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RECOMMENDATIONS

Recommendations for the use of endoscopic lung volume reduction in South Africa: Role in the treatment of emphysema

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Emphysema is a very common cause of morbidity and mortality in South Africa (SA). Therapeutic options in severe emphysema are limited. Endoscopic lung volume reduction (ELVR) is increasingly being used internationally for the treatment of advanced emphysema in a subset of patients with advanced disease, aiming to obtain the same functional advantages as surgical lung volume reduction while reducing risks and costs. In addition to endobronchial valves, ELVR using endobronchial coils is 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 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.

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Chronic obstructive pulmonary disease (COPD) is one of the most common causes of morbidity and mortality in South Africa (SA).[1-3] 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.[4] In addition, poverty has been shown to be associated with an increased burden of COPD.[5] Pharmacotherapy and guidance on smoking cessation continue to form the backbone of management guidelines for COPD in SA.[1,6]

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.[7] Endoscopic lung volume reduction (ELVR) refers to bronchoscopically facilitating volume loss to improve pulmonary mechanics and compliance,[8,9] 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,[8] 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.[10]

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 devices used for ELVR. The aim is to provide SA pulmonologists with an overview of the efficacy of the various techniques and evidence for their use, and to suggest an evidence-based approach for the appropriate local use of these devices.

1. Modalities and devices currently available in SA

1.1 Unidirectional endobronchial and intrabronchial valves

Unidirectional valves block entrance of air during inspiration, but permit exhalation of air and secretions, causing partial or complete

lobar collapse. The valves are self-expanding devices that are implanted via a catheter introduced through the working channel of a flexible bronchoscope.[8] 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).[8] 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).

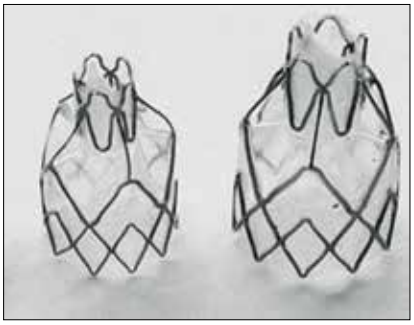

Fig. 1. Endobronchial (Zephyr) valves of varying diameters for lobar or segmental occlusion.

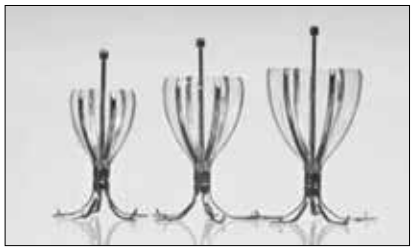

Fig. 2. Intrabronchial (IBV) valves of varying diameters.

Two major caveats for the use of valves and other bronchial blocking devices are the presence of either a homogeneous distribution of emphysema or significant collateral ventilation.[8] The degree of heterogeneity can be judged either by visual inspection of a high-resolution chest computed tomography (HRCT) scan or with specifically designed software. Heterogeneous emphysema is denoted by a >25% difference in emphysema score between ipsilateral upper and lower lobes, measured at a threshold of <−950 Hounsfield units.[11] In the absence of heterogeneous emphysema, bronchial blocking devices are unlikely to be successful. 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.[12] 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.[12]

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.[13-19] 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.

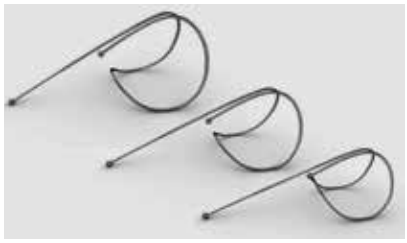

Fig. 3. Endobronchial (RePneu) coils of varying lengths.

Current evidence (Table 2) suggests that candidates with both heterogeneous and homogeneous emphysema can experience clinically significant benefit from ELVR using coils.[10,20-23] 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.[23] 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

Study details	Design	Primary efficacy measures	Major outcomes	Major adverse events	Comments
Snell *et al.*,[13] 2003 Number enrolled: 10	Case series: bilateral ELVR (feasibility study)	NA	No major change in radiological findings, lung function or 6MWD; DL_{CO} improved from mean (SD) 7.47 (2.0) to 8.26 (2.6) mL/min/mmHg (p=0.04)	No major complications (at 30 days). Minor complications included exacerbation of COPD (n=3), asymptomatic pneumothorax (n=1) and pneumonia (n=1)	Showed that ELVR with valves was feasible and safe, but that further studies were needed to explore patient characteristics that determine symptomatic efficacy
Toma *et al.*,[14] 2003 Number enrolled: 8	Case series: unilateral ELVR (feasibility study)	NA	Median FEV_1 increased from 0.79 to 1.06 L (p=0.028) and median DL_{CO} from 3.05 to 3.92 mL/min/mmHg (p=0.017)	Pneumothorax (n=2)	Acceptable short-term safety
VENT (USA) trial (Sciurba *et al.*[15]), 2010 Number enrolled: 321	RCT (2:1): unilateral ELVR v. standard medical care	Changes in FEV_1 and 6MWD at 6 months	FEV_1 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)	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%)	Greater radiographic evidence of emphysema heterogeneity and fissure completeness was associated with an enhanced response to treatment
VENT (Europe) trial (Herth *et al.*[16]), 2012 Number enrolled: 60	RCT (2:1): unilateral ELVR v. standard medical care	Changes in FEV_1, cycle ergometry and SGRQ at 6 months	Mean change in FEV_1 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)	Pneumothorax (n=5). No difference in COPD exacerbation rates	Superior clinical results with computed tomography suggestive of complete fissures and with successful lobar occlusion
Ninane *et al.*,[17] 2012 Number enrolled: 73	Sham-controlled study (1:1): bilateral ELVR without lobar collapse	≥4-point improvement in SGRQ	24% responders in treated group v. 0% in control group (p=0.002)	COPD exacerbation 13% v. 9% (p=0.595)	Not effective in majority; major finding was that complications are due to bronchoscopy itself rather than device
Eberhardt *et al.*,[18] 2012 Number enrolled: 22	RCT (1:1): bilateral (incomplete occlusion) v. unilateral (for total occlusion) treatment	FEV_1, 6MWD, SGRQ	FEV_1 improved in unilaterally treated group but not in the other group (21.4% v. 0.03%) (p=0.002)	Respiratory failure (n=2), pneumothorax (n=1)	Unilateral valve placement with complete occlusion superior to bilateral partial occlusion
STELVIO trial (Klooster *et al.*[19]), 2015 Number randomised: 68	RCT (1:1): unilateral ELVR (collateral ventilation excluded) v. standard medical care	FEV_1, FVC, RV and 6MWD at 6 months	FEV_1 22.7%, FVC 442 mL, RV −831 mL, 6MWD 106 m and SGRQ −14.7 points superior in treated group (all p<0.001)	Pneumothorax 17.6%	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

RCT = randomised controlled trial; NA = not applicable; FEV_1 = 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; DL_{CO} = carbon monoxide diffusing capacity; SD = standard deviation.

Table 2. Summary of key clinical studies that evaluated the safety and efficacy of ELVR with coils

Study details	Design	Efficacy measures	Outcome	Major adverse events	Comments
Herth *et al.*,[10] 2010 Number enrolled: 11	Case series (feasibility study)	NA	NA	COPD exacerbations (mild), no pneumothorax	ELVR with coils was deemed safe and feasible
Slebos *et al*,[20] 2012 Number enrolled: 16	Prospective cohort pilot study	SGRQ, FEV_1, FVC, RV, 6MWD	SGRQ improved by 14.9 points (in 11 patients by >4 points), FEV_1 by 14.9%, FVC by 13.4%, RV by 11.4% and 6MWT by 84.4 m (all $p<0.005$)	Pneumothorax ($n=1$), pneumonia ($n=2$), COPD exacerbation ($n=6$), chest pain ($n=4$), mild (<5 mL) haemoptysis ($n=21$)	First study to show significant improvements in pulmonary function, exercise capacity, and quality of life
RESET trial (Shah *et al.*[21]), 2013 Number enrolled: 47	RCT (1:1): bilateral ELVR v. standard medical care	SGRQ	−8.63 ($p=0.04$)	COPD exacerbation (4%)	Evidence of improved quality of life
Deslee *et al.*,[11] 2014 Number enrolled: 60	Prospective multicentre cohort trial	SGRQ, pulmonary function testing, mMRC and 6MWD up to 12 months	ΔSGRQ −11.1 points, Δ6MWD +51.4 m, ΔFEV_1 +0.11 L, and ΔRV −0.71 (all $p<0.01$)	COPD exacerbation (6.1%), pneumonia (5.2%), pneumothorax (3.5%), haemoptysis (0.9%)	Significant responses for both heterogeneous and homogeneous emphysema
Klooster *et al.*,[22] 2014 Number enrolled: 10	Prospective single-centre cohort trial	Change in 6MWD at 6 months	6MWD improved from 289 to 350 m ($p=0.005$), 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 ($p=0.028$)	Pneumothorax ($n=1$), slight (<5 mL) haemoptysis ($n=5$), chest discomfort ($n=6$), COPD exacerbation ($n=5$)	The benefit of LVR coil treatment is not limited to patients with heterogeneous emphysema
Hartman *et al.*,[23] 2015 Number enrolled: 38	Prospective single-centre cohort trial	mMRC, pulmonary function testing and 6MWD at 5 years	Significant improvement in mMRC score remained, with 40% of the patients reaching the 6MWD MICD and 59% the SGRQ MICD	No device-related complications	Best long-term data on safety of coils

NA = not applicable; SGRQ = St George's respiratory questionnaire; FEV_1 = 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, Pulmonx Inc.) uses synthetic polymeric foam to obtain atelectasis. A recent multi-centre randomised controlled trial, terminated early for financial reasons, confirmed significantly 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.[8] 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.[28]

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.[8] 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.[29-31]

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 fissures 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), RV/total lung capacity (TLC), 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 contraindications 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. homogeneous disease), degree of tissue destruction, the presence of collateral ventilation and pulmonary impairment.

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

Indications
40 - 75 years
Heterogeneous emphysema and no collateral ventilation (valves)*
Dyspnoea despite maximal medical therapy and pulmonary rehabilitation
FEV_1 15 - 45%
Hyperinflation with TLC >100% and RV >150 - 175%
$PaCO_2$ <6.7 kPa (50 mmHg)
PaO_2 >6 kPa (45 mmHg) while breathing ambient air
6MWD ≥140 m (after rehabilitation)
Contraindications
Homogeneous emphysema (valves)*
Collateral ventilation/non-intact fissures (valves)*
>75% parenchymal destruction on HRCT (coils)†
Current smoking (past 6 months)
DL_{CO} <20% (relative)
Giant bullae (>1/3 of hemithorax)
Alpha-1-antitrypsin deficiency
Previous thoracotomy, pleurodesis or chest wall deformity
Excessive sputum
Severe pulmonary hypertension (>50 mmHg)
Active infection
Unstable cardiac conditions
Significant pleural or interstitial changes on HRCT
Any type of antiplatelet or anticoagulant therapy that cannot be stopped for 7 days prior to procedure

FEV_1 = forced expiratory volume in 1 second; TLC = total lung capacity; RV = residual volume; $PaCO_2$ = partial pressure of carbon dioxide; PaO_2 = partial pressure of oxygen; 6MWD = 6-minute walking distance; DL_{CO} = carbon monoxide diffusing capacity.
*Specific for endobronchial and intrabronchial valves.
†Specific for endobronchial coils.

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.[8] 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.[7-9,16,19]

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 consultant work for PulmonRx, PneumRx, Uptake Medical and Aeris. The remaining authors have nothing to declare.

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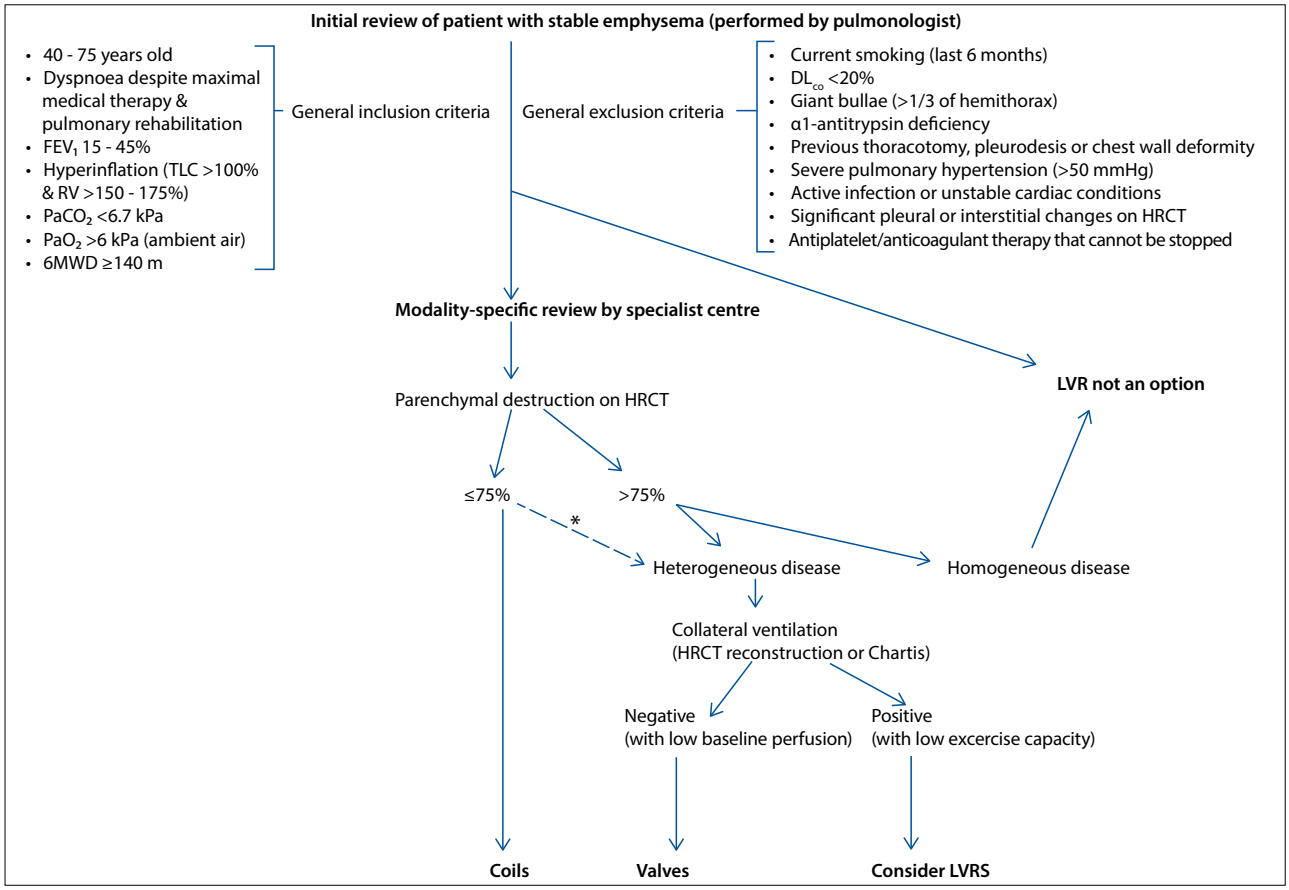

*Fig. 4. Suggested approach to ELVR in SA. (*Patients with 25 - 75% of tissue destruction and no collateral circulation may also benefit from valves, although the reported response rates and improvements in functional status and pulmonary function test seem to favour ELVR with coils. LVR = lung volume reduction; LVRS = lung volume reduction surgery; FEV_1 = forced expiratory volume in 1 second; TLC = total lung capacity; RV = residual volume; $PaCO_2$ = partial pressure of carbon dioxide; PaO_2 = partial pressure of oxygen; 6MWD = 6-minute walking distance; DL_{CO} = carbon monoxide diffusing capacity.)*

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