where studies give results for 3 and 6 months the 6 month results only are presented)</i>									
Argenziano ²⁴ (66)	0.52 (0.19)	0.78 (0.38)	0.26‡	22 (8)	34 (14)	12‡	176 (96)	273 (96)	96‡
Bagley ²⁵ (55)*	N/A	N/A	0.19 (0.0002)	N/A	N/A	N/A	N/A	N/A	32 (0.042)
Benditt ⁴¹ (21)	1.12‡	1.12‡	0.00‡	24‡	28‡	4‡	N/A	N/A	N/A
Bousamra ²⁶ (45)*	0.68 (0.23)	0.97 (0.38)	0.29 (0.005)	26 (9)	40 (15)	14 (0.002)	N/A	N/A	N/A
Cooper ³⁹ (101)*	0.70‡	1.06‡	0.36 (<0.001)	25‡	38‡	13‡	338‡	402‡	64 (<0.001)
Cordova ⁴⁰ (25)*	0.68 (0.19)	0.93 (0.29)	0.25 (<0.001)	27 (8)	37 (12)	10‡	257 (113)	338 (80)	80 (0.001)
Criner ²⁷ (2)	0.41 (0.00)	0.90 (0.36)	0.49‡	38 (1)	38 (2.80)	0‡	N/A	N/A	N/A
Daniel ²⁸ (17)	0.73‡	1.02‡	0.29 (<0.0001)	25‡	36‡	11‡	N/A	N/A	N/A
Eugene ²⁹ (44)	0.41 (0.01)	0.62 (0.03)	0.21‡	15‡	23‡	8‡	N/A	N/A	N/A
Eugene ³⁰ (25)	0.68 (0.05)	0.91 (0.35)	0.23 (<0.001)	N/A	N/A	N/A	N/A	N/A	N/A
Keller ³¹ (25)*	0.80 (0.33)	1.05 (0.41)	0.25 (<0.001)	33 (8.40)	35 (7.90)	2‡	289 (96)	322 (64)	32 (0.01)
Kotloff (MS) ³² (80)	0.73 (0.24)	1.02 (0.40)	0.29‡	27‡	38‡	11‡	N/A	N/A	N/A
Kotloff (VATS) ³² (40)	0.73 (0.24)	1.00 (0.37)	0.27‡	25‡	36‡	11‡	N/A	N/A	N/A
Little ³³ (28)*	0.74 (0.07)	0.85 (0.06)	0.11 (0.009)	N/A	N/A	N/A	N/A	N/A	N/A
McKenna ⁴² (166)	0.68‡	0.94‡	0.26 (<0.0001)	26‡	36‡	10 (<0.0001)	N/A	N/A	N/A
Miller ³⁴ (53)	0.56‡	1.10‡	0.54‡	24‡	52‡	28‡	241‡	482‡	241‡
Sciurba ³⁵ (20)	0.87 (0.36)	1.11 (0.45)	0.24 (<0.001)	32 (11)	41 (14)	9‡	241 (80)	273 (80)	32 (0.05)
Snell ³⁶ (20)*	0.72 (0.19)	1.07 (0.30)	0.35 (<0.001)	28 (6)	42 (11)	14 (<0.001)	306 (129)	434 (129)	129 (<0.001)
Stammberger ³⁷ (42)	0.80 (0.24)	1.18 (0.44)	0.38 (<0.001)	29 (7)	41 (13)	12‡	241 (96)†	338 (96)†	96 (0.001)†
Zenati ³⁸ (35)	0.64 (0.22)	0.97 (0.38)	0.33 (<0.0001)	22‡	35‡	13‡	273 (80)	306 (64)	32 (<0.05)
IQ range	0.64–0.74	0.91–1.07	0.23–0.36	24–28	35–40	9–13	241–290	306–434	32–96
<i>Long term 1 year follow up</i>									
Cooper ³⁹ (56)*	0.69‡	1.00‡	0.31‡	24	36	12‡	354	418	64‡
Cordova ⁴⁰ (13)*	0.66 (0.17)	0.90 (0.35)	0.22 (<0.05)	N/A	N/A	N/A	N/A	N/A	N/A
<i>18 months to 2 years follow up</i>									
Cooper ³⁹ (20)*		1.25‡	0.42‡	27	42	15‡	370	450	80‡
Cordova ⁴⁰ (6)*	0.69 (0.20)	0.91 (0.37)	0.22 (<0.12)	N/A	N/A	N/A	N/A	N/A	N/A

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

*Baseline data appear to have been obtained after pulmonary rehabilitation in the majority of patients.

†12MWD halved.

‡Standard deviations/p value not given.

Table 5 Results of quality of life data for included studies

Reference (n)	Measurement tool	Results
Bagley ²⁵ (55)	Chronic Respiratory Disease Questionnaire	Mean pre/post test difference: Fatigue - 3.16 (p=0.0001) Emotional function - 4.84 (p=0.0031) Mastery - 3.61 (p=0.0005)
Cooper ³⁹ (101)	SF36	Compared with 1 year ago: 78% much better 20% somewhat better 1% about the same 1% somewhat worse 0% much worse
	Nottingham Health Profile	Areas where statistically significant improvements occurred: Physical mobility Energy Vitality
		Non-statistically significant improvements were observed in most other areas
Cordova ⁴⁰ (25)	Sickness Impact Profile	Mean scores: Pre Post p value Overall 18 7 <0.0002 Physical 13 4 <0.008 Psychosocial 11 4 <0.02
Daniel ²⁸ (17)	Non-validated patient based questionnaire	79% expressed a marked improvement 17% felt somewhat better 4% felt worse

used validated standardised tools. The most commonly used tool was the modified (American Thoracic Society) Medical Research Council of Great Britain scale (MMRC).⁴⁷ The MMRC scale results for 403 patients are presented in table 6.

Bagley *et al*²⁵ used the CRQ⁴³ and recorded a mean improvement of 5.84 (p=0.0001). The Borg scale was used in two studies.⁴⁸ In the series reported by Eugene *et al*²⁹ the mean score decreased from 7.6 before surgery to 4.65 post-operatively, and Zenati *et al*³⁸ 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*²⁹ were all very ill.) The Mahler baseline dyspnoea index (BDI) and transitional dyspnoea index (TDI) were used by a number of studies.⁴⁹ Three studies reported scores for the functional impairment component individually^{31 38 39} 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*⁵¹ reported an overall baseline focal score (BFS) of 3.36 and a transitional focal score (TFS) of 6.12, and Scirbia *et al*⁵⁵ 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 hospital 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*³⁹ 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 FEV₁, 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 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.

Table 6 Individual study results for the MMRC dyspnoea scale

Study (n)	Mean (SD) pre-test score	Mean (SD) post-test score	Mean difference
Argenziano ²⁴ (66)	4.1 (0.8)	1.7 (1.3)	-2.4
Cooper ³⁹ (101)	2.8	1.2	-1.6
Eugene ²⁹ (44)	3.9	2.35	-1.55 (p<0.01)
McKenna ¹² (166)	2.9	1.9	-1.0 (p<0.0001)
Snell ³⁶ (20)	3.4 (0.5)	2.1 (0.8)	-1.3 (p<0.001)
Stammberger ³⁷ (42)	3.5 (0.7)	1.6 (1.0)	-1.9

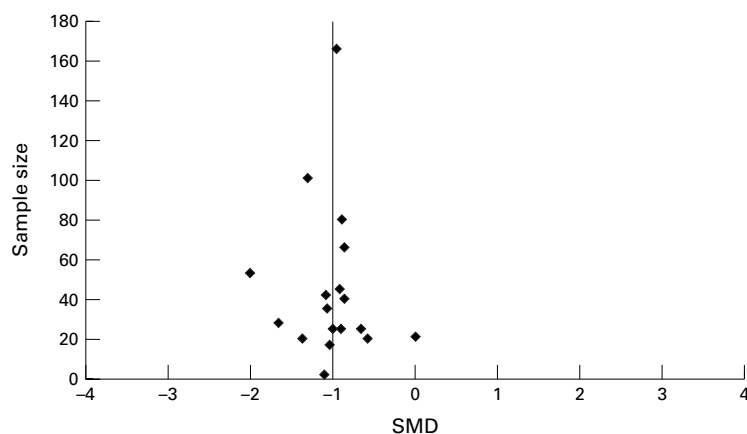


Figure 1 Funnel plot of 18* standardised mean differences (SMD) for forced expiratory volume in one second (FEV_1) by sample size. *Excludes one extreme outlier⁵⁰ which extended the x axis and hampered interpretation of the plot.

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 fig 1 which plots sample size against the standardised mean difference for FEV_1 in the included studies acts as a crude visual check on the likelihood of missing studies.⁵⁰ 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.⁵¹ Where outcome measurements can be made before and after an intervention, as is the case for FEV_1 , 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.²³

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, FEV_1 , 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 FEV_1 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.⁵²

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

costs. Thus, although this systematic review supports LVRS as a promising option in the management of patients with severe end stage emphysema, it also explains current uncertainty and supports the view that further rigorous research, particularly randomised controlled trials, are required to resolve this. One such trial is currently in progress in the UK which will incorporate an economic evaluation,⁵³ and another is ongoing in the USA.⁵⁴ Until the results of these are available, debate will continue on whether LVRS has a secure place among routinely available treatments for end stage COPD secondary to severe emphysema.

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