

Review Article **Update on Nonsurgical Lung Volume Reduction Procedures**

J. Alberto Neder and Denis E. O'Donnell

Division of Respiratory and Critical Care Medicine, Department of Medicine, Queen's University and Kingston General Hospital, Kingston, ON, Canada K7L 2V6

Correspondence should be addressed to Denis E. O'Donnell; odonnell@queensu.ca

Received 28 May 2015; Accepted 2 July 2015

Copyright © 2016 J. A. Neder and D. E. O'Donnell. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

There has been a surge of interest in endoscopic lung volume reduction (ELVR) strategies for advanced COPD. Valve implants, coil implants, biological LVR (BioLVR), bronchial thermal vapour ablation, and airway stents are used to induce lung deflation with the ultimate goal of improving respiratory mechanics and chronic dyspnea. Patients presenting with severe air trapping (e.g., inspiratory capacity/total lung capacity (TLC) < 25%, residual volume > 225% predicted) and thoracic hyperinflation (TLC > 150% predicted) have the greatest potential to derive benefit from ELVR procedures. Pre-LVRS or ELVR assessment should ideally include cardiological evaluation, high resolution CT scan, ventilation and perfusion scintigraphy, full pulmonary function tests, and cardiopulmonary exercise testing. ELVR procedures are currently available in selected Canadian research centers as part of ethically approved clinical trials. If a decision is made to offer an ELVR procedure, one-way valves are the first option in the presence of complete lobar exclusion and no significant collateral ventilation. When the fissure is not complete, when collateral ventilation is evident in heterogeneous emphysema or when emphysema is homogeneous, coil implants or BioLVR (in that order) are the next logical alternatives.

1. Clinical Problem

The efficacy of pharmacological approaches in promoting lung deflation in COPD is limited when the main mechanism of lung hyperinflation is no longer bronchial constriction and airway narrowing but the anatomical consequences of extensive alveolar destruction. Ever since the encouraging results of the landmark National Emphysema Treatment Trial (NETT), there has been a surge of interest in novel nonsurgical lung volume reduction (LVR) strategies for advanced COPD. Endoscopic procedures (ELVR) (Table 1) [1-4], in particular, have gained momentum due to the excess morbidity and mortality found in some specific NETT subgroups. By promoting lung deflation, these procedures are aimed at improving respiratory mechanics with the ultimate goal of ameliorating the distressing symptom of chronic dyspnea. Unfortunately, there remains a lack of evidence-based recommendations to assist the selection of patients who are most likely to benefit from various current interventions. In order to help the clinician decide on the best option for individual patients, this focused review will critically appraise the current evidence on the topic. We recovered pertinent publications in English that were retrieved from PubMed[™]

up to May 2015, with particular consideration of randomized controlled trials (RCTs) and meta-analyses.

2. Physiological Rationale for Lung Deflation in COPD

Severe lung hyperinflation places the inspiratory muscles, especially the diaphragm, at a significant mechanical disadvantage by shortening its fibers and compromising its force generating capacity. The increase in dyspnea intensity at any given ventilation during exercise in advanced COPD ultimately reflects the inability of the compromised respiratory system to respond appropriately to increasing respiratory neural drive, that is, neuromechanical dissociation [5]. It follows that reduction in lung hyperinflation following endoscopic LVR should help reduce respiratory discomfort.

While surgical LVR (SLVR) excises lung areas of predominant high ventilation/perfusion ratios, endoscopic LVR (ELVR) may decrease or, ideally, obliterate ventilation to those areas. Thus, physiological dead space is expected to decrease in response to effective LVR and, with it, respiratory neural drive and ventilatory requirements for a given

Technique	Dependence on collateral ventilation	Reversibility	Mechanisms of action	Principal complications
Valve implantation	Yes	Fully reversible	Prevention of inspired air from entering target airways whilst allowing exit of trapped air	Pneumothorax, hemoptysis
Coil implantation	No	Partially reversible (within 4 weeks)	Torquing of the bronchi (intrabronchial) Increased radial tension of adjacent airway network (endobronchial)	Hemoptysis, COPD exacerbations
Bronchoscopic thermal vapour ablation	No	Irreversible	Inflammatory reaction	Local and systemic inflammatory reaction
Airway stent	Yes	Partially reversible	Bypassing airway	Stent loss, stent obliteration

TABLE 1: Overview of the currently available procedures for lung volume reduction (LVR) in advanced emphysema.

external power output. Improvements in cardiopulmonary interactions may also occur due to enhancement of venous return and lower right ventricle afterload with benefits for left ventricular filling, When these mechanical and cardiocirculatory improvements are coupled with reduced respiratory neural drive (due to improved pulmonary gas exchange), the net effect is reduced neuromechanical dissociation of the respiratory system and improved activity-related dyspnea.

2.1. Endoscopic One-Way Valve Implantation. The one-way valves are intended to work by preventing inspired air from entering target airways whilst allowing exit of trapped air from distal airways (Table 1). The umbrella-like "intrabronchial valve" (IBV) is deployed bilaterally to the upper lobes to redistribute ventilation to less emphysematous areas. The mouth-fish appearing "endobronchial valve" (EBV) is deployed unilaterally to induce total lobar atelectasis. There is growing evidence that EBV is more effective than IBV [1]. Regardless of the valve that is used, best results are obtained in heterogeneous emphysema when lobar ventilation can be isolated; that is, there is little collateral ventilation. Heterogeneity can be defined, for instance, as the difference in the quantitative emphysema score between the targeted lobe and the adjacent ipsilateral nontargeted lobe. A key anatomical feature associated with lung deflation, therefore, is a "complete" fissure as suggested by the absence of a parenchymal bridge connecting the lobes for >10% of the fissure [2]. When both complete fissure and lobar occlusion are present, substantial increments in FEV1 (up to 26%, on average) have been reported in 6 months and sustained at 12 months. It should be noted that only ~20% of patients met these strict criteria. Assessment of fissure integrity also requires radiological expertise but specific software packages are available. There is recent evidence, however, that CT scans overestimate completeness of the right minor fissure and underestimate completeness of the right major fissure [25]. Alternatively, or in addition, a dedicated endobronchial balloon and flow-transducer system can be used to assess collateral ventilation.

The most recent meta-analyses showed that one-way valves were associated with minor, but significant, increases in mean FEV₁ (\sim 7%) compared to standard medical care in patients with severe to very severe COPD (Table 2) [3, 4]. Statistically significant changes were also seen in chronic dyspnea; however, improvements were modest and only marginally greater than the minimally important difference (MID). Increases in peak work rate during an incremental cycle test were also significant (~5 W) but also lower than the suggested MID (10 W). Six-minute walking distance failed to significantly increase. The rate of adverse events tended to be greater with EBV but this was mostly related to nonmassive hemoptysis and, less commonly, pneumothorax and pneumonia [3, 4]. Unfortunately, effective postprocedure lobar atelectasis which might be associated with better functional results was also associated with a greater incidence of pneumothorax.

2.2. Coil Implants. With this method, a deployed coil conforms to a predetermined shape ("memory-shape" coil). By bending in the airway and causing compression of adjacent lung tissue, it induces local LVR (intrabronchial coil). Alternatively, multiple endobronchial coils may be implanted throughout a lobe achieving deflation through increased radial tension across the airway network which might also open small airways by increased tethering effects. A potential advantage is that the implants do not depend on (the absence of) collateral ventilation and therefore could be useful for patients with relatively homogeneous emphysema (Table 1). Conversely, patients with large bullae are unlikely to benefit from this technique since the proposed mechanism is shortening of the airways. Effectiveness and a good safety profile have been reported in small cohorts of patients with heterogeneous emphysema. A single, relatively small RCT involving patients with heterogeneous and homogeneous

Prospective multicenter registry $n = 98$ 90 days11 ± 3%1RCTComplete fistor ($n = 68$)6 months16%1Multicenter prospective cohort studyHigh heterogeneity ($n = 90$)12 months16%1Multicenter prospective cohort studyTreatment group ($n = 11$)21 ± 10%11%8CTComplete fistor ($n = 00$)6 months $26 \pm 39\%$ 21 ± 11%0Prospective, randomized, noncontrolledComplete fistor ($n = 10$)3 months21 ± 11%1RCTComplete fistor ($n = 20$)3 months21 ± 11%1Prospective, noncontrolledComplete fistor ($n = 11$)3 months21 ± 11%1Prospective, noncontrolledComplete fistor ($n = 20$)1 month21 ± 11%1Prospective, noncontrolledCV positive ($n = 29$)1 months $1 \pm 15\%$ 1Prospective, noncontrolledTreatment group ($n = 142$)6 months $1 \pm 15\%$ 1Open-label, multicenter, non-RCTTreatment group ($n = 23$)3 months $1 \pm 15\%$ 1Open-label, multicenter, non-RCT $n = 21$ $1 = 23\%$ $1 = 0.000$ 1Open-label, multicenter non-RCT $n = 21$ $1 = 23\%$ $1 = 0.000$ 1Prospective analysis from multicenter non-RCT $n = 21$ $1 = 23\%$ $1 = 0.000$ 1Open-label, multicenter non-RCT $n = 21$ $1 = 22\%$ $0 = 0.000$ 1Multicenter open-label, multicenter non-RCT $n = 21$ $1 = 23\%$ $0 = 0.000$ 2Mult		Auutor, year	Study design	Patient population	TILLE POINT	ΔFEV_1	$\Delta 6-MWD$	DAUKU (units)
Sciurba et al. 2010 [7]RCTTreatment group ($n = 214$) 4% Sciurba et al. 2010 [8]Multicenter prospective cohort studyHigh hereogeneity ($n = 90$) 11% 5% Sterman et al. 2012 [9]RCTComplete fissure ($n = 68$)6 months 11% $2 \pm 12\%$ Sterman et al. 2012 [9]RCTComplete fursiture ($n = 30$)12 months $-2 \pm 12\%$ Shehant et al. 2012 [10]Prospective, randomized, noncontrolledComplete unilateral occlusion ($n = 20$) $2n + 11\%$ $21 \pm 11\%$ Ninane et al. 2012 [11]RCTComplete unilateral occlusion ($n = 11$) $3m onths$ $21 \pm 11\%$ Ninane et al. 2012 [12]Prospective, noncontrolledCV negative ($n = 37$) $3m onths$ $21 \pm 15\%$ Ninane et al. 2013 [12]Prospective, noncontrolledCV negative ($n = 37$) $3m onths$ $-3 \pm 5\%$ Shebos et al. 2013 [13]RCTTreatment group ($n = 11$) $3m onths$ $-21 \pm 5\%$ Shah et al. 2013 [15]RCTTreatment group ($n = 12$) $1m onth$ $16 \pm 22\%$ Shah et al. 2013 [16]RCTTreatment group ($n = 32$) $1m onth$ $16 \pm 22\%$ Shah et al. 2013 [16]RCTTreatment group ($n = 120$) $10 + 122$ 14% Shah et al. 2012 [16]Prospective, non-ontrolled $n = 16$ $n = 16$ 1242 Shah et al. 2012 [16]RCTTreatment group ($n = 22$) 110% 14% Refere et al. 2012 [16]Retra 2009 [17]Open-label, non-RCT $n = 21$ $3m onths$ 13% Refere et al. 2012 [20]R		Wan et al. 2006 [6]	Prospective multicenter registry	n = 98	90 days	$11 \pm 3\%$	$37 \pm 90 \text{ m}$	I
Sciurba et al. 2010 [7]RCTComplete fissure ($n = 68$)6 months16%Herth et al. 2010 [8]Multicenter prospective cohort studyHigh heterogenetry ($n = 90$)12 months $-2 \pm 12\%$ Sterman et al. 2010 [8]Multicenter prospective cohort studyTreatment group ($n = 111$)2 months $-2 \pm 12\%$ Bebehaardt et al. 2012 [10]Prospective, randomized, noncontrolledComplete fissure, lobar occlusion ($n = 20$)6 months $7 \pm 20\%$ Bebehaardt et al. 2012 [11]RCTComplete insure, lobar occlusion ($n = 11$)3 months $21 \pm 11\%$ Ninane et al. 2012 [12]Prospective, noncontrolledCV negative ($n = 37$)3 months $-2 \pm 5\%$ predWood et al. 2014 [13]RCTPartial bilateral occlusion ($n = 11$)3 months $-2 \pm 5\%$ predStebos et al. 2013 [12]Prospective, noncontrolledTreatment group ($n = 142$)3 months $-2 \pm 5\%$ predStebos et al. 2013 [13]RCTTreatment group ($n = 142$)5 months $-2 \pm 5\%$ predStah et al. 2013 [14]Prospective, noncontrolledTreatment group ($n = 32$)1 month $1 \pm 15\%$ Stah et al. 2012 [16]RCTTreatment group ($n = 32$)5 months $-2 \pm 5\%$ predStah et al. 2012 [16]RCTTreatment group ($n = 32$)5 months $-2 \pm 5\%$ Stah et al. 2012 [16]RCTTreatment group ($n = 32$)5 months $-2 \pm 5\%$ Submot et al. 2012 [16]RCTTreatment group ($n = 32$)2 months $-2 \pm 5\%$ Submot et al. 2012 [16]Open-label, multicenter, non-RCT			- 8	Treatment group ($n = 214$)		4%	9 m	-3
Retman et al. 2010 [8]Multicenter prospective cohort studyHigh heterogeneity ($n = 90$)11%sHerth et al. 2012 [9]RCTComplete fisure, lobar occlusion ($n = 11$)2 months $-2 \pm 12\%$ berhardt et al. 2012 [10]Prospective, randomized, noncontrolledTreatment group ($n = 11$)3 months $2.6 \pm 24\%$ berhardt et al. 2012 [10]Prospective, randomized, noncontrolledComplete tuilateral occlusion ($n = 11$)3 months $2.6 \pm 24\%$ Niname et al. 2012 [11]RCTComplete tuilateral occlusion ($n = 11$)3 months $2.1 \pm 11\%$ Niname et al. 2013 [12]Prospective, noncontrolledCV negative ($n = 51$)1 month $1.6 \pm 22\%$ Wood et al. 2014 [13]RCTTreatment group ($n = 142$)6 months $-2 \pm 5\%$ predSlebos et al. 2013 [15]Prospective, noncontrolledTreatment group ($n = 23$)3 months $1.6 \pm 22\%$ Slebos et al. 2013 [15]RCTTreatment group ($n = 23$)3 months $1.2 \pm 5\%$ Slah et al. 2013 [15]RCTTreatment group ($n = 23$)3 months $1.2 \pm 5\%$ Slah et al. 2015 [16]Open-label, multicenter, non-RCT $n = 16$ $n = 20$ $3 = 0.01$ RHerth et al. 2012 [19]Rtern et al. 2012 [10]Rtern et al. 2012 [20] $3 = 0.05\%$ RHerth et al. 2012 [20]Open-label, multicenter, non-RCT $n = 21$ $3 = 0.01$ Suble et al. 2012 [20]Multicenter open-label non-RCT $n = 23$ $3 = 0.01$ RHerth et al. 2012 [20]Multicenter open-label non-RCT $n = 28$		Sciurba et al. 2010 [7]	RCT	Complete fissure $(n = 68)$	6 months	16%	8 m	I
Sterman et al. 2010 [8]Multicenter prospective cohort study $n = 91$ 12 months $-2\pm 12\%$ $Berhardt et al. 2012 [9]RCTComplete instanct group (n = 11)7\pm 20\%7\pm 20\%Berhardt et al. 2012 [10]Prospective, randomized, noncontrolledComplete unilateral occlusion (n = 11)3 \mod hs21\pm 11\%Ninane et al. 2012 [10]Prospective, noncontrolledComplete unilateral occlusion (n = 11)3 \mod hs21\pm 10\%Ninane et al. 2012 [11]Prospective, noncontrolledCynegitive (n = 2)3 \mod hs-3\pm 15\%Nood et al. 2013 [12]Prospective, noncontrolledCynegitive (n = 2)1 \mod h1\pm 15\%Nood et al. 2013 [13]RCTTreatment group (n = 12)3 \mod hs-2\pm 5\% predShelo at al. 2013 [14]Prospective, noncontrolledTreatment group (n = 2)1 \mod h1\pm 15\%Shelo at al. 2013 [16]RCTTreatment group (n = 2)1 \mod h1\pm 25\%Shelo at al. 2013 [16]RCTTreatment group (n = 2)1 \mod h1\pm 25\%Shelo at al. 2013 [16]RCTTreatment group (n = 2)1 \mod h1\pm 25\%Shelo at al. 2012 [10]Ropen-label, multicenter, non-RCTn = 166 \mod h9 \pm 22\%Shelo at al. 2012 [10]Multicenter non-RCTn = 211 \mod h9 \pm 22\%Shelo at al. 2012 [20]Multicenter non-RCTn = 211 \mod h9 \pm 22\%Shelo at al. 2012 [20]Multicenter non-RCTn = 211 \mod h1 \mod hShel at al. 2012 [20]<$				High heterogeneity ($n = 90$)		11%	12 m	I
Herth et al. 2012 [9]RCTTreatment group ($n = 111$) $7 \pm 20\%$ Se herth et al. 2012 [10]Prospective, randomized, noncontrolledComplete unliateral occlusion ($n = 20$) $5 \mod 13$ $26 \pm 24\%$ Eberhardt et al. 2012 [10]Prospective, randomized, noncontrolledComplete unliateral occlusion ($n = 11$) $3 \mod 18$ $25 \pm 25\%$ Niname et al. 2012 [11]RCTComplete unliateral occlusion ($n = 11$) $3 \mod 18$ $-9 \mod 1$ Niname et al. 2013 [12]Prospective, noncontrolledCV negative ($n = 50$) $1 \mod 11$ $-1 \pm 15\%$ Wood et al. 2014 [13]RCTCV negative ($n = 50$) $1 \mod 1$ $1 \pm 15\%$ Wood et al. 2015 [16]RCTTreatment group ($n = 142$) $6 \mod 18$ $26 \pm 125\%$ Shah et al. 2015 [16]RCTTreatment group ($n = 23$) $3 \mod 18$ $9 \pm 22\%$ Shah et al. 2016 [16]Nonc et al. 2012 [19]Retrospective, non-RCT $n = 16$ $6 \mod 18$ $9 \pm 22\%$ Shah et al. 2010 [18]Open-label, multicenter, non-RCTIneutent group ($n = 23$) $3 \mod 18$ $9 \pm 22\%$ Magnussen et al. 2012 [19]Retrospective, analysis from multicenter, non-RCT $n = 21$ $3 \mod 18$ $9 \pm 22\%$ Magnussen et al. 2012 [19]Retrospective, analysis from multicenter, non-RCT $n = 21$ $3 \mod 18$ $9 \pm 22\%$ Shah et al. 2012 [20]Multicenter sigle-arm prospective studies $n = 21$ $3 \mod 18$ $9 \pm 22\%$ Shah et al. 2017 [23]Multicenter open-label non-RCT $n = 21$ $3 \mod 18$ $12 \times 6\%$ Shah et al. 2017 [23]Multicenter open-label		Sterman et al. 2010 [8]	Multicenter prospective cohort study	n = 91	12 months	$-2 \pm 12\%$	$14 \pm 104 \mathrm{m}$	-8.2 ± 16
sThe complete fissure, lobar occlusion ($n = 20$)Of the cubic of $n = 11$)26 ± 24%Eberhardt et al. 2012 [10]Prospective, randomized, noncontrolledComplete fissure, lobar occlusion ($n = 11$)3 months26 ± 24%Niname et al. 2012 [11]RCTComplete milateral occlusion ($n = 11$)3 months-9 mLHerth et al. 2013 [12]Prospective, noncontrolledCV negative ($n = 51$)1 month-9 mLWood et al. 2014 [13]RCTCV negative ($n = 20$)1 month16 ± 22%Wood et al. 2013 [15]RCTTreatment group ($n = 20$)1 month16 ± 22%Shah et al. 2013 [15]RCTTreatment group ($n = 23$)3 months9 ± 22%Shah et al. 2015 [16]Open-label, multicenter, non-RCTHigh-dose hydrogel ($n = 23$)3 months9 ± 22%RHerth et al. 2012 [19]Open-label, multicenter, non-RCTN = 280 months9 ± 22%RHerth et al. 2012 [10]Open-label, multicenter, non-RCTN = 2812 months9 ± 22%RHerth et al. 2012 [20]Multicenter, non-RCTN = 2812 months9 ± 22%RMagnussen et al. 2012 [20]Multicenter, non-RCTN = 2812 months9 ± 22%RMagnussen et al. 2012 [20]Multicenter, non-RCTN = 2812 months9 ± 22%RMagnussen et al. 2012 [20]Multicenter, non-RCTN = 2812 months14%RHerth et al. 2012 [20]Multicenter, non-RCTN = 2812 months25%RMagnussen et al. 20		Herth et al 2012 [9]		Treatment group ($n = 111$)	6 months	$7 \pm 20\%$	$15 \pm 91 \mathrm{m}$	-5 ± 14
Eberhardt et al. 2012 [10]Prospective, randomized, noncontrolledComplete unilateral occlusion $(n = 11)$ 3 months $21 \pm 11\%$ Niname et al. 2012 [11]RCTPartial bilateral occlusion $(n = 11)$ 3 months $-3 \pm 15\%$ Herth et al. 2013 [12]Prospective, noncontrolledCV negative $(n = 37)$ 3 months $-2 \pm 5\%$ Wood et al. 2014 [13]Prospective, noncontrolledCV negative $(n = 29)$ 1 month $1 \pm 15\%$ Wood et al. 2012 [14]Prospective, noncontrolledCV negative $(n = 29)$ 1 month $-2 \pm 5\%$ predSubb et al. 2013 [15]RCTTreatment group $(n = 142)$ 6 months $-2 \pm 5\%$ predSubb et al. 2013 [15]Prospective, noncontrolledTreatment group $(n = 23)$ 3 months 14% Subb et al. 2012 [16]Open-label, multicenter, non-RCTInvestment group $(n = 23)$ 3 months $9 \pm 22\%$ RHerth et al. 2010 [18]Open-label, multicenter, non-RCTInvestment group $(n = 22)$ $3 months3.3 \pm 3.2\%RHerth et al. 2012 [19]Retrospective analysis from multicenter non-RCTn = 213.3 months3.3 \pm 3.2\%RMagnussen et al. 2012 [20]Multicenter, non-RCTn = 213.0 \pm 1243.3 \pm 3.2\%RRHerth et al. 2012 [21]Nuntlicenter, non-RCTn = 213.3 \pm 3.2\%RRHerth et al. 2012 [22]Multicenter, non-RCTn = 213.3 \pm 0.221RSell et al. 2012 [22]Multicenter, non-RCTn = 213.3 \pm 0.234RSell et al. 2012 [22]$	Valves		VC1	Complete fissure, lobar occlusion ($n = 20$)		$26 \pm 24\%$	$22 \pm 38\%$	-10 ± 15
Minane et al. 2012 [11] Troppetitye, nationated, interval occlusion $(n = 37)$ 3 months $-3 \pm 15\%$ Ninane et al. 2012 [11] Prospective, noncontrolled CV negative $(n = 51)$ 1 month $1 \pm 15\%$ Herth et al. 2013 [12] Prospective, noncontrolled CV negative $(n = 29)$ 3 months $-2 \pm 5\%$ pred Wood et al. 2014 [13] RCT Treatment group $(n = 129)$ 6 months $-2 \pm 5\%$ pred Shah et al. 2015 [14] Prospective, noncontrolled Treatment group $(n = 142)$ 6 months $-2 \pm 5\%$ pred Shah et al. 2015 [16] RCT Treatment group $(n = 123)$ 3 months $9 \pm 22\%$ Zoumot et al. 2015 [16] Open-label, multicenter, non-RCT Invedose hydrogel $(n = 28)$ 6 months $9 \pm 22\%$ R Herth et al. 2010 [18] Open-label, multicenter, non-RCT Invedose hydrogel $(n = 28)$ 6 months $33 \pm 3.2\%$ R Herth et al. 2012 [20] Multicenter open-label, multicenter non-RCT $n = 21$ $n = 21$ $3 \pm 25\%$ R Herth et al. 2012 [20] Multicenter open-label non-RCT $n = 28$ $12 \pm 215\%$ $9 \pm 25\%$ Nagnussen et al. 2012 [20] Multicenter non-RCT $n = 28$ $12 \pm $	E	herhardt et al. 2012 [10]	Duranting undernized noncontrolled	Complete unilateral occlusion ($n = 11$)	3 monthe	$21 \pm 11\%$	$49 \pm 53 \mathrm{m}$	-12 ± 11
Ninane et al. 2012 [11] RCT Partial occlusion ($n = 37$) 3 months -90 mL Herth et al. 2013 [12] Prospective, noncontrolled CV positive ($n = 51$) 1 month $16 \pm 22\%$ Wood et al. 2014 [13] Prospective, noncontrolled CV positive ($n = 29$) 1 month $16 \pm 12\%$ Wood et al. 2013 [13] Prospective, noncontrolled Treatment group ($n = 142$) 6 months $-2 \pm 5\%$ pred Slab et al. 2015 [14] Prospective, noncontrolled Treatment group ($n = 142$) 6 months 14% Slab et al. 2015 [16] RCT Treatment group ($n = 23$) 3 months $9 \pm 22\%$ Counce tet al. 2016 [16] Open-label, multicenter, non-RCT Ineaton ($n = 23$) 100 mths $9 \pm 22\%$ R Herth et al. 2010 [18] Open-label, multicenter, non-RCT 10% dose hydrogel ($n = 22$) 6 months $33 \pm 3.2\%$ R Magnussen et al. 2012 [19] Renomental coup ($n = 21$) 3 months $3.3 \pm 3.2\%$ R Matter et al. 2012 [20] Multicenter on n-RCT $n = 28$ 12 months $3.3 \pm 3.2\%$ R Herth et al. 2012 [21]	1		г юзреснуе, тапионныен, понсоннонен	Partial bilateral occlusion $(n = 11)$		$-3 \pm 15\%$	$-52 \pm 81 \mathrm{m}$	2 ± 9
Herth et al. 2013 [12] Prospective, noncontrolled CV negative $(n = 51)$ I month $16 \pm 22\%$ Wood et al. 2014 [13] RCT Treatment group $(n = 142)$ 6 months $12 \pm 5\%$ pred Slebos et al. 2012 [14] Prospective, noncontrolled CV positive $(n = 29)$ 6 months $15 \pm 17\%$ Slebos et al. 2013 [15] RCT Treatment group $(n = 142)$ 6 months $15 \pm 17\%$ Slebos et al. 2013 [16] RCT Treatment group $(n = 23)$ 3 months $15 \pm 17\%$ Slebos et al. 2015 [16] RCT Treatment group $(n = 23)$ 3 months $15 \pm 17\%$ Criner et al. 2015 [16] RCT Treatment group $(n = 23)$ 3 months $9 \pm 22\%$ Criner et al. 2016 [18] Open-label, multicenter, non-RCT Low-dose hydrogel $(n = 22)$ $9 \pm 22\%$ $9 \pm 22\%$ R Herth et al. 2012 [19] Retrosective non-RCT Low-dose hydrogel $(n = 22)$ $9 \pm 12.9\%$ $6 \times 112.9\%$ R Magnussen et al. 2012 [19] Retrosective non-RCT $n = 21$ $12 \times 12.9\%$ $6 \times 12.9\%$ R Magnussen et al. 2012 [19] Retrosective, non-RCT		Ninane et al. 2012 [11]	RCT	Partial occlusion $(n = 37)$	3 months	-90 mL	7 m	-4
Interferent et al. 2015 [L2] Trospective, noncontrolled CV positive $(n = 29)$ I month 1 ± 15% Wood et al. 2012 [14] Prospective, noncontrolled Treatment group $(n = 142)$ 6 months $15 \pm 17\%$ Slebos et al. 2012 [14] Prospective, noncontrolled Treatment group $(n = 23)$ 3 months 14% Slebos et al. 2015 [16] RCT Treatment group $(n = 23)$ 3 months 14% Shah et al. 2015 [16] RCT Treatment group $(n = 23)$ 3 months $9 \pm 22\%$ Criner et al. 2016 [17] Open-label, multicenter, non-RCT Herth et al. 2010 [18] $9 \pm 22\%$ $6 \pm 12.9\%$ R Herth et al. 2010 [18] Open-label, multicenter, non-RCT $n = 21$ 13% $6 \pm 12.9\%$ R Herth et al. 2012 [20] Multicenter, non-RCT $n = 21$ $3 \mod nths$ $3.3 \pm 3.2\%$ R Herth et al. 2012 [20] Multicenter open-label non-RCT $n = 21$ $12 \mod nths$ $25.0 \pm 33.4\%$ Kramer et al. 2012 [20] Multicenter open-label non-RCT $n = 21$ $12 \mod nths$ $25.0 \pm 33.4\%$ Kramer et al. 2012 [21] Prospective st			Durantizza and controlled	CV negative $(n = 51)$	1 month	$16 \pm 22\%$	$24 \pm 57 \mathrm{m}$	-10 ± 13
Wood et al. 2014 [13] RCT Treatment group (n = 142) 6 months $-2\pm 5\%$ pred Slebos et al. 2012 [14] Prospective, noncontrolled n = 16 6 months 15 \pm 17\% Shah et al. 2013 [15] RCT Treatment group (n = 23) 3 months 14% Shah et al. 2013 [15] RCT Treatment group (n = 23) 3 months 9 \pm 22% Zoumot et al. 2016 [16] Open-label, multicenter, non-RCT Inworks by drogel (n = 23) 12 months 9 ± 22% TR Herth et al. 2010 [18] Open-label, multicenter, non-RCT High-dose hydrogel (n = 22) 6 months 15.6 ± 16.8% TR Herth et al. 2012 [29] Romuths 120 months 3.3 ± 3.2% 0.201.1 Magnussen et al. 2012 [20] Multicenter open-label non-RCT $n = 28$ 12 months 25.0 ± 33.4% Kramer et al. 2012 [20] Multicenter open-label non-RCT $n = 44$ 6 months 17% Herth et al. 2012 [20] Multicenter single-arm prospective studies $n = 37$ 12 months 86 ± 174 mL Kramer et al. 2012 [22] Two multicenter non-RCT $n = 37$ 12 months		Herth et al. 2015 [12]	r 10spectave, moncomu oned	CV positive $(n = 29)$	11110111 1	$1 \pm 15\%$	$10 \pm 57 \text{ m}$	-5 ± 15
Slebos et al. 2012 [14] Prospective, noncontrolled $n = 16$ 6 months $15 \pm 17\%$ Shah et al. 2013 [15] RCT Treatment group ($n = 23$) 3 months 14% Shah et al. 2013 [15] RCT Treatment group ($n = 35$) 12 months $9 \pm 22\%$ Zoumot et al. 2016 [16] RCT Dow-dose hydrogel ($n = 35$) 12 months $9 \pm 22\%$ Teatment group ($n = 35$) 12 months $9 \pm 22\%$ $1.56 \pm 16.8\%$ $6 = 7 \pm 12.9\%$ TR Herth et al. 2010 [18] Open-label, multicenter, non-RCT High-dose hydrogel ($n = 22$) $3 \mod hs$ $3.3 \pm 3.2\%$ TR Magnussen et al. 2012 [19] Retrospective analysis from multicenter non-RCT $n = 21$ $3 \mod hs$ $3.3.4\%$ Magnussen et al. 2012 [20] Multicenter open-label non-RCT $n = 28$ $12 \mod hs$ $25.0 \pm 33.4\%$ Kramer et al. 2012 [20] Prospective, noncontrolled $n = 44$ $6 \mod hs$ 17% Herth et al. 2012 [22] Two multicenter non-RCT $n = 37$ $12 \mod hs$ $25.0 \pm 33.4\%$ Kramer et al. 2017 [22] Two multicenter non-RCT $n = 44$ $6 \mod hs$ 1.7% Kall et al. 2017 [22] M		Wood et al. 2014 [13]	RCT	Treatment group $(n = 142)$	6 months	$-2 \pm 5\%$ pred	$-24 \pm 69 \text{ m}$	2 ± 16
Shah et al. 2013 [15] RCT Treatment group ($n = 23$) 3 months 14% Zoumot et al. 2015 [16] RCT Treatment group ($n = 35$) 12 months 9 ± 22% Zoumot et al. 2016 [16] RCT Low-dose hydrogel ($n = 28$) 6 months 9 ± 22% R Herth et al. 2010 [18] Open-label, multicenter, non-RCT Low-dose hydrogel ($n = 22$) 6 months 15.6 ± 16.8% R Herth et al. 2010 [18] Open-label, multicenter, non-RCT High-dose hydrogel ($n = 22$) 3 months 3.3 ± 3.2% R Magnusser et al. 2012 [19] Retrospective analysis from multicenter non-RCT $n = 21$ 3 months 3.3 ± 3.2% R Magnusser et al. 2012 [20] Multicenter open-label non-RCT $n = 28$ 12 months 25.0 ± 33.4% R Herth et al. 2012 [20] Multicenter open-label non-RCT $n = 44$ 6 months 17% R Herth et al. 2012 [22] Two multicenter non-RCT $n = 37$ 12 months 86 ± 174 mL R Shah et al. 2011 [24] Multicenter NCT $n = 36$ 6 months 0.6%		Slebos et al. 2012 [14]	Prospective, noncontrolled	n = 16	6 months	$15 \pm 17\%$	$84 \pm 73 \text{ m}$	-15 ± 12
Zoumot et al. 2015 [16]RCTTreatment group $(n = 35)$ 12 months $9 \pm 22\%$ Criner et al. 2009 [17]Open-label, multicenter, non-RCTLow-dose hydrogel $(n = 28)$ 6 months $6.7 \pm 12.9\%$ Herth et al. 2010 [18]Open-label, multicenter, non-RCTHigh-dose hydrogel $(n = 22)$ 6 months $15.6 \pm 16.8\%$ Magnussen et al. 2010 [19]Retrospective multicenter, non-RCT $n = 21$ 3 months $3.3 \pm 3.2\%$ Magnussen et al. 2012 [19]Retrospective multicenter non-RCT $n = 28$ 12 weeks $19.1 \pm 21.5\%$ ($0.18 \pm 0.22 \text{ L}$)Knamer et al. 2012 [20]Multicenter poen-label non-RCT $n = 18$ 12 months 2.7% Snell et al. 2012 [21]Prospective, noncontrolled $n = 44$ 6 months 17% Herth et al. 2012 [22]Two multicenter non-RCT $n = 37$ 12 months 2.06% Shah et al. 2017 [23]Multicenter non-RCT $n = 36$ 6 months 0.6% Shah et al. 2017 [24]Multicenter non-RCT $n = 208$ 12 months 0.6%	Coils	Shah et al. 2013 [15]	RCT	Treatment group $(n = 23)$	3 months	14%	52 m	-8
Criner et al. 2009 [17]Open-label, multicenter, non-RCTLow-dose hydrogel ($n = 28$)6 months $6.7 \pm 12.9\%$ Herth et al. 2010 [18]Open-label, multicenter, non-RCTHigh-dose hydrogel ($n = 22$)5 months $5.6 \pm 16.8\%$ Magnussen et al. 2012 [19]Retrospective analysis from multicenter non-RCT $n = 21$ 3 months $3.3 \pm 3.2\%$ Kramer et al. 2012 [20]Multicenter open-label non-RCT $n = 28$ 12 weeks $191 \pm 21.5\%$ (0.18 ± 0.221)Kramer et al. 2012 [21]Prospective, non-RCT $n = 18$ 12 weeks $191 \pm 21.5\%$ (0.18 ± 0.221)Herth et al. 2012 [22]Two multicenter open-label non-RCT $n = 44$ 6 months 17% Cardoso et al. 2017 [22]Two multicenter single-arm prospective studies $n = 37$ 12 months 86 ± 174 mLShah et al. 2012 [22]Multicenter non-RCT $n = 37$ 12 months 6.6 months 1.7% Shah et al. 2017 [23]Multicenter non-RCT $n = 37$ 12 months 0.6% Shah et al. 2011 [24] $m = 208$ 12 months -20 ± 300 mL	- 4	Zoumot et al. 2015 [16]	RCT	Treatment group $(n = 35)$	12 months	$9 \pm 22\%$	$34 \pm 52 \mathrm{m}$	-6 ± 14
Criter et al. 2019[17]Open-tades, numericates, non-NC1High-dose hydrogel $(n = 22)$ 0 months15, 6 \pm 16, 8%Herth et al. 2010[18]Open-tabel, multicenter, non-RCT $n = 21$ 3 months3.3 \pm 3.2%Magnussen et al. 2012[19]Retrospective analysis from multicenter non-RCT $n = 28$ 12 weeks $191 \pm 21.5\%$ (0.18 ± 0.221)Kramer et al. 2012[20]Multicenter open-tabel non-RCT $n = 28$ 12 weeks $191 \pm 21.5\%$ (0.18 ± 0.221)Kramer et al. 2012[21]Prospective, noncontrolled $n = 44$ 6 months 17% Herth et al. 2012[22]Two multicenter single-arm prospective studies $n = 37$ 12 months 86 ± 174 mLCardoso et al. 2007[23]Multicenter non-RCT $n = 36$ 6 months 0.6% Shah et al. 2011[24]Multicenter non-RCT $n = 208$ 12 months 0.6%			Onon label multiconton non DCT	Low-dose hydrogel ($n = 28$)	6 monthe	$6.7 \pm 12.9\%$	$25.5 \pm 53.2 \mathrm{m}$	-6.9 ± 8.8
Herth et al. 2010 [18]Open-label, multicenter, non-RCT $n = 21$ 3 months $3.3 \pm 3.2\%$ Magnussen et al. 2012 [19]Retrospective analysis from multicenter non-RCTs $n = 28$ 12 weeks $191 \pm 21.5\%$ (0.18 ± 0.22 L)Kramer et al. 2012 [20]Multicenter open-label non-RCT $n = 18$ 12 months $25.0 \pm 33.4\%$ Snell et al. 2012 [21]Prospective, noncontrolled $n = 44$ 6 months 17% Herth et al. 2012 [22]Two multicenter single-arm prospective studies $n = 37$ 12 months 86 ± 174 mLCardoso et al. 2007 [23]Multicenter non-RCT $n = 36$ 6 months 0.6% Shah et al. 2011 [24]Multicenter RCT $n = 208$ 12 months 0.6%		Criner et al. 2009 [17]		High-dose hydrogel ($n = 22$)		$15.6 \pm 16.8\%$	$9.9 \pm 51.2 \mathrm{m}$	-9.7 ± 18.8
Magnussen et al. 2012 [19]Retrospective analysis from multicenter non-RCTs $n = 28$ 12 weeks19.1 ± 21.5% (0.18 ± 0.22.1.)Kramer et al. 2012 [20]Multicenter open-label non-RCT $n = 18$ 12 months25.0 ± 33.4%Snell et al. 2012 [21]Prospective, noncontrolled $n = 44$ 6 months25.0 ± 33.4%Herth et al. 2012 [22]Two multicenter single-arm prospective studies $n = 37$ 12 months86 ± 174 mLCardoso et al. 2007 [23]Multicenter non-RCT $n = 36$ 6 months0.6%Shah et al. 2011 [24]Multicenter RCT $n = 208$ 12 months 0.6%		Herth et al. 2010 [18]	Open-label, multicenter, non-RCT	n = 21	3 months	$3.3 \pm 3.2\%$	$10.8\pm8.8\%$	-7.8 ± 3.7
Kramer et al. 2012 [20]Multicenter open-label non-RCT $n = 18$ 12 months25.0 ± 33.4%Snell et al. 2012 [21]Prospective, noncontrolled $n = 44$ 6 months 17% Herth et al. 2012 [22]Two multicenter single-arm prospective studies $n = 37$ 12 months 86 ± 174 mLCardoso et al. 2007 [23]Multicenter non-RCT $n = 36$ 6 months -20 ± 200 mLShah et al. 2011 [24]Multicenter RCT $n = 208$ 12 months -20 ± 200 mL	Μ	[agnussen et al. 2012 [19]	Retrospective analysis from multicenter non-RCTs	n = 28	12 weeks	$19.1 \pm 21.5\% (0.18 \pm 0.22 \text{ L})$	$30.9 \pm 50.2 \text{ m}$	-11.6 ± 12.4
Snell et al. 2012 [21]Prospective, noncontrolled $n = 44$ 6 months17%Herth et al. 2012 [22]Two multicenter single-arm prospective studies $n = 37$ 12 months $86 \pm 174 \text{ mL}$ Cardoso et al. 2007 [23]Multicenter non-RCT $n = 36$ 6 months 0.6% Shah et al. 2011 [24]Multicenter RCT $n = 208$ 12 months $-20 \pm 200 \text{ mL}$	ľ	Kramer et al. 2012 [20]	Multicenter open-label non-RCT	n = 18	12 months	$25.0 \pm 33.4\%$	$8.6\pm65.2\mathrm{m}$	-7.0 ± 15.8
Herth et al. 2012 [22]Two multicenter single-arm prospective studies $n = 37$ 12 months $86 \pm 174 \text{ mL}$ Cardoso et al. 2007 [23]Multicenter non-RCT $n = 36$ $6 \mod hs = 0.6\%$ Shah et al. 2011 [24]Multicenter RCT $n = 208$ $12 \mod hs = -20 \pm 200 \text{ mL}$	DTVA	Snell et al. 2012 [21]	Prospective, noncontrolled	n = 44	6 months	17%	47 m	-14
Cardoso et al. 2007 [23]Multicenter non-RCT $n = 36$ 6 months 0.6% Shah et al. 2011 [2.4]Multicenter RCT $n = 208$ $12 months$ $-20 \pm 200 \text{ mL}$	WA TO	Herth et al. 2012 [22]	Two multicenter single-arm prospective studies	n = 37	12 months	$86 \pm 174 \text{ mL}$	$18.5 \pm 63.7 \mathrm{m}$	-11 ± 14
Shah et al. 2011 [24] $n = 208$ $n = 208$ $12 months$ $-20 \pm 200 mL$		Cardoso et al. 2007 [23]	Multicenter non-RCT	n = 36	6 months	0.6%	-12 m	-1.8
	Stents	Shah et al. 2011 [24]	Multicenter RCT	n = 208	12 months	$-20 \pm 200 \text{ mL}$ $-0.15 \pm 7\%$	-21 m	-1

1	
4	
6	
SS	
ğ	
rei	
efe	
Ĵ	,
na	
ser	
N	
ac	
en	
ed	
ŭ	
vaj	
ad	
0L	
fc	
LVR	
5	
ic	
ŏ	
SC	
p	
en	
g	
s	
lie	
Ĕ	
l s₁	
je	
isł	
ldi	
b	
er	
arg	0
, la	
he	
Jf 1	
s	
- me	
ō	
nt	
ō	
pu	
sa	
Li.	
rist	
tei	
Je.	
lar	
J D	
ä	
LE	
LABLI	
L	

Severe symptomatic COPD, dyspnea and exercise limitation optimal medical management including pulmonary rehabilitation RV > 225% pred and/or TLC > 150% pred and/or IC/TLC \leq 25% 20% pred < FEV₁ < 50% pred and 20% pred < DL_{CO} < 70% pred

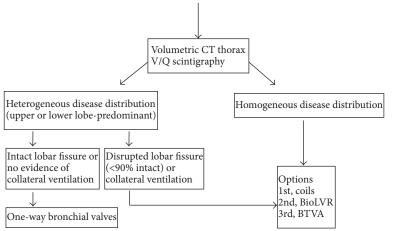


FIGURE 1: Algorithm for endoscopic LVR evaluation and selection of procedure. BioLVR: biological lung volume reduction; BTVA: bronchial thermal vapour ablation; CT: computed tomography; IC: inspiratory capacity; pred: predicted; RV: residual volume; TLC: total lung capacity; V/Q: ventilation/perfusion.

disease found a significant improvement in quality of life which was maintained up to one year following procedure. This was accompanied by improvements in FEV_1 and decrements in pulmonary gas trapping (but not total lung capacity (TLC)) [16]. The most frequently reported adverse events were pneumonia and COPD exacerbation, both <10% (Table 2).

2.3. Biological LVR (BioLVR). BioLVR aims to promote LVR through intra-airway polymerization of fibrinogen suspension and thrombin solution with the purpose of inducing a localized inflammatory reaction (Table 1) [1]. The ensuing irreversible atelectasis and tissue remodeling are expected to induce lung contraction and volume reduction in 1-2 months. An alternative Japanese approach using autologous blood and thrombin has been used in a small number of selected patients with very severe COPD [26]. The biological sealants can also work regardless of the integrity of the interlobar fissure [1]. Several observational or pilot studies found positive effects on lung hyperinflation, exercise tolerance, and quality of life with an acceptable safety profile (Table 2). The first RCT with BioLVR confirmed these preliminary findings regarding efficacy [27]. Unfortunately, the study was prematurely terminated for business-related reasons after only 95 of the planned 300 were randomized. Of note, despite only 2 deaths, the number of serious adverse events was markedly greater in the treatment versus control groups.

2.4. Bronchial Thermal Vapour Ablation (BTVA) Therapy. BTVA uses heated water (steam) to produce thermal injury of the target tissue, usually a segmental airway. Similar to BioLVR, the treatment aims to induce lung volume reduction regardless of the presence of collateral ventilation (Table 1). As expected, patients with higher inflammatory responses can achieve better clinical outcomes. More experience has been gained with patients showing heterogeneous upper lobepredominant emphysema who do not present with a bulla of more than a third of the lobar volume. The largest multicenter trial to date reported improved lung function, exercise tolerance, and quality of life (Table 2) [21]. The magnitude of these benefits, however, lessened at 6 months, suggesting progression of COPD or compensatory hyperinflation. Serious adverse events were observed: COPD exacerbation, pneumonia, and respiratory tract infection were the most common complications. A multicenter, randomized trial evaluating safety and efficacy following segmental, bilateral BTVA in patients with severe emphysema is underway in Europe and Australia and results are expected in 2015/2016.

2.5. Airway Bypass Stents. Airway bypass stents have been used to create and maintain passages between the bronchi and emphysematous lobes. Efficacy of the technique, therefore, depends strongly on the lack of collateral ventilation (Table 1). Despite promising initial results, the largest trial to date (n = 208) failed to show significant improvement in the main functional outcomes at 1, 3, 6, and 12 months (Table 2) [23, 24]. Moreover, the stents were lost in most cases possibly due to chronic cough and expectoration. There was also significant granulation and occlusion in remaining stents. A recent meta-analysis confirmed that, among the available endoscopic approaches, the stents had the least impressive performance to date [3].

3. Recommendations

(i) Patients presenting with severe air trapping (e.g., inspiratory capacity (IC)/TLC < 25%, residual volume > 225% predicted) and thoracic hyperinflation (TLC > 150% predicted) have the greatest potential to derive benefit from ELVR procedures (Figure 1). Very severe functional impairment (FEV1 and/or DL_{CO} ≤

20% predicted) is an established contraindication for ELVR.

- (ii) Pre-LVRS or ELVR assessment should ideally include cardiological evaluation, high resolution CT scan, ventilation and perfusion scintigraphy, full pulmonary function tests, cardiopulmonary exercise testing, and measurements of quality of life and dyspnea (Figure 1). Careful computer-based assessment of fissure integrity on chest CT and endobronchial balloon-occluding systems to assess distal flow are recommended before ELVR.
- (iii) If a decision is made to offer an ELVR procedure, one-way valves are the first option in the presence of complete lobar exclusion and no significant collateral ventilation (Figure 1). It should be expected, however, that only 1 in 5 eligible patients will meet these anatomic features. When the fissure is not complete, when collateral ventilation is evident in heterogeneous emphysema or when emphysema is homogeneous, coil implants or BioLVR (in that order) are the next logical alternatives. These nonreversible techniques (BioLVR and BTVA) appear to be less desirable owing to greater risk of persistent harm to already-frail patients. Nevertheless, benefits may accrue in highly selected patients in specialized centers. Currently, there appears to be insufficient evidence to support the use of airway bypass stents in the management of advanced emphysema.
- (iv) No ELVR procedures have been approved by Health Canada. To date (June 2015), they are available except in research centers as part of clinical trials.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

References

- D. Gompelmann, R. Eberhardt, and F. Herth, "Endoscopic volume reduction in COPD-a critical review," *Deutsches Ärzteblatt International*, vol. 111, no. 49, pp. 827–833, 2014.
- [2] I. H. Iftikhar, F. R. McGuire, and A. I. Musani, "Predictors of efficacy for endobronchial valves in bronchoscopic lung volume reduction: a meta-analysis," *Chronic Respiratory Disease*, vol. 11, no. 4, pp. 237–245, 2014.
- [3] I. H. Iftikhar, F. R. McGuire, and A. I. Musani, "Efficacy of bronchoscopic lung volume reduction: a meta-analysis," *International Journal of Chronic Obstructive Pulmonary Disease*, vol. 9, pp. 481–491, 2014.
- [4] M. Choi, W. S. Lee, M. Lee et al., "Effectiveness of bronchoscopic lung volume reduction using unilateral endobronchial valve: a systematic review and meta-analysis," *International Journal of Chronic Obstructive Pulmonary Disease*, vol. 10, pp. 703–710, 2015.
- [5] D. A. Mahler and D. E. O'Donnell, "Recent advances in dyspnea," *Chest*, vol. 147, no. 1, pp. 232–241, 2015.

- [6] I. Y. P. Wan, T. P. Toma, D. M. Geddes et al., "Bronchoscopic lung volume reduction for end-stage emphysema: report on the first 98 patients," *Chest*, vol. 129, no. 3, pp. 518–526, 2006.
- [7] F. C. Sciurba, A. Ernst, F. J. F. Herth et al., "A randomized study of endobronchial valves for advanced emphysema," *The New England Journal of Medicine*, vol. 363, no. 13, pp. 1233–1244, 2010.
- [8] D. H. Sterman, A. C. Mehta, D. E. Wood et al., "A multicenter pilot study of a bronchial valve for the treatment of severe emphysema," *Respiration*, vol. 79, no. 3, pp. 222–233, 2010.
- [9] F. J. F. Herth, M. Noppen, A. Valipour et al., "Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort," *European Respiratory Journal*, vol. 39, no. 6, pp. 1334– 1342, 2012.
- [10] R. Eberhardt, D. Gompelmann, M. Schuhmann et al., "Complete unilateral vs partial bilateral endoscopic lung volume reduction in patients with bilateral lung emphysema," *Chest*, vol. 142, no. 4, pp. 900–908, 2012.
- [11] V. Ninane, C. Geltner, M. Bezzi et al., "Multicentre European study for the treatment of advanced emphysema with bronchial valves," *European Respiratory Journal*, vol. 39, no. 6, pp. 1319– 1325, 2012.
- [12] F. J. F. Herth, R. Eberhardt, D. Gompelmann et al., "Radiological and clinical outcomes of using ChartisTM to plan endobronchial valve treatment," *European Respiratory Journal*, vol. 41, no. 2, pp. 302–308, 2013.
- [13] D. E. Wood, D. A. Nader, S. C. Springmeyer et al., "The IBV valve trial: a multicenter, randomized, double-blind trial of endobronchial therapy for severe emphysema," *Journal of Bronchology and Interventional Pulmonology*, vol. 21, no. 4, pp. 288–297, 2014.
- [14] D.-J. Slebos, K. Klooster, A. Ernst, F. J. F. Herth, and H. A. M. Kerstjens, "Bronchoscopic lung volume reduction coil treatment of patients with severe heterogeneous emphysema," *Chest*, vol. 142, no. 3, pp. 574–582, 2012.
- [15] P. L. Shah, Z. Zoumot, S. Singh et al., "Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomised controlled trial," *The Lancet Respiratory Medicine*, vol. 1, no. 3, pp. 233–240, 2013.
- [16] Z. Zoumot, S. V. Kemp, S. Singh et al., "Endobronchial coils for severe emphysema are effective up to 12 months following treatment: medium term and cross-over results from a randomised controlled trial," *PLoS ONE*, vol. 10, no. 4, Article ID e0122656, 2015.
- [17] G. J. Criner, V. Pinto-Plata, C. Strange et al., "Biologic lung volume reduction in advanced upper lobe emphysema: phase 2 results," *American Journal of Respiratory and Critical Care Medicine*, vol. 179, no. 9, pp. 791–798, 2009.
- [18] F. J. Herth, R. Eberhard, D. Gompelmann, D.-J. Slebos, and A. Ernst, "Bronchoscopic lung volume reduction with a dedicated coil: a clinical pilot study," *Therapeutic Advances in Respiratory Disease*, vol. 4, no. 4, pp. 225–231, 2010.
- [19] H. Magnussen, M. R. Kramer, A.-M. Kirsten et al., "Effect of fissure integrity on lung volume reduction using a polymer sealant* in advanced emphysema," *Thorax*, vol. 67, no. 4, pp. 302–308, 2012.
- [20] M. R. Kramer, Y. Refaely, N. Maimon, D. Rosengarten, and O. Fruchter, "Bilateral endoscopic sealant lung volume reduction therapy for advanced emphysema," *Chest*, vol. 142, no. 5, pp. 1111–1117, 2012.
- [21] G. Snell, F. J. F. Herth, P. Hopkins et al., "Bronchoscopic thermal vapour ablation therapy in the management of heterogeneous

emphysema," *European Respiratory Journal*, vol. 39, no. 6, pp. 1326–1333, 2012.

- [22] F. J. F. Herth, A. Ernst, K. M. Baker et al., "Characterization of outcomes 1 year after endoscopic thermal vapor ablation for patients with heterogeneous emphysema," *International Journal* of Chronic Obstructive Pulmonary Disease, vol. 7, pp. 397–405, 2012.
- [23] P. F. G. Cardoso, G. I. Snell, P. Hopkins et al., "Clinical application of airway bypass with paclitaxel-eluting stents: early results," *Journal of Thoracic and Cardiovascular Surgery*, vol. 134, no. 4, pp. 974–981, 2007.
- [24] P. L. Shah, D.-J. Slebos, P. F. G. Cardoso et al., "Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomised, sham-controlled, multicentre trial," *The Lancet*, vol. 378, no. 9795, pp. 997–1005, 2011.
- [25] M. S. Kent, C. Ridge, D. O'Dell, P. Lo, R. Whyte, and S. P. Gangadharan, "The accuracy of computed tomography to predict completeness of pulmonary fissures. A prospective study," *Annals of the American Thoracic Society*, vol. 12, no. 5, pp. 696–700, 2015.
- [26] Y. Mizumori, Y. Mochiduki, Y. Nakahara et al., "Effects of bronchoscopic lung volume reduction using transbronchial infusion of autologous blood and thrombin in patients with severe chronic obstructive pulmonary disease," *Journal of Thoracic Disease*, vol. 7, no. 3, pp. 413–421, 2015.
- [27] C. E. Come, M. R. Kramer, M. T. Dransfield et al., "A randomised trial of lung sealant versus medical therapy for advanced emphysema," *European Respiratory Society*, vol. 16, no. 3, pp. 651–662, 2015.





The Scientific World Journal



Research and Practice









Computational and Mathematical Methods in Medicine

Behavioural Neurology





Oxidative Medicine and Cellular Longevity