Review Article

Pneumothorax as a result of bronchoscopic lung volume reduction with endobronchial valves: a clinical practice review of risk and management strategies

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Abstract: Bronchoscopic lung volume reduction (BLVR) with endobronchial valves for patients with severe emphysema and absence of collateral ventilation is suggested as a treatment strategy in both the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the National Institute for Health and Care Excellence (NICE) guidelines. BLVR has demonstrated favorable outcomes for patients with severe emphysema by improving lung function, symptoms, quality of life, and possibly mortality. Pneumothorax is the most common complication of BLVR and is caused by the rapid expansion of the ipsilateral non-target lobe with a resulting alveolar or bronchopleural fistula. While concerning due to the potential for short-term acute management, available studies have concluded that pneumothorax following BLVR has not contributed to serious long-term consequences. This article offers a review of the approach to BLVR pre-procedural evaluation and post-procedural management strategies. Additionally, special circumstances including emphysema phenotype, pleural disease, and partial treatment when considering the risk of pneumothorax is also discussed. Initial BLVR pre-procedural evaluation requires a comprehensive history and physical including comorbidities, imaging review, along with assessment of patient function and pulmonary physiology. Post-BLVR procedural monitoring and expert recommendations for pneumothorax management strategies should be followed to help guide clinicians' approach to the care of advanced emphysema patients.

Keywords: Bronchoscopic lung volume reduction (BLVR); pneumothorax; complications after BLVR

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Introduction

As described in the National Emphysema Treatment Trial (NETT), lung volume reduction surgery (LVRS) improved exercise capacity, but a survival benefit was only observed for the subset of patients with both upper-lobe predominant emphysema and low baseline exercise capacity. The subset of patients without upper lobe predominant emphysema and high baseline exercise capacity was found to have an increased mortality along with negligible functional gain (1). Due to the risk of post-operative complications, patients may be reluctant to pursue a surgical approach. As a result, several minimally invasive bronchoscopic methods have been investigated, including bronchial valves, coils, thermal vapor ablation, sealants, and airway bypass stents.

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Currently, of these options, only endobronchial valves are approved for use in the United States. Commercially available Zephyr® endobronchial valve (Pulmonx Corp., Redwood City, CA, USA) and the intrabronchial Spiration® Valve System (Olympus, Tokyo, Japan) are commonly used for bronchoscopic lung volume reduction (BLVR). The LIBERATE, TRANSFORM, IMPACT, and STELVIO studies evaluated the outcomes of the Zephyr® valve system (2-5), while the EMPROVE and REACH studies evaluated the outcomes of the Spiration® Valve System (6,7). The studies concluded that there was improved lung function, exercise capacity, dyspnea, and quality of life after BLVR with either of the valve systems. Since 2019, BLVR utilizing valves is suggested as a treatment strategy in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (Level A evidence) for patients with severe emphysema with hyperinflation and no collateral ventilation between the target and ipsilateral lobe(s) (8,9). More recently, in a study of 1,471 patients, the median survival of patients who underwent treatment with BLVR was found to be longer (1.7 years) compared with those who did not receive the treatment, suggesting that BLVR in patients with severe hyperinflation may also lead to a survival benefit. Notably, BLVR in this study was performed using both valves and coils and was found to be an independent predictor of survival after adjusting for other survival-influencing factors such as age, gender, or severity of disease (10).

However, there are potential complications of the BLVR procedure with valves. While the most common of these is pneumothorax, other complications have also been described including chronic obstructive pulmonary disease (COPD) exacerbation, pneumonia, hemoptysis, valve migration/expectoration, and granulation tissue formation (3-5,11-13). Notably, based on other major trials, these other complications did not show significantly higher prevalence in patients treated with valves compared with controls (3,5,11-13). This review will summarize pertinent studies and expert statements discussing BLVR related pneumothorax risk, evaluation, and management.

Technical aspects of endobronchial valve placement

Patient selection

Candidates for BLVR should undergo a thorough evaluation and meet certain criteria prior to consideration of the procedure. Patients should receive optimal medical therapy as defined by the GOLD guidelines, participate in a pulmonary rehabilitation or comparable physical therapy program, and have quit smoking for at least 4 months. Evaluation should include a full medical assessment, complete lung function measurements, high resolution computed tomography (HRCT) scan, transthoracic echocardiogram (TTE), arterial blood gas (ABG) on room air, and a 6-minute walk test (6MWT). Patients who may be eligible for endobronchial valves must have severe emphysema (GOLD stages 3 and 4 with an FEV_1 of 15–45%) with hyperinflation [residual volume (RV) >175% predicted in heterogenous emphysema (EMPROVE study was 150%), RV >200% predicted in homogenous emphysema (only Zephyr approved in the US for homogenous disease)] and absence of collateral ventilation between the target and ipsilateral lobe(s) as can be reviewed in *Table 1* (2,6). Additionally, eligible patients should not have any contraindications including inability to tolerate a bronchoscopic procedure, severe gas exchange impairment [PaO_2 ≤45 mmHg on room air, $PaCO_2$ ≥50 mmHg on room air, diffusing capacity of carbon monoxide (DLCO) <20% predicted], frequent exacerbations, suspicious pulmonary nodules, large bullae occupying more than one-third of the lung, severe heart failure, uncontrolled pulmonary hypertension, or any allergy to the valve material (14-16). In the case of multiple possible target lobes, nuclear scanning can be performed to identify the lobe with the least perfusion to minimize the amount of ventilation/perfusion (V/Q) mismatching that occurs with lobar occlusion after valve placement (17,18).

Valve sizing and placement

The Zephyr® valve system utilizes a HRCT for initial screening which is uploaded and analyzed. Afterwards, a StratX® report is generated based on the computed tomography (CT) analysis, reporting emphysema severity, fissure integrity, and heterogeneity. The Zephyr® valve is a one-way valve that has a duckbill design (*Figure 1A*) and is made of a self-expanding nitinol frame with a silicone cover that exerts radial force against the airway wall. There are two valve sizes (4.0 and 5.5 mm diameter) which both expand by 3 mm with the option for a "low-profile" (LP) version that has a reduced length (14). Valve sizing is determined using sizing wings on the deployment catheter which approximates the size of the airway diameter and measurement marks to determine length. Use of the Chartis® (Pulmonx Inc., Redwood City, CA, USA) system

Table 1 BLVR eligibility criteria

Evaluation/testing	Result
Clinical history	Symptomatic emphysema despite optimal medical therapy
	Complete participation in pulmonary rehabilitation program
	Clinically stable on ≤20 mg prednisone (or equivalent)/day
	Smoking cessation for ≥4 months
	Able to tolerate anesthesia/sedation-based procedure
	BMI <35 kg/m^2
Pulmonary function tests	FEV_1 15–45% predicted
	RV ≥175% predicted
	TLC ≥100% predicted
	6MWD between 100–500 m
	DLCO >20% predicted
Imaging	Emphysema on CT scan
Collateral ventilation	Target lobe must have absence of collateral ventilation

BLVR, bronchoscopic lung volume reduction; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; RV, residual volume; TLC, total lung capacity; 6MWD, 6-minute walk distance; DLCO, diffusing capacity of carbon monoxide; CT, computed tomography.

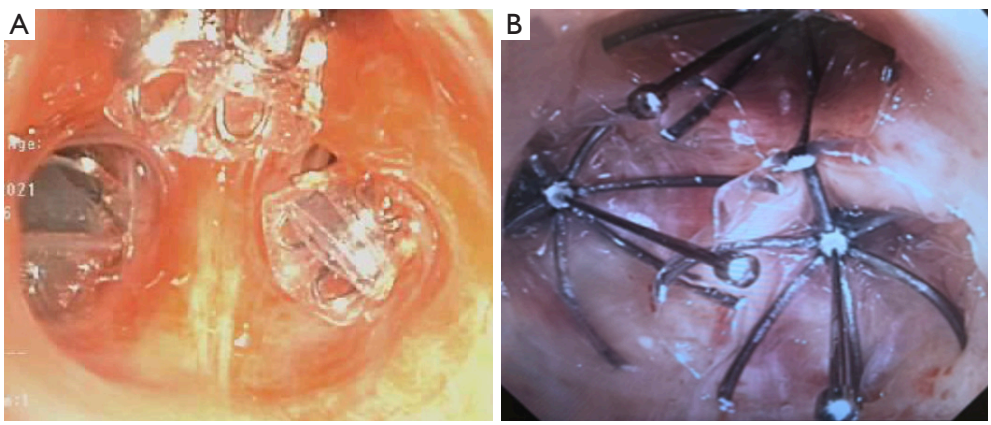

Figure 1 Endobronchial valves in the right upper lobe bronchial segments. (A) Zephyr valves. (B) Spiration valves.

which uses a balloon occlusive catheter system to measure distal airflow is recommended intra-procedurally to evaluate for the presence of collateral ventilation prior to valve insertion for patients who have been found to have partially complete (80–95%) fissures on the StratX® report (15,19). The valves are then deployed using a catheter system that extends through a 2.8 mm bronchoscope working channel.

The Spiration® Valve System recommends patients receive a HRCT scan as part of the evaluation for BLVR. This scan gets uploaded for screening by SeleCT®, a quantitative tomography system, which provides a report of emphysema severity, fissure integrity, and heterogeneity. The valve has an umbrella design (*Figure 1B*), which allows for air and mucus to drain, and is made of nitinol supporting a polyurethane cover with anchor tips at the base to prevent valve migration. The valve is also designed with a removal rod to assist with retrieval and is available in sizes from 5.0–9.0 mm. Valve sizing is determined using a

preoperatively calibrated balloon catheter that is then used during the procedure to evaluate airway diameter. Deployment requires unsheathing of the valve via a catheter that extends through a 2.8 mm bronchoscope working channel (6).

Pneumothorax and persistent air leak after BLVR

Pneumothorax occurs in up to 34% of treated patients due to compensatory overexpansion of the ipsilateral untreated lobe(s) (2,17). A meta-analysis by Labarca and colleagues, found an incidence of pneumothorax of 26% (79/293 patients) with no difference in the rate found in subgroup analysis based on emphysema distribution (20). Notably, there has been a higher prevalence of the development in pneumothorax after BLVR in recent studies, likely because of better patient selection when assessing for the absence of collateral ventilation (3,5,13). As a result, there has been debate as to whether pneumothorax post valve placement should even be considered a true complication or a treatment effect. A retrospective analysis by Gompelmann and colleagues of 70 patients with pneumothorax after BLVR found that this complication generally has no negative impact on long term clinical status (21). Another large retrospective analysis by Gompelmann and colleagues found that the occurrence of pneumothorax did not influence survival (22). The LIBERATE study also did not find differences in outcomes for patients who developed a pneumothorax compared with those that did not (2). In another multicenter study by Fiorelli and colleagues of 423 treated patients treated with endobronchial valves for severe heterogeneous emphysema (17.3% pneumothorax rate), the authors concluded that complications do not seem to have a significant impact on clinical outcomes in patients who achieve lobar atelectasis (23). Though pneumothorax is of significant concern after BLVR, Gompelmann and colleagues noted that most cases resolved either with observation or with the insertion of a chest tube. These patients with resolved pneumothorax showed substantial reductions in the target lobar volume at follow up (24). Adequate lung volume reduction with greater than 50% reduction in target lobar volume has demonstrated clinically significant benefits in hyperinflation, exercise capacity, quality of life, and airflow obstruction. An approach with complete lobar occlusion and a higher risk of pneumothorax may be superior to incomplete lobar occlusion when considering patient outcomes (25,26). These studies suggest that pneumothorax should be considered as a possible treatment effect with no bearing on outcomes or expected benefits.

Mechanism of pneumothorax after BLVR

The mechanism of pneumothorax after BLVR is secondary to the ipsilateral non-target lobe rapid expansion which can contribute to an injury in that lobe resulting in an alveolar or bronchopleural fistula (27). An alternate mechanism is a pneumothorax ex-vacuo. In this scenario, a vacuum develops in the pleural space surrounding the collapsed lobe and gas from ambient tissue and blood are subsequently drawn into the pleural space. However, in this case, the seal between the visceral and parietal pleura remains intact and patients are generally asymptomatic with pleural air expected to resolve spontaneously over time without need for chest tube insertion (28,29). A pneumothorax might also theoretically originate from a barotrauma response to the acute volume reduction in the treated lobe. In this instance, the valves may be closing the originating bronchi which may prevent an air leak. These cases of pneumothorax are expected to be less extensive on chest X-ray, and patients may also be relatively asymptomatic (17).

Risk factors for the development of pneumothorax after BLVR

Several studies have looked at identifying risk factors for the development of pneumothorax after BLVR. Such risk factors have been found to include patients with significant pleural adhesions in the target lung, significant paraseptal emphysema, large difference in volume of the target lobe compared with the ipsilateral lobe(s), high emphysematous destruction score of the ipsilateral nontreated lobe(s), and rapid onset of atelectasis (17). The risk is the highest in the first 72 hours post procedure, and hence, it is recommended that patients get admitted to the hospital for observation post procedure for 48–72 hours (23). Pneumothorax as a complication from BLVR has been seen more frequently in patients with valve placement in the left upper lobe. For example, the rates of right and left side upper lobe pneumothorax were reported as 8% and 52%, respectively in the TRANSFORM study, while 6.3% and 66.4%, respectively, in the LIBERATE study (2,3). However, comparatively, in a study by Fiorelli and colleagues in 36 procedures which were followed up for 5 years, despite left upper lobe treatment in 72%, pneumothorax complication

was only seen in 6% (30). Another risk factor to consider is whether BLVR was performed on the most diseased lobe. A *post-hoc* analysis of data from the LIBERATE trial found that patients who were not treated in the most diseased lobe had worse outcomes with a higher risk of a complex pneumothorax (which was defined as leading to death or requiring valve removal) (2).

Rupture of blebs, bullae, and fragile lung tissue in the ipsilateral non-treated lobe are believed to be important contributing causes to the development of pneumothorax (31). While clinical trials did not find an elevated pneumothorax risk in patients with paraseptal bullae or blebs, an expert panel noted that this could be influenced by selection bias as these patients were commonly excluded from participating in trials investigating valve treatment (17). Interestingly, successful cases using endobronchial valves for management of bullae have been described (32-35). Having ipsilateral surgery or interventions with resultant pleural adhesions or having de-novo pleural adhesions in the untreated lobe can lead to a higher rate of pneumothorax. A study by van Geffen and colleagues demonstrated that patients with a higher pleural adhesion score based on a pre-intervention HRCT suffered a higher rate of pneumothorax after BLVR (36). Authors from this study recommend that a prolonged observation time in the hospital or serial chest X-ray may be helpful. The presence of pleural adhesions, however, has not consistently shown to be associated with a higher rate of pneumothorax as noted by Gompelmann and colleagues in the post-hoc analysis of the LIBERATE trial (37). Nevertheless, an expert panel does regard the presence of pleural adhesions an important risk factor after valve treatment (17). A prospective study evaluating pleural adhesion using ultrasound or HRCT may be beneficial.

The risk of pneumothorax is reportedly higher when upper lobes are treated in general when compared to the lower lobes. Two trials demonstrated a nonsignificant trend toward more pneumothoraces when treating upper lobes as opposed to lower lobes (13,26). However, there was no consensus within the expert panel regarding this possible risk factor (17).

Gompelmann and colleagues identified low attenuation volume of the ipsilateral untreated lobe, ipsilateral untreated lobe volume/hemithorax volume ratio, emphysema type, pleural adhesions, and RV as significant predictors of pneumothorax (37). However, no single risk factor has been identified that could influence decision making as to whether a patient should be treated or excluded from valve therapy. A thorough work up during the patient selection process and identifying risk factors such as a high destruction score in the non-treated ipsilateral lobe, target lobe volume to total lung volume ratio, RV, structural deformities as described would be helpful to predict outcomes and guide physicians in discussion with patients regarding proceeding with BLVR.

Reducing risk of pneumothorax after BLVR

In a multicenter, randomized, sham procedure controlled double-blind trial, bilateral-partial lobar bronchial valve occlusion of both upper lobes of patients with severe emphysema was found to have shifted lung volume from the treated lobes to the untreated lobes to a significant degree. Though device safety was confirmed and pneumothorax was found to be reduced, this trial did not achieve clinically meaningful results (38). Similarly, in a randomized, blinded, and sham procedure-controlled study Ninane and colleagues demonstrated that incomplete occlusion was safe without reports of pneumothorax but not effective in the majority of patients (39). In a retrospective study, Egenod and colleagues found that a two-staged approach to BLVR can lead to progressive lung volume reduction as well as reduced pneumothorax risk. Initially, valves were placed in all but the most proximal segment or sub-segment with the remaining segment treated in a follow up procedure with only 4 of 58 (7%) of treated patients suffering a pneumothorax. However, in this study, only 31% of patients had complete atelectasis (40). To date, there is no definitive BLVR procedural modification that is recommended to reduce pneumothorax risk.

Physical strain and cough have been hypothesized as possible causes for spontaneous pneumothorax. One retrospective analysis by Herzog and colleagues reported that cough suppressants and bed rest for 48 hours post BLVR reduced the rate of post procedural pneumothorax from 25% to 5% (41). However, there is limited data to routinely prescribe this modified medical therapy for all patients post BLVR.

Management of pneumothorax after BLVR

Post procedural care is critical after BLVR and includes hospitalization for at least 3 nights, appropriate staff training for pneumothorax recognition, serial follow up chest X-rays, patient/caregiver education, and an emergency pneumothorax kit available on the ward with all necessary chest tube placement supplies (17). Valipour and colleagues as well as van Dijk and colleagues have developed expert

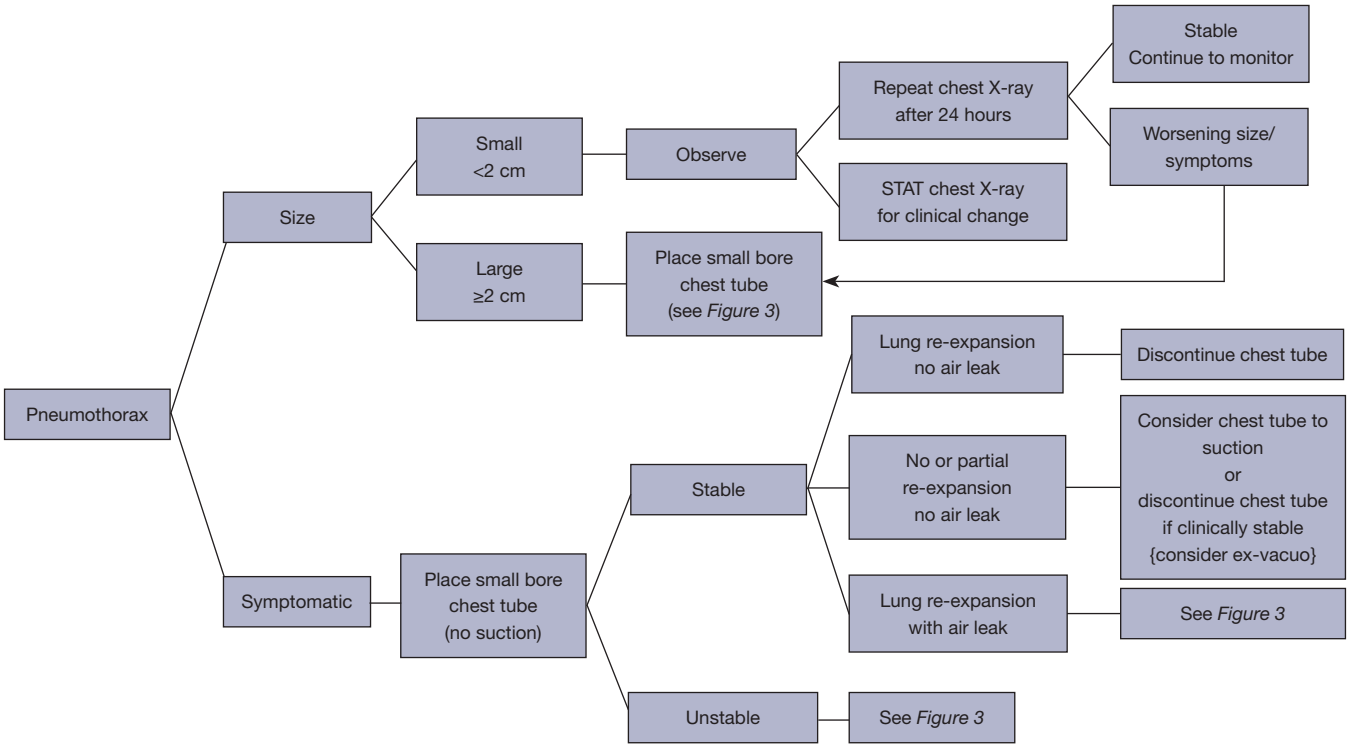

Figure 2 Pneumothorax post BLVR management algorithm. BLVR, bronchoscopic lung volume reduction.

statements and suggest treatment algorithms for patients who develop pneumothorax after BLVR (17,42). A summary of these recommendations can be reviewed in *Figures 2,3*. In general, first, the size or extent of the pneumothorax is assessed based on the amount of pleural separation. A pneumothorax is determined to be small if there is less than 2 cm of pleural separation or large if there is 2 or more cm of pleural separation. Additionally, a functional assessment is made, whether the patient is symptomatic or asymptomatic. Clinical observation is recommended if a pneumothorax is small and the patient is asymptomatic. Serial chest X-rays to monitor for any progression is recommended in this case. If a pneumothorax is enlarging, or clinical symptoms deteriorate, small-bore chest tube placement is suggested (though, a larger bore chest tube may be required if respiratory failure or subcutaneous emphysema result). A follow up CT scan of the chest may be helpful to localize and evaluate the extent of a pneumothorax as well as guide further treatment options or manage aberrant chest tube placement (17,42).

Management of persistent air leak after BLVR

Should a patient develop a post BLVR persistent air leak (considered when an air leak is present for a week or more after chest tube placement), the decision must then be made as to whether one or more bronchial valves should be removed. By removing one or more valves, the target lobe could re-expand with pleural apposition and promote healing of an alveolar or bronchopleural fistula. In the case of valve removal, the most proximal one is suggested to be removed since this will improve airflow throughout the lobe distal to the valve allowing at least partial lobe re-expansion. Additionally, the most proximal valve is likely to be anatomically easiest to replace. If the air leak stops after valve removal and does not reappear after discontinuation of the chest tube, valve replacement can be considered 6–8 weeks after chest tube removal (24,42). If a persistent air leak for at least one week after valve removal occurs, mechanical or chemical pleurodesis, use of a Heimlich valve, or surgical approach should be considered (17,42). *Figure 4* demonstrates a case where a left sided pneumothorax developed 7 days after successful BLVR of the left upper lobe. Due to persistent air leak and substantial respiratory symptoms with development of severe subcutaneous emphysema, all the valves were ultimately removed with resolution of the pneumothorax, air leak, and subcutaneous emphysema.

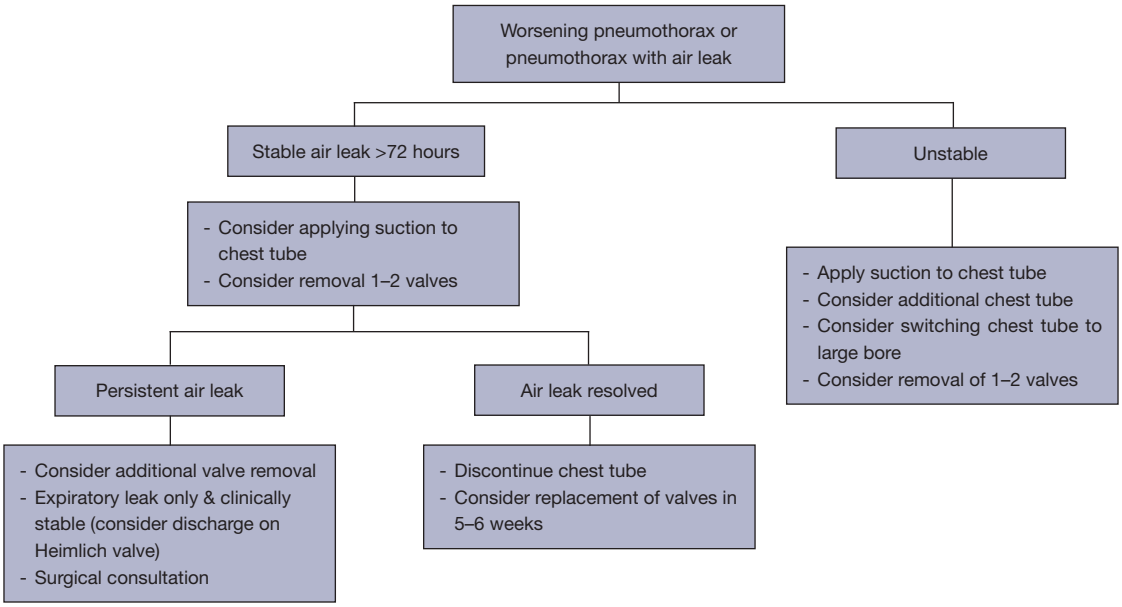

Figure 3 Worsening pneumothorax or persistent air leak post BLVR algorithm. BLVR, bronchoscopic lung volume reduction.

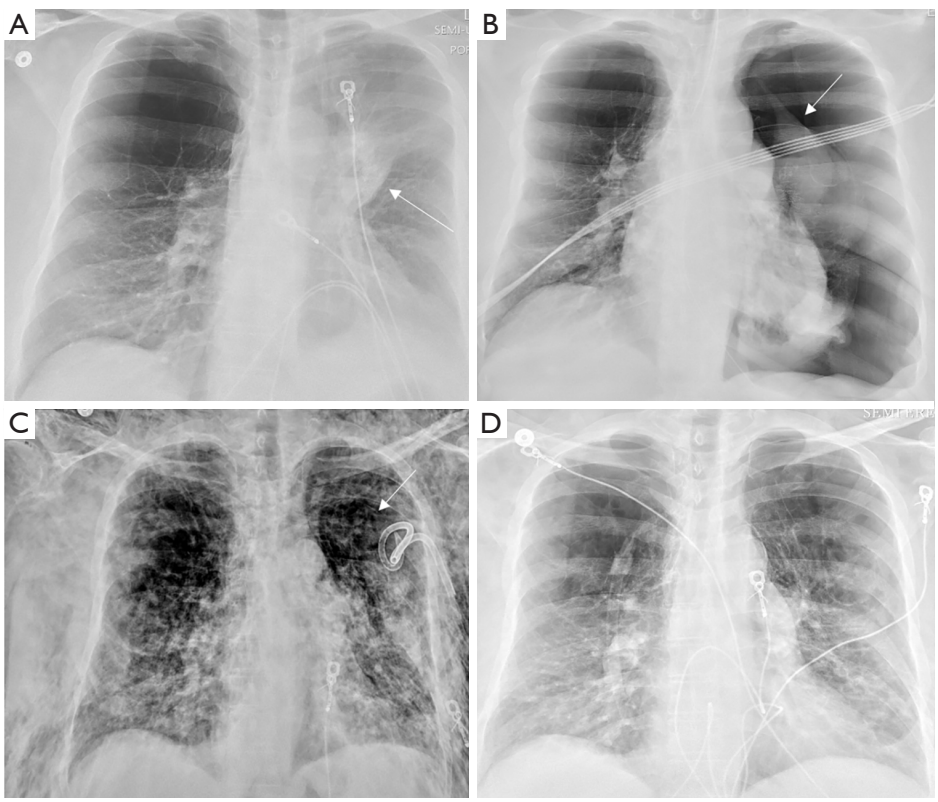

Figure 4 Case of BLVR resulting in pneumothorax. (A) Chest X-ray with left upper lobe atelectasis (arrow) after BLVR. (B) Chest X-ray with left-sided pneumothorax (arrow) 7 days after BLVR. (C) Chest X-ray demonstrating severe subcutaneous emphysema with pneumothorax (arrow) after BLVR with chest tube in place and persistent air leak. (D) Chest X-ray after all valves removed with resolution of pneumothorax and subcutaneous emphysema. BLVR, bronchoscopic lung volume reduction.

Follow-up after BLVR

Bianchi and colleagues discovered that participation in pulmonary rehabilitation after BLVR yielded further improvement in exercise tolerance (43). To monitor progress after BLVR, quality of life questionnaires, repeat lung function tests with 6-minute walk testing, chest X-ray or CT scan are typically ordered. Additionally, patients are recommended to continue their prior COPD routine with supplemental O_2 if needed, bronchodilator/respiratory treatments, exercise, and preventive care (including vaccinations) (44).

Conclusions

BLVR has been found to be a safe and reversible procedure which is effective at improving the lung function, symptoms, quality of life, and possibly even mortality of patients affected by severe emphysema. Additionally, the use of valves for BLVR is not prohibitive for future LVRS or lung transplant. Pneumothorax is the most common and concerning complication after BLVR and there are recommended strategies to evaluate and manage this occurrence. Initially, careful preprocedural evaluation of patients including assessment of risk for the development of complications is an important part of patient selection. Post valve care with hospitalization for at least 3 nights with easy access to chest tube supplies is critical should a pneumothorax develop during this period. Patients and hospital staff should be educated in ensuring prompt identification should such a complication arise. Finally, managing a BLVR related pneumothorax and persistent air leak requires a thoughtful and stepwise approach to both avoid and mitigate this complication to achieve the best result for the patient. Expert statements have been published to help guide clinicians' assessment and management of this post procedural complication. Further research is needed to help identify and manage risk factors to help reduce the development of pneumothorax after BLVR.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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