Risk factors of prolonged air leaks

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Abstract: Prolonged air leaks are one of the major and most common postoperative complications after thoracic surgery and are associated with significant morbidity. Many risk factors including gender, age, body mass index (BMI), preoperative lung disorders, postoperative predicted lung function, pleural adhesions, preoperative serum albumin levels, air leakage on postoperative day 1 (POD) and surgical technique have been described. The clinical impact of these parameters varies greatly and risk scores have been developed to better detect high-risk patients.

Keywords: Prolonged air leak (PAL); risk factor; thoracic surgery; pulmonary resection

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Introduction

Prolonged air leakage (PAL) after thoracic surgery is a common problem leading to an increased length of stay (LOS), a higher complication rate and increased medical costs (1-3). Several definitions of PAL exist in literature. The traditional definition is an air leakage, which persists for more than 7 postoperative days (PODs) (4). Another, more current definition is that of air leaks leading to an increased LOS compared to an otherwise uncomplicated postoperative course (1). According to this definition, PAL is defined as that lasting for more than 5 days after standard pulmonary resections. The Society of Thoracic Surgeons and European Society of Thoracic Surgeons both use this definition of PAL. Other less frequently used definitions suggest the term PAL already after 3 or 4 days.

There are two major ways to grade air leakage in postoperative patients with chest drains. Grading can be done either conventionally by water seal systems or through digital drainage systems. The traditional water seal systems offer an easy and cheap way to visualize air leaks by means of bubbling in the water seal chamber. The most common classifications of air leakage grade the severity based on whether the leak is seen on forced expiration only (grade 1) on expiration (grade 2), or continuous (grade 3) (5) and the amount of air leakage from absent (grade 0), mild (grade 1), mild to moderate (grade 2) and severe (grade 3) (6,7). The newer digital chest drainage systems offer an objective quantification of air flow through the drainage system. The flow is displayed along with the pleural pressure difference in real time.

Incidence and sequelae of air leaks

PAL throughout the literature (1-3) markedly increases the morbidity after thoracic surgery, prolongs the hospital stay and thus leads to higher medical costs (*Table 1*). In a retrospective analysis of 726 patients undergoing pulmonary lobectomy a higher rate of empyema (8.2% to 10.4%) in patients with air leak lasting more than 7 days versus a rate of only 0% to 1.1% in patients with lesser air leaks was found (8). Increased pulmonary morbidity, including pneumonia, atelectasis and empyema (risk-ratio: 2.78) as well as an increased length of hospital stay was observed in a series of 238 lobectomy patients with air leaks lasting for at least 5 days (2). Prolonged air contributed to higher costs of

Table 1 Overview of studies on risk factors for prolonged air leaks (PAL)

Publish year	Author	Period	Total cases	Population	PAL def.	Incidence of PAL (%)	Identified risk factors
2004	Brunelli *et al.*	1995–2003	588	Lobectomy	>7 days	15.6	Reduced ppoFEV1; pleural adhesions; upper resections
2005	Stolz *et al.*	2003–2004	134	Lobectomy	≥7 days	9.7	COPD
2006	DeCamp *et al.*	1998–2002	580	Bilateral LVRS	>7 days	–	Low DLCO; pred. upper lobe or diffuse; extensive pleural adhesions
2010	Brunelli *et al.*	2000–2009	685	Lobectomy	>7 days	13	Age >65 years; adhesions; FEV1 <80%; BMI <25.5 kg/m^2
2011	Rivera *et al.*	2004–2008	24,113	Lung resections	≥7 days	6.9	Male gender; adhesions; LVRS; upper lobectomy; bilateral procedures
2011	Petrella *et al.*	2004–2007	121	Lobectomy	≥ POD 5	–	Male gender; right side; age >58 years
2012	Elsayed *et al.*	2002–2007	1,911	Lung resections	>6 days	6.7	Low FEV1; lobectomy; upper lobe; different surgeon
2013	Liang	2008–2010	380	Lung resections	≥ POD 5	18	Severe radiologic emphysema; histopathologic emphysema; FEV1 <80%; lobectomy
2017	Pompili *et al.*	2007–2015	5,069	VATS lobectomy	>5 days	9.9	Male gender; FEV1 <80%; BMI <18.5 kg/m^2
2017	Li *et al.*	2014–2016	442	VATS anatomic resections	>5 days	11.8	BSA >1.68 m^2
2017	Zhao *et al.*	2014–2015	1,051	VATS major pulmonary resection	>5 days	10.6	Extensive pleural adhesions
2017	Okada *et al.*	2010–2015	146	Lobectomy	>5 days	16	Serum albumin (≤4.0 g/dL); air leak on POD1

BMI, body mass index; POD, post-operative day; FEV1, forced expiratory volume in 1 second; LVRS, lung volume reduction surgery; BSA, body surface area; COPD, chronic obstructive pulmonary disease; VATS, video-assisted thoracoscopic surgery.

more than 13,000€ per year in this series. The percentage of patients exhibiting an air leak peaks immediately after pulmonary resections. More than 57% of patients have an air leak present on the first POD (8). Air leakage decreases in the subsequent PODs (9).

In high-risk populations, such as patients undergoing lung volume reduction surgery (LVRS) for severe emphysema within the National Emphysema Treatment Trial (NETT) the incidence of postoperative air leak is as high as 90% within 30 days after LVRS in patients undergoing bilateral procedures (10). This does not necessarily translate into a prolonged air leakage in all patients, however the presence of an air leak on POD 1 has been described as a risk factor for the development of PAL. A variety of studies have shown an incidence of PAL (with different definitions) of 6.7–26% (3,10-15). This incidence is similar after open and VATS approach.

In this article we will focus on PAL resulting from alveolar-pleural fistula defined as a communication between the pulmonary parenchyma distal to a segmental bronchus and the pleural space in spontaneously breathing patients. Mechanical ventilation predisposes to prolonged air leakage due to increased intrapulmonary pressure. Other, more rare causes of PAL after thoracic surgery include bronchopleural fistulas as well as leakage from bronchial anastomoses.

Several risk factors for PAL that have been identified. They can be classified in patient related risk factors and surgery related risk factors.

Patient-related factors

Gender and age

There is conflicting evidence whether gender is a risk factor for PAL. In several studies male gender has been described as a risk factor for PAL (10,12,16,17). Other studies did not find a significant difference between the two genders (4,18) and one study found female gender to be a significant factor for developing PAL in the univariate analysis (3). There is however evidence that the incidence of PAL increases with higher age. This can be explained by the fact that elderly patients may have a more fragile lung parenchyma, which may predispose to the occurrence of this complication. A recent Asian study classified 2.292 patients undergoing video-assisted thoracoscopic surgery (VATS) for spontaneous pneumothorax into three groups and found the incidence of PAL in patients aged 13 to 49 years, 50 to 69 years, and 70 to 85 years to be 3.55%, 13.1%, and 49.1%, respectively. Age was an independent risk factor the multivariate analysis (19). The exact cut-off for increased risk varies with some authors suggesting an age above 65 (1) and others an age above 58 years to be a risk factor for PAL (17).

Body mass index (BMI) and body surface area (BSA)

There is also conflicting data whether a low BMI is a risk factor for the development of PAL. The cut-off for being a significant risk factor ranged in positive studies from 25.5 kg/m^2 (1) to 18.5 kg/m^2 (13). However, low BMI did not remain a significant risk factor in multivariate analysis in one study (3) while others found no statistical difference in BMI between the groups with and without PAL (18,20).

The BSA was postulated as well to be a risk factor for PAL. In a single-center retrospective analysis of 442 patients undergoing VATS anatomical resections for lung adenocarcinoma a PAL rate of 11.8% was found. Patients with BSA >1.68 m^2 had a significantly higher incidence of PAL (P=0.006) compared to those with BSA ≤1.68 m^2 (21). Among the explanations for this finding the authors stated that a larger pleural cavity might have larger area related to severe pleural adhesions, which needed to be dissected and divided during the VATS procedure, resulting in a higher probability of air leak.

Blood values

In a retrospective analysis of 146 patients who underwent pulmonary lobectomy for lung cancer it was shown that a low preoperative serum albumin and the presence of a major air leak at rest on POD 1 were independent predictors of PAL (14). The authors hypothesized that hypoalbuminemia indicates malnutrition, which is associated with poor tissue healing and decreased collagen synthesis in surgical wounds. Consistent with these results an association between low serum albumin level and PAL was shown by others several years ago (20) as well as in a recent Asian retrospective study (5).

Smoking history, chronic obstructive pulmonary disease (COPD) and Emphysema

Smoking history and preoperative respiratory comorbidities predispose to structural lung changes and seem logical risk factors as well as the presence of pleural adhesions. Yet available data vary between different patient cohorts. In a very recent analysis of the Western China lung Cancer Database covering more than thousand patients only the presence of pleural adhesions remained a significant risk factor in the multivariate analysis (16).

In another study of 380 patients undergoing pulmonary resections patients in the prolonged alveolar air leak group had higher pack-years of smoking (41.5 *vs.* 38.5 pack-years) (22). Elsayed confirmed the finding that a higher pack-year history of smoking is one of the significant factors in the development of PAL (3). In a Japanese study a smoking history of ≥40 pack years was a significant risk factor only in the univariate analysis (14). In the study of Okereke *et al.* smoking history did not emerge as a risk factor for occurrence of air leak (23). Jiang did not find smoking history to be a significant risk factor for developing PAL in his cohort of spontaneous pneumothorax patients undergoing VATS (19).

COPD is a major patient-related risk factor for developing PAL. Preoperative lung function tests reflect the severity of COPD. Accordingly, patients with a reduced postoperative predicted forced expiratory volume in 1 second (FEV1) are prone to PAL (13,18). In a large series of 588 patients undergoing lobectomy or bilobectomy for non-small cell cancer Brunelli *et al.* found out that among patients at greatest risk for developing PAL were those with a lower mean FEV1 (mean FEV1 79% *vs.* 90%;

P<0.0001), lower mean forced vital capacity (FVC), lower FEV1/FVC ratio (mean 0.66 *vs.* 0.71; P<0.0001), lower predicted postoperative FEV1 (mean 63% *vs.* 72%; P<0.0001 (4). In contrast to many authors, Okereke *et al.* did not report a low FEV1 as a risk factor of PAL (23).

In patients with severe emphysema undergoing LVRS there is a high risk for the development of PAL due to the poor quality of the lung parenchyma. In contrary to PAL after anatomic resection PAL after LVRS is more frequent and lasts longer. In the NETT the incidence of PAL in the cohort of 552 patients undergoing bilateral LVRS was 50% (10). The surgical approach does not seem to influence the PAL rate in LVRS patients (10). In the NETT low carbon monoxide diffusion in the lung (DLCO) was identified as a risk factor for developing PAL as well.

Liang et al found in a retrospective analysis of 380 patients undergoing pulmonary resections that emphysema seen on preoperative CT scan, a predicted postoperative FEV-1 less than 80% and FEV-1/FVC less than 70% are significant risk factors for severe PAL (22). In multivariate analysis, one of the main risk factors for developing PAL included a low predicted FEV-1 (pFEV1) (P<0.001) in Elsayed's study as well (3).

Infectious disease

Infectious conditions and chronic inflammation like tuberculosis and aspergillosis have been reported to increase the risk of PAL. In a cohort of 23 patients undergoing anatomic pulmonary resections for human immunodeficiency virus–negative multidrug-resistant tuberculosis Mohsen *et al.* stated a postoperative complication rate of 34.7%, PAL (longer than 7 days) being the major one. Out of all patients undergoing lobectomy 33.3% had PAL (range, 11 days–7 months). The authors traced the high incidence of PAL in their cohort to the peripheral disease with extensive adhesions affecting the whole hemithorax and not only the diseased lobe and to the extrapleural approach in order to avoid bleeding and operining cavities. Most air leaks were at the fissure area (24). In another series of 72 patients undergoing major surgical resection for pulmonary tuberculosis the PAL incidence was 21% (25). A similar incidence of PAL after resection for Mycobacterium xenopi pulmonary infection has been shown by Lang-Lazdunski *et al.* Five of 18 patients had PAL after pulmonary resection (26).

Chen *et al.* investigated 256 patients who underwent surgical treatment for aspergilloma. Among the major postoperative complications was PAL (2.1% in simple aspergilloma and 3.8% in complex aspergilloma) (27). In their study of 30 patients operated upon for aspergilloma Farid *et al.* noticed an even higher rate of PAL of 7.23% (28). In a North American cohort of 60 patients who underwent surgery for pulmonary aspergilloma the postoperative morbidity rate was 30%. The most frequent postoperative complication was PAL in 15%, the majority of these in the complex aspergilloma group (29). In 23 out of 71 patients with PAL and/or residual air space after resections for pulmonary aspergillosis, complications were observed more frequently in patients with greater cavitation near the chest wall (30).

Steroid treatment and induction chemotherapy

Patients with preoperative inhalative or oral steroid treatment greater than 10 mg daily or for longer than 1 month are considered to be at higher risk for PAL (10,31). DeCamp *et al.* stated that preoperative use of inhalative steroids but not oral steroids was an independent predictor of air leak duration (10). The exact mechanism for this finding is still unclear. The authors hypothesize that corticosteroids inhibit wound healing and may prolong healing of visceral pleural injury after LVRS.

Preoperative induction chemotherapy was not proven to be a significant risk factor for PAL. Petrella *et al.* noted that induction treatment (P=0.9405) was not related to prolonged postoperative air leak. Preoperative chemotherapy did not affect air leak status (17). Other studies confirmed this finding (18,23).

Surgery-related risk factors

Surgeon-related factors

There is no consistent clear evidence that the surgeon's specialisation correlates with PAL. In a retrospective study surgeons were divided into two groups according to their background and focus (lung and mediastinal diseases *vs.* esophageal diseases) and no differences were observed (16). Within the NETT, air leak occurrence and duration was neither surgeon- nor operation-dependent (10).

In contrast to this, Okereke and colleagues found that the risk of PAL is surgeon-dependent and might be linked to the number of anatomic lung resection performed by an individual surgeon (23). This finding was confirmed by Elsayed *et al.* (3).

Surgical site and resection extent

An association of upper lobectomies and bilobectomies with PAL was observed in several studies (3,4,12,32). In a study of 319 lobectomies Okereke and colleagues found that left lower lobectomy had a lower incidence of any air leak compared with other lobectomies (23). However, Brunelli *et al*. could not confirm this finding in a different population (1).

Right-sided lobectomies have been shown to be a risk factor for developing PAL in a retrospective analysis of 241 lobectomies performed for lung cancer (17). Multivariate logistic regression analysis showed that right side of operation (P=0.0010) was significantly related to prolonged postoperative air leak. The authors explain the effect of the right-sided operations due to two fissures requiring a more extensive parenchymal dissection. In addition, complete fissure is more common on the left side.

In contrast to most authors identifying that the type of lobectomy is a risk factor for developing PAL, Stolz *et al.* did not find significant differences in the type of lobectomy in their retrospective study of 134 patients undergoing lobectomy for lung tumor (18). In many series, performing a lobectomy was more likely to cause PAL than a wedge resection or a segmentectomy. Upper lobectomy was a greater risk factor for developing PAL compared to sublobar resections, presumably because a larger residual pleural space precludes the parietal-visceral pleural apposition (3,9).

Fissure status

A less developed or incomplete fissure is considered a risk factor for PAL in some series (1,33,34). This is mainly due to the parenchymal dissection in the fissure leading to air leaks. Nevertheless, fissure status was not found as an independent risk factor for PAL in a population of 1,051 patients undergoing VATS major pulmonary resection. This was traced back to a "single-direction/fissure last" surgical technique, which divided the lung parenchyma as last step during surgery and avoided to mobilize the pulmonary artery through the lung fissures (16).

Presence of adhesions

Many studies detected the presence of severe pleural adhesions as a relevant risk factor for PAL. Obviously the definition of severe pleural adhesions is based on subjective interpretation. Mobilization of the lung during the division of the adhesions may cause lung parenchyma injuries, particularly when blind maneuvers of blunt dissection are performed. Brunelli *et al.* found that the presence of dense pleural adhesions increased the risk of PAL and was the only significant independent variable predicting PAL after both upper and lower resections (1).

The NETT reached the same conclusion stating that the occurrence of PAL was more common and the duration prolonged in patients with extensive pleural adhesions (10). Rivera *et al.* found a PAL frequency of 10.4% in patients with pleural adhesions requiring intraoperative adhesiolysis (12). In a recent study, Kouritas *et al.* investigated 144 patients undergoing major lung resection retrospectively (35). The authors showed that that the presence of pleural adhesions during major lung resections is associated with a longer duration of PAL (P=0.03) than in the non-adhesion group. Zhao *et al.* identified extensive pleural adhesions as the only independent risk factor for PAL in their study of 1,051 patients after VATS major pulmonary resection for lung cancer (16). Okereke *et al.* could not support above mentioned finding though grading the pleural adhesions in their study of 319 patients undergoing anatomic lobectomy (23).

Pneumothorax

In a retrospective study including 2,292 patients operated on for spontaneous pneumothorax by VATS Jiang *et al.* detected age, American Society of Anesthesiologists (ASA) scores, bliateral procedures and bullae diameter as independent risk factors of PAL (19).

Surgical technique-related factors

Most studies investigating the risk factors for PAL were performed with patients operated by a thoracotomy approach (2,11,23). A recent investigation of more than 1,000 patients of the Western China Lung Cancer Database operated only by video-thoracoscopy (VATS) and undergoing major pulmonary resections for lung cancer demonstrated that an incomplete fissure was not a risk factor for PAL. This was attributed to the "fissure-last"-technique used in all patients (16). The fissureless technique appears to be a superior approach for fused fissures (33).

In a prospective randomized study Lequaglie and colleagues detected a significantly lower incidence of PAL in patients treated with a synthetic polyethylene glycol matrix compared to the control group (36). In general, the occurrence and duration of air leaks seems to be associated rather with characteristics of patients and their disease than with a specific surgical technique (10).

Risk scores

Since there are conflicting data on many individual risk factors for the development of PAL an integration of several factors into risk scores might give a more meaningful risk assessment of patients prior to surgery. Several studies developed risk scores to predict the incidence of PAL. Most of these PAL scores were published for open lobectomies. Brunelli *et al.* developed a four factor weighted score from a single center database (11). In 2011, Rivera *et al.* published a risk model developed from the French Society of Cardiovascular and Thoracic Surgery database (12). Four years later a validation score in a population of VATS lobectomy patients was published (37). Pompili *et al.* recently published a VATS-specific risk score based on the ESTS database (13).

The rationale behind above mentioned risk scores is to deliver reliable information about the risk of patients developing PAL after lung resection. On the basis of these scores patients at high risk of developing PAL can be selected who may benefit most from intraoperative preventative measures to minimize the occurrence of this complication.

Summary

Prolonged air leakage after thoracic surgery is a common complication, which extends the hospital stay and can lead to an increased morbidity and result in higher medical costs. Its incidence is highest after LVRS. The risk for PAL after lobectomies is higher compared to sublobar resections.

Several studies have investigated risk factors for developing prolonged air leaks after thoracic surgery in different populations. In general, these risk factors can be classified into two categories: patient-related and surgery-related risk factors. Patient-related risk factors include emphysema, reduced FEV1 and DLCO, advanced age, pleural adhesions, underlying infectious disease male gender, low BMI and BSA, chronic steroid use, low serum albumin levels and air leak on POD 1.

Surgery-related risk factors include the surgeon's case volume, the site and extent of resection, fissure completeness and the management of extensive adhesions.

For several of these risk factors there are conflicting data about the actual relevance.

Risk scores using above-mentioned risk factors have been developed to to better identify high-risk patients.

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Footnote

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