Lung volume reduction surgery: results from a randomised trial re-analysed and re-interpreted using longitudinal data analyses methodology

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Abstract

Background

The largest randomised controlled trial evaluating the results of lung volume reduction surgery (LVRS) was conducted by the National Emphysema Treatment Trial (NETT) that published a series of reports for outcomes up to 24 months. However, patient outcomes were difficult to interpret due to limitations in and the presentation of conventional statistical analyses applied to repeated measures (longitudinal) data.

We aimed re-evaluated the results from NETT using longitudinal data methodology to report longer term outcomes to facilitate interpretation by clinicians and patients who are considering LVRS in the management of emphysema.

Methods

Trial data was released by the United States National Institute of Health and the United States National Heart, Lung and Blood Institute, and analysed using a mixed effects model. 5 year data was estimated and presented in the baseline units of the original measurement.

Results

The five-year differences in patients randomised to LVRS was a small but sustained improvements in lung function parameters of FEV1, FVC and RV of +1.4% ($P<0.001$), +3.44% (($P<0.001$) and -19.49% ($P<0.001$) of the predicted values respectively. With regards to physiological parameter function, the five year difference in patients randomised to LVRS was an overall 0.89 Watt improvement in maximum workload (P=0.069), -4.12 improvement in shortness of breath score (P<0.001) and a 0.088 improvement in quality of well-being score (P=0.102).

Conclusions

Our results suggest that LVRS continues to have an important role in the management of patients with severe emphysema with long term benefits to lung function parameters and a sustained improvement to the relief of dyspnoea.

Introduction

The largest randomised controlled trial evaluating the results of lung volume reduction surgery (LVRS) was conducted by the National Emphysema Treatment Trial (NETT) that published a series of reports for outcomes up to 24 months.[1-3]

A decade later, the effects of LVRS on patient outcomes remain difficult to interpret by the majority of clinicians and therefore impossible to explain to our patients due to limitations in limitations in the way the data has been presented. We cannot advise patients on either the degree of benefit nor the proportion of patients who respond according to conventional measures. The original paper focussed on mortality and the other patient related outcomes such as quality of life and breathlessness were difficult to interpret. The impact of the results was to significantly reduce referral for lung volume reduction surgery. Consequently there has been a dramatic decrease in the number of procedures performed despite its overwhelming efficacy in appropriately selected patients.

The statistical analyses and time series outcomes depicted as multiple histograms in the NETT publication provide a good overview to a complicated question, but does not take into account complexities such as correlation structures (within patient, between patients and between groups) within longitudinal data and therefore cannot provide easily interpretable information such as the average effect of LVRS versus medical therapy with time.

The purpose of this study is to re-evaluate the results from the NETT using longitudinal data methodology to report longer term outcomes interpretable by clinicians and patients who are considering LVRS in the management of emphysema.

Methods

Data was obtained by joint permission from the United States National Institute of Health and the United States National Heart, Lung and Blood Institute, and interrogated using longitudinal data analysis techniques to estimate the differences in the survivors of the 608 surgical and 610 medical participants on age, sex and height adjusted (percentage predicted) values for lung volumes. The entry criteria of the study and trial results have been previously published.[1, 4]

For each response variable we applied a mixed effects model, with an expected population average incorporating components for the effects of medical and surgical treatments.[5] The model allows interpretation of the effect of medical treatment as linear with a monthly rate of change. The difference between medical treatment and surgical is given by the sum of a parameter that represents the immediate effect of surgery and a non-linear term that allows for an exponential decay of the surgical effect. We did not specify a correlation structure between errors as we adopted a saturated model to account for this. A full description of the statistical methodology used in this paper can be obtained on request.

To facilitate clinical interpretation, assessment of efficacy for each major outcome was plotted on the estimated values and differences in patients randomised to LVRS or medical therapy using measurement values of each reference test, in units of the original test results and displayed as a time series plot.

Results

Longitudinal measurements of lung function were evaluated in 1218 patients in the cohort at 6, 12, 24, 36, 48 and 60 months. The results have been presented in two formats, the first is a plot of the individual estimated values in each group and the adjacent plot is the difference between patients randomised to LVRS versus medical treatment. A summary of the estimated differences at the immediate and 5 year period is provided in table 1.

For FEV1, in patients randomised to LVRS, there was an immediate improvement in compared to medical therapy with an estimated decline to baseline approximately 5 years after randomisation with a residual difference of +1.47% of predicted in favour of LVRS at the 5 year interval (Figure 1). Similarly, all other parameters that experienced initial improvement showed evidence of returning to baseline (albeit at a varying rate) within the 5 year follow up interval. The differences RV/TLC ratio can be seen in Figure 2. Other mechanical effects such as residual volume (Figure 3), forced vital capacity (Figure 4) also showed evidence of returning towards baseline but remained at -19.49% predicted ($P<0.001$) and +3.44% predicted ($P<0.001$) in favour of LVRS at the 5 year time point.

In patients randomised to LVRS exercise performance measured as maximum workload increased initially but effects returned to baseline by 5 years with a residual difference of +0.89 W ($P=0.069$) in favour of LVRS (Figure 5). The physiological effect of improving arterial oxygenation was sustained at +5.96 mmHg in favour of LVRS but the difference was no longer statistically significant at P=0.480 (Figure 6). Symptomatic improvements to shortness of breath was sustained at -4.12 points (P<0.001) in favour of LVRS (Figure 7) but the overall quality of well-being score was still in favour of LVRS although the difference at the 5 year interval was small at 0.09 and not statistically significant (Figure 8).

Discussion

Longitudinal data analysis is now an established sub-specialist area of statistics and regarded as a breakthrough method in the analysis of repeated measures data.[6] Application of this technique for the first time on the NETT data has revealed a number of insightful observations.

The effects of LVRS in general have been evaluated in three broad outcomes, survival, lung function and quality of life. Data from the original NETT had revealed no difference in overall survival, however identified a sub-group of patients with upper lobe predominant heterogeneous emphysema and low baseline exercise capacity who are expected to derive a survival advantage with LVRS.[1]

In this study, we profile the time differences in lung function measures between the two groups and categorise them as lung function and quality of life outcomes. The lung function improvements of LVRS such as immediate increase in FEV_1, FVC, reduction in RV, TLC and RV/TLC ratio support the efficacy of LVRS as surgical therapy. The improvements however, the increments each show a tendency to return to baseline, albeit at different rates. The improvements to exercise work load seem to mirror that of the mechanical lung function results.

The increase in PaO_2 appeared sustained but was not statistically significant at the 5 year interval. Detailed analyses of the LVRS study from our institution identified that the increase in Kco (the transfer factor for carbon monoxide) paralleled that of the arterial oxygenation, suggesting that the effects of LVRS may also be in part due to improvements in the redistribution of blood flow, by resecting severely diseased lung tissue.[7]

Although no overall survival benefit has been demonstrated, lung function measures provide objective measures of benefit and we argue that patient related outcomes such as improvement to dyspnoea, quality of life and exercise capacity are more important. From the longer term results that we report, the most pertinent observation is the sustained improvement to the UCSD shortness of breath score (a five point difference has been reported as a reasonably minimally important difference[8]).

Our results suggest that LVRS continues to have an important role in the management of patients with severe emphysema with long term benefits to lung function parameters and a sustained improvement to the relief of dyspnoea. LVRS should be undertaken with a view to improve patient symptoms rather than overall survival.

Conclusions

The effects of LVRS are an improvement to lung function and exercise workload that returning to baseline within a 5 year period. Although LVRS may not improve survival the procedure continues to have an important role in patients with severe emphysema with a sustained improvement to dyspnoea as far out as 5 years after surgery.

Acknowledgements

The authors are grateful for the assistance of Professor Steven Piantadosi and for the data released to us by the United States National Institute of Health and the United States National Heart, Lung and Blood Institute.

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Table 1. Estimated immediate and 5 year effects on lung function parameters

Response	Estimated immediate effect	p-value	Estimated difference at 5 years	p-value
FEV1 (% predicted)	+8.28	<0.001	+1.47	<0.001
FVC (% predicted)	+12.13	<0.001	+3.44	<0.001
RV (% predicted)	-55.08	<0.001	-19.49	<0.001
TLC (% predicted)	-15.09	<0.001	-5.24	<0.001
RV/TLC	-0.26	<0.001	-0.09	<0.001
PaO2 (mmHg)	+5.10	<0.001	+5.96	0.480
Maximum Workload	+7.97	<0.001	+0.89	0.069
Shortness Breath Score	-21.13	<0.001	-4.12	<0.001
Quality of Well Being Score	+0.16	<0.001	+0.09	0.102

Figure 1. Results for FEV1

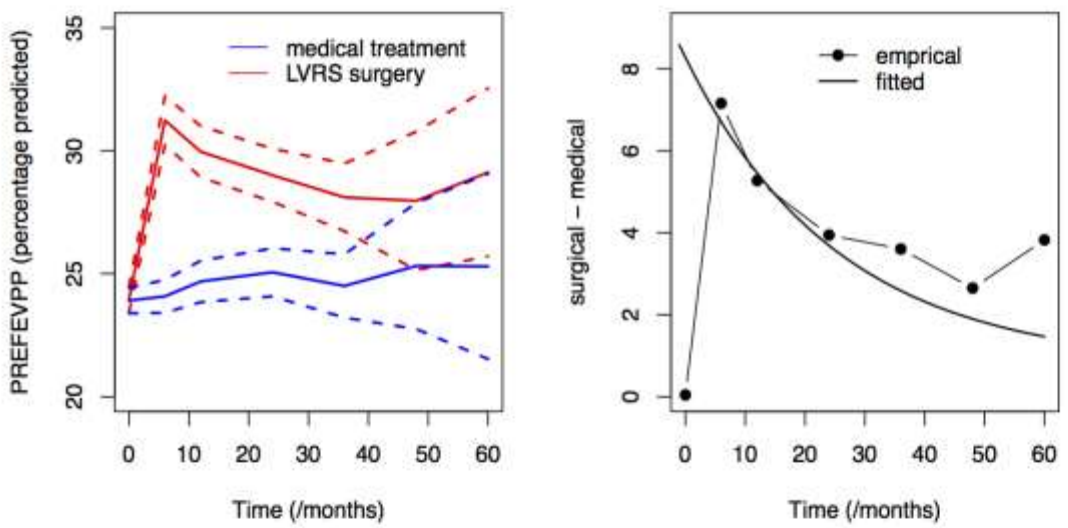

Figure 2. Results for the RV/TLC ratio

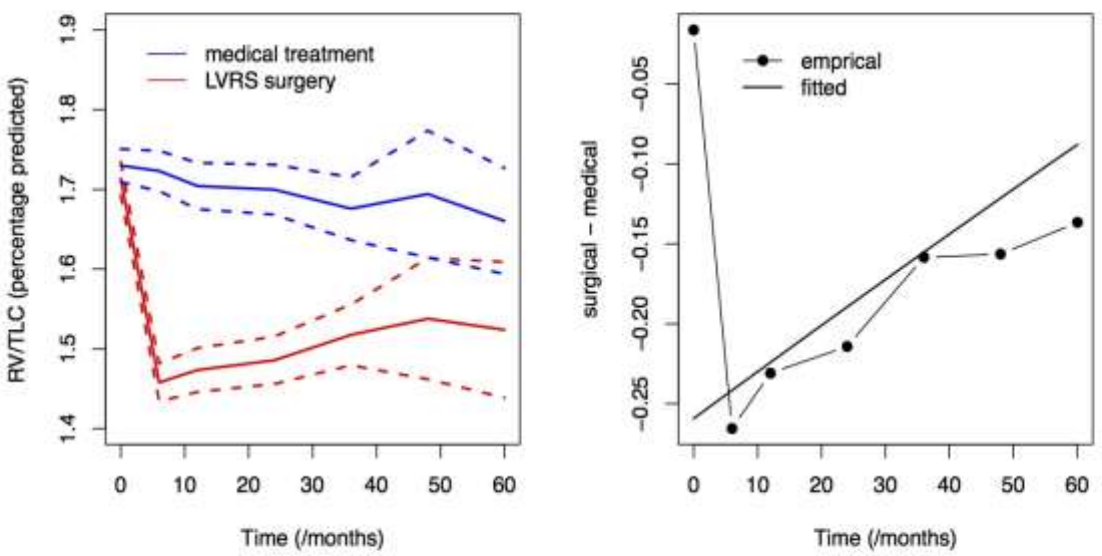

Figure 3. Results for residual volume

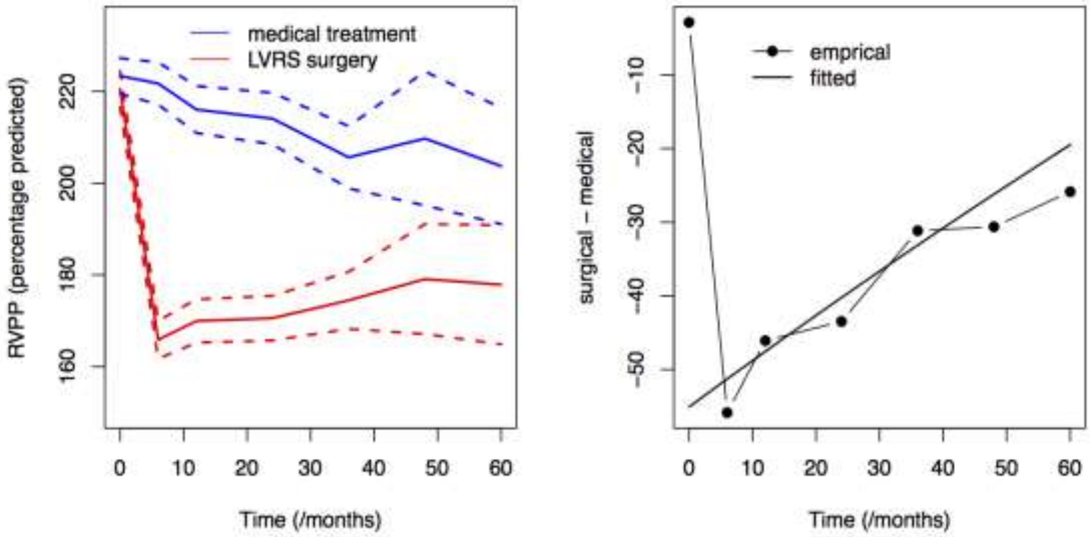

Figure 4. Results for forced vital capacity

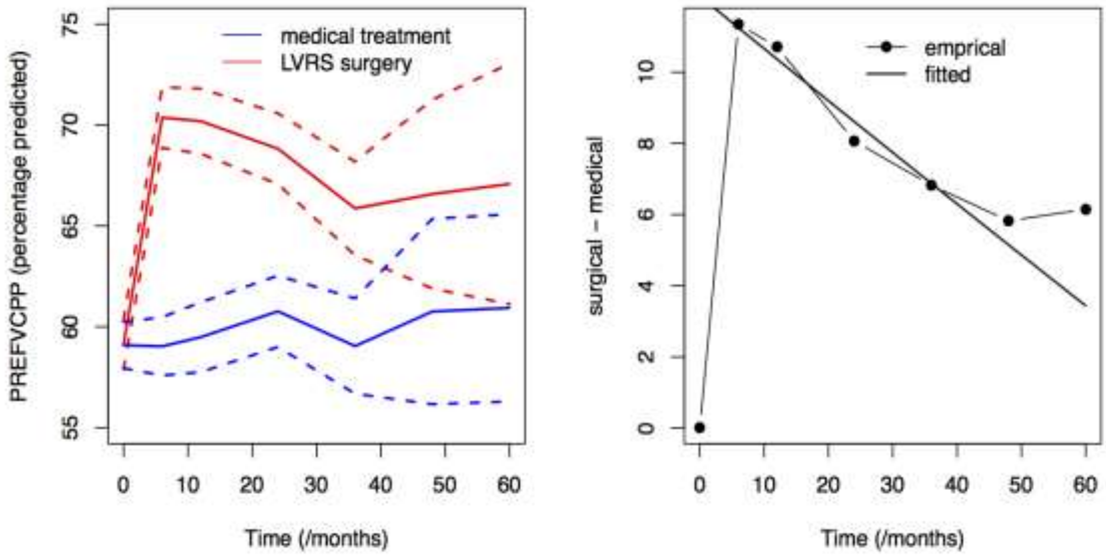

Figure 5. Results for maximum workload

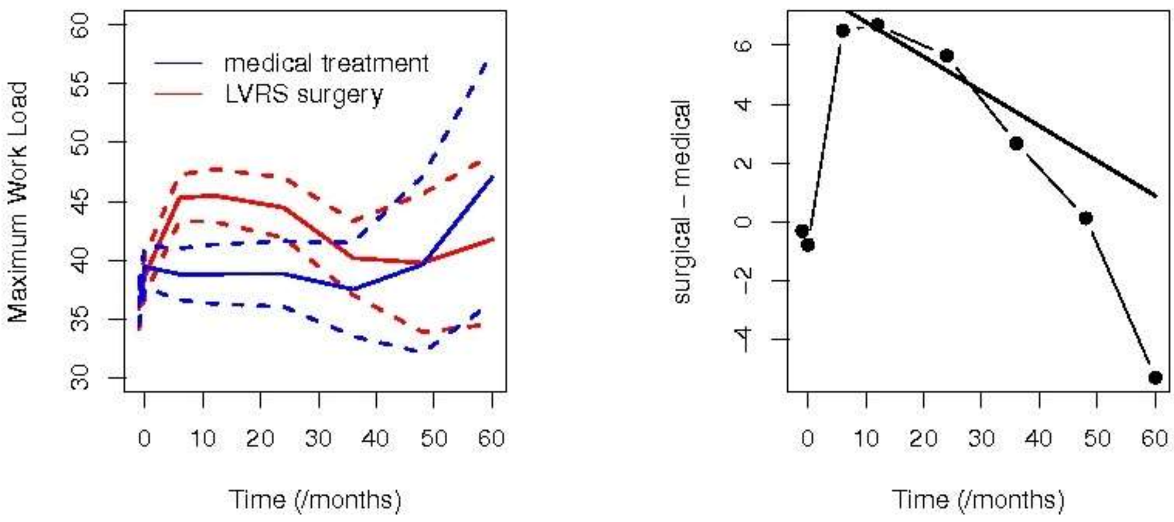

Figure 6. Results for arterial oxygenation

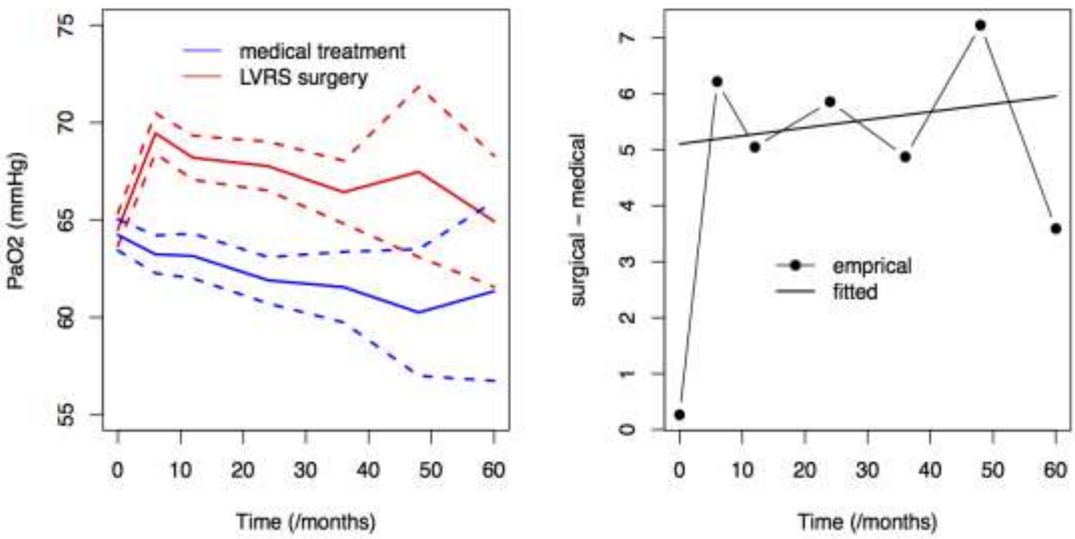

Figure 7. Results for shortness of breath score

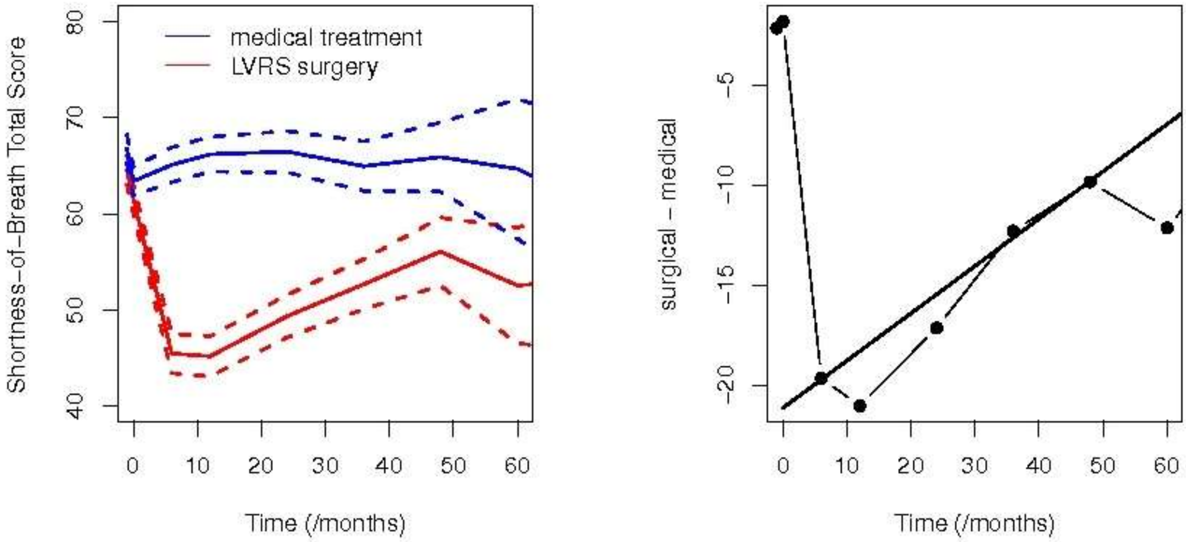

Figure 8. Results of quality of well being score