REVIEW

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Late-stage emphysema: When medical therapy fails

ABSTRACT

Although most patients with emphysema are managed medically, a small subset of severely disabled patients may become candidates for surgery. This paper discusses for the internist who works with emphysema patients the risks, benefits, patient selection criteria, and outcome data for three procedures in current use: bullectomy, lung transplantation, and a new procedure which provides an alternative to transplantation—lung volume reduction.

KEY POINTS

All patients with emphysema require maximal maintenance medical therapy for functional relief and also as a prerequisite for surgical intervention.

Patient selection for bullectomy is based on symptoms, comorbid states, pulmonary function tests, imaging studies, and, above all, the size of the bullae.

Studies fail to show any statistical advantage of double lung vs single lung transplantation as late as 5 years after surgery; thus, since donor lungs are scarce, double lung transplantation should be reserved for select cases.

In lung volume reduction, abnormal and nearly functionless emphysematous lung tissue comprising 20% of the lung is resected, thus reducing the hyperinflated lungs closer to normal lung volume.

MOST PATIENTS with chronic obstructive pulmonary disease (COPD) are managed medically, but a small subset of patients who experience a progressive and accelerated decline in lung function, increasing symptoms, and severe disability[1] may be candidates for one of three surgical treatments:

- Bullectomy
- Lung transplantation
- Lung volume reduction.

This article will briefly touch on medical management of emphysema, and then review the rationale, indications, patient selection, and outcome data for each surgical approach.

ELEMENTS OF MAXIMAL MEDICAL THERAPY

Smoking cessation and oxygen therapy are the cornerstones of management for all patients with severe airflow obstruction and functional limitation. All patients require maximal maintenance medical therapy—not only for functional relief, but also as a prerequisite for any surgical intervention.

Specific components of medical therapy include pharmacotherapy, pulmonary rehabilitation, preventive vaccination, smoking cessation, and long-term oxygen therapy. When these treatments do not provide enough relief and the patient is able to undergo surgery, consideration of bullectomy, lung transplantation, or lung volume reduction is appropriate.

Drug therapy

Pharmacologic interventions aim to relieve symptoms and include short-acting and long-acting beta-2 agonists (albuterol, salmeterol), anticholinergic agents (antimuscarinics), methylxanthines, and steroids.[2,3–7] The role of

TABLE 1

Indications for long-term oxygen therapy*

Partial pressure of oxygen (PaO_2) ≤ 55 mm Hg
or oxygen saturation ≤ 88%

PaO_2 56 to 59 mm Hg or oxygen saturation 89%, if
Electrocardiographic evidence of cor pulmonale, or
Edema due to congestive heart failure, or
Hematocrit > 56%

Medicare-reimbursable to correct hypoxemia during
Exercise, if PaO_2 ≤ 55 mm Hg or oxygen saturation ≤ 88%
Sleep, if PaO_2 ≤ 55 mm Hg or oxygen saturation ≤ 88%
Drop in PaO_2 > 10 mm Hg or oxygen saturation > 5% with signs or symptoms of hypoxia

*Medicare requires recertification and retesting in 60 to 90 days if PaO_2 > 55 mm Hg, or oxygen saturation > 88% when oxygen was prescribed; recertification in all patients required after 1 year

Smoking cessation and oxygen therapy are still the cornerstone of management

steroids in slowing the rate of decline in FEV_1 is still unclear; results from ongoing long-term studies (ISOLDE, EUROSCOP) are expected shortly. Steroids seem to offer clear-cut benefit when used during acute exacerbations.[8] Similar benefits during an acute exacerbation have also been shown with the use of antibiotics compared with placebo.[9]

Vaccination

Preventive vaccination against pneumococcus and annual vaccination against influenza are advised.

Pulmonary rehabilitation

All patients with emphysema should undertake a pulmonary rehabilitation program and should continue a home-based exercise program for life.[10–12] An 8-week comprehensive rehabilitation program has been shown to result in a greater increase in maximal exercise tolerance, oxygen uptake, and exercise endurance, with improvement in perceived breathlessness and muscle fatigue when compared to a similar period of education alone.[13] Similar improvement in exercise tolerance and quality of life (for parameters of dyspnea, fatigue, emotion, and mastery) has been observed with home rehabilitation compared to controls.[14]

Only smoking cessation and long-term oxygen therapy improve survival

The above interventions are associated with symptomatic improvement, but survival benefits have been demonstrated only with smoking cessation and long-term oxygen therapy.

Smoking cessation. Although smoking cessation fails to regain lost FEV_1, it reduces the accelerated annual rate of decline in FEV_1 seen in smokers, and may even reduce the decline to levels seen in lifetime nonsmokers if stopped at an early stage.

Oxygen therapy. Both the Medical Council Research trial and the Nocturnal Oxygen Therapy Trial demonstrated a survival benefit from continuous oxygen therapy, with survival directly related to the total number of hours of oxygen used.[15,16] In patients in whom conventional oxygen delivery systems may be problematic or fail to achieve adequate oxygenation, a transtracheal oxygen system may be a more effective alternative to achieve therapeutic blood oxygen levels with lower flow rates.[17] Physiologic improvement from long-term oxygen therapy includes reduction in dyspnea, maximal voluntary ventilation, polycythemia, pulmonary hypertension, hypoxia associated with rapid eye movement during sleep, and nocturnal arrhythmias. It also results in improved arterial oxygenation, neuropsychiatric function, and exercise tolerance (TABLE 1).

BULLECTOMY

A bulla is an airspace greater than 1 cm in diameter formed as a result of pulmonary tissue destruction.[18] It maintains direct communication with bronchioles, but its walls lack vascularity. Thus, the bulla does not participate in gas exchange and acts more like a space-occupying lesion with compressive effects on surrounding parenchyma.

Patient selection for bullectomy

Patient selection for bullectomy should be based on symptoms, comorbid states, pulmonary function tests, imaging studies, and, above all, the size of the bullae. Bullae in patients with emphysema are generally from 1 cm to 4 cm in diameter, but are sometimes much larger, occupying more than one third of

the hemithorax.[19] The larger the bulla, the stronger the indication for surgery.

Bullae predispose patients to pneumothorax. In one series of patients with bullous emphysema,[20] the incidence of pneumothorax was 15.7% among patients followed without surgery. In the same series, pneumothorax was the indication for bullectomy in 19% of cases.

Asymptomatic patients, irrespective of the size of the bulla, generally are not operated on unless they work at a job that puts them at high risk for pneumothorax (eg, commercial airline pilots).[21]

Significant dyspnea remains the most common indication for bullectomy.

The bullae should be the likely cause of symptoms. If dyspnea and reduced pulmonary function are caused by widespread emphysema rather than by a giant bulla, then bullectomy may have no effect on symptoms or lung function. For example, if a bulla is not a giant bulla (ie, it occupies less than 30% of the hemithorax) but the patient has a severely reduced FEV_1, a reduced diffusing capacity, hypoxia, hypercarbia, and disabling dyspnea, then symptoms are likely due to the underlying emphysema rather than to the bulla.

On the other hand, in a symptomatic patient with a giant bulla and normal surrounding lung tissue, significant improvement can be expected. Younger patients with no comorbid conditions, an FEV_1 > 40% of predicted,[22] normal diffusing capacity,[22–24] and normal blood gases[22,24] are good candidates for bullectomy and show a reduction in dyspnea, improved exercise tolerance, increased FEV_1, and sustained benefits over years.

Evaluation for bullectomy

Chest computed tomography (CT) is currently the preferred method of evaluation in these patients. It easily demonstrates the size of the bulla, the status of surrounding pulmonary vasculature, and underlying lung disease.

Bullectomy outcomes

Physiological improvement following bullectomy is manifested by decreased airway and pulmonary vascular resistance, reduced functional residual capacity, and increased elastic recoil of the lung. Furthermore, the resulting decrease in total lung volume may improve diaphragmatic contour. Reduction in physiologic dead space is unlikely, as bullae normally do not participate in gas exchange.

Long-term results in properly selected patients have been good. The best outcome has been seen in patients with giant bullae occupying more than 50% of the hemithorax[25] and near-normal underlying lung functions. Subjective improvement in symptoms is often greater than objective increases in lung function.[26,27] Despite return of symptoms in some patients because of continued smoking,[24] functional improvements in the majority have been sustained over 5 to 10 years, and even as long as 24 years.[20,28,29]

Bullectomy is generally for bullae that occupy at least 30% of the hemithorax

TABLE 2

Selection criteria for lung transplantation

Between 70% and 130% of ideal body weight

Taking only a minimal dose of steroids (≤ 20 mg of prednisone)

Approximate maximum age (years):
- 65 (single lung recipients)
- 60 (double lung recipients)
- 55 (heart-lung recipients)

No substance abuse for more than 6 months

Creatinine clearance > 50 mg/mL/min

Chronic obstructive pulmonary disease
- FEV_1 < 25% of predicted (without reversibility)
- Hypercapnia ($PaCO_2$ > 55 mm Hg)
- Pulmonary hypertension
- Progressive disease (eg, cor pulmonale)

LUNG TRANSPLANTATION

Lung transplantation is the ultimate option for patients with severe end-stage lung disease, and emphysema remains the most common indication for transplantation.

Patient selection

A number of general-health criteria and disease-specific characteristics need to be fulfilled before patients are considered good candidates (TABLE 2). In general, prerequisites for successful lung transplantation include:

- Severe disease with significantly impaired activities of daily living

- Motivated patient with no associated comorbid conditions
- Completion of maximal medical therapy and optimal pulmonary rehabilitation.

The goal of lung transplantation is improved quality of life rather than prolonged survival. Acutely ill, unstable patients on mechanical ventilation are not candidates. However, stable patients on noninvasive ventilation may be evaluated for transplantation. Hypercapnia and significant pulmonary hypertension are acceptable in lung transplantation candidates, whereas this is not true for candidates for lung volume reduction.

Contraindications

Hepatitis B surface antigen positivity, hepatitis C with histologic evidence of liver disease, human immunodeficiency virus infection, and progressive neuromuscular disease are among the absolute contraindications to transplantation (TABLE 3). For patients treated for cancer, a 2-year disease-free interval is recommended before transplantation, except for basal and squamous cell skin carcinoma, in which case there is no such requirement. However, in the case of breast cancer (stage 2 or higher), extracapsular renal cell tumor, colon carcinoma (> Duke A), and melanoma (level III or deeper), most lung transplantation centers opt for a 5-year disease-free interval before considering transplantation.

Relative contraindications. Symptomatic osteoporosis is a relative contraindication to lung transplantation. Patients with marked kyphosis or significant back pain may be denied transplantation. Patients with less than normal bone densitometry T scores in the hip or spine are placed on therapy, usually oral bisphosphonates. Asymptomatic patients with T scores of less than -2.5 standard deviations from the mean are considered at high risk and receive preoperative intravenous bisphosphonate therapy. All attempts should be made to discontinue use of corticosteroids.

Patients need to weigh between 70% and 130% of their ideal body weight. Periodic biochemical monitoring is recommended to satisfy compliance with freedom from substance abuse. Psychosocial issues that may negatively impact patient outcome should be resolved, and noncompliance with medical care or treatment plans should be addressed.

Attempts should be made to eradicate colonization with fungal and atypical mycobacterial species. However, adequately treated mycobacterial disease is not a contraindication to lung transplantation.

TABLE 3

Absolute and relative contraindications to lung transplantation

Absolute

- Hepatitis B surface antigen positivity, hepatitis C with liver disease
- Malignancy within 2 years, except skin cancer
- Significant untreatable coronary artery disease or left ventricular dysfunction, except for heart-lung recipients
- Progressive neuromuscular disease
- HIV infection
- Creatinine clearance < 50 mg/mL/min

Relative

- Colonization with fungal or atypical mycobacterial infections
- Symptomatic osteoporosis
- Systemic disease with end-organ damage
- Kyphoscoliosis
- Sputum with panresistant organisms
- Unresolved psychosocial issues
- Mechanical ventilation (invasive)
- Noncompliance to medical therapy

Single lung transplantation: Preferred method despite drawbacks

Single lung transplantation is the preferred method of transplantation now offered to emphysema patients. Most clinicians report good early and intermediate results,[30] and it allows for a larger number of recipients than double lung transplant.

Hyperinflation of the native lung is an important complication of single lung transplantation. It may occur if the donor lung is small, if there is significant bullous disease present in the native lung, or if there is early allograft rejection or other pulmonary complication. Although this problem is reported by many physicians, overall impact on patient outcome appears small. In the rare cases of significant graft compression, several corrective options (eg, pneumonectomy, lobectomy, bullectomy, lung volume reduction) are available.

Emphysema is the most common indication for lung transplant

Infection of the native lung is another problem, with the potential of contamination of the transplanted lung, threatening its function. Of particular concern is *Aspergillus* colonization of the native lung which may act as a reservoir for persistent infection.[31]

Double lung transplantation: reserve for select patients

Although early functional outcomes are better with double lung transplantation and the potential for certain complications is much less than with single lung transplantation, survival data have failed to show any statistically significant advantage of double lung over single lung transplantation up to 5 years after surgery. Thus, in view of the great shortage of donor lungs, double lung transplantation should be reserved either for very young patients or for those in whom there is a compelling reason to remove both lungs, such as concomitant bronchiectasis or giant bullous disease.

Lung transplantation mortality and complications

The number of patients with end-stage disease far exceeds the donor organ supply

Perioperative mortality for lung transplantation has decreased significantly during the past decade, and both single lung and double lung methods in emphysema patients have less than a 10% operative mortality.[32] Causes of early mortality (< 90 days) include infection (35%), early graft failure due to reperfusion injury (15%), cardiac dysfunction, rejection, bleeding, and anastomotic breakdown.[32]

Late mortality is primarily related to infection, chronic rejection, or bronchiolitis obliterans. Aggressive infection prophylaxis can restrict infectious complications in the immediate perioperative period, but opportunistic infections related to immunosuppressive agents are a constant danger.

Complications of drug-induced immunosuppression in the posttransplantation period include lymphoreticular and non-lymphoreticular malignancies, hypertension, renal toxicity (from cyclosporine and tacrolimus), gastrointestinal problems, cyclosporine-induced neurotoxicity, osteoporosis, and hyperlipidemia.

Transplantation outcomes

After transplantation, most patients exhibit an improvement in dyspnea from New York Heart Association class 3 or 4 to class 1. Single lung transplantation patients may achieve an FEV_1 measurement of more than 50%[33] and a marked improvement in both graded and nongraded exercise capacity.[34] Maximum oxygen uptake ranges from 45% to 60%, similar to that for double lung transplant recipients,[35] with a marked increase in 6-minute walking distances by 3 months after transplantation.[36]

LUNG VOLUME REDUCTION

The number of emphysema patients with end-stage lung disease presenting to transplantation centers far exceeds the number of donor organs available, so alternatives to transplantation are necessary. Lung volume reduction is an effective alternative gaining popularity.

Lung volume reduction seeks to correct a variety of physiologic variables in the emphysematous lung, specifically elastic lung recoil pressure and expiratory flow. Abnormal and nearly functionless emphysematous lung tissue comprising 20% of the lung is resected, thus reducing the hyperinflated lungs closer to normal lung volume.

In emphysematous lungs, lung volumes are increased, the elastic properties are lost, and circumferential pull on the bronchioles is impaired, especially during expiration, leading to a greater degree of obstruction. After lung volume reduction surgery, the increased lung volumes are reduced, and the physiologic circumferential pull is partially restored. Reduction in lung volumes also allows the diaphragm to attain a more dome-shaped contour that permits it to function more effectively, and the thoracic cage to assume a more normal shape.

This procedure was developed between 1957 and 1961, but a high complication rate and an unacceptable mortality rate led to its abandonment until its revision and resurgence in the early 1990s.[37]

Patient selection

The general medical patient selection criteria are less stringent for lung volume reduction than for lung transplantation, but the disease-

TABLE 4

Eligibility factors for lung transplantation and lung volume reduction

FACTORS	LUNG TRANSPLANTATION	LUNG VOLUME REDUCTION
Age > 65 years	Not allowed	Allowed
Coexistent pulmonary infection or bronchiectasis	Not allowed	Allowed
Homogeneous disease distribution	Allowed	Possibly allowed
Previous thoracotomy	Allowed	Not allowed
Social support system	Important	Less important
Financial issues	Important	Less important
FEV_1 < 20% of predicted	Usually required	Not required
Total lung capacity	No minimum	> 100% required
PaO_2 (on room air)	No minimum	> 45% required
$PaCO_2$	No maximum	< 60 mm Hg required
Pulmonary arterial pressure (mean)	No maximum	< 35 mm Hg required

specific criteria are more restrictive (TABLE 4). For example, there is no age restriction, some comorbid disease states are allowed, and a solid psychosocial support system is not considered as crucial. Although patients have significant functional disabilities, the ability to complete a pulmonary rehabilitative program and some exercise tolerance (such as the ability to walk at least 140 meters) are essential prerequisites for lung volume reduction surgery (TABLE 5).

Choosing between lung volume reduction and transplantation

Despite the differences in specific criteria for lung volume reduction vs lung transplantation, a small group of patients qualifies for either procedure, and the choice of treatment must be individualized.

For older groups of patients closer to the transplantation age restriction (see TABLE 2), the benefits of lung volume reduction should be weighed against those obtained from lung transplantation.

For example, lung function is improved much more with transplantation than with lung volume reduction, although at 1 year the exercise tolerance is the same.[38] Thus, although some would offer lung transplantation, the choice is controversial and individual preferences should be clarified. For younger patients, lung volume reduction may provide enough improvement to postpone the need for transplantation. Furthermore, in either group of patients, lung volume reduction may be a bridge to transplantation while patients await a donor organ. For a patient whose FEV_1 is severely reduced (< 15%), pulmonary damage may be so severe that lung transplantation is the only option.

Air leaks are the most common complication after lung volume reduction

Complications

Persistent air leaks are the most common complication following lung volume reduction. Other complications include pneumonia, reintubation, need for tracheostomy, wound infection, arrhythmias, phrenic nerve palsies, gastrointestinal problems including bowel perforation, development of postoperative pulmonary hypertension, thrombophlebitis, myocardial infarction (in older patients), and significant anxiety and panic attacks. Anxiety and panic attacks have been associated with an increase in morbidity.

Careful attention to preoperative exacerbation, early management of anxiety and panic attacks, avoidance of narcotic analgesics beyond the first couple of days to reduce bowel problems, extubation within

TABLE 5

Criteria for lung volume reduction surgery

- No age restriction
- Marked disability after completing pulmonary rehabilitation (see text)
- No tobacco use for at least 4 months
- Imaging must show heterogeneous disease (homogeneous disease has more stringent criteria)
- Pulmonary function tests (all after bronchodilator administration; lung volumes measured by plethysmography)
  - Forced expiratory volume in 1 second (FEV_1) ≤ 45%; if age > 70 years, an FEV_1 ≥ 15% predicted)
  - Total lung capacity ≥ 110%
  - Residual volume ≥ 150%
  - Diffusing capacity of the lung for carbon monoxide ≤ 70%
  - Absence of bronchodilator response (FEV_1 change ≤ 30% and 300 mL)
- $PaCO_2$ < 60 mm Hg
- PaO_2 > 45 mm Hg on room air
- Mean pulmonary artery pressure ≤ 35 mm Hg or peak systolic pressure ≤ 45 mm Hg

the operating or recovery room, and reinstitution of postoperative pulmonary rehabilitation as soon as possible could help obviate some complications and permit an earlier hospital discharge.

Perioperative mortality is reported between 0% and 18%, with most centers under 10%.[19,39]

Lung volume reduction outcomes

Successful lung volume reduction results in a variable improvement in elastic lung recoil.[38] Cumulative evidence suggests an increase in FEV_1 of 13% to 96% in a diverse population of patients utilizing different surgical techniques and variable follow-up.[19] Upper lobe predominance and elevated baseline plethysmographic residual volume are associated with a good outcome. There may be a disproportionate subjective improvement in symptoms (eg, quality of life) compared with objective findings in lung function studies.

Long-term follow-up data are still not available, and it is not clear how long the improvement in lung function seen after lung volume reduction will persist. Maximal improvement in lung function indices are seen at 6 months after surgery, and although improvements are maintained at 1 year, there may be a trend towards falling indices compared with the 6-month values.[40,41] Long-term improvement in measurements of other functional aspects such as dyspnea, which may or may not be related to commonly measured pulmonary function, has not been carefully studied.

Lung volume reduction: major questions

Lung volume reduction is a palliative procedure that does not halt, but only slows, the rate of functional decline for emphysema patients. The disease will progress, and symptoms will likely worsen. Still, data suggest that significant short-term improvement and partial reversal of the physiologic derangements can be obtained.

Major questions remain about the role of lung volume reduction:

- Who are the best candidates for the procedure, and does the procedure have an acceptably good effect?
- If there is a benefit, how long does it last, and does it justify both the risk to potential transplantation candidates and the cost in money and resources?

The role of lung volume reduction vs maximal medical therapy and pulmonary rehabilitation need to be more carefully assessed in patients with advanced COPD. Can medical therapy and rehabilitation alone result in improvements similar to those reported for lung volume reduction?

To answer some of these tethering issues, a multicenter study is underway. This study, the National Emphysema Treatment Trial, is a 17-center prospective trial involving 4,700 patients randomized either to medical therapy and rehabilitation or to surgery. Patients will be followed for 5 years.

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