Chronic obstructive pulmonary disease (COPD) is one of the most common causes of morbidity and mortality in South Africa (SA). While smoking remains the most common risk factor for the development of COPD locally, long-term biomass fuel exposure, tuberculosis and HIV also contribute significantly to the disease burden. In addition, poverty has been shown to be fuel exposure, tuberculosis and HIV also contribute significantly of management guidelines for COPD in SA.

In advanced emphysema, therapeutic options are limited. Surgical lung volume reduction is known to improve functional status and mortality, but only in the subgroup of patients with predominant upper-lobe emphysema and low exercise capacity, and at the cost of high morbidity. Endoscopic lung volume reduction (ELVR) refers to bronchoscopically facilitating volume loss to improve pulmonary mechanics and compliance, and is now increasingly being used internationally for the treatment of advanced emphysema. The aim of ELVR is to obtain the same functional advantages as surgical lung volume reduction, with reduced risks and costs. These techniques aim to achieve regional reductions in lung volume, thereby decreasing dynamic hyperinflation, with resultant improvement in diaphragm and chest wall mechanics. In addition, endobronchial coils in particular re-tension the airway network and in so doing mechanically increase elastic recoil in the emphysematous lungs, tethering open airways and thereby preventing airway collapse.

There is a growing body of evidence that certain patients with advanced emphysema benefit from ELVR, provided that a systematic approach is followed and selection criteria are met. In addition to endobronchial valves, endobronchial coils for ELVR are now available in SA. The high cost of these interventions underscores the need for careful patient selection to best identify those who may or may not benefit from ELVR-related procedures.

The Assembly on Interventional Pulmonology of the South African Thoracic Society appointed a committee comprising both local and international experts to review the evidence and provide advice on the use of ELVR in SA based on published evidence, expert opinion and local access to the various devices. The Assembly on Interventional Pulmonology of the South African Thoracic Society appointed a committee comprising both local and international experts to extensively review all relevant evidence and provide advice on the use of ELVR in SA based on published evidence, expert opinion and local access to the various devices.
lobar collapse. The valves are self-expanding devices that are implanted via a catheter introduced through the working channel of a flexible bronchoscope.\(^{10}\) Currently, Zephyr endobronchial valves (Pulmonx Inc., USA) and IBV intrabronchial valves (Olympus Respiratory America, USA) are commercially available in SA.

Zephyr valves (Fig. 1) are made of a nitinol (nickel titanium) mesh covered by silicone and contain a double silicone membrane that opens during expiration and closes during inspiration. They are available in two sizes, one for segmental (4.0 - 9.0 mm) and one for lobar bronchi (5.5 - 8.5 mm).\(^{30}\) IBV valves (Fig. 2) are umbrella-shaped devices made of a nitinol mesh covered by a polyurethane membrane, and available in four different sizes (5, 6, 7 and 9 mm).

Similarly, endobronchial blocking devices are unlikely to be beneficial in the presence of significant interlobar collateral ventilation. Such collateral ventilation prevents atelectasis and thereby subverts the deflating effect of the devices. The presence of incomplete fissures, seen on an HRCT scan, is considered a proxy for physiological interlobar collateral ventilation. Recent evidence suggests that if the fissures are <75% intact, further evaluation should not be performed as collateral ventilation is always present, whereas with >90% complete fissures, collateral ventilation is practically never present. The Chartis system is an endobronchial catheter system (Chartis Pulmonary Assessment System; Pulmonx Inc.) used to directly measure the percentage of interlobar collateral ventilation in patients with between 75% and 90% fissural integrity.\(^{20}\) The system is made up of a balloon catheter that is connected to a console and inserted into an airway via a bronchoscope. Once inflated it occludes the bronchus, preventing direct outflow of inspired air. A near-constant rate of expiratory airflow during the assessment is observed in cases with collateral ventilation, whereas a steady reduction in flow is observed in the absence of collateral ventilation.\(^{21}\)

The current evidence for the use of endobronchial and intrabronchial valves is summarised in Table 1. Although numerous observational and randomised trials showed statistical benefits in respect of practically all functional parameters, minimal clinically important differences (MICDs) were significantly more likely to be observed in patients with advanced heterogeneous emphysema and no collateral ventilation and in those in whom unilateral valve placement achieved complete lobar collapse.\(^{13-16}\) The most common reported adverse events were pneumothoraces (5 - 10%), mild haemoptysis (2 - 6%) and exacerbations of underlying COPD (8 - 40%).

The recently completed STELVIO trial provided the strongest evidence for use of valves in patients without collateral ventilation.\(^{19}\) Dutch investigators randomised 68 patients with severe heterogeneous emphysema on HRCT with visual estimation of complete or near-complete fissures to endobronchial Zephyr valve treatment (n=34) or standard medical care (n=34). The primary outcome measures were change in spirometric measures and 6-minute walking distance (6MWD) at 6 months. Clinical relevance was assessed relative to MICDs. At 6 months, the MICDs were attained in all parameters in the treated group compared with controls (p<0.001 for all endpoints).

### 1.2 Coils

Coils (RePneu; BTG Inc., USA) are nitinol devices (Fig. 3) designed to be straightened for deployment into a subsegmental airway, and thereafter to resume their preformed shape.\(^{10}\) This conformational shape change after deployment results in parenchymal retraction with volume loss, while maintaining airway patency.\(^{10}\) The device is currently available in three lengths (100, 125 and 150 mm) to accommodate different-sized airways. The coils are implanted via a flexible bronchoscope under general anaesthesia or conscious sedation and fluoroscopic guidance using a proprietary delivery system.

Current evidence (Table 2) suggests that candidates with both heterogeneous and homogeneous emphysema can experience clinically significant benefit from ELVR using coils.\(^{16,20-23}\) This benefit is obtained regardless of the presence of collateral ventilation, or complete lobar collapse post-insertion, but requires that no more than 75% of the total lung parenchyma is destroyed by emphysema prior to insertion.\(^{11,22}\) Approximately 75 - 80% of patients will experience MICDs in lung function and quality of life, while mild haemoptysis of <5 mL (50 - 75%), exacerbations of COPD (5 - 12%), mild chest discomfort (15 - 50%) and infrequent pneumothoraces (3%) are the described adverse events.\(^{11,22}\) A recent report on the 3-year follow-up data of 38 patients who underwent ELVR using coils suggested that the coil treatment was safe; no late pneumothoraces, coil migrations or unexpected adverse events occurred.\(^{12}\) Although clinical benefit declined gradually over time, at 3 years after treatment approximately 50% of patients maintained improvements in 6MWD and subjective dyspnoea, as well as quality of life scores.
Table 1. Summary of key clinical studies that evaluated the safety and efficacy of ELVR with valves

<table>
<thead>
<tr>
<th>Study details</th>
<th>Design</th>
<th>Primary efficacy measures</th>
<th>Major outcomes</th>
<th>Major adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snell et al.,[13] 2003 Number enrolled: 10</td>
<td>Case series: bilateral ELVR (feasibility study)</td>
<td>NA</td>
<td>No major change in radiological findings, lung function or 6MWD; DLCO improved from mean (SD) 7.47 (2.0) to 8.26 (2.6) mL/min/mmHg (p=0.04)</td>
<td>No major complications (at 30 days). Minor complications included exacerbation of COPD (n=3), asymptomatic pneumothorax (n=1) and pneumonia (n=1)</td>
<td>Showed that ELVR with valves was feasible and safe, but that further studies were needed to explore patient characteristics that determine symptomatic efficacy</td>
</tr>
<tr>
<td>Toma et al.,[14] 2003 Number enrolled: 8</td>
<td>Case series: unilateral ELVR (feasibility study)</td>
<td>NA</td>
<td>Median FEV1 increased from 0.79 to 1.06 L (p=0.028) and median DLCO from 3.05 to 3.92 mL/min/mmHg (p=0.017)</td>
<td>Pneumothorax (n=2)</td>
<td>Acceptable short-term safety</td>
</tr>
<tr>
<td>VENT (USA) trial (Sciurba et al.[15]), 2010 Number enrolled: 321</td>
<td>RCT (2:1): unilateral ELVR v. standard medical care</td>
<td>Changes in FEV1 and 6MWD at 6 months</td>
<td>FEV1 1.9% higher (p=0.007) and 6MWD 19.1 m more (p=0.02) in treated group; SGRQ decreased by 3.4 (p=0.04)</td>
<td>COPD exacerbation requiring hospitalisation (7.9% v. 1.1%) (p=0.03) and haemoptysis (6.1% v. 0% (p=0.01). Pneumonia in target lobe (4.2%)</td>
<td>Greater radiographic evidence of emphysema heterogeneity and fissure completeness was associated with an enhanced response to treatment</td>
</tr>
<tr>
<td>VENT (Europe) trial (Herth et al.[16]), 2012 Number enrolled: 60</td>
<td>RCT (2:1): unilateral ELVR v. standard medical care</td>
<td>Changes in FEV1, cycle ergometry and SGRQ at 6 months</td>
<td>Mean change in FEV1 7.0% v. 0.5% (p=0.067); cycle ergometry 2W v. 3W (p=0.04); SGRQ −5 v. 0.3 points (p=0.047)</td>
<td>Pneumothorax (n=5). No difference in COPD exacerbation rates</td>
<td>Superior clinical results with computed tomography suggestive of complete fissures and with successful lobar occlusion</td>
</tr>
<tr>
<td>Ninane et al.[17] 2012 Number enrolled: 73</td>
<td>Sham-controlled study (1:1): bilateral ELVR without lobar collapse</td>
<td>≥4-point improvement in SGRQ</td>
<td>24% responders in treated group v. 0% in control group (p=0.002)</td>
<td>COPD exacerbation 13% v. 9% (p=0.595)</td>
<td>Not effective in majority; major finding was that complications are due to bronchoscopy itself rather than device</td>
</tr>
<tr>
<td>Eberhardt et al.,[18] 2012 Number enrolled: 22</td>
<td>RCT (1:1): bilateral (incomplete occlusion) v. unilateral (for total occlusion) treatment</td>
<td>FEV1, 6MWD, SGRQ</td>
<td>FEV1 improved in unilaterally treated group but not in the other group (21.4% v. 0.03%) (p=0.002)</td>
<td>Respiratory failure (n=2), pneumothorax (n=1)</td>
<td>Unilateral valve placement with complete occlusion superior to bilateral partial occlusion</td>
</tr>
<tr>
<td>STELvio trial (Klooster et al.[19]), 2015 Number randomised: 68</td>
<td>RCT (1:1): unilateral ELVR (collateral ventilation excluded) v. standard medical care</td>
<td>FEV1, FVC, RV and 6MWD at 6 months</td>
<td>FEV1 22.7%, FVC 442 mL, RV −831 mL, 6MWD 106 m and SGRQ −14.7 points superior in treated group (all p&lt;0.001)</td>
<td>Pneumothorax 17.6%</td>
<td>Best evidence that ELVR with valves in the absence of collateral ventilation results in statistically and clinically significant improvements in pulmonary function, exercise capacity and quality of life</td>
</tr>
</tbody>
</table>

RCT = randomised controlled trial; NA = not applicable; FEV1 = forced expiratory volume in 1 second; 6MWD = 6-minute walking distance; SGRQ = St George’s respiratory questionnaire; W=watt; FVC = forced vital capacity; RV = residual volume; DLCO = carbon monoxide diffusing capacity; SD = standard deviation.
Table 2. Summary of key clinical studies that evaluated the safety and efficacy of ELVR with coils

<table>
<thead>
<tr>
<th>Study details</th>
<th>Design</th>
<th>Efficacy measures</th>
<th>Outcome</th>
<th>Major adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herth et al.[10], 2010</td>
<td>Case series (feasibility study)</td>
<td>NA</td>
<td>NA</td>
<td>COPD exacerbations (mild), no pneumothorax</td>
<td>ELVR with coils was deemed safe and feasible</td>
</tr>
<tr>
<td>Slebos et al.[20], 2012</td>
<td>Prospective cohort pilot study</td>
<td>SGRQ, FEV₁, FVC, RV, 6MWD</td>
<td>SGRQ improved by 14.9 points (in 11 patients by &gt;4 points), FEV₁ by 14.9%, FVC by 13.4%, RV by 11.4% and 6MWD by 84.4 m (all p&lt;0.005)</td>
<td>Pneumothorax (n=1), pneumonia (n=2), COPD exacerbation (n=6), chest pain (n=4), mild (&lt;5 mL) haemoptysis (n=21)</td>
<td>First study to show significant improvements in pulmonary function, exercise capacity, and quality of life</td>
</tr>
<tr>
<td>RESET trial (Shah et al.[21]), 2013</td>
<td>RCT (1:1): bilateral ELVR v. standard medical care</td>
<td>SGRQ</td>
<td>−8.63 (p=0.04)</td>
<td>COPD exacerbation (4%)</td>
<td>Evidence of improved quality of life</td>
</tr>
<tr>
<td>Deslee et al.[22], 2014</td>
<td>Prospective multicentre cohort trial</td>
<td>SGRQ, pulmonary function testing, mMRC and 6MWD up to 12 months</td>
<td>ΔSGRQ −11.1 points, Δ6MWD +51.4 m, ΔFEV₁ +0.11 L and ΔRV −0.71 (all p&lt;0.01)</td>
<td>COPD exacerbation (6.1%), pneumonia (5.2%), pneumothorax (3.5%), haemoptysis (0.9%)</td>
<td>Significant responses for both heterogeneous and homogeneous emphysema</td>
</tr>
<tr>
<td>Klooster et al.[23], 2014</td>
<td>Prospective single-centre cohort trial</td>
<td>Change in 6MWD at 6 months</td>
<td>6MWD improved from 289 to 350 m (p&lt;0.005), FVC from 2.17 to 2.55 L (p=0.047), RV from 5.04 to 4.44 L (p=0.007) and SGRQ from 63 to 48 points (p=0.028)</td>
<td>Pneumothorax (n=1), slight (&lt;5 mL) haemoptysis (n=5), chest discomfort (n=6), COPD exacerbation (n=5)</td>
<td>The benefit of LVR cooling treatment is not limited to patients with heterogeneous emphysema</td>
</tr>
<tr>
<td>Hartman et al.[24], 2015</td>
<td>Prospective single-centre cohort trial</td>
<td>mMRC, pulmonary function testing and 6MWD at 5 years</td>
<td>Significant improvement in mMRC score remained, with 40% of the patients reaching the 6MWD MICD and 59% the SGRQ MICD</td>
<td>No device-related complications</td>
<td>Best long-term data on safety of coils</td>
</tr>
</tbody>
</table>

NA = not applicable; SGRQ = St George’s respiratory questionnaire; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; RV = residual volume; 6MWD = 6-minute walking distance; mMRC = modified Medical Research Council dyspnoea score; Δ = change.

2. Modalities not available in SA

2.1 Bronchial spigots

Watanabe Spigots (Novatech, France) have been used successfully in the management of pulmonary fistula and persistent pneumothorax with continuous air leakage.[24] Despite many reports describing successful treatment of persistent air leaks using endobronchial Watanabe Spigots, evidence for their use in the context of ELVR for emphysema is lacking.

2.2 Sealants

The AeriSeal system (Aeris Therapeutics Biological, Pulmonix Inc.) uses synthetic polymeric foam to obtain atelectasis. A recent multicentre randomised controlled trial, terminated early for financial reasons, confirmed significant improvements from baseline in lung function, dyspnoea and quality of life when compared with controls at 3 months, but the fact that 44% of treated patients experienced adverse events requiring hospitalisation (including two deaths) raised some safety concerns.[25]

2.3 Vapour

Bronchoscopic thermal vapour ablation (InterVapor; Uptake Medical, USA) uses high-temperature water vapour delivered into the target lung segments through a catheter with precise amount of energy, thereby inducing thermal damage resulting in permanent airway fibrosis.[6] Although one potential advantage of this technology is that it is not influenced by interlobar collateral ventilation, it has been shown to have a relatively modest effect on lung function.[26,27] Adverse events, particularly COPD exacerbations, are frequently observed.[24]

2.4 Airway bypass

The technique of airway bypass is based on the creation of extra-anatomical passages between the hyperinflated lung parenchyma and larger airways.[4] Evidence suggests that although some short-term benefit may be achieved in patients with severe hyperinflation, pulmonary function appears to return to baseline within 3 months.[28-31]
3. Evaluation of candidates for potential lung volume reduction

The initial screening of potential candidates with stable disease should ideally be performed by pulmonologists, and should include an assessment of severity of dyspnoea, functional impairment, past thoracic surgery, comorbidities and smoking status.

Routine special investigations should include an HRCT scan (to estimate heterogeneity, integrity of fissions and degree of tissue destruction, and to exclude occult malignancy), full pulmonary function testing (including measurements of forced expiratory volume in 1 second, forced vital capacity, residual volume (RV), total lung capacity (TLC), carbon monoxide diffusing capacity and 6MWD, arterial blood gas measurement and echocardiography (to exclude pulmonary artery pressures >50 mmHg).

The general indications for and contra-indications to valves and coils are summarised in Table 3. ELVR should not be offered to active smokers, patients with pulmonary hypertension, unstable cardiac pathology, active respiratory infections, a very poor exercise tolerance or no clear evidence of hyperinflation, or to patients on any type of long-term antiplatelet or anticoagulant therapy that cannot be stopped 7 days before the procedure.

Appropriate or borderline candidates should be referred to a centre with the capacity to evaluate and treat them and follow them up, including managing complications and removal of devices if required. These centres should individualise the interventions on the basis of disease phenotype (e.g. heterogeneous v. homogenous disease), degree of tissue destruction, the presence of collateral ventilation and pulmonary impairment.

4. Suggested approach to ELVR in SA

There is currently no official guideline from any of the major thoracic societies and no head-to-head evidence comparing the various techniques and devices. The Assembly on Interventional Pulmonology of the SA Thoracic Society has therefore based the approach summarised in Fig. 4 on the available published evidence, availability of the devices in SA and international expert opinion.

The degree of severity of emphysema, the degree of tissue destruction, heterogeneity of the disease and the presence of collateral ventilation are all important factors in the final selection process. The algorithm presented in Fig. 4 should not be viewed as a rigid guideline, and the clinician should still use discretion, especially in those patients who may potentially benefit from either coils or valves. For example, patients with 25 - 75% tissue destruction and no collateral ventilation may also benefit from valves, although the reported response rates and improvements in functional status and pulmonary function tests seem to be greater with coils.

It is recommended that all ELVR procedures should be performed in the context of a local and/or international registry. The Assembly on Interventional Pulmonology of the SA Thoracic Society is willing to assist potential centres wanting to establish an ELVR service in terms of training and accreditation.

5. Conclusions

Appropriate candidates with marked hyperinflation and relatively preserved lung parenchyma are more likely to benefit from ELVR with bilateral coils, irrespective of the collateral ventilation and heterogeneity of the disease. In contrast, patients with heterogeneous disease and no collateral ventilation are more likely to benefit from unilateral ELVR with valves, aiming to achieve complete lobar collapse. A well-structured evidence-based approach to ELVR, including initial screening and subsequent referral to a specialised centre, is important to avoid inappropriate use of devices, which may be both wasteful and harmful.

Author contributions. The article was written by CFNK and JT, and extensively reviewed by KD, JWB, BWA, MJV, FvG-B, D-JS, PLS and FJFH.

Conflicts of interest. FJFH and D-JS have performed consultative work for PulmonRx, PneumRx, Uptake Medical and Aeris. The remaining authors have nothing to declare.

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Table 3. General indications for and contraindications to ELVR with endobronchial and intrabronchial valves and coils in patients with stable emphysema

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 - 75 years</td>
<td>Homogeneous emphysema and no collateral ventilation (valves)*</td>
</tr>
<tr>
<td>Heterogeneous emphysema and no collateral ventilation (valves)*</td>
<td>Hyperinflation with TLC &gt;100% and RV &gt;150 - 175%</td>
</tr>
<tr>
<td>Dyspnoea despite maximal medical therapy and pulmonary rehabilitation</td>
<td>PaCO₂ &lt;6.7 kPa (50 mmHg)</td>
</tr>
<tr>
<td>FEV₁ &lt;15 - 45%</td>
<td>PaO₂ &gt;6 kPa (45 mmHg) while breathing ambient air</td>
</tr>
<tr>
<td>Hyperinflation with TLC &gt;100% and RV &gt;150 - 175%</td>
<td>6MWD ≥140 m (after rehabilitation)</td>
</tr>
</tbody>
</table>

*Specific for endobronchial and intrabronchial valves.
†Specific for endobronchial coils.
FORUM

Initial review of patient with stable emphysema (performed by pulmonologist)

- Current smoking (last 6 months)
- DLco <20%
- Giant bullae (>1/3 of hemithorax)
- α-antitrypsin deficiency
- Previous thoracotomy, pleurectomy or chest wall deformity
- Severe pulmonary hypertension (>50 mmHg)
- Active infection or intolerance to lung volume reduction treatments
- Significant pleural or interstitial changes on HRCT
- Antiplatelet/anti-coagulant therapy that cannot be stopped

- 40 - 75 years old
- Dyspnoea despite maximal medical therapy & pulmonary rehabilitation
- FEV1, 15 - 45%
- Hyperinflation (TLC >100% & RV >150 - 175%)
- PaCO2 >6.7 kPa
- PaO2 >6 kPa (ambient air)
- 6MWD >210 m

General inclusion criteria

- Positive (with low exercise capacity)
- Negative (with low baseline perfusion)
- Heterogeneous disease
- Homogeneous disease
- Parenchymal destruction on HRCT

General exclusion criteria

- LVR not an option

Modality-specific review by specialist centre

- Coils
- Valves
- Consider LVRs

![Diagram](http://dx.doi.org/10.1183/09031936.00161611)

Fig. 4. Suggested approach to ELVR in SA. (*Patients with 25 - 75% of tissue destruction and no collateral circulation may also benefit from valves, although the reported response rates and improvements in functional status and pulmonary function test seem to favour ELVR with coils. LVR = lung volume reduction; LRS = lung volume reduction surgery; FEV1 = forced expiratory volume in 1 second; TLC = total lung capacity; RV = residual volume; PaCO2 = partial pressure of carbon dioxide; PaO2 = partial pressure of oxygen; 6MWD = 6-minute walking distance; DLco = carbon monoxide diffusing capacity.)