Successful use of endobronchial valve for persistent air leak in a patient with COVID-19 and bullous emphysema

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SUMMARY
Patients with SARS-CoV-2 pneumonia can suffer from pneumothorax and persistent air leak (PAL). The pneumothorax occurs with or without pre-existing lung disease. PAL refers to air leak lasting more than 5–7 days and arises due to bronchopleural or alveolopleural fistula. The management of PAL can be challenging as a standard management guideline is lacking. Here we present the case of a 42-year-old smoker with COVID-19 who presented to the hospital with fever, cough, acute left-sided chest pain and shortness of breath. He suffered from a large left-sided pneumothorax requiring immediate chest tube drainage. Unfortunately, the air leak persisted for 13 days before one-way endobronchial valve (EBV) was used with complete resolution of the air leak. We also review the literature regarding other cases of EBV utilisation for PAL in patients with COVID-19.

BACKGROUND
Endobronchial valve (EBV) is a bronchoscopically inserted one-way valve that prevents the airflow to the distal airways while allowing exhalation and proximal drainage of airway secretion. In the USA, EBV is approved by the Food and Drug Administration (FDA) for bronchoscopic lung volume reduction in a select group of patients with chronic obstructive pulmonary disease (COPD) and severe heterogeneous emphysema.[1 2] Additionally, EBV can be used for 'compassionate use' for postlung resection persistent air leak (PAL).[3] Although not technically approved by the FDA, there are many reports of 'off label' EBV use for PAL due to bronchopleural fistula (BPF) or alveolopleural fistula (APF) in the setting of primary or secondary spontaneous pneumothorax. The definition of PAL is somewhat arbitrary. Most clinicians would agree that an air leak lasting more than 5–7 days despite drainage of the pleural space would be an acceptable time frame.[4]

SARS-CoV-2 is the causative organism for COVID-19.[5] Although most patients suffer from mild disease, lower respiratory tract infection with SARS-CoV-2 can lead to acute respiratory distress syndrome with significant mortality.[6] Among different manifestations of pleural involvement by SARS-CoV-2, pneumothorax is potentially life-threatening.[7 8] Pneumothorax can occur in patients with or without pre-existing lung disease and the presence or absence of mechanical ventilation.[9 10] We report the case of a young man with SARS-CoV-2 pneumonia who developed secondary spontaneous pneumothorax (SSP) with PAL that was successfully treated with EBV placement. We also review the literature to identify additional cases where EBV was used for a similar indication in patients with COVID-19.

CASE PRESENTATION
A 42-year-old man presented to the hospital with left-sided chest pain that started approximately 2 hours ago. He was exposed to a patient with COVID-19 about 2 weeks ago and had been quarantining at home. He has been suffering from fever, rhinorrhoea, cough, sputum production and shortness of breath for the past week. The patient developed acute severe left anterior chest pain after a bout of vigorous coughing, prompting the visit to the emergency department (ED). He had no medical history and was on no medication at home routinely. He was an active smoker with a 40-pack year history of smoking.

In the ED, the patient was in visible distress from the pain. His vital signs were as follows: blood pressure 134/90 mm Hg, pulse 112 beats per minute, temperature 37.1° C, respiratory rate 27 breaths per minute, and oxygen saturation 84% on room air that corrected to 92% with 6 L oxygen via nasal cannula (NC). Chest auscultation revealed absent breath sound in the left hemithorax and diffuse wheezing on the right.

INVESTIGATIONS
The laboratory work-up showed mild leucocytosis and evidence of haemoconcentration. A portable chest radiography revealed large left-sided pneumothorax (figure 1A). A large-bore (36 Fr) chest tube was emergently inserted with a significant improvement of the pneumothorax (figure 1B). Left lung infiltrate with retrocardiac dense consolidation was also seen. Air leak was noted during inspiration, expiration and forced expiratory manoeuvre, and −20 cm of water suction was applied through the chest tube. Rapid antigen test for SARS-CoV-2 and reverse transcriptase-PCR were both positive.

TREATMENT
The patient was started on remdesivir, dexamethasone and empiric antibiotics.

OUTCOME AND FOLLOW-UP
Over the next 7 days, his oxygen requirement improved, requiring 2 L oxygen via NC. However, attempts to manage the air leak with only water seal

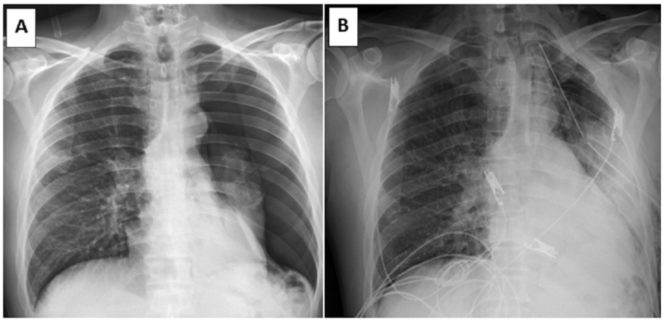

Figure 1 Portable chest X-ray demonstrating large left-sided pneumothorax with collapsed lung without any evidence of tension (A). Chest X-ray following chest tube insertion revealed expansion of the lung with small residual pneumothorax (B). Dense retrocardiac consolidation and mid-lung zone infiltrate were also seen.

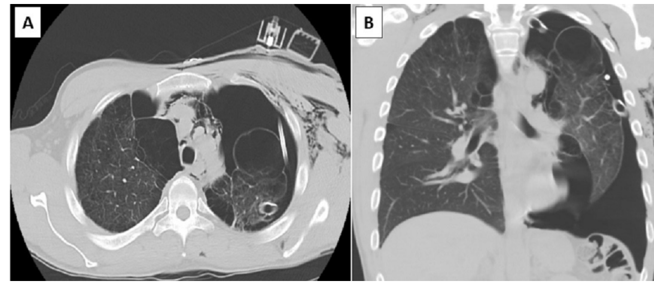

Figure 3 CT of the chest in axial (A) and coronal (B) views showing bilateral bullous emphysema in the lung apices. Persistent large left-sided pneumothorax, pneumomediastinum and subcutaneous emphysema were clearly evident.

drainage worsened pneumothorax and subcutaneous emphysema. Two additional small-bore chest tubes (thoracic vents) were inserted to assist with the pleural space drainage, but the pneumothorax persisted (figure 2). A CT of the chest revealed large left-sided pneumothorax despite three pleural drainage catheters. Bilateral apical bullous disease with emphysema was also noted (figure 3). The occurrence of bullous emphysema was attributed to prolonged smoking. Twelve days after his hospital admission, the patient still had PAL with expiration and coughing, and the decision was made to use EBV to treat the BPF. Given the patient's significant bullous disease and recent SARS-CoV-2 pneumonia, a video-assisted thoracoscopic surgery (VATS) or thoracotomy for bullectomy or partial lung resection was deemed to be high risk.

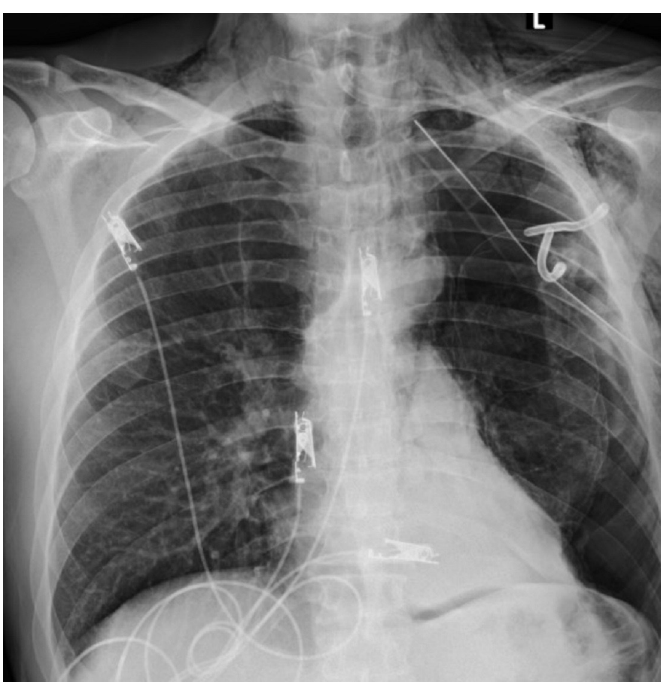

Figure 2 Anteroposterior chest X-ray showing large left-sided pneumothorax. The chest radiography was performed while the patient was on water seal drainage without any suction. One large-bore chest tube and two additional thoracic vents were inserted in the pleural space at this time. Significant subcutaneous emphysema was also present.

The patient underwent EBV placement on day 13 of PAL. The procedure was performed under general anaesthesia. A significant air leak was noted in the water seal drainage system with positive pressure ventilation before EBV deployment. Using a Fogarty balloon catheter, the site of the air leak was first identified. Occlusion of the left main stem or left upper lobe bronchus resulted in complete resolution of the air leak. However, occlusion of the segmental bronchi of the left upper lobe was not successful in abolishing the air leak. After appropriate size determination, three EBV (spiration valve system (SVS); SVS Olympus Respiratory America, Redmond, Washington, USA), all 9 mm, were deployed in the apicoposterior, anterior and lingular bronchus (figure 4). The air leak resolved completely. Within the next 36 hours, all pleural drainage catheters were removed (figure 5). The patient was discharged home 2 days after the procedure. The patient did well after discharge. The EBVs were removed 6 weeks later without any complications. Chest X-ray immediately following the procedure revealed partial expansion of the left upper lobe with residual areas of atelectasis (figure 6).

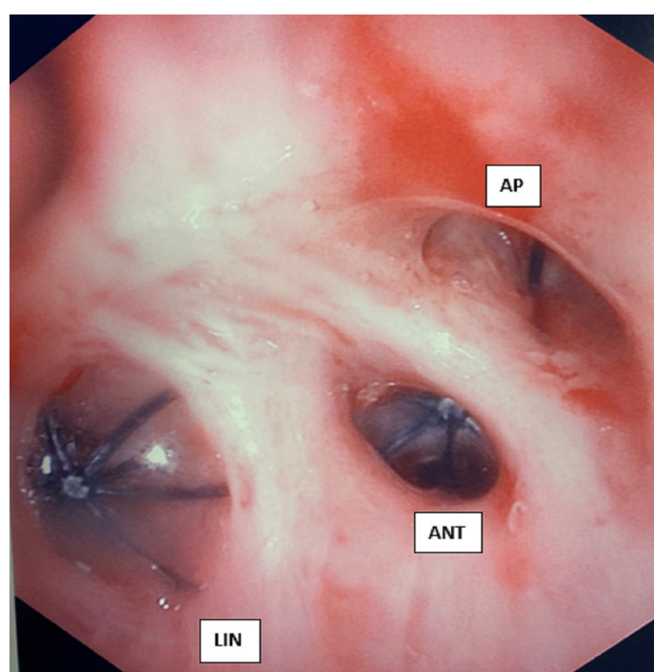

Figure 4 Bronchoscopic view following endobronchial valve (spiration valve system) insertion in the left upper lobe. ANT, anterior segment; AP, apicoposterior segment; LIN, lingular segment.

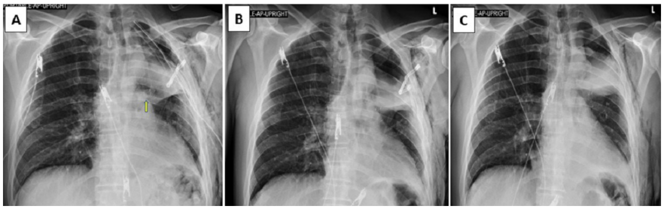

Figure 5 Serial chest radiography following endobronchial valve placement. Chest X-ray, 1 hour post procedure, revealed collapsing left upper lobe with small pneumothorax (A). The endobronchial valves are indicated by the green arrow. Chest X-ray 4 hours following removal of the large-bore chest tube (approximately 24 hours after the procedure) showed atelectatic left upper lobe, loss of lung volume and stable pneumothorax (B). Chest X-ray following removal of all chest drainage catheter (30 hours after procedure) demonstrating stable pneumothorax and improved subcutaneous emphysema (C).

DISCUSSION

We have reported the case of a young man with SSP in the setting of COVID-19 and PAL lasting 13 days who improved promptly following EBV placement. Our literature search identified three more cases where EBV was successfully used for PAL in patients with COVID-19 (table 1).[11–13]

All reported patients were men in their fifth and sixth decades of life. All patients had unilateral pneumothorax, with two patients having involvement of the right side.[12 13] All patients required tube thoracostomy for management of the pneumothorax. One patient required more than one pleural drain.[11] The air leak was localised to one lung lobe in two cases.[11 12] The other patient had bilobar involvement.[13] SVS was used in two individuals, whereas the other patient received Zephyr valve. The number of deployed valves ranged from 1 to 6. The patient who required six valves had bilobar involvement and underwent two bronchoscopy sessions for valve deployments.[13] All authors reported a significant improvement in air leak following the procedure. In our patient, we observed complete resolution of the air leak at the completion of the procedure, which was not reported in other studies. However, a complete resolution of air leak within a few days of bronchoscopy was reported in all patients. Two patients were discharged within a week of the procedure.[11 12] The exact time of discharge was not specified for one patient.[13] No immediate complications were reported in any patients. Migration of the Zephyr valve on routine bronchoscopy after 1 month occurred in one patient. This patient developed recurrent pneumothorax and eventually required VATS and pleurodesis.[11]

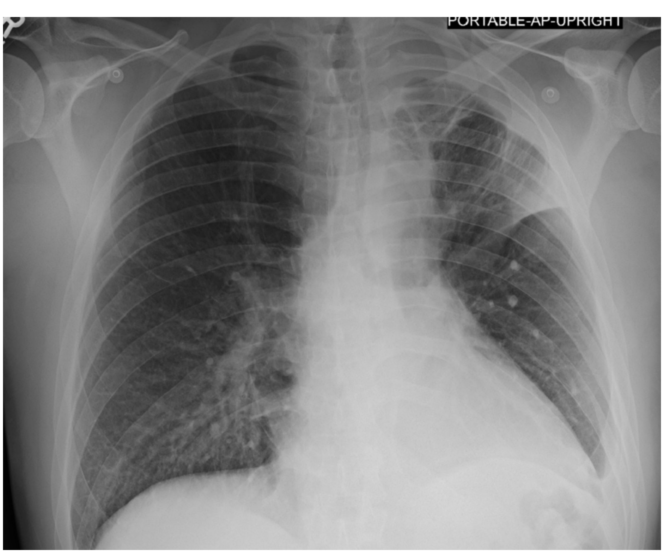

Figure 6 Portable chest X-ray following removal of the endobronchial valves revealed partial expansion of the left upper lobe with areas of streak-like opacities consistent with atelectasis. There was no pneumothorax.

In addition to affecting pulmonary parenchyma, SARS-CoV-2 can also cause pleural complications. Commonly reported pleural abnormalities include pleural thickening, pleural retraction, pleural effusion and pneumothorax.[14 15] Moreover, pneumomediastinum and subcutaneous emphysema in the absence of pneumothorax can also occur.[16] Although initially thought to be a rare complication (approximately 1% of patients), the incidence of pneumothorax is much higher in critically ill patients with COVID-19.[14] Based on recent studies, the incidence is approximately 10%.[7 14] Pneumothorax is commonly seen in middle-aged men, predominantly affecting the right side, occurring in both mechanically ventilated and non-ventilated patients. Smoking status has not been implicitly associated with a higher risk.[16 17] The occurrence of pneumothorax may or may not be independently associated with higher mortality.[7 16–18]

The term SSP describes the occurrence of spontaneous pneumothorax in a patient with pre-existing lung disease. Virtually any lung disease can be implicated in the pathogenesis of SSP, but the most common cause is COPD.[19 20] Air leak is not an uncommon problem in patients with SSP. Although the majority of air leaks resolve spontaneously, nearly 40% of patients suffer from PAL.[21] PAL occurs due to an abnormal connection between the pleural space and airways (BPF) or alveolus (APF). The pathogenesis of pneumothorax in patients with SARS-CoV-2 pneumonia is unclear. There is likely a contribution from viral invasion, inflammation of the pulmonary parenchyma and microangiopathy, as well as barotrauma in the setting of mechanical ventilation. The pulmonary parenchymal involvement is predominantly subpleural with SARS-CoV-2. The anatomical proximity can lead to damage to the adjacent visceral pleura, leading to the formation of APF, pneumothorax and subsequently PAL.[14] Like our patient, one other reported individual also suffered from bullous emphysema.[11] It is difficult to ascertain the individual contribution of the emphysema or SARS-CoV-2 pneumonia to the pathogenesis of APF in these patients.

The management of PAL can be challenging. Uncertainty arises due to the lack of a predictive model that can identify patients in whom a resolution of air leak is likely if followed conservatively. As a result, management strategies have been highly variable among different centres. Two consensus guidelines have recommended early consideration of surgery for air leak persisting beyond 4 days.[22 23] It is crucial to emphasise that these cut-off values are essentially arbitrary and expert opinions, and no solid evidence exists to support them. In fact, resolution of air leak in SSP was reported in up to 80% of patients when they were managed conservatively for 14 days.[21] However, there are some suggestions that multiple pleural interventions and a delay in surgery may detrimentally affect surgical outcomes, such as longer postoperative hospital stay.[24] Moreover, the development of empyema or pleural adhesion may make VATS impossible, requiring thoracotomy, which is inherently more invasive.[24] Therefore, an individualised approach to PAL may be beneficial for patients. For example, patients in whom the degree of air leak shows gradual improvement may be managed expectantly rather than early surgery. On the other hand, patients on mechanical ventilation with non-resolving large air leaks could be an excellent candidate for early surgery. A relatively

Table 1 Reported cases of endobronchial valve for persistent air leak in patients with COVID-19

Author	Age	Gender	Comorbidity	Site of pneumothorax	Present on admission	Tension	Pleural drainage	Number of pleural drain	Mechanical ventilation	Duration of air leak (days)	Site of BPF	Type of valve	Number	Postprocedure air leak	Outcomes	Complications
Szewczyk *et al*[11]	69	Male	Severe bullous emphysema	Left	Yes	No	Tube thoracostomy	2	Yes, developed during the course of illness	17	LUL	Zephyr	3	Reduced from grade 5 to 1.	Discharged 22 days after initial chest tube placement.	Migration of the valve in the anterior segment of LUL after 1 month. Recurrence of pneumothorax; the patient underwent VATS and pleurodesis.
Talon *et al*[12]	64	Male	Recurrent right-sided empyema	Right	Yes	No	Tube thoracostomy	1	No	NS	RML	Spiration	1	Air leak reduced by 60%–70%.	Discharged 1 week after the procedure. Chest tube removed after 6 weeks. EBV removed after 13 weeks.	None.
Pathak *et al*[13]	55	Male	None	Right	No, developed on day 10	No	Tube thoracostomy	1	Yes	31	RML and RLL	Spiration	6 RML: 2; RLL: 4 (performed in 2 bronchoscopy sessions; 4 in the first, 2 later)	Complete resolution after a few days of the second bronchoscopy.	The patient survived the hospitalisation. Required tracheostomy that was decannulated. The patient was ambulatory after 3 months without dyspnoea or oxygen desaturation.	None.
Our case	42	Male	Bullous emphysema	Left	Yes	Yes	Tube thoracostomy	3	No	13	LUL	Spiration	3	Complete resolution of air leak. Small apical pneumothorax.	The patient was discharged 2 days after the procedure.	None.

BPF, bronchopleural fistula; EBV, endobronchial valve; LUL, left upper lobe; NS, not specified; RLL, right lower lobe; RML, right middle lobe; VATS, video-assisted thoracoscopic surgery.

new approach in the management of PAL is the use of EBV. EBV deployment is minimally invasive and is achieved by flexible bronchoscopy. The two available EBV systems are SVS and Zephyr. Both EBVs have shown good results controlling air leaks in small cohorts and case reports.[4 25 26]

EBVs are one-way valves that prevent airflow to the distal airways while allowing for exhalation and drainage of airway secretion from those airways. Due to its inherent mechanism of action, EBV appears to be an excellent option for the treatment of PAL. However, the valves are expensive and may not be effective in all patients unless carefully chosen.[27] The efficacy of the EBV to completely abolish or significantly reduce air leak depends on appropriate localisation of the airway(s) and estimation of collateral ventilation. The localisation of the affected airway is generally performed by 'balloon occlusion technique'. A Fogarty balloon catheter is bronchoscopically introduced to progressively occlude the main stem, lobar, segmental and subsegmental airways to isolate the culprit airway. It may take several respiratory cycles for the air leak to cease completely. Sometimes, a partial improvement may be seen. Reduction of air leaks by more than 50% could be clinically beneficial. Unlike bronchoscopic lung volume reduction, routine assessment of collateral ventilation prior to EBV deployment is not routinely performed in patients with PAL.[28] However, the persistence of air leak following occlusion of lobar bronchus could be suggestive of incompleteness on ipsilateral major fissure and presence of collateral ventilation. BPF or APF affecting more than one lung lobe could also be responsible. A second method of BPF localisation using capnography has also been reported.[29] In this technique, a catheter is passed through the working channel of the bronchoscope and sequentially placed in each segment of the lung after the chest tube is opened to the atmosphere. A capnograph is attached to the proximal hub of the catheter to measure end-tidal carbon dioxide. If the catheter is placed in the airway with BPF, the capnogram demonstrates quick flattening of the curve to a straight line. This technique has been used to successfully localise the affected airway in patients after failed 'balloon occlusion technique'.[30] Identification of BPF by methylene blue has been practised for many decades but rarely used for PAL.[31]

Air leak following lung resection or lung volume reduction surgery is also a common occurrence. The incidence of air leak on the first postoperative day has varied between 24% and 48%.[32–35] The incidence of PAL (after 5 days), however, is approximately 10%.[36] The risk of air leak varies depending on the type of lung resection.[33] A number of risk factors for PAL have also been identified. These include increased age, female gender, COPD or other underlying lung disease, low forced expiratory volume in the first second and carbon monoxide diffusion capacity, pleural adhesion, and chronic steroid use, among others.[37–39] PAL is associated with increased length of hospital stay and higher morbidity and mortality. Due to its efficacy in small cohorts, the FDA approved humanitarian use of EBV for postlung resection PAL in 2008.[40]

Several studies prior to the COVID-19 pandemic demonstrated high efficacy of EBV for PAL in non-lung resection patients. The effectiveness has ranged from 57% to 96% in complete resolution or a significant improvement of the air leak.[4] Based on our review in patients with COVID-19, the EBV appears to be efficacious for PAL, with or without pre-existing emphysema. As many of these patients are critically ill, they may not tolerate a thoracotomy well and EBV could potentially be considered prior to surgical intervention.

One unique risk associated with bronchoscopic EBV placement in patients with COVID-19 is the risk of aerosolisation and dissemination of SARS-CoV-2 during bronchoscopy. However, based on recent data, the risk of SARS-CoV-2 transmission among healthcare workers during bronchoscopy appears to be low when appropriate personal protective equipment is used.[41] Other complications include worsening hypoxia, which was not observed in our patient or the other reported cases. Valve migration, atelectasis and empyema are rare complications.[31] Despite being expensive, cost analysis studies have shown EBV to be a cost-effective procedure as well.[3 4] Although we were able to localise the BPF to the left upper lobe in our patient, it is important to emphasise that appropriate localisation may be challenging even with the use of the 'balloon occlusion technique', at least for some patients. These patients may require additional EBVs to occlude airways beyond the segmental bronchi in a single lung lobe, further increasing the cost of the procedure.

EBV could potentially be an exciting alternative to surgical intervention for PAL. Bronchoscopic EBV deployment is minimally invasive and associated with a high success rate for resolution of air leak. With the ongoing COVID-19 pandemic and a significant number of critically ill patients developing pneumothorax, the use of EBV may become a crucial technique to manage the air leak as surgical intervention may pose a significant perioperative risk. Prospective trials with a larger patient population will provide more definitive data regarding the cost-effectiveness of this technique.

Patient's perspective

I was in the hospital for 13 days waiting to go home to my kids. The procedure allowed me to go home within 2 days. I couldn't ask for anything more.

Learning points

- Pneumothorax and persistent air leak (PAL) could complicate SARS-CoV-2 pneumonia.
- Endobronchial valve (EBV) appears to be effective for bronchopleural fistula in patients with COVID-19.
- EBV should be considered for PAL prior to surgical intervention in patients with COVID-19, given the minimally invasive nature of the procedure.

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