Long-Term Survival Analysis of the Canadian Lung Volume Reduction Surgery Trial

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Background. The Canadian Lung Volume Reduction Surgery (CLVRS) trial was a multicentered randomized controlled trial that concluded that lung volume reduction surgery improves functional status and health-related quality of life (for at least 2 years) in selected patients with advanced emphysema.

Methods. This retrospective observational study assessed the long-term survival of patients enrolled in the CLVRS at 8 to 10 years after randomization. Vital statistics were gathered through telephone contact, physician records, and municipal obituaries. Survival analysis was undertaken using Kaplan-Meier and the Cox proportional hazards models.

Results. Fifty-two patients (84% of the initial 62 patients randomized) had a median survival time of 4.11 years. A 16-month survival advantage and a 20% reduction in mortality was observed in the LVRS group as compared with the best medical care group. Although clinically meaningful, these differences were not statistically significant.

Conclusions. These findings echo those of other published reports and demonstrate the potential long-term benefit of LVRS in the treatment of end-stage emphysema.


Chronic obstructive pulmonary disease (COPD) was the fourth leading cause of death in Canada in 2009, and accounted for 10,515 deaths nationwide [1]. In 2009, 4.2% of Canadians aged 35 years and older reported that they had been diagnosed with COPD [1]. Unlike other disease states that similarly have a high mortality, there has been little progress in reducing mortality from COPD and the death rate continues to climb, increasing by as much as 16% in the last 20 years [2]. The morbidity, resource consumption, hospitalizations, and mortality associated with COPD carry a significant social and economic burden [3]. Information about the utility of lung volume reduction in a Canadian setting has been slow to emerge.

Medical management consisting of bronchodilators, corticosteroids, smoking cessation and exercise programs, noninvasive ventilator support, and oxygen therapy are currently the most commonly used forms of treatment for severe emphysema. Smoking cessation and oxygen therapy have the only established survival benefit. Lung volume reduction surgery (LVRS), despite its proven benefit, has failed to find a clinical role in the management of end-stage emphysema [4]. By reducing lung volumes, the mechanics of breathing, which have been restricted by the oversized, inelastic lungs of emphysema, are improved. Previous studies have shown that patients with heterogeneous emphysema (mainly apical disease) stand to benefit the most from LVRS [5, 6]. Despite the results of these and several other randomized trials demonstrating a benefit, physicians remain reluctant to recommend surgery [7–13].

The Canadian Lung Volume Reduction Surgery (CLVRS) trial was a multicentered randomized controlled trial conducted between 2000 and 2002, with the purpose of comparing the health utility, quality of life, and pulmonary function of patients who were treated with either LVRS or best medical care including pulmonary rehabilitation [14]. Over the first 2 years after randomization, the study demonstrated a 30% increase in forced expiratory volume in 1 second of 0.265L ($p = 0.013$), an improvement in 6-minute walk test of 78 m ($p = 0.045$), and a gain of 0.21 quality-adjusted life-years ($p = 0.19$) [14]. The study demonstrated that for selected patients, LVRS improved the health utility and quality of life and pulmonary function of patients with advanced emphysema over the 2 years of assessment. Current Canadian Thoracic Surgery guidelines for the management of COPD support the use of LVRS for selected patients but acknowledge it is resource intense and costly, and note that adopting LVRS as part of a treatment plan should be balanced against the available resources [4]. As data accumulate regarding the long-term outcomes of LVRS, BRAHMS20130102134057
its efficacy and benefit will become clearer. The aim of this study is to assess the long-term survival of all patients enrolled in the CLVRS trial, 8 to 10 years after its completion. The results will add to the body of information about the long-term survival of the patients who have under gone LVRS.

**Patients and Methods**

This retrospective observational study of patients in the CLVR study was undertaken to assess long-term survival after receiving approval from the Ethic Boards in each of the five centers in the Canadian study. All-cause mortality was measured as the number of months survived since randomization. The CLVRS trial randomly assigned 62 patients with end-stage emphysema to either bilateral lung volume reduction surgery through median sternotomy in addition to best medical care (BMC) or to BMC alone [14]. The BMC included completion of a 6-week period of standardized pulmonary rehabilitation. The two groups were demographically similar, 32 patients were assigned to the LVRS arm and 30 patients to the BMC arm (Table 1). Original outcomes were assessed using intention-to-treat analysis. One of the 3 patients randomized to LVRS who did not undergo surgery withdrew from the study and refused follow-up. Follow-up of the patients randomly allocated to BMC did not demonstrate any crossover to the surgical arm before the completion of the index CLVRS trial. This absence of crossover was believed to be due to disease progression which had rendered patients unacceptably poor surgical candidates.

We established the patient’s status (alive or dead) by first contacting the patient or the patient’s family by phone. Each patient’s phone number on record was called until the patient or next of kin was reached. In the case of identified deaths, family members who were reached were asked to provide a date of death to serve as the censoring event in the survival analysis. When patients were unreachable by phone, physicians’ charts (surgeon and primary care physician) and hospital charts were checked to establish the patient’s survival status. Finally, all information retrieved through next of kin or physician records was verified using municipal obituaries to confirm the death dates. Any identifiable deaths (and the time from randomization) were therefore recorded based on the available information. For the purposes of survival analysis, censoring events included death after randomization or last date of known follow-up (ie, in the case of patients who could not be contacted and were lost to follow-up by their surgeon or family practitioner). For such patients, the last recorded follow-up date served as the last date at which they were known to be alive.

Survival analysis was conducted using both the Kaplan-Meier [15] and Cox proportional hazards models [16]. Kaplan-Meier analysis yielded treatment specific survival curves with median survival in months after randomization. The survival curves were compared using the log rank test. Analysis using the Cox proportional hazards model provided time specific, as well as overall hazards ratio for each intervention arms. Considering the lack of statistically significant differences in baseline characteristic and to prevent the introduction of bias through inadvertent imbalance between the randomized groups, a crude unadjusted Cox proportional regression analysis was performed. Sensitivity analysis did not demonstrate a difference in Cox regression when adjusting for age and sex. All data were analyzed using SPSS version 18.0 statistical software (SPSS, Chicago, IL). Differences were deemed statistically significant when a p value of less than 0.05 was achieved.

**Results**

All patients randomized in the CLVRS trial were eligible. Data were acquired on 52 of the 62 patients and were part of this analysis. One patient in the surgery arm was excluded before undergoing treatment. Nine other patients were lost to follow-up (5 from the LVRS arm and 4 from the BMC arm). Information could not be confirmed because phone contact was not possible and there was no other contact information, nor was there any evidence of death in office or hospital charts or obituaries. The 10 patients lost to follow-up had baseline characteristics similar to those of the group identified in this study (Table 2). In total, 26 patients were analyzed in each arm, totaling 84% of the patients randomized in the original study (Fig 1). Seven of the deaths recorded were found only in the municipal obituaries of local papers. The proportion of patients surviving 3, 5, and 10 years in the LVRS group was 52%, 46%, and 7% respectively, compared with 31%, 25%, and 0% in the BMC group.

Kaplan-Meier analysis illustrates a trend toward a long-term survival benefit in the LVRS group (Fig 2). The overall median survival was 59 months. Median survival in the LVRS group was 63 months, and 47 months in the BMC group (p = 0.20), yielding a difference of 16 months. LVRS appeared to improve survival by nearly a year, and a third longer than patients treated by BMC alone (Table 3). Although not statistically

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**Table 1. Patient Baseline Characteristics as per the CLVRS Trial**

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>LVRS</th>
<th>BMC</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>Age, years (range)</td>
<td>64.1 (48–78)</td>
<td>63.7 (50–75)</td>
</tr>
<tr>
<td>Male:female</td>
<td>22:10</td>
<td>19:11</td>
</tr>
<tr>
<td>Smoking pack-years</td>
<td>59.5</td>
<td>44.1</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.4 ± 4.0</td>
<td>23.6 ± 4.0</td>
</tr>
<tr>
<td>RV (L)</td>
<td>5.4 ± 1.0</td>
<td>5.4 ± 1.2</td>
</tr>
<tr>
<td>Total lung capacity</td>
<td>136%</td>
<td>138%</td>
</tr>
<tr>
<td>FEV1</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>DLCO</td>
<td>31%</td>
<td>35%</td>
</tr>
<tr>
<td>Six-minute walk test, m</td>
<td>340</td>
<td>320</td>
</tr>
</tbody>
</table>

BMC = best medical care; CLVRS = Canadian Lung Volume Reduction Surgery; DLCO = diffusion capacity of lung for carbon monoxide; FEV1 = forced expiratory volume in 1 second; L = liter; LVRS = lung volume reduction surgery; RV = residual volume.
significant (given the overlap of the confidence intervals), this difference is nonetheless clinically substantial, considering the standard error (SE) in both groups—with the difference in survival being clearly greater than the 6.7 months SE in the surgery group and the 12.0 months SE in the BMC group.

The Cox proportional hazards model demonstrated a favored survival in the LVRS arm (Fig 3). The curves overlap earlier on and then diverge later in the follow-up period, illustrating a greater survival difference over time. The overall hazard ratio was 0.81 (confidence interval: 0.41 to 1.57), a 20% reduced rate of death in the LVRS group as compared with the BMC group. This apparent benefit is upheld at various periods throughout this long-term evaluation. Specifically, at 4 years, the survival rate was 56% in the LVRS groups versus 45% in the BMC group. At 6 and 8 years, the survival rates were 42% versus 33% and 37% versus 26%, respectively (Table 4). It is important to note that, despite the trend toward survival advantage in the LVRS group, the confidence intervals of the overall HR crosses the line of no effect, implying no statistical significance ($p = 0.37$). This is, however, likely an effect of lack of power in the study given the limited sample size.

Comment

The improved health utility, health-related quality of life, and functional improvements after LVRS for patients with end-stage emphysema are well established. Nonetheless, surgery for patients with advanced emphysema has not been adopted as a standard option for these sick patients. Bias and high resource utilization appear to limit its appeal. Despite several randomized controlled trials showing LVRS as beneficial, and national COPD treatment guidelines endorsing LVRS, only a handful of patients in Canada and a few hundred patients in the United States underwent LVRS last year. The clinical uncertainty of LVRS value prompted a review of the final outcomes of our CLVR study patients to see if we might better understand this

![Diagram of Canadian Lung Volume Reduction Surgery trial long-term survival analysis consort diagram.](image-url)
unexplained clinical trend. The aim of this study was to specifically compare the survival of LVRS versus BMC alone in the long term.

Using the cohort of randomized patients from the original CLVR trial, this study captured 84% of the previously enrolled patients through phone contacts or access to hospital/physician records. The median survival of 4.11 years is similar to that reported by the long-term follow-up to the National Emphysema Treatment Trial [5, 6]. At the time of this study the majority of the CLVRS patients in both groups were dead, reflecting the advanced stage of disease. This, along with resource limitations, made the assessment of functional status in long-term survivors not possible. At 5 years, more than half of the LVRS group had died and only a quarter of the BMC group was alive. By 10 years, the only surviving patients were 2 who had been randomly assigned to the LVRS group. With only these few patients alive at the time of this review, we were limited to a survival analysis.

Survival analysis conducted in this study demonstrated a trend toward a survival benefit after LVRS. Both the Kaplan-Meier survival curves and the Cox proportional hazards model demonstrated a greater mortality immediately after surgery. This early mortality in the LVRS group is quickly (within a few months) transformed to a survival advantage. Patients surviving the critical early postoperative period appear to soon after benefit from the surgery. This initial mortality toll blunts the long-term survival advantage seen by the patients who successfully undergo LVRS.

The results of our review of this small group of patients in the Canadian study is not statistically significant. Initial sample size calculations for the CLVR study required 350 patients to establish a difference of the desired effect size [14]. With the challenges of recruitment, the CLVR trial only enrolled 20% of that initial sample size calculated. A small sample size study faces the challenge of type II error with a clear disadvantage of being underpowered. Yet in this review both the Kaplan-Meier model and the Cox proportional hazards model are nonetheless clinically meaningful. The 16 months’ survival advantage is reflected by a 20% reduction in mortality seen after LVRS, and is better than BMC alone. On careful review, the magnitude of the SE is relatively small as compared with the magnitude of the clinical improvement. The difference in survival (16 months) is much greater than the 6.7 months SE in the surgery group and the 12.0 months SE in the BMC group.

This finding leads us to believe that if we had a larger sample size we would see statistical significance. That is also supported by other long-term studies all showing a similar benefit. It is important to note that the inclusion criteria of the CLVRS trial was less restrictive than other similar trials, and included a more functionally compromised sample population (diffusion capacity of lung for carbon monoxide of 30% to 35% approached the exclusion criteria of the NETT trial) [13]. This, in combination with the lack of power could potentially explain the inability to reach a statistically significant difference. We offer our data to the body of information available in the hope that a future meta-analysis will provide

Table 3. Kaplan-Meier Estimates of Medians for Survival Time

<table>
<thead>
<tr>
<th>Allocation</th>
<th>Median Estimate</th>
<th>SE</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Lung volume reduction surgery</td>
<td>63.0</td>
<td>6.7</td>
<td>49.9-76.1</td>
</tr>
<tr>
<td>Best medical care</td>
<td>47.0</td>
<td>12.0</td>
<td>23.5-70.5</td>
</tr>
<tr>
<td>Overall</td>
<td>59.0</td>
<td>10.4</td>
<td>38.6-79.4</td>
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CI = confidence interval; SE = standard error.
sufficient sample sizes to achieve not only this important clinical finding of improved survival but also will add statistical significance.

The CLVRS trial, like others, has provided evidence of a multifaceted value to LVRS in the treatment of end-stage emphysema. The initial trial demonstrated clinical and statistical benefit with regards to impairment (as measured by improved posttreatment forced expiratory volume in 1 second), disability (as measured using the 6-minute walk test), and quality-of-life (as measured through the Chronic Respiratory Disease Questionnaire). Moreover, the long-term follow-up study demonstrated a clinically meaningful, but not statistically significant, survival difference. What appears to be an initial postoperative mortality is offset by long-term survival benefit.

In conclusion, this follow-up study failed to demonstrate a statistically significant difference in long-term survival between the two groups. Despite the depicted crude long-term clinical advantage of LVRS over BMC alone, the study was likely underpowered to capture a mortality difference. Survival with advanced emphysema is dismal, with a mean overall survival of 4.11 years. A 16 months, increased median survival and a 20% reduction in mortality was demonstrated after LVRS. We are encouraged by the success of surgical intervention in this lethal disease. These findings support other evidence that LVRS offers improved outcomes for patients who survive the increased mortality of the postoperative period. We hope LVRS surgery will find a useful place in the management of advanced emphysema.

References
9. Pompeo E, Marino M, Nofroni I, Matteucci G, Mineo TC. Reduction pneumoplasty versus respiratory rehabilitation in

<table>
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<tr>
<th>Follow-Up</th>
<th>LVRS</th>
<th>BMC</th>
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<tr>
<td>Four years</td>
<td>56%</td>
<td>45%</td>
</tr>
<tr>
<td>Six years</td>
<td>42%</td>
<td>33%</td>
</tr>
<tr>
<td>Eight years</td>
<td>37%</td>
<td>26%</td>
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BMC = best medical care; LVRS = lung volume reduction surgery.

DISCUSSION

DR SYED QUADRI (Worcester, MA): Thank you for a great presentation. As you know, the numbers of lung volume reduction cases in the United States has declined quite a bit since the heyday about 10 years ago, primarily due to the National Emphysema Treatment Trial and the conflicting results and so on. What has your experience been in Canada with the volume of LVR surgery over the past 5 to 10 years?

DR AGZARIAN: They’re very similar I think in terms of the amount of volume reduction surgeries being performed in Canada since it’s also declined substantially. It’s not commonly practiced. And obviously we have fewer tertiary care centers, and if so, it does happen in those settings. But on an overall basis, it’s not as common. It’s kind of echos what’s happening in the States as well.

DR QUADRI: Thank you.

DR JOSHUA R. SONETT (New York, NY): Excellent paper. It agrees with our huge national study in the United States, and it still hasn’t changed practice patterns. The question is what can we do differently? I mean, I would urge you, if we’re going to publish this, publish this in a medical journal and not in our surgical journal, because as small as this room is or even if it’s bigger, we’re the believers. And we can present all day to ourselves, but I’m not sure how to convince the pulmonologists who, A, got scared away from the high-risk group; and, B, who are looking at endobronchial lung volume reduction surgery the way stents were looked at early in the coronary artery bypass graft experience and thinking they’re going to do it just as well. So we have a long uphill battle I think to get it back. But I think it’s got to start with at least proving to the medical people in their journals and in their meetings that it’s the real deal in terms of survival.

DR AGZARIAN: Yes, I agree. I think that’s a very good point. My humble opinion on the matter is that the pulmonologists, they see the whole conglomerate of patients, and really patient selection is very important. And I think initially when this treatment was first instituted, I think some of the selection criteria were a little more liberal and that led to increased complications. So I really think education is very important, where we present these findings is important, as well as addressing which patients benefit best. And that’s been kind of discussed previously in the National Emphysema Treatment Trial and such.

DR STEPHANIE HELMER (Jacksonville, FL): I’ve spent a lot of time in Canada, growing up in Montreal. I’ve got a question. It looked like your randomization was a little bit skewed to the fact that there were more smokers in your lung volume reduction surgery group. Was that true?

DR AGZARIAN: You mean more patients were in the surgery group?

DR HELMER: One of your slides appeared to show that more patients in the surgery group were smoking. I assume that most of the patients were smokers at one time, but did they continue smoking?

DR AGZARIAN: I think in terms of whether they continued smoking or not, I don’t have the exact number, to be honest with you. I don’t know exactly how many of the patients continued smoking afterward, but I presume it would be comparable in both arms. But I don’t know, to be honest.

DR ROBERT DUANE DAVIS (Durham, NC): Do you have any idea how many of them crossed over and had transplant afterward?

DR AGZARIAN: That’s a good question. It’s pertinent to the room we’re in right now, but I don’t know how many of them. What we do know is at 5 years, 25% of the patients in the medical care arm were alive as compared with 36% in the surgical arm. So most of the patients at this follow-up study institution had passed away by that point.

DR DAVIS: And you don’t have a national—in the United States, we have the national security database that you can always use. There is no equivalent in Canada?

DR AGZARIAN: No. We don’t have a national database with that regard. We only have three or four centers that would do transplants in the first place.

DR DAVIS: For the manuscript, it would be really important, given the lack of statistical significance, of trying to reduce the loss to follow-up component. Thank you very much.