

This article has been adapted from an ERS Research Seminar held in Como, Italy in 2007. The original slides and other material can be found at www.ers-education.org

Endobronchial blockers for lung volume reduction



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Competing interests

The author's group has received unrestricted research grants from Emphasys, PortAero and Broncus, all of which own technologies relating to minimally invasive non-drug approaches to emphysema.

Provenance

Adapted from an ERS Research Seminar

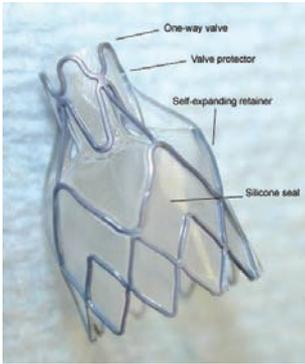
Educational aims

- › To understand how endobronchial valves can improve symptoms in patients with emphysema and to convey current opinion regarding optimal patient selection.

Summary

Surgical lung volume reduction can, under certain circumstances, improve forced expiratory volume in one second (FEV₁), indices of resting hyperinflation and quality of life [1] in patients with emphysema. However, a significant proportion of patients (between one-quarter and one-third) fail to derive significant benefit from the procedure. This in itself might not matter were it not that, in large series, the mortality rate has been at least 4–5% [1–3]. While this risk might be acceptable if success were guaranteed, it is less appealing otherwise. Another issue is that, in order to reduce mortality and morbidity, most groups impose safety criteria so that patients who are too disabled are not eligible for lung volume reduction surgery (LVRS).

These factors suggest a need for a treatment which is more likely to be effective and is less dangerous and/or reversible. Two principal approaches have been described. In one, an extrapulmonary pathway is created, which allows increased expiratory flow from the lung. In the other, which will be discussed in this article, an endobronchial blocker or valve is positioned with the aim of achieving distal collapse; the tissue engineering approach, using instilled glues, is a variant of this technique.

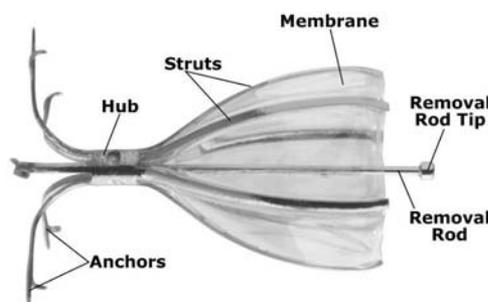


Collapsing diseased lung

An English surgeon, S. Sabanathan, first suggested endobronchial blockade as an alternative approach to the problem of reducing lung volume. His preliminary data, from procedures performed between November 1996 and April 1997 [4] were published posthumously and showed that significant improvement was possible using this approach. However, the blockers initially used had not been designed for endobronchial occlusion. Significant problems were observed with migration of the blockers or if blocker disintegration occurred. Additionally, only very limited pulmonary function data were reported.

Biotechnology companies have now taken up the challenge, and two devices designed specifically for the purpose are commercially available. The Emphasys system (Emphasys Medical Inc, Redwood City, CA, USA; figure 1a) uses a one-way duckbill valve that is inserted in such a way that air is permitted to leave the subtended segment but not to enter it. The valve is secured and supported by a collapsible metal framework. The early valves were inserted over a guide wire, but current models can be inserted through the working channel of a fiberoptic bronchoscope. Five human studies with the valve have been published [5–9] and the company has recently reported the combined data (*i.e.* a summation and duplication) [10].

The Spiration device (Spiration Inc, Redmond, WA, USA; figure 1b) is an 'umbrella' arrangement, inserted so that the convex surface is positioned distally with the aim once again, of allowing expiratory but not inspiratory flow; to the best of the current author's knowledge, the only human data so far reported are in abstract form from an uncontrolled study of 30 patients [11], who were subjected to bilateral upper lobe placement. The reported safety data were satisfactory but less than one third of patients showed improvements in FEV₁ or 6-min walking test >15%.



Similarly, although animal data exist for a tissue engineering approach to lung volume reduction [12], human data so far are confined to subsegments of a single lung in six subjects [13]. Again, the safety profile was satisfactory.

Experience with endobronchial therapy

In 2003, TOMA *et al.* [9] reported the use of the Emphasys valve for unilateral bronchoscopic lung volume reduction (BLVR), giving data from eight patients. Despite the small sample size, a statistically significant improvement in FEV₁ was seen, with an increase from 0.79 L (range 0.61–1.07) to 1.06 L (0.75–1.22; difference 34%; $p=0.028$). Dynamic hyperinflation was not measured, but a nonsignificant improvement in indices of resting hyperinflation as judged by whole-body plethysmography was noted.

A study of bilateral lung volume reduction using an early version of the Emphasys valve found no improvement in any parameter except transfer factor of the lung for carbon monoxide (T_{LCO}), although the authors also found valve insertion to be safe and well tolerated [5].

Two further studies presented data from mixed samples of patients who had undergone either unilateral or bilateral BLVR. The study of YIM *et al.* [6] looked at 20 patients, of whom 12 underwent unilateral and eight bilateral valve insertion, mostly but not exclusively in the upper lobes. There was a significant improvement in FEV₁ from 0.73 L to 0.92 L 3 months after the operation ($p=0.009$), but trends towards improvement in gas transfer and plethysmographic lung volumes failed to reach statistical significance. VENUTA *et al.* [7] studied 13 patients undergoing unilateral or bilateral BLVR ($n=2$), mostly but not exclusively in the upper lobes. There was a significant improvement in FEV₁ from 0.75 L to 1.00 L at 3 months ($p=0.01$). In addition, significant falls were observed in plethysmographic lung volumes. Mean T_{LCO} rose from 33% to 50% predicted.

Only one study of BLVR has measured dynamic hyperinflation directly [8]. A total of 19 patients were treated with unilateral endobronchial valve insertion and key measurements were made 4 weeks after the procedure. As in previous studies, statistically significant improvements in mean FEV₁ (28.4 to 31.5% pred; $p<0.05$) and in mean T_{LCO} (36 to 41% pred; $p=0.016$) were observed (table 1). Statistically significant improvements in total

Table 1 Lung function before and 4 weeks after BLVR

	Baseline	4 weeks
FEV ₁ % pred	28.4±11.9	31.5±13.2*
TLC L	9.1±1.5	8.8±1.5*
RVL	5.8±1.7	5.23±1.7
FRC L	7.09±1.5	6.61±1.7*
T _{L,CO} mmol·min ⁻¹ ·kPa ⁻¹	3.3±1.1	3.7±1.2*
K _{CO} mmol·min ⁻¹ ·kPa ⁻¹ ·L ⁻¹	0.68±0.2	0.73±0.2*

Data are presented as mean±sd. TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; K_{CO}: carbon monoxide transfer coefficient. *: p<0.05. Data taken from [8], with permission from the publisher.

lung capacity and functional reserve capacity were observed, though improvement in residual volume was not statistically significant. Patients were divided into improvers and non-improvers, the former being defined as patients who were able to show an increase of both 60 s and 30% in endurance time on the constant-rate cycle endurance test. Overall, nine (47%) out of 19 patients met this criterion. In a stepwise regression analysis, only changes in resting inspiratory capacity and in T_{L,CO} were retained as independent predictors, producing an equation that explained 81% of the variation in endurance time (p<0.0001). If patients with atelectasis were excluded, again only the same two variables were retained in the model (r²=0.61; p=0.002).

A dataset combining the above studies has

recently been reported [10]: 98 patients were studied, with an average number of four valves per patient. The majority of patients underwent complete unilateral (48%) or bilateral (21%) lobar occlusion. Significant improvements were observed in FEV₁ (mean 60 mL, 10%) and in walking distance (37 m, 23%).

The results of a multicentre randomised controlled trial were presented at the 2007 European Respiratory Society Congress. Because this was a "Hot Topic symposium", no written record of the data exists at the time of writing but a peer-reviewed paper is expected shortly.

While clinically these mean improvements are at the lower range of what might be considered worthwhile, the safety profile of BLVR compares favourably with surgical LVRS. *Post hoc* subset analysis showed that the biggest improvements were seen in those patients submitted to complete lobar occlusion, and those who had the lowest pre-operative FEV₁ and the greatest hyperinflation.

Conclusion

Given careful patient selection, LVRS has been shown to be effective in improving emphysema patients' lives. However, the failure and mortality rates remain high. BLVR, a less traumatic procedure, has a better safety profile. Although early indications are promising, data from randomised controlled trials on its efficacy have so far been lacking.

References

- Cooper JD, Patterson GR, Sundaresan RS, et al. Results of 150 consecutive bilateral lung volume reduction procedures in patients with severe emphysema. *J Thorac Cardiovasc Surg* 1996; 112: 1319–1330.
- 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: 239–245.
- Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003; 348: 2059–2073.
- Sabanathan S, Richardson J, Pieri-Davies S. Bronchoscopic lung volume reduction. *J Cardiovasc Surg (Torino)* 2003; 44: 101–108.
- Snell G, Holsworth L, Borrill ZL, et al. The potential for bronchoscopic lung volume reduction using bronchial prostheses. *Chest* 2003; 124: 1073–1080.
- Yim AP, Hwang TM, Lee TW, et al. Early results of endoscopic lung volume reduction for emphysema. *J Thorac Cardiovasc Surg* 2004; 127: 1564–1573.
- Venuta F, de Giacomo T, Rendina EA, et al. Bronchoscopic lung-volume reduction with one-way valves in patients with heterogeneous emphysema. *Ann Thorac Surg* 2005; 79: 411–416.
- Hopkinson NS, Toma TP, Hansell DM, et al. Effect of bronchoscopic lung volume reduction on dynamic hyperinflation and exercise in emphysema. *Am J Respir Crit Care Med* 2005; 171: 453–460.
- Toma TP, Hopkinson NS, Hillier J, et al. Bronchoscopic volume reduction with valve implants in patients with severe emphysema. *Lancet* 2003; 361: 931–933.
- Wan IY, Toma TP, Geddes DM, et al. Bronchoscopic lung volume reduction for endstage emphysema: report on the first 98 patients. *Chest* 2006; 129: 518–526.
- Wood DE, McKenna RJ Jr, Yusef RD, et al. A multicenter trial of an intrabronchial valve for treatment of severe emphysema. *J Thorac Cardiovasc Surg* 2007; 133: 65–73.
- Ingenito EP, Berger RL, Henderson AC, Reilly JJ, Tsai L, Hoffman A. Bronchoscopic lung volume reduction using tissue engineering principles. *Am J Respir Crit Care Med* 2003; 167: 771–778.
- Reilly J, Washko G, Pinto-Plata V, et al. Biological lung volume reduction: a new bronchoscopic therapy for advanced emphysema. *Chest* 2007; 131: 1108–1113.