Review Article

Minimally invasive persistent air leak management

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Abstract: Persistent air leak (PAL) management is a complex clinical entity with a variety of underlying etiologies and treatment options. Imprecise use of nomenclature associated with this condition has confounded the situation. Guidelines on the subject are antiquated and do not include modern therapeutic modalities. Bronchoscopic options, namely endobronchial valves, have revolutionized PAL treatment in patients who are poor surgical candidates. The paucity of high-quality data has prohibited revision of older guidelines. Development of evidence-based treatment algorithms is necessary to advance the quality and consistency of care for this serious clinical problem.

Keywords: Endobronchial valves; airway valves; persistent air leak (PAL); bronchoscopy; pneumothorax

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Introduction

Management of persistent air leaks (PAL) is a challenging issue for thoracic surgeons and interventional pulmonologists. The multitude of underlying etiologies means each instance is unique and must be addressed accordingly. Air leak localization is often challenging and requires a meticulous approach. Antiquated guidelines fail to address contemporary, minimally invasive therapeutic modalities, many of which are bronchoscopic in nature. This has led to wide variation in treatments depending on local expertise and experience.

Definitions

PALs may be caused by an alveolar pleural fistula (APF) or a bronchopleural fistula (BPF). These terms are often used interchangeably but represent distinct entities. An APF refers to a pathologic communication between the subsegmental bronchus or a more distal portion of the airway and the pleural space. Conversely, when the source of air is at the segmental bronchus or more proximal, it is termed a BPF. Management is generally similar for these two entities, so precision in nomenclature is usually not critical. Regardless of where the defect is located, the end result is the same—continued entry of air (i.e., air leak) into the pleural space.

An air leak is indicated when there are bubbles in the water seal chamber of a collection system that is connected to a pleural drain. The water seal chamber typically contains an air leak meter, represented by numbered columns, that indicates the degree of an air leak. The higher the numbered column through which bubbling occurs, the larger the air leak.

When an air leak continues beyond 5–7 days, it is classified as being persistent by convention. This threshold originates from surgical experience following lung resection, where several days of air leak is not unexpected. Fortunately, continuation of an air leak only occurs in a minority of cases.

Classification of severity

The grading system for air leaks is based on the amount of

Table 1 Cerfolio classification of air leaks

Grade 1, FE
During forced expiration only, typically when asking the patient to cough
Grade 2, E
Expiration only
Grade 3, I
Inspiration only
Grade 4, C
Continuous bubbling present in the air leak chamber during both inspiration and expiration

leak and the phase of respiration during which it occurs. The most cited classification of air leak severity was developed by Robert Cerfolio (*Table 1*) and was designed for the post-operative setting (1). A continuous air leak occurs during both inspiration and expiration and represents the most severe form of leak. Leaks that occur only during inspiration are unusual. Expiratory leaks are the most common type of leak and generally evolve to occur only during forced expiration as the fistula heals.

The advent of digital chest drainage systems has enabled more precise quantification of air leak severity, supplanting the need for subjective estimation based on the observation of bubbles in sequentially numbered columns of traditional collection devices (2). These devices display air flow into the collection system and the pleural pressure difference in real time. A chest tube can generally be safely removed when the air leak has decreased to <20 mL/min (3). Studies have demonstrated earlier chest tube removal and hence decreased hospital length of stay (LOS) with these devices (4,5). As affordability improves, increased utilization will hopefully lead to improved PAL management in the form of more expedient chest tube discontinuation.

Incidence & etiology

The incidence of PALs is variable. Potential etiologies include pulmonary infections, mechanical ventilation, chest trauma, thoracic surgery, and pneumothorax. Right-sided pneumonectomy and secondary spontaneous pneumothorax are associated with higher rates of PAL development than their counterparts (6,7). It can occur in up to 26% of cases following lobectomy and in 24–46% of lung volume reduction surgery (LVRS) cases (8-12). A leak of >50 mL/min on the digital drainage device was predictive of developing a PAL in patients undergoing lobectomies (13). The type of operation and surgical technique are also major determinants. The incidence rates following transthoracic needle aspiration and transbronchial biopsies are unknown but likely exceedingly low given the low rate of clinically significant pneumothoraces in these two procedures. The rate of PAL with mechanical ventilation is unknown in the low tidal volume era. An older study found a 2% incidence of PAL in patients on mechanical ventilation, but the average tidal volume of patients in the study was 14.6 mL/kg (14). Such large tidal volumes are rarely, if ever, employed today, even in non-acute respiratory distress syndrome (ARDS) patients.

Risk factors

Risk factors largely depend on the underlying etiology and vary among surgical lung resection procedures. Risk factors for the development of PAL with spontaneous pneumothorax include underlying lung disease (i.e., secondary pneumothorax), older age, and large bullae diameter (15). With LVRS, lower DLCO and forced expiratory volume in one second (FEV1), along with marked pleural adhesions, and upper lobe predominant and diffuse emphysema all predispose to PAL development (12). Numerous risk factors have been identified for PAL development following lobectomy as follows (6,8,9,16-21):

(I) COPD;
(II) Female sex;
(III) Lower FEV1;
(IV) Smoking history;
(V) Diabetes mellitus;
(VI) Chronic steroid use;
(VII) Residual cancer at the resection margin;
(VIII) Post-operative positive pressure ventilation;
(IX) Neoadjuvant chemotherapy and/or radiation.

Complications

In post-LVRS patients, thirty-day mortality was similar in those with and without an air leak (12). PAL still remains a significant source of morbidity, resource utilization, and health care expense. Susceptibility to pneumonia is increased, along with readmission rate to the intensive care unit (ICU) and hospital LOS (9,12). After lobectomy, the average LOS for a non-PAL and PAL patient is 7.9±1.44 days and 13.7±3.92 days, respectively (8,12). After LVRS,

Table 2 Anecdotal approaches to persistent air leak

Method	Type of study (no. of patients)	% with air leak improved or resolved	Complications
Fibrin sealant (27)	3 case reports (1 patient each)	100%	None
Platelet gel (28)	Case report (n=1)	100%	None
Ethanolamine (29,30)	2 case series (n=15 & 5)	80%, 100%	Fever, chest pain, pulmonary infiltrates, and hydropneumothorax. None in the second case series
Metal coils (32)	Case series (n=5)	80%	None
Watanabe spigots (31)	Case series (n=60)	97%	Pneumonia, dyspnea, fever
Laser (33)	Case series (n=13)	85%	None
Synthetic hydrogel (34)	Case series (n=22)	86%	Gel expectoration, hypoxia

Adapted with permission from Dugan *et al*. (35).

the average LOS for a non-PAL and PAL patient is 7.6±4.4 and 11.8±6.5 days, respectively (12).

Guidelines

The variable management strategies for PALs stem from the paucity of up-to-date guidelines on the subject. The American College of Chest Physicians (ACCP) 2001 guidelines on the management of spontaneous pneumothorax recommends surgical evaluation for pleurodesis via video-assisted thoracoscopic surgery (VATS) and actually advises against bronchoscopic treatment (22). The 2010 British Thoracic Society (BTS) guidelines on pleural procedures recommends early thoracic surgical opinion (23). Management of patients who are poor surgical candidates is simply not addressed, creating a conundrum for clinicians and highly variable practice patterns.

Treatment

Volume, duration, and trend are the primary factors that must be considered when evaluating an air leak. A larger leak that has been present longer and is not diminishing has a low likelihood of resolution without intervention (24). Traditional management included options such as prolonged thoracostomy tube drainage with or without continuous wall suction, flutter valve, VATS with parenchymal stapling or mechanical pleurodesis, and thoracotomy if VATS was not feasible. For patients on a mechanical ventilator, adjustments can also be made to reduce airflow through the fistula. These include decreasing the inspiratory time, positive end-expiratory pressure (PEEP), and tidal volume (25). These changes, along with a daily spontaneous breathing trial (SBT) will facilitate early liberation from the ventilator.

A multitude of anecdotal approaches exist but are not widely accepted, have only limited supporting data, and are not approved by the United States (US) Food and Drug Administration (FDA) (26-34). These techniques generally fall into two broad categories: implantation of a device or administration of a chemical agent (*Table 2*). Devices include Watanabe spigots, Amplatzer occluders, and metallic stents. Chemical agents include tissue adhesives, hemostatic agents, submucosal injections, and thermal therapy. Studies involving these mechanisms are limited by their small sample size and multiple inherent sources of bias. Some of these devices are more widely accepted in other countries. Watanabe spigots are an established treatment modality for intractable pneumothorax in Japan and are frequently used for this purpose.

Chemical pleurodesis involves the use of sclerosants to cause an inflammatory response. Talc, doxycycline, tetracycline, minocycline, and bleomycin are some of the commonly used agents. Side effects include chest pain, fever, acute lung injury, and empyema. Multiple retrospective studies have demonstrated a high rate of success with these agents (8). Direct apposition of the visceral and parietal pleura is required for success (36).

Autologous blood patch pleurodesis is another modality that has been utilized for over 30 years (37). Studies have demonstrated a success rate of >90% with PALs following pulmonary resection or spontaneous pneumothorax (38). The procedure involves obtaining 50 to 100 mL of peripheral venous blood and then injecting it into the chest tube, which is then flushed and clamped (39). This approach

relies on two processes—the immediate sealing effect of clotted blood and the resultant pleural inflammation and consequential symphysis of the two pleural layers.

The most recent, and perhaps innovative, management strategy centers around the use of endobronchial (EBV: Zephyr, PulmonX Inc.) and intrabronchial (IBV/SVS system, Spiration, Inc.) valves. Intrabronchial valves were originally conceived and evaluated as a minimally invasive alternative to lung volume reduction surgery. They were developed to treat patients with emphysema and hyperinflation. The first reported case of airway valves in humans to control an air leak was published in 2005 (40). Since then, valves have increasingly been employed for this purpose. These one-way valves are deployed using a flexible bronchoscope and prevent continued airflow through a fistula by occluding segmental and subsegmental bronchi. The Spiration valve is classified as a humanitarian exemption device (HDE) by the FDA and is approved for prolonged or significant air leaks complicating surgical lung resection. A HDE is a medical device intended to benefit patients with a particular disease or condition that is not manifested by more than 8,000 individuals in the United States per year.

Potential complications include valve malpositioning, expectoration, pneumonia, and desaturation. Both valves are constructed on a Nitinol framework. Nitinol is an amalgamation of nickel and titanium that produces a flexible, yet extremely durable, compound that enables valves to conform to the airway by expanding and contracting with respiration. The Spiration valve is umbrella-shaped and made of polyurethane, while the Zephyr valve has a duck bill appearance and is made with silicone. The Spiration valve comes in four sizes, ranging from 5 to 9 mm, while the Zephyr valve is available in two sizes. Their configuration allows air and secretions to escape during exhalation but prevents air from passing through during inhalation. The hypothesis relies on tissue healing during the time air flow through the fistula is blocked. After the defect has healed, valve removal can occur using a flexible bronchoscope. Valves are removed *en-bloc*.

Sequential balloon occlusion, the primary strategy for identifying the origin of an air leak, was first described by Ratliff and colleagues in 1977 (41). This method involves occlusion of segmental airways, moving proximally to distally, starting at the mainstem bronchi. During periods of occlusion, observation of the air leak chamber for 4–5 ventilatory cycles is imperative as residual air is washed out. Other methods of leak location identification are also available and include instillation of methylene blue, oxygen insufflation, ventilation scintigraphy, and the Chartis system (Pulmonx, Redwood City, CA, USA) (42). With the first method, methylene blue is instilled on the pleural side, while direct bronchoscopic visualization is maintained. Oxygen insufflation involves directed application of oxygen through the suction channel and assessment for increasing leak in the water seal chamber. The Chartis system involves a balloon catheter with a flow and pressure sensor. An abnormal pleural communication is suggested when the pressure remains persistently negative after occluding airflow through a segment. Locating the site of a post-surgical leak is typically less challenging since it is usually located at the bronchial stump. Pinpointing a non-operative APF or BPF is often much more rigorous.

Relative to the anecdotal approaches, valves are supported by more robust data from larger studies. The earliest case series was published in 2009 and included 40 patients who received the Zephyr valve (43). A mean of 2.9±1.9 valves were placed in each patient with an overall procedural success rate of 93% and a complication rate of 15%. The pleural drain was removed after a mean of 7.5 days. Valves were only retrieved in 20% of subjects. Gillespie *et al.* published the first case series using the Spiration valve in 2011. In 8 valve placement procedures, the mean duration of air leak after the procedure was 4.5 days, a median of 3.5 valves were used, and all removals were successful. There were no procedural or valve-related complications (44). In the largest study of Spiration valves to date (N=75 patients), Gilbert *et al.* demonstrated resolution or diminution of air leak in 56% of patients overall (45). In unsuccessful cases, chemical pleurodesis or autologous blood patch pleurodesis may be necessary as complementary therapy.

Seventy percent of patients in the study by Gilbert *et al.* had valves placed for a non-FDA approved indication (45). Valves are commonly inserted prior to postoperative day 5 in an effort to minimize morbidity associated with PAL. This should be a consideration in patients with chronic obstructive pulmonary disease (COPD) who develop a pneumothorax, since these patients have a higher complication and mortality rate than their non-COPD counterparts (46,47). While valves may not completely eliminate a vigorous air leak, they can often sufficiently reduce it so that wall suction is no longer required. In this scenario, patients may be discharged with a chest tube attached to a Heimlich valve or portable collection system that can be removed on an outpatient basis after the fistula tract has healed.

Widespread off-label use reflects an unacceptable

paucity of high quality data and the consequential lack of supporting guidelines. Even the prospective studies that have been conducted thus far have not included a control group. The first randomized controlled trial of intrabronchial valves is currently enrolling participants, with a goal of 200. The Valves Against Standard Therapy (VAST) study is examining time to air leak cessation as the primary outcome. The experimental arm contains patients who receive the Spiration valve system, while the control group receives standard of care interventions. Data from this study and others will hopefully enable development of new guidelines that incorporate valves into the treatment algorithm for PAL.

Conclusions

Modern, minimally invasive treatment modalities for PAL have revolutionized management of a challenging clinical problem. Variable practice patterns stem from the lack of up-to-date guidelines on the subject. As more high-quality data become available, particularly from the upcoming VAST study, guideline development and revision will be necessary. This will enable a more standardized approach to a common clinical dilemma and form the foundation for continued advancement in this area.

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Footnote

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