Diplomarbeit

Spontaneous Pneumothorax: Evaluation of the histology of wedge resections and clinical-pathological correlation – a pilot study

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Graz, am 20.7.2016 *Klara Barthofer eh.*

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„Wir behalten uns von unseren Studien am Ende doch nur das, was wir praktisch anwenden."

Johann Wolfgang von Goethe

Abstract

BACKGROUND: Spontaneous pneumothorax (PTX) may occur with no apparent underlying disease or may be associated with a broad variety of pulmonary disorders. Recently, the presence of fibroblastic foci in the lung tissue of PTX has been described, however, this has not been investigated systematically so far. The aim of our study was to elucidate the frequency of these lesions in pulmonary tissue and to illustrate any clinicopathologic correlations.

METHODS: One-hundred and fifty nine consecutive cases of spontaneous pneumothorax, treated with surgery and obtainment of the lung tissue, were enrolled. Cases of PTX were retrieved for a 10-year period between 1994 and 2014. Patients were analysed regarding their personal and histological features with a special focus on fibroblastic foci. Statistical analysis was performed to reveal the commonalities within the study group and also to illustrate the differences between patients with or without fibroblastic foci, patients with no relapse and relapses and patients with a different number of relapses.

RESULTS: Out of 159 patients 74% are male, 26% are female. The midpoint for female patients shows an age of 36 years, 1.65m in height, 57kg in weight. The midpoint for male patients shows an age of 30 years, 1.82m in height, 70kg in weight. 67% of all male patients are smokers with an amount of 9 PY, 57% of all female patients are smokers with an amount of 8 PY. 73% of all patients present a history of lung diseases, 16% present a history of systemic diseases. 31% show no relapse, 52% a single relapse, 25% a two-times relapse and 18% three-times or more relapses.

89% of the cases present interstitial inflammation with lymphocytes dominating, 85% present smoker´s macrophages, 79% fibrosis, 73% pleuritis, 58% mesothelial reaction, 55% fibroblastic foci, and 42% bullae. The presence of fibroblastic foci is associated with male sex, younger age, height, a lower BMI and a lower amount of PY compared to the group without fibroblastic foci. Also fibrosis, bullae and lymphocytes are more frequently found in patients with fibroblastic foci. There are no significant associations between fibroblastic lesions and the number of episodes of PTX (relapses/no relapses).

CONCLUSION: Patients with pneumothoraces show common personal and histological features. Both, physical predispositions like slim, tall habitus with an underweight BMI, smoking and lung disease as well as changes of the lung tissue including smoker´s macrophages, fibroblastic foci, fibrosis, eosinophilic granulocytes, mesothelial reaction and interstitial inflammation with lymphocytes are seen in tissue of patients with PTX. Young patients who were assumed as healthy without any underlying lung disease may

show histopathologic changes of the lung tissue inlcuding a high incidence of fibroblastic foci, fibrosis, bullae as well as interstitial inflammation. Fibroblastic foci are surprisingly often seen in our cohort of patients with PTX. However, it still cannot be determined whether these lesions contribute to the pathogenesis of this disease or whether they are a hallmark of wound healing in affected tissue. Their role in the context of PTX remains elusive. Further studies in this respect are warranted to gain more information.

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Abbreviations

PTX	pneumothorax
1° PTX	primary spontaneous pneumothorax
2° PTX	secondary spontaneous pneumothorax
ELCs	emphysema-like changes
CT	computed tomography
Chr	chromosome
EEA	exogenous allergic alveolitis
COPD	chronic obstructive pulmonary disease
CF	cystic fibrosis
AIDS	autoimmune deficiency syndrome
X-ray	X-radiation
HIV	human immundeficiency virus
RB-ILD	respiratory bronchiolitis associated interstitial lung disease
HR-CT	high resolution computed tomography
G	gauge
Fr	french
VATS	video-assisted thoracoscopic surgery
ARDS	acute respiratory distress syndrome
min	minute
mm	millimeter
O_2	oxygen
H_2O	water
%	percent
PY	packyear
ASA	American Society of Anesthesiologists
ILD	interstitial lung disease
SRIF	smoking-related interstitial fibrosis
H&E	hematoxylin and eosin
ADHD	attention deficit hyperactivity disorder
M	mean
SD	standard deviation
t	t-test for independent sampling
χ^2	Pearson´s chi-square test for independence

n	number in a subsample
N	total number in a sample
P	probability

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1 Introduction

1.1 Pneumothorax

Pneumothorax (PTX) is the presence of air within the pleural space (1), (2), (3). The term pneumothorax was used first in 1803 by Itard and published in 1903 by Emerson (4). Air enters the pleural space via a leak from a hole in the underlying lung or as a result of chest penetrating injury. A pneumothorax can be classified in traumatic and spontaneous pneumothorax (1), (2), herein, we will focus on spontaneous pneumothorax. The intrapleural pressure is normally negative, caused by the retractive force of lung elastic recoils. In case of a connection between the atmosphere and the pleural space, air is sucked in and the lung collapses. Air flows from the lung or from the outside into the pleural space till there is an equal pressure on both sides (2).

1.2 Spontaneous pneumothorax

1.2.1 Definition and epidemiology

In contrast to the traumatic pneumothorax a spontaneous pneumothorax is defined as an air entrapment in the pleural space without traumatic history. This can happen in apparently healthy lungs without underlying lung disease (1° PTX) or it can be associated with the presence of lung diseases (2° PTX) (1). Incidences vary from study to study from 9 to 17/100 000 inhabitants per year (5), (6). A biphasic age distribution with the first peak between 15 and 35 years (mainly 1° PTX) and the second peak over 55 years (mainly 2° PTX) is described (6). Women (1.2-6 /100 000) are less frequently affected than men (5) and tend to be affected later in life (7). The cause for this sex-related difference remains unknown, but features associated in male patients (cigarette smoking and tall leptosome habitus) are less frequently found in women (8), (9).

1.2.2 Etiology and pathogenesis

A spontaneous pneumothorax occurs when air enters the pleural space. There are different mechanisms how air enters the pleural space (5), (2), (10), but the exact pathogenesis of the PTX still remains unknown (11). Frequently, a connection between the alveolar spaces and the pleura is found (14).

Most authors believe that the underlying cause of PTX is the spontaneous rupture of a subpleural bleb, or bulla of an otherwise normal lung tissue, which leads to 1° PTX (1), (6), (10), (12). 76 to 100% of patients show subpleural bullae, treated with video-assisted thorascocopic surgery (VATS) or thoracotomy. Computed tomography of the chest shows ipsilateral bullae in 89% of patients with 1° PTX, as compared to 20% of controls (14).

The mechanism of bullae formation remains speculative, but blebs or bullae may originate from early emphysematous-like changes (ELCs) without underlying clinical disease (2), (5), (10). ELCs are described as pneumatized epipleural chambers which are linked to the lung parenchyma. Often the rupture of the pleura is found in the area of ELCs. The bullae or the ELC can be caused by genetic predisposition, respiratory bronchiolitis or disorders of the contralateral ventilation (5), (13). On CT scans ELCs were present in 89% of patients on the ipsilateral side and in up to 80% on both lung sides (15), (16). In the control group, consisting of healthy volunteers matched for age and smoking behaviour, only 20% showed ELCs (16). ELCs were also present in 81% of patients with healed 1° PTX, who had never smoked (17).

Inflammatory changes also play an important role in the formation of ELCs and bullae (18). Inflammation, also caused by smoking, leads to a degradation of elastic fibers. The so-called elastolysis is caused by an imbalance between proteases and antiproteases and oxidants and antioxidants and a higher amount of macrophages and neutrophiles in that tissue (19), (20), (21), (22). This also leads to bronchiolar wall fibrosis and destruction of the pulmonary parenchyma, resulting in ELCs (23).

Smoking increases the number of inflammatory cells, especially macrophages in small airways. Macrophages release potent chemotactic factors, resulting in accumulation of neutrophiles in small airways (24), (25). Cigarette smoke itself leads to an influx of neutrophiles caused by loss of functional activity of chemotactic factors inactivator (26). All the inflammatory cells accumulate in the endobronchial system between the pulmonary parenchyma and the bronchial tree leading to an endobronchial obstruction. The obstruction induces an overpressure in the alveolar tissue resulting in rupture of pulmonary parenchyma (27), (28).

Pleural perforation can also occure with inflammation caused by destroying abscesses, tumors (lung carcinoma, lung metastasis) or other pathological processes of the lung (e.g. pulmonal Langerhans-all-Histiocytosis) (5).

Most pneumothoraces occur in the lung apex as ELCs are mostly located in the lung apices. In addition, the interpleural pressure is more negative in the lung apex than in the basal lung area (5), (10), (29). This results in a higher wall tension in the alveolar space, which leads to a higher predisposition to tissue rupture.

Predispositions and risk factors for PTX are (1), (2), (5) (11), (13), (28) (30), (31), (32), (33):

- tall leptosomal habitus
- age between 20-40 years or >60 years
- low body mass index
- lung diseases
- systemic diseases (eg collagen vascular diseases)
- cigarette or cannabis smoking
- endometriosis
- genetic predisposition such as the rare Birt-Hogg-Dubé syndrome, an autosomal mutation in folliculin gene Chr 17 which causes renal and skin tumours and pulmonary cysts
- physical exertion, especially in combination with high intraabdominal pressure (eg during defecation, coughing).
- atmospheric pressure changes (divers, fighter pilots)
- exposure to loud music.

Out of these risk factors for PTX, cigarette smoking is the major one. The risk of suffering from a PTX in healthy men increases from 0.1% in non-smokers up to 12% in smokers. Smoking causes distal airway inflammation, disturbance of collateral ventilation as well as anatomic and morphometric alterations which may contribute to increased visceral pleural porosity and thus to ruptures and air leakage. The risk is also dose-related: Light smokers (1 to 12 cigarettes/day) have a 7 times higher risk, moderate smokers (12 to 22 cigarettes/day) have a 21 times higher risk and those smoking more than 22 cigarettes/day have a 102 times higher chance of the occurrence of a pneumothorax. Of note, this association is more apparent in men than in women. Cannabis consume is associated with bullous lung disease and thus related to the risk of pneumothorax (10).

Changes of the lung tissue can occur with specific profession, leading to pneumoconiosis, exogenous allergic alveolitis (EAA), chronic obstructive pulmonary disease (COPD) and more. These below listed professions and workplaces are associated with a higher risk of involving lung diseases: farmers, workplaces with agricultural products, antibiotics and enzymes, food industry, bakers, forestry and wood processing, textile industry and processing, waste, waste water and recycling industry, composting plant industry, plastic industry, hairdressers, hospital workers, metal industry and handicraft industry (35).

1.2.3 Forms

There are two big groups of spontaneous pneumothorax, the primary spontaneous pneumothorax (1° PTX) and the secondary spontaneous pneumothorax (2° PTX). Rare forms of spontaneous pneumothoraces are the catamenial pneumothorax and the tension pneumothorax (2), (10). Differentiation between these groups is important leading to specific management and prognosis (10).

1.2.3.1 Primary spontaneous pneumothorax (1° PTX)

The primary spontaneous pneumothorax occurs without any significant underlying disease. It especially appears in young men between the age of 20 and 30 years who are tall and slim to thin (5), (13). This can be explained by the fact that tall and thin patients show an increased pressure gradient from lung base to apex which leads to a higher risk of lung rupture (10). Often patients have a history of smoking or asthma (13). Kroegel et al. (2014) claims that 90% of patients with a 1° PTX are smokers or ex-smokers (5). In French the 1° PTX is also called "Pneumothorax du jeune Conscrit", meaning pneumothorax of the young selectee because predisposed persons remind of young men when entering the military service. The cause of 1° PTX is a rupture of a mainly apically located subpleural bulla, which is seen in 75% of patients undergoing thoracoscopic treatment (5), (10), (13). Even more likely is the pre-existence of emphysema-like changes (ELCs). Physical effort reportedly does not correlate with the incidence of 1° PTX (5), (13).

1.2.3.2 Secondary spontaneous pneumothorax (2° PTX)

The secondary spontaneous pneumothorax occurs due to underlying lung disease, often causing subpleural bullae (2). It has a peak age around 60 which correlates with a high incidence of COPD. The most frequent diseases associated with 2° PTX are COPD, interstitial lung diseases (ILD) and cystic fibrosis (CF) (5). The cause can also be preceeding viral bronchitis or pneumonia (13). In contrary to 1° PTX the causes of 2° PTX follow distinct pathological changes of the lung and the pleura. These develop from obstructive ventilation disorders (volume trauma) or from formation of bullae or cyst- like lung lesions due to emphysema, tuberculosis, cystic fibrosis, Langerhans cell histiocytosis and lung fibrosis. Other underlying lung diseases which variably are associated with 2° PTX are pulmonary diseases like status asthmaticus and bronchial or pleural carcinoma, congential cysts and bullae, bacterial pneumonia, whooping cough, esophageal rupture, lymphangioleiomyomatosis, sarcoidosis stadium IV, pulmonary infections like

pneumocystis jiroveci (AIDS), necrotizing pneumonia and gynecological diseases like endometriosis (1).

Independent of the underlying lung disease, chronic nicotine abuse is the most significant risk factor. The risk of developing a pneumothorax in a life of a smoker is much more higher (12%), compared to a non-smoker (0.1%). Jeske et al. (1993) described 710 patients with a spontaneous pneumthorax in an observation time of 20 years. 21% suffered from lung disease and out of that more than 60% were smokers (1).

Compared to the 1° PTX the 2° PTX shows symptoms earlier and the complication rate is higher. This is based of the missing compensation linked with the underlying pulmonary disease (13).

The symptoms range from dyspnea to orthopnea. In contrast to this 1° PTX can be asymptomatic. The manifestation of complications like tension pneumothorax and mediastinal emphysema is also nearly exceptional detected within the 2° PTX (5).

1.2.3.3 Catamenial pneumothorax

The catamenial pneumothorax is a special form of the 2° PTX. It occurs in women between the age of 30 and 40, suffering from endometriosis. Pneumothorax appears within the first 3 days of menstruation and is situated mainly on the right lung side. As an explanation of the pathogenesis an endometriosis of the pleura tissue can be seen (5). The catamenial pneumothorax is treated with hormonal substitutions. If the above mentioned treatment is inefficient, pleurectomy is performed and requires cooperation of thoracic surgeons and gynecologists (5), (32).

1.2.3.4 Tension pneumothorax

The tension pneumothorax is an emergency situation requiring immediate treatment (1). It is characterized by air enterings the pleural space following a valve mechanism. The connection of the lung to the pleural space functions as a valve allows air to enter but not to flow out in expiration. Thus, air accumulates in the pleural space leading to an increased pleural pressure. The lung is pushed down, the mediastinum is shifted to the opposite side of the lung and the venous return to the heart and cardiac output are impaired (2).

1.3 Diagnostics

Typical physiognomy and the clinical history linked with the appearance of the patient can already lead to the diagnosis of a pneumothorax. Chest X-ray may confirm the suspected diagnosis but CT scan is seen as the gold standard (5).

1.3.1 Clinical observation

1.3.1.1 Medical history

- young men, <30 years, leptosomal habitus (tall, thin, slim and light bones) are associated with 1° PTX
- clinical history of pulmonary diseases and other systemic diseases like cystic fibrosis, tuberculosis, lungfibrosis, lymphangioleiomyomatosis, HIV infection, COPD, emphysema, alpha-1 antitrypsin deficiency are more associated with 2° PTX (5).

1.3.1.2 Symptoms

Symptoms depend on the dimension of the pneumothorax and the underlying disease. It generally occurs unilateral (29). Small amounts of air trapped in the pleura cavity can be asymptomatic and it may resolve itself without any intervention within a few days (5), (29). But only 5% of pneumothoraces are asymptomatic (13). A significant pneumothorax shows a sudden onset, starting with localized pain at the affected thorax side and breathlessness (5), (13), (29). In 2° PTX dyspnea is the most prominent clinical feature whereas dyspnea is often absent or mild in 1° PTX. In 1° PTX patients more often suffer from a sudden ipsilateral chest pain (11).

Healthy young adults may tolerate a pneumothorax quite well and do not complain about impairing symptoms (2). Therefore, younger patients are often hospitalized 1-2 days after the real onset of the lung collapse (13). Older patients with underlying lung diseases often develop severe respiratory distress (2).

Cough can also appear in an early stage of PTX. Tussis occurs because the two pleural layers vanish apart from each other. In the beginning the sudden pain is depending on the breathing movement caused by the touching of the pleural layers while breathing. For this reason patients avoid inhaling deeply, called inspiration-blockage or doorstop-phenomenon. In the later stage pain can diminish or desist when the interpleural air contempt is large enough to keep the two pleural layers apart from each other (5).

Instead of this dyspnoe (exertional) may appear caused by the increased lung collapse.

If air is trapped in the pleural space, it is called a tension pneumothorax. In that case tachypnoea, cyanosis, cardiovascular depression and later on pulsus paradoxus may occur. The arterial blood gas analysis shows hypoxia and hypercapnia when disturbance or underlying disease is substantial (5).

1.3.1.3 Physical examination

On physical examination suspecting a pneumothorax these listed features may be seen:

- tachypnoea
- relieving posture (13)
- hypersonic percussion sound “acoustic sound of a carton“
- diminished or missing vocal fremitus
- attenuated or abolished breathing sounds (5)
- Hamman´s sign, a click on auscultation in time with the heart sound
- bubbles and crackles under the skin of the torso and neck if there is subcutaneous emphysema (1).

The hypersonic percussion sound results of the higher amount of air in the chest cavity and so forth a hollow percussion tone, like drumming on a thick carton (“carton ton“) (5).

A tension pneumothorax can also present with tachycardia, pulsus paradoxus, marked jugular venous distension, decreased blood pressure, cyanosis, mediastinal emphysema till to cardiogenic schock (13).

1.3.2 Body-imaging

1.3.2.1 Chest X-ray in expiration

1.3.2.1.1 Direct signs

The chest X-ray, performed in two levels (anterior-posterior as well as lateral), still represents the gold standard in imaging. A typical chest X-ray in expiration of a patient with pneumothorax shows a structure free airspace between the collapsed lung and the chest wall, seen in figure 1. The features of a pneumthorax on a posteroanterior (PA) erect chest X-ray are:

- visible pleura line, hairline (see Figure 1)
- enhanced transparency lateral of the collapsed lung
- absent pulmonary vascular markings (5).

In addition tension pneumothorax shows

- an asymmetry of volume, as the affected lung appears larger
- the mediastinum can be shifted to the direction of the healthy thorax side
- widened intercostal space at the affected lung side
- the diaphragm can be flattened and deeper.

These signs can be missing if the visceral pleura and the parietal pleura are stucked together by adhesions (5).

1.3.2.1.2 Indirect signs

The above described direct signs can not be seen when the X-ray is made on a recumbent patient. The leaked air accumulates in the ventral thorax while the lateral lung still sticks to the chest wall. The characteristical indirect features of a recumbent chest X-ray are

- accented border of heart, mediastinum and diaphragm caused by the missing contact between lung parenchym and mediastinum, heart or diaphragm
- increased transparency especially in the lower lung areas
- a wide and deep costodiaphragmatical cavity ("deep sulcus sign") caused by the missing negative pressure in the pleural space.

Skin folds seen on a reclining patient may lead to false positive diagnosis of a pneumothorax (5). Tiny pneumothoraces which are often not detected on an erect chest X-ray may be diagnosed by lateral chest or decubitus radiographs (1). The identification of a convex pleural line may help to distinguish between a pneumothorax and large bullae (2).

Figure 1: Erect chest X-ray (PA) of a right sided PTX. Typical hairline marking the collapsed lung (⟹). (Kindly provided by Assoz.Prof.PD Dr. Jörg Lindenmann)

1.3.3 Computed tomography of the thorax

The computed tomography (CT) scan of the thorax is the best diagnostic option to confirm or to exclude a pneumothorax which is not clearly visible on the chest X-ray (5). A typical presentation of a pneumothorax is seen in Figure 2. Small amounts of air in the pleura space can be detected in the so called lung window. The identification of a pneumothorax of an anterior (small) or anterolateral (bigger) may be useful for the implantation of an intercostal suction drainage (5). In some cases CT scans may help to distinguish between emphysema, bullae, other bullous diseases and pneumothorax (1),(5). Furthermore CT may be useful in detecting underlying lung diseases (1).

Figure 2: CT scan right sided PTX. Lung margin (⟹) . (Kindly provided by Assoz.Prof.PD Dr. Jörg Lindenmann)

1.3.3.1 Transthoracic sonography

The ultrasound of the thorax describing a pneumothorax is characterised by

- the absence of the synchronic breathing movement of the hyperechoic pleura lung border reflex, seen as a "slide sign" or "curtain phenomenon"

- missing of the “tail of the comet phenomenon artifact“ or torch phenomenon
- the absence of the slightly pulse synchronic movability of the visceral pleura
- increased regular replication echoes (reverberation) of the air filled pleura space (5)
- the passage between the air filled lung and pneumothorax (6).

1.3.4 Pathological features

Jeske et al. (1993) described 710 patients with PTX: 80% had a totally collapsed lung, 20% had an apical pneumothorax and less than 10% developed bilateral pneumothoraces (13), (34). Pneumomothorax commonly occurs unilateral (29). PTX can affect one of both sides of the lung. It is not shown that one of the lung side is affected more often (1).

Spontaneous pneumothorax is caused due to some pathological changes of the lung, usually emphysema. Especially in healthy young individuals the lung appear to be normal. But when a thoracotomy was performed these people show common histological changes, illustrated in table 1 (29).

Pathological features
- Emphysema
- Fibrosis
- Bullae
- Pleural porosity
- Inflammation
- Alveolar collapse
- Mesothelial hyperplasia
- Eosinophilic pleuritis
- Fibroblastic foci
- Pigmented macrophages

Table 1: Pathological features (29)

Fibrosis is usually found at the apex of the lung and can extend up to 2-3 cm. If fibrosis is overlapped of one or more bullae (> 1cm) it is called apical cap. There can be a hole in the pleural surface, connecting the pleura and the bullae (29), although only a minority of

blebs are actually ruptured at the time of thoracoscopy or surgery. Therefore, blebs and bullae are related to the occurrence of pneumothorax but account seldomly as the triggering factor (36), (37), (38).

More important are other lesions, especially pleural porosity, areas of disrupted mesothelial cells at the visceral pleura, replaced by an inflammatory elastofibrotic layer with increased porosity, allowing air leak into the pleural space (11).

Histology shows alveolar collapse, chronic inflammation and reactive mesothelial hyperplasia with eosinophils dominating. One of the most common seen pathological features in spontaneous pneumothorax is pulmonary fibrosis. Pulmonary fibrosis is an unspecific reaction of lung tissue (29). It especially occurs in alveolar septa or as a circumscribed lesion, a so called scar (39). Pulmonary fibrosis involves the gradual change of normal lung parenchyma with fibrotic tissue, represented by an excessive fibrous connective tissue. The replacement of normal lung with scar tissue causes irreversible decrease in oxygen diffusion capacity and the resulting stiffness or decreased compliance makes pulmonary fibrosis a restrictive lung disease (40). Pulmonary fibrosis is maintained by aberrant wound healing, rather than chronic inflammation (41). The cause of pulmonary fibrosis can be a secondary effect of other diseases like autoimmune disorders, viral infections, bacterial infections (tuberculosis), toxic inhalation (cigarette smoking, asbestosis, silicosis) leading to interstitial lung disease (41). If the cause is unknown it is called idiopathic pulmonary fibrosis, also known as usual interstitial pneumonia (UIP) (42).

Normally, the reactive eosinophilic pleuritis affects only the surface of the pleura and penetrates only a short distance into the lung tissue. If air is trapped in the pleural cavity for a longer time also mesothelial changes, especially squamous changes can occur. These can develope into malignant formations. Often there is no underlying disease or tuberculosis to be found (29).

Especially inflammatory changes lead to obstruction check-valve mechanism that can be seen as the real cause of pneumothorax (11).

The changes in the apical region of the lung may develop themselves out of rapid somatic growth in tall, thin men. When these people stay erect the apices are being particularly poorly perfused and cause ischaemia. This leads to direct damage of the apices or fibrosis. This apical changes often affects both lung sides therefore there is a high risk of recurrence on the opposite side. Rarely, there can be minor anatomical anomalies of the bronchi detected when pneumothorax occurs cumulative in one family (29).

Cigarette smoking is the major risk factor of evolving a pneumothorax (10). Smoking may cause degradation of elastic fibers due to influx of neutrophils and macrophages in the lung. This degradation causes an imbalance in the protease-antiprotease and oxidant-antioxidant system. After bullae have been formed, inflammation-induced obstruction of the small airways increases alveolar pressure, resulting in an air leakage into the lung interstitium. Air then moves into the hilum, causing pneumomediastinum. This leads to a higher mediastinal pressure and rupture of the mediastinal parietal pleura, causing pneumothorax (14). The phagocytic capabilities of macrophages provide the first line of defense against toxic agents in the distal lung and is also shown by ingested coarse-grained pigments resulting in brown macrophages (43), (44), (45). Macrophages have a defensive role in the lung and at the same time they may be important in the pathogenesis of pulmonary disease. The release of enzymes and chemical mediators from alveolar macrophages may result in pulmonary fibrosis and also play an important role in the pathogenesis of emphysema (46), (47). Cigarette smoke not only induces changes of macrophages, it also leads to an accumulation of pigmented alveolar macrophages (48).
Nevertheless, blebs and bullae also occur in up to 15% of normal lung tissues without any pathological features (30), (49), (50).
For the first time, Deborah et al. (2012) identified in a 92 case study a distinct pattern of pneumothorax associated with fibroblastic lesions in a subset of cases of PTX. 12% of all patients with PTX presented a pattern of pleural fibrosis with islands of fibroblastic foci within a myxoid stroma at the pleural-parenchymal interface or leading edge. It still remains unknown whether this fibroblastic pattern are related to the pathogenesis (51). Fibroblastic lesions (see Figure 13) usually are found in paraseptal and subpleural areas where they protrude into the alveolar spaces. They are covered with epithelium, show a myxoid stroma and usually lack inflammatory infiltrates. They are thougt to represent the manisfestion of wound healing in ongoing lung injury. In general, fibroblastic lesions are regarded as the hallmark lesion in the histological pattern of usual interstitial pneumonia (UIP), seen in idiopathic pulmonary fibrosis (IPF), a rare idiopathic interstitial pneumonia. This enigmatic disease which carries a grave prognosis usually is diagnosed in male patients above the age of 50.
Furthermore, smokers often present respiratory bronchiolitis associated interstitial lung disease (RB-ILD). RB-ILD is almost exclusively apparent in heavy smokers and it is defined as accumulation of pigmented macrophages in the alveolus and interstitium with chronic bronchitis and a mild fibrotic-inflammatory interstitial reaction (45), (52).

1.3.5 Staging and evaluation of the pneumothorax extent

Pneumothorax can be staged with histological criterias (Verschoof) (5). Nowadays the characterization of Vanderschueren using high resolution computed tomography (HR-CT), as illustrated in table 2, is more common (5), (53).

Evaluation of the pneumothorax extent can be made easily with chest X-ray. Chest X-ray allows to measure the extent of the pneumothorax. The width of the rim of air surrounding the lung is used to classify pneumothoraces into small (rim of air measured at the level of hilum ≤ 2cm) and larger (>2cm). A 2cm rim of air approximately equates to a 50% pneumothorax in volume (1), (2).

Stage	Vanderschueren	Verschoof
I	Idiopathic pneumothorax, endoscopic normal lung	Pneumothorax without histological verifiable results
II	Pneumothorax with pleuropulmonal adhesions	Pneumothorax with an apical bullae
III	Pneumothorax with a single bulla (< 2cm in diameter)	Pneumothorax with general cystic lung disease
IV	Pneumothorax with multiple bullae (>2cm diameter)	

Table 2: Staging of the pneumothorax (5)

1.4 Therapy

1.4.1 Therapy decision

There are three international guidelines (the American College of Chest Physicians Delphi consensus statement, the British Thoracic Society guidelines and the Belgian Society of Pulmonology) which contrast sharply in many aspects of proposed treatment (7). Treatments of pneumothorax shown in Figure 3 are mostly based on the guidelines of the he British Thoracic Society.

The aim of the pneumothorax therapy is the evacuation of the pleura space as soon as possible. This will lead to a re-dilatation of the collapsed lung (5).

For initial management it should be determined whether the pneumothorax is 1° or 2°. Patients with a 2° PTX tolerate the pneumothorax less well and also show a significant higher mortality with 10% and therefore should be managed more aggressively (1), (32). Therefore, patients with 2° PTX always have to be hospitalized for at least 24 hours (32). The underlying lung disease should also be treated (1).

One of the most important factors for therapy decision is the severity of breathlessness. Breathlessness indicates the need for active intervention as well as supportive treatment (32). The decision of the therapy of a pneumothorax based on clinical presentation is illustrated in figure 3.

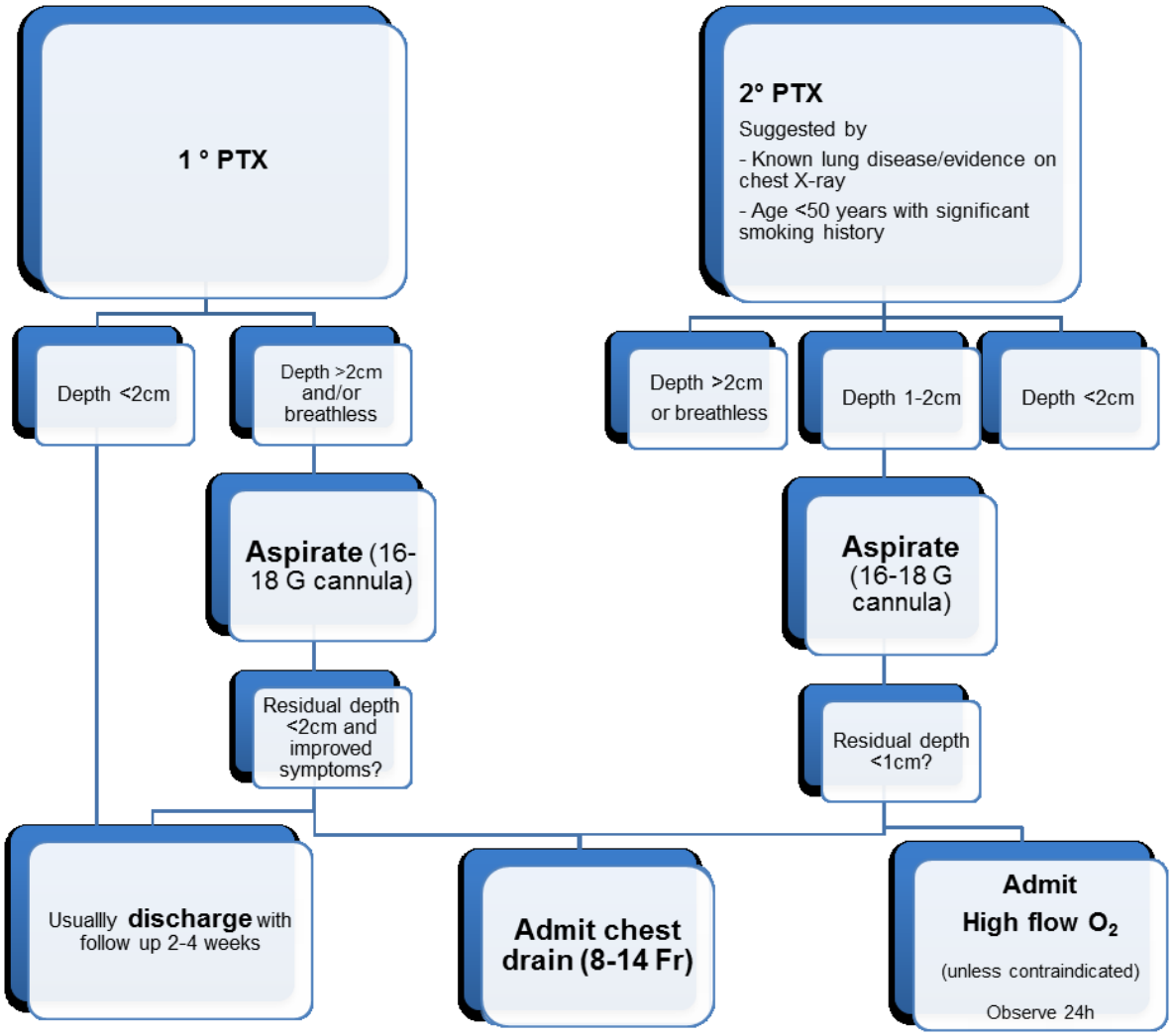

Figure 3: Algorithm for treatment of spontaneous pneumothorax (1)

Furthermore the decision of therapy depends on the following facts:

- clinical presentation of the patient including breathlessness, hypoxia, haemodynamic compromise
- presence of underlying lung disease

- probability of spontaneous regression
- probability of a relapse
- progression of the pneumothorax between 9 and 96 hours
- current dimension of the pneumothorax (5).

1.4.2 Observation range

The evaluation of a patient with pneumothorax include:

- re-evaluation of the clinical stage
- chest X-ray controls
- re-evaluation of the size of the pneumothorax.

There are no guidelines regarding chest X-ray controls.

After an uncomplicated pneumothorax the lung may expands itself 3 weeks after the event (5).

1.4.3 Conservative treatment

Discharge combined with frequent controls: Patients with a small 1° PTX without breathlessness can be considered for discharge with early outpatient review. These patients should receive clear written advice to return in the event of worsening breathlessness (32).

Observation (without oxygen): If the patient has no symptoms and the pneumothorax is small the patient can be observed and controlled within small breaks. The precondition is that there is no progression of the PTX (5). Observation is the treatment of choice especially in small 1° PTX without any significant breathlessness. Also selected asymptomatic patients with a large 1° PTX may be managed by observation alone (32). Each day 1.25% of the PTX-volumes will be reabsorbed spontaneously (5). Such patients may be discharged advised to return to the hospital as soon as symptoms worsen (2).

Observation (with oxygen): The reabsorbed range is 4 times bigger if the patient gets high-flow oxygen (> 3L/min) trough a nasal cannula, with appropriate caution in patients with COPD (1), (2) . Oxygen also reduces dyspnea and hypoxaemia. However acording to Stephen Chapam (1) every hospitalized patient should get high flow (10L/min) inspired O_2. Inhalation of oxygen displaces the nitrogen in the pleura space which leads to a bigger difference between the total gas pressure in the pleural space and the pressure in the pleural capillaries. This leads to faster reabsorption of the air which is trapped in the pleura space (2).

Aspiration: A simple needle aspiration using a small gauge-needle (12-14 French) to suck out air of the pleural space can relieve symptoms. A part of the PTX-volume can be

aspirated by hand. The patient has to sit up straight and before inserting the needle local anesthetic should be injected (2), (5). Between the 2nd and 3rd intercostal space the needle is placed medioclaviculary. After aspiration of 150-500ml the needle is removed. Indication for small needle aspirations are small and uncomplicated pneumothoraces. In 70% of PTX cases this treatment is sufficient. Small needle aspiration accelerates the degeneration of the pneumothorax and also the duration of hospitalization can be reduced (5), (32). Also a 14-16 gauge-needle is as effective as large-bore (> 20 French) chest drains and should be preferred. A needle aspiration should not be repeated unless there were technical difficulties. If a needle aspiration failed a small bore (< 14 French) chest drain insertion is indicated (32).

Small caliber drainage: A plastic or teflon drainage (e.g. Matthys-catheter, pleura-cath) is inserted into the 2nd or 3rd intercostal space mediaclaviculary using the Seldinger technique (2). There is a minor risk of hurting the expanded lung because of the elastic material which is used (5). In spontaneous pneumothorax, small caliber (smaller than 14 French) tubes may be inserted, larger tubes do not have an advantage (54).

Portable chest tube or intercostal tube drainage: Chest tubes are usually not required in the majority of patients with a 1° PTX. They are more common in the management of critical ill patients with severe diseases including a higher risk of morbidity and mortality (1). Small caliber chest drains are preferred for chest tube treatment (32). The external part of the chest tube stays open with a one-way valve system like the Heimlich valve or with a water seal. The Heimlich valve is more often used because it can be used without hospitalization and it may even reduce the duration of the hospital stay. This sort of drain allows the air to escape but not to re-enter without an extra negative pressure circuit and also avoids a tension pneumothorax. The normal movement of the patient leads to a higher interpleural pressure so that air escapes through out the drainage. 75% of the patients with a portable drainage may not suffer from a relapse. It can also be used if patients have to be transported (5). The tube is left in place until no air is seen to escape from it for a period of time, and X-rays confirm re-expansion of the lung (54), (55). Chest tubes are used first-line when pneumothorax occurs in people with AIDS, frequently due to underlying pneumocystis pneumonia, as this condition is associated with prolonged air leakage. Bilateral pneumothorax is relatively common in people with pneumocystis pneumonia, and surgery is often required (54).

Thoracotomy with continuous negative pressure circuit: It is used as the first-line therapy of a 2° PTX or if there is a high risk of relapse and persistent leakage. Frequently small

calibre (7-14 Fr) chest tubes are sufficient. Bigger caliber tubes (> 24 Fr) are used if higher sucking is needed to expand the lung (5). High-volume low-pressure suction systems with 10-30cm H_2O are recommended (5), (32).
Big caliber tubes are inserted into the 4^{th}-7^{th} intercostal space in the middle or frontal axillary line after a local anesthetic is applied (5).

A chest tube is indicated

- when the distance between the apical thorax and the lung apex is bigger or even 3cm
- if the pneumothorax takes more than 15% of the size of the hemithorax
- if there is a high risk of progression or relapse
- if the patient is cardiopulmonary prestressed (5).

Removal of the chest tube
The chest tube can be removed after several (5-7) days when there is no suspicion of a persistent air leak and the daily chest X-ray shows a fully expanded lung. The most important step is that a positive intrapleural pressure is preserved at the moment of removal. The patient should be in a comfortable position and should take a deep breath. While the patient exhales, the drain is pulled out as a whole at one time. 12-24 hours after the removal a chest X-ray is indicated (5). The sucessful therapy is shown in Figure 4.

1.4.4 Surgery

Usually a first time pneumothrax can be treated with conservative measures. The aim of the surgical treatment is the repair of the apical hole or bleb and to close the pleural space. A relapse of a pneumothorax is an indication for surgical therapy. As well as persistent air leak over 7 days, second ipsilateral 1° PTX, first contralateral 1° PTX, bilateral 1° PTX, spontaneous haemothorax, first time 1° PTX in patients with profession at risk like pilots or underwater divers and first time manifestation of a 2° PTX in patients with underlying diseases (1), (5).

1.4.4.1 VATS

Video-assisted thoracoscopic surgery (VATS) is a type of thoracic surgery performed using a small video camera that is introduced into the patient's chest via a scope. Instruments can be inserted through separate holes in the chest wall called “ports”. Because of the small skin entrances the risk of infektion or wound dehiscence is minor. This leads

to faster and better wound healing and a quicker postoperative recovery (56). Nowadays, VATS is standard due to minimal invasion, little postoperative pain and minor complication rate. The pleura can be observed, bullae can be removed and also partial pleural abrasion can be performed. VATS also prevents big skin scaring, offers a shorter in-hospital stay and reduces postoperative lung problems (5), (54). 2° PTX, re-occurred 1° PTX as well as primary 1° PTX can be treated with VATS. Especially in young patients with 1° PTX VATS is the gold standard (1). The relapse rate after VATS is 2-14% which is much smaller than the relapse rate after chest tube therapy (30%) (5).

1.4.4.2 Thoracotomy

A thoracotomy is much more complex than VATS. Also the patient has to be hospitalized longer then treated with VATS. In contrast to this, thoracotomy has the lowest relapse rate (0-7 %) (5).

1.4.4.3 Transaxillary mini-thoracotomy

Transacillary mini-thoracotomy is a variation of thoracotomy using a minimal axillary incision. It is a reasonable alternative to the conventional thoracotomy due to less invasiveness (1).

1.4.4.4 Pleurodesis

If a persistent leak allows air to flow out of the pleura space a pleurodesis is indicated. As first-line therapy talcum or tretracycline is used to provoke a sclerosis to artificially obliterate the pleural space (1), (5). It can be instilled through an intercostal drain or directly during VATS, thoracotomy or pleurectomy. As a requirement the lung has to touch the pleura. After pleurodesis patients have the smallest relapse rate (<10 %). But chemical pleurodesis has a failure rate of 10-20% (1). The talcum is instilled via the chest tube or directly and after 3 hours a suction is applied to ensure a pleuropleural contact. Five minutes after instilling the talcum patients claim about lot of pain thus local and intrapleural anesthesia with xylocain is necessary. Furthermore a systemic pain killer like opiates or sedatives can be used. As a rare complication acute respiratory distress syndrome (ARDS) may occur especially when the talcum dose needed is higher than 4 g (5).

1.4.5 Complications

Not only the lungs can collapse but there may occur other complications. Also specific situations like tension pneumothorax and catamenial pneumothorax require different management strategy.

Subcutaneous emphysema: Air is trapped in the layer of skin under pressure from the pleural space, coming from the chest cavity travelling along the fascia. The cause can be a large air leakage, especially when underlying lung disease such as COPD is present. In most cases it is harmless but rarely can cause a respiratory compromise from upper airway compression. Subcutaneous emphysema can be treated with high-flow (10L/min) inspired O_2. If the emphysema resists the treatment can be expanded with large-caliber chest drain on suction (1).

Re-expansion pulmonary edema: In 14% of pneumothorax cases patients suffer from breathlessness and cough, accompanied by edema in the re-expanded lung, visible in the chest X-ray. It occurs more frequently in young patients with large 1° PTX and if the use of a chest drain on suction is applied between the first 48 hours. In most cases it is self-resolving and no treatment is needed.

Tension pneumothorax: A tension pneumothorax is a case of emergency. If there is any suspicion of a tension pneumothorax high-flow O_2 is indicated and the insertion of a large bore cannula is needed. If the sound of hiss of escaping air is noticeable the diagnosis of a tension pneumothorax can be made. Also immediate chest X-ray should be done. Tension pneumothorax is treated with air aspiration until the the patient is less distressed and after that a chest drain should be inserted and should stay there until no air comes out and the underwater seal is bubbling satisfactorily.

Catamenial pneumothorax: When the occurrence of pneumothorax happens at time of menstruation and it is recurrent, the diagnosis of catamenial pneumothorax is likely. It can be treated with VATS, pleurodesis and/or ovulation-suppressing drugs (1).

1.4.6 Relapse therapy

Young patients without any underlying disease should have surgery to prevent the recurrence of a pneumothorax. Nowadays VATS is standard due to minimal invasion, little postoperative pain and a minor complication rate. The pleura can be observed macroscopically, bullae can be removed and also partial pleural abrasion can be performed. VATS also prevents big skin scars, offers shorter in-hospital stays and reduces postsurgical lung problems. The relapse rate is lower than 1% after surgical intervention (5), (54).

The most significant risk factors for recurrence of a pneumothorax are large size pneumothoraces with persistent air leakage treated with conservative therapy. Other factors such as smoking status, BMI and number of bullae are not showing a significantly higher recurrence rate (57). Although rarely seen in women the occurrence of 1° PTX in women of childbearing age is not unusual. There appears to be an increased risk of recurrence of pneumothorax during pregnancy and during parturition (32).

1.4.7 Follow-up care

After successful re-dilatation of the collapsed lung a chest X-ray should be performed 7-10 days after discharge. Patients also should be advised not to travel by plane or do longer travels until the lung is again fully extended (1), (5). During a plane flight, barometic pressure is reduced at altitudes and this can cause expansion of enclosed thoracis air pockets (2). Also patients should never dive in the future, unless he or she has undergone definitive surgical procedure. Especially during therapy the patient should avoid smoking but also in long-term prognosis chronical smoking should be stopped (1), (5), (32).

Figure 4: Before and after treatment. Figure 4a shows a right sided total PTX, (⟹) illustrating the folded lung. Figure 4b shows fully extended lungs after efficient treatment with intercostal tube (⟹) . (Kindly provided by Assoz.Prof.PD Dr. Jörg Lindenmann)

1.4.8 Differential diagnosis

The guideline symptoms of a pneumothorax are thoracic (breath depending) pain, dispnoea and worst case scenario cardiovascular depression. This following diseases have to be excluded as a differential diagnosis:

- ischemic heart diseases: sudden left situated thoracic pain
- pericarditis: dull, not acute thoracic pain
- aorta dissection: acute and intense thoracic pain
- pleuritis: associated with a respiratory tract infection
- lung embolism: sudden, breath depending pain without preferred localization
- intercostal neuralgia: dragging intercostal pain
- acute abdomen: acute to recurrent pain
- exacerbation of a chronic lung disease: unspecific and diffuse pain (COPD, CF).

Differential diagnostic of 2° PTX is difficult to distinguish because the underlying disease covers PTX associated symptoms. In case of an exacerbation the possibility of a pneumothorax should be considered. Especially the reoccurrence rate of 2° PTX is much higher than of 1° PTX (39-47% in COPD; 50-83% in cystic fibrosis) (5).

1.4.9 Prognosis and development

The development of an uncomplicated pneumothorax can take from hours to days. In contrast, tension pneumothorax may develop rapidly within a few minutes.

Generally speaking there is always the possibility of a recurrence after the first pneumothorax. The relapse rate lies between 20 and 30% after the first occasion of a pneumothorax. With every ipsilateral relapse the probability rises (50% after the first, 80-100% after the second relapse) (5). For 1° PTX there is a probability of 30% (13-54.2 %) and for 2° PTX there is 39-47% chance of a second episode of a pneumothorax (1).

2 Materials and methods and Aim of the study

This retrospective study was carried out at the Department of Thoracic Surgery and at the Department of Pathology of Medical University Graz. One hundred and fifty nine consecutive cases of spontaneous pneumothoraces, treated with surgery and obtainment of lung tissue, were enrolled. Cases of PTX between 1994 and 2014 were retrieved. We aimed to illustrate the histopathologic findings in a cohort of PTX; in particular we were interested in the frequency of fibroblastic lesions as the presence of those only recently was described in PTX. Next, we were interested whether histopathologic findings are associated with clinical findings.

2.1 Study population

The computer files of all patients were searched in the open medocs system for stationary patients who had a wedge resection and the diagnosis spontaneous PTX at the ward for thoracic surgery. All cases of PTX were retrieved, regardless of clinical impression of etiology (primary or secondary). One hundred and fifty nine patients fulfilled the inclusion criteria, demonstrated in table 3. The study was approved by the local ethical committee of the Medical University Graz (EK number: 27-119 ex 14/15).

Inclusion criteria:

Patients with the diagnosis of spontaneous PTX and available lung tissue were recruited to this study. Patient`s age ranged from 18-99 years. Furthermore, there had to be the complete information about the personal criteria's such as birth date, sex, body height, body weight, affected lung side, number of relapses, general diseases, lung diseases, ASA

classification, number of the histological sample and smoking habits in pack-years. When the information about the patient`s profession was present, it was also included.

Exclusion criteria:

Patients with another kind of pneumothorax, than spontaneous pneumothorax were excluded. Also patients who had a spontaneous pneumothorax, but the obtainment of lung tissue was not available were excluded from the study. If one personal criterion was missing the patient was not included.

2.2 Data collection

2.2.1 Personal data

The personal data (table 3) were collected from the medical history, searched in the open medocs system.

Personal data
- Birth date
- Sex
- Height
- Weight
- BMI
- Age at surgery
- Smoking habits in pack-years (PY)
- Affected lung side
- Number of relapses
- Systemic disease
- Lung disease: COPD, inflammation (respiratory bronchiolitis, bronchopneumonia, chronic bronchitis, pleuritis), asthma, lymphangioleiomyomatosis, tuberculosis, sarcoidosis, SRIF, interstitial lung disease (ILD), lung changes (atelectasis, fibrosis, lung cyst, emphysema, bronchiectasia, pleural effusion, pleurahyalinosis), pulmonary embolism,

mesothelioma, lung infarction, bronchial or pleural carcinoma, whooping cough, pneumocystis jiroveci (AIDS), Langerhans-Cell-Histiocytosis, endometriosis.
- Profession (Dust exposure/no dust exposure)
- American Society of Anesthesiologists (ASA) classification (1-6)

Table 3: Personal data

2.2.2 Histological criteria

We used formalin-fixed paraffin-embedded material from the archive of the Institute of Pathology, Medical University Graz. Two µm thick H&E-stained sections (hematoxylin and eosin) were examined with light microscopy. The lung tissue was analyzed based on the common pathological features associated with pneumothorax (see table 4).

Histological criteria
- Smoker´s macrophages
- Fibroblastic foci
- Fibrosis
- Mesothelial reaction
- Eosinophilic pleuritis
- Bullae
- Emphysema
- Interstitial inflammation: neutrophils, - Leukocytes, plasma cells
- Other features

Table 4: Histological criteria

2.3 Statistical analysis

Statistical analysis was performed by using the Statistical Program for Social Sience (IBM SPSS Statistic for Windows, Version 22 Armonk, NY: IBM). The student test for independent samples was used to compare continous variables and the Chi-squared test was used to compare the nominal data. The regression analysis was used to check if there was a connection between two continous variables. All statistical hypothesis tests were two tailed and a *P* value of less than 0.05 was considered to be significant.

3 Results

3.1 Personal data

The information about age, height, weight, smoking habit, lung disease, systemic disease, occupation, ASA classification and number of relapses was analyzed in every patient. The results of the statistical analysis of the personal criteria are summarized in Table 5.

The analysis of the personal data shows that there are in total 159 patients who were diagnosed with spontaneous pneumothorax between the years 1994 and 2014. Of these, 118 (74 %) patients are male and 41 (26 %) patients are female (see Figure 5).

	Men (118 male patients	**Women** (41 female patients
Age (yr)	30 ± 12 (18-80)	36 ± 14 (18-81)
Height (m)	1.82 ± 0.07 (1.67-1.98)	1.65 ± 0.07 (1.55-1.86)
Weight (kg)	70 ± 10 (40-105)	57 ± 7.6 (42-80)
Smokers/Nonsmoker (%)	67/33	56/44
Smoking (PY)	9 ± 15 (0-105)	8 ± 10 (0-30)
Lung disease (%)	73	
Systemic disease (%)	16	
Dust exposure (%)	11	
ASA (1-4)	1: 45 % 2: 47 % 3,4: 7 %	
Relapse (%)	0: 31 1: 52 3: 16 >3: 2	

Table 5: Demographic details of personal criteria. Data are shown as midpoint ± SD. Smoking habits shown in pack years (PY).

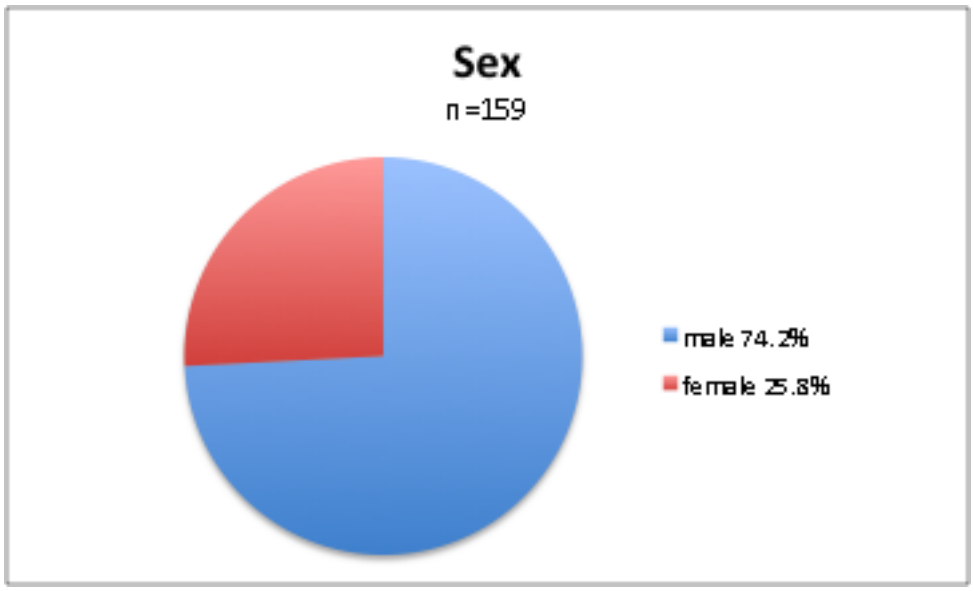

Figure 5: Sex distribution

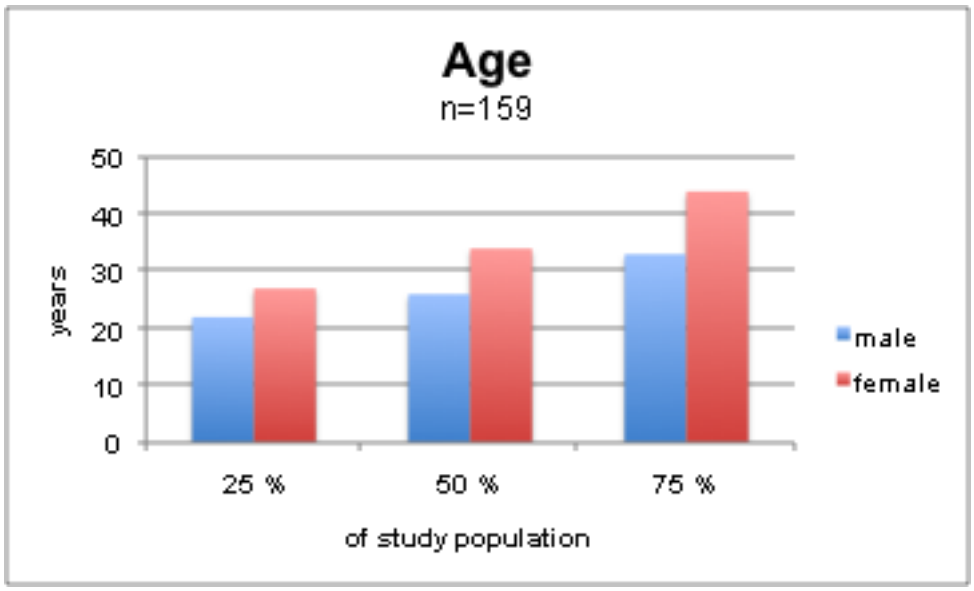

Figure 6: Age distribution

The midpoint of the age at operation, which presents the age of the onset of the first PTX, of male patients is 31.4 years with a standard deviation of 18.7 years (31,4 ± SD 18,7; range 18-80,9 years). The midpoint of age at onset in male patients is 29.7 years (±SD 12.1). The midpoint of age at onset in female patients is 36.2 years (± SD 13.6). Women are significantly older than men when the first PTX occurs (P = 0.04). For the age distribution, see Figure 6.

The midpoint of body height in men is 1.80m (±SD 0.07; range 1.67m - 1.98m). The midpoint of body height in women is 1.65m (±SD 0.06; range 1.55m - 1.86m).

The midpoint of body weight in male patients is 70.4kg (±SD 10.3, range 40kg - 105kg).

The midpoint of body weight in female patients is 56.6kg (±SD 6, range 42kg - 80kg).

The midpoint of the BMI in male patients is 21.3 (±SD 3.1, range 14.17 - 38.08), indicating that 16% of men have a lower BMI then 18.5 and are therefore called underweight.

The midpoint of the BMI in female patients is 20.7 (±SD 2.8, range 16.6 - 30.5), indicating that 27% of women are underweight (BMI ≤ 18.5).

Of all patients, 102 are smokers (64%), illustrated in Figure 7. In total, 23 women (56%) and 79 men (67%) smoke.

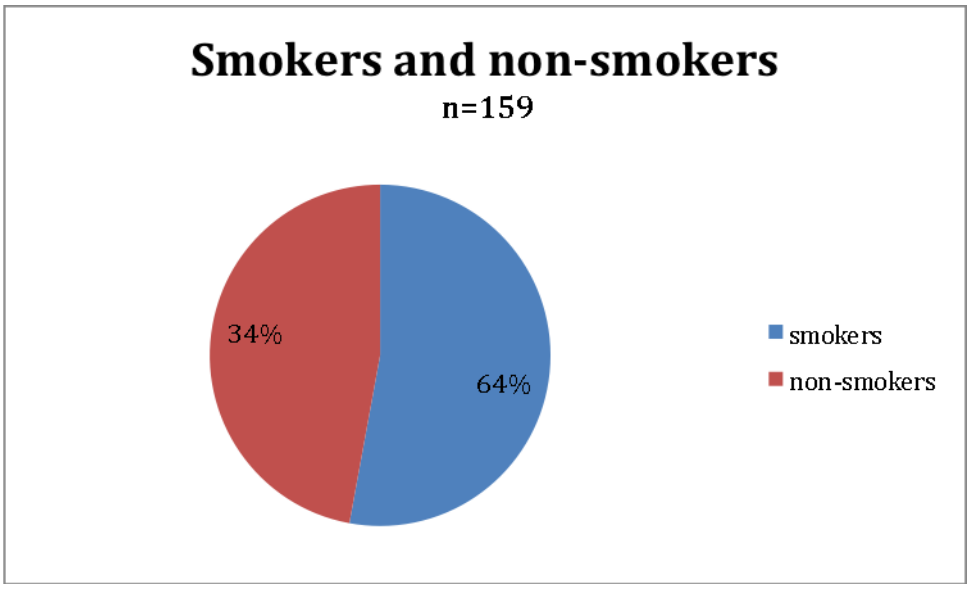

Figure 7: Smokers and non-smokers

Smoking habits are demonstrated in Figure 8. Of all female smokers 83% quote to have a history of lower than 15 pack years, 5% smoked between 15 and 25 PY and 12% >25 PY. Of all female patients 56% are smokers, 67% of all male patients are smokers. Of all male smokers 86% have a history of <15 PY, 6% smoked between 15 and 25 PY and 9% >25 PY.

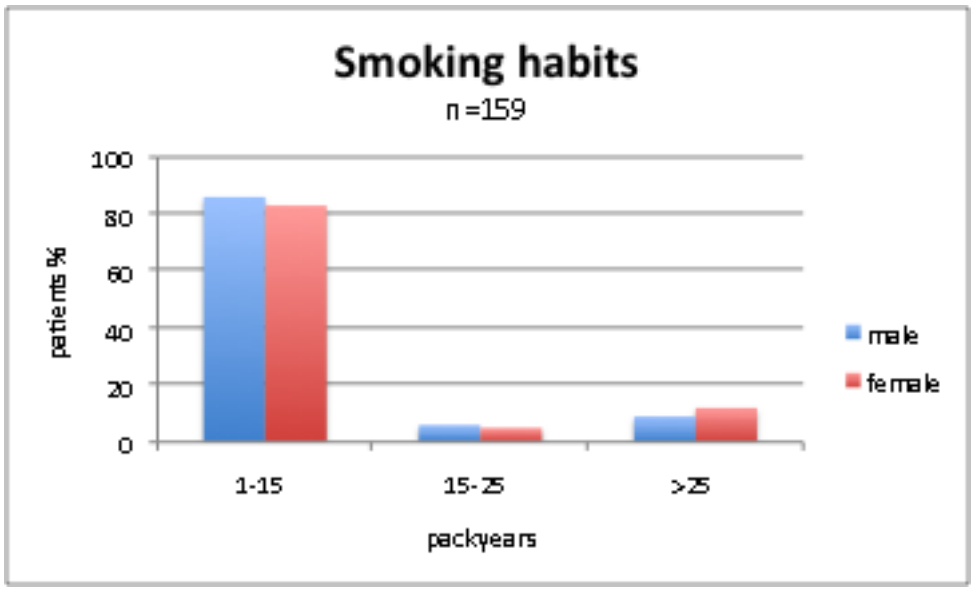

Figure 8: Smoking habits divided into packyears

43 patients of the study population (27%) show no lungs disease in the medical history.

116 patients (73%) present a history of lung disease with emphysema, respiratory bronchiolitis and pleural diseases as the most common diseases. The distribution of the different clinically known lung diseases is shown in Table 6,

	Patients (%)	Patients (number)
No lung disease	**27**	**43**
Lung disease	**73**	**116**
- Emphysema	60	95
- Inflammation	42	67
- Respiratory bronchiolitis	21	35
- Pleural disease	21	33
- Fibrosis	21	11
- COPD	6	9
- Pneumonia	5	8
- ILD	3	5
- Bronchial asthma	3	5
- Others >3 %	10	29

Table 6: Lung diseases – distribution

133 (84%) of the study population do not suffer from systemic diseases. The remaining 26 patients (16%) show the presence of systemic diseases such as a history of alcoholism (4%) and thromboembolism (3%). Less than 3% of patients suffer or had suffered from other diseases such as hypertension, Ehlers-Danlos syndrome, endometriosis, substance

abuse, hepatitis A, Scheuermann`s disease, testicular carcinoma, ADHD, epilepsy, stroke, renal carcinoma and Crohn´s disease.

Out of 124 patients, 107 male and female patients (in total 67%) do not show a history of occupational dust exposure. Of note, information regarding the profession is missing in 35 cases. 17 patients (11%) experienced dust exposure in their occupational careers.

Of all patients 92% show an ASA score of 1 or 2, demonstrated in Figure 9. Out of , 71 patients (45%) were graded of the anesthetists into ASA score 1. 75 patients (47%) were classified into ASA score 2, 8 patients (5%) show an ASA score of 3 and 3 patients (2%) were diagnosed with an ASA score 4. The information about the ASA score of 2 patients was not available.

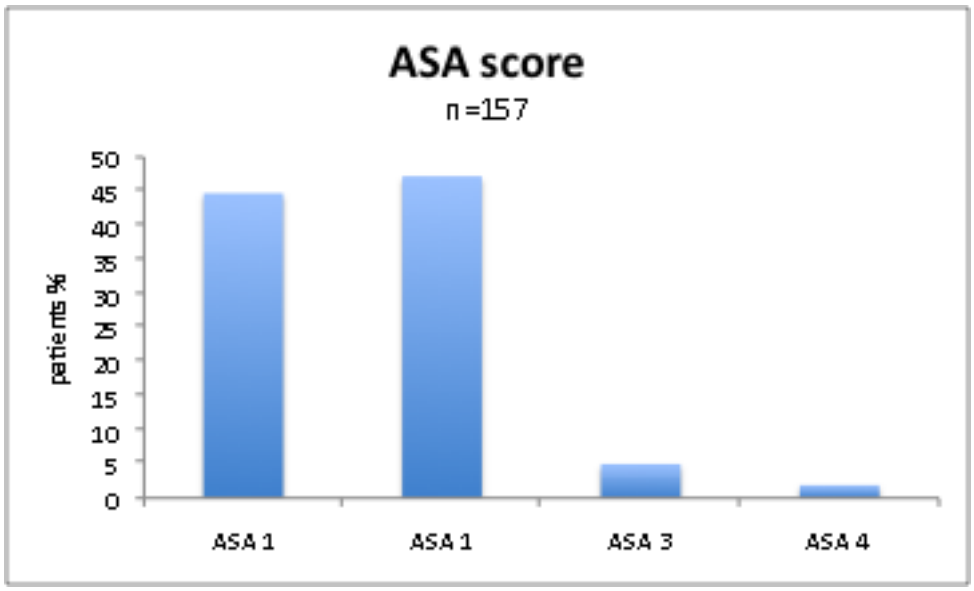

Figure 9: ASA score distribution

49 patients (31%) did not experience a relapse, illustrated in Figure 10. 110 patients (69%) show a history of at least one relapse: Out of these, 82 patients (52%) suffered a singular relapse, 25 patients (16%) two relapses and 2 patients (1%) even three relapse. Four and six relapses were seen in 1 patient each. There is no association ($P = 0.636$) of the amount of PY and the probability for a second episode of pneumothorax (relapse). In addition, no association between dust exposure and relapse number is seen ($P = 0.331$).

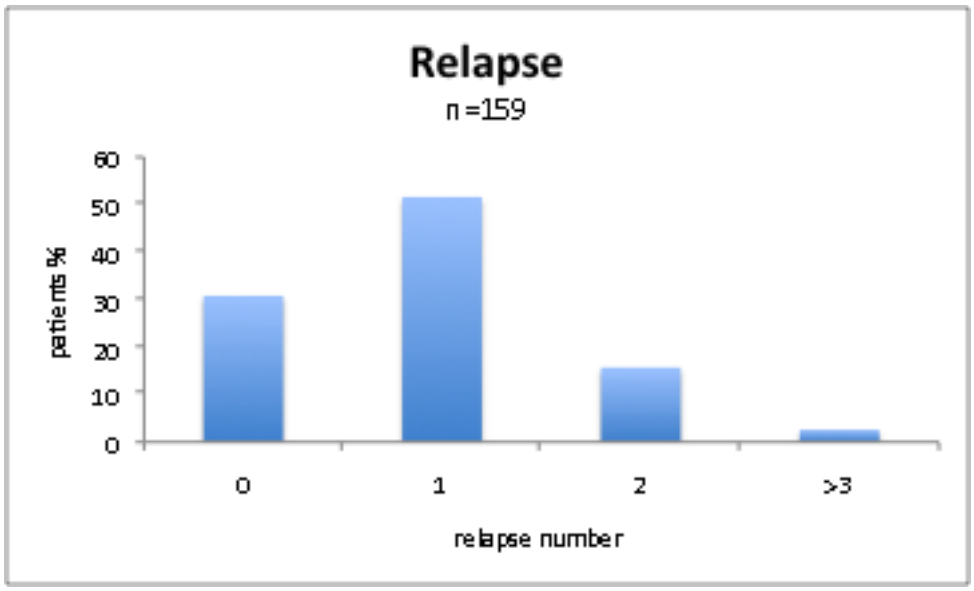

Figure 10: Relapse rate

3.2 Histological criteria

The results of statistical analysis of the histological criteria are summarized in table 6 and in Figure 11.

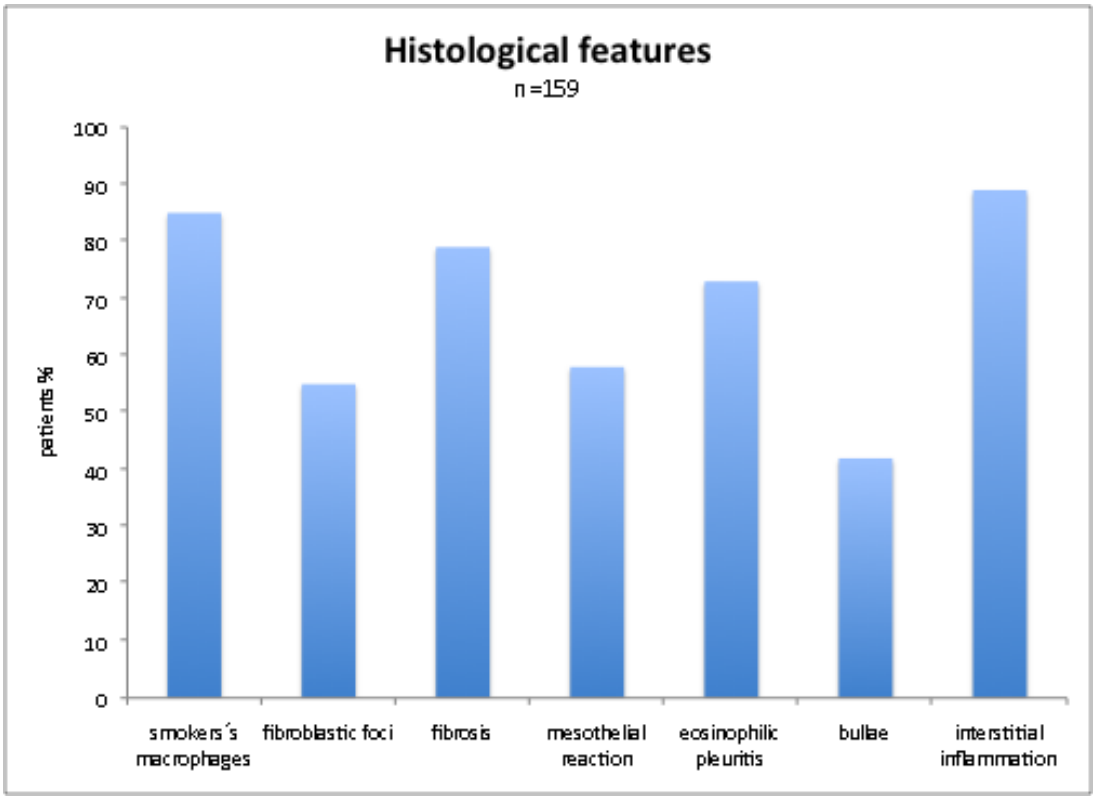

Figure 11: Histological features

	Patients (%)	Patients (number)
Smoker`s macrophages	85	135
Fibroblastic foci	55	88
Fibrosis	79	126
Mesothelial reaction	58	92
Eosinophilic pleuritis	73	116
Bullae	42	68
Interstitial inflammation	89	141
- Lymphocytes	87	139
- Plasma cells	21	33
- Neutrophils	20	32

Table 7: Demographic table of histological criteria

The majority of patients (135 patients, 85%) show the existence of smoker´s macrophages, seen on Figure 11. 97 patients (61%) present few smoker´s macrophages, 35 patients (22%) several smoker´s macrophages and 3 patients (2%) have numerous smoker´s macrophages. In only 24 patients (15%) no smoker´s macrophages are detected. Out of the group that denied cigarette smoking (36%, 61 patients), 20 patients do not show the presence of smoker´s macrophages. However, 37 patients, who also denied smoking present smoker´s macrophages. There is a strong association between the existence of smoker´s macrophages and pack-years ($P = 0.001$).

Figure 12a and b: Smoker´s macrophages: numerous heavily brown pigmented macrophages (hematoxylin-eosin, original magnification x200 [A], x400[B])

Out of 159 patients 88 patients (55%) present fibroblastic foci, demonstrated in Figure 13. 14 of all women (34%) show the presence of fibroblastic foci. 74 of all men (62%) show the presence of fibroblastic foci. Male patients show a higher presence of fibroblastic foci than women. The presence of fibroblastic foci is neither associated with the previous clinical history of lung disease (P = 0.368) nor the presence of a systemic disease (P = 0.476).

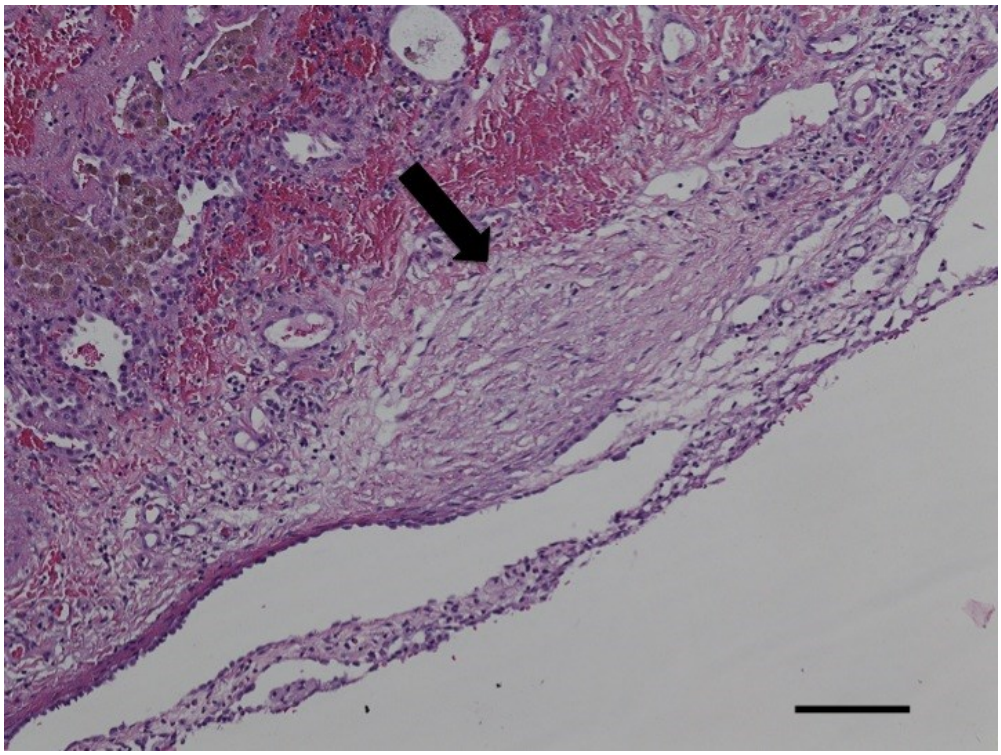

Figure 13: Fibroblastic focus (hematoxylin-eosin, original magnification x100)

Most patients, 126 patients (79%) present fibrosis in histological analysis, illustrated in Figure 14. Out of that 113 patients (71%) show few fibrosis, 13 patient (8%) show plenty of fibrosis. 33 patients (20%) do not present fibrosis.

Figure 14: Fibrosis. Formation of subpleural (➡) and septal (▼) fibrous connective tissue, thickening of alveolar walls (◆) (hematoxylin-eosin, original magnification x20)

More than half, 92 patients (58%) show mesothelial reaction, seen in Figure 15. Out of that, 71 patients (45%) present few mesothelial reaction and 21 patients (13%) show numerous mesothelial changes. In 67 cases (42%) no mesothelial reaction was found.

Figure 15: Mesothelial reaction. Proliferation of mesothelial cells (⟵) (hematoxylin-eosin, original magnification x 40)

In 116 patients (73%) eosinophilic pleuritis is detected. Out of that, 98 patients (62%) show few eosinophilic pleuritis, 17 patients (11%) moderate eosinophilic pleuritis and 1 patient (1%) suffers from severe eosinophilic pleuritis. Over half of the study population does not show the presence of one or more bullae, 91 patients (57%) had no sign of bullae. 66 patients (42%) present bullae, the histological findings are demonstrated in Figure 16.

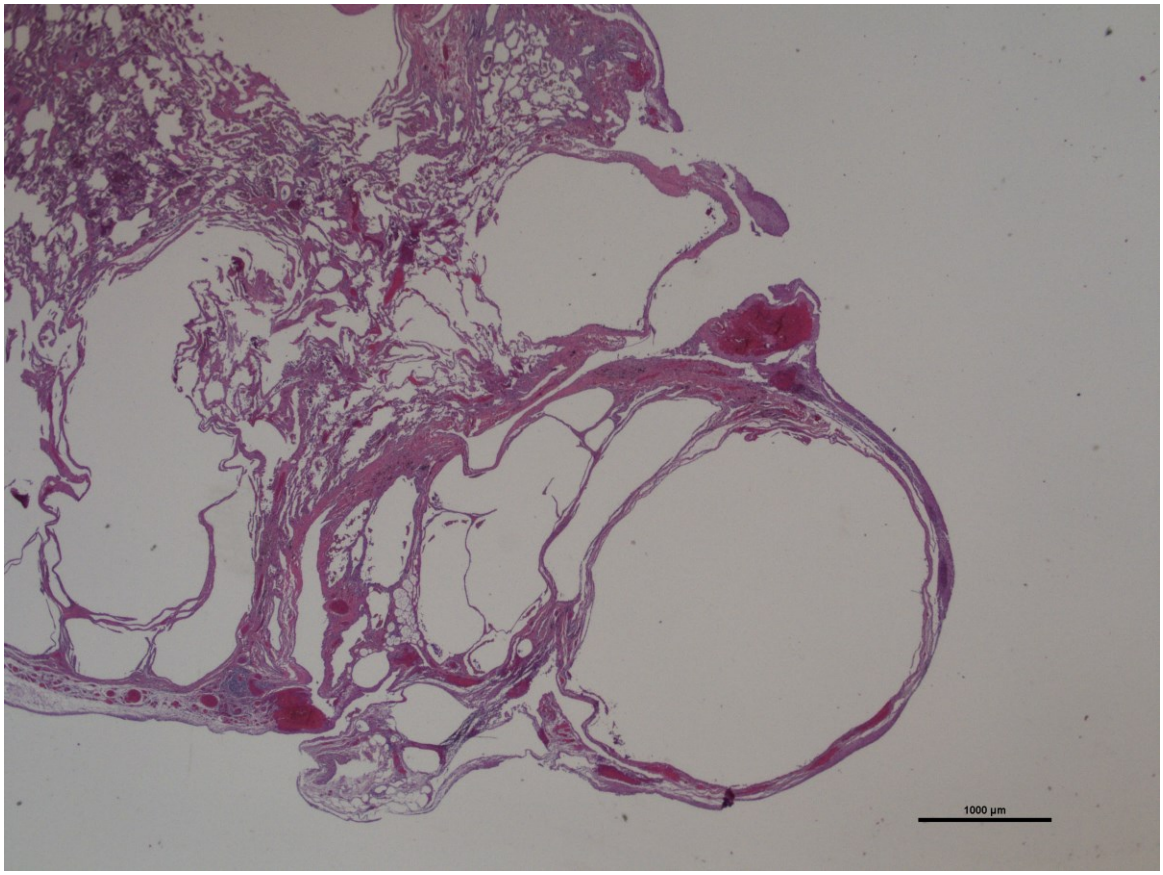

Figure 16: Bulla. Well-defined cavitiy > 1cm in size with a thin wall (hematoxylin-eosin, original magnification x10)

Nearly all patients, 141 patients (89%) show inflammatory reaction in histology samples, shown in Figure 17. 18 patients (11%) show no sign of inflammation in the lung tissue.
In inflammatory infiltrates, lymphocytes are dominating, to a variable extent, also plasma cells as well as neutrophile granulocytes are found.

Figure 17: Lung tissue with numerous lymphocytes (hematoxylin-eosin, original magnification x40)

3.3 Comparison fibroblastic foci - no fibroblastic foci

Fibroblastic foci are regarded as hallmark lesions of the pattern of usual interstitial pneumonia, a severe interstitial lung disease with a grave prognosis. However, their role in the context of spontaneous pneumothorax has not been studied in detail. In order to see whether these fibroblastic foci are associated with demographic or clinical parameters, we stratified our patients into two groups depending on the presence (88 patients, 55%) or absence (71 patients, 45%) of fibroblastic foci. Statistical analysis shows significant differences between the two groups in age, height, BMI and PY as illustrated in Table 8.

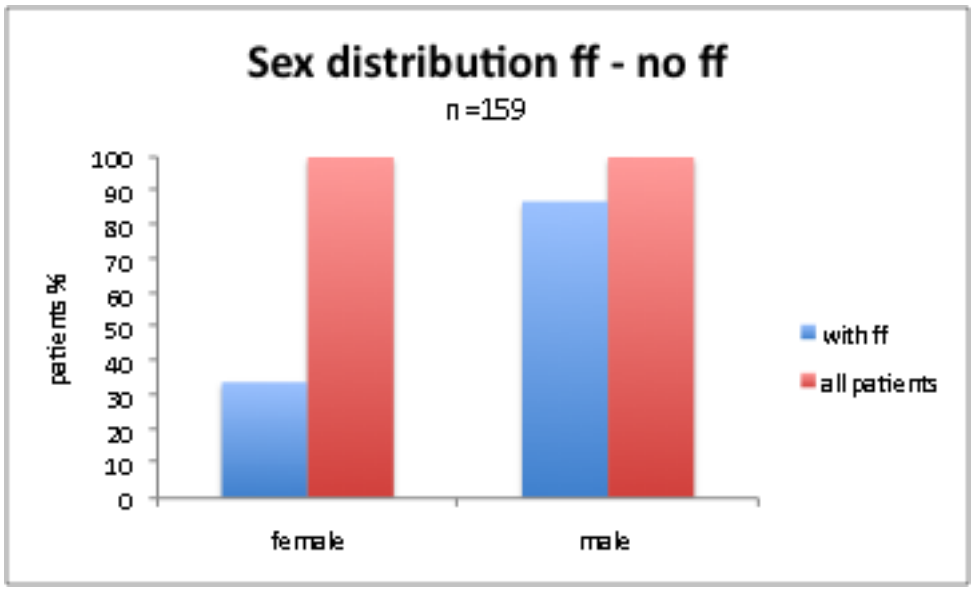

Figure 18: Sex distribution. Female and male patients and the amount of fibroblastic foci (ff) within the group.

Patients with fibroblastic foci are younger (27.8 years ± SD 10.7) than patients without fibroblastic foci (35.8 ± SD 13.8, $P = 0.008$).

In the group with fibroblastic foci patients are significantly taller (1.79m ± SD 0.09) than in the group without fibroblastic foci (1.75m ± SD 0.11, $P = 0.012$).

Patients with the presence of fibroblastic foci show a lower BMI (20.4 ± SD 2.4) than patients without the fibroblastic foci pattern (22.1 ± SD 3.5, $P= 0.001$).

The pack-year amount in the group with fibroblastic foci is lower (6.5 ± SD = 9.3) than in the group without fibroblastic foci (10.2 ± SD 17.9, $P = 0.063$).

There was a significant association between the sex and fibroblastic foci, ($P = 0.002$) as fibroblastic foci tend to occur more often in male patients (87% of men) than female patients (34% of women), as seen in Figure 18.

There was a significant association between fibrosis and fibroblastic foci. Fibrosis is more common in patients with fibroblastic foci ($P = 0.004$).

77 patients (61%) with fibroblastic foci show fibrosis, compared to 49 patients (39%) without fibroblastic foci but fibrosis.

There was a significant association between bullae and fibroblastic foci ($P = 0.04$). Bullae are more common in patients with fibroblastic foci (65%) than in patients without fibroblastic foci (35%).

There was a significant association between lymphocytic interstitial inflammation and fibroblastic foci ($P = 0.015$). 82 patients (59 %) with fibroblastic foci show presence of lymphocytes, compared to 57 patients (41 %) without fibroblastic foci.

	Patients with ff	Patients without ff
Age (yr)	28 ± 11	36 ± 14
Height (m)	1.8 ± 0.09	1.75 ± 0.11
BMI	20.4 ± 2.4	22.1 ± 5.5
PY	6.5 ± 9.3	10.2 ± 17.9
Fibrosis (%)	61	49
Bullae (%)	65	35
Lymphocytes (%)	59	41

Table 8: Demographic table showing the differences between patients with fibroblastic foci (ff) and patients without fibroblastic foci. Data are shown as ± SD.

3.4 Comparison no relapse – relapse

Two groups were formed, dividing patients with no relapse and patients with relapse. Personal and histological criteria were compared and analyzed. The first group includes patients with the one or more relapse of pneumothorax (n = 110), the second group includes patients without relapse (n = 49). Statistical analysis shows no significant differences between the two groups in all histological and personal criteria.

3.5 Comparison one relapse – more relapses

Two groups were formed, dividing patients with a singular relapse and patients with multiple relapses. Personal and histological criteria were compared and analyzed. The first group includes patients with only one relapse of pneumothorax (n = 66), the second group includes patients with more than one relapse (n = 19). Statistical analysis shows no

significant differences between the two groups regarding all histological and personal criteria.

4 Discussion

Spontaneous pneumothorax may occur with no underlying disease or may be associated with a wide variety of disorders (lung diseases and systemic diseases alike). Most authors believe that the underlying cause of PTX is a spontaneous rupture of a subpleural bleb or bulla. In 2012, the presence of fibroblastic foci in a subset of spontaneous PTX was described by Deborah for the first time. With that in mind we carefully reanalysed the lung tissue of 159 patients with PTX as well as their clinical history to see if and to which extent this specific pattern also exists in our study group. In addition, patients with and without relapses and also in the group of different relapse frequency were compared and analysed. Furthermore, we aimed to elucidate associtions of certain histopathological and clinical findings.

Analyses show that the average pneumothorax patient is male and around 1.8 m tall. The BMI is in the range between underweight and normal. In general, PTX patients are smokers, but interestingly, the number of PY is in the lower range. The bigger part of the group shows the presence of lung disease, in most cases emphysema and interstitital inflammation. Systemic diseases are not frequently encountered. Patients show an ASA score between 1 and 2, meaning most patients are healthy or show a mild systemic disease. PTX may occur once, however, it may come in several episodes. If PTX occurs in female patients, the onset of the first PTX is later than in men. More women present with an underweight BMI than men.

Histological features with a high incidence are smoker´s macrophages, fibroblastic foci, fibrosis, eosinophilic granulocytes, mesothelial reaction and interstitial inflammation with lymphocytes predominating. In the majority of patients fibroblastic lesions are seen.

Patients with fibroblastic foci tend to be male, younger than the other PTX patients, taller, show a lower BMI and a shorter history of smoking. Patients with fibroblastic lesions also show a higher incidence of fibrosis, bullae and interstitial lymphocytic infiltrates.

There are no significant differences between patients with one PTX, two or more.

Bösch et al. (2014) claims that there is a biphasic age distribution, the first peak between 15 and 35 years (mainly 1° PTX) and the second peak over 55 years (mainly 2° PTX) (6), however, in our cohort we cannot confirm that finding. Most of the patients (75%) are younger than 37 years old, although we did not divide the study population in 1°

PTX and 2° PTX. Further studies are required with a higher number of patients in order that a statement can be made.

The epidemiological study by Gupta et al. (2000) found out that in women the PTX onset is later (between 30 and 34 years) than in men (7). Our research confirms that with the median age of 36 in female patients, compared to men with the median age of 30. Gupta et al. (2000) also argues that the cause for this gender-related difference remains still unknown, but features associated in male patients (cigarette smoking and tall leptosome habitus) are less frequently found in women (8), (9). Also, we can not confirm the leptosome habitus in women because we do not have a control group with healthy lungs for body weight and size which is the major limitation of the study presented herein. Women also show a lower incidence of smoking than men. Therefore, the lower amount of smoking may be the real reason for a lower incidence of PTX in female patients.

Predispositions such as tall slim habitus, low BMI, lung dissease (1), (2), (5), (30), (31) are also found in our majority of the study population and may be assumed to take part of the cause of the formation of a PTX.

Kroegel (2014) claims that the relapse rate is between 20 and 30% after the first episode of a pneumothorax (5). Our study shows that the relapse rate is in fact much higher as even 52% suffer from a second pneumothorax after the first onset. Only 30% suffer from a one-time PTX. It may be possible that our relapse rate is higher than compared to other studies because our study includes already selected patients. Histological features such as emphysema, fibrosis, bullae, inflammation, mesothelial reaction and pigmented macrophages (29) can also be seen in the majority of our cases. Altough we claim that not only the signs mentioned above are the common pathological features, also fibroblastic foci are a feature frequently encountered in PTX. Deborah et al. (2012) reports an association between the incidence of fibroblastic foci and PTX for the first time. We can confirm this, although we do not have a control group with healthy lungs. Our study also demonstrates that fibroblastic foci occur more often in younger, taller PTX patients and show a lower BMI compared to the other PTX patients. Although patients with fibroblastic foci are younger than the patients without fibroblastic foci the incidence of fibrosis, bullae and lymphocytes are higher in the group with fibroblastic foci. Kroegel (2014) and Hien (2014) say that patients, who suffer from 1° PTX are normally younger and do not present any underlying lung disease (5), (13). In our studies younger patients with fibrolastic foci show a higher incidence of fibrosis, bullae and lymphocytes. There are no differences in patients with only one PTX or one or even more relapses. Chih-Yung Chiu et al. (2014)

also claims that factors such as smoking status, BMI and number of bullae are not showing a significant higher recurrence rate (57). We assume that the incidence of relapses does not correlate with our analysed features. Also the lungs may not change from one relapse to another. Spezialised researches show more detailed information, which would have gone beyond of scope in this thesis.

Patients with pneumothoraces show common personal and histological features. On the one hand predispositions like slim, tall habitus with an underweight BMI, smoking and lung disease lead to PTX and the other hand changes of the lung tissue including smoker´s macrophages, fibroblastic foci, fibrosis, eosinophilic granulocytes, mesothelial reaction and interstitial inflammation are frequently seen. Young patients who were assumed as healthy without any underlying lung disease show definitive changes of the lung tissue inlcuding a higher incidence of fibroblastic foci, fibrosis, bullae and lymphocytes.

Fibroblastic foci are surprisingly often seen in our cohort of patients with PTX. However, it still cannot be determined whether these lesions contribute to the pathogenesis of this disease or whether they are a hallmark of wound healing in affected tissue. Their role in the context of PTX remains elusive. Further studies in this respect are warranted to gain more information.

5 Bibliography

(1) Stephen Chapman, Grace Robinson, John Stradling, Sophie West, John Wrightson: Oxford Handbook of Respiratory Medicine. Oxford University Press, 2014. P. 371-381
(2) Stephen J. Bourke and Graham P. Burns: Respiratory Medicine lecture Notes. Eight Edition, John Wiley & Son, 2011. P. 167-173
(3) Fraser John H Brims, Nick A Maskell: Ambulatory treatment in the management of pneumothorax: a systematic review of the literature. Thorax 2013; 68: 664–669. doi:10.1136/thoraxjnl-2012-202875
(4) Emerson C. Pneumothorax: a historical, clinical, and experimental study. John Hopkins Hosp Rep 1903;11:1–450
(5) Claus Kroegel, Urlich Costabel: Klinische Pneumologie. Thieme Verlag, 2014. P. 525-538
(6) Dennis Bösch, Jan Steffel, Thomas Lüscher: Lunge und Atemwege. Springer Verlag, 2014. ISBN 978-3-642-28222-5. P. 141-145 (german)
(7) Gupta D, Hansell A, Nichols T,et al: Epidemiology of pneumothorax in England. Thorax 2000;55:666–71
(8) Lippert HL, Lund O, Blegvad S, et al.: Independent risk factors for cumulative recurrence rate after first spontaneous pneumothorax. Eur Respir J 1991;4:324–31
(9) Bense L, Eklund G, Wiman LG. Smoking and increased risk of contracting spontaneous pneumothorax. Chest 1987;92:1009–12
(10) Stephen G. Spiro, Gerard A. Silvestri, Alvar Agusti: Clinical Respiratory Medicine. Fourth edition, Elsevier Saunders, 2012. P. 831-836
(11) Noppen M, Schramel F. Pneumothorax. Eur Respir 2002; 22: 279–296
(12) Light RW. Management of spontaneous pneumothorax. Am Rev Respir Dis 1993; 148: P.245–248
(13) Hien: Praktische Pneumologie. 2.Auflage. Springer Verlag Berlin, Heidelberg, 2014. (German) 10.1007/978-3-642-10209-7. ISBN 978-3-642-10207-3
(14) Steven A. Sahn, M.D., and John E. Heffner, M.D.: Spontaneous Pneumothorax. N Engl J Med 2000; 342:868-874. DOI: 10.1056/NEJM200003233421207
(15) Mitlehner W , Friedrich M, Dissmann W.: Value of com-puter tomography in the detection of bullae and blebs in patients with primary spontaneous pneumothorax. Respiration 1992; 59: 221–227
(16) Lesur O, Delorme N, Fromaget JM, et al.: Computed tomography in the etiologic assessment of idiopathic spontaneous pneumothorax. Chest 1990; 98: 341–347
(17) Lesur O, Delorme N, Fromaget JM, Bernadac P, Polu JM.: Computed tomography in the etiologic assessment of idiopathic spontaneous pneumothorax. Chest 1990; 98: 341–347
(18) Schramel, Postmus, Vanderschueren.: Current aspects of spontaneous pneumothorax. Eur Respir J 1997; 10: 1372–1379 DOI: 10.1183/09031936.97.10061372
(19) Fukuda Y , Haraguchi S, T anaka S, Y amanaka N.: Pathogenesis of blebs and bullae of patients with spontaneous pneumothorax: ultrastructural and immunohis- tochemical studies. Am J Respir Crit Care Med 1994; 149: A1022
(20) Tetely TD. Proteinase imbalance: its role in lung disease. Thorax 1993; 48: 560–565.
(21) Wallaert B, Gressier B, Marquette CH, et al.: Inactivation of alpha1-proteinase inhibitor by alveolar inflammatory cells from smoking patients with or without emphyse- ma. Am Rev Respir Dis 1993; 147: 1537–1543
(22) Kondo T, Tagami S, Yohioka A, Nishiruma M, Kawakami Y.: Current smoking of elderly men reduces antioxidants in alveolar macrophages. Am Rev Respir Dis 1991; 143: 144–149
(23) Adesina AM, Vallyathan V, McQuillen EN, Weaver SO, Craighead JE.: Bronchiolar inflammation and fibrosis associated with smoking: a morphologic cross-sectional population analysis. Am Rev Respir Dis 1991; 143: 144–149
(24) Hunninghake GW, Crystal RG.: Cigarette smoking and lung destruction: accumulation of neutrophils in the lungs of cigarette smokers. Am Rev Respir Dis 1983; 128: 833–838
(25) Sibille Y., Reynolds HY : Macrophages and polymor- phonuclear neutrophils in lung defense and injury: state of the art. Am Rev Respir Dis 1990; 141: 471–501
(26) Robbins RA, Gossman GL, Nelson KJ, Koyama S, Thompson AB, Rennard SI.: Inactivation of chemotacic factor inactivator by cigarette smoke: a potential mechanism of modulating neutrophil recruitment to the lung. Am Rev Respir Dis 1990; 142: 763–768
(27) Dermksian G, Lamb LE.: Spontaneous pneumothorax in apparently healthy flying personnel. Ann Intern Med 1959; 51: 39–51
(28) Weiss LD, van Meter KW.: Cerebral air embolism in asthmatic scuba divers in a swimming pool. Chest 1995; 107: 1653–1654
(29) Bryan Corrin, Andrew G. Nicholson: Pathology of the lungs. Second Edition, Churchill Livingstone, 2006. P. 694-695

(30) Amjadi K, Alvarez GG, Vanderhelst E, et al.: The prevalence of blebs and bullae among young healthy adults: a thoracoscopic evaluation. Chest 2007; 132: 1140–1145. doi: 10.1631/jzus.B1000131
(31) Coxson HO, Chan IHT, Mayo JR, et al.:Early emphysema in patients with anorexia nervosa. Am J Respir Crit Care Med 2004; 170: 748–752
(32) MacDuff A, Arnold A, Harvey J: BTS Pleural Disease Guideline Group (December 2010). "Management of spontaneous pneumothorax: British Thoracic Society pleural disease guideline 2010". Thorax 65 (8): ii18–ii31. doi:10.1136/thx.2010.136986. PMID 20696690.
(33) Dermksian G, Lamb LE.: Spontaneous pneumothorax in apparently healthy flying personnel. Ann Intern Med 1959; 51: 39–51
(34) Wolfgang Hien: Arbeitspapiere Berufskrankheiten Nr. 1 Arbeits- und berufsbedingte obstruktive Lungenerkrankungen – Kenntnisstand und Hinweise für die Praxis des Berufskrankheiten-Verfahrens. Bremen 2014 (german)
(35) Jeske A et al. (1993) Results of thoracocscopy and pleurodesis with talc poudrage and thoracotomy. Chest. 103:345-347
(36) Randomsky JBD, Hartel W.: Pleuraporosität bei idiopatischen Spontanpneumothorax. Pneumologie 1989; 43: 250-253.
(37) Masshof W, Hofer W: Zur Pathologie der sogenanntenn idiopathischen Spontanpneumothorax. Deutsche Medizinische Wochenzeitschrift 1973; 98: 801- 805
(38) Olhata M, Suzuki H: Pathogenesis of spontaneous pneumothorax. With special reference to the ultrastructure of emphysematous bullae. Chest 1980; 77: 771-776
(39) C. Thomas et al.: Spezielle Pathologie. Schattauer Verlag, 1996. ISBN 3-7945-2326-1. P. 129 (german)
(40) Mayo Clinic Staff. "Complications". Mayo Foundation for Medical Education and Research. Retrieved 26th July 2014
(41) Gross TJ, Hunninghake GW. (2001).: "Idiopathic pulmonary fibrosis". N Engl J Med 345: 517–525. doi:10.1056/NEJMra003200
(42) Mayo Clinic Staff. "Causes". Mayo Foundation for Medical Education and Research. Retrieved 26th July 2014
(43) Reynold HY.: Respiratory infections may reflect deficiencies in host defence mechanisms. Diseases Monthly 1985;31:1-98
(44) Sibille Y, Reynolds HZ.: Macrophages and polymorphonuclear neutrophils in lung defence and injury. State of the Art. Am Rec Respir Dis 1990;141:471-501
(45) Konietzko, Wendel, Wiesner: Erkrankungen der Lunge. De Gruyter. Berlin, 1994. ISBN: 3-11-012130-1. P. 214 (german)
(46) Rennard SI, Hnninghake GW, Bitterman PB, Crystal RG.: Production of fibronectin by the human alveolar macrophage: mechanisms of the recruitment of fibroblasts to sites of tissue injury in interstitial lung disease. Proc Natl Acad Sci 1981;78:7147-51
(47) D Macridou, D Laws: Case Report: Respiratory bronchiolitis associated interstitial lung disease (RB-ILD): a case of an acute presentation.Thorax 2004;59:910-911 doi:10.1136/thx.2003.011080
(48) Dennis E. Niewoehner, M.D., Jerome Kleinerman, M.D., and Donald B. Rice, M. Div: Pathologic Changes in the Peripheral Airways of Young Cigarette Smokers. N Engl J Med 1974; 291:755-758 October 10, 1974DOI: 10.1056/NEJM197410102911503
(49) Bense L, Lewander R, Eklund G, et al.: Non-smoking, non-alpha 1 antitrypsin deficiency-induced emphysema in nonsmokers with healed spontaneous pneumothorax, identified by computed tomography of the lungs. Chest 1993; 103: 433–438
(50) Lesur O, Delorme N, Fromaget JM, et al.: Computed tomography in the ethiologic assessment of idiopathic spontaneous pneumothorax. Chest 1990; 98: 341-347
(51) Deborah A. Belchis, MD; Kris Shekitka, MD; Christopher D. Gocke, MD.A Unique, Histopathologic Lesion in a Subset of Patients With Spontaneous Pneumothorax. Arch Pathol Lab Med. 2012;136:1522–1527; doi: 10.5858/arpa.2012-0330-OA
(52) KM Müller, M Kenter: Tabak-assoziierte siderophile und conchoide Speicherphänomene in Rauchermakrophagen mit Riesenzellen. Pneumologie 2013; P. 67 - 44 DOI: 10.1055/s-0033-1334697. (german)
(53) http://www.vbdo.at/artikel/einblick/blick11/index.htm Austria: VBDO – Verband für Bildgebende Diagnostik Österreich, updated June 2001, seen on 30th July 2015 (german)
(54) MacDuff A, Arnold A, Harvey J: Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. Thorax 65(Suppl 2):ii18–ii31. doi:10.1136/thx.2010.136986
(55) Baumann MH, Strange C, Heffner JE, Light R, Kirby TJ, Klein J, Luketich JD, Panacek EA, Sahn SA (February 2001): "Management of spontaneous pneumothorax: an American College of Chest

Physicians Delphi consensus statement". Chest 119 (2): 590–602. doi:10.1378/chest.119.2.590. PMID 11171742
(56) Shields, Thomas: General Thoracic Surgery. Lippincott Williams & Wilkins, 2004. P. 524 ISBN 978-0-7817-3889-7