

## Ⓜ Lung Volume Reduction: Apex Treatments and the Ecology of Chronic Obstructive Pulmonary Disease Care

The care system for people with chronic obstructive pulmonary disease (COPD) includes, but is not limited to, interactions between and choices made by health and social care professionals, patients, and their families and carers. Actors within this system will have varying degrees of agency, be constrained by factors including culture and economics, and have varying and potentially conflicting motivations. This sort of complex network can be thought of as a kind of ecosystem, which in the case of COPD is anything but healthy. A majority of patients with the condition miss out on basic aspects of care, such as evidence-based smoking cessation support, pulmonary rehabilitation, and effective self-management, with substantial unwarranted variation in outcomes (1) and considerable unmet need among breathless patients (2). Developing the analogy, there is growing understanding of the wide effect that apex predators have across ecosystems; for example, by reducing herbivore and mesopredator numbers, apex predators can increase diversity in populations of small mammals and plant species (3). Poor COPD care in part reflects nihilism about the effectiveness of treatment, but evidence now shows clearly that in appropriately selected patients with the condition, lung volume reduction (LVR) surgery and endobronchial valve placement can have substantial benefits on lung function, exercise capacity, health status, and even survival (4–9). LVR procedures thus provide a system incentive to ensure that patient assessment, and care in general, is optimized so that those patients who are eligible can be identified and benefit. As such, LVR procedures have the potential to take on this “apex” role in the COPD care ecosystem, providing a treatment that, although only a proportion of patients are eligible, still provides a “pull factor” that could drive up standards of care more broadly.

The recent National Institute for Health and Care Excellence COPD guideline update (10) outlines a stepwise system approach to evaluation for LVR (Table 1). At the end of pulmonary rehabilitation, patients' condition and their pharmacotherapy should have been optimized as far as is possible. If at that point they are still limited by breathlessness, the plausibility of LVR should be considered in all individuals. In the absence of obvious contraindications such as frailty or multimorbidity, a respiratory assessment including computed tomography thorax and lung function testing should be performed. Where emphysema and significant hyperinflation are identified, suggesting LVR is a possibility, a review by an LVR multidisciplinary team, able to assess

technical suitability and weigh different options to establish whether any LVR approach is likely to be beneficial, should be considered. Obviously, to get to this final point, the healthcare system requires breathless patients with COPD actually to be offered and be able to access pulmonary rehabilitation, receive smoking cessation support, and have appropriate pharmacotherapy.

Most studies of LVR with endobronchial valves have used the Zephyr valve (4–9, 11). This contains a duckbill valve inside a nitinol/silicone frame and is held in place against the airway mucosa, as the device expands when deployed. A recent meta-analysis of trials using the Zephyr device found that in patients without collateral ventilation, valve placement improved residual volume by 0.57 L (95% confidence interval,  $-0.71$  to  $-0.43$ ), FEV<sub>1</sub> by 21.8% (17.6–25.9%), and 6-minute-walk test by 49 m (95% confidence interval, 32–66 m) (12).

An alternative device, the Spiration valve, constructed of nitinol coated with polyurethane, has an umbrella design and, when deployed, fixes onto the airway wall with five anchor hooks. Initial, unsuccessful clinical trials with this valve did not use the whole-lobe approach to treatment (13), which is now acknowledged to be necessary for endobronchial valve treatment to be effective. In this issue of the *Journal*, Criner and colleagues (pp. 1354–1362) describe the results of the EMPROVE study, which investigated the effect of lobar occlusion with this valve in patients with heterogeneous emphysema, hyperinflation, and intact interlobar fissures assessed as >90% intact on computed tomography bounding the target lobe (14). In a multicenter study, 172 participants were randomly assigned 2:1 to valve placement or usual care. In terms of technical efficacy, 75% of those treated had at least a 350-ml reduction in target lobe volume, and 40% had complete atelectasis of the target lobe. There was 101 ml between group difference in change in FEV<sub>1</sub> at 6 months, favoring valve placement accompanied by a between group change in residual volume of 361 ml. Health status and breathlessness improved, but there was no effect on walking distance.

Safety outcomes were similar to those seen in previous valve studies: 12.4% of patients treated with valves experienced a serious pneumothorax. Of these, around two thirds required one or more valve to be removed, although in half of these cases it was possible to replace the valves subsequently with good long-term outcomes. Two thirds of pneumothoraces occurred within 3 days of the procedure, underlining the importance of in-patient observation for 3 nights after endobronchial valve placement. By 12 months, 9% of treated and 7% of control patients had died. Only one death occurred within 3 months of the procedure (from sepsis at 26 d), and only one death, from a lung abscess in the target lobe 353 days postprocedure, was judged as likely to be related to the device.

There are some technical issues to the study. The study did not include a sham procedure (5) and so was unblinded. This is less

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**Table 1.** A Stepwise Approach to Assessment for LVR Procedures in COPD

Ensure that the five fundamentals of COPD care are in place

1. Treatment and support to stop smoking
2. Pneumococcal and influenza vaccinations
3. Pulmonary rehabilitation
4. Codeveloped personalized self-management plan
5. Identified and optimized treatment for comorbidities

At the end of pulmonary rehabilitation, the condition of a person with COPD should have been optimized as far as is going to be possible, including exercise training, self-management, psychological support, optimal pharmacotherapy, and smoking cessation

At this point:

1. Consider whether LVR is a plausible intervention, based on the following criteria:
  - FEV<sub>1</sub> < 50%
  - Still limited by breathlessness (typically MRC breathlessness score of 4 or 5)
  - Ex-smoker
  - Able to walk at least 140 m in 6-minute-walk test or incremental shuttle test
2. If yes, offer a respiratory review to further assess whether LVR is possible:
  - Lung function shows hyperinflation (plethysmographic RV > 170%) and T<sub>lCO</sub> above 20%
  - CT thorax shows emphysema
  - Treatment of comorbidities has been optimized
  - Absence of potential contraindications (comorbidities, lung fibrosis, and substantial sputum burden)
3. If yes, refer to a specialist LVR team to consider technical suitability for LVR (surgical or bronchoscopic)

*Definition of abbreviations:* COPD = chronic obstructive pulmonary disease; CT = computed tomography; LVR = lung volume reduction; MRC = Medical Research Council; RV = residual volume; T<sub>lCO</sub> = carbon monoxide transfer factor.

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likely to have affected lung function measures but may have influenced health status and exercise assessments. The effectiveness and adverse effect profile of valve placement depends on patient selection. Substantial improvement is only seen where collateral ventilation is absent, but this also increases the risk for pneumothorax occurring as the ipsilateral lung remodels in response to atelectasis in the target lobe. Visual inspection of interlobar fissures was used. This seems to have been a reasonably effective approach, as the 40% rate of target lobe atelectasis was similar to other trials using collateral flow measurement (15) (e.g., 38% in BeLieVeR-HIFI [5]), as was the proportion of individuals who had target lobe volume reduction of >350 ml: 75% versus 90% in the TRANSFORM trial (7) and 84% in LIBERATE (8).

Taken together, these data suggest that the Spiration valve is an effective means to achieve lung volume reduction with an acceptable risk/benefit ratio. Although direct comparison trials are needed to evaluate its effectiveness compared with the more established device (and of bronchoscopic approaches more generally to lung volume reduction surgery [16]), the presence of a new “predator” should stimulate both interest in LVR and activity, so that more patients can access effective treatments and overall COPD care improves beyond current inadequate levels (17, 18). ■

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Nicholas S. Hopkinson, M.B. B.S., Ph.D.  
National Heart and Lung Institute  
Imperial College  
London, United Kingdom

ORCID ID: 0000-0003-3235-0454 (N.S.H.).

## References

1. Royal College of Physicians. Primary care: Time to take a breath [accessed 2017 Mar 24]. Available from: <https://www.rcplondon.ac.uk/projects/outputs/primary-care-time-take-breath>
2. Elbhairi AF, Quint JK, Rogers J, Laffan M, Polkey MI, Hopkinson NS. Patterns of breathlessness and associated consulting behaviour: results of an online survey. *Thorax* 2019;74:814–817.
3. Ritchie EG, Johnson CN. Predator interactions, mesopredator release and biodiversity conservation. *Ecol Lett* 2009;12:982–998.
4. Criner GJ, Cordova F, Sternberg AL, Martinez FJ. The National Emphysema Treatment Trial (NETT) part II: lessons learned about lung volume reduction surgery. *Am J Respir Crit Care Med* 2011;184:881–893.
5. Davey C, Zoumot Z, Jordan S, McNulty WH, Carr DH, Hind MD, et al. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFI study): a randomised controlled trial. *Lancet* 2015;386:1066–1073.
6. Klooster K, Slebos DJ, Zoumot Z, Davey C, Shah PL, Hopkinson NS. Endobronchial valves for emphysema: an individual patient-level reanalysis of randomised controlled trials. *BMJ Open Respir Res* 2017;4:e000214.
7. Kemp SV, Slebos D-J, Kirk A, Kornaszewska M, Carron K, Ek L, et al.; TRANSFORM Study Team \*. A multicenter randomized controlled trial of Zephyr endobronchial valve treatment in heterogeneous emphysema (TRANSFORM). *Am J Respir Crit Care Med* 2017;196:1535–1543.
8. Criner GJ, Sue R, Wright S, Dransfield M, Rivas-Perez H, Wiese T, et al.; LIBERATE Study Group. A multicenter randomized controlled trial of Zephyr endobronchial valve treatment in heterogeneous emphysema (LIBERATE). *Am J Respir Crit Care Med* 2018;198:1151–1164.
9. Garner J, Kemp SV, Toma TP, Hansell DM, Polkey MI, Shah PL, et al. Survival after endobronchial valve placement for emphysema: a 10-year follow-up study. *Am J Respir Crit Care Med* 2016;194:519–521.
10. Hopkinson NS, Molyneux A, Pink J, Harrisingh MC; Guideline Committee (GC). Chronic obstructive pulmonary disease: diagnosis and management: summary of updated NICE guidance. *BMJ* 2019;366:14486.
11. Scirba FC, Ernst A, Herth FJF, Strange C, Criner GJ, Marquette CH, et al.; VENT Study Research Group. A randomized study of endobronchial valves for advanced emphysema. *N Engl J Med* 2010;363:1233–1244.
12. van Geffen WH, Slebos D-J, Herth FJ, Kemp SV, Weder W, Shah PL. Surgical and endoscopic interventions that reduce lung volume for emphysema: a systemic review and meta-analysis. *Lancet Respir Med* 2019;7:313–324.
13. Ninane V, Geltner C, Bezzi M, Foccoli P, Gottlieb J, Welte T, et al. Multicentre European study for the treatment of advanced emphysema with bronchial valves. *Eur Respir J* 2012;39:1319–1325.
14. Criner GJ, Delage A, Voelker K, Hogarth DK, Majid A, Zgoda M, et al.; IMPROVE Study Group. Improving lung function in severe heterogeneous emphysema with the Spiration valve system (IMPROVE): a multicenter, open-label randomized controlled clinical trial. *Am J Respir Crit Care Med* 2019;200:1354–1362.
15. Koster TD, van Rikxoort EM, Huebner RH, Doellinger F, Klooster K, Charbonnier JP, et al. Predicting lung volume reduction after

endobronchial valve therapy is maximized using a combination of diagnostic tools. *Respiration* 2016;92:150–157.

16. Buttery S, Kemp SV, Shah PL, Waller D, Jordan S, Lee JT, *et al*. CELEB trial: comparative Effectiveness of Lung volume reduction surgery for Emphysema and Bronchoscopic lung volume reduction with valve placement: a protocol for a randomised controlled trial. *BMJ Open* 2018;8:e021368.
17. Whittaker H, Connell O, Campbell J, Elbehairy AF, Hopkinson NS, Quint JK. Eligibility for lung volume reduction surgery in chronic obstructive

pulmonary disease patients identified in a UK primary care setting. *Chest* [online ahead of print] 2 Aug 2019; DOI: 10.1016/j.chest.2019.07.016.

18. Philip K, Gaduzo S, Rogers J, Laffan M, Hopkinson NS. Patient experience of COPD care: outcomes from the British Lung Foundation Patient Passport. *BMJ Open Respir Res* 2019;6:e000478.

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## ⊗ Maximal Lung Recruitment in Acute Respiratory Distress Syndrome: A Nail in the Coffin

The traditional way to reverse hypoxemia in acute respiratory distress syndrome (ARDS) is the use of positive end-expiratory pressure (PEEP). Ideally, PEEP is to be used to maximize alveolar recruitment and to minimize alveolar overdistension during tidal ventilation, more than for improving gas exchange. The notion of recruitment implies aeration of previously nonaerated lung regions. There is no uniform definition of recruitment (1). Recruitment has been estimated from gas entering either nonaerated or nonaerated and poorly aerated regions when using thorax computed tomography (CT) scanning (1, 2) or from gas entering previously nonaerated and poorly inflated regions using lung mechanics or gas dilution (1).

The CT scan imaging shows that ARDS lungs are heterogeneous. This means that nonaerated, poorly aerated, normally aerated, and overdistended regions coexist in ARDS lungs. In addition, the overall effects of PEEP on recruitability are complex. In patients with ARDS, the percentage of potentially recruitable lung when going from 5 to 45 cm H<sub>2</sub>O airway pressure is highly variable, and 24% of the lung could not be recruited at this high pressure (3). Other authors (4), however, have found that the lungs of selected patients with ARDS can be fully recruited with maximal recruitment maneuvers (i.e., PEEP up to 45 cm H<sub>2</sub>O and 60 cm H<sub>2</sub>O end-inspiratory airway pressure).

In the last years, numerous investigators have compared different PEEP setting strategies in patients with ARDS. These studies have essentially compared low/moderate PEEP levels with higher PEEP levels. Different methods have been used: comparison of PEEP levels according to high/low PEEP–F<sub>I</sub>O<sub>2</sub> tables with or without recruitment maneuvers (5, 6), individual PEEP titration to reach a plateau airway pressure of 28–30 cm H<sub>2</sub>O (7), PEEP titration based on respiratory system compliance after performing maximal recruitment maneuvers (8, 9), and PEEP titration based on end-expiratory transpulmonary pressure (10). Very disappointingly, these trials have shown no benefits in terms of relevant patient-centered outcomes. Yet signals of harm have emerged from the maximal recruitment trials.

The PHARLAP (Permissive Hypercapnia, Alveolar Recruitment and Low Airway Pressure) study in this issue of the *Journal* by Hodgson and colleagues (pp. 1363–1372) is a well-conducted randomized clinical trial in patients with moderate to severe ARDS, comparing a maximal recruitment strategy with a control group managed with low V<sub>T</sub> and moderate PEEP (11). The maximal recruitment strategy was a combined open lung procedure that included a staircase recruitment maneuver using 15 cm H<sub>2</sub>O pressure control ventilation and stepwise increases in PEEP up to 40 cm H<sub>2</sub>O, a PEEP titration maneuver in which the PEEP was decreased in steps of 2.5 cm H<sub>2</sub>O until a derecruitment PEEP was reached (defined as a decrease in Sp<sub>O<sub>2</sub></sub> by 2% or more or a PEEP of 15 cm H<sub>2</sub>O was reached), and when derecruitment PEEP was reached, a new brief (2 min) recruitment maneuver was again repeated. These maneuvers were conducted from the day of randomization to day 5. A total of 102 combined open lung procedures were performed in 56 patients in the intervention group, and 12 patients in the control group received nonprotocolized recruitment maneuvers. The enrollment in the study was aborted when the results of the Alveolar Recruitment Trial were published (9) because of safety concerns and perceived loss of equipoise, and after 115 of 340 planned patients had been randomized.

Although the study by Hodgson and colleagues is negative, the authors are to be commended for rigorously conducting and reporting this important trial. No differences were found in ventilator-free days (the primary outcome) or mortality rate, barotrauma, new use of hypoxemia adjuvant therapies, and length of stay (secondary outcomes) between the intervention and the control groups. Importantly, a significantly higher rate of new cardiac arrhythmias, defined as rapid atrial fibrillation, ventricular tachycardia, or ventricular fibrillation, was found in the intervention group (29%) compared with the control group (13%). Performing the combined open lung procedure was not simple, and during the maneuvers, transient episodes of hypotension and desaturation often occurred in spite of patients' optimization in terms of vascular volume before the maneuvers. In 13% of instances, the hypotension during the maneuvers was severe enough to trigger an increase in the vasopressor infusion rate. The whole process was complex and time consuming, and safety issues were relevant. Of note, very few patients (less than 10%), received ventilation in prone position. The PHARLAP trial strongly suggests that the cardiovascular consequences and, quite likely, the overdistension induced by the procedures outweigh the

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