# Original Article

# Radiological profile of the ideal candidate for lung volume reduction surgery to treat emphysema: a systematic review*

PAULA ANTONIA UGALDE FIGUEROA**, MARTHA SILVIA MARTINEZ-SILVEIRA, EDUARDO PONTE***, AQUILES CAMELIER***, JORGE L. PEREIRA-SILVA***

**Background:** Lung volume reduction surgery is an alternative treatment for advanced pulmonary emphysema. Radiological evaluation of the type and distribution of emphysema, together with the results of pulmonary function testing, seem to be the main criteria used in deciding whether or not the procedure is indicated.

**Objective:** To determine the extent of scientific evidence available regarding the radiological profile of the ideal candidate for lung volume reduction surgery.

**Method:** A systematic review of the literature from January 1994 to January 2004 using the following databases: MEDLINE, EMbase, LILACS, The Cochrane Library and EBM Reviews.

**Results:** Of 208 articles identified, 16 met the study criteria. Two were randomized (one multicentric, named the 'National Emphysema Treatment Trial' and including 1218 patients, and the other including only 30 patients). The other 14 articles were observational studies. The National Emphysema Treatment Trial identified a subgroup of patients with favorable prognoses when submitted to lung volume reduction surgery. This group consisted of patients with advanced heterogeneous pulmonary emphysema with upper lobe predominance, diffuse pulmonary distention and low exercise capacity. The pattern of the results obtained in the remainder of the studies was consistent with the individual analyses, despite their heterogeneity. In the observational studies, surgical benefit, mortality rates and quality of life were assessed.

**Conclusion:** The radiological pattern, characterized by the type, heterogeneity, distribution and diffuse distention, together with the degree of emphysema severity, represents the main predictor of a positive surgical outcome. Due to the paucity of studies in the literature, this is a grade B recommendation.

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**Key words:** Pulmonary emphysema. Lung surgery. Tomography X-ray computed. Review.

*Study carried out at the Universidade Federal da Bahia, Salvador. BA.
Correspondence to: Paula Antonia Ugalde Figueroa. Rua Emilio Odebrecht 254/102. CEP: 41830-300 Salvador, BA.
Phone. 55 71 3203-3488. E-mail: paugalde@terra.com.br
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## INTRODUCTION

Chronic obstructive pulmonary disease is a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is accompanied by an abnormal pulmonary inflammatory response to noxious particles and gases, primarily caused by cigarette smoking[1].

Pulmonary emphysema, which is one of the main components of chronic obstructive pulmonary disease, is defined as an abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, followed by the destruction of their walls, with no evident fibrosis[2]. The major functional disturbance caused by emphysema is the loss of lung elastic recoil of the lungs, resulting in reduced expiratory airflow and air trapping, which are responsible for lung hyperinflation[3]. Emphysema is usually caused by cigarette smoking, although other types of environmental exposure may be involved in the pathogenesis of the disease(4). In some cases, emphysema is accompanied by α-1 antitrypsin deficiency, which can aggravate the condition in smokers[4]. Emphysema is a chronic, progressive, incapacitating disease and can cause intense prolonged suffering for patients and their families, as well as great expenditure of health resources. Emphysema is one of the major causes of premature mortality in the modern world[5]. In 1997, according to data collected in the USA, there were 16,365,000 outpatient consultations and 448,000 hospitalizations directly related to chronic obstructive pulmonary disease[6].

In Brazil, according to data from the Sistema de Informações Hospitalares do Sistema Único de Saúde (SIH/SUS, Hospital Information Service of the Unified Health System) of the Ministry of Health, 66,711,853 Brazilian reals (US$22,846,526) were spent due to 182,035 hospitalizations of patients older than 49 years of age and diagnosed with chronic obstructive pulmonary disease[7].

Although clinical treatment may result in symptom relief and reduce the duration of each exacerbation, there is no definite proof that it can alter the natural course of the disease or reduce mortality[1]. Lung volume reduction surgery (LVRS) is a therapeutic alternative that can provide symptom relief, increase exercise capacity and improve quality of life if surgical candidates are selected carefully[8].

In order to determine the potential surgical benefit, is necessary to use imaging techniques to perform qualitative and quantitative evaluations[9]. Through a systematic review, we attempted to determine whether the radiological profile, characterized by the type, heterogeneity, anatomical distribution and distension of the emphysema, as well as by the degree of emphysema severity, would be predictive of a positive surgical outcome.

## METHODS

Studies regarding LVRS were selected from the following databases: MEDLINE, EMbase, LILACS, The Cochrane Library and EBM Reviews. Studies published from January 1994 to January 2004 were reviewed. Keywords used in the systematic review were, in accordance with the database terminology: "lung volume reduction surgery"; "LVRS"; "Lung/Surgery"; "Pulmonary surgical procedures"; "pneumoplasty"; pneumonectomy"; "computed tomography"; "Tomography"; "X-ray, computed" "Tomography"; "X-Ray"; "pulmonary emphysema". The best keywords for use in the search strategy were selected on the basis of a careful study of the National Library of Medicine Medical Subject Headings, EMbase database keywords and Biblioteca Virtual em Saúde - Descritores em Ciências da Saúde (Virtual Library of Health - Health Science Keywords) sites. Studies of interest were selected after the titles and the abstracts had been read. At that stage, the full versions of all potentially relevant studies were obtained.

The search strategy followed a methodology involving three steps[10]: inclusion of terms related to the condition ("pulmonary emphysema" vs. "LVRS"); insertion of terms related to the intervention ("tomography", "X-ray, computed", etc.); and inclusion of terms related to the methodology of the clinical studies[11]. Following these steps increased the sensitivity of this review. At each step, studies involving experimental animals were excluded. We also analyzed the references of the studies, trying to identify studies that might have been overlooked in the databases. We also carried out a manual search of non-indexed publications and contacted specialists to inquire about potential unpublished studies.

TABLE 1
The Cochrane Collaboration classification regarding the risk of bias in randomized studies

| Individual bias risk | Interpretation | Relationship with individual criteria |
|---|---|---|
| A. Low | Plausible bias that is unlikely to severely affect the results | All criteria met |
| B. Moderate | Plausible bias, results can become doubtful partially met | One or more criteria |
| C. High | Plausible bias, seriously affecting the reliability of results | One or more criteria not met |

In order to be included in this systematic review, studies must have been published between January 1994 and January 2004 and had to meet at least one of the following criteria: having either a randomized or observational design; involving patients diagnosed with advanced pulmonary emphysema and submitted to LVRS, regardless of the approach taken; assessing the prognostic value of pre or postoperative radiological evaluation (chest X-rays or computed tomography) of LVRS candidates; correlating functional and radiological findings with surgical outcomes; evaluating postoperative follow-up treatment, including functional and radiological parameters; determining morbidity, mortality and quality of life of patients submitted to LVRS. Studies in English, Portuguese and Spanish were reviewed.

Review articles, studies of bullous emphysema and studies that involved laser ablation for the surgical treatment of emphysema were excluded.

Two independent reviewers made the final selection and the independent analysis of each of the studies. Information such as demographics, sample size, study characteristics, methodology, interventions, results and follow-up evaluations, were collected from every selected study. If there was disagreement, the studies were reviewed, aiming at a consensual position and, in case a consensus was not reached, a third reviewer was included in the process.

Considering the objective of this systematic review, we followed the established criteria[12-14], formulating specific questions for each of the reviewed studies and, if those questions were answered by the methodology of a given study, it was immediately selected. The Cochrane Collaboration helped define variables used to evaluate not only the scientific quality of a study but its level of evidence as well[15]. These variables were allocation (appropriate, inappropriate or indefinite); blind study for the intervention and results; loss analysis and follow-up evaluation.

The risk of bias in a study is directly related to the previously defined criteria. Table 1 shows the classification regarding the risk of bias in a randomized study, in accordance with the Cochrane Reviewer Handbook[15].

In general, the same sources of bias seen in randomized studies can be applied to cohort studies[15].

The authors assume that the patients involved in the studies included in the present study were not blinded as to the study design since written informed consent is required prior to the performance of the surgical procedure.

The statistical analysis was descriptive, based on simple frequency and score distribution

## RESULTS

Using the above-mentioned search strategy, we identified a total of 208 articles in the following databases: MEDLINE, EMbase, LILACS, The Cochrane Library and EBM Reviews (Table 2). After their titles and abstracts had been read, 38 were selected. These 38 were submitted to the previously defined inclusion and exclusion criteria[8,16-30], resulting in the exclusion of 22 articles (Table 3).. Therefore, the final selection comprised 16 articles, all of which were fully analyzed and accepted by both reviewers.

The 16 remaining articles clearly referred to the theme "radiological profile of the ideal candidate for lung volume reduction surgery", evaluated the prognostic value of the type and distribution of the pulmonary emphysema, and correlated those data with the surgical outcome. Of the 14 observational studies selected, 13 were

TABLE 2

**Search results by database and by strategy**

| Database | LVRS vs. PE | LVRS vs. PE vs. CT | LVRS vs. PE vs. CT vs. CRCS |
|---|---|---|---|
| MEDLINE | 1312 | 247 | 155 |
| EMbase | 732 | 151 | 51 |
| LILACS | 32 | 10 | 0 |
| EBM Reviews | 14 | 4 | 2 |
| Total | 2090 | 412 | 208 |

LVRS: lung volume reduction surgery; PE: pulmonary emphysema; CT: computed tomography; CRCS: controlled randomized clinical studies, excluding those involving experimental animals

cohort studies, 5 of which prospective[8, 18-21], 8 of which were retrospective[22-29], and 1 was a case series study[30].

The 13 cohort studies[8,18-29] were paired for group analysis since they presented the same design, evaluated the same disease and intervention, measured the prognosis, described the follow-up evaluation of all participants and calculated the losses. Table 4 shows the individual characteristics of each of these studies.

Of the 16 selected articles, only 2 were randomized studies; the National Emphysema Treatment Trial [16] presented low risk of bias, and that conducted by Cassina et al.[17] presented a moderate risk of bias (Table 5).

The Cassina et al. study[17] was a randomized study, carried out from March 1995 to November 1996, comprising 30 patients subdivided into two distinct groups. Group 1 comprised 12 consecutive patients diagnosed with pulmonary emphysema due to α-1 antitrypsin deficiency, whereas group 2 comprised 18 patients with heterogeneous emphysema related to smoking. Patients from both groups were submitted to LVRS. There was a follow-up period of 2 years, and all losses were registered. The objective was to compare functional results during the follow-up period between patients diagnosed with α-1 antitrypsin deficiency and those with heterogeneous emphysema related to smoking. This was because, up to that point, α-1 antitrypsin deficiency was used as an exclusion criterion in many clinical trials or because this condition had not been studied separately. All participants were submitted to the same clinical evaluation protocol and preoperative pulmonary rehabilitation program. In-hospital mortality was nil in both groups. However,

TABLE 3

**Article exclusion criteria**

| Exclusion criteria | Reference |
|---|---|
| Review article | Kazerooni EA et al., 1997, 1998, 1999; Ramsey SD et al, 2003; Gierada DS et al., 2002; Bloch KE et al., 2002; Russi EW et al., 1999 |
| Computed tomography not used as a predictor for surgical treatment | Szekely LA et al., 1997; Ingenito EP et al., 2001; Sugi K et al., 2001; Baldwin JC et al, 2000; Maki DD et al, 1999; Kotloff RM et al, 2001 |
| Radiological profile of ideal candidate for surgery not evaluated | Bae KT et al., 1997; Cederlund K et al, 2002; Brenner M et al, 1997; Cleverley JR et al., 2000; Wisser W et al., 1998; Hunsaker AR et al., 1998; |
| Editorials | Gevenois PA et al., 2001; Salzman SH et al., 2000 |
| Artcle in Italian | Bonfioli C et al., 1997 |

TABELA 4 - Característica dos estudos de coorte selecionados

| Reference | Study design | Inclusion criteria | Exclusion criteria | Intervention | Outcome | Follow-up |
|---|---|---|---|---|---|---|
| Mc Kenna, 1997 | 154 consecutive patients from May 1995 to May 1996 | Severe heterogeneous emphysema, $FEV_1$ normal cardiologic evaluation from 40% to 20% of predicted values | Current smoker, homogeneous emphysema, age > 80 years, severe heart disease, cancer MV use, previous thoracic surgery | LVRS | Mortality, morbidity, radiologic pattern, age, $FEV_1$ | 3 months |
| Flaherty, 2001 | 89 consecutive patients from August 1994 to April 1998 | Severe heterogeneous emphysema, $FEV_1$ from 40% to 20% of predicted values, normal cardiologic evaluation | Chronic bronchitis, severe heart disease, smoking, á-1 antitrypsin deficiency | LVRS and type of emphysema detected by CT | Mortality, morbidity, functional evaluation, walk test, CT | 3 years |
| Coxson, 2003 | 21 patients from June 1994 to June 1997 | Patients who completed radiological, cardiopulmonary and physiological evaluation | Undefined | LVRS | $FEV_1$, exercise testing, radiological pattern | 3 months |
| Yusen, 2003 | 200 consecutive patients from 1993 to 1998 | Severe heterogeneous pulmonary emphysema, adequate cardiologic evaluation | Another airway disease, severe comorbidities, pulmonary hypertension > 45mmHg, unilateral LVRS unilateral or candidates for bullectomy | Preoperative pulmonary rehabilitation and LVRS | $FEV_1$, dyspnea, morbidity, mortality, quality of life | 5 years |
| Hamacher, 1999 | 37 consecutive patients from August 1994 to December 1998 | Adequate radiologic, physiologic and cardiopulmonary evaluation | á-1 antitrypsin deficiency | LVRS and type of emphysema detected by CT | Respiratory function testing and survival rate | 2 years |
| Weder, 1997 | 37 consecutive patients from August 1994 to December 1996 | Severe emphysema, dyspnea upon minimal exertion or at rest | Smokers, bullous disease | LVRS and type of emphysema detected by CT | Respiratory function testing and survival | 3 months |
| Gierada, 1997 | 46 consecutive patients, from January 1993 to February 1996 | Severe emphysema, without severe comorbidities | Bullous disease | LVRS and type of emphysema detected by CT | Respiratory function testing and quality of life | 6 months |
| Slone, 1997 | 50 consecutive patients from January 1993 to October 1994 | Pulmonary rehabilitation, severe emphysema | Smoking | LVRS | Respiratory function testing and radiological improvement | 6 months |
| Thurnheer, 1999 | 70 consecutive patients from August 1994 to November 1997 | Severe emphysema, dyspnea upon minimal exertion or at rest | Hypercapnia ($PaCO_2$ > 55 mmHg), advanced coronary disease, DLCO < 20% and bullous disease | LVRS | Respiratory function testing and radiological evaluation | 3 months |
| Gierada, 2000 | 70 consecutive patients from December 1993 to May 1995 | Adequate radiologic, physiologic and cardiopulmonary evaluation | Inadequate distribution of the emphysema for the study or poor physical condition | LVRS | Respiratory function testing and radiological evaluation | 6 months |
| Pompeo, 2000 | 52 consecutive patients from October 1995 to March 1998 | Severe pulmonary emphysema, preoperative pulmonary rehabilitation | Suppurative lung disease, bullous disease, asthma, metastatic cancer, smoking | LVRS and type of emphysema detected by CT | Respiratory function testing and radiological evaluation | No |
| Rogers, 2000 | 35 consecutive patients from October 1994 to February 1997 | Severe pulmonary emphysema, Adequate radiologic, physiologic and cardiopulmonary evaluation | Oxygen arterial saturation < 84% for 3 min in cycle ergometry without load | LVRS and type of emphysema detected by CT | Respiratory function testing and radiological evaluation | 3 months |
| Hunsaker, 2002 | 39 consecutive patients from October 1994 to January 1999 | Severe pulmonary emphysema with radiologic and cardiopulmonary evaluation | Not defined | LVRS, lung tomography and scintigraphy | Respiratory function testing, radiological and scintigraphic evaluation | Undefined |

$FEV_1$: forced expiratory volume in one second; MV: mechanical ventilation; LVRS: lung volume reduction surgery; CT: computed tomography; DLCO: diffusing capacity for carbon monoxide.

TABLE 5

**Characteristics of the randomized studies**

| | |
|---|---|
| Reference | |
| | Cassina, 1998 |
| | NETT, 2003 |
| Study design | |
| | Randomized, uncontrolled; 30 participants, 12 with de á-1 antitrypsin deficiency and 18 with acquired emphysema. One study group submitted to LVRS |
| | Randomized, controlled; multicentric; 1218 participants, 608 in the surgical group and 610 in the clinical group |
| Comparison | |
| | Functional results over a two-year follow-up period |
| | LVRS versus best clinical treatment, both groups were submitted to pulmonary rehabilitation prior to treatment |
| Inclusion and exclusion criteria | |
| | Severe emphysema $FEV_1$< 1 L, dyspnea score > 2, poor quality of life, heterogeneous emphysema, excluding bullous |
| | Emphysema or bronchiectasis, active smoker, body mass index < 18 kg/m$^2$ and hypercapnia |
| | Criteria defined by the NETT in 1999[21] |
| Intervention | |
| | LVRS X-ray CT |
| | LVRS X-ray CT |
| Outcome | |
| | Mortality, morbidity, complications and respiratory function testing |
| | Mortality, morbidity, maximal exercise capacity, evaluation of pulmonary function and quality of life |
| Follow-up period | |
| | 6, 12 and 24 months |
| | 5 years |

$FEV_1$: forced expiratory volume in one second; LVRS: lung volume reduction surgery; CT: computed tomography;

the number of complications was significantly higher in group 1. Functional improvement for the patients in group 1 peaked at 6 months. However, after a one-year follow-up period, there was a significant decline in pulmonary function, which returned to basal levels. On the other hand, functional improvement for the patients in group 2 was consistent and continued for at least two years.

The National Emphysema Treatment Trial(16) was a multicentric, randomized, controlled study, in which patients were subdivided into two treatment groups, and was carried out from January 1998 to July 2002. The study comprised a total of 1218 patients. Patients diagnosed with advanced bilateral pulmonary emphysema were selected. After randomization, 610 patients were submitted to clinical treatment and 608 to both clinical and surgical treatment. All patients were submitted to the same clinical evaluation protocol and the same pulmonary rehabilitation program (16 to 20 sessions, over a 6- to 10-week period). The study identified a subgroup of patients with favorable prognoses when submitted to LVRS. This group consisted of patients with advanced heterogeneous pulmonary emphysema presenting upper lobe predominance, diffuse pulmonary distension and low exercise capacity.

Functional improvement and the improvement in patient quality of life after 6, 12 and 24 months favored the surgical group. Within 24 months, exercise capacity significantly improved in the surgical group when compared to those patients submitted to clinical treatment alone (16% vs. 3%; $p < 0.001$). Improvement in exercise capacity

was observed in 28%, 22% and 15% of the patients at postoperative months 6, 12 and 24, respectively, compared to 4%, 5% and 3% of the patients in the clinical treatment group ($p < 0.001$).

In conclusion, in surgical group patients diagnosed with heterogeneous pulmonary emphysema presenting upper lobe predominance, diffuse pulmonary distention and low exercise capacity, functional improvement was greater and mortality rates were lower. The greatest surgical benefit was observed in those patients whose symptoms improved to the point of increasing their exercise capacity. For those patients, even a minimal functional improvement can have a significant impact on their quality of life.

## DISCUSSION

Lung volume reduction surgery is a procedure that should be indicated only when strict selection criteria are met since treatment success fundamentally depends on precise identification of good candidates for surgery[13].

In the present study, we tried to use a nonquantitative systematic review in order to determine whether there was an ideal radiological pattern that correlated with the postintervention prognosis. The National Emphysema Treatment Trial[16] is the only study using a methodology appropriate for evaluating this question. The article by Cassina et al.[17] was also a randomized study. However, the allocation of patients was inadequate and the patient sample was small (n = 30), insufficient to reject the type 2 error hypothesis, potentially affecting the interpretation of results. In addition, the authors evaluated a heterogeneous population of patients, if we consider that the evolution and the biological behavior of emphysema caused by α-1 antitrypsin deficiency differ from the characteristics of emphysema associated with smoking. Nevertheless, the study helped us conclude that patients diagnosed with heterogeneous emphysema related to smoking presented higher survival rates and functional improvement when submitted to LVRS than did patients diagnosed with emphysema caused by α-1 antitrypsin deficiency who were also submitted to that type of surgery.

The lack of randomized studies in the literature prevented us from performing a quantitative analysis of the systematic review, or meta-analysis. The other 14 studies were observational studies and were considered in this review. All came to the same conclusion: patients with severe, apical and heterogeneous emphysema have lower mortality rates and higher improvement in their pulmonary function and quality of life. The main bias that resulted from this type of study was related to the lack of a control group, which reduced the acceptance of these conclusions in clinical practice. Since they were observational studies, they did not allow the comparative analysis of outcome measures after an intervention, such as mortality, functional evaluation and quality of life. Although the conclusions drawn by the authors of these studies do not have the same force or scientific validity as those resulting from randomized studies[15], they should be considered applicable to the population.

In view of the need to evaluate the true efficacy of LVRS, we carried out this systematic review and discovered that there was a lack of appropriately designed studies in the literature. This surgical procedure has typically been recommended based on data collected in observational studies. We found only one A-level randomized study[16] evaluating this theme.

This systematic review allowed us to conclude that the radiological profile, characterized by the type, heterogeneity, distribution and diffuse distention of emphysema, together with the degree of emphysema severity, characterized by pulmonary function testing and the evaluation of exercise capacity, represents the main predictor of a positive surgical outcome. Due to the paucity of studies in the literature, this is a grade-B recommendation. Further studies should be carried out in order to provide this recommendation with a higher degree of scientific consistency.

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