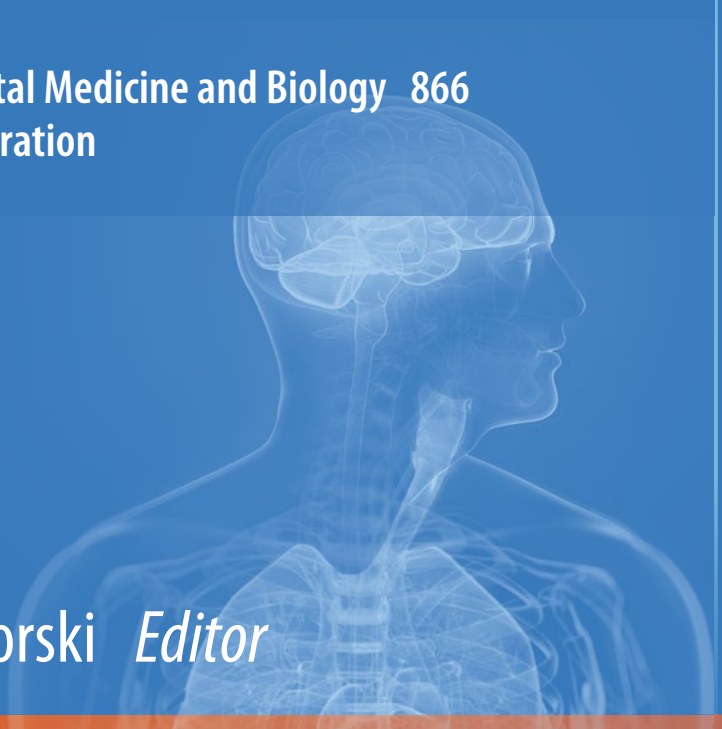
Advances in Experimental Medicine and Biology 866
Neuroscience and Respiration



Mieczyslaw Pokorski *Editor*

Noncommunicable Diseases

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Advances in Experimental Medicine and Biology

Neuroscience and Respiration

Volume 866

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Noncommunicable Diseases

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Preface

The book series *Neuroscience and Respiration* presents contributions by expert researchers and clinicians in the field of pulmonary disorders. The chapters provide timely overviews of contentious issues or recent advances in the diagnosis, classification, and treatment of the entire range of pulmonary disorders, both acute and chronic. The texts are thought as a merger of basic and clinical research dealing with respiratory medicine, neural and chemical regulation of respiration, and the interactive relationship between respiration and other neurobiological systems such as cardiovascular function or the mind-to-body connection. The authors focus on the leading-edge therapeutic concepts, methodologies, and innovative treatments. Pharmacotherapy is always in the focus of respiratory research. The action and pharmacology of existing drugs and the development and evaluation of new agents are the heady area of research. Practical data-driven options to manage patients will be considered. New research is presented regarding older drugs, performed from a modern perspective or from a different pharmacotherapeutic angle. The introduction of new drugs and treatment approaches in both adults and children also is discussed.

Lung ventilation is ultimately driven by the brain. However, neuropsychological aspects of respiratory disorders are still mostly a matter of conjecture. After decades of misunderstanding and neglect, emotions have been rediscovered as a powerful modifier or even the probable cause of various somatic disorders. Today, the link between stress and respiratory health is undeniable. Scientists accept a powerful psychological connection that can directly affect our quality of life and health span. Psychological approaches, by decreasing stress, can play a major role in the development and therapy of respiratory diseases.

Neuromolecular aspects relating to gene polymorphism and epigenesis, involving both heritable changes in the nucleotide sequence and functionally relevant changes to the genome that do not involve a change in the nucleotide sequence, leading to respiratory disorders will also be tackled. Clinical advances stemming from molecular and biochemical research are but possible if the research findings are translated into diagnostic tools, therapeutic procedures, and education, effectively reaching physicians and patients. All these cannot be achieved without a multidisciplinary, collaborative, bench-to-bedside approach involving both researchers and clinicians.

The societal and economic burden of respiratory ailments has been on the rise worldwide, leading to disabilities and shortening of life span. COPD alone causes more than three million deaths globally each year. Concerted efforts are required to improve this situation, and part of those efforts are gaining insights into the underlying mechanisms of disease and staying abreast with the latest developments in diagnosis and treatment regimens. It is hoped that the books published in this series will assume a leading role in the field of respiratory medicine and research and will become a source of reference and inspiration for future research ideas.

I would like to express my deep gratitude to Mr. Martijn Roelandse and Ms. Tanja Koppejan from Springer's Life Sciences Department for their genuine interest in making this scientific endeavor come through and in the expert management of the production of this novel book series.

Opole, Poland Mieczyslaw Pokorski

Volume 15: Noncommunicable Diseases

Diseases of the respiratory system often cause multisystem dysfunction and morbidity. Respiratory diseases not transmissible by a direct contact are rarer than those of inflammatory or infectious background. Such noncommunicable diseases, often entailing genetic and immune aspects, are areas of limited understanding; sarcoidosis being a case in point. This book tackles the issues relevant to such diseases. The research on novel cytokine markers, which may help in the diagnosis and management of sarcoidosis, is described. Modern approaches to the management of pneumothorax, a frequent accompaniment of lung diseases or chest wall trauma are dealt with as well. There are also chapters that underscore the immuno-inflammatory mechanisms of disorders seemingly unrelated to respiration, such as obesity or aplastic anemia, which may appreciably affect the control of the respiratory system and thus its vulnerability to diseases. The book will be of interest to clinicians and medical researchers.

Contents

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Interleukin-33 as a New Marker of Pulmonary Sarcoidosis

W. Naumnik, B. Naumnik, W. Niklińska, M. Ossolińska, and E. Chyczewska

Abstract

The mechanisms of sarcoidosis (Besniera-Boeck-Schaumann disease, BBS) remain incompletely understood, although recent observations suggested an important contribution of interleukin-33 (IL-33). So far, there are no data about bronchoalveolar lavage fluid (BALF) concentration of IL-33 in patients with BBS. In the present study we attempted to relate the concentration of IL-33 to IL-18, a well-known marker of BBS activity, in BALF of BBS patients. We examined 24 BBS patients (stage II). The age-matched control group consisted of 24 healthy subjects. The levels of IL-33 and IL-18 in BALF were higher in BBS patients than in the control group [IL-33: 4.8 (0.1–12.5) *vs.* 3.4 (0.6–56.9) pg/ml, p = 0.024; IL-18: 33.2 (5.7–122.0) *vs.* 10.8 (1.9–45.8) pg/ml, p = 0.002]. In the BBS group, the correlations between IL-33 and IL-18 (r = 0.606, p = 0.002), and between IL-33 and diffusion lung capacity for carbon monoxide (DLCO) (r = −0.500, p = 0.035) were found. The receiver-operating characteristic curves were applied to find the cut-off serum levels of IL-33 and IL-18 in BALF (BBS *vs.* healthy: IL-33 2.7 pg/ml and IL-18 16.4 pg/ml). We conclude that IL-33 appears an important factor of pulmonary BBS activity.

Keywords

Bronchoalveolar lavage fluid • Interleukin-33 • Interleukin-18 • Disease marker • Sarcoidosis

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1 Introduction

Sarcoidosis is a multisystem immunologic disorder of unknown etiology, characterized initially by a Th (T-helper) lymphocyte/macrophage alveolitis and later by the formation of epithelioid cell granulomas (Cui et al. 2010). The mechanisms of sarcoidosis (Besniera-Boeck-Schaumann disease, BBS), the most common interstitial lung disease (ILD), remain incompletely understood, although recent observations have suggested an important contribution of interleukin 33 (IL-33) (Luzina et al. 2013). IL-33 can be classified as an alarmin because it is released into the extracellular space following cell damage or tissue injury and acts as an endogenous danger signal by sending out warning signals to alert neighbouring cells and tissues (Liew et al. 2010). IL-33 was thought to be mainly involved in initiating and perpetuating Th2-driven responses and activating mast cells, due to the fact that these two cell types express high amounts of ST2 (the interleukin-1 receptor family member), the cell-surface receptor of IL-33 (Schmitz et al. 2005). Recently many studies have revealed that IL-33 is associated with suppressing of Th1 responses, which plays a major role in patients with sarcoidosis (Rostan et al. 2013; Smithgall et al. 2008). Moreover, IL-33 is involved in the control of cell cycle progression in endothelial cell and regulation of angiogenesis (Martin 2013). Li et al. (2014) showed that IL-33 promotes lung fibrosis in mice. Some patients with BBS can develop lung fibrosis at a later stage of disease (Cui et al. 2010). Angiogenesis may contribute to fibroproliferation, which may lead to novel therapeutic options. According to some authors there is an association between interleukin 18 (IL-18) and activity of pulmonary sarcoidosis (Liu et al. 2010). There have been no data about concentrations of IL-33 in patients with sarcoidosis so far. Therefore, in the present study we aimed to compare the concentration of IL-33 to IL-18.

2 Methods

The study was conducted in conformity with the Declaration of Helsinki for Human Experimentation of the World Medical Association. The protocol was approved by a local Ethics Committee and written informed consent was obtained from all participants.

2.1 Patients and Control Subjects

The study group included 24 patients with lung sarcoidosis (BBS). Patients were in stage 2 of BBS (bilateral hilar lymphadenopathy and pulmonary infiltrations: F/M - 5/19, mean age 40 ± 8 years) recruited at the Department of Lung Diseases, the Medical University of Białystok in Poland, in 2009–2013. We diagnosed patients according to the current clinical and pathological guidelines (Statement on sarcoidosis 1999). The control group consisted of 24 healthy volunteers (F/M - 5/19, mean age 39 ± 9 years) without any inflammatory conditions. All patients and control subjects underwent BALF and lung function tests (vital capacity, VC, and diffusing capacity for carbon monoxide, DLCO) (Standardization of Spirometry 1994 Update. American Thoracic Society 1995). We performed bronchofiberoscopy with BALF as part of a routine clinical management. We used fiberoptic bronchoscope (Pentax FB 18 V, Pentax Corporation, Tokyo, Japan) under local anesthesia with lidocaine, following premedication with intramuscular atropine and hydroxyzine as a sedative. The bronchoscope was inserted and wedged in the right middle lobe, and three 50 ml aliquots of sterile saline solution, warmed to 37 °C, were instilled and recovered from the subsegmental bronchus by suction. The recovered fluid was filtered through 2 layers of sterile gauze and subsequently centrifuged at 800 rpm for 10 min at 4 °C. Supernatant was stored at −70 °C until use. BALF samples were analyzed for total and differential cell counts, flow cytometry to measure CD4+, and CD8+ lymphocyte counts, and for IL-33 and IL-18 detected by Elisa. Cell differentials were made on smears stained by Grünwald-Giemza by counting at least 400 cells under a light microscope (magnification × 1000). Another part of the BALF (cell suspension) was

incubated with phycoerythrin-labeled anti-CD4 antibody and fluorescein isothiocyanate-labeled anti-CD8 antibody (Becton Dickinson, Mountain View, CA) for 20 min, washed twice. Flow cytometry was performed using Becton Dickinson flow cytometer that detects lymphocytes by fluorescence. The percentages of positively stained cells were scored to determine the number of CD4 and CD8 cells.

2.2 Concentrations of IL-33 and IL-18 in BALF

Concentrations of IL-33 were measured by commercially available enzyme-linked immunosorbent assays (ELISA) (eBioscience, San Diego, CA) and (MBL International, Woburn, MA, respectively). The assays were performed according to manufacturers' recommendations. The minimum detectable levels of IL-33 and IL-18 were 0.2 pg/mL and 1.5 pg/ml, respectively.

2.3 Statistical Analysis

The Shapiro-Wilk test was used for data distribution analysis. We used a *t*-test to calculate the parametrical data. The Mann-Whitney U and Wilcoxon tests were used for the features inconsistent with normal data distribution. Spearman's rank test was used to calculate correlations between the parameters and receiver-operating characteristics (ROC) curves to find the cut-off levels of IL-33 and IL-18. A value of $p < 0.05$ was considered to indicate statistical significance. We used Statistica 10.0 software (StatSoft Inc., Tulsa, USA) for all analyses.

3 Results

There were no appreciable differences in age or gender between the patient and control groups. Concerning pulmonary function, BBS patients had lower %VC and %DLCO than those in healthy persons (%VC: 82.1 ± 21.2 *vs.* 96.4 ± 6.0, p = 0.02; %DLCO: 80.1 ± 25.0 *vs.* 95.3 ± 9.0, p = 0.01).

The levels of IL-33 and IL-18 in BALF were higher in the BBS patients than those in the control group [IL-33: 4.8 (0.1–12.5) pg/ml *vs.* 3.4 (0.6–56.9) pg/ml, p = 0.024; IL-18: 33.2 (5.7–122.0) pg/ml *vs.* 10.8 (1.9–45.8) pg/ml, p = 0.004] (Fig. 1a, b). There was a positive correlation between BALF levels of IL-33 and IL-18 in the BBS group (r = 0.606, p = 0.002) (Fig. 2).

The ROC curves show that specificity and sensitivity of BALF IL-33 in the BBS patients in relation to healthy people were 59 % and 95 %, respectively, at a cut-off value of 2.699 pg/ml. Specificity and sensitivity of BALF IL-18 in the BBS patients in relation to healthy people were 28 % and 80 %, respectively, at a cut-off value of 16.436 pg/ml. The areas under the curve for IL-33 and IL-18 in BALF were 0.683 and 0.781, respectively (Fig. 3).

In the BBS group, DLCO% correlated negatively with IL-33 (r = −0.512, p = 0.035) (Fig. 4a), and IL-18 (r = −0.596, p = 0.009; not shown) in BALF. Moreover, a positive correlation was found between IL-33 and the percentage of lymphocytes (r = 0.45, p = 0.032) in BALF (Fig. 4b).

The percentage of lymphocytes was higher, and that of macrophages was lower in BALF of BBS patients compared with those in the healthy group (%lymphocytes: 46.7 ± 28.0 *vs.* 16.1 ± 7.0, p = 0.002; %macrophages: 59.4 ± 23.1 *vs.* 82.1 ± 15.0, p = 0.003). The BBS patients had a higher percentage of CD4+ in BALF than healthy subjects (%CD4+: 48.4 ± 13.2 *vs.* 8.1 ± 0.3, p = 0.003). There were no significant differences between the percentage of CD8+ in BALF of BBS and control groups (CD8+: 15.3 ± 3.1 *vs.* 16.8 ± 4.2, p = 0.422).

4 Discussion

Mortality in patients with sarcoidosis is higher than that in the general population, due mainly to pulmonary fibrosis (Valeyre et al. 2014). The

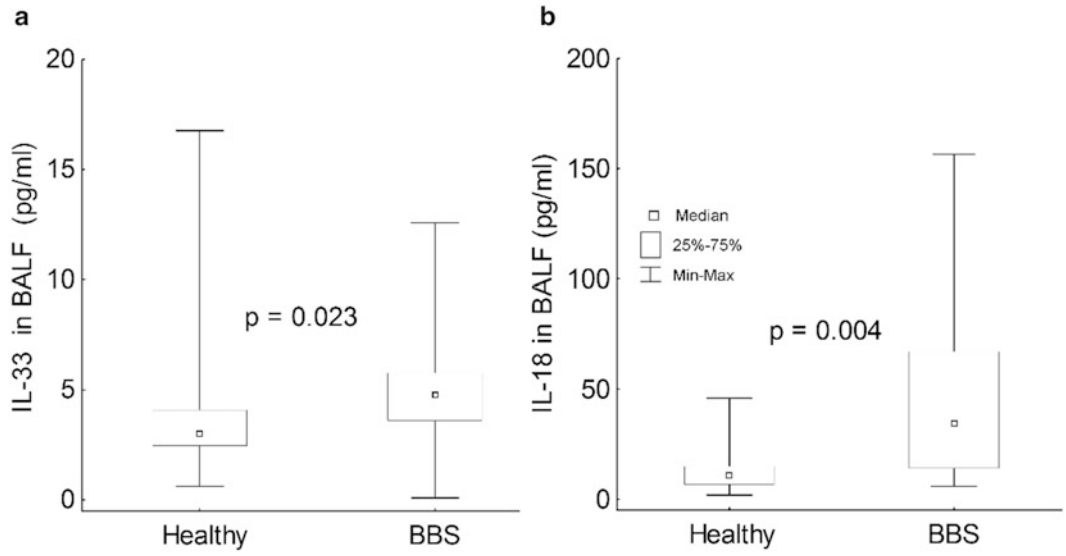

Fig. 1 **IL-33** (**a**) **and IL-18** (**b**) concentrations in BALF from sarcoidosis (BBS) patients and control subjects

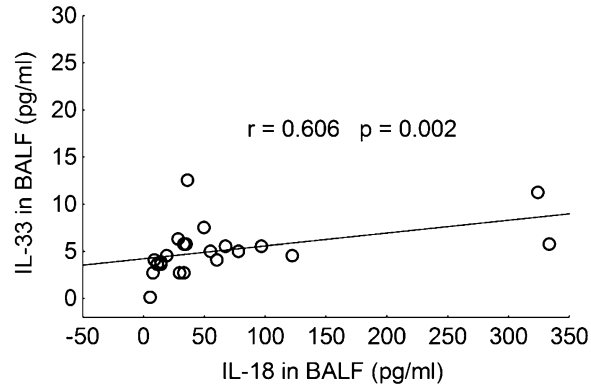

Fig. 2 **Correlation between IL-33 and IL-18** concentrations in BALF from sarcoidosis (BBS) patients

finding of the underlying mechanism of sarcoidosis and the elucidation of relevant biomarkers is key for future therapeutic advances. In the resent study, BBS patients had higher levels of IL-33 than those in healthy subjects. This observation is consistent with the study of Yang et al. (2011). Those authors described that IL-33 can contribute to the development of Th1-type of immune response as well as enhanced IL-18 secretion. There are many publications about Th1 immune responses in BBS, substantially less is known about cellular sources of IL-33. We found a correlation between the level of IL-33 and the percentage of lymphocytes in BALF from BBS patients. That may suggest that IL-33 is released from lymphocytes in these patients. The result is in line with a study of Zissel et al. (2010) who showed that an exaggerated immune response stemming from the close interaction between macrophages and T cells causes the formation of sarcoid lesions. Our observations are not in accord with a study of Baekkevold et al. (2003) who described that IL-33 is released by endothelial and epithelial cells, but are consistent with a study of Kempf et al. (2014) who demonstrated that granulomas are a source of interleukin-33 expression in pulmonary and extrapulmonary sarcoidosis. Summarising, it is possible that IL-33 is released from both lymphocytes and epithelial cells. Epithelioid-cell-rich granulomas and

stimulation of T-cells plays a key role in the pathogenesis of sarcoidosis (Chen et al. 2011). IL-33 is released from stressed or damaged cells to the tissue microenvironment. This cytokine stimulates the proinflammatory interferon gamma and profibrotic factors such as transforming growth factor, insulin-like growth factor, and matrix metalloproteinases. All these factors are present at sites of inflammation in individuals with BBS (Kempf et al. 2014; Kakkar et al. 2012).

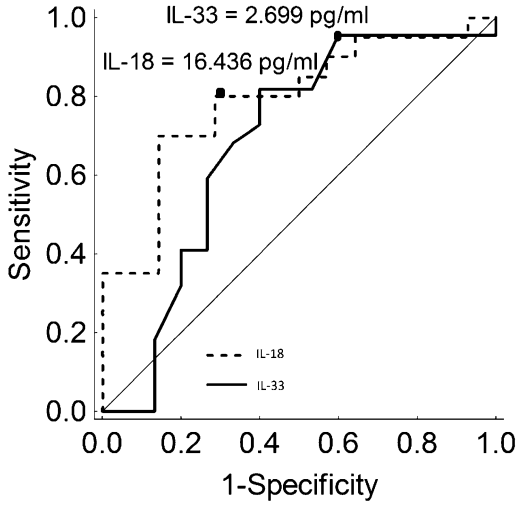

Fig. 3 Receiver operating characteristic (ROC) curve for IL-33 and IL-18 in BALF differentiating sarcoidosis (BBS) and healthy subjects (AUC 0.683 and 0.781, respectively)

IL-18 expression is increased in airway epithelial cells in active BBS (Kieszko et al. 2007). That finding is in accord with the present study in which BBS patients had a higher level of IL-18 in BALF than that in healthy subjects. IL-18 is defined as an inducer of Th1 response. This cytokine is produced by macrophages, dendritic cells, and airway epithelial cells (Okamura et al. 1995). IL-18 is considered as a good marker of BBS activity (Kieszko et al. 2007). In the present study, we found a strong correlation between the concentration of IL-33 and IL-18 in BALF from BBS patients. Moreover, the level of IL-33 correlated with DLCO. These results are consistent with the findings of Li et al. (2014) who showed that IL-33 could promote, enhancing the production of profibrotic factors, the process of chronic inflammation and fibroproliferation, contributing to pulmonary fibrosis and lung dysfunction. In order to fully verify this issue, sarcoidosis patients should be investigated at sequential stages of the disease. Our present patients were at stage II of BBS, without lung fibrosis. Liu et al. (2011) postulate that the measurement of circulating IL-18 might be of potential clinical utility in the differential diagnosis of BBS *versus* idiopatic pulmonary fibrosis.

We surmise that IL-33 may be a potent marker of BBS activity that can be used in clinical practice. A recent study of Kempf et al. (2014)

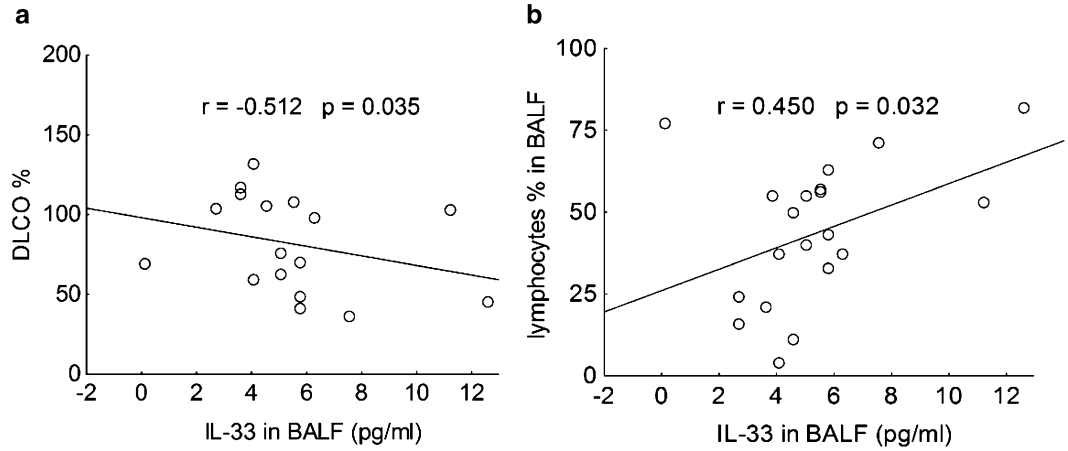

Fig. 4 Correlations between IL-33 and (a) DLCO and (b) %lymphocytes in BALF from sarcoidosis (BBS) patients

reported that IL-33 plays a critical role in the pathogenesis and progression of sarcoidosis. IL-33 expression in sarcoidosis seems to depend on the specific tissue microenvironment of sarcoid granulomas and represents a novel biomarker for systemic involvement. In summary, our present findings point to the possibility of practical use of IL-33 measurements. That could contribute to a more individualized treatment of patients.

Conflicts of Interest The authors had no conflicts of interest to declare in relation to this article.

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Finite Elements Modeling in Diagnostics of Small Closed Pneumothorax

J. Lorkowski, M. Mrzygłód, and O. Grzegorowska

Abstract

Posttraumatic pneumothorax still remains to be a serious clinical problem and requires a comprehensive diagnostic and monitoring during treatment. The aim of this paper is to present a computer method of modeling of small closed pneumothorax. Radiological images of 34 patients of both sexes with small closed pneumothorax were taken into consideration. The control group consisted of X-rays of 22 patients treated because of tension pneumothorax. In every single case the model was correlated with the clinical manifestations. The procedure of computational rapid analysis (CRA) for *in silico* analysis of surgical intervention was introduced. It included implementation of computerize tomography images and their automatic conversion into 3D finite elements model (FEM). In order to segmentize the 3D model, an intelligent procedure of domain recognition was used. In the final step, a computer simulation project of fluid-structure interaction was built, using the ANSYS\Workbench environment of multi-physics analysis. The FEM model and computer simulation project were employed in the analysis in order to optimize surgical intervention. The model worked out well and was compatible with the clinical manifestations of pneumothorax. We conclude that the created FEM model is a promising tool for facilitation of diagnostic procedures and prognosis of treatment in the case of small closed pneumothorax.

Keywords

Artificial intelligence • Computer modeling • Diagnostic • Finite elements method • In silico analysis • Pneumothorax

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1 Introduction

Pneumothorax means the presence of the air between parietal and visceral pleura, which entails lung collapse. As a consequence, there are a mediastinal shift to the opposite side, hemodynamic imbalance due to disordered perfusion/ventilation ratio, and hypoxia. Pneumothorax symptoms can be divided into early and late ones. The former are anxiety, tachypnea, respiratory distress, increased breathing effort, shock (hypotension and tachycardia), hyper-resonance and decreased breath sounds on the ipsilateral side, emphysema, and engorged neck veins if there is no hypovolemia. The latter appear as cyanosis and a shift of trachea to the opposite side. Cardiorespiratory failure and sudden cardiac arrest also can be observed, especially in case of tension pneumothorax. Tension pneumothorax is a serious clinical problem, which requires accurate and, quite often, rapid diagnostics and monitoring. One of the causes of tension pneumothorax is trauma. We distinguish closed, open, small closed, and tension type of pneumothorax, which can occur immediately or with some delayed after trauma (Plourde et al. 2014). It is known that mild general trauma involves the chest in about 12 %, while major trauma is accompanied by chest trauma in 47 % (Lorkowski et al. 2014a, b). Tension pneumothorax appears in about 5 % of major trauma victims in the pre-hospital setting and in 1–3 % of patients in intensive care units (Roberts et al. 2014). The small closed pneumothorax caries the lowest risk for patients (Lorkowski et al. 2013; Ball et al. 2005).

A problematic issue concerning pneumothorax is the choice of an optimal method for its diagnostic and treatment. In case of small pneumothorax, up to 15 % of lung volume or size less than 1.5 cm, conservative treatment and monitoring are advocated. Our earlier study shows that conservative treatment may possibly be extended to pneumothorax the size of up 2 cm (Lorkowski et al. 2013). A multicenter study performed in 569 blunt trauma patients shows that occult pneumothorax can be treated conservatively when linked with monitoring. An increase in the pneumothorax size or ongoing signs of respiratory failure necessitate the undertaking of invasive approach, such as decompression and drainage (Moore et al. 2011). Concerning the diagnostic methods, the choice is the following: auscultation and percussion, ultrasonography, radiography, and computer tomography. The ultrasound effectiveness depends much on the operator's skills and experience, but it shows higher sensitivity compared with radiography (Alrajab et al. 2013; Alrajhi et al. 2012; Ding et al. 2011). The value of the ultrasound examination has been appreciated in emergency in case of major trauma patients (Ianniello et al. 2014) and in positive-pressure ventilated patients (Oveland et al. 2013). Nevertheless, ultrasonography has limited diagnostic power in case of subcutaneous emphysema, obesity, adhesive pleura diseases, or emphysema (Kreuter and Mathis 2014). Among new methods developed for the diagnosis of pneumothorax, the measurements or computer analysis of pulmonary acoustic transmission, the latter connected with visualization are of note, but do not settle all the diagnostic difficulties involved (Hayashi 2011; Mansy et al. 2002a, b). Therefore, the aim of the present paper was to present a new method of modeling of small closed pneumothorax based on *in silico* mechanical-fluid analysis using fast 3D finite elements modeling (FEM).

2 Methods

The study was accepted by an institutional Review Board for Human Research and was performed in accord with the Declaration of Helsinki for Medical Research Involving Human Subjects. Radiological images of 34 patients, F/M – 11/23, mean age 48.5 years (range 20–84 years), with small closed pneumothorax were taken into consideration. The pneumothorax size was assessed on the basis of widely accepted criteria as a distance between visceral and parietal pleura, which in the anterior-posterior radiographic projection ranged from 0.5 to 2.0 cm (Henry et al. 2003). The

Table 1 Sequential steps of computational rapid analysis (CRA) using 3D finite elements modeling (FEM)

1	Computed tomography (CT) scanning
2	Conversion of CT images into 3D FEM model
3	Assignment of material properties to greyscale shades of bitmaps
4	Use of artificial intelligence analysis to the 3D model segmentation
5	Assignment of equivalent material properties to designated subdivisions, using a multiscale approach (for each elementary volume one finite element of averaged mechanical properties was assigned).
6	FEM simulation: static structural, computational fluid dynamics (CFD), fluid-structure interaction (FSI), multi-body simulation (MBS), explicit dynamics analysis, remodeling/healing simulation.

patients were treated conservatively with no pleural drainage. The results of treatment were satisfactory, with decreasing size of pneumothorax in consecutive radiograms, and its complete resolution in each case after a month.

The control group consisted of 22 patients, F/M – 5/17, mean 48.8 years (range 21–85 years). Those were trauma patients with tension pneumothorax at the time of admission. Pneumothorax was treated with pleural drainage in this group and the course of treatment was monitored radiologically. Normalization of blood gas content and other laboratory tests was present in 20 cases in which pneumothorax was resolved and the symptoms of lung contusion disappeared after a month. Two of these patients died during treatment of polytrauma, but pneumothorax was not the cause of death in either case.

Chest radiograms of all patients were analyzed. Based on computer tomography results, a reference computer model was made. In each case, the reference model was correlated with the clinical presentation of pneumothorax. The procedural elaboration consisted of an algorithm called 'computational rapid analysis' (CRA) for *in silico* analysis and optimization of surgical intervention. The sequential procedural steps are shown in Table 1.

Computed tomography (CT) chest images of the patients were taken. Then, a set of CT images was processed into an FEM model. Considering the size of the model derived (~20 GB of database file), only a representative model part was chosen for further simulation (Fig. 1a). This fragment underwent a further processing to decrease and optimize the database size. Finally, the model was limited to its minimal volume, covering the following subdivisions: chest cavity with the lung and the pneumothorax area, and a layer of surrounding tissues (Fig. 1b). In order to separate those divisions, an artificial intelligence (AI)-based filtration procedure was used. The procedure enabled to identify subdomains' boundaries and to assign equivalent material properties (Fig. 1c). Afterward, an attempt was made to transfer the database into a multiphysics simulation project of ANSYS/Workbench environment. Unfortunately, the model size made this procedure unworkable. The procedure turned out to be time-consuming and, with the available equipment base, could not be effectively implemented (10 % of single subdivision preprocessing required a time longer than 4 h). Therefore, an alternative model in the CATIA V5 program was prepared (Fig. 2a). Then, a simplified geometric 3D model of the investigated tissues was loaded into the computerized fluid dynamic (CFD) flow analysis of the ANSYS WB program (Fig. 2b).

3 Results

The analyzed fluid, designated as the air of temperature of 25 °C, was assumed for further analysis. After defining the boundary conditions and loads of the analysis (Fig. 3a, b), dynamic calculations of the fluid (air) flow in the chest cavity were made. This enabled to determine the distribution of pressure acting on the lung and the chest walls (Fig. 3c). Transferring the results of CFD analysis to the structural analysis environment allowed making the next methodological step, which was to create a conjugated fluid-structure analysis (FSI) (Fig. 4a). For the