



Editorial

Pros and Cons of Endoscopic Treatment of Emphysema

Luces y sombras del tratamiento endoscópico del enfisema

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Pros and Cons of Endoscopic Treatment of Severe Asthma

For a long time now, pulmonologists have been searching for a minimally-invasive alternative to lung volume reduction surgery, especially since the NETT study demonstrated that the surgical technique improves the functional capacity and quality of life of some patients with severe emphysema.¹ What is most striking of the NETT study is that a subgroup of patients with emphysema, predominantly in the upper lobes and with poor tolerance to effort, reached an unprecedented increase in survival. As strange as it may seem, it was that same assay that led to the demise of lung volume reduction surgery in the United States when evidence was given of the high price that some patients had to pay for improvement (5.5% mortality and morbidity higher than 50%), including a notable increase in mortality of some high-risk subgroups.² Currently, and despite the positive results of NETT, less than 200 surgical interventions are performed annually in the US.³ The paradoxical failure of the NETT study gave rise to a spectacular proliferation of medical mechanisms whose goal is to find a minimally-invasive alternative to surgery.

The pioneers of the endoscopic treatment of emphysema tried to reproduce the benefits of the NETT, avoiding the frequent complications of this therapeutic option, such as air leaks and prolonged hospitalizations. The initial postulated research hypothesis was aimed at achieving a clear improvement in respiratory functional tests, selecting patients with heterogeneous emphysema predominantly in the upper lobes. Later, the paradigm changed. Some opted to avoid lung volume reduction and center on redistribution, using computed tomography (CT) as a scale instead of the functional tests. In addition, less ambitious objectives were posed as alternatives to spirometry, above all the improvement of specific quality-of-life questionnaires, such as St. George's (SGRQ). This change in strategy, evidenced in the randomized studies of the IBV® system by Spiration,^{4,5} aspires to a modest benefit in exchange for guaranteeing patient safety. Needless to say, patients with severe emphysema are extremely delicate, and even an endoscopic treatment can have fatal consequences. The change in paradigm was also motivated by the observation that the magnitude of endoscopic

lung volume reduction was less than that of surgery and the fact that the subjects that experimented clear improvement in spirometry usually had a greater risk of complications.⁶ Furthermore, in the Spiration valve pilot study, it became obvious that endoscopic treatment, despite not improving either functional or aerobic capacity or a manifested reduction in lung volume, can improve the quality of life of patients with severe emphysema (averaging 8 points of the SGRQ).⁷ All this is open to debate, and various alternatives continue to be explored. Some researchers, such as Felix Herth in Heidelberg, are of the opinion that lung volume reduction is indispensable and should be the main objective of these techniques. He therefore advocates lobar exclusion in most cases (personal communication, Hamburg 2010).

Treatment with endobronchial valves, which without a doubt has been the most widely-studied treatment to date, seems to have raised more questions than it has given answers. So much so, that the first device to apply for FDA approval failed by a wide margin after the panel of experts considered that the results of the VENT study were not solid enough.⁸ The multi-center clinical assay was well-designed and controlled (although not by placebo) with a considerable sample size, using Zephyr® valves by Emphasys. The results were statistically significant, but not conclusive. Improvement was observed in FEV1 (60 ml), 6-minute walk test (19 meters), and favorable changes in the SGRQ with the treatment (average 3.4 points).⁹ Although these results can be considered hopeful due to their statistical significance, the number of hospitalizations due to COPD exacerbations was much greater in the treatment group (17 vs. 1) as was the incidence of hemoptysis. The fear of worsening things was greater than the hope deposited in these meek, favorable results.

The European study of the Spiration valves, smaller than the VENT study but controlled by placebo, has also been unable to demonstrate that endoscopic techniques represent a clear alternative to surgery. The patients treated in this study, in which two Spanish centers participated, presented an initial improvement of more than 4 points on the SGRQ combined with a significant reduction of the lung volume of the upper lobes. Curiously enough, the magnitude of the placebo effect was similar at three months, the time at which the patients of the control group received valves as required by the protocol and by logical medical ethics. At the end of the study, 31% of the patients treated experienced a decrease of 8 points on the SGRQ

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and a significant reduction in the lung volume of the upper lobes treated.¹⁰ The parallel assay done in the United States will tone down the impact of the placebo effect as the randomization is prolonged for 6 months.

Those of us who continue to research the possibilities of endobronchial valves keep our hope up, as our aim is to find a minimally-invasive option over surgery. The most obvious advantages would be its low morbidity and mortality, but amongst the other advantages is its reversibility. The option of withdrawing valves from the airway in the event of complications is especially attractive, and in fact this was necessary in 20% of the patients in the Spiration pilot assay.⁷ Unfortunately, we still do not know whether we should concentrate on bilateral or unilateral treatment. We have no idea whether it is preferable to treat the most damaged lobe or if we should follow the path of the NETT and treat only patients with upper lobar emphysema. It is not clear how to avoid collateral ventilation in order to achieve a greater reduction in lung volume in those patients undergoing lobar exclusion (the Chartis® endobronchial device was developed by Pulmonx for this goal).¹¹ On the other hand, we are still searching for a scientific explanation to justify the improvement in the quality of life of subjects who experience no functional changes, improvement in gas exchange, or greater tolerance to effort. Nor is it clear whether the demonstrated changes in the SGRQ are sufficient enough for the treatment to be worth it. One of the great unknowns, and perhaps the most interesting observation of the randomized assays completed to date, is the magnitude of the placebo effect of bronchoscopy. This finding is in common with other endoscopic techniques, such as bronchial thermoplasty,¹² and is a powerful impediment when interpreting questionnaires like the SGRQ in assays that are not controlled by placebo. Last of all, the high cost of the treatment, estimated at \$12,000-\$20,000 per patient,¹³ is worrisome.

Aside from the growing debate involving unidirectional valves, other techniques have emerged that rival these in scientific theory and are currently being studied. Among these are treatment with biological glue, lung volume reduction by thermal vapor and the placement of transbronchial prostheses to aide in the exhalation of trapped air. Bioglue and bronchi prostheses offer the possibility for treatment in patients with homogeneously-distributed emphysema.¹⁴ The former, developed by Aeris in the US, has yielded a polymer that will be studied in 2011 in a multi-center study in Spain. For now, bioglue is achieving improvements in lung function and quality of life, associated with the healing of treated subsegments.¹⁵ This system has the advantage of producing a progressive volume reduction, avoiding the risk for pneumothorax. Fortunately, as it is a gel that covers the subsegmental surface, it is not jeopardized by collateral ventilation, which is quite problematic for other endoscopic options such as endobronchial valves. Its greatest disadvantage is the inflammation that it produces, with the consequent risk of COPD exacerbation, and the fact that it is an irreversible treatment. In the event the patient's condition worsens, there is no turning back. Furthermore, the healing that it produces in high-risk patients makes interpreting future tomographies difficult when screening for lung cancer.

Prostheses have been studied in the randomized multi-center, placebo-controlled assay known as EASE. The results were presented in the European Congress in Barcelona this year. More than 300 patients were included from all over the world, and although an improvement in FEV1 could not be demonstrated, a significant

reduction was reached in residual volume, with a mean of about half a liter. It once again became clear that endoscopic treatment of emphysema, homogenous in this case, results in an improvement in the quality of life of patients with severe emphysema.¹⁶ Unfortunately, the improvement was not lasting and, as was to be expected, more adverse effects were observed in the treatment group than in the control group.

For the moment, it is apparent that there is much left to be done. We know that the endoscopic treatment of emphysema allows for a limited reduction in regional or global lung volume depending on the technique used, and a significant improvement in quality of life in exchange for fewer morbidities and less mortality compared with surgery. The glass seems half empty when we compare the magnitude of the effect of endoscopic treatments with the benefits obtained with surgery, but half full when the comparison is with the pharmacological treatment of COPD. Improvements of 8 points on the SGRQ are not paltry when we compare this improvement with the changes of less than 4 points reported in emblematic studies such as TORCH or UPLIFT.^{17,18}

References

1. 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.
2. National Emphysema Treatment Trial Research Group. Patients at high risk of death after lung-volume-reduction surgery. *N Engl J Med.* 2001;345:1075-83.
3. Naunheim KS. Lung volume reduction surgery: A vanishing operation? *J Thorac Cardiovasc Surg.* 2007;133:1412-3.
4. Sterman D, González X, Springmeyer SC, Mehta A. Design of a multicenter, double-blinded, randomized and sham-controlled study to evaluate the ibv valve system for the treatment of severe emphysema in USA. World Congress of Bronchology 2008, Tokyo, Japan.
5. Ninane V. European Multicenter, Blinded and Randomized Study Design to Evaluate the Effectiveness of Bronchoscopic Airway Valve Placement for the Treatment of Advanced Emphysema. *Eur Respir J.* 2007;17th ERS conference: 106s.
6. Wan IY, Toma TP, Geddes DM, Snell G, Williams T, Venuta F, et al. Bronchoscopic lung volume reduction for end-stage emphysema: report on the first 98 patients. *Chest.* 2006;129:518-26.
7. Sterman DH, Mehta AC, Wood DE, Mathur PN, McKenna RJ, Ost DE, et al, IBV Valve US Pilot Trial Research Team. A multicenter pilot study of a bronchial valve for the treatment of severe emphysema. *Respiration.* 2010;79:222-33.
8. Available from: <http://www.fda.gov/ohrtms/dockets/ac/08/transcripts/2008-4404-t001.pdf>.
9. Sciruba FC, Ernst A, Herth F, Strange C, Criner GJ, Marquette CH, et al. A Randomized Study of Endobronchial Valves for Advanced Emphysema. *N Engl J Med.* 2010;363:1233-44.
10. Abstract europeo.
11. Mantri S, Macaraeg C, Shetty S, Aljuri N, Freitag L, Herth F, et al. Technical Advances: Measurement of Collateral Flow in the Lung With a Dedicated Endobronchial Catheter System. *J of Bronchology.* 2009;16:141-4.
12. Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade M, Shah PL. Effectiveness and Safety of Bronchial Thermoplasty in the Treatment of Severe Asthma. A Multicenter, Randomized, Double-Blind, Sham-Controlled Clinical Trial. *Am J Respir Crit Care Med.* 2010;181:116-24.
13. Berger RL, DeCamp MM, Criner GJ, Celli BR. Lung Volume Reduction Therapies for Advanced Emphysema: An Update. *Chest.* 2010;138:407-17.
14. Refaely Y, Criner G, Dransfield M, Leeds W, Tewari S, Gildea T, et al. Safety and Efficacy of Biologic Lung Volume Reduction (BLVR) in Patients with Advanced Homogeneous Emphysema. *Am J Respir Crit Care Med.* 2009;179:A4392.
15. Criner GJ, Pinto-Plata V, Strange C, Dransfield M, Gotfried M, Leeds W, et al. Biologic Lung Volume Reduction in Advanced Upper Lobe Emphysema: Phase 2 Results. *Am J Respir Crit Care Med.* 2009;179:791-8.
16. Sius, EASE trial results. ERS Barcelona, 2010.
17. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med.* 2007;356:775-89.
18. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease. *N Engl J Med.* 2008;359:1543-54.