Lung volume reduction surgery: results of a Canadian pilot study

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Objective: To present preliminary experience with lung volume reduction surgery (LVRS) before the institution of the Canadian LVRS trial.

Design: A prospective case series between December 1995 and January 1997.

Setting: University hospitals in London and Hamilton, Ont.

Patients: Forty-nine patients who had disabling dyspnea or emphysema with hyperinflation, able to participate in respiratory rehabilitation. Twenty-three patients were excluded because of comorbid conditions precluding surgery, pulmonary hypertension, excessive steroid dependence, malnutrition, obesity, previous thoracotomy, large solitary bullae, concurrent malignant disease, chronic bronchitis, hypercapnia or psychiatric illness.

Interventions: Preoperative respiratory rehabilitation followed by LVRS via median sternotomy.

Main outcome measures: Impairment, disability and handicap were assessed before and 12 months after LVRS. Impairment was assessed by changes in pulmonary function test results and blood gas measurements, disability by the 6-minute walk test and cardiopulmonary exercise test, and handicap by the disease-specific chronic respiratory disease questionnaire (CRQ), the generic medical outcomes survey short form 36 (SF-36) and the generic health utilities index mark III (HUI-III).

Results: Two patients died of respiratory failure while in rehabilitation. Twenty-four patients (17 men, 7 women) successfully completed rehabilitation and underwent LVRS. The mean age was 63 years (range from 49 to 78 years) and the median length of hospital stay was 12.5 days (range from 7 to 90 days). Two patients (8%) died in the early postoperative period (within 30 days) of pneumonia. One patient died of respiratory failure 8 months after LVRS after a difficult 90-day postoperative hospital stay. There were 27 major complications. There was a 36% relative increase in the mean forced expiratory volume in the first second ($p = 0.01$) and a 10% relative increase in the 6-minute walk test ($p = 0.06$). The mean CRQ dyspnea score increased 2.3 points ($p = 0.01$), and the SF-36 general health domain increased 20 points ($p = 0.01$). There was no significant change in the HUI-III ($p = 0.73$).

Conclusion: LVRS appears to lessen the respiratory impairment and handicap for at least 1 year in selected patients with advanced emphysema.

Objectif : Présenter l'expérience préliminaire tirée de l'intervention chirurgicale de réduction du volume pulmonaire (ICRVP) avant le lancement de l'étude canadienne en la matière.

Conception : Étude de cas prospective réalisée entre décembre 1995 et janvier 1997.

Contexte : Hôpitaux universitaires de London et de Hamilton (Ontario).

Patients : Quarante-neuf patients atteints d'une dyspnée invalidante ou d'emphysème avec hyperinflation, capables de participer à une réadaptation respiratoire. On a exclu 23 patients pour les raisons suivantes : problèmes comorbides empêchant une intervention chirurgicale, hypertension pulmonaire, dépendance excessive aux stéroïdes, malnutrition, obésité, thoracotomie antérieure, importantes bulles isolées, tumeur maligne simultanée, bronchite chronique, hypercapnie ou maladie psychiatrique.

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INTERVENTIONS : Réadaptation respiratoire préopératoire suivie d'une intervention chirurgicale de réduction du volume pulmonaire par sternotomie médiane.

PRINCIPALES MESURES DE RÉSULTATS : On a évalué la déficience, l'incapacité et le handicap avant l'ICRVP et 12 mois après. On a évalué la déficience en fonction des changements des résultats des tests de fonction pulmonaire et des mesures de gaz sanguins, l'incapacité au moyen de l'épreuve de marche de six minutes et de l'épreuve d'exercice cardio-pulmonaire, et le handicap au moyen du questionnaire sur les maladies respiratoires chroniques (CRQ) spécifique à la maladie, du questionnaire générique abrégé 36 (SF-36) sur les résultats médicaux et de l'indice générique des facteurs utilitaires de la santé mark III (HUI-III).

RÉSULTATS : Deux patients sont morts d'insuffisance respiratoire au cours de la période de réadaptation. Vingt-quatre patients (17 hommes, 7 femmes) ont terminé avec succès la réadaptation et ont subi une intervention chirurgicale de réduction du volume pulmonaire. Leur âge moyen était de 63 ans (plage de 49 à 78 ans) et la durée médiane de l'hospitalisation a atteint 12,5 jours (plage de 7 à 90 jours). Deux patients (8 %) sont morts d'une pneumonie au début de la période postopératoire (dans les 30 jours). Un patient est mort d'insuffisance respiratoire huit mois après l'intervention chirurgicale, après un difficile séjour de 90 jours à l'hôpital qui a suivi l'intervention. Il y a eu 27 complications majeures. On a constaté une augmentation relative de 36 % du volume expiratoire maximal moyen par seconde (p = 0,01) et une augmentation relative de 10 % lors de l'épreuve de marche de 6 minutes (p = 0,06). Le résultat moyen de dyspnée CRQ a augmenté de 2,3 points (p = 0,01), et le domaine général de santé indiqué par le questionnaire SF-36 a augmenté de 20 points (p = 0,01). Le résultat de l'indice mark III HUI-III n'a pas changé pour la peine (p = 0,73).

CONCLUSION : L'ICRVP semble réduire la déficience et le handicap respiratoires pendant au moins un an chez certains patients atteints d'emphysème avancé.

The results from case series reported from the United States, Australia and Europe of patients who have undergone lung volume reduction are encouraging, but to date there are no data from Canadian centres. In Canada, chronic obstructive pulmonary disease (CPOD) is the fourth leading cause of death.[1] In 1994, COPD was diagnosed in 750 000 Canadians, representing 3.1% of the population.[2] There were 8920 deaths due to chronic bronchitis and 1059 deaths due to emphysema. In 1993, over 116 500 Canadians were admitted to hospital, resulting in over 1.1 million hospital-days and over $632 million in expenditures for the treatment of COPD. Lung volume reduction surgery (LVRS) appears to improve functional and physiologic parameters in patients with emphysema.[3] It has not, however, clearly been shown to improve the quality of life as assessed by valid instruments. Two Canadian university centres began collaborative work in 1995 to assess the physiologic and health-related quality-of-life changes after LVRS. We present the results of our pilot project, examining the effectiveness of LVRS for the treatment of emphysema in a Canadian population before the institution of the Canadian lung volume reduction surgery trial. The purpose of this study was to evaluate outcomes in patients with advanced emphysema who have undergone LVRS, specifically, to examine the change in patients' quality of life after LVRS, to aid in the sample-size calculation and to refine the inclusion–exclusion criteria for the Canadian lung volume reduction surgery trial.

METHODS

Inclusion criteria

Consecutive patients referred for LVRS from 2 university centres in London and Hamilton, Ont., were assessed between December 1995 and March 1997. Patients were screened by history, physical examination, routine laboratory tests, pulmonary function tests, chest computed tomography, nuclear lung perfusion scanning, echocardiography, and right heart catheterization if needed. Patients were considered eligible if they were between 40 and 79 years of age, had disabling dyspnea, emphysema with hyperinflation and agreed to participate in respiratory rehabilitation and LVRS (Table I).

Exclusion criteria

Patients were excluded if they had any comorbid conditions precluding surgery, pulmonary hypertension, excessive steroid dependence (more than 10 mg/d of prednisone), malnutrition, obesity, previous thoracotomy, large solitary bullae (more than 20% of hemithorax), concurrent malignant disease, chronic bronchitis (daily sputum production for more than 3 months per year), hypercapnia (partial pressure of carbon dioxide [P_{CO_2}] more than 55 mm Hg) or psychiatric illness (Table II).

Procedure

All patients had a respiratory assessment and underwent at least 6 weeks of respiratory rehabilitation. Once rehabilitation had "medically" optimized the patients' health, they underwent bilateral LVRS as previously described.[3] Antibiotics (1 g cefazolin intravenously or 1 g vancomycin) were given prophylactically 30 minutes before skin incision. A thoracic

epidural catheter was inserted preoperatively and pre-emptive analgesia was provided with rectal administration of indomethacin (100 mg). General anesthesia consisted of intravenous propafol (2 mg/kg) or sodium thiopental (3 to 5 mg/kg); nitrous oxide was avoided and systemic use of narcotics minimized. A left-sided double-lumen endotracheal tube provided single lung ventilation. A standard median sternotomy incision was made and the most severely affected lung was managed first. Single lung ventilation was used on the contralateral side and the collapsed lung elevated with posteriorly placed moist packs or saline. The total lung volume was reduced by 20% to 30% by removing the most destroyed lung with linear staplers (GIA-90 stapler; Auto Suture, Norwalk, Conn.). The staple line was buttressed with bovine pericardium to reduce postoperative air leaks.[4] Efforts were made to maintain the normal shape and configuration of the lung. An apical parietal pleurectomy was performed in some patients to encourage pleurodesis and help reduce air leaks. The procedure was repeated on the other side. Each pleural space was drained using 2 chest tubes attached to underwater seal.

Postoperative analgesia was provided by a mixture of 0.25% bupivacaine and fentanyl 20 mg/mL administered through the thoracic epidural catheter and titrated as required. To prevent respiratory depression and help reduce the need for narcotic agents, rectal indomethacin suppositories were administered (100 mg every 12 hours). Misoprostol 200 mg 3 times per day was given orally to prevent gastrointestinal ulcers while indomethacin was being given. Routine physiotherapy was initiated as early as possible postoperatively.

Table I

Criteria for Inclusion in the Study
Disabling dyspnea (CRQ dyspnea score < 5)
Impaired quality of life
Age between 40 and 79 yr
Post-bronchodilator FEV_1 ≤ 40% predicted
Diffusion capacity (DLCO/VA) ≤ 60%
Total lung capacity (by whole-body plethysmography) ≥ 120% *or*
Residual volume (by whole-body plethysmography) ≥ 200%
Able to attend a respiratory rehabilitation program preoperatively

CRQ = chronic respiratory disease questionnaire, FEV_1 = forced expiratory volume in the first second, DLCO/VA = diffusion capacity of carbon monoxide corrected for alveolar volume.

Outcomes

The outcome measurements in this pilot study included an assessment of impairment, disability and handicap as defined by the World Health Organization in 1980.[5] Impairment (any loss or abnormality of function) was measured using pulmonary function tests and blood gas measurements. Disability (any restriction in the ability to perform an activity in the manner considered normal for a human being) was assessed using the maximum exercise capacity from the stage 1 exercise test and by the 6-minute walk test.[6] Handicap (the disadvantage resulting from an impairment or disability that limits or prevents the fulfilment of a role that is normal for that individual) was scored using health-related quality-of-life instruments. The quality-of-life assessment included a portfolio of 3 validated instruments: the disease-specific chronic respiratory disease questionnaire (CRQ);[7] the generic medical outcomes survey short form 36 (SF-36);[8,9] and the generic health utilities index mark III (HUI-III).[10,11]

Chronic respiratory questionnaire

The CRQ is a 20-item questionnaire that is interviewer-administered and disease specific. It measures patients' symptoms in the areas of dyspnea (5 items), fatigue (4 items), emotional function (7 items) and mastery (4 items) during self-selected day-to-day activities. Each domain is scored on a scale of 1 (worst) to 7 (best). It

Table II

Criteria for Exclusion of Patients From the Study
Medical conditions, other than emphysema, that might limit exercise tolerance, participation in a rehabilitation program or cognitive functions, e.g.,
ischemic heart disease
peripheral vascular disease
neuromuscular disease
Pulmonary hypertension by right heart catheterization (systolic pressure > 50 mm Hg or mean > 35 mm Hg)
Excessive corticosteroid therapy (prednisone > 10 mg/d)
Malnutrition (body mass index < 20 kg/m^2)
Obesity (body mass index > 30 kg/m^2)
Previous thoracotomy
Solitary bullae (bulla > 20% of hemithorax)
Concurrent malignant disease
Chronic bronchitis (daily sputum production > 3 mo/yr)
Hypercapnia (P_{CO_2} > 55 mm Hg)
Asthma (increase in FEV_1 > 20% and > 200 mL post bronchodilator)

P_{CO_2} = partial pressure of carbon dioxide, FEV_1 = forced expiratory volume in the first second.

takes 20 minutes to administer. Its performance in subjects with COPD has been tested and its validity, responsiveness and interpretability are established.[7,12–15] A change in score of 0.5 per item has been associated with a minimally important health-related difference in quality of life, a change of 1 is moderate, and a change of more than 1 a large difference.[16]

Medical outcomes study short form 36

The SF-36 is a commonly used and reliable generic tool. This instrument measures 8 heath-related concepts: physical function; role limitations secondary to physical health problems; social function; mental health; role limitations secondary to emotional problems; pain; vitality; and general health perceptions. The scores range from 0 (worst) to 100 (best). The SF-36 provides data that are comparable for different health states and interventions.[9,17,18] The scores on several subscales correlate significantly with severity of chronic lung disease expressed by forced expiratory volume in the first second (FEV_1), baseline dyspnea index or clinical criteria.[19,20] It can discriminate among people with different severity of COPD.[21] It is highly reproducible among patients with chronic airflow limitation and it shows responsiveness in a variety of clinical surgical interventions.[22,23] Validity and reliability have been established in 11 186 adult English-speaking patients. The test takes less than 10 minutes as an interviewer-administered questionnaire in elderly people and it can be self- or interviewer-administered.[18] Its utility in patients who undergo LVRS is unknown.

The health utilities index mark III

The HUI-III is a generic preference-based approach to the measurement of health status and assessment of health-related quality of life. It is a 15-item self-administered questionnaire that has been designed to ask the minimum number of questions required to classify health status. Health status as described in the HUI-III system is valued according to a multiplicative multi-attribute utility function estimated from preference scores that are obtained from a random sample of the general public.[10,24] The scoring function for the HUI-III is based on standard gamble preference measurements. The scoring function for the HUI-III assigns a single summary score in the interval between 0.00 (dead) and 1.00 (perfect health).

Analysis

The preoperative values after respiratory rehabilitation and before operation were compared with the postoperative values at 12 months. The scoring of the CRQ has been described previously.[7] Scores for each of the 8 dimensions of health on the SF-36 were calculated by summation of the Likert scales for each item.[9] The sums were transformed to a percentage of the possible range of scores for each dimension using SAS software and the program provided in the user's manual.[25] Scoring for the HUI was based on the mark III version.[11] All available paired data were summarized as the mean (and 1 standard deviation) and the range and compared with a paired *t*-test using the SPSS.[26] The absolute and relative changes between preoperative and postoperative values are presented with the 95% confidence interval and the probability value.

RESULTS

The demographic details of all patients from both centres are shown in Table III. Forty-nine patients were referred for consideration for LVRS to the centres after being screened by their referring respirologists using the eligibility criteria outlined in Tables I and II. Twenty-three candidates were excluded from the protocol for the reasons listed in Table IV. Two additional patients were assessed and accepted for the procedure but had respiratory failure and died before operation. Twenty-four patients successfully completed the rehabilitation and underwent LVRS. One patient had α-1 antitrypsin deficiency. One patient was considered a good candidate for surgery but had an initial P_{CO_2} of 68 mm Hg. After much consideration he underwent surgery

Table III

Demographic Features of 24 Patients (17 Men, 7 Women) Who Underwent Lung Volume Reduction Surgery

Demographic feature	Mean (and SD)	Range
Age, yr	62.8 (7.5)	49 – 78
Intensive care unit stay, d	4.8 (12.0)	0 – 60
Hospital stay, d*	18.3 (18.5)	7 – 90

*Median hospital stay was 12.5 d.

Table IV

Reasons for Exclusion of 23 Patients From the Study

Reason	No. of patients
Not hyperinflated (TLC < 120%)	1
Not disabled enough	6
Unsuspected lung cancer	4
Hypercarbia (P_{CO_2} > 55 mm Hg)	1
Comorbidities	4
Pneumothorax and air leak	5
End-stage respiratory failure	2

TLC = total lung capacity, P_{CO_2} = partial pressure of carbon dioxide.

and did well .[27] No other patient underwent LVRS outside the defined inclusion criteria.

Complications

Two patients died of pneumonia, both on the 18th postoperative day. The early morbidities (within 30 days) are listed in Table V. One patient died 8 months postoperatively after surviving a difficult 90-day initial hospital stay and a second patient had respiratory failure requiring ventilation 16 months postoperatively. He recovered and at the time of writing was doing well.

Table V

Early Complications or Death (Within 30 Days)

Complication/death	No. (%)
Prolonged air leak (> 10 d)	6 (25)
Tracheobronchitis	5 (21)
Ventilation required (BiPAP or mechanical)	4 (17)
Panic attacks	3 (13)
Pneumonia	3 (13)
Supraventricular tachycardia	1 (4)
Leg thromboembolism	1 (4)
Horner's syndrome	1 (4)
Gastrointestinal bleeding	1 (4)
Heparin-induced skin necrosis	1 (4)
Death	2 (8)

BiPAP = bi-level positive airway pressure.

Impairment

At 12 months there was a 36% relative improvement in FEV_1 and an absolute improvement of 8% (95% CI 2% to 13%) ($p = 0.008$) after LVRS. There were no significant changes in partial pressure of oxygen, PCO_2, diffusion capacity or total lung capacity (Table VI). The residual volumes significantly decreased by 78% (95% CI –120% to –36%), Home oxygen requirements decreased from 11 of 24 (46%) preoperatively to 3 of 20 (15%) postoperatively.

Disability

There was no significant improvement in the degree of patient disability. The maximum exercise capacity increased 55% or 161 kpm (95% CI –9 to 331 kpm) ($p = 0.3$) and the 6-minute-walk improved 10% or 34 m (95% CI –35 to 104 m) ($p = 0.06$) (Table VII).

Handicap

There was a significant amelioration of dyspnea, as detected by an increase in the CRQ dyspnea score of 2.3 (95% CI 0.8 to 3.7, $p = 0.006$). Two of the 8 domains of the generic SF-36 improved significantly. The physical role domain improved by 182% ($p = 0.04$) and the general health domain improved by 49% ($p = 0.01$). The HUI-III showed a slight but insignificant improvement in quality of life (0.03; 95% CI –0.14 to 0.20, $p = 0.07$).

Discussion

LVRS appears to improve the health of selected patients with emphysema as suggested by the measurement of impairment, disability and handicap. Many studies have already shown improvements in physiology, pulmonary function and the 6-minute walk test; however, improvements in handicap have yet to be documented well.[28–31]

The disease-specific CRQ has been tested, and its validity, responsiveness and interpretability are established in patients having emphysema.[7,12–15] The changes in the dyspnea and mastery domains of the CRQ were clinically and statistically significant after LVRS (Table VIII).[6] The generic SF-36 showed improvements in 2 of the 8 domains, although all other domains, except for the pain index, did show some improvement.

The HUI-III produced insightful results. HUI is a preference-based in-

Table VI

Changes Resulting From Lung Volume Reduction Surgery With Respect to Impairment

	Measurement						
	Preoperative		Postoperative		Change		
Outcome measure	Mean (and SD)	No. of patients	Mean (and SD)	No. of patients	Absolute (95% CI)	Relative, %	*p* value
FEV_1, % predicted	22 (7)	18	30 (13)	18	8 (2 to 13)	36	0.008
PO_2, mm Hg	64 (9)	11	62 (9)	11	–1 (–9 to 6)	–7	0.696
PCO_2, mm Hg	45 (8)	11	42 (6)	11	–3 (–7 to 1)	–7	0.147
DLCO/VA, % predicted	44 (13)	15	45 (15)	15	1 (–5 to 7)	2	0.679
TLC, % predicted	128 (19)	16	124 (16)	16	–5 (–14 to 5)	–4	0.311
RV, % predicted	256 (62)	12	178 (61)	12	–78 (–120 to –36)	–31	0.002

FEV_1 = forced expiratory volume in the first second, PO_2 = partial pressure of oxygen, PCO_2 = partial pressure of carbon dioxide, DLCO/VA = diffusion capacity of carbon monoxide corrected for alveolar volume, TLC = total lung capacity, RV = residual volume.

strument that takes into account the values and beliefs of the patients. It permits the integration of both mortality and morbidity and when assessed over time produces a measure of quality adjusted life years (QALYs). QALYs have become essential outcome measures for clinical trials and are recommended by an expert panel of the United States Public Health Service.[32] A panel of experts, consisting of thoracic surgeons, respirologists and methodologists estimated that a change in the HUI score of 0.1 would be a clinically significant change. The mean change of 0.03 seen after LVRS is informative. Although the disease-specific CRQ demonstrated significant improvements, the HUI did not. The HUI does not specifically address the disabilities and handicaps of emphysematous patients but does provide an overall assessment of the impact of LVRS from the patient's perspective. It also will allow comparisons among different health states to help establish health care policies. We believe the HUI is the instrument of choice as the primary outcome indicator in LVRS research.[33]

A number of questions remain:

- Will LVRS prove to be better than the best medical management?
- Who are the best candidates?
- What are the mechanisms of clinical and physiologic improvement?
- What are the costs of the procedure to the health care system?

Our early experience suggests that LVRS may benefit some patients with dyspnea due to end-stage emphysema. A prospective randomized trial to fully evaluate its effectiveness is needed. The Canadian Lung Volume Reduction Surgery Study, currently under way, is a multicentred randomized trial comparing medical and surgical management. The data acquired from our preliminary pilot work has allowed us to refine the study entry criteria, outcomes and sample size for this trial.[33] The study will address these questions and help to establish the role of LVRS in Canada.

Conclusions

This pilot study demonstrates that LVRS is associated with improvement in measurements of impairment and handicap at 1 year postoperatively in a sample of 24 highly selected patients with advanced emphysema. These short-term results suggest that LVRS

Table VIII

Changes Resulting From Lung Volume Reduction Surgery With Respect to Handicap

	Measurement		Change		
	Preoperative, mean (and SD)	Postoperative, mean (and SD)	Absolute (95% CI)	Relative, %	*p* value
CRQ, *n* = 11					
Dyspnea	2.9 (1.3)	5.2 (1.4)	2.3 (0.8 to 3.7)	79	0.006
Fatigue	3.7 (1.1)	5.0 (1.2)	1.3 (–0.04 to 2.6)	35	0.056
Mastery	4.5 (1.3)	6.4 (0.8)	1.9 (0.9 to 2.9)	42	0.002
Emotion	5.0 (1.3)	5.9 (0.8)	0.9 (–0.3 to 2.1)	18	0.120
SF-36, *n* = 7					
Physical functioning	21 (21)	33 (29)	11 (–12 to 35)	52	0.274
Physical role	11 (20)	31 (39)	20 (0.9 to 40)	182	0.043
Pain index	88 (16)	85 (21)	–4 (–22 to 15)	–5	0.660
General health	41 (10)	61 (14)	20 (7 to 33)	49	0.009
Vitality	45 (22)	56 (21)	11 (–5 to 27)	24	0.130
Social functioning	48 (31)	75 (16)	27 (–1 to 55)	56	0.057
Emotional role	57 (46)	81 (38)	24 (–37 to 85)	42	0.376
Mental health Index	76 (17)	83 (16)	7 (–5 to 20)	9	0.186
Health utilities index mark III, *n* = 22	0.58 (0.28)	0.61 (0.32)	0.03 (–0.14 to 0.20)	5	0.728

Table VII

Changes Resulting From Lung Volume Reduction Surgery With Respect to Disability

	Measurement						
	Preoperative		Postoperative		Change		
Outcome measure	Mean (and SD)	No. of patients	Mean (and SD)	No. of patients	Absolute (95% CI)	Relative, %	*p* value
Maximum exercise capacity, kpm	292 (134)	5	453 (188)	5	161 (–9 to 331)	55	0.310
6-minute walk, m	346 (100)	17	381 (134)	17	34 (–35 to 104)	10	0.058

involves significant risk to patients but can result in measurable improvement in health. HUI-III, SF-36 and CRQ are useful in assessing patients who undergo this procedure.

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