# A Randomized Clinical Trial of Lung Volume Reduction Surgery Versus Best Medical Care for Patients With Advanced Emphysema: A Two-Year Study From Canada

John D. Miller, MD, Richard A. Malthaner, MD, Charles H. Goldsmith, PhD, Ronald Goeree, MS, David Higgins, MDCM, P. Gerard Cox, MB, Lawrence Tan, MD, and Jeremy D. Road, MD, for the Canadian Lung Volume Reduction Surgery Study

Division of Thoracic Surgery, McMaster University/St. Joseph's Hospital, Hamilton, Ontario, Division of Thoracic Surgery, University of Western Ontario, London, Ontario, Division of Thoracic Surgery, University of Manitoba, Winnipeg, Manitoba, and Respiratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada

*Background.* **We present a summary report evaluating the efficacy of lung volume reduction surgery (LVRS) in patients with advanced emphysema in the Canadian setting.**

*Methods.* **Quality of Life measures assessed the efficacy of adding LVRS to best medical care including rehabilitation in this blinded randomized multicentered controlled trial with 2 years of follow-up. Health utility and quality-adjusted life years (QALY) were outcomes central to our economic assessment.**

*Results.* **None of the 32 patients randomized to the LVRS arm or 30 patients in the best medical care (BMC) arm crossed-over and no patients were lost to follow-up. Overall surgical mortality was 16% at 2 years while the overall medical mortality was 13% ($p$ = 0.914). There were no 30-day postoperative deaths but 2 deaths (6%) occurred within 90 days of randomization. Surgery reduced the residual volume measured at 6 months by 23% (5,385 mL to 4,322 mL, $p$ = 0.007). There was an increase in forced expiratory volume in 1 second ($FEV_1$) of 30% (265 mL, $p$ = 0.013) from baseline, an improvement in the six minute walk test (6MWT) of 78 meters ($p$ = 0.045), and an increase in Health Utility Index 3 (HUI3) which peaked at 6 months with a difference of 0.16 ($p$ = 0.129). There was a gain in QALYs of 0.21 ($p$ = 0.19) in the LVRS-arm over the BMC-arm. The LVRS costs an additional $28,119 Canadian dollars (CAD) compared with BMC or $133,900/QALY gained.**

*Conclusions.* **The addition of LVRS to best medical care including pulmonary rehabilitation improves pulmonary function, exercise activity, and quality of life in selected patients with advanced emphysema. Cost is high but in keeping with other treatment modalities currently available.**

**(Ann Thorac Surg 2006;81:314–21)**


Chronic obstructive pulmonary disease is the fifth most common cause of death and is the only leading cause of death that is rising in prevalence. Despite the results of seven randomized trials and several case series demonstrating a benefit to patients, physicians remain routinely reluctant to recommend surgery to their patients with emphysema as a palliative measure [1–10]. Information about the risks, benefits, and costs of lung volume reduction in a Canadian setting has been lacking. We report the final clinical and economic results of a multicenter Canadian trial with 2-year follow-up.

## Patients and Methods

### *Patient Selection*

Five Canadian centers enrolled patients into the CLVR study conditional on specific inclusion and exclusion criteria (Table 1). Patients were not excluded for homogeneous disease. After screening, patients who qualified for the trial were referred for a standardized pulmonary rehabilitation program. Medical therapy was optimized [11], baseline testing (prerandomization) was performed (Table 2), and patients who qualified were randomized in a 1:1 allocation ratio between lung volume reduction surgery (LVRS) and optimal medical therapy. Patients assigned to LVRS proceeded to surgery within 2 weeks. All outcome events were attributed on an intent-to-treat basis. Crossover between study arms was not permitted. Recruitment started July 1997 and finished January 2001. Institutional ethics approval of this study was obtained on June 1996 and each patient within the study gave informed consent for serving as a subject.

### *Surgical Technique and Best Medical Care*

Surgical technique was standardized. Preoperative high resolution computed tomographic scan and ventilation-perfusion scan were used to determine target areas that were resected through a median sternotomy. Approximately 20% to 30% of the total lung volume was removed and the staple line was buttressed with either bovine

Accepted for publication July 18, 2005.

Presented at the Forty-first Annual Meeting of The Society of Thoracic Surgeons, Tampa, FL, Jan 24–26, 2005.

Address correspondence to Dr Miller, McMaster University, 50 Charlton Avenue East, Hamilton, Ontario, Canada, L8N 4A6; e-mail: jmiller@mcmaster.ca.



0003-4975/06/$32.00
doi:10.1016/j.athoracsur.2005.07.055

*Table 1. Entrance Criteria*

| |
|---|
| Inclusion: |
| Disabling dyspnea (CRQ - dyspnea score < 5) |
| Age between 40 and 79 years |
| Postbronchodilator $FEV_1 \leq 40\%$ predicted |
| Diffusing capacity (DLCO/VA) ≤ 60% |
| Total lung capacity ≥ 120% or |
| Residual volume ≥ 200% |
| Able to attend a respiratory rehabilitation |
| Exclusion: |
| Presence of significant: |
| Ischemic heart disease, |
| Peripheral vascular disease |
| Neuromuscular disease |
| Pulmonary hypertension (systolic > 50 or mean > 35 mm Hg) |
| Excessive corticosteroid therapy (prednisone > 10 mg/day) |
| 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 malignancy |
| Chronic bronchitis (daily sputum production > 3 months per year) |
| Hypercapnia ($PCO_2$ > 55 mg Hg) |
| Asthma (increase in $FEV_1$ > 20% and > 200 mL postbronchodilator) |

CRQ = chronic respiratory disease questionnaire; DLCO/VA = diffusing capacity of lung for carbon monoxide; $FEV_1$ = forced expiratory volume in 1 second; $PCO_2$ = partial pressure of carbon dioxide.

pericardium or polytetrafluoroethylene (GOR-TEX; W L Gore & Assoc, Flagstaff, AZ) to reduce postoperative air leaks [12]. Best medical care was standardized by following the recommendations of the American Thoracic Society [11] and Canadian Thoracic Society [13]. Best medical care (BMC) included additional pulmonary rehabilitation and was offered postoperatively as required.

### *Outcome Measures*

Outcome measurements included assessment of body function, activity, and participation. Body function was measured using pulmonary function and blood gases. Activity level was assessed by the six minute walk test (6MWT). The predetermined minimally clinically important difference (MCID) for $FEV_1$ was determined to be 200 mL or an increase from baseline of 20% [14] and a MCID for 6MWT was considered to be 30 meters [15]. Participation was assessed by Quality of Life (QOL) questionnaires; the disease-specific Chronic Respiratory Disease questionnaire (CRQ) [16], the generic Medical Outcomes Survey Short-Form 36 (SF-36) [17], and the most general Health Utility Index (HUI3), our primary outcome [18].

The CRQ is an interviewer-administered questionnaire that measures the patients' physical and emotional symptoms as they relate to emphysema. Each item is scored on a 7 point modified Likert Scale from 1 (maximum impairment) to 7 (no impairment). Changes in the score of 0.5, 1.0, and 1.5 were regarded as small, moderate, and large effects, respectively [19].

The Medical Outcome Study Short Form (SF-36) is a self-administered questionnaire with 8 domains and two components. Each domain is scored 0 to 100 with the highest number representing the best health state, while the Physical and Mental Component Summaries have a mean score of 50 and a standard deviation of 10. In this study 5 was considered a small clinical change while 10 was a large change. The HUI3 is a generic preference-based approach to the measurement of health status and health-related quality-of-life [20]. The scoring for HUI3 assigns a single summary number in the interval between 0.00 (death) and 1.00 (perfect health) with negative values for health states worse than death. The HUI3 difference between intervention arms over the 2 years of the study is expressed in quality-adjusted life years (QALYs) gained. A MCID of 0.05 was determined by review with a panel of stakeholders and experts, consisting of patients, thoracic surgeons, respirologists, and a methodologist. The QALYs have become essential outcome measures for clinical trials and are recommended by the United States Public Health Commission on Research in Health and Medicine [21].

A trained individual who was blinded to the patient treatment allocation administered all measurement of the 6MWT, pulmonary function studies, CRQ, and HUI3. The incremental cost-effectiveness of LVRS compared with BMC alone over a 2-year time horizon was assessed and was defined as the ratio of the difference between treatment groups in mean costs to the difference in quality-adjusted life years (cost per QALY). The economic analysis was conducted from the viewpoint of a provincial government healthcare payer.

Price weights were applied to resource use data to estimate the total healthcare cost for each patient. Price weights for hospital resources were provided by a large Ontario Case Costing Project teaching hospital in Ontario [22] that was participating in the CLVR study. Costs of physician services were taken from the Ontario Sched-

*Table 2. Demographics*

| | LVRS Arm | Best Medical Care Arm |
|---|---|---|
| Age mean (min–max) | 64.1 (48–78) | 63.1 (50–75) |
| Gender M:F | 22:10 | 19:11 |
| Smoking pack years | 59.5 | 44.1 |
| BMI kg/m$^2$ | 24.4 (15.0–33.0) | 23.6 (17.1–32.5) |
| RV (L) (min-max) | 5.40 (3.70–7.37) | 5.37 (3.49–8.22) |
| $FEV_1$ (ml) (% predicted) | 726 (25%) | 653 (23%) |
| TLC (L) (% predicted) | 8.20 (136%) | 7.78 (138%) |
| DLCo (% predicted) | 8.18 (31%) | 8.92 (35%) |
| 6 MWT (min-max) | 340 (107–649) | 319 (133–468) |

BMI = body mass index; DLCO = diffusing capacity of lung for carbon monoxide; $FEV_1$ = forced expiratory volume in 1 second; LVRS = lung volume reduction surgery; MWT = minute walk test; RV (L) = residual volume (lung); TLC = total lung capacity.

ule of Benefits [23]. Unit costs for drugs were derived from the Ontario Drug Benefits Schedule [24]. Costs are reported in 2004 Canadian dollars (CAD).

*Statistical Analysis*

The primary outcome of the trial was the difference in QALYs between the two intervention arms using HUI3 as the basis of this calculation. The primary analysis was a two-way analysis of variance with center blocking and treatment as the two factors. Blocking was done in groups of 2 or 4. Randomization, in a 1:1 allocation ratio between treatment arms with surgeon stratification, was performed at the Data Coordinating Center to ensure concealment of the process. The sample size calculation was based on a two-tailed type I error rate, alpha of 5%, with a power of 90%, and clinically important difference of 0.10 over the 2-year period. We estimated a need of 350 patients. Nonparametric bootstrap methods were used to calculate a 95% interval for the incremental cost effectiveness ratio.

*Quality-Adjusted Values*

While it is common to integrate (health) utility values collected over time by using the area under the curve drawn between multiple time points to compute QALYs, this procedure is less common with clinical outcomes. Recent literature [20] has suggested that any measure that is either interval or a ratio, can be integrated to get an overall assessment over the time course of the trial. In this study, we used the outcome measures at each and every time point where the data were recorded. We then used the area over the 2 years (730 days) of the trial to determine a value. Dividing this value by 730 resulted in a quality-adjusted value for each patient for that variable. Comparing each arm of the study using this quality-adjusted value would measure the impact of surgery relative to medicine. This approach was preferred to comparing multiple values over time that are not statistically independent such that any differences could lead to confusion. The quality-adjusted value provides a global average assessment of each outcome and is intuitive and simple to interpret because it uses the same units as the original measurements.

## Results

Sixty-two patients completed pulmonary rehabilitation and were candidates for randomization. Thirty-two patients were randomized to surgery and 30 to best medical care. The demographics of all patients randomized are outlined in Table 2. All patients were followed to 2 years or to their death.

There were 3 patients randomized to the LVRS arm who did not undergo LVRS. One withdrew from the study prior to the scheduled surgery date and refused to be followed further. A second patient's operation was postponed and on reassessment, four months later, he felt too well to accept the risks of surgery. All scheduled outcome measures were obtained for this patient and were included in the surgical cohort results (intent-to-treat). A third patient was disqualified in error because of an unexpected intraoperative discovery of a lung malignancy. Subsequent assessment of this patient was not carried out by the local study center.

*Mortality*

There were no 30-day postoperative deaths and 2 of 32 (6%) patients died within 90 days of surgery. There was a 1 of 30 (3%) patient death in the best-medical-care arm during the first 90 days. The overall 2-year survival was similar in each arm of the study: LVRS arm 5/32 deaths (16%) and the BMC arm 4/30 deaths (13%) ($p = 0.935$).

*Participation: CRQ and SF-36*

The difference between groups at 2 years in all four domains of the CRQ achieved statistical significance (Table 3). The quality-adjusted values were clinically important and statistically significant for all four domains. The CRQ-dyspnea domain score was better for the LVRS patients when compared with patients treated in the medical arm over the 2 years of the study (−1.14, 95% confidence interval [CI; 0.33–1.95]; ($p = 0.008$).

Eight of 10 domains of the SF-36 achieved the MCID at 2 years, but only one achieved statistical significance. The physical functioning domain was both clinically important and statistically significant at the 2-year assessment (26.42, 95% CI 11.3–41.5; $p = 0.0016$). The quality-adjusted value was clinically important in 9 of 10 domains and statistically significant in 4 of these domains (Table 3).

*HUI3*

The HUI3 showed a clinically important improvement in quality of life at the 2-year assessment (0.104) but had only an 80% certainty that the observation was a true finding (Table 4, Fig 1). The difference failed to achieve statistical significance (0.104, 95% CI −0.06–0.27; $p = 0.19$).

*RV and $FEV_1$*

Lung reduction after surgery was achieved as evidenced by a reduced of 26% from baseline (Table 5). Mean residual volume for the surgical patients at baseline was 5,400 mL and 4,017 mL at 6 months ($p = 0.007$).

There was an absolute increase in $FEV_1$ of 263 mL (30% from baseline, $p = 0.055$) at 6 weeks. This improvement persisted to a lesser extent through 3, 6, 12, and 18 months but disappeared by 24 months. Twenty-nine of 32 (91%) surgical patients had a measurable increase in their $FEV_1$ after LVRS, while 10 of 30 (33%) patients treated medically showed an improvement in their $FEV_1$ over the 2-year study. ($X^2 = 22.62$, $p < 0.0001$; Fisher exact $p2 < 0.0001$). Patients in the surgical arm had an improvement in the quality-adjusted $FEV_1$ of 267 mL ($p = 0.013$) compared with the patients in the medical arm.

*Oxygen Requirement*

There were no significant changes in arterial blood gas measurements over the 2-year study and no significant changes after LVRS. A small but not statistically significant difference between groups was observed in $Paco_2$ at 6 months (−4.3 mm Hg [standard error 2.23]) ($p = 0.07$),

*Table 3. Changes in Participation: Quality-Adjusted Value for CRQ and SF36: Difference Between LVRS and BMC Arms Through 24 Months*

| | Quality Adjusted Value | | | |
|---|---|---|---|---|
| CRQ Domain | Mean | {95% CI} | (df) | *p* |
| Dyspnea | 1.14 | {0.33 to 1.95} | (24) | 0.0079 |
| Fatigue | 0.90 | {0.04 to 1.76} | (24) | 0.0414 |
| Mastery | 1.00 | {0.13 to 1.87} | (24) | 0.0261 |
| Emotional function | 0.87 | {0.09 to 1.64} | (24) | 0.0308 |
| SF-36 Domain | | | | |
| Physical functioning | 17.06 | {6.28 to 27.84} | (28) | 0.0031 |
| Role physical | 17.61 | {−0.44 to 35.65} | (15) | 0.0551 |
| Bodily pain | 10.85 | {0.81 to 20.89} | (28) | 0.0351 |
| General health | 17.48 | {7.48 to 27.48} | (28) | 0.0013 |
| Vitality | 9.16 | {−2.85 to 21.17} | (28) | 0.1293 |
| Social functioning | 12.03 | {−0.49 to 24.56} | (28) | 0.0591 |
| Role emotional | 10.26 | {−4.87 to 25.39} | (26) | 0.1751 |
| Mental health | 10.58 | {−0.96 to 22.11} | (28) | 0.0707 |
| Mental component score | 3.89 | {−3.42 to 11.20} | (28) | 0.2852 |
| Physical component score | 6.67 | {1.93 to 11.40} | (28) | 0.0075 |

CI = confidence interval; CRQ = chronic respiratory disease questionnaire; df = degrees of freedom.

but this difference vanished by 12 months. Home oxygen was required by 37% of the patients before LVRS. This percentage was reduced to 28% postoperatively ($p$ = 0.09). Six patients (50%) required less oxygen support and 3 patients (25%) required an increase in their oxygen.

## *Six Minute Walk Test*

The 6MWT improved by 93.8 meters (95% CI [15.4–172.1]) ($p$ = 0.021) over the 2-year period (Table 5). Twenty-two of the 32 patients (69%) in the surgical arm had a measurable increase in their six minute walk test while 10 (31%) patients deteriorated. In the medical arm 8 of 30 (27%) had a measurable increase in their 6MWT while 22 of the 30 (73%) patients deteriorated as the 2-year study progressed (Xi2 = 10.98, $p < 0.0009$; Fisher exact $p2 < 0.0011$).

*Table 4. Changes in Health-Related Quality of Life HUI3: Difference Between LVRS and BMC Arms Changes in HUI3 Through 24 Months*

| | HUI-3 Score | | | |
|---|---|---|---|---|
| | Mean | {95% CI} | (df) | *p* |
| 3 month | 0.13 | {−0.07 to 0.32} | (19) | 0.1806 |
| 6 month | 0.16 | {−0.05 to 0.36} | (16) | 0.1285 |
| 12 month | 0.13 | {−0.13 to 0.39} | (15) | 0.3087 |
| 24 month | 0.12 | {−0.12 to 0.35} | (13) | 0.2991 |
| Quality-adjusted value[a] | 0.104 | {−0.06 to 0.27} | (13) | 0.1911 |
| QALY | 0.21 | {−0.12 to 0.53} | (13) | 0.1911 |

[a] With interpolation; Mean = adjusted mean post randomization scores minus adjusted mean baseline scores.

BMC = best medical care; CI = confidence interval; df = degrees of freedom; LVRS = lung volume reduction surgery; QALY = quality-adjusted life years.

## *Cost Effectiveness Analysis*

Price weights and utilization of selected resource use by treatment group are presented (Table 6). Thirty-two patients were randomized to LVRS, and 30 to BMC. Three patients (1 LVRS, 2 BMC) were excluded from the economic analysis because of no data. Two LVRS patients did not undergo surgery but were included in this intent to treat analysis. The mean length-of-stay for the initial hospitalization was 31.1 days in the surgery group including a mean of 11.3 days in the intensive care unit. Over the 2 years of the study, the LVRS group experienced a mean of 0.8 hospitalization per patient and a mean number of hospital days of 10.3 compared with the medical care group who experienced a mean of 1.6 hospitalizations per patient and each hospitalization was 17.2 days in duration. The LVRS patients had a mean of 7.3 months of home oxygen vs 10.3 months for patients in the BMC arm. Of the LVRS patients, 51% returned to a rehabilitation program while 39% of the patients in the BMC arm went back into a rehabilitation program.

The mean cost related to the index hospitalization was $33,622 per patient in the LVRS group and $0 per patient in the BMC group (Table 7). This includes a mean of $4,684 for the surgery (includes bronchoscopy and/or tracheotomy costs) and $28,938 for length of stay hospitalization costs. Follow-up costs were $5,503 lower among surgery patients compared with the BMC group ($16,154 vs $21,657). Contributing to the lower follow-up costs were lower hospitalization costs ($7,204 vs $12,155), oxygen costs ($2,781 vs $3,927), and medication costs ($1,175 vs $1,400). The cost for rehabilitation was ($3,469 vs $2,647) in the LVRS arm vs BMC arm. The total mean cost over the 2-year period was $49,776 in the surgery group and $21,657 in the BMC group. This results in an incremental cost of LVRS of $28,119 (95% CI $5756 to $22362).

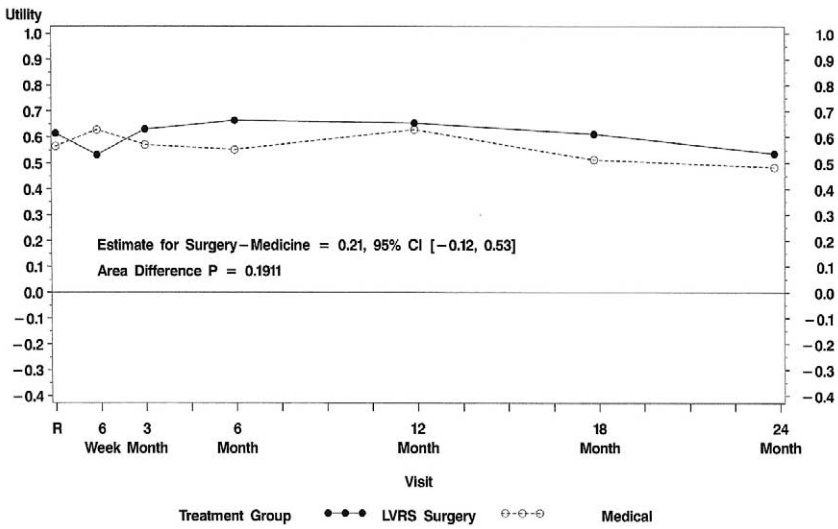


*Fig 1. Health Utility Index (HUI3): Each treatment group is illustrated by a line marking the average value of the HUI3 at each of the assessment times of the study. The area under the line represents the accumulated value of the HUI3 for that treatment group. The area between the two lines (groups) is the difference between the two treatment arms and is conceptually the quality-adjusted value gained (or lost) over the 2-year study. Closed circles represent the LVRS group; open circles represent the medical group. (CI = confidence interval; LVRS = lung volume reduction surgery.)*

The LVRS patients were found to have 0.21 more quality-adjusted life years than BMC patients over a 2-year time horizon. Dividing the incremental mean cost of LVRS patients ($28,119) by their incremental QALYS (0.21) results in an incremental cost-effectiveness ratio of $133,900 per QALY (95% CI 26,000 to undefined).

## Comment

Across the five centers, 467 candidates were screened and 405 were excluded from the protocol. Sixty-two patients were selected. This ratio of successful selection was similar to the experience of others [6, 8]. The most common reasons for exclusion in our study were patients who were too ill with multisystem disease (25%) or not ill enough with lung volumes too small (24%). Other reasons included single large bullae (20%); 68 patients (17%) were excluded and considered for transplantation. Patients declined because of unwillingness to be randomized (9%). Twenty patients were excluded because they were referred while in an intensive care unit and were requiring mechanical ventilation. We hoped to enroll 350 patients, but stopped recruiting when 18% of our target number was met. This poor accrual was the result of several factors. Economics, politics, shifts in patients' perception, medical preference, and regional strategic needs all contributed to our failure to meet our goal and are a subject of another paper. Similar trials have met with similar struggles. The National Emphysema Treatment Trial (NETT) recruited 27% of their original target (1,200/4,500). Despite the fact that our study was underpowered for its primary outcome, it was well-powered for all other outcomes assessed.

The incremental cost effectiveness ratio of patients randomized to lung volume reduction surgery in this study was found to be $133,900/QALY gained. Based on conventional cost-effectiveness threshold where $20,000/QALY is within most healthcare budgets, treatments that cost more than $100,000/QALY are considered to be outside budget limits [25], LVRS would not be considered a cost-effective intervention. Nonetheless, society continues to subscribe to other treatments with similar or greater costs per QALY. The Harvard Center for Risk Assessment reports several such treatments [26]. Laparoscopic hernia repair costs $140,000/QALY gained when compared with open hernia repair. Lung transplantation costs $137,000 to $294,000 per QALY gained when compared with best care with no transplantation; radiologic

*Table 5. Changes in Body Function and Activity Pulmonary Function and Six Minute Walk Test (MWT): Difference Between LVRS and BMC Arms Through 24 Months*

| | $FEV_1$ Liters | | | | 6MWT Meters | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean | {95% CI} | (df) | *p* | Mean | {95% CI} | (df) | *p* |
| 3 month | 0.26 | {0.05 to 047} | (25) | 0.0172 | 29.36 | {−20.85 to 79.58} | (21) | 0.2374 |
| 6 month | 0.27 | {0.02 to 0.51} | (19) | 0.0329 | 58.02 | {−1.08 to 117.12} | (19) | 0.0539 |
| 12 month | 0.07 | {−0.16 to 0.30} | (18) | 0.5439 | −3.44 | {−61.65 to 54.77} | (17) | 0.9021 |
| 24 month | 0.06 | {−0.14 to 0.27} | (15) | 0.5148 | 40.84 | {36.68 to 118.37} | (14) | 0.2775 |
| Quality-adjusted value[a] | 0.22 | {0.07 to 0.38} | (24) | 0.0065 | 93.76 | {15.39 to 172.12} | (22) | 0.0210 |

[a] With interpolation; Mean = adjusted mean post randomization scores minus adjusted mean baseline scores.

BMC = best medical care; CI = confidence interval; df = degrees of freedom; $FEV_1$ = forced expiratory volume in 1 second; LVRS = lung volume reduction surgery.

*Table 6. Price Weights and Utilization for Selected Resources*

| | Price Weights | Utilization | |
|---|---|---|---|
| | | LVRS (n = 31) | BMC (n = 28) |
| Initial hospitalization | | | |
| Number with LVRS surgery (%) | $4,315/surgery | 28 (90%) | 0 (0) |
| Mean total length of stay | | 31.1 | 0 |
| Mean ICU length of stay | $1,446/day | 11.3 | 0 |
| Mean non-ICU length of stay | $626/day | 19.8 | 0 |
| Follow-up (means) | | | |
| Admissions | | 0.8 | 1.6 |
| Days in hospital | $626/day | 10.3 | 17.2 |
| GP visits | $54/visit | 8.0 | 6.9 |
| ER visits | $123/visit | 1.1 | 3.0 |
| Specialist visits | Varies | 5.6 | 5.9 |
| Months on oxygen | $383/month | 7.26 | 10.33 |
| Number of patients in rehab(%) | $56/outpatient | 16 (51%) | 11 (39%) |

ER = emergency room; GP = ICU = intensive care unit; LVRS = lung volume reduction surgery.

screening for foreign bodies before MRI costs $504,000/QALY gained, autologous blood transfusion program costs between $420,000 and $42,000,000/QALY gained.

Our results are consistent with findings of other small randomized clinical trials, and the National Emphysema Treatment Trial (NETT) [1–10]. These studies suggest that the clinical and physiologic improvements peak 6 to 12 months after LVRS and are sustained for two years before an important decline in benefits is observed.

In the surgical arm of this study QOL measures improved after LVRS; however, this small improvement did not always achieve MCID. When comparison is made with the medical group who continued to deteriorate, however, the benefit of LVRS was clearly seen easily surpassing the MCID and achieving statistical significance in most domains. Although LVRS offers some improvements in QOL the major gain realized by the surgical patient is that while both groups deteriorate over the 2-year time horizon, the surgical group does so at a level persistently above the medical group.

Lung volume reduction surgery, in addition to best medical care including pulmonary rehabilitation, provides meaningful physiologic changes that reduces a patient's dyspnea and improves quality of life. Lung volume reduction surgery is feasible and is relatively safe. The cost to provide LVRS is high but in keeping with other treatment modalities currently available.

The Canadian Institute of Health Research (CIHR), MT-14386, funded the Canadian Lung Volume Reduction Surgery Study trial.

*Table 7. Cost Per Patient by Treatment Group and Cost Effectiveness*

| | LVRS (n = 31) | BMC (n = 28) | Difference (LVRS-BMC) |
|---|---|---|---|
| Index hospitalization | | | |
| Surgery | 4,684 | 0 | |
| Length of stay | 28,938 | 0 | |
| Total index hospitalization | 33,622 | 0 | 33,622 (16,309; 50,935) |
| Follow-up | | | |
| Hospitalizations | 7,204 | 12,155 | |
| Rehabilitation | 3,469 | 2,647 | |
| Oxygen | 2,781 | 3,957 | |
| Medications (copd, antiinfectives) | 1,175 | 1,400 | |
| Outpatient[a] | 1,524 | 1,498 | |
| Total follow-up costs | 16,154 | 21,657 | −5,503 (−19,812; 8,804) |
| Total costs | 49,776 | 21,657 | 28,119 (5,756, 22,362) |
| Quality adjusted life years | 1.29 | 1.08 | 0.21 (−0.12, 0.53) |
| Increment cost-effectiveness Ratio: cost/QALY | | | 133,900 (26,000; undefined) |

[a] Includes emergency room visits, nonprotocol specialist visits, nonprotocol investigations.

BMC = best medical care; copd = chronic obstructive pulmonary disease; LVRS = lung volume reduction surgery; QALY = quality-adjusted life years.

## References


1. Criner GJ, Cordova FC, Furukawa S, et al. Prospective randomized trial comparing bilateral lung volume reduction surgery to pulmonary rehabilitation in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;160:2018–27.
2. Geddes D, Davies M, Koyama H, et al. Effect of lung-volume-reduction surgery in patients with severe emphysema. N Engl J Med 2000;343:239–45.
3. Pompeo E, Marino M, Nofroni I, Matteucci G, Mineo TC. Reduction pneumoplasty versus respiratory rehabilitation in severe emphysema: a randomized study. Ann Thorac Surg 2000;70:948–53.
4. Lofdahl CG, Hillerdal G, Strom K. Randomized controlled trial of volume reduction surgery—preliminary results up to 12 months. Am J Respir Crit Care Med 2000;161:585.
5. Goodnight-White S, Jones JW, Baaklini WA, et al. Prospective, randomized, controlled trial comparing bilateral lung volume reduction surgery (LVRS) to medical therapy alone in patients with severe emphysema. Chest 2000;118(suppl 4):102S (abstract)
6. Goldstein RS, Todd TR, Guyatt G, et al. Influence of lung volume reduction surgery (LVRS) on health related quality of life in patients with chronic obstructive pulmonary disease. Thorax 2003;58:405–10.
7. The National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003;348:2059-73.
8. Cooper JD, Trulock EP, Triantafillou AN, et al. Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. J Thorac Cardiovasc Surg 1995;109:106–16.
9. Young J, Fry-Smith A, Hyde C. Lung volume reduction surgery (LVRS) for chronic obstructive pulmonary disease (COPD) with underlying severe emphysema. Thorax 1999; 54:779–89.
10. Malthaner RA, Miller JD. Lung volume reduction surgery: results of a Canadian pilot study. Can J Surg 2000;43:377–83.
11. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995;152(pt 1):S77–S121.
12. Hazelrigg SR, Boley TM, Naunheim KS, et al. Effect of bovine pericardial strips on air leak after stapled pulmonary resection. Ann Thorac Surg 1997;63:1573–5.
13. Guidelines for the assessment and management of chronic obstructive pulmonary disease. Canadian Thoracic Society Workshop Group. CMAJ 1992;147:420-8.
14. Redelmeier DA, Goldstein RS, Min ST, Hyland RH. Spirometry and dyspnea in patients with COPD. When small differences mean little. Chest 1996;109:1163–8.
15. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the Six-Minute-Walk-test in chronic lung disease patients. Am J Respir Crit Care Med 1997;155:1278–82.
16. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. Thorax 1987;42:773–8.
17. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 Health Survey Manual and Interpretation Guide. 1st ed. Boston, MA: New England Medical Center, The Health Institute, 1993.
18. Feeny D, Furlong W, Torrance GW, et al. Multiattribute and single-attribute utility functions for the health utilities index mark 3 system. Med Care 2002;40:113–28.
19. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials 1989;10:407–15.
20. Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2. Med Care 1996;34:702–22.
21. Gold MR, Seigel JE, Russel LB, Weinstein MC. Cost-effectiveness in health and medicine. 1st ed. New York, NY: Oxford University Press Inc, 1996.
22. Ontario Case Cost Project. Ontario Case Cost Project (OCCP): Ontario Guide to Case Costing. 1.1 ed. Ottawa: Ontario Case Cost Project, 1995.
23. Ontario Ministry of Health. Schedule of Benefits: 1st ed. Toronto: Queen's Printer, 1998.
24. Ontario Ministry of Health. Ontario Drug Benefit Formulary. 1st ed. Ottawa: Ontario Ministry of Health, 1992.
25. Laupacis A, Feeny D, Detsky AS, Tugwell PX. Tentative guidelines for using clinical and economic evaluations. CMAJ 1992;146:473–81.
26. Harvard School of Public Health. Cost-utility analyses 1976 to 2001. Cancer Care Ontario Practice Guidelines: http://www.hsph.harvard.edu/cearegistry/1976-2001_CEratios_comprehensive_4-7-2004.pdf.Accesssed 10-16-2004.


## DISCUSSION

**DR MALCOLM M. DECAMP** (Boston, MA): As you just heard, emphysema is one of the leading causes of adult death in North America; just yesterday it claimed the life of Johnny Carson. Along with ischemic heart disease, stroke, and lung cancer, emphysema is a major source of tobacco-related mortality and morbidity and healthcare expenditure. In their manuscript, Dr Miller points out that 62 million Canadian dollars were spent on the management of COPD (chronic obstructive pulmonary disease) in 1990, and those figures in the United States in the mid-1990s was estimated between $1 and $4 billion.

Unlike coronary artery disease and lung cancer, little new has been published regarding effective treatment for emphysema. The only therapy providing any documented survival advantage for this disease was the use of, first, nocturnal and then continuous ambulatory oxygen therapy, and these findings were published almost three decades ago.

Reintroduced by Cooper in the early 90s, lung volume reduction surgery has recently been validated as effective therapy for emphysema, especially by the National Emphysema Treatment Trial. For the first time since the publication of the supplemental oxygen trials, an intervention for emphysema has been shown to improve exercise capacity, quality of life and, in selected patients, survival.

Dr Miller and his colleagues should be congratulated for the design and execution of a multicenter prospective randomized trial of lung volume reduction surgery versus best medical therapy within the Canadian healthcare system. Five centers participated, though only four were clinically active.

There were several similarities with the NETT (National Emphysema Treatment) trial. Patients were similar with regard to age and the severity of their emphysema. There was no overall difference in survival in either study, but because of the smaller sample size in the Canadian study, no subsets could be analyzed. There was significant improvement in general and respiratory-specific quality of life that persisted throughout follow-up in both studies, and overall, the incremental cost, as you just heard at the conclusion of the presentation, was about 134,000 Canadian dollars for quality-adjusted life year. That figure for the overall group in the NETT trial was about $100,000, but again, because of the small sample size, they could not discern or perform any subset analysis.

There were some important differences between this study and the NETT trial. There was statistically significant improvement in respiratory function in this trial in $FEV_1$ and six-minute walk distance, but compared to the patient's baseline, these deteriorated in the first six to 12 months follow-up. Patient accrual of 62 patients represents only 5% of the 1,200 patients accrued in the NETT study, and accrual was only 18% of their target. The mean hospital length of stay was a little over one month, twice that seen in the NETT trial and the mean ICU length of stay in these patients was about 11 days; again, twice that ICU length of stay seen in the NETT trial.

I have four questions for the authors. First, your primary end point was quality-adjusted life years measured by the Health Utility Index. Unfortunately this outcome was not statistically different between treatment groups, yet you claimed that the observed difference was "clinically" important. How can you justify this concept of minimally clinically important difference for such a diffuse measure as Health Utility Index?

Why was your accrual so poor? Over what time period did you recruit centers and patients, and did you exclude centers and why?

Third, you conclude that LVR is feasible in small surgical volume centers, but I am not sure that your 6% to 10% operative mortality and one-month hospital length of stay, 11 days in the ICU, supports this. Were there non-study LVR patients operated on in these institutions during this study, and what is the minimum center and surgeon volume and experience that you think is necessary to run an LVR program?

And finally, your analysis reports results as comparisons of medicine versus surgery in terms of mean values relative to their baseline. How do you account for the heterogeneity of response following surgery or even following pulmonary rehabilitation? Would you continue to use the study inclusion and exclusion criteria for selection of patients for lung volume reduction surgery or would you modify these based on the heterogeneity of response that you saw in your patients or in those reported by other authors?

I would like to thank you for the manuscript in advance and the Society for the privilege of discussing this important paper.

**DR MILLER**: Thank you, Dr DeCamp, for your kind comments. The poor accrual I guess is a similar situation to all. I think the NETT trial accrued about 22 or 27% of their predicted numbers of 4,500, and this was 12%. So similar features, very complicated stories of each one, and again, would be reported elsewhere.

I think you are right, the fact that it can be done by this trial in small centers in Canada does not necessarily mean that that's a subscription for all small centers to start. We were highly specialized centers and had a run-in period with a larger volume of experience before we started. So I think that it implies that it can be done in small centers if they are highly qualified. I think the differences in numbers and experiences are generally reflective in the two groups, the medical system in Canada and the U.S.

Thank you again.